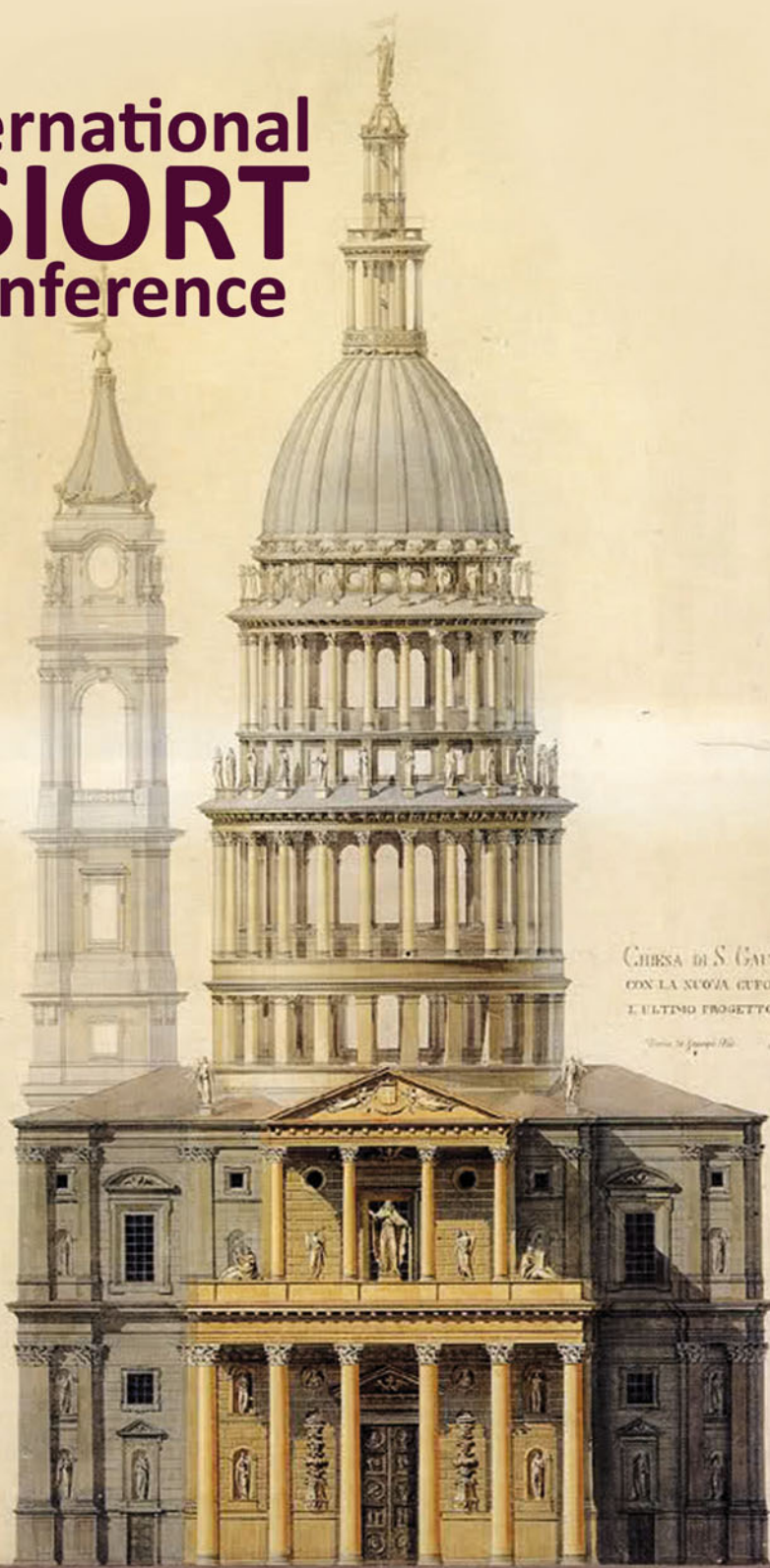
9th International ISIORT Conference

Final Programme

June 24/25th 2016 - Novara, Italy



ISIORT
INTERNATIONAL SOCIETY of
INTRAOPERATIVE RADIATION THERAPY

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Dear Colleagues,

on behalf of the ISIORT, we welcome you to the 9th International ISIORT Conference held in Novara, Italy, June 24-25, 2016. It is hoped that the rich and intense scientific programme will make this meeting a fruitful event with emphasis not only on the current clinical standard but also on the new opportunities and future views of our discipline.

Marco Krengli
President, ISIORT

Under the auspicies of

ESTRO European Society for RADIOTHERAPY & ONCOLOGY

esso The European Society of Surgical Oncology — Endorsed

ALATRO Asociación Ibero Latinoamericana de Terapia Radiante Oncológica

RAO Associazione Italiana di Radioterapia Oncologica

RAB Società Italiana di Radiobiologia

aifm Associazione Italiana di Fisica Medica

UPO Università del Piemonte Orientale

Azienda Ospedaliero-Universitaria Maggiore della Carità di Novara

PROGRAM

Friday, June 24

08:15 REGISTRATION

08:50 – 13:00 **_Educational course: IORT in Partial Breast Irradiation_**

8:50 *Introduction:* **Marco Krengli**

Clinical basis

Chair: **Felix Sedlmayer, Alberto Luini**

Update of results of randomized trials:

9:00 TARGIT
Elena Sperk

9:20 ELIOT
Roberto Orecchia

9:40 Discussion

9:50 UPDATE OF ASTRO/GEC-ESTRO RECOMMENDATIONS FOR PATIENT SELECTION
Maria Cristina Leonardi

10:10 Discussion

10:20 Coffee break

Practical aspects of the IORT procedure

Chair: **Claudia Schumacher, Michele Avanzo, Antonella Ciabattoni**

IORT by electrons

10:40 SURGICAL ASPECTS
Alberto Luini

10:55 PHYSICAL ASPECTS
Stefania Comi

11:10 Discussion

IORT by Kv x-rays

11:20 SURGICAL ASPECTS
Marc Sütterlin

11:35 PHYSICAL ASPECTS
Frank Schneider

11:50 Discussion

New perspectives in translational research

Chair: **Hugo Marsiglia, Robert Krempien**

12:10 BIOMOLECULAR AND HISTOLOGICAL PROGNOSTIC FACTORS FOR IN BREAST RECURRENCES AFTER IORT AS A BOOST IN BREAST CANCER
Gerd Fastner

12:30 GENOMIC SELECTION OF PATIENTS IN PBI
Pedro Lara

12:50 Discussion

13:00 Lunch

14:00 **Welcome address**

14:20 – 15:40 *Evidence Based Medicine and IORT*

Chair: **Felipe Calvo, Umberto Ricardi**

14:20 BREAST CANCER
Antonella Ciabattoni

14:40 GASTRO-INTESTINAL TUMORS
Michael Haddock

15:10 SARCOMA
Falk Roeder

15:30 Discussion

15:40 – 17:00 *Selected oral presentations: breast I*

Chair: **Antonella Ciabattoni, Mikheil Janjalia**

15:40 FULL-DOSE 21 Gy INTRAOPERATIVE ELECTRON RADIOTHERAPY IN EARLY BREAST CANCER: RESULTS AFTER A MEDIAN 5.2 -YEARS FOLLOW UP IN 758 PATIENTS FROM A SINGLE ITALIAN INSTITUTION
Takanen S., Gambirasio A., Gritti G., Källi M., Andreoli S., Fortunato M., Feltre L., Filippone F.r., Iannacone E., Maffioletti L., Muni R., Piccoli F., Mauri E.m.p., Giovannelli M., Burgoa L., Paludetti A., Ferro M., Palamara F., Fenaroli P., Cazzaniga L.f. (Bergamo, Italy)

15:50 BREAST CONSERVING SURGERY: INTRAOPERATIVE RADIOTHERAPY USING NOVAC 7, EXPERIENCE WITH 703 CASES AT CITTÀ DI CASTELLO HOSPITAL
Alessandro M., Ferranti F., Massetti M., Corazzi F., Angelini M., Pentiricci A., Rossi G. (Città di Castello, Perugia, Italy)

16:00 PARTIAL BREAST WITH ELECTRONS: PRELIMINARY RESULTS OF THE MULTICENTER GROUP OF THE EMILIA ROMAGNA REGION ITALY
Stefanelli A., Zini G., Baldissera A., Frezza G., Iotti C., Venturini A., Perini F. (Ferrara, Italy)

16:10 LOCAL RECURRENCE IN BREAST CANCER PATIENTS TREATED WITH IORT vs CONVENTIONAL EBRT IN EARLY STAGE BREST CANCER: OUR SINGLE CENTRE RETROSPECTIVE CASE-CONTROL STUDY, TREVISO HOSPITAL
Lekaj M., Cesaro G., Gava A. (Padova, Italy)

16:20 INTRAOPERATIVE RADIOTHERAPY FOR EARLY BREAST CANCER: A MONOCENTRIC EXPERIENCE
Baldissera A., Giaccherini L., Marinelli I., Mosconi F., Manganelli F., Guidi E., Romagnoli R., Magi S., Ricci R., Palombarini M., Parisi A., Cucchi M.C., Ferrarini R., Frezza G. (Bologna, Italy)

16:30 ANALYSIS OF DATA FROM THREE CENTERS IN TURKEY ON INTRAOPERATIVE RADIOTHERAPY OF BREAST CANCER
Bese N., Altinok A., Alan O., Dizdar N., Caglar H., Ince U., Uras C. (Istanbul, Turkey)

16:40 WHICH FACTORS CONTRIBUTE TO EARLY TUMOR CONTROL FAILURE AFTER APBI/IOERT FOR ELDERLY BREAST CANCER PATIENTS?
Koper P., Fisscher U., Mast M., Petoukhova Anna L., Marinelli A., Van Der Sijp J., Franssen J., Merkus J., Jannink I., Gescher F., Speijer G., Roeloffzen E., Zwanenburg A., Francken A.b., Struikmans H. (The Hague, The Netherlands)

16:50 TARGIT E(LDERLY) - PROSPECTIVE PHASE II STUDY OF INTRAOPERATIVE RADIOTHERAPY (IORT) IN ELDERLY PATIENTS WITH SMALL BREAST CANCER
Sperk E. (Mannheim, Germany)

17:00 Coffee break

17:20
18:10

Selected oral presentations: breast II

Chair: **Elvio Russi, Claudia Schumacher**

17:20 IOERT AS ANTICIPATED TUMORBED BOOST IN BREAST CANCER OF CLINICAL STAGES I-III:UPDATED 10-YEARS RESULTS
Fastner G., Kaiser J., Kronberger C., Moder A., Kopp P., Wallner M., Reitsamer R., Fischer Th., Fussl C., Zehentmayr F., Sedlmayer F. (Salzburg, Austria)

17:30 INTRAOPERATIVE ULTRASOUND ROLE IN BREAST INTRAOPERATIVE ELECTRON RADIATION THERAPY (B-IOERT) BOOST
Vidali C., Severgnini M., Bortul M., Bellio G., Urbani M., Toscano L., De Denaro M., Beorchia A. (Trieste, Italy)

17:40 INTRAOPERATIVE ELECTRON BOOST RADIOTHERAPY (IOERT) FOR EARLY STAGE BREAST CANCER: INSTITUTIONAL EXPERIENCE (2009-2015)
Calín A., Muñoz M., Blanco J., Guerrero L., Sierra I., Santos M., Arnaiz J., Davo A., Lozano M., Alvarado E., Lizarraga S., **Calvo F.** (Madrid, Spain)

17:50 INTRAOPERATIVE RADIATION THERAPY FOR BREAST CANCER:
A PHYSICAL AND CLINICAL REVIEW OF IRANIAN EXPERIENCE
Mahdavi S.R.M., **Akbari M.E.**, Nafisi N., Mirzaei H.R. (Tehran, Iran)

18:00 RISK FACTORS FOR IPSILATERAL BREAST CANCER RECURRENCE AFTER INTRAOPERATIVE RADIOTHERAPY (IORT)
Sperk E., Teich P., Weiss C., Sütterlin M., Wenz F. (Mannheim, Germany)

18:10
18:30 **Lecture: Imaging in IORT: any progress?**

Introduction: **Felipe Calvo**
Speaker: **Javier Pascau**

18:30
18:50 **Lecture: Potential Clinical Trials with IORT and Immunotherapy**

Introduction: **Michael Haddock**
Speaker: **John Grecula**

20:00 Social Dinner

Saturday, June 25

08:00 – 09:20 *Selected oral presentations: various tumor sites*

Chair: **Carlos Ferrer, Sergio Gentilli**

08:00 RADIOLOGICAL PELVIC CHANGES AFTER INTENSE ADJUVANT LOCAL THERAPY INCLUDING INTRAOPERATIVE PRESACRAL ELECTRON BOOST IN LOCALLY ADVANCED RECTAL CANCER: PREDICTIVE ANALYSIS
Muñoz M., Serrano J., Alvarado E., Guerrero L., Santos M., Lozano M., **Calvo F.** (Madrid, Spain)

08:10 INTRA-OPERATIVE RADIOTHERAPY WITH ELECTRONS (IOERT) AND SURGERY IN PRIMARY RECTAL TUMORS:RESULTS OF OUR INSTITUTION
Morillo Macías V., Bouché A., Ferrer C., López J., Boldó E., Lozoya R., Mayol A. (Castellón, Spain)

08:20 INTRA-OPERATIVE RADIOTHERAPY WITH ELECTRONS (IOERT) AND SURGERY IN PELVIC RECURRENCE: RESULTS OF OUR INSTITUTION
Morillo Macías V., López J., Bouché A., Ferrer C., Boldó E., Lozoya R., Mayol A. (Castellón, Spain)

08:30 PANCREATIC CANCER: RESULTS AFTER RESECTION AND OPTIMIZED ESCALATED IRRADIATION
Muñoz M., Alvarado E., Sierra I., Guerrero L., Santos M., Arnaiz J., Garcia Sabrido G., Ascensio J., Gómez M., **Calvo F.** (Madrid, Spain)

08:40 EXTREMITY PRESERVATION IN PRIMARY SOFT TISSUE SARCOMAS AFTER RADICAL INTENT SURGERY AND DOSE-DENSE RADIOTHERAPY"
Calvo F. (Madrid, Spain)

08:50 INCLUDING INTRAOPERATIVE RADIOTHERAPY IN THE THERAPEUTIC SCHEME RESULTS IN SIMILAR LOCAL CONTROL IN HIGH AND LOW RISK SARCOMA
Boldo E., Piquer T., Mayol A., Lozoya R., Bouche A., Morillo V., Lopez Tarjuelo J., Ferrer C. (Castellón, Spain)

09:00 INTRAOPERATIVE RADIOTHERAPY AND VASCULAR RESECTION
Boldo E., Piquer T., Lozoya R., Mayol A., Molina J., Admeller X., Bouche A., Morillo V., Ferrer C. (Castellón, Spain)

09:10 USER EVALUATION OF AN IOERT DEDICATED ONLINE INTERACTIVE SCIENTIFIC PLATFORM
Alvarado E., Silos m., Sierra I., Guerrero L., Pascau J., **Calvo F.** (Madrid, Spain)

09:20 – 10:30 *Physics Session*

Chair: **Wilhelmus Dries, Frank Hensley**

09:20 SAFETY IN IORT PROCESS AND QA ISSUES
Karla Torszok

09:40 IN VIVO DOSIMETRY IN IORT TREATMENTS
J. Lopez-Tarjuelo

10:00 CHALLENGES IN IORT DOSIMETRY: THE MISSION OF THE AIFM WORKING GROUP, ITS EXPERIENCE AND WORKING HYPOTHESES
Loris Menegotti

10:20 Discussion

10:30
12:00

Radiobiology Session

Chair: **Renzo Corvò, Elena Sperk**

10:30 RADIOBIOLOGY OF LOW-ENERGY X-RAYS AND HIGH SINGLE DOSES
Elena Sperk

10:50 MICROENVIRONMENT BY X-RAYS IORT
Gustavo Baldassarre

11:10 INTRAOPERATIVE RADIOTHERAPY IMPAIRS BREAST CANCER STEM CELL PHENOTYPE INCREASED BY SURGICAL WOUNDING
David Murawa

11:30 Discussion

running coffe break 10:30/11:30

11:40
12:30

Satellite Symposium (see pag. 10)

12:30 Lunch

13:15
13:45

General Assembly

13:45
14:30

Lecture: Long term survivors after IORT: a lesson to be learned

Introduction: **Roberto Orecchia**
Felipe Calvo, Michael Haddock, Felix Sedlmayer

14:30
15:40

Selected oral presentations: biology and physics

Chair: **Giovanni Ivaldi, Gianfranco Loi**

14:30 RADIOBIOLOGICAL ASPECTS OF INTRA OPERATIVE RADIOTHERAPY
Akbari M.E., Nafisi N., Mirzaei H.R., Mahdavi S.R.M. (Tehran, Iran)

14:40 APOPTOTIC PATHWAY ACTIVATION IN PROSTATE NEOPLASTIC CELLS AFTER 12 GY-IORT
Pisani C., Domagala N., Copes F., Mercalli F., Volpe A., Beldì D., Boccafoschi F., Boldorini R., Krengli M. (Novara, Italy)

14:50 IN VIVO DOSIMETRY BY EBT3 GAFCHROMIC FILMS DURING IORT BREAST TREATMENT
Manco L., Stefanelli A., Zini G., De Troia A., Carcoforo P., Hernandez Flores F., De Guglielmo E., Fabbri S., Turra A. (Ferrara, Itay)

15:00 VARIABLES AFFECTING DISC ATTENUATOR ALIGNMENT IN BREAST INTRAOPERATIVE RADIOTHERAPY (IORT)
Ivaldi G.B., Tabarelli De Fatis P., Liotta M., Malovini A. (Pavia, Italy)

15:10 BREAST IOERT AND SHIELDING DISCS – MORE THAN A SIDEKICK?
Hamedinger D., Track C., Moser K., Bräutigam E., Wiesauer K., Putz E., Geinitz H. (Linz, Austria)

15:20 COMPARING THE DOSIMETRIC CHARACTERISTICS OF THE ELECTRON BEAM FROM DEDICATED INTRAOPERATIVE AND CONVENTIONAL RADIOTHERAPY ACCELERATORS
Mirzaei H.R., Baghani H.R., Aghamiri S.M.R., Mahdavi S.R.M., Akbari M.E., Nafisi N. (Tehran, Iran)

15:30 COMPARISON OF MOBETRON 1000 AND MOBETRON 2000 FOR IOERT
Petoukhova Anna L., Wingerden K.V., Egmond J.V., Koper P., Ceha H., Stam T., Peeters M., El Kadaoui M., Tan J., Struikmans H. (The Hague, The Netherlands)

15:40 / 16:50 *Ongoing Trials and Prospective Studies*

Chair: **Antonino De Paoli, Ignacio Azinovic**

15:40 HIOB PROTOCOL
Gerd Fastner

15:50 MULTI-INSTITUTION PHASE II TRIAL OF INTRAOPERATIVE ELECTRON BEAM RADIOTHERAPY BOOST AT THE TIME OF BREAST CONSERVING SURGERY WITH ONCOPLASTIC RECONSTRUCTION IN WOMEN WITH EARLY-STAGE BREAST CANCER
Jose Bazan

16:00 MULTIDISCIPLINARY MANAGEMENT IN SPINE METASTASIS (V-IORT)
Roberto Orecchia

16:10 IORT IN RECONSTRUCTION SURGERY
Luis Marin

16:20 RETROPERITONEAL SARCOMA
Falk Roeder

16:30 IORT IN HIGH-RISK PROSTATE CANCER
Michele Billia

16:40 CURRENT STATUS OF THE ISIORT REGISTRY
Marco Krengli

16:50 / 17:00 **Closing remarks**

FACULTY

Michele Avanzo	*Aviano, Italy*
Ignacio Azinovic	*Madrid, Spain*
Gustavo Baldassarre	*Aviano, Italy*
Jose Bazan	*Columbus, USA*
Michele Billia	*Novara, Italy*
Felipe Calvo	*Madrid, Spain*
Antonella Ciabattoni	*Rome, Italy*
Stefania Comi	*Milan, Italy*
Renzo Corvò	*Genova, Italy*
Antonino De Paoli	*Aviano, Italy*
Wilhelmus Dries	*Eindhoven, The Netherlands*
Gerd Fastner	*Salzburg, Austria*
Carlos Ferrer	*Castellon, Spain*
Sergio Gentilli	*Novara, Italy*
John Grecula	*Ohio State, USA*
Michael Haddock	*Rochester, USA*
Frank Hensley	*Heidelberg, Germany*
Giovanni Ivaldi	*Pavia, Italy*
Mikheil Janjalia	*Tbilisi, Georgia*
Robert Krempien	*Berlin, Germany*
Marco Krengli	*Novara, Italy*
Pedro Lara	*Gran Canaria, Spain*
Maria Cristina Leonardi	*Milan, Italy*
Gianfranco Loi	*Novara, Italy*
Alberto Luini	*Milan, Italy*
Luis Marin	*Santiago, Chile*
Hugo Marsiglia	*Santiago, Chile*
Loris Menegotti	*Trento, Italy*
David Murawa	*Poznan, Poland*
Roberto Orecchia	*Milan, Italy*
Javier Pascau	*Madrid, Spain*
Umberto Ricardi	*Turin, Italy*
Falk Roeder	*Munich, Germany*
Elvio Russi	*Cuneo, Italy*
Frank Schneider	*Mannheim, Germany*
Claudia Schumacher	*Colonia, Germany*
Felix Sedlmayer	*Salzburg, Austria*
Elena Sperk	*Mannheim, Germany*
Marc Sütterlin	*Mannheim, Germany*
Juan Lopez-Tarjuelo	*Castellon, Spain*
Karla Torszok	*Santiago, Chile*

11:40 Intrabeam overwiev on new IORT applicators and protocols
Roberta Lazzari, IEO, Milan Italy

In cooperation with ZEISS

11:55 A real time in vivo dosimeter integrated in the RP disk for IOeRT breast treatment
Giuseppe Felici, R&D Manager S.I.T. - Sordina IORT Technologie

In cooperation with SIT Sordina IORT Technologies

12:10 Worldwide Technical and Clinical Review of Mobetron Usage
Sebastian Adamczyk, Associate Director Physics, IntraOp

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GENERAL INFORMATION

MEETING VENUE

Auditorium Banca Popolare di Novara
Via Carlo Negroni, 11 - 28100 Novara (Italy)

The Auditorium is located in the heart of the historic centre of Novara, just a few steps from Basilica of San Gaudenzio.

REGISTRATION FEES *in Euro VAT included*

Conference

REGULAR	*€ 150,00*
RESIDENTS*	*free*
FACULTY	*free*

* only attached the attendance certificate

SOCIAL DINNER

Social Dinner, included in the regular Conference fee, will be held on Friday, June 24 - 20:00 hrs at **Club Unione** Via Giacomo Puccini 2, Novara

REGULAR FEE COVERS

Admittance to the scientific session of the congress, congress material, access to technical exhibition, refreshments during breaks and lunches as indicated in the final program, social dinner.

RESIDENTS REGISTRATION COVERS

Admittance to the scientific session of the congress, congress material, access to technical exhibition, refreshments during breaks and lunches as indicated in the final program.

BEST ORAL PRESENTATION AWARD

The best oral presentation selected by the ISIORT Board will be awarded.
The award amount of € 600,00 is supported by ISIORT.

LANGUAGE

The official language of the Meeting is English.

ATTENDANCE CERTIFICATE

At the end of the Meeting, an attendance certificate will be issued to all registrered Participants.

VARIATIONS

The Scientific and the Organizing Secretariat reserve the right to make whatever change to the program they deem necessary for scientific and/or technical reasons.

PRIVACY

Information according to Legislative Decree 30/06/2003 No. 196 ("Law regarding the protection of personal data"): your personal data provided on this occasion will be processed manually and electronically in order to document your participation in Congresses, Events, Meetings and other Events organized by Ad Arte Srl and treatments arising from legal obligations. They will be communicated to suppliers and third parties involved or participating in the Event, as well as to the competent authorities, in compliance with the law and will be used for sending the periodic Newsletter containing update on the events of your interest organized by Ad Arte . Providing data for such purposes, it is compulsory for your participation in the Congress, the refusal will prevent participation. The data controller is Ad Arte Srl - Via M. D'Azeglio 51 2-40123 Bologna, Italy. You shall have all the rights under Title II of the Legislative Decree 30/06/2003 No. 196. The signature on the forms prepared for Congress (registration form, sponsor and speakers forms, etc.) constitutes acknowledgment of this Notice and the rights set out above, and enables the processing of personal data and the communication for the above purposes.

NOTE

NOTE

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ORGANIZATION

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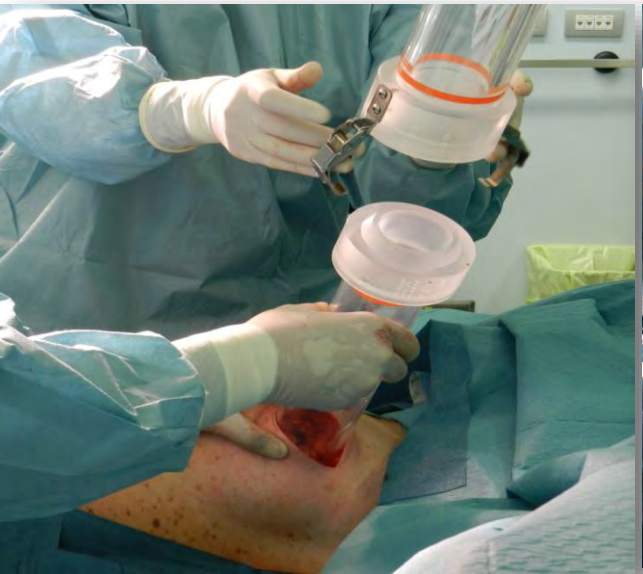
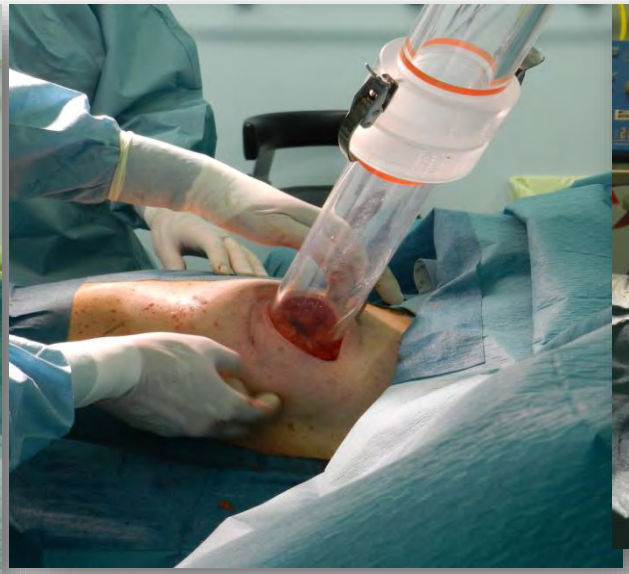
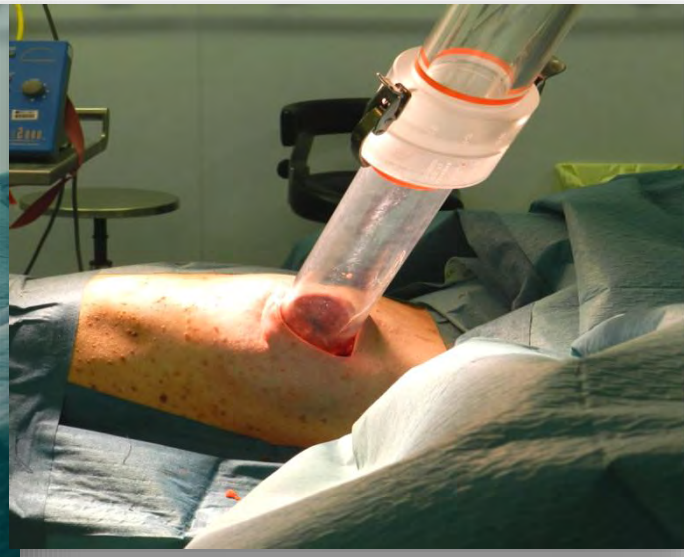
Surgical aspects of Intraoperative Radiotherapy with Electrons

Alberto Luini- Fabio Bassi
European Institute of Oncology
MILAN

Multidisciplinarity is an integral part of the treatment of breast cancer.
Breast conserving surgery and personalized medical therapy are now accompanied by extremely focused and precise radiotherapy.
With this approach, ELIOT is a new way of improving the adjuvant treatment

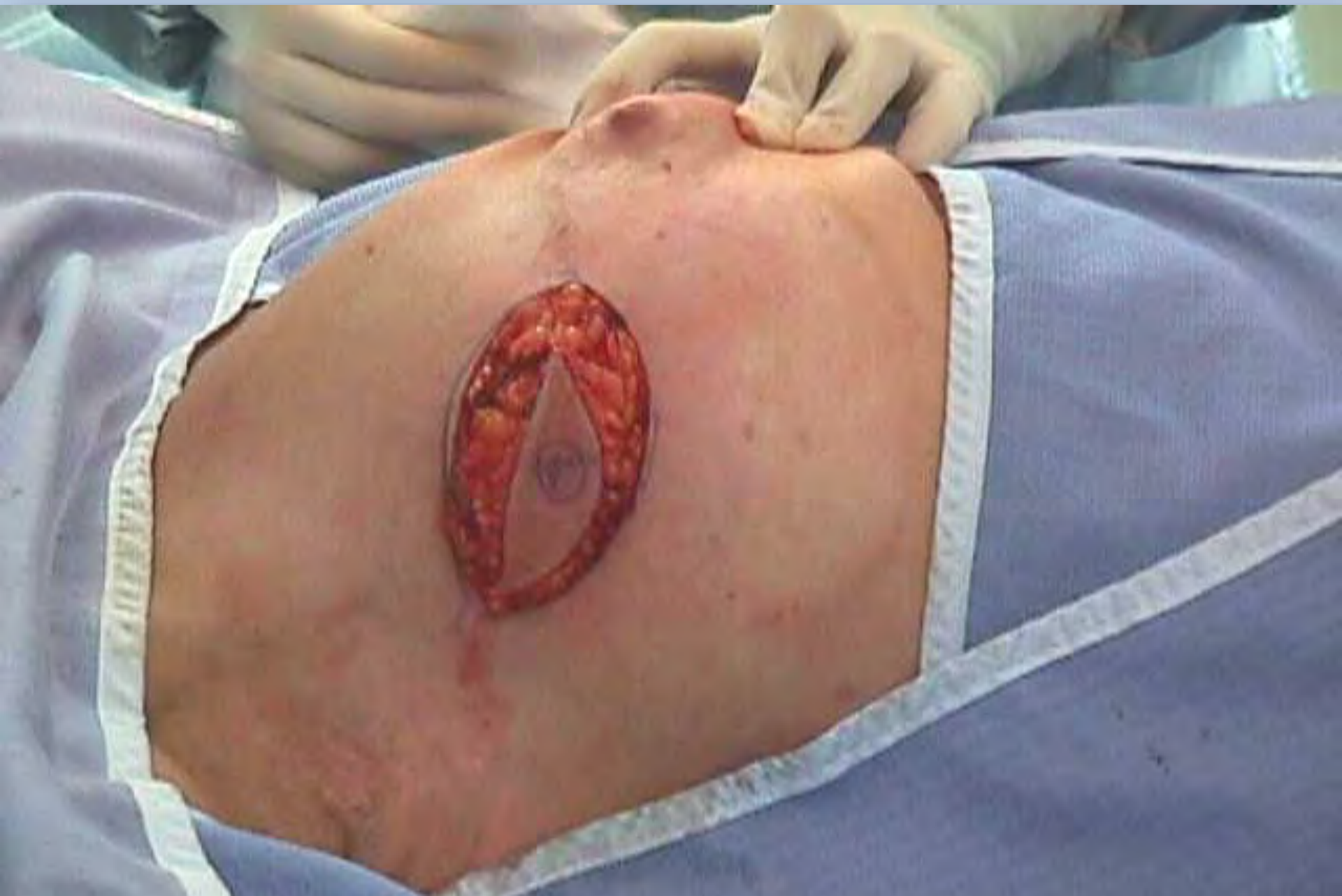




Six steps for the ELIOT procedure

1. Tumor removal
2. Thoracic wall protection
3. Temporary breast gland reconstruction
4. Collimator placement
5. Radiotherapy
6. Breast reconstruction

The first step:
tumor removal by quadrantectomy or partial resection.

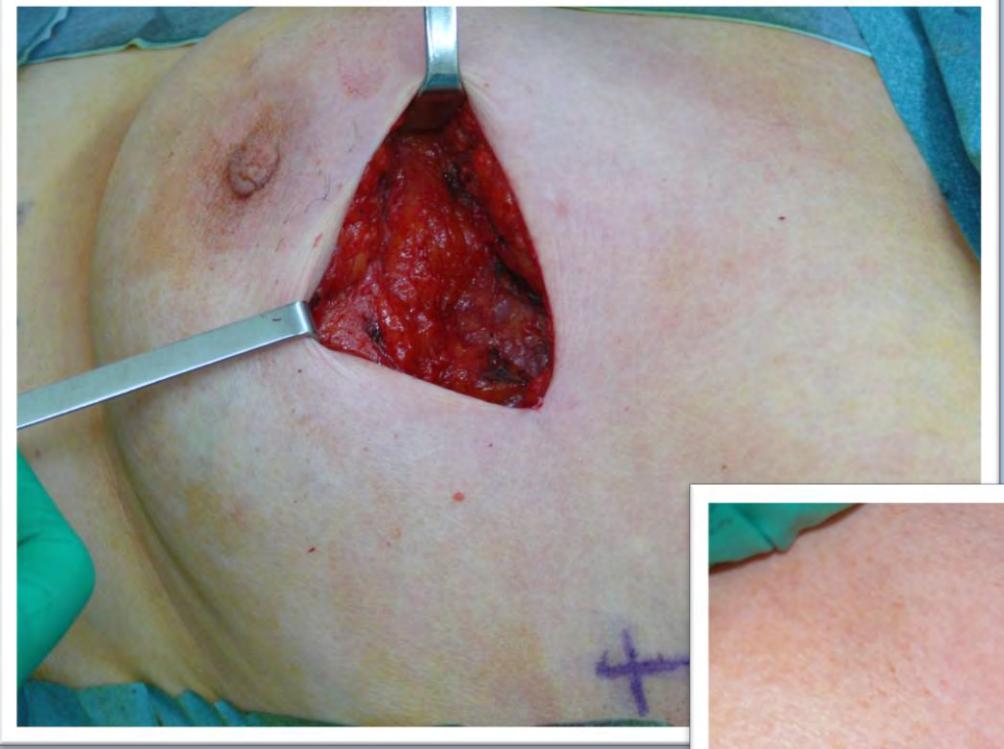
quadrantectomy

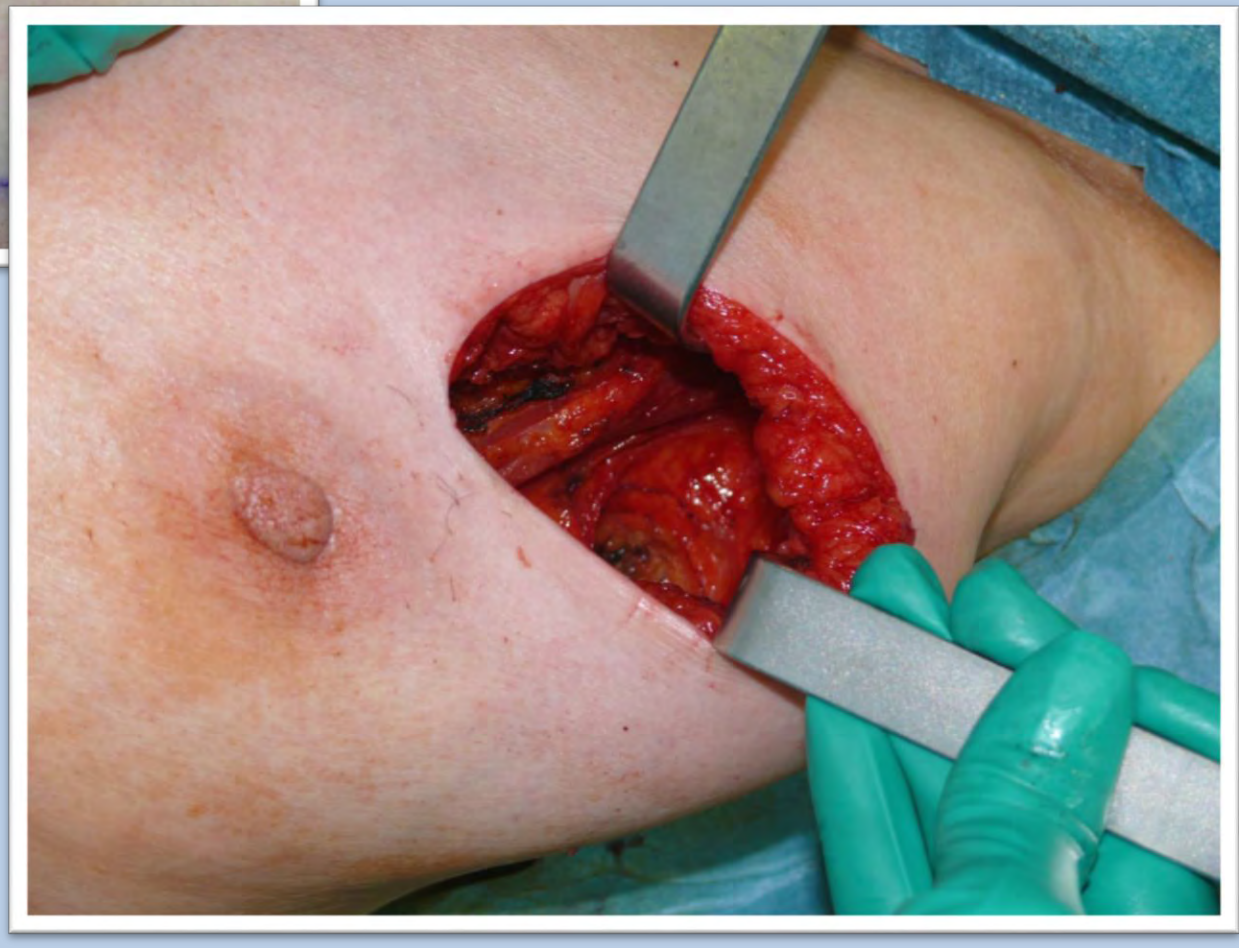


Cancer removal

The wide breast resection is done in the same manner as in standard BCS: radial skin incision centered on the tumor or periareolar incision for tumors relatively close to the areola.

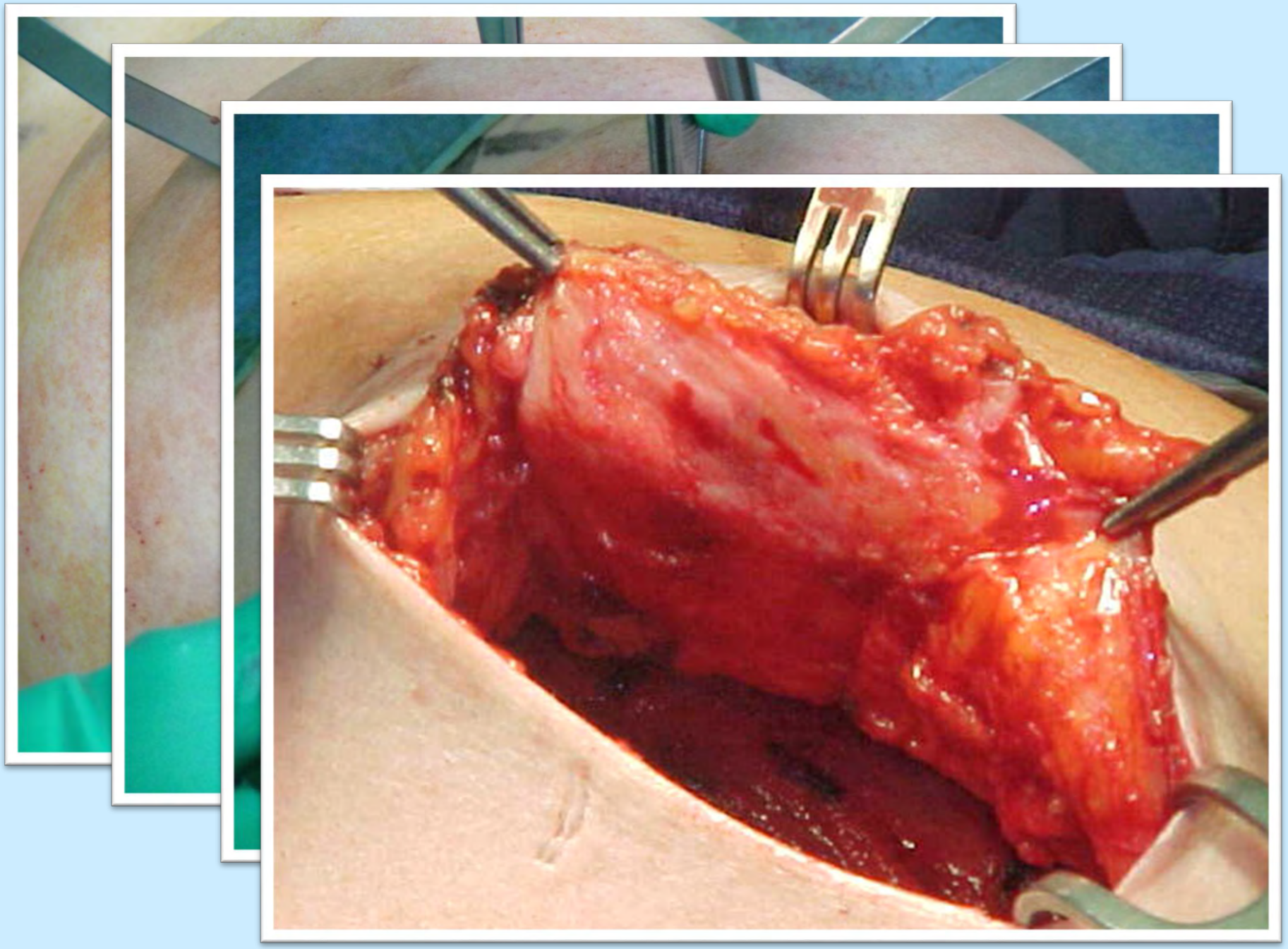
The ELIOT procedure does not interfere with the oncological criteria of "classic" BCS (1 cm grossly free margins of resection, usually including a small ellipse of skin). The excision deeply extends to the fascia of the pectoralis major muscle, which is usually spared.

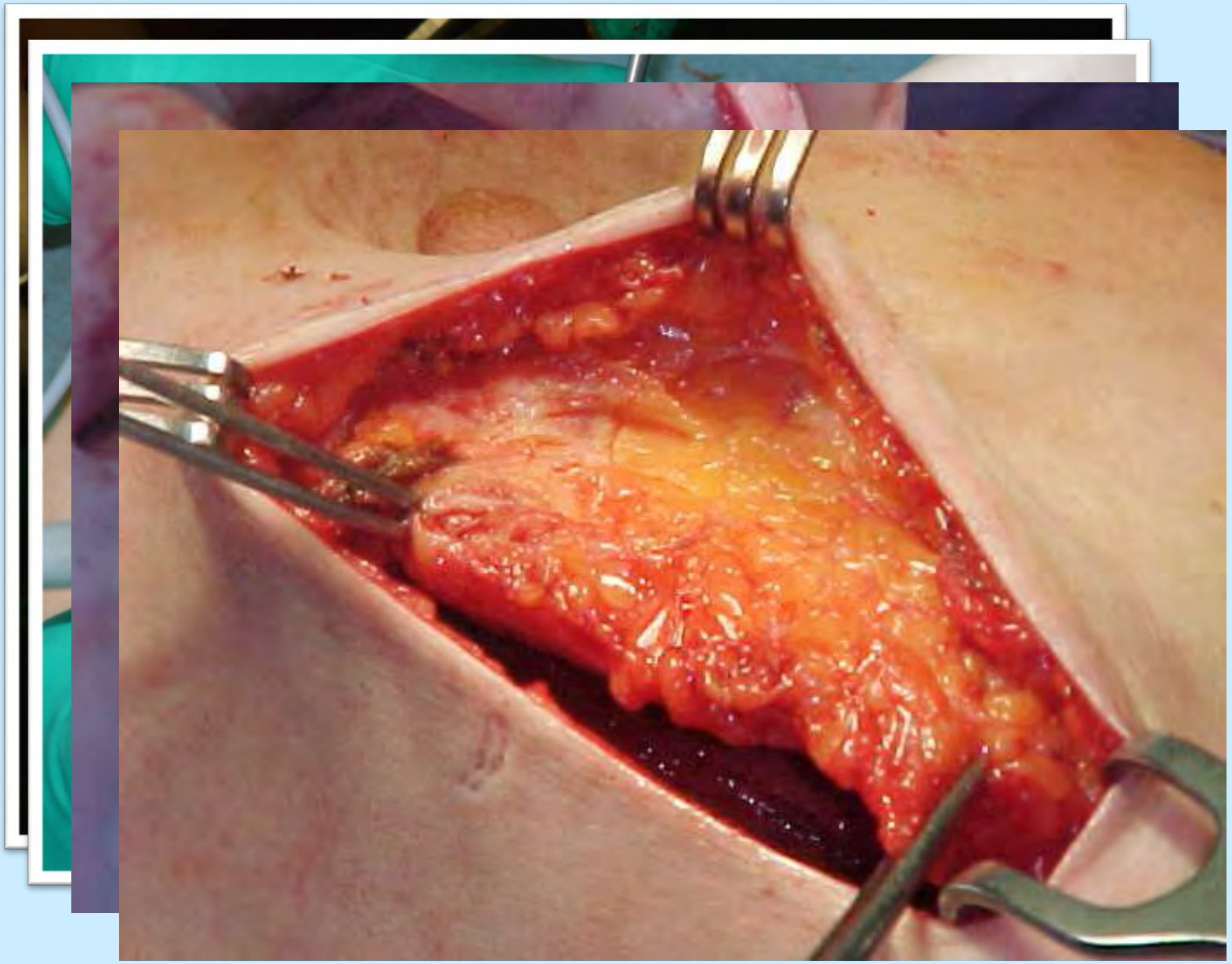




Breast mobilization

The wide mobilization of the mammary gland from the surrounding fascia of the pectoralis major and, superficially, from the skin, represents a critical step, permitting the optimal exposure of the "target" to the radiation beam.





The second step: after the isolation of an adequate area all around the surgical breach, protection of the thoracic wall using lead and aluminium disks.

Thoracic wall protection

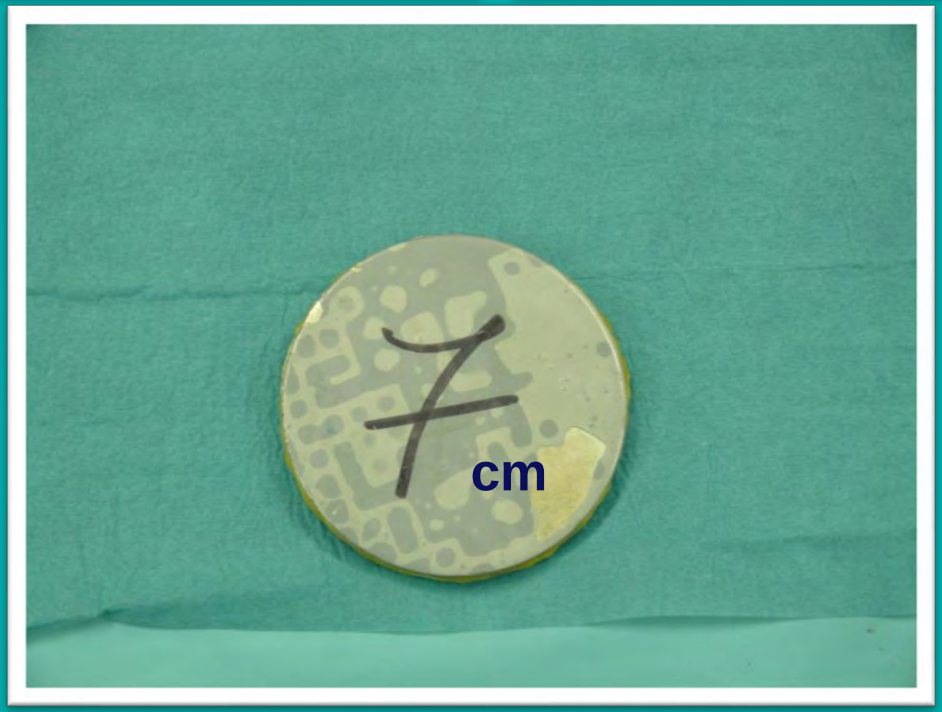
To minimize the irradiation delivered to the thoracic wall and to guarantee the delivery of the full radiation dose, a dedicated lead disk 5 mm thick and an aluminum disk 4 mm thick, available in various diameters (4,5,6, 8 and 10 cm), are commonly used as protective devices.

Thoracic wall protection

The disks are inserted together in the space between the gland and the pectoral muscle. Wall protection is guaranteed by the absorption properties of the lead disk combined with the aluminum disk for the absorption of the electrons back-scattered by the lead disk itself. Moreover, the 9-mm distance created by the two disks represents an additional guarantee of thoracic protection.

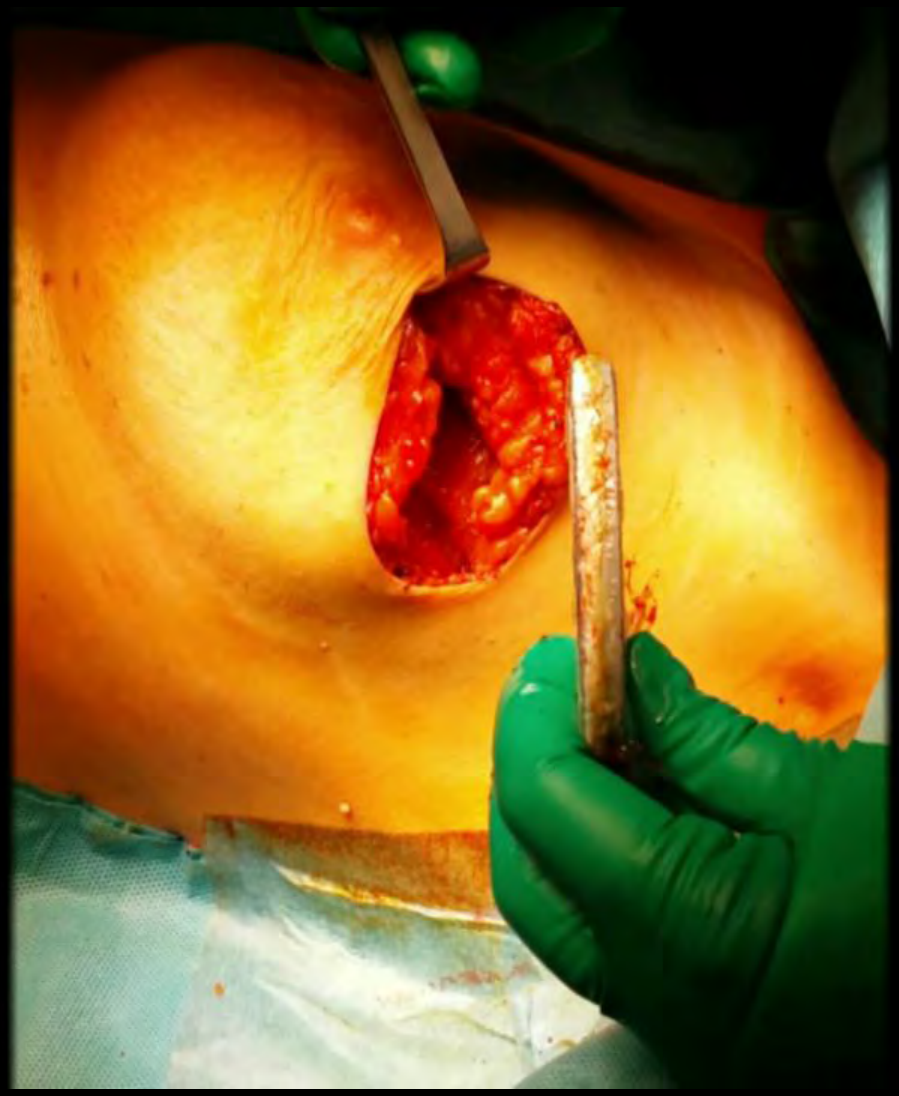

Alluminium face

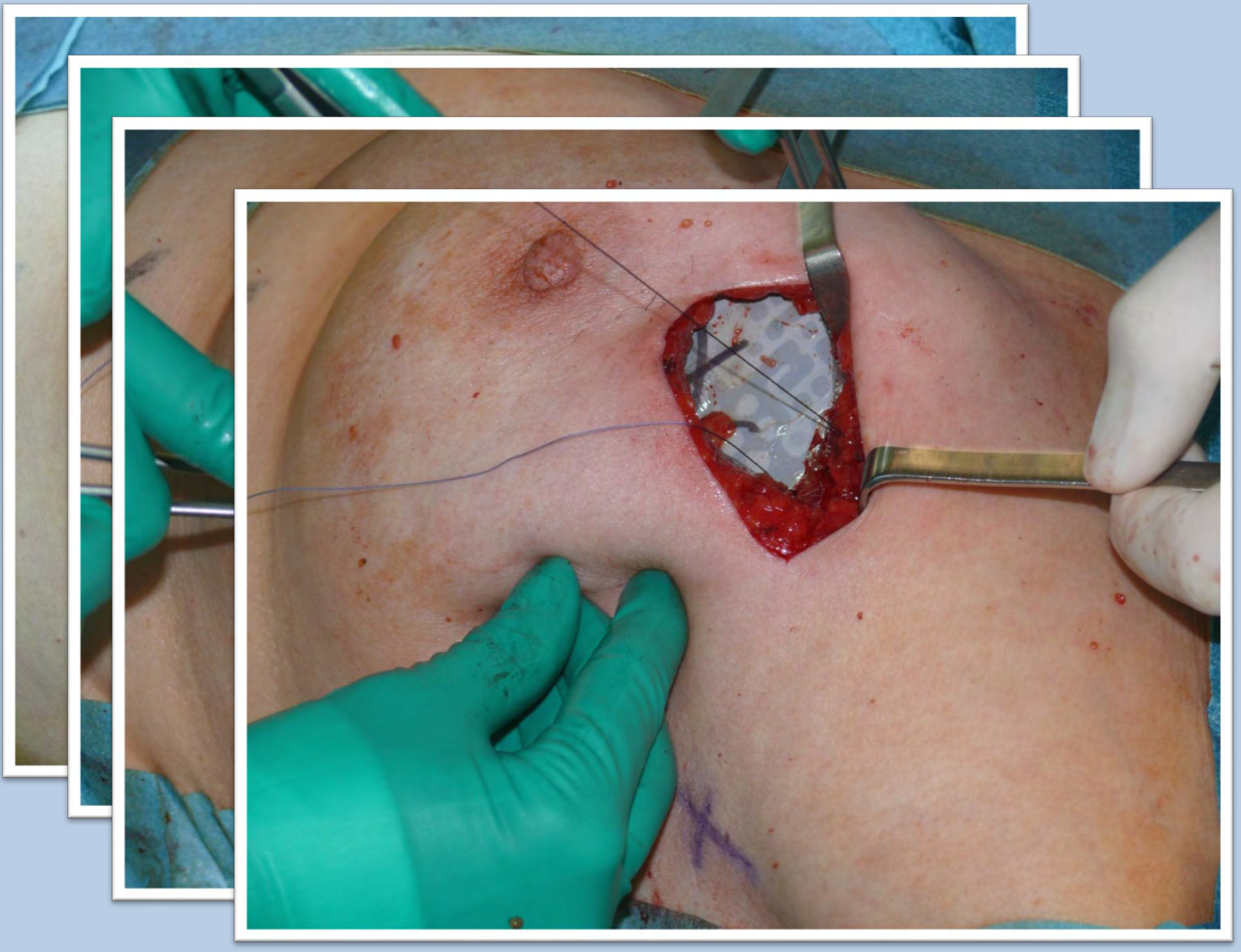

Lead face
8 cm

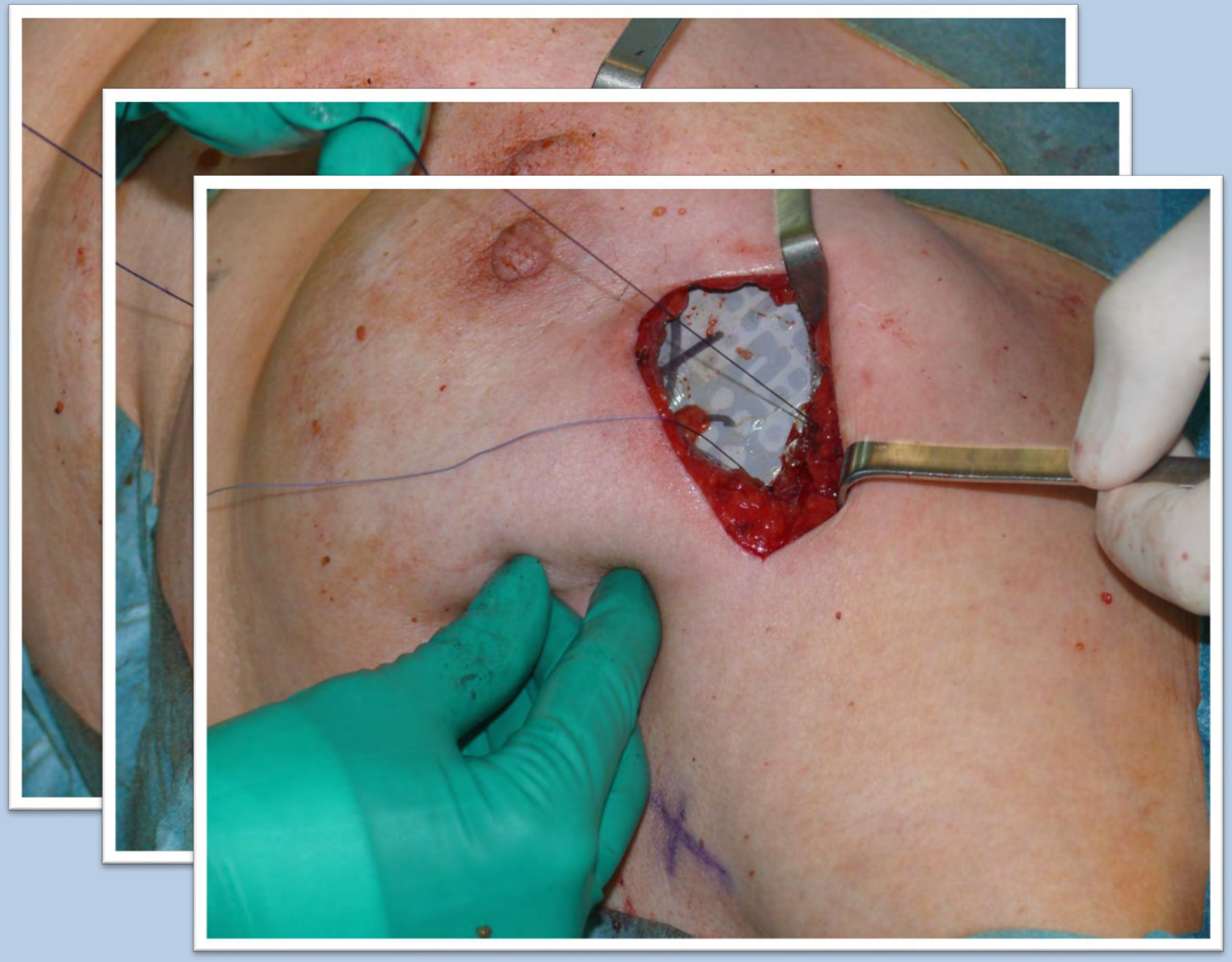

7 cm

Thoracic wall protection

To allow the best protection of the thoracic wall, the disks must be at least equal or greater in size to the breast target size. According also to the width of the skin incision, the largest disks must be chosen and placed exactly under the mammary target to be irradiated.







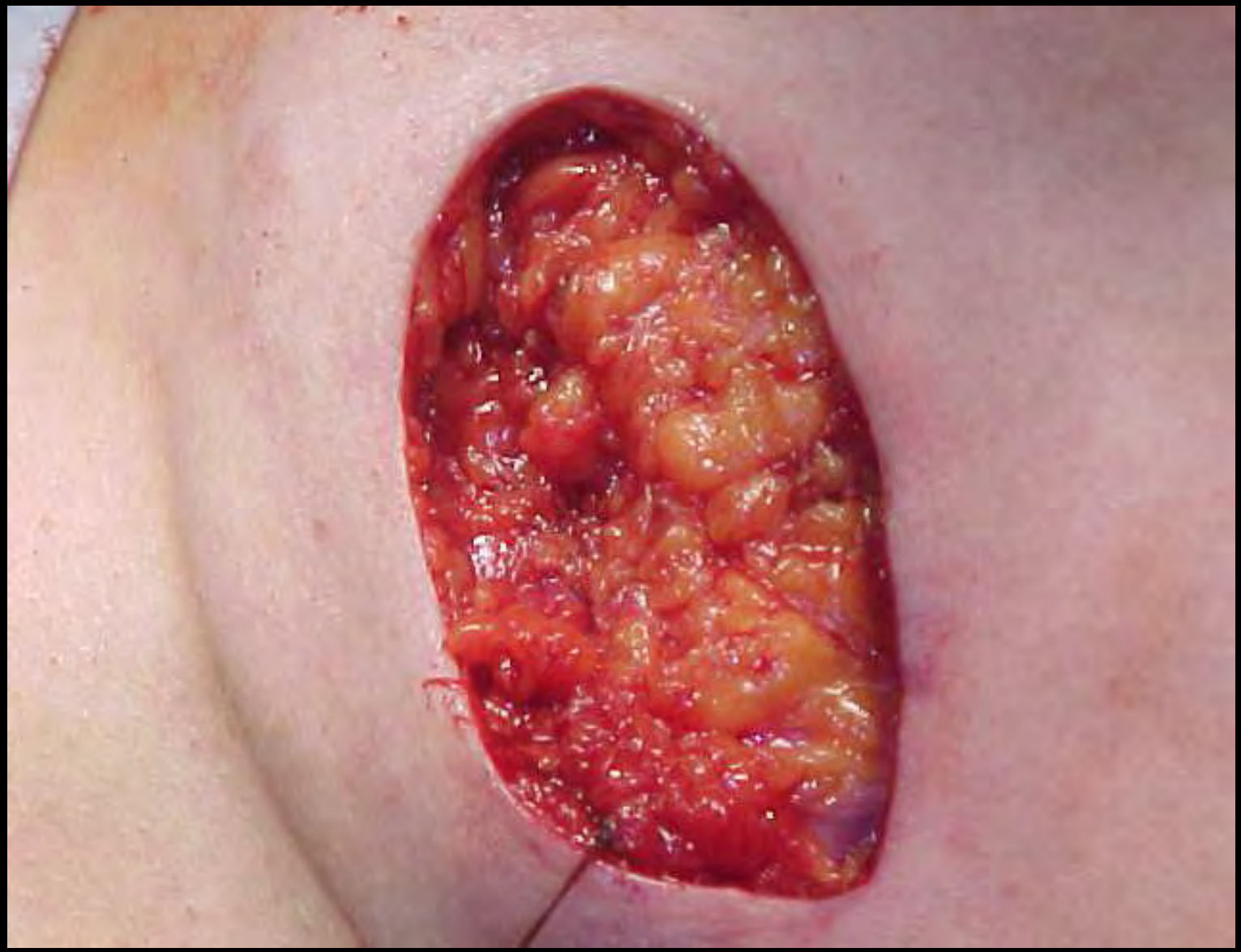
Breast gland reconstruction

The gland must be reconstructed over the disks avoiding excessive non-homogeneity in the shape of the target volume. In fact, the electron beam energy is chosen on the basis of the thickness of the target volume, and the best dose distribution of radiotherapy in the gland is achieved if the thickness of the irradiated target remains as homogeneous as possible.

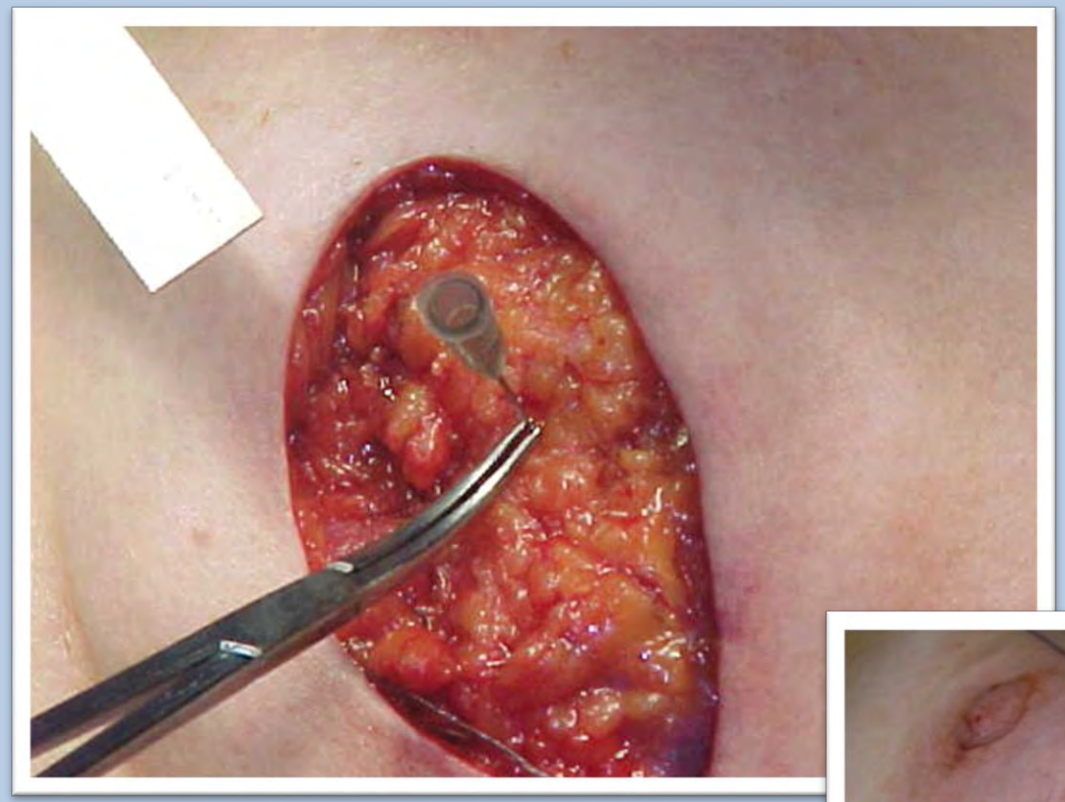
Breast gland reconstruction

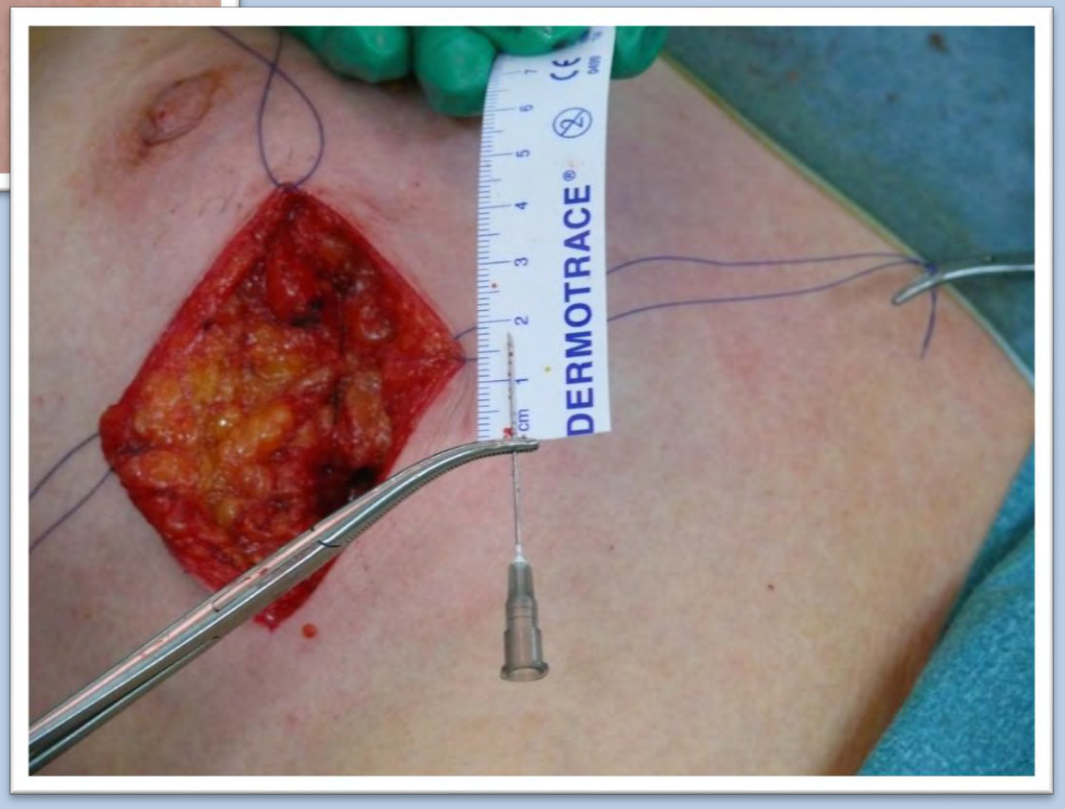
The gland is sutured by temporary separated stitches in one single plane, taking the entire thickness of the breast. The final result is the perfect restoration of the anatomy and of the thickness of the gland, with the protection of the thoracic wall lying under the gland.

Breast gland reconstruction



The third step: breast gland thickness measurement and collimator placement



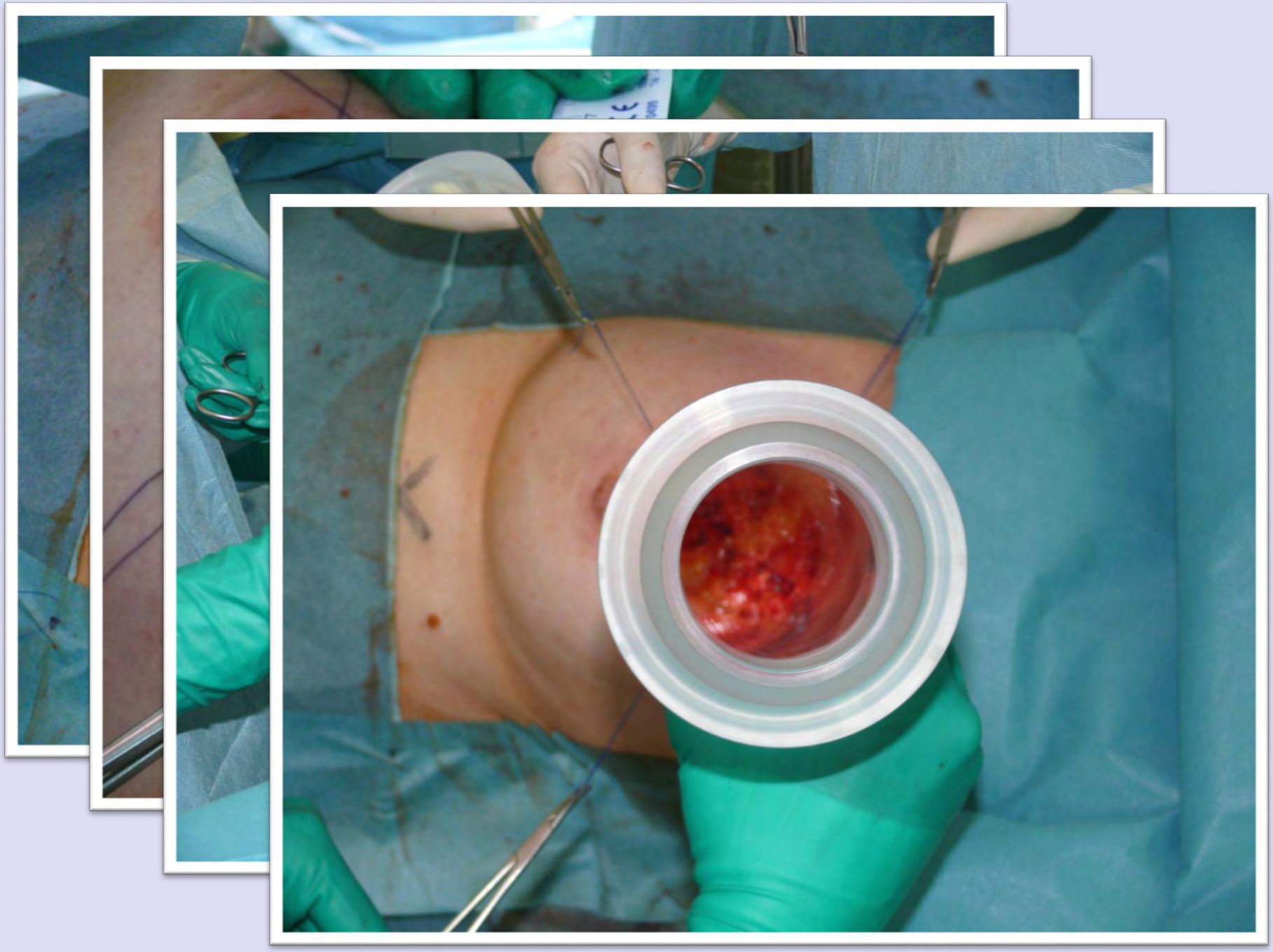

DERMOTRACE®
cm

Collimator placement

The collimator of the LINAC is introduced through the skin incision and placed directly in contact with the breast target. The skin margins of the surgical incision are everted out, far from the target. The portion of the breast that needs to be irradiated (clinical target volume) is an area of 4 to 5 cm of minimum diameter around the cancer resection site but, depending on the breast size, the cancer localization, and the technical possibility of mobilizing the gland, it is possible to irradiate up to 10 cm of the breast parenchyma.

Collimator placement

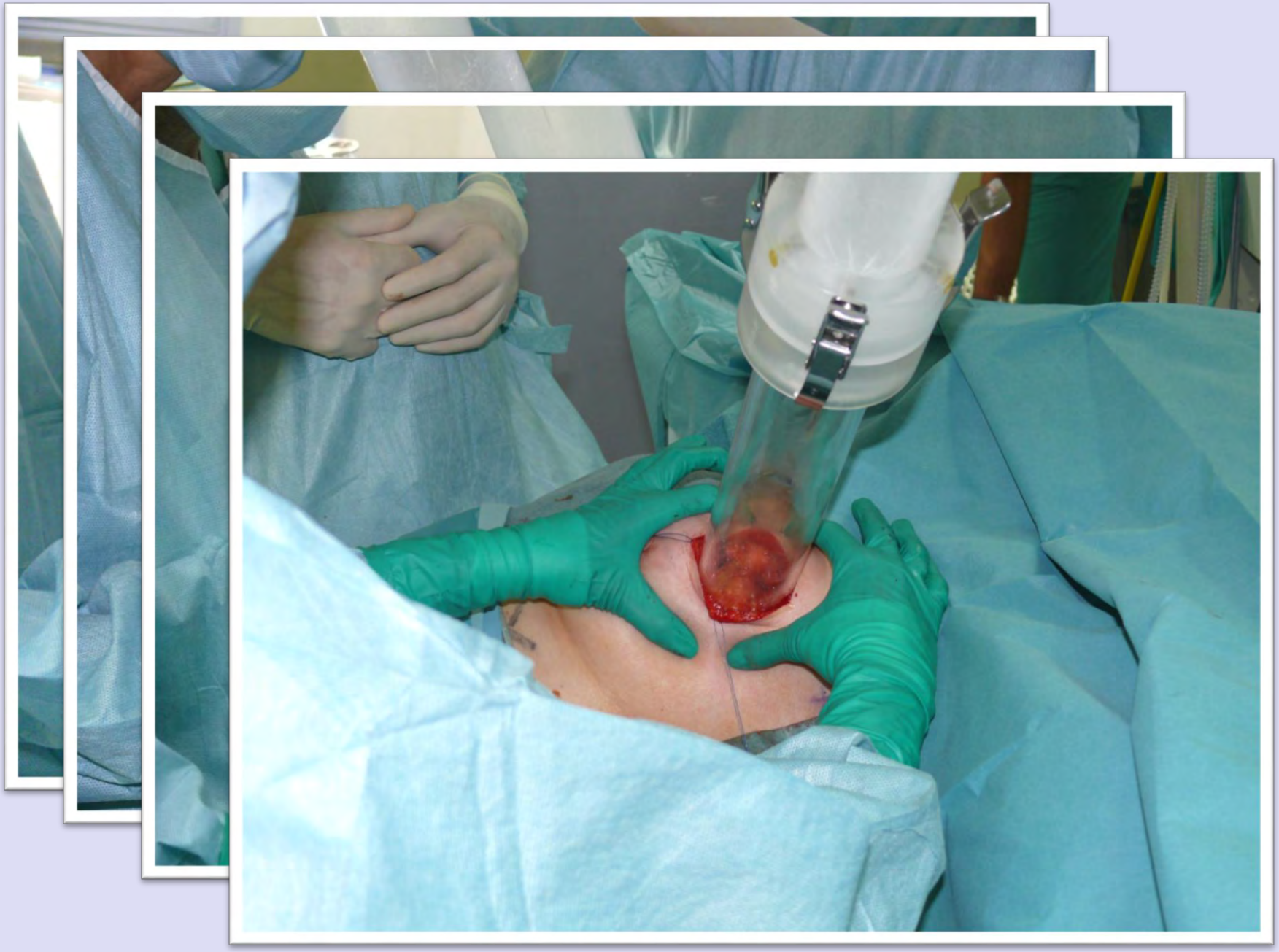
The collimator is placed directly in contact with the breast gland. Great care should be taken to avoid the involuntary creation of an herniation of the gland into the collimator, the result in this case could be an increase in the dose delivered to the superficial part of the target.



Connection to the LINAC

The remote control of the LINAC allows the gentle movement of the machine in every direction. The radiation technologist moves the LINAC, and the connection to the distal part of the applicator is performed in the exact position chosen.

Connection to the LINAC



The fourth step: RADIOTHERAPY

ELIOT

(**EL**ectron **I**ntra **O**perative **T**herapy

Full dose (21Gy) or BOOST (12Gy) in three minutes

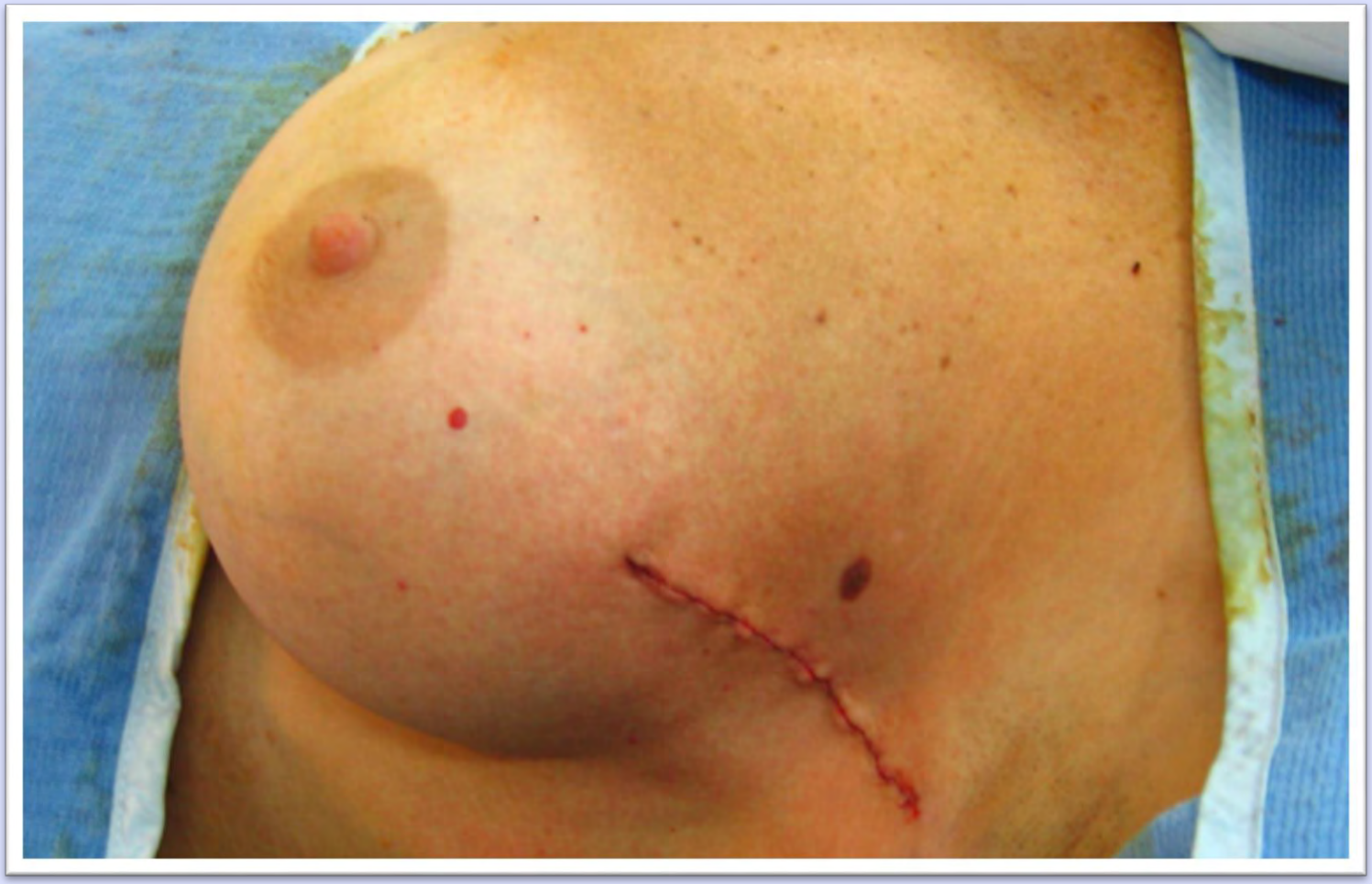
IEO Arc

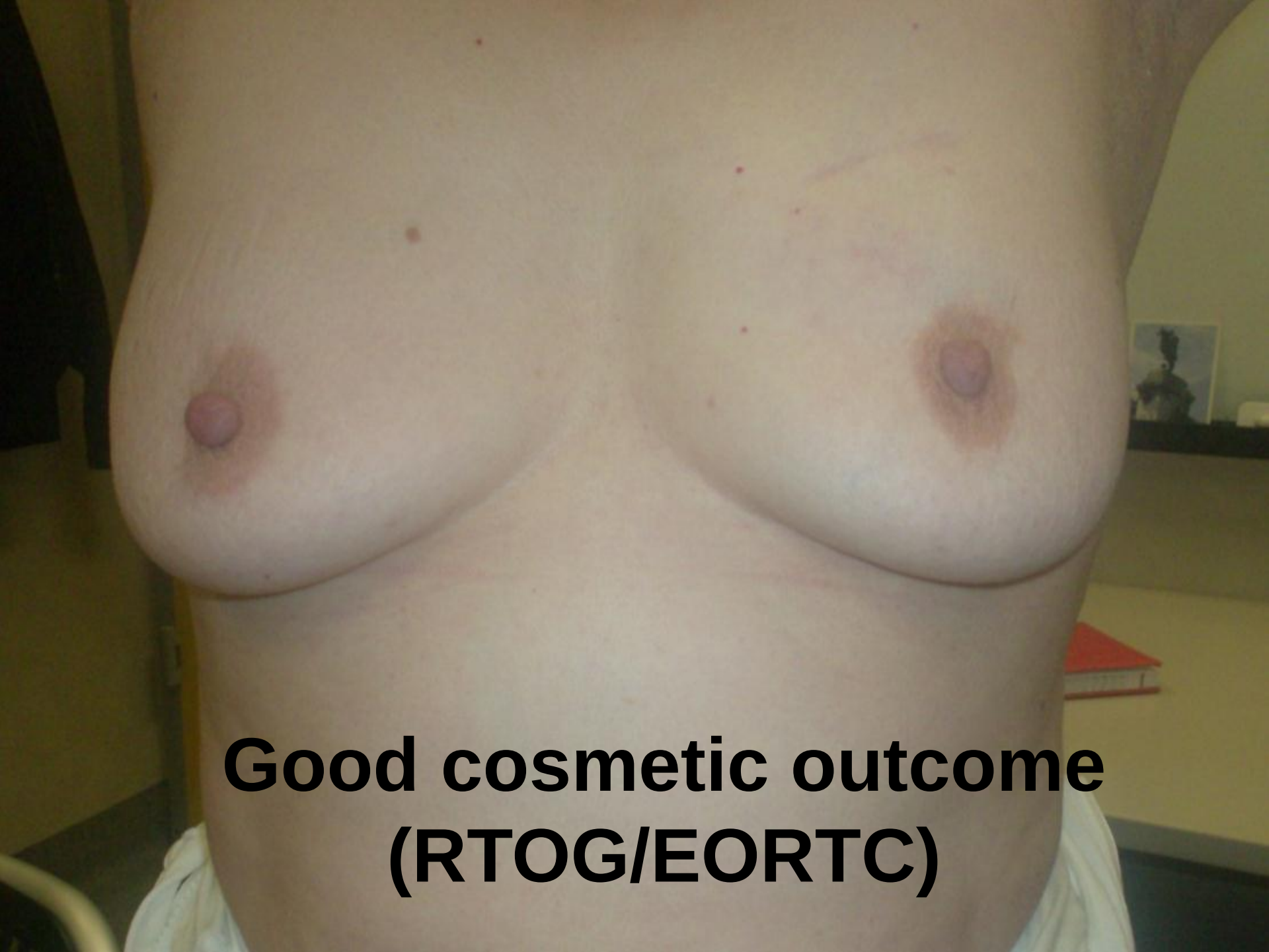
IEO Istituto Europeo di Oncologia

Removal of ELIOT Devices and Wound Synthesis

After the delivery of the radiation dose, the collimator is immediately removed from the surgical breach, and the LINAC is placed far from the operating table. The suture of the gland is partially or completely undone to allow the removal of the disks. The gland is then reconstructed again, being the reconstruction facilitated by the previous breast mobilization that created glandular flaps.

Result




Good cosmetic outcome
(RTOG/EORTC)

ELIOT: advantages

- Collimator is placed under the direct control of the surgeon, and the dose – intensity evaluation is made by the radiotherapist and physicist directly there.



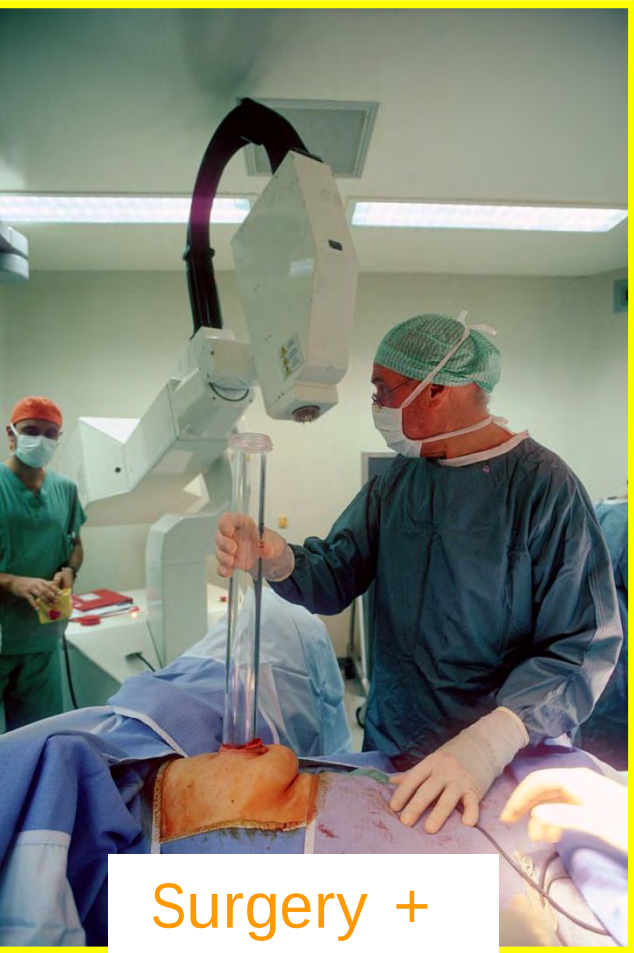

Advantages of ELIOT

<u>Short irradiation</u>:

-Unique dose (21 Gy) vs. 6 weeks of fractionated doses (50+10Gy)

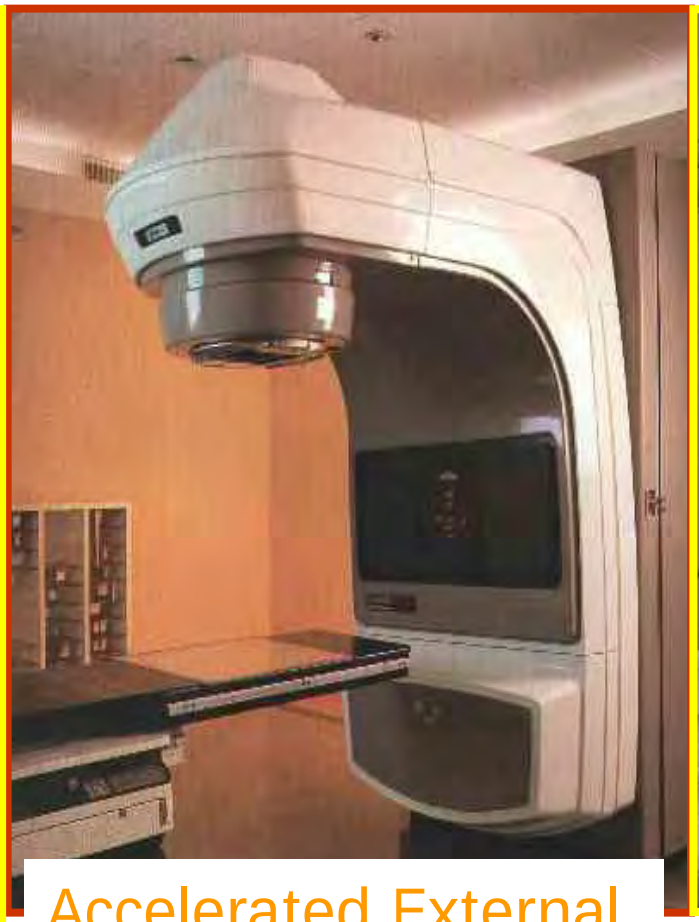
-The problem of the difficult access to radiotherapy centers is solved

Advantage: to avoid delay of radiotherapy



Surgery + ELIOT boost

1



Accelerated External Radiotherapy

21

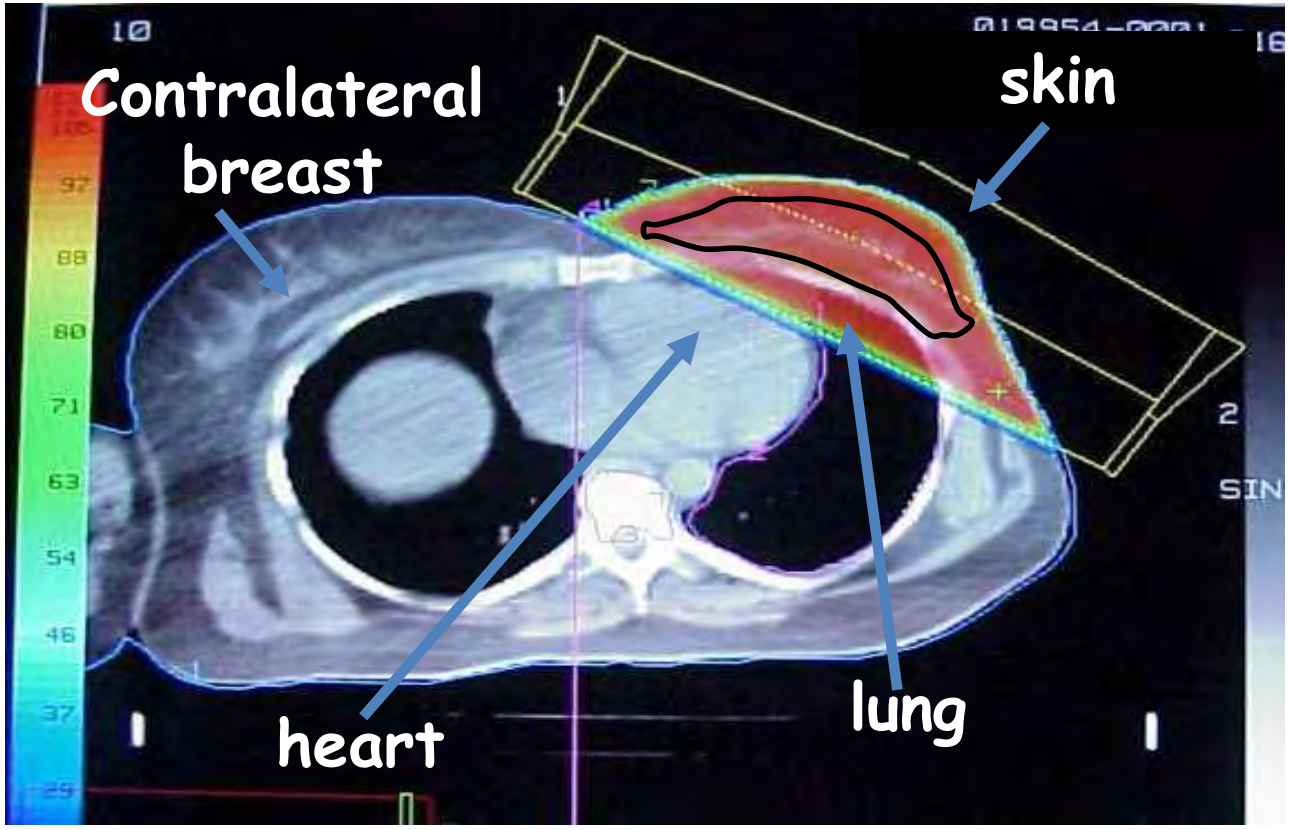
days

Systemic treatments

34-38

Advantages of ELIOT

Radiation exposure to the skin, subcutaneous tissue, lung, heart and contralateral breast is dramatically reduced



External RTP: contraindications

- Hodgkin Disease
- Severe cardiopathy
- Additive mastoplasty
- Skin lesions
- Previous RTP for breast cancer

IEO Arc

… conclusion

Indication for ELIOT

- Biological evaluation
- Breast dimension and tumor site
- Type of skin incision
- Additive prosthesis
- Type of collimator and disks
- Cosmetic result

MOBILE LINEAR ACCELERATOR FOR IOERT:

DOSIMETRIC AND TECHNICAL ASPECTS

Comi Stefania

Medical Physics Department

European Institute of Oncology, Milano

Novara 24 June 2016

LIAC 001

A mobile dedicated linac for IORT, working in an existing OR

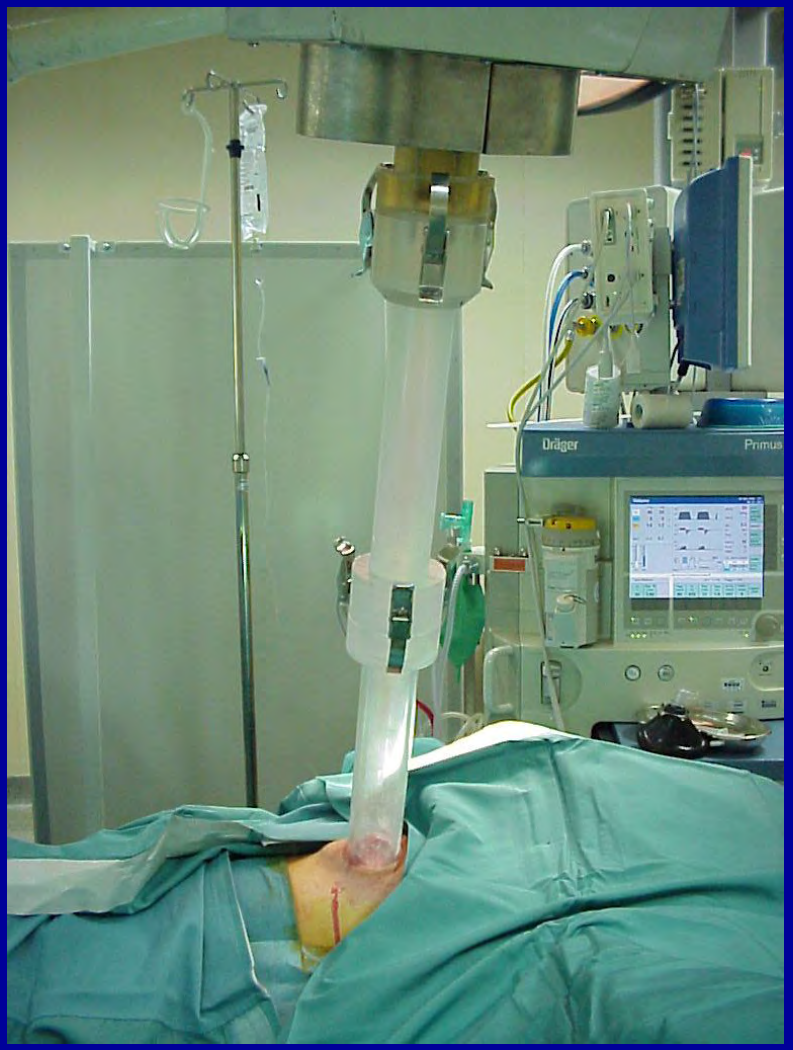
Electron beams (4,6,8,10 MeV) (4 energy levels) with high dose/pulse values

LIAC 023

A mobile dedicated linac for IORT, working in an appropriate shielding OR

Electron beams (6,8,10,12 MeV) (4 energy levels) with high dose/pulse values

Dose rate: 3-40 Gy/min



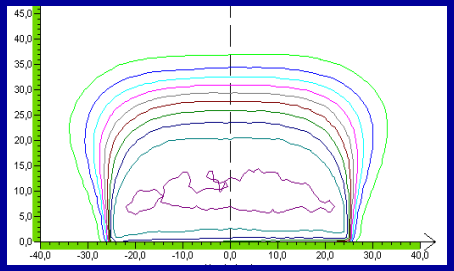
hard-docked, transparent PMMA applicators

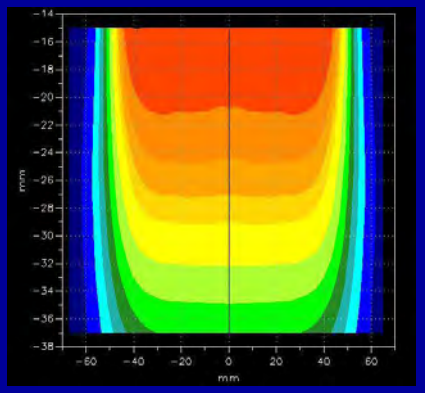
LIAC

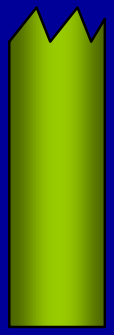
no beam bending system

no scattering foils

no photon jaws





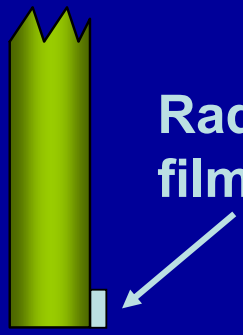


5-mm perspex round applicators (hard docking)

Ø : 4 - 5 - 6 – 7 - 8 cm and 10 cm

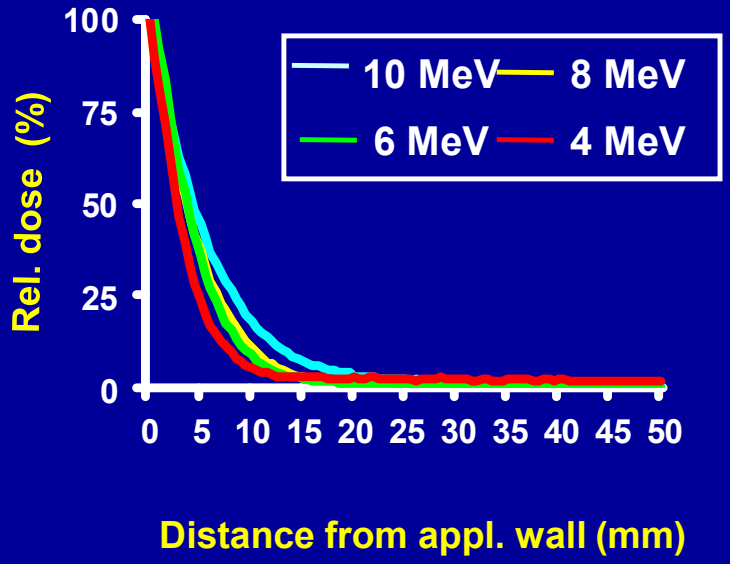
flat-ended and beveled (15°, 30°,45°)

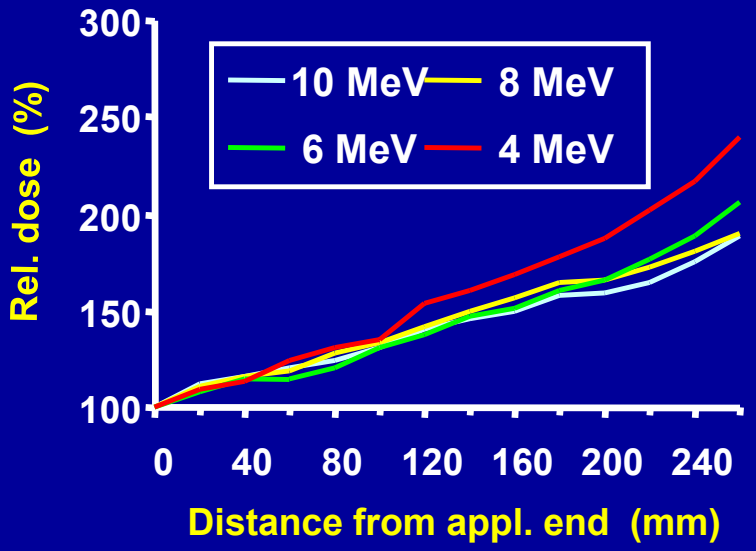
Transmitted radiation through the applicator walls

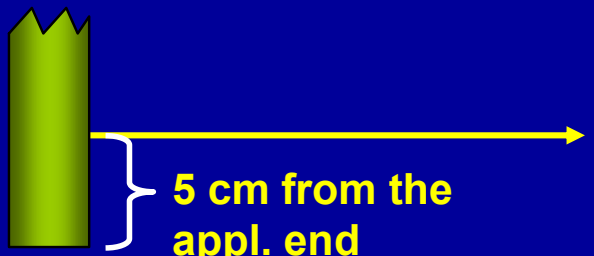


Radiochromic film

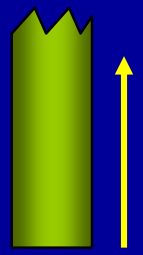
10 MeV	Ø 6	on the wall	4%
8 MeV	Ø 6	on the wall	4%
6 MeV	Ø 6	on the wall	4%
4 MeV	Ø 6	on the wall	3%







5 cm from the appl. end



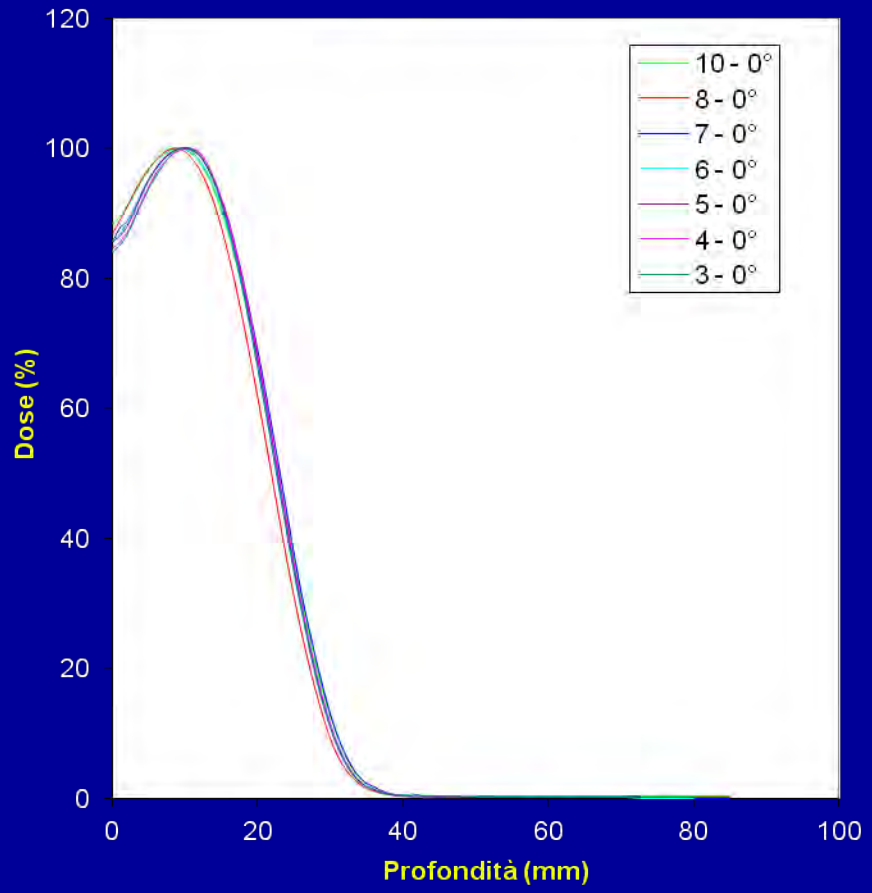
2 mm from the appl. wall

Relative dosimetry

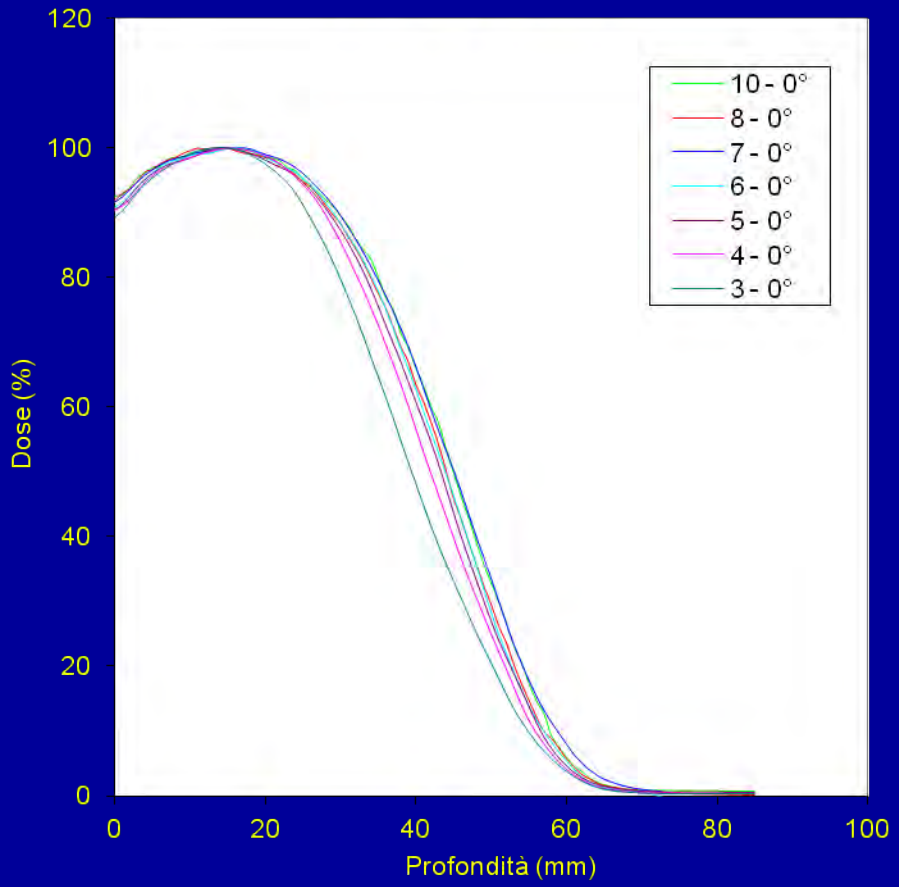
(thin silicon detector in a water phantom)

Deep Dose Distribution LIAC 023 PDD 0°

PDD 6 MeV



PDD 12 MeV

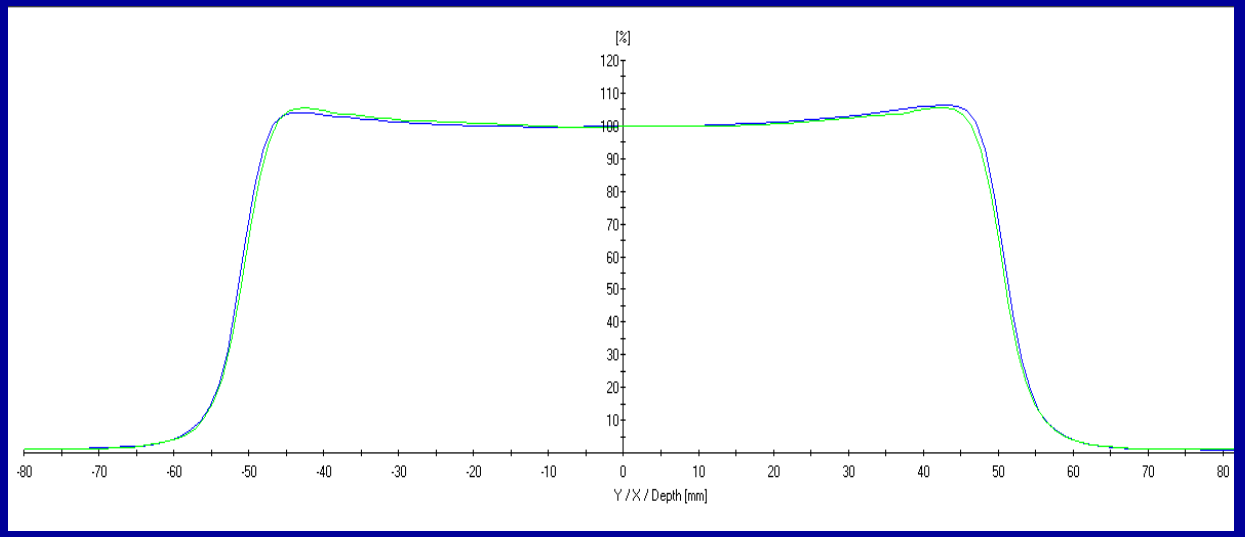


Dose Profiles

Appl Ø 10 - 0°

6MeV

Relative dose (%)

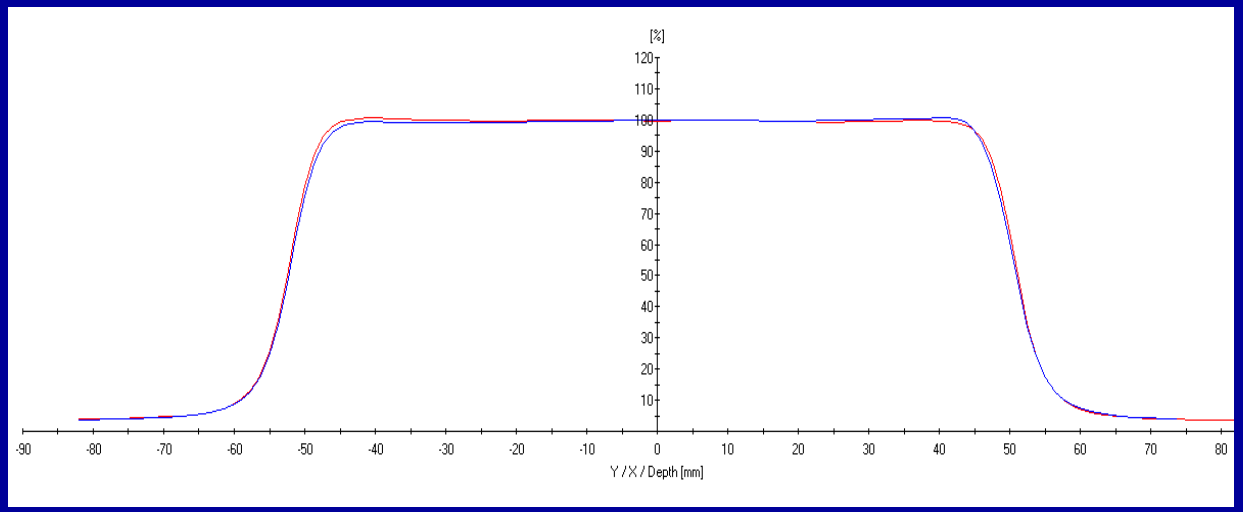


Distance from central axis (mm)

Appl Ø 10 - 0°

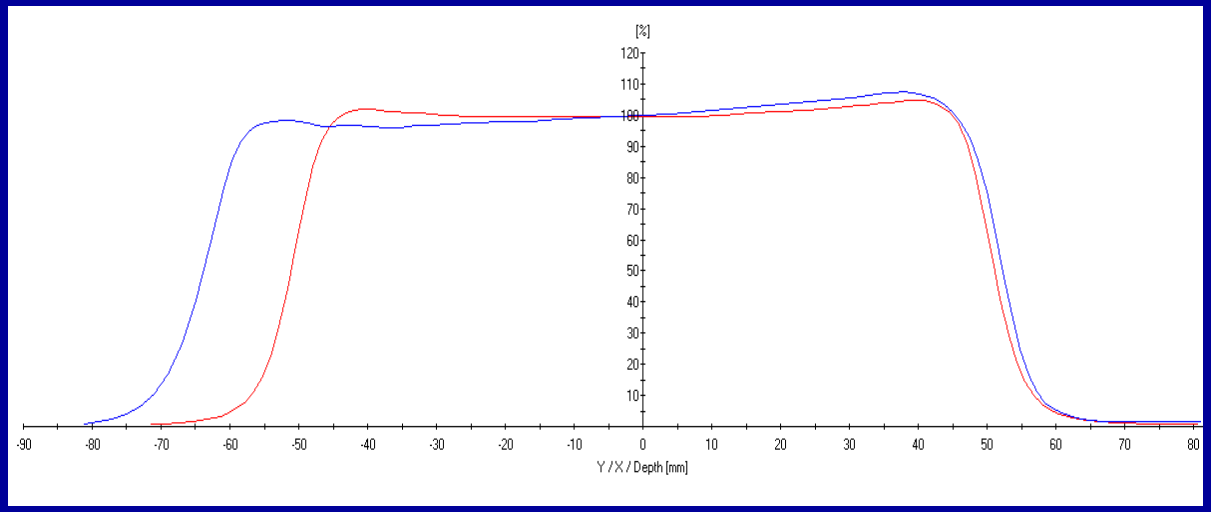
12MeV

Relative dose (%)



Dose Profiles

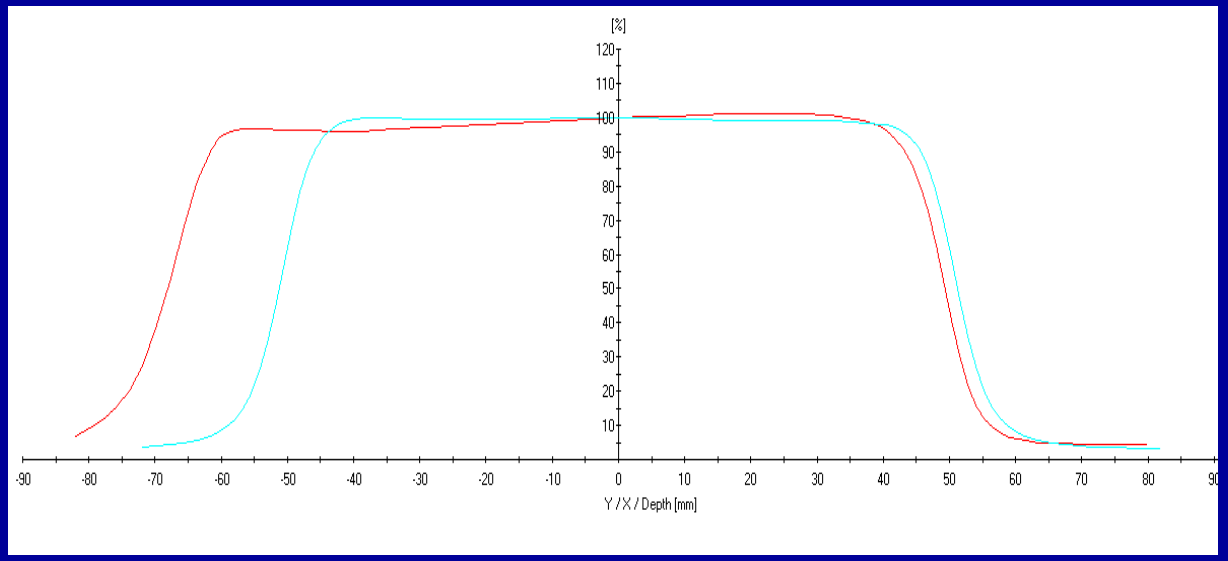
Appl Ø 10 - 30°
6MeV



Distance from central axis (mm)

Tilted profile

Appl Ø 10 - 30°
12MeV



Data sheets for MU calculation during IORT with LIAC 023

E (MeV)	Applicator (mm)	Isodose Prescription (%)	Dose prescribed (cGy)	MU	time limit (s) *
12	100	90	1200	1327	56
	80			1133	48
	70			1063	45
	60			962	40
	50			880	37
	40			821	34
	30			811	34
10	100	90	1200	1351	77
	80			1151	66
	70			1066	61
	60			976	56
	50			893	51
	40			840	48
	30			846	48
8	100	90	1200	1330	83
	80			1126	70
	70			1052	66
	60			965	60
	50			892	56
	40			848	53
	30			902	56
6	100	90	1200	1321	111
	80			1126	94
	70			1063	89
	60			977	82
	50			917	77
	40			882	74
	30			992	83

E (MeV)	Applicator (mm)	Isodose Prescription (%)	Dose prescribed (cGy)	MU	time limit (s) *
12	100	0,90	2100	2323	98
	80			1984	83
	70			1860	78
	60			1684	71
	50			1540	65
	40			1436	60
	30			1419	60
10	100	0,90	2100	2365	136
	80			2014	115
	70			1865	107
	60			1708	98
	50			1562	90
	40			1470	84
	30			1480	85
8	100	0,90	2100	2328	145
	80			1971	123
	70			1842	115
	60			1688	105
	50			1561	97
	40			1484	92
	30			1578	98
6	100	0,90	2100	2313	194
	80			1970	165
	70			1860	156
	60			1709	143
	50			1605	134
	40			1544	129
	30			1736	145

QUALITY ASSURANCE PROTOCOL

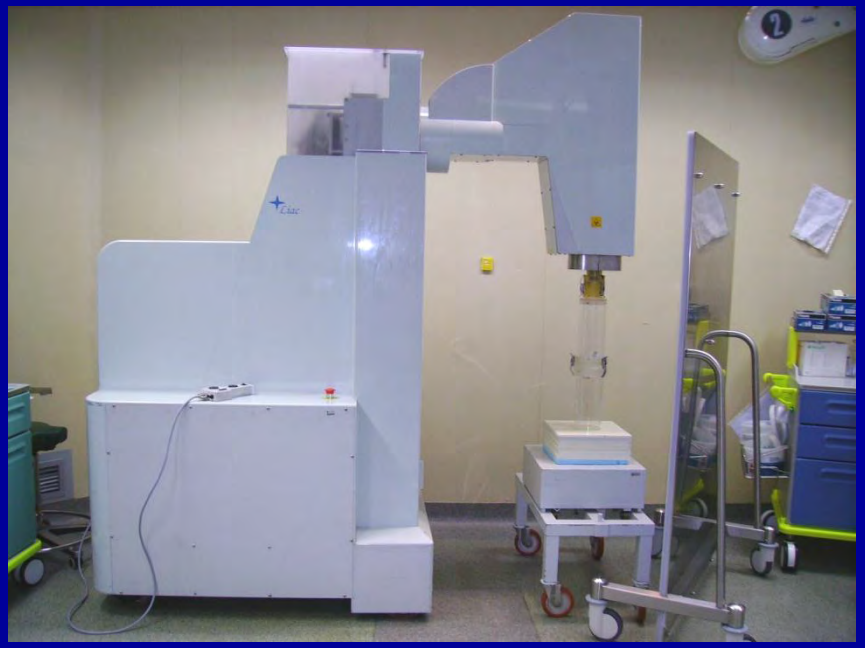
- ✓ QA program modified from those developed for conventional linacs
- ✓ Specific features of LIAC and RP limitations in the OR

Daily checks (in the 12 hours before treatments)

PARAMETER	TOLERANCE LEVEL	EQUIPMENT
safety systems, warning devices, mechanical movements	functional	= =
dose monitoring system: constancy	2%	flat chamber in solid phantom

PARAMETER	TOLERANCE	EQUIPMENT
Monthly checks		
radiation beam energy	2 mm @ D80%	verific. films in solid ph.
flatness and symmetry	10% (flatness); 3% (symmetry)	verific. films in solid ph.
dose monitoring system: short-term reproducibil.	1%	flat chamber in solid ph.
status of accessories	not damaged	= =
6-monthly checks		
dose monitoring system: linearity	2%	flat chamber in solid ph.
stray radiation	as low as possible	radiation monitor, film badges, TLDs
Yearly checks		
photon contamination	< 1%	verific. films in solid ph.
beam dose calibration	2%	MD-55-2 films in solid ph., Fricke dos. in water (2 yrs)

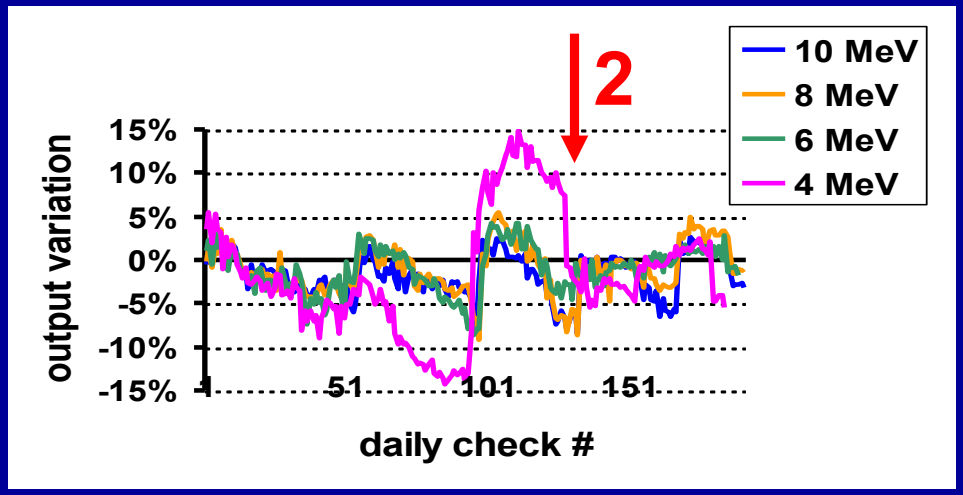
Analysis of dose output long-term stability



- Dec 04 – Jul 07: 182 daily checks (4 energies)
- PTW Roos flat ion chamber
- mean variation and 1 SD

Daily output variations (%)

	overall	after upgrade 2
4 MeV	-1.6 ± 6.9	-1.5 ± 2.3
6 MeV	-1.1 ± 2.7	-0.3 ± 1.3
8 MeV	-1.0 ± 2.9	-0.0 ± 2.4
10 MeV	-1.8 ± 2.5	-1.1 ± 2.5

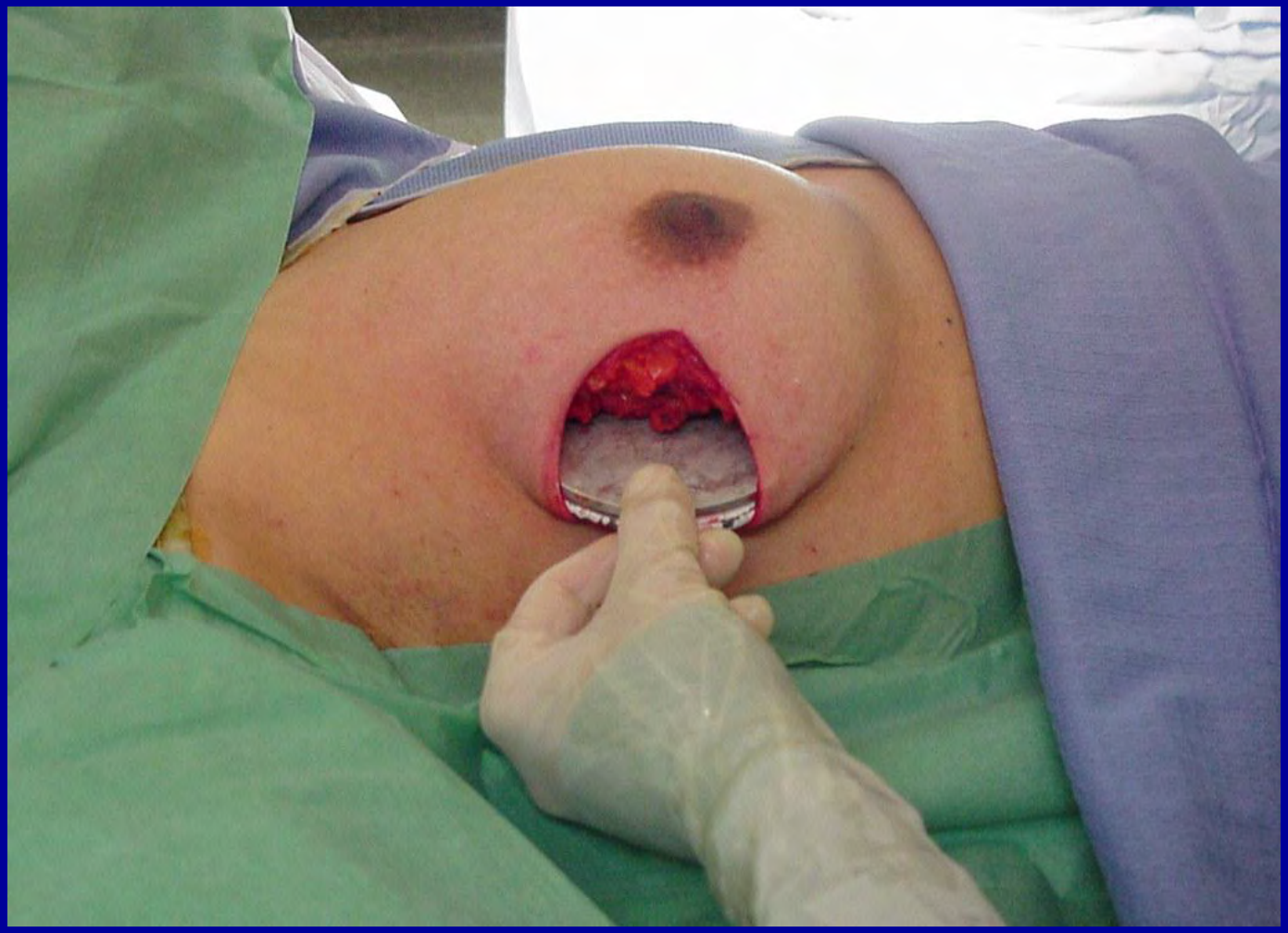


SD (%)

Liac : ~ 2 - 2.5 (1 yr)

- Liac vs conventional linacs (and Mobetron): lower stability as a price to pay for high mobility and compactness, as well as use of high dose/pulse beams
- Severe QA program, including preventive maintenance at a regular basis, is mandatory in the clinical practice!

Internal shieldings



Which type of disks?

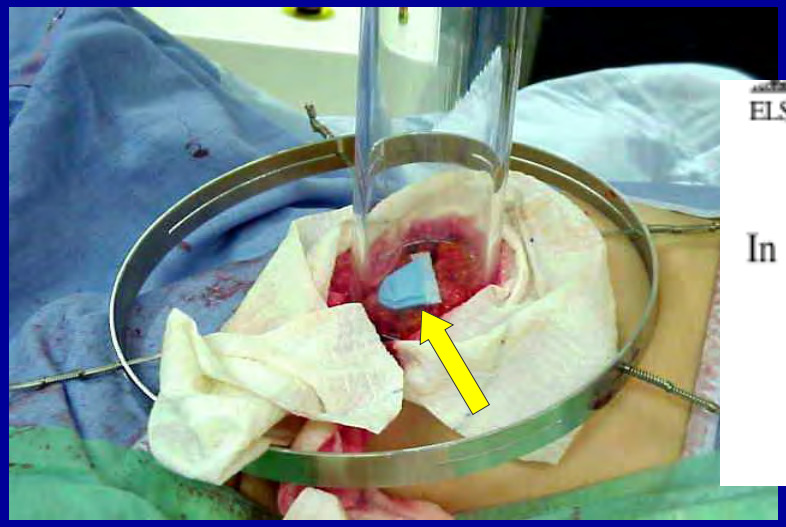
Electron backscatter effect from lead		
10 MeV	at interface	1.58
	5 mm RW3	1.18
	10 mm RW3	1.00
	2 mm Al	1.24
	4 mm Al	1.11

We use: 2 mm Lead + 4 mm Aluminium

Shielding transmission LIAC 023

Disc	Nominal energy			
	6 MeV	8 MeV	10 MeV	12 MeV
2mmPb+4mmAl	0,37%	0,66%	1,32%	2,13%
4mm Pb+4mmAl	0,29%	0,51%	0,87%	1,13%

In vivo dosimetry



ELSEVIER

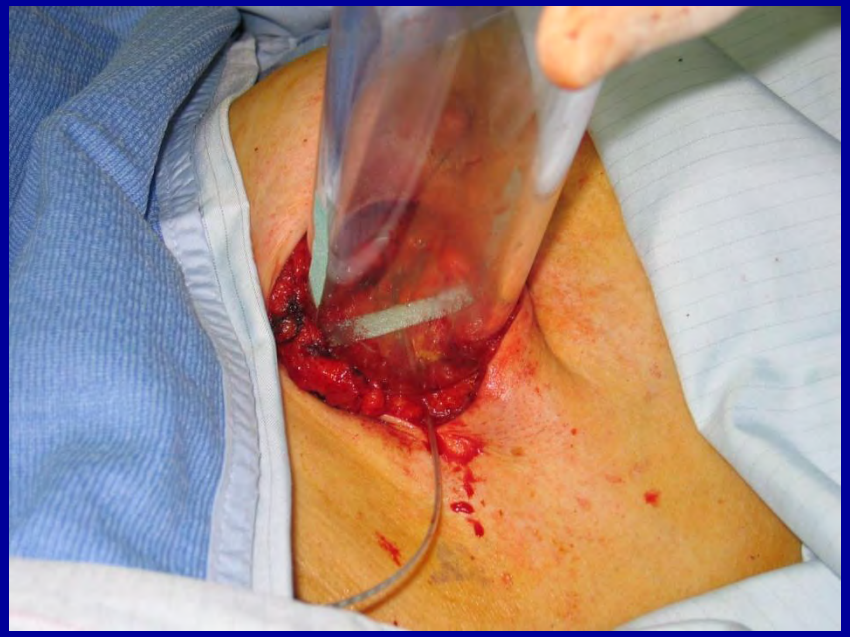
Radiotherapy and Oncology 69 (2003) 285–289

www.elsevier.com/locate/radonline

In vivo dosimetry using radiochromic films during intraoperative electron beam radiation therapy in early-stage breast cancer

Mario Ciocca[a,*], Roberto Orecchia[b], Cristina Garibaldi[a], Elena Rondi[a], Alberto Luini[c], Giovanna Gatti[c], Mattia Intra[c], Paolo Veronesi[c], Roberta Lazzari[b], Giampiero Tosi[a], Umberto Veronesi[c]

- entrance dose (dmax) derived by surface measurements
- 2 radiochromic films in a sterile thin envelope
- negligible field perturbation
- 24-72 hrs (48 hrs pref.) post-irradiation time
- temperature dependence : 5%
- estimated overall uncertainty (1 SD): 4 %



Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 3, pp. 952–960, 2005

0360-3016/05/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2005.02.049

PHYSICS CONTRIBUTION

IN VIVO DOSIMETRY WITH MOSFETS: DOSIMETRIC CHARACTERIZATION AND FIRST CLINICAL RESULTS IN INTRAOPERATIVE RADIOTHERAPY

Rita Consorti, Ph.D.,* Assunta Petrucci, Ph.D.,* Falbo Fortunato,*
Antonella Soriani, Ph.D.,† Simona Marzi, Ph.D.,† Giuseppe Iaccarino, Ph.D.,†
Valeria Landoni, Ph.D.,† and Marcello Benassi, Ph.D.†

Radiotherapy and Oncology 78 (2006) 213–216
www.thegreenjournal.com

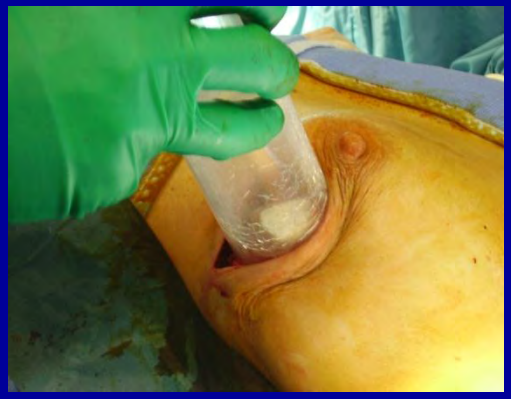
IORT dosimetry

Real-time in vivo dosimetry using micro-MOSFET detectors during intraoperative electron beam radiation therapy in early-stage breast cancer

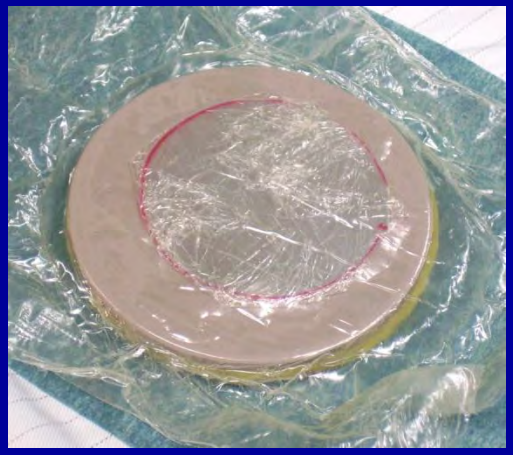
Mario Ciocca[a,*], Valeria Piazzi[a], Roberta Lazzari[b], Andrea Vavassori[b], Alberto Luini[c], Paolo Veronesi[c], Viviana Galimberti[c], Mattia Intra[c], Andrea Guido[b], Giampiero Tosi[a], Umberto Veronesi[c,d], Roberto Orecchia[b]

[a]Department of Medical Physics, [b]Division of Radiation Oncology, [c]Division of Senology, and [d]Scientific Director, European Institute of Oncology, Milano, Italy.

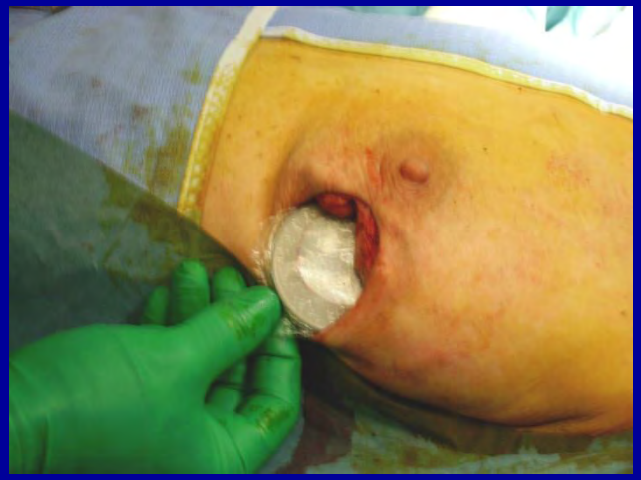
IN VIVO DOSIMETRY : recent developments



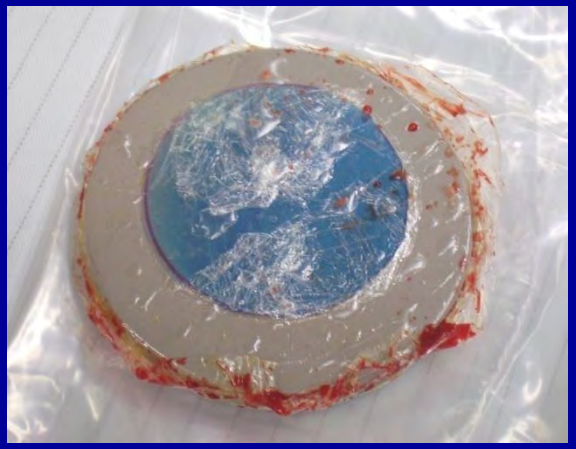
• **entrance dose** (at d_{max}) derived from surface dose measurement (2 **small** films)

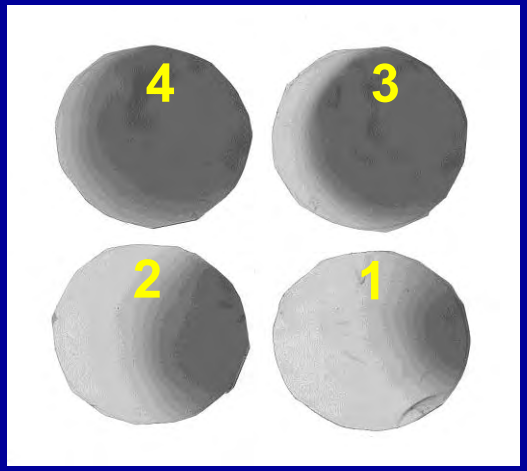


• **exit dose**: 1 **large area** (Ø 4 cm) film on top of Pb/Al shielding disc (inserted between mammary gland and pectoral muscle)



Measured vs expected dose (based on isodose chart and gland thickness measured by surgeon using a needle and ruler)





Evaluation of disk alignment: score 1 (bad) to 4 (excellent)

Alignment of the shielding disk

	all pts	larger disks*
score 1	2/35 (6%)	=
score 2	10/35 (29%)	1/7 (14%)
score 3	15/35 (43%)	2/7 (29%)
score 4	8/35 (23%)	4/7 (57%)
score 3+4	23/35 (66%)	6/7 (86%)

* : disk diameter > 6 cm (6.5-7 cm)

MOST IMPORTANT RADIATION PROTECTION ITEMS

- positioning of protective barriers around operating table (building 1)

or

- positioning of accelerator with respect to floor protection (building 2)

- Nobody in the OR during irradiation

Nobody in the dirty corridor during irradiation^:

an audible alarm and a signal light are activated 30 s before irradiation start

^ or in the patient preparation / operators' washing room (building 1) except operators at the treatment console

Special IORT applications in breast patients

1. Pregnant women

2. Cardiac implantable electronic devices carriers

Pregnant women

Is electron beam intraoperative radiotherapy safe in pregnant women with early breast cancer?

In vivo dosimetry to assess fetal dose

A couple of TLDs were positioned on non pregnant patients skin in 4 different positions and in uterus

Prescribed dose	Right ovary	Left ovary	Suprapubic	Sub-diaphragmatic	Uterus
Gy	mGy	mGy	mGy	mGy	mGy
21	0.925	1.001	0.776		0.57
21	0.453	0.443	0.384	1.639	0.3
12	0.677	0.557	0.435	2.902	0.366
21	0.881	0.814	0.682	1.98	0.485
12	0.314	0.293	0.576	7.758	0.261

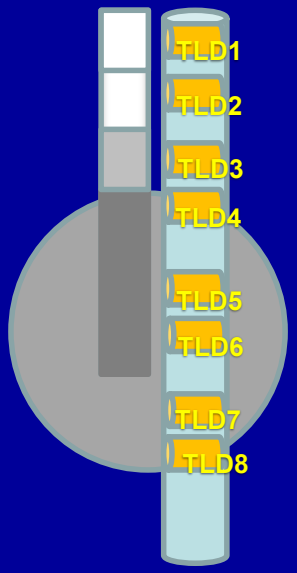
In December 2011 a pregnant woman, affected by early stage breast cancer, underwent conservative surgery and ELIOT full dose (21 Gy at 90% isodose) during the 15th gestation week

Comparing the data on the skin between non pregnant women and the pregnant one, we evaluated that the expected dose to the foetus should have been 0.84 mGy

ELIOT offers the pregnant woman the choice of receiving breast-conserving surgery, without exposing her baby to a significant radiation risk, and preserves her breast

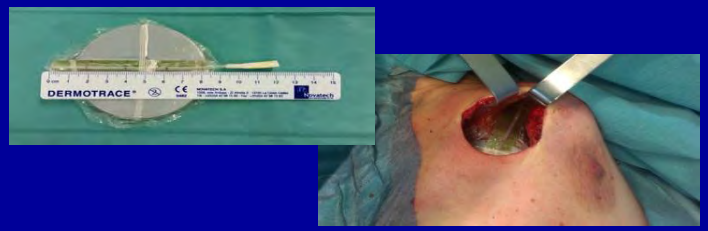
Cardiac implantable electronic devices carriers

Two catheters with 8 TLDs

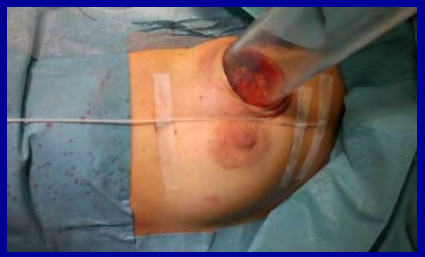


The first catheter was attached to the thoracic shielding

The catheter tip was positioned in the subclavicular region, where a cardiac device would be placed



The second catheter was placed on the patient skin, parallel to the first one, next to the applicator



ELIOT seems to be safe for patients using cardiac devices as long as the minimum distance of 2.5 cm is kept between the cardiac device edge and the applicator wall

Conclusions

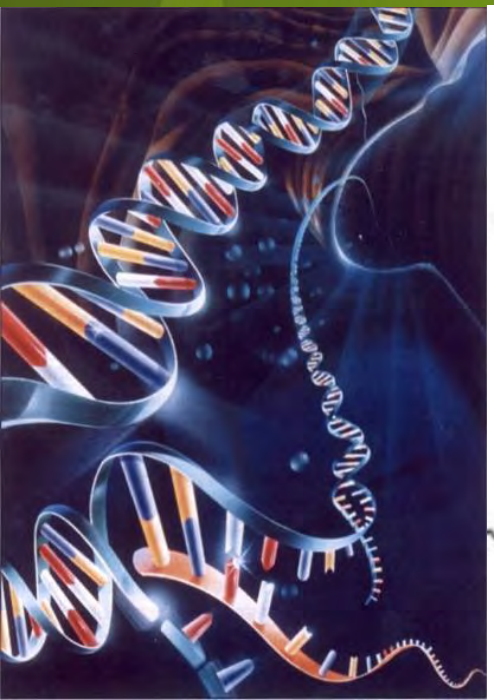
Work in progress:

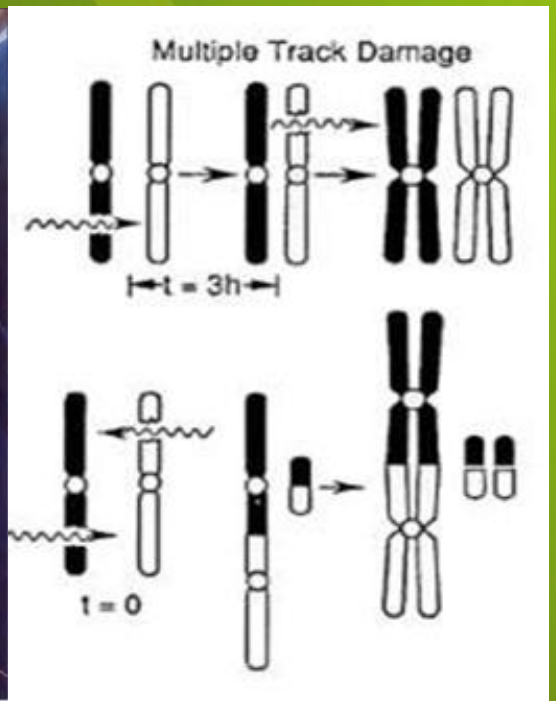
- **TPS for IORT**
- **In vivo dosimetry**

UNIVERSITY HOSPITAL
UNIKLINIKUM
SALZBURG

Biomolecular and histological prognostic factors

for in breast recurrences after IORT as a Boost in breast cancer?





Fastner G, Zehentmayr F, Sedlmayer F

UC Radiotherapy and Radio-Oncology
University Hospital, Paracelsus Medical University, Salzburg

predictors for IBR ?

Impact of Pathological Characteristics on Local Relapse After Breast-Conserving Therapy: A Subgroup Analysis of the EORTC Boost Versus No Boost Trial

Heather A. Jones, Ninja Antonini, Augustinus A.M. Hart, Johannes L. Peterse,† Jean-Claude Horiot, Françoise Collin, Philip M. Poortmans, S. Bing Oei, Laurence Collette, Henk Struikmans, Walter F. Van den Bogaert, Alain Fourquet, Jos J. Jager, Dominic A.X. Schinagl, Carla C. Wárlám-Rodenhuis, and Harry Bartelink

n = 1616

Table 5. Multivariable Analysis of Time to Local Relapse for All Patients

Parameter	*P*	Hazard for Local Failure	
		Estimate	95% CI
Randomized treatment 50 Gy WBI, 0 Gy *v* 16 Gy	.0006	0.47	0.31 to 0.73
Age, > 50 *v* ≤ 50 years	< .0001	0.42	0.28 to 0.65
Systemic treatment, yes *v* no	.088	0.66	0.41 to 1.06
Differentiation grade of the invasive tumor, high *v* low/intermediate	.026	1.67	1.06 to 2.62
Differentiation grade of DCIS			
High *v* low/intermediate	.96	1.02	0.54 to 1.93
No DCIS *v* high	.39	0.80	0.48 to 1.33
Margin of invasive tumor, not involved *v* involved	.33	0.78	0.49 to 1.27

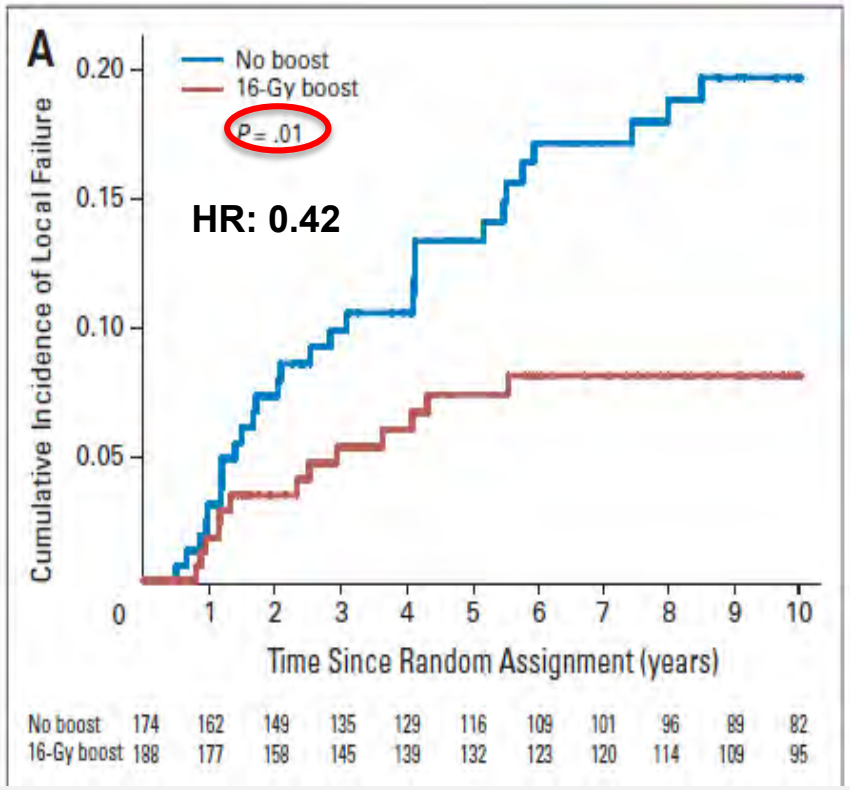
Abbreviations: WBI, whole breast irradiation; DCIS, ductal carcinoma in situ.

VOLUME 27 · NUMBER 30 · OCTOBER 20 2009

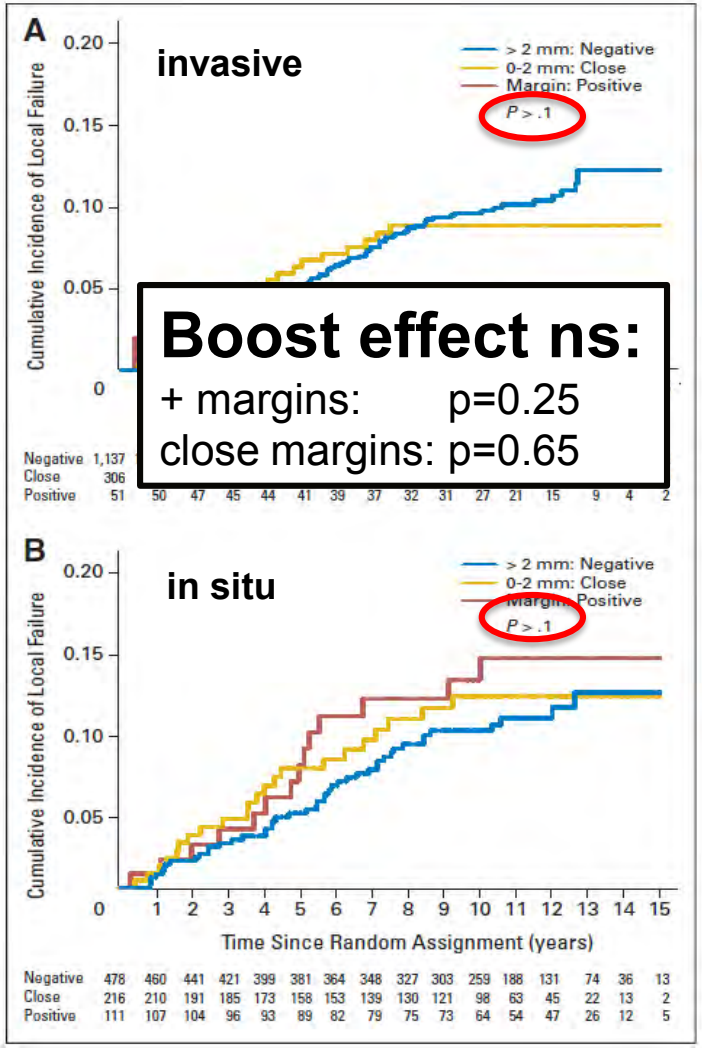
JOURNAL OF CLINICAL ONCOLOGY

Boost effect in G3 tumors or close/+ margins?

High-grade



margin status



Clinical experiences after
IORT - BOOST?

"Classical & biological" arguments

Visualization/definition of the tumorbed

Complete skin protection (electrons)

High **Oxygenation** intraoperatively

Immunological effects:

- **Blockade of cell proliferation (wound fluid)**

  (Belletti et al Clin Cancer Res. 2008)
- **Induction cytokines**

  (Vaidya et al , Herskind et al, 2009 Int J Radiat Oncol Biol Phys).
- **Antiangiogenic effects**

  (Flickinger et al Technol Cancer Res Treat 2003,
  Chang et al Nat Med 2005)

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Biomolecular mode of action

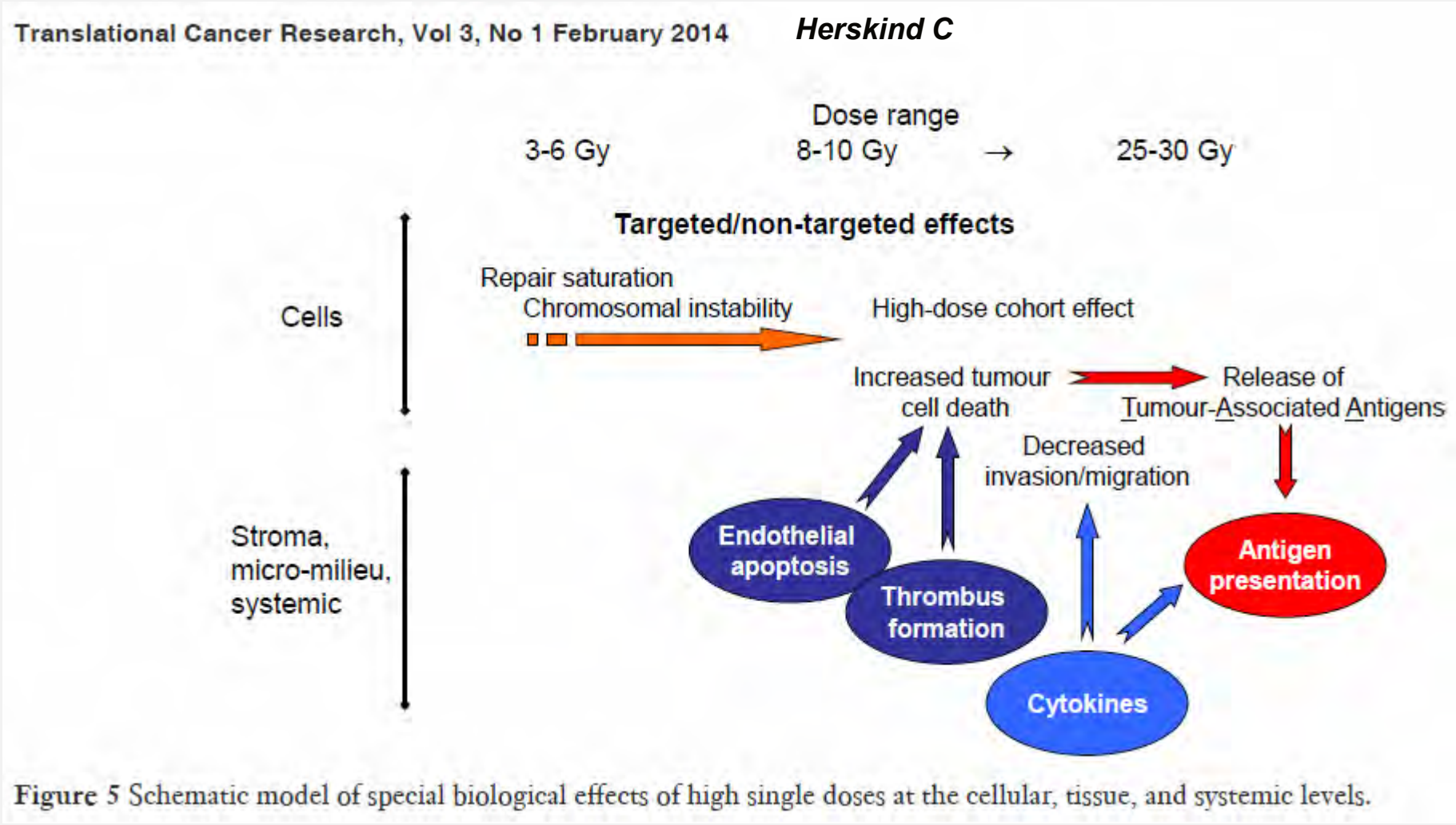
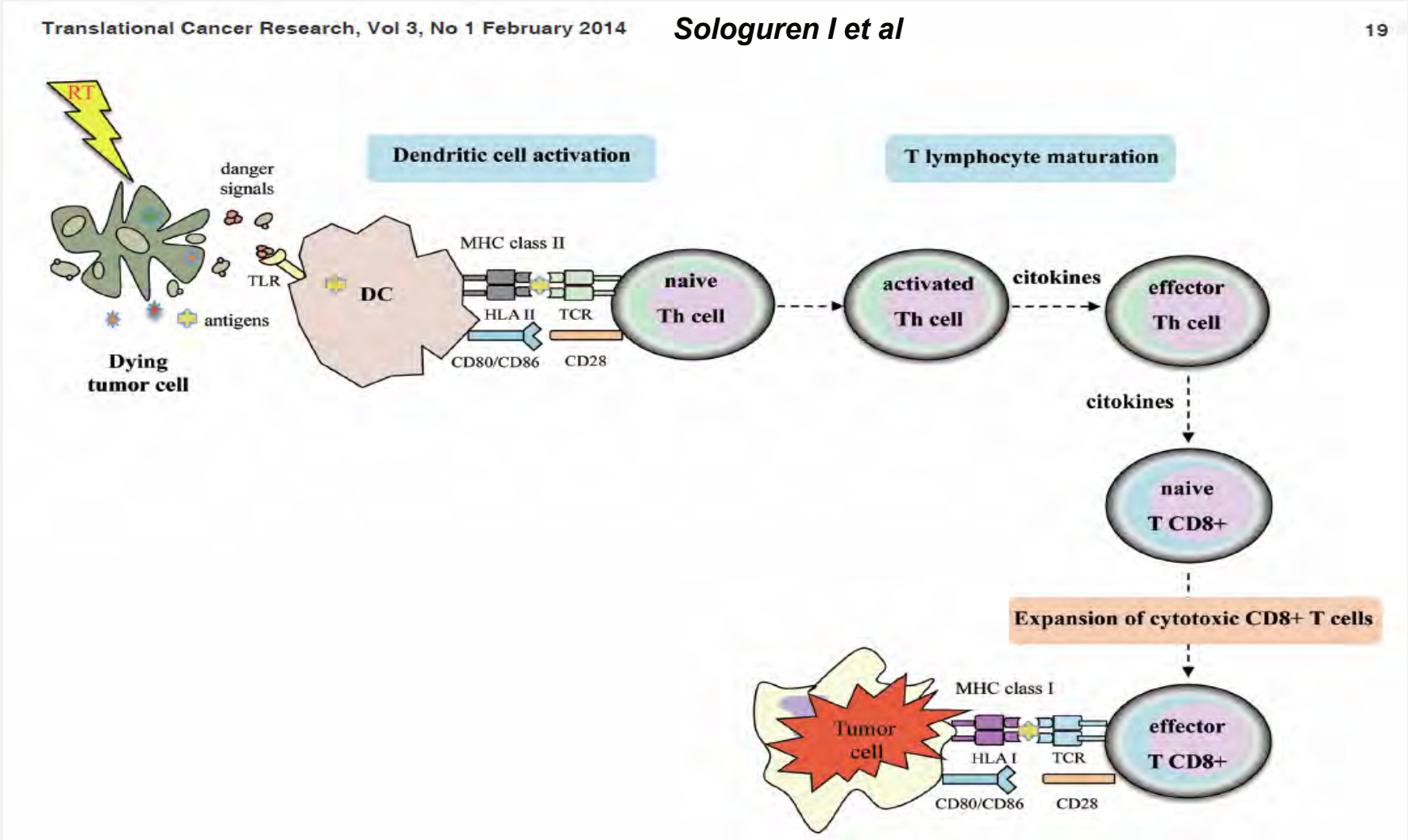


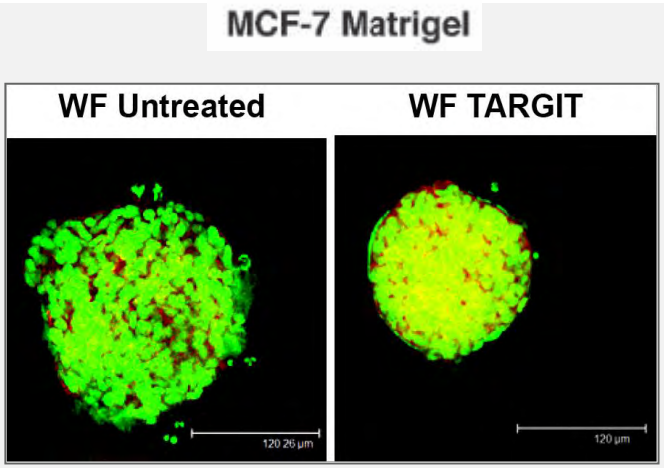
Figure 5 Schematic model of special biological effects of high single doses at the cellular, tissue, and systemic levels.

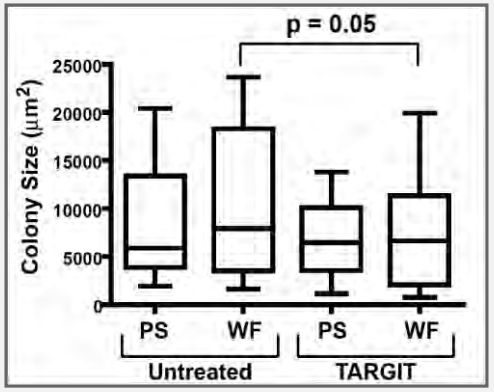
Immunological effects

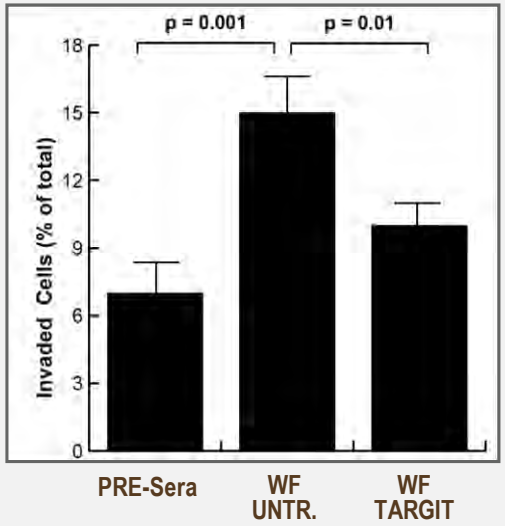


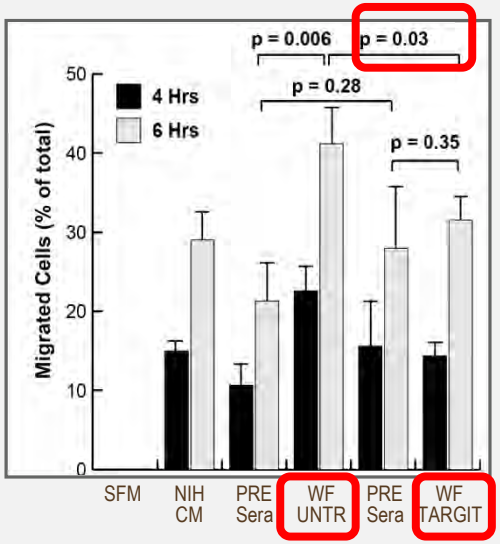
Wound fluid and cell proliferation ?

[Belletti et al, Clin Cancer Res 2008]







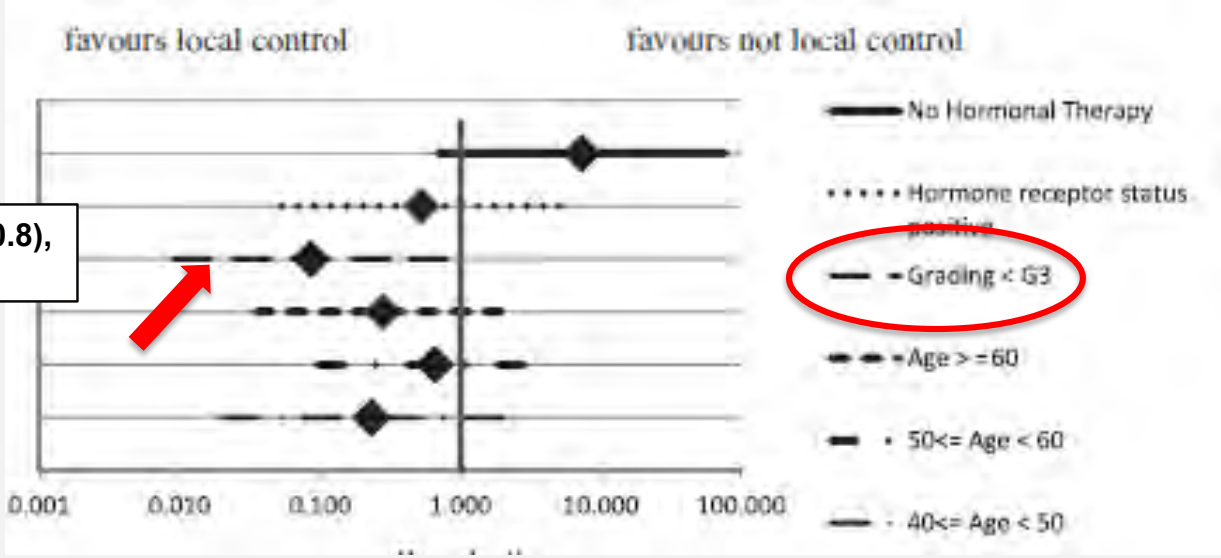


predictors for IBR

European pooled analysis

IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: Long term results of an ISIORT pooled analysis

Gerd Fastner [a,*,1], Felix Sedlmayer [a,1], Florian Merz [a,1], Heinrich Deutschmann [a,1], Roland Reitsamer [b,c,1], Christian Menzel [b,1], Christoph Stierle [b,c,1], Armando Farmini [b,c,1], Torsten Fischer [b,c,1], Antonella Ciabattoni [d,1], Alessandra Mirri [d,1], Eva Hager [e,1], Gabriele Reinartz [f,1], Claire Lemanski [i,1], Roberto Orecchia [g,1], Vincenzo Valentini [h,1]



HR 0.09 (0.01-0.8), p = 0.031

Radiotherapy and Oncology 108 (2013) 279–286

„Possible“ predictors for IBR

10-years FUP of Salzburg cohort

∑ 21 recurrences (n=770)

Factor	Patients (n)/%
G3	**8 / 38**
≥ T2	5 / 24
Non Luminal	3 / 14
Triple negative	**7 / 33**
< 50 Y	**9 / 43**
Multifocality	**6 / 29**
Tube < 6 cm	**11 / 52**

Predictors for IBR

BC-subtypes

Breast Cancer Subtype Approximated by Estrogen Receptor, Progesterone Receptor, and HER-2 Is Associated With Local and Distant Recurrence After Breast-Conserving Therapy

Paul L. Nguyen, Alphonse G. Taghian, Matthew S. Katz, Andrzej Niemierko, Rita F. Abi Raad, Whitney L. Boon, Jennifer R. Bellon, Julia S. Wong, Barbara L. Smith, and Jay R. Harris

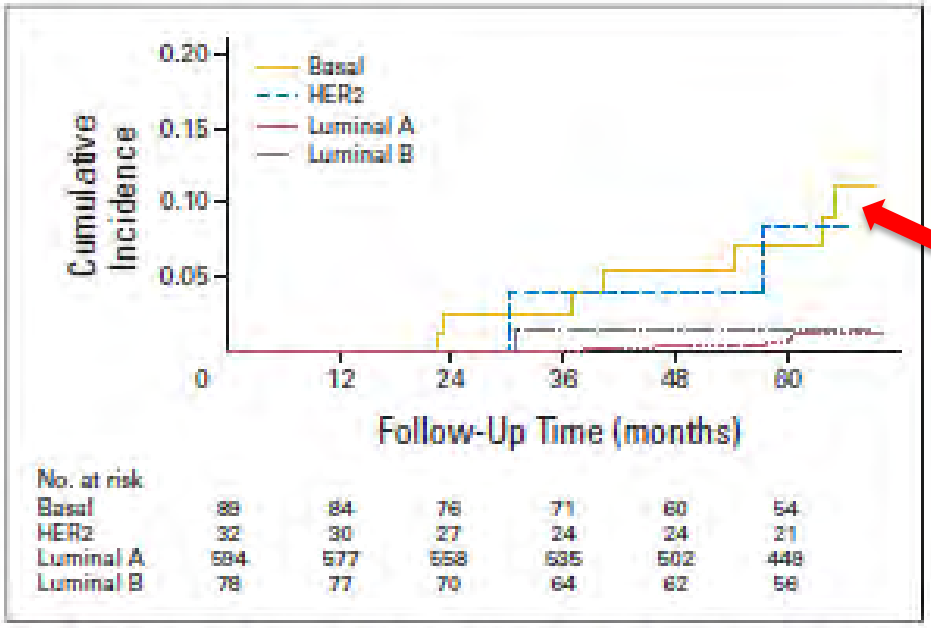


Fig 1. Cumulative incidence of local recurrence by breast cancer subtype. HER2, human epidermal growth factor receptor 2.

Compared to Luminal A, 5-year LR-rate:

TN: HR **7.1** (95% KI, 1.6-31), **p=0.009**

Her-2 (non-luminal): **9.2** (95% KI, 1.6-51), **p=0.012**

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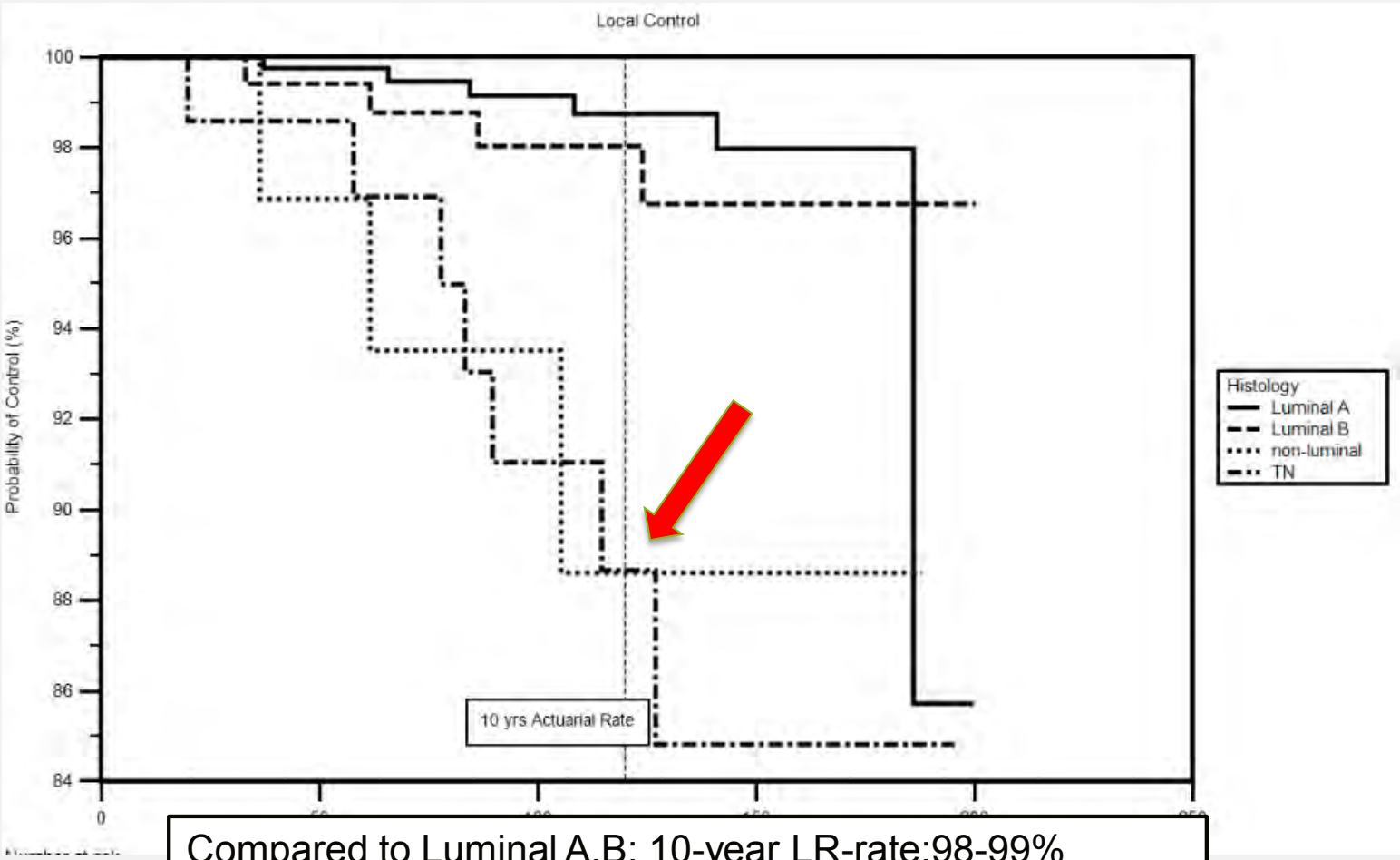
Predictors for IBR

BC-subtypes after IOERT



Compared to Luminal A,B: 10-year LR-rate:98-99%

TN: 88.7% (95% KI,76-95), p = 0.005

non-luminal: 88.6% (95% KI,68-96), p = ≤0.05

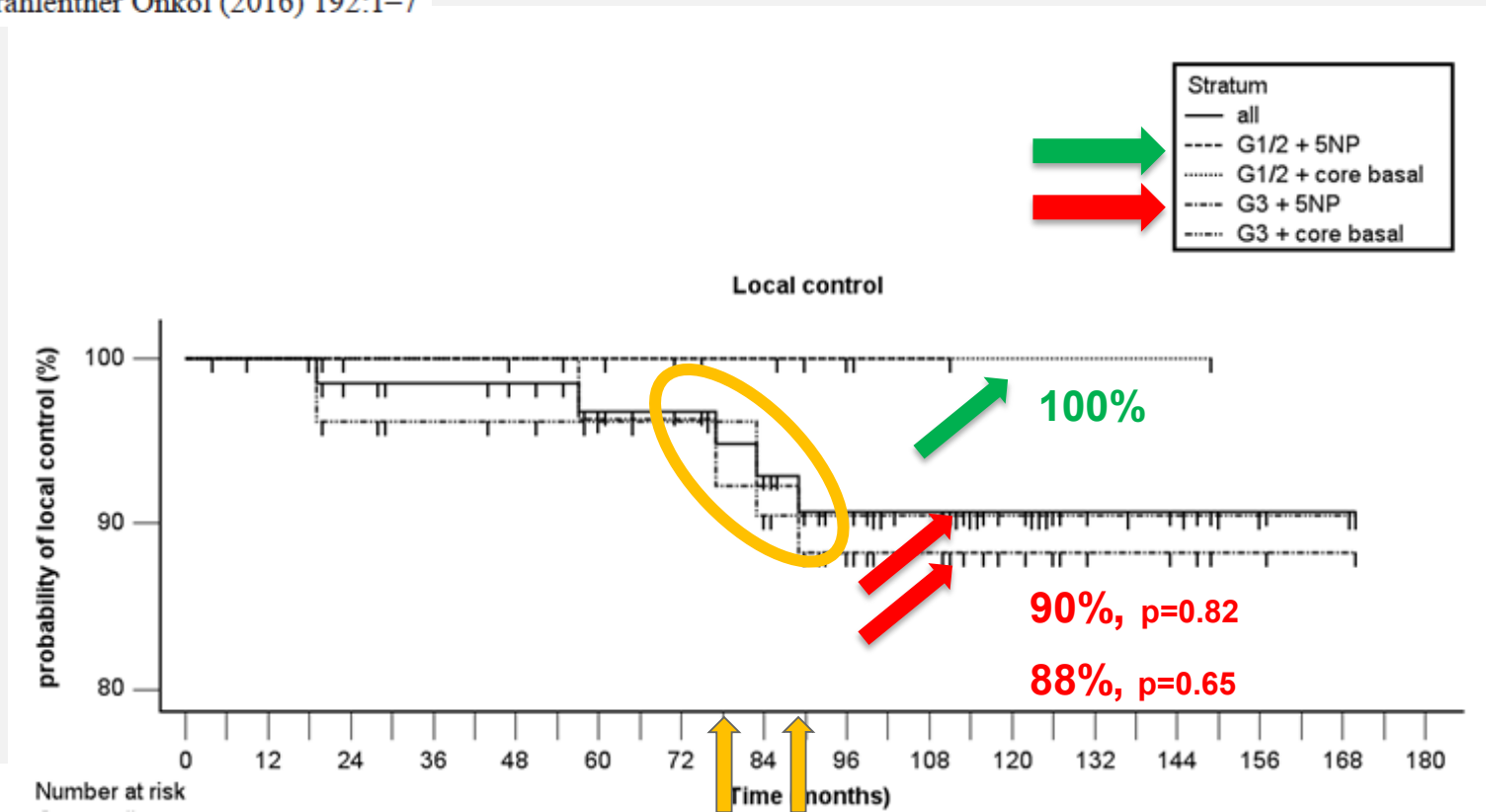
Predictors for IBR

BC-subtypes after IOERT

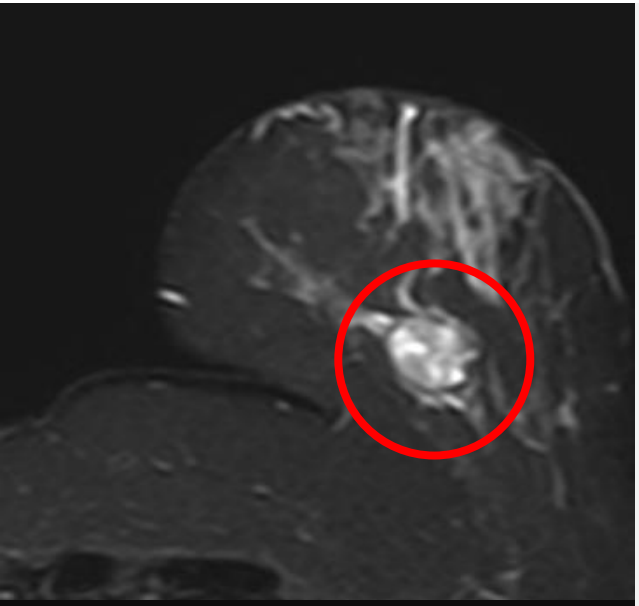
Survival and local control rates of triple-negative breast cancer patients treated with boost-IOERT during breast-conserving surgery

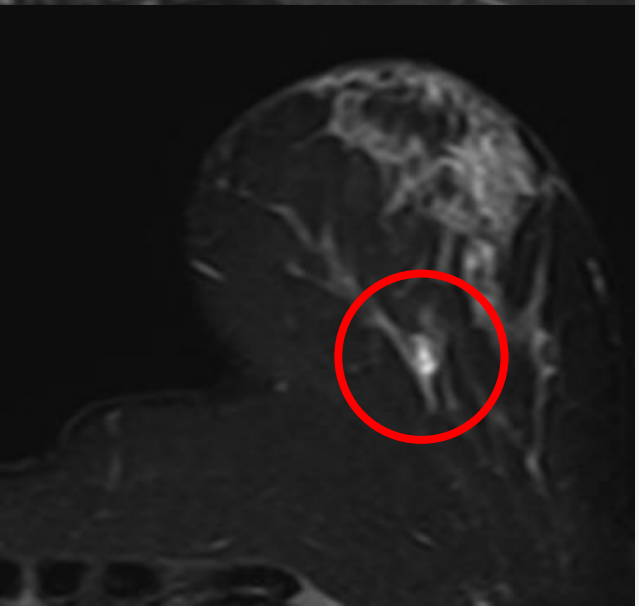
Gerd Fastner · Cornelia Hauser-Kronberger · Angelika Moder · Roland Reitsamer · Franz Zehentmayr · Peter Kopp · Christoph Fussl · Thorsten Fischer · Heinrich Deutschmann · Felix Sedlmayer

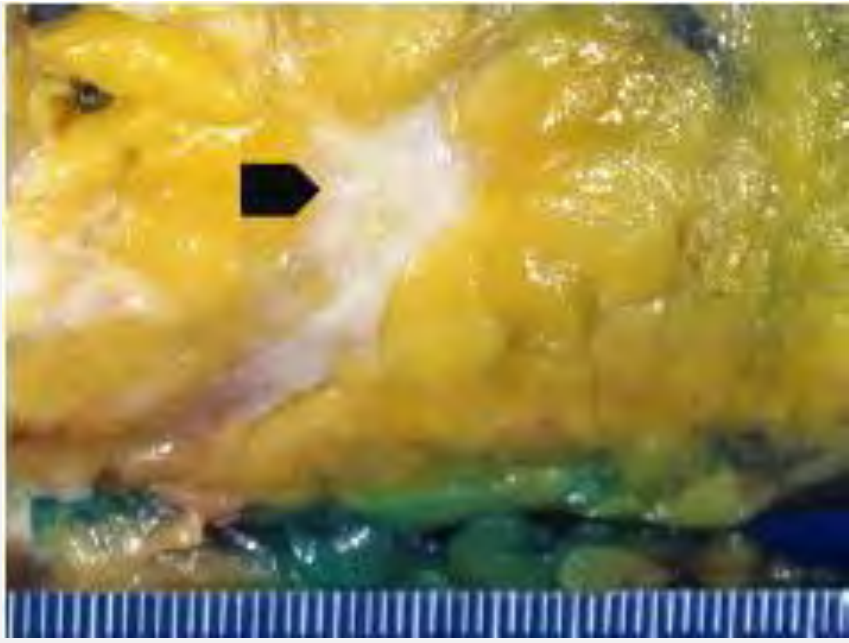
Strahlenther Onkol (2016) 192:1–7

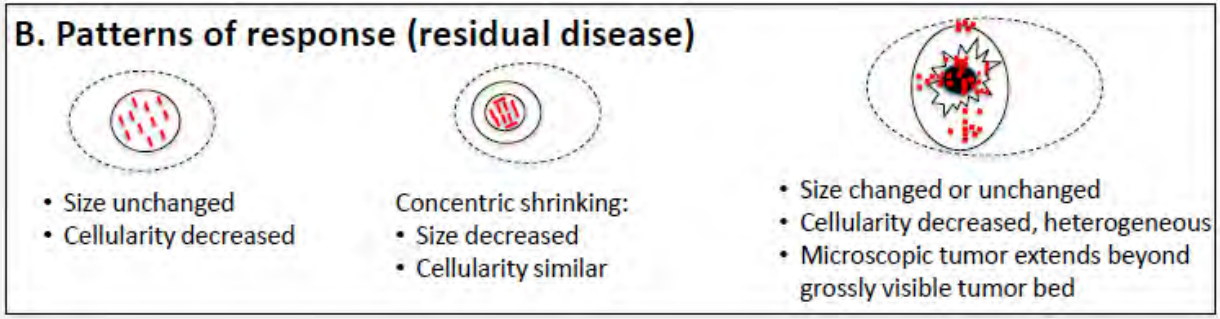


Predictors for IBR after PST









BIG-NABCG: Bossuyt V et al (Yale Un., US)
Ann Oncol. 2015 ;26:1280-91

BIG-NABCG: Provenzano E et al (MD Anderson CC, US)
Mod Pathol. 2015 ;28:1185-201

Predictors for IBR after PST

Mamounas PE et al, 2012 JCO

Age < 50:

- ypN+
- No breast pCR

Chen A. et al, 2004 JCO

cN 2-3
ypT2 (>2cm)
cT3-4 / res. multifocality
res. multifocality (univariat)

Min SY et al, 2011 Int J Radiat Oncol Biol Phys

stage III
cN2-3
G3
ER neg
KI 67≥ 15%

} univariat

Predictors for IBR

IOERT after PST

IOERT as anticipated tumor bed boost during breast-conserving surgery after neoadjuvant chemotherapy in locally advanced breast cancer—Results of a case series after 5-year follow-up

Gerd Fastner[1], Roland Reitsamer[2], Ingrid Ziegler[1], Franz Zehentmayr[1], Christoph Fussl[1], Peter Kopp[1], Florentia Peintinger[2], Richard Greil[3], Thorsten Fischer[2,4], Heinrich Deutschmann[1] and Felix Sedlmayer[1]

Int. J. Cancer: 136, 1193–1201 (2015)

Table 3. Characteristics of IBTR, RR and DM

	Group 1			Group 2		
Characteristics	IBTR (2)	RR (1)	DM (11)	IBTR (2)	RR (1)	DM (6)
Primary tumor size, ≥30 mm	2	1	9	0	0	2
pPR	2	1	8	2	1	6
ypN+	1	1	8	1	1	6
Premenopausal status	2	0	5	2	1	3
Triple negative status	1	0	5	2	1	2
G3	1	0	6	2	1	2

Biomolecular predictors for IBR ?

The role of mi-RNA

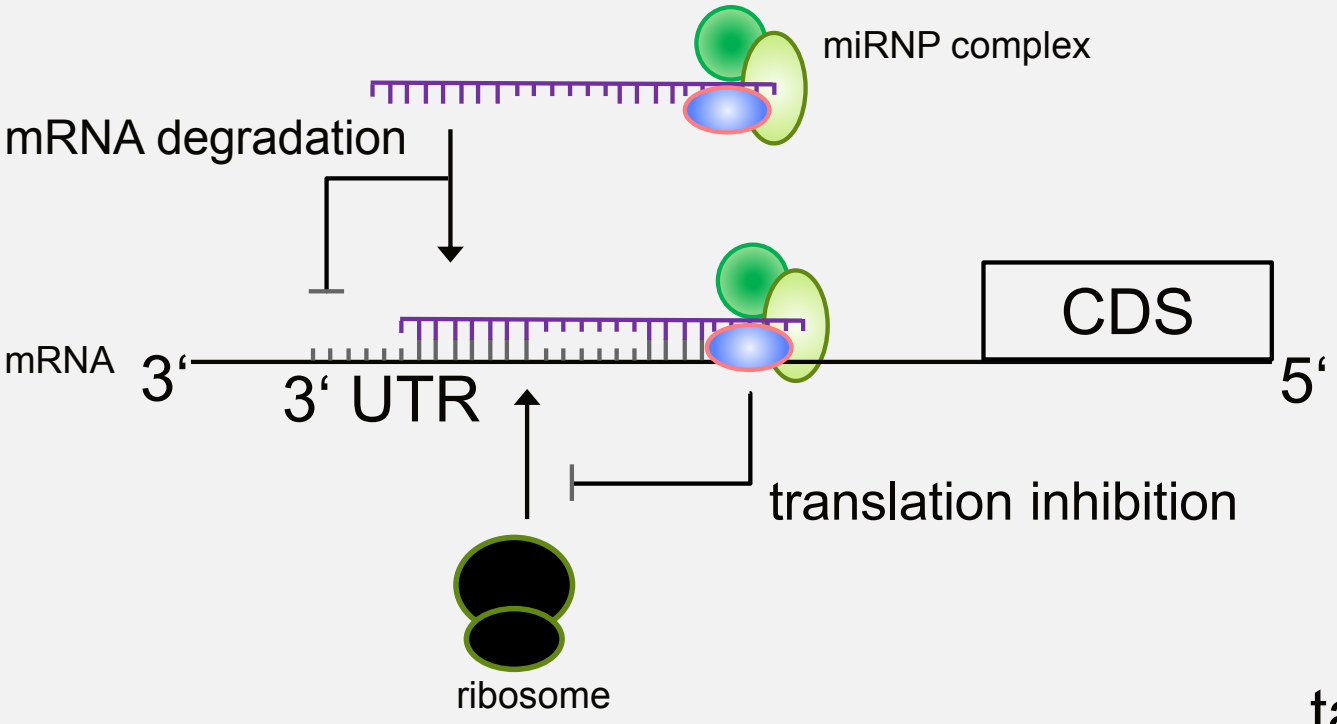
- **What** are miRNAs (miRs, microRNAs)?
  - Small non-coding RNAs (20-25 nucleotides)

- What is the **biological function** of miRs?
  - Blocking of translation by miR-mRNA-binding

- What could be **the role** of miRs in cancer tissue / patients?
  - Oncogene
  - Tumor suppressor

Biomolecular predictors for IBR ?

The role of mi-RNA



target protein

3‘ UTR… untranslated region
CDS… coding sequence

The role mi-RNA

Aim

- **To identify miRs** that predict local control in early stage breast cancer patients after breast conserving therapy

Study design: retrosp.matched-pair 147 patients, early stage

- **Pilot study** (microarray, 1200 miRs): 16 patients with local relapse versus 16 controls without local relapse
- **Validation study** (RT-qPCR, 8 miRs): 30 patients with local relapse versus 85 patients without local relapse
- **FFPE samples** of the resected untreated tumor

The role mi-RNA

Method: Fold change (fc)

Definition: fc is a measure for the different expression levels of two molecules measured by PCR

Pilot: miR-pattern distinguishes relapse from control patients

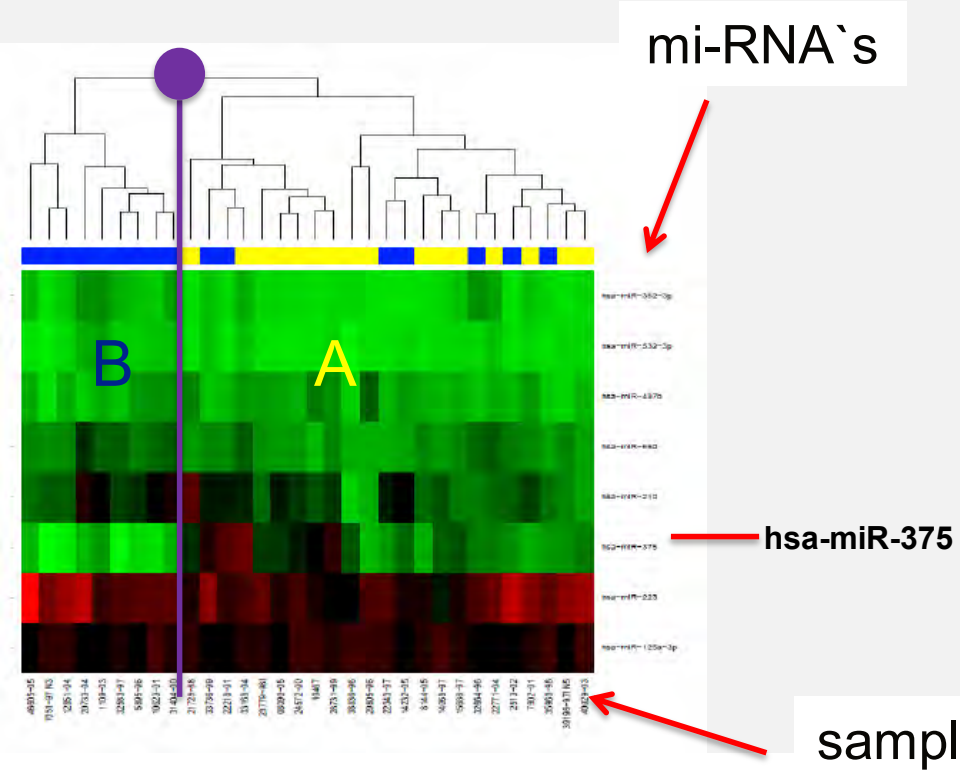


Figure 1
By means of hierarchical clustering a heat-map was generated. The dendrogram on top depicts the grouping of patients according to their pattern of candidate miRs **(yellow: patient with local relapse; blue: patient without local relapse).** The intensity values of a given miR are shown in **green (low intensity)** and **red (high intensity).** On the right side the eight candidate miRs are listed. At the bottom the sample numbers are shown. The first knot in the dendrogram separates a group of patients **without relapse (pattern B)** from the **rest of the cohort (pattern A).**

The role mi-RNA

Pilot: predictive value of the pattern verified in 32 patients

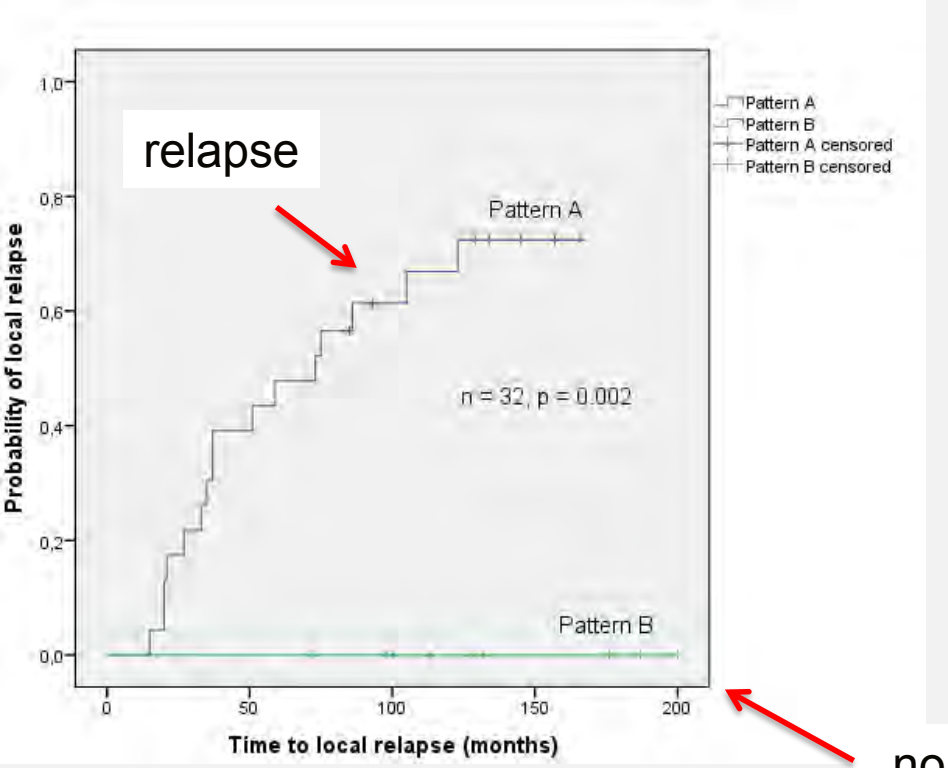


Figure 2
This plot shows the log-rank comparison of **pattern A versus pattern B**. The pattern of **eight miRs** (hsa-miR-362-3p, hsa-miR-532-3p, hsa-miR-487b, hsa-miR-660, hsa-miR-210, hsa-miR-375, hsa-miR-223, hsa-miR-125a-3p) was able to differentiate between relapse group and control group.

The role mi-RNA

Pilot: *MiR-375* is the most prominent single miR in the pattern

expression level of „hsa-miR-375“

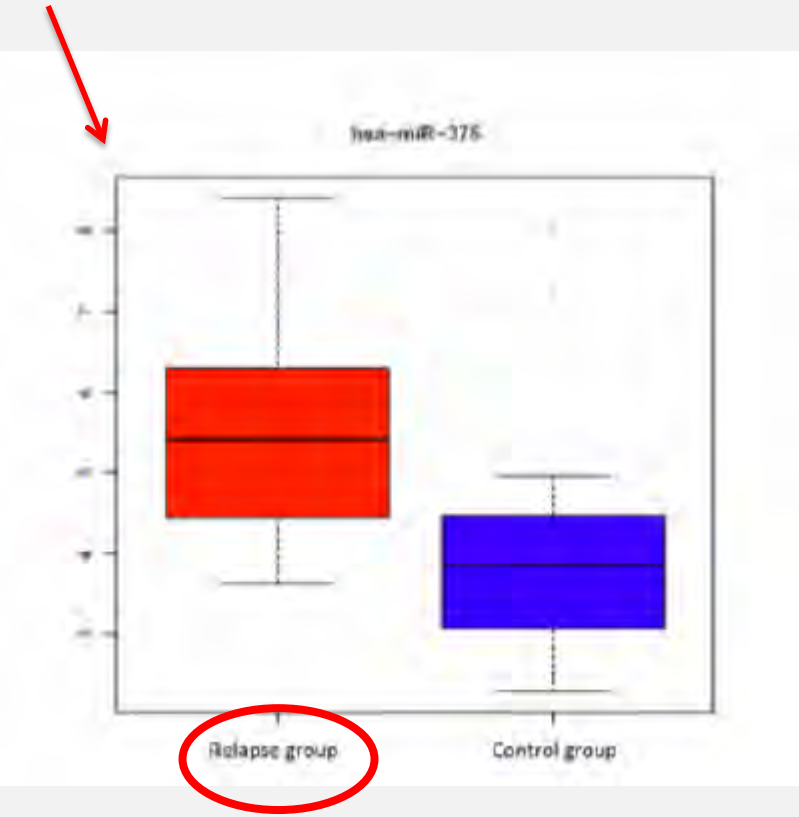


Figure 3:
The most prominent single miR that could differentiate relapse from control patients was **hsa-miR-375** (LIMMA, raw p-value 0.009). The box plot shows relapse versus control group, the expression values of hsa-miR-375 are shown on the y-axis.

The role mi-RNA

Validation: predictive value of hsa-miR-375 verified in 115 patients

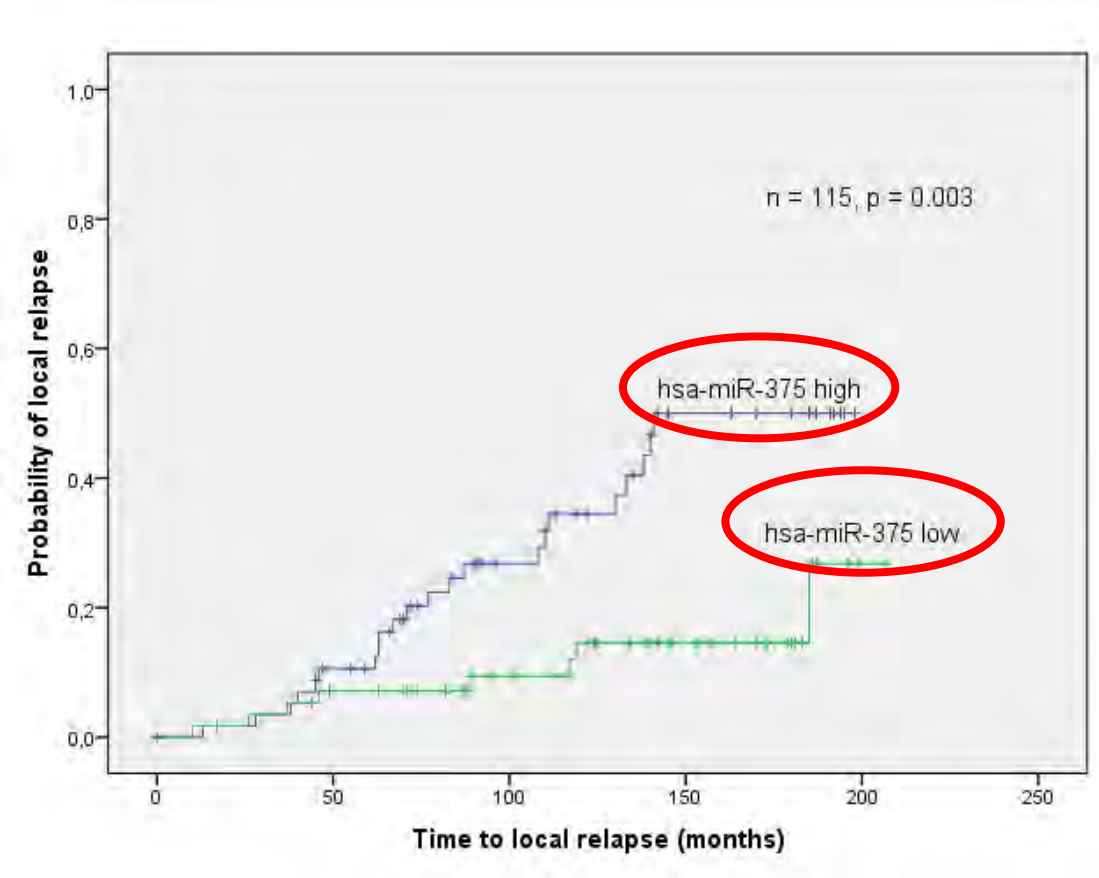


Figure 5:
In a time-to-event analysis (event = local relapse) hsa-miR-375 was able to separate the relapse from the control group (log-rank p = 0.003): **high expression levels were correlated with a higher probability of local relapse.**

The role mi-RNA

Zehentmayr et al. Clinical Epigenetics (2016) 8:28
DOI 10.1186/s13148-016-0198-1

Clinical Epigenetics

RESEARCH Open Access

Hsa-miR-375 is a predictor of local control in early stage breast cancer

Franz Zehentmayr[1,2*], Cornelia Hauser-Kronberger[3], Barbara Zellinger[2,3], Falk Hlubek[5], Claudia Schuster[5], Ulrich Bodenhofer[6], Gerd Fastner[1], Heinz Deutschmann[1,2], Philipp Steininger[2], Roland Reitsamer[4], Thorsten Fischer[4] and Felix Sedlmayer[1,2]

Further steps:

- identification of target genes for hsa-miR-375
- changes in microRNA profiles in woundfluid after IOERT (HIOB-trial)

Conclusion

Growing scientific visibility of biological efficacy higher dosages:

- *influence on wound fluid* to impair cell ploriferation
- *immunological effects* (cytokine induction, Antigene presentation)
- *antiangiogenic effects* (endothelial apoptosis, thrombus formation)
- *Repair saturation of DNA-damages* by increasing single dosages

Histological predictors - LR:

Without PST:
- G3
- BC-subtypes: TN, non-luminal

After PST:
- G3 ER neg
- TN KI67≥ 15%
- age < 50
- cT: at least ≥ 2 cm
- stage III
- res. multifocality disease in the breast
- no pCR (breast a/o nodes)
- higher cN+ (N2-3)

Biomolecular predictors - LR:

mi-RNA:
- hsa-miR-375

Further steps:
- Testing for target genes
- Testing mi-RNA profiles in the woundfluid

Update of ASTRO/GEC-ESTRO recommendations for patient selection

		ASTRO GUIDELINES			GEC-ESTRO GUIDELINES		
		SUITABLE	CAUTIONARY	UNSUITABLE	GOOD CANDIDATES	POSSIBLE CANDIDATES	CONTRA-INDICATION
Patient factors							
Age	AGE	≥60 y	50-59	<50	>50 y	>40-50	≤40
BRCA1/2 mutation	-	Absent	Absent	Present	-	-	-
Pathologic factors							
Tumor size	Diametro T	≤ 2cm	2.1- 3cm	>3cm	≤ 3cm	≤3cm	>3cm
pT	pT	pT1	pT0 or pT2	pT3-pT4	pT1-pT2	pT1-pT2	pT2(>3cm) pT3-pT4
Margins	MARGINI	Negative	Close	Positive	Negative	Close	Positive
Grade	G	Any	Any	Any	Any	Any	Any
LVI	IVP	No	Limited/focal	Extensive	Not allowed	Not allowed	Present
ER status	ERP	Positive	Negative	Any	Any	-	-
Multicentricity	-	Uncentric	Unicentric	Present	Uncentric	Unicentric	Present
multifocality	Focalità	Unifocal	Unifocal	Multifocal	Unifocal	Multifocal ≤2cm	Multifocal>2cm
Histology	ID_istologia	Inv. Ductal*	Inv. lobular	Any	Inv. Ductal*	Inv. lobular	Any
Pure DCIS	ID_istologia	Not allowed	≤3 cm	>3 cm	Not allowed	Allowed	-
EIC (is)	Componente in situ	Not allowed	≤3 cm	>3 cm	Not allowed	Not allowed	Present
Nodal factors							
N stage	PNnew N__se_dissez	pN0 (i^-,i^+)	pN0 (i^-,i^+)	pN1,pN2,pN3	pN0	pN1mi pN1a (by ALND)	pNx; ≥pN2a (≥4 positive nodes)
Nodal surgery	ID_Tipo interv Ntot	SNB or ALND	SNB or ALND	Not performed	SNB or ALND	SNB or ALND	Not performed
Treatment factors							
Neoadj. CT	NEOADJ	Not allowed	Not allowed	Yes	Not allowed	Not allowed	Yes

BreastCare

Consensus

Breast Care 2015;10:211–219
DOI: 10.1159/000433590

Published online: June 23, 2015

14th St. Gallen International Breast Cancer Conference 2015: Evidence, Controversies, Consensus – Primary Therapy of Early Breast Cancer: Opinions Expressed by German Experts

Partial Breast Radiation after BCS

The majority of the St. Gallen panelists believe that partial irradiation without whole breast radiation is possible for patients who are classified as 'suitable' according to the ASTRO (American Society for Radiation Oncology) and ESTRO (European Society for Radiotherapy and Oncology) criteria

2009

Phase III trials
Phase II studies
Comparative studies
subanalyses

2016

	Variable DB ELIOT-OUT	ASTRO GUIDELINES			GEC-ESTRO GUIDELINES		
		SUITABLE	CAUTIONARY	UNSUITABLE	GOOD CANDIDATES	POSSIBLE CANDIDATES	CONTRA-INDICATION
Patient factors							
Age	AGE	≥60 y	50-59	<50	>50 y	>40-50	≤40

AGE

50 y

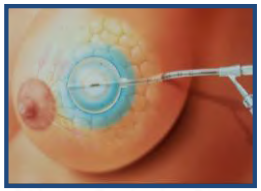
Trial	AGE	% < 50	<50>
TARGIT	≥ 45	9%	No differ
ELIOT	> 48	7%	No differ
GEC-ESTRO	≥ 40	14%	No differ
Florence Univ.	>40	16%	No differ
NSABPB- 39 RTOG-413	≥ 18	NA	
RAPID	≥ 40	NA	
IMPORT LOW	≥ 50		
IRMA	≥ 49	ongoing	
SHARE	≥50	ongoing	
HUNGARIAN	>40	20%	(30-40 excluded later on - high LR)

APBI: the AGE

Age	Overall LR	
	%	Ann.rat
<50 (368 pts) 21%	7.07	2.28
51-59 (665 pts)	3.3	1.05
>60 (789 pts)	2.28	0.8

Table 5 Multivariate analysis of clinical outcomes for patients with breast cancer treated with full-dose intraoperative radiotherapy with electrons categorized according to the American Society for Radiation Oncology (ASTRO) consensus statements

Variable	Ipsilateral breast tumor recurrence		Regional lymph node failure		Distant metastases	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, year						
<50	1.00		1.00		1.00	
50–59	0.48 (0.28–0.84)	0.01	4.40 (0.54–35.6)	0.16	0.87 (0.28–2.71)	0.80
60+	0.41 (0.23–0.72)	0.002	4.13 (0.51–32.3)	0.18	2.27 (0.83–6.20)	0.11



International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation: Breast Cancer

Predictors of Local Recurrence Following Accelerated Partial Breast Irradiation: A Pooled Analysis

Chirag Shah, M.D.,* John Ben Wilkinson, M.D.,* Maureen Lyden, M.S.,† Peter Beitsch, M.D.,‡ and Frank A. Vicini, M.D.*

Table 3 Univariate analysis of IBTR

Variable	ASBS (n = 1,449)		WBH (n = 529)		Pooled (n = 1,978)	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age at diagnosis <50 years vs. ≥50	1.40 (0.59–3.36)	0.45	3.16 (0.98–10.16)	0.05*	1.80 (0.90–3.58)	0.10
Age (continuous variable)	0.99 (0.97–1.02)	0.87	0.94 (0.90–0.99)	0.02*	0.99 (0.96–1.00)	0.20
Tumor stage T1 vs. T2	0.69 (0.16–2.90)	0.61	1.64 (0.21–12.76)	0.64	0.95 (0.53–1.71)	0.87
Tumor size ≤20 mm vs. >20 mm	1.61 (0.39–6.74)	0.51	1.13 (0.15–8.82)	0.91	1.45 (0.45–4.70)	0.53
Tumor size (continuous variable)	0.98 (0.93–1.04)	0.51	1.01 (0.93–1.10)	0.79	0.99 (0.95–1.04)	0.68
Estrogen receptor status (negative vs. positive)	3.61 (1.85–7.04)	<0.001*	1.11 (0.25–5.06)	0.89	2.82 (1.55–5.13)	<0.001*
Margin status (positive/close vs. negative)	2.13 (0.98–4.64)	0.06	0.97 (0.27–3.48)	0.97	1.60 (0.82–3.10)	0.16
Nodal status (positive vs. negative)	0.79 (0.11–5.88)	0.82	0.72 (0.09–5.60)	0.75	0.75 (0.18–3.15)	0.70
ASTRO consensus (suitable/cautionary vs. unsuitable)	0.95 (0.46–1.95)	0.88	0.37 (0.13–1.03)	0.06	0.71 (0.39–1.28)	0.25
ASTRO consensus (suitable vs. cautionary/unsuitable)	0.63 (0.32–1.24)	0.18	0.95 (0.34–2.65)	0.92	0.71 (0.40–1.25)	0.23

		ASTRO GUIDELINES			GEC-ESTRO GUIDELINES		
		SUITABLE	CAUTIONARY	UNSUITABLE	GOOD CANDIDATES	POSSIBLE CANDIDATES	CONTRA-INDICATION
Pathologic factors							
Tumor size	Diametro T	≤ 2cm	2.1- 3cm	>3cm	≤ 3cm	≤3cm	>3cm

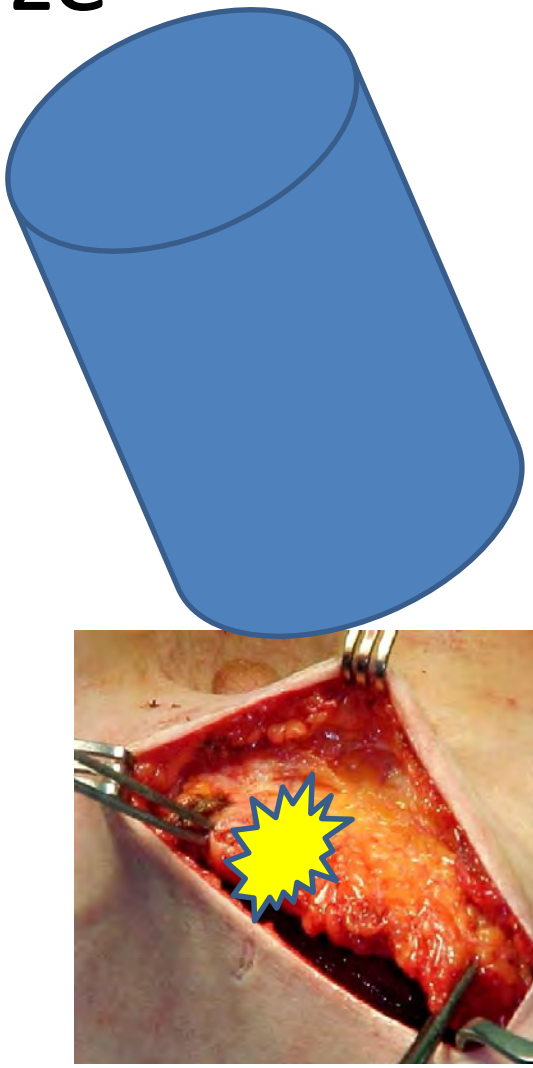
T size

≤ 2 cm

Trial	PBI technique	eligibleT size	T size> 2cm
TARGIT	Intraop photons	≤3.5 cm	12%
ELIOT	Intraop electr	≤ 2.5 cm	12%
GEC-ESTRO	HDR/PDR BRT	≤3cm	11%
Florence Univ.	IMRT	≤ 2.5 cm	5.4%%
NSABPB- 39 RTOG-413	HDR BRT/MammoSite BT/3D CRT	≤3cm	NA
RAPID	3D CRT	≤3cm	NA
IMPORT LOW	IMRT	<3cm	NA
IRMA	3D CRT	<3cm	ongoing
SHARE	3D CRT	≤ 2cm	ongoing
HUNGARIAN	HDR BT/ext e-	≤ 2cm	0%

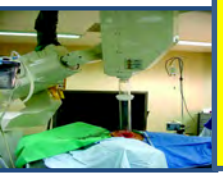
IORT-applicator size

Studies	T size > 2cm	Median cone size or range	Local relapse
ELIOT trial	12%> 2cm	4cm	11% (70 mo)
Verona	26% > 2cm	6 cm	1.8% (51 mo)
Trento	0%>2 cm	5-6 cm	0% (48 mo)
Montpellier	0% > 2cm	4-6 cm	9.5% (72 mo)
North Carolina U.	17% > 2cm	5.5 cm	15% (69 mo)
Udine	0%>2cm	NA	2% (72 mo)



ELIOT TRIAL

	Patients (n/N)	IBTR 5-year event rate (95% CI)	Log-rank p value*
Total	35/651	4·4% (2·7–6·1)	..
Pathological size			
≤1 cm	5/199	1·9% (0·0–4·0)	..
1–1·5 cm	13/243	4·2% (1·5–6·9)	..
1·5-2·0 cm	7/120	4·7% (0·7–8·8)	..
>2·0 cm	10/83	10·9% (3·7–18·1)	0·006

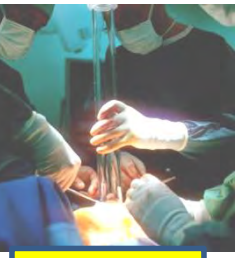


ELIOT out TRIAL

Variable	Ipsilateral breast tumour recurrence		Regional lymph node failure		Distant metastases	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
pT						
pT1	1.00		1.00		1.00	
pT2	2.42 (1.46–4.01)	0.0006	3.83 (1.48–9.87)	0.006	2.22 (1.03–4.77)	0.04

		ASTRO GUIDELINES			GEC-ESTRO GUIDELINES		
		SUITABLE	CAUTIONARY	UNSUITABLE	GOOD CANDIDATES	POSSIBLE CANDIDATES	CONTRA-INDICATION
Patient factors							
		≥2mm			≥2mm		
Margins	MARGINI	Negative	Close	Positive	Negative	Close	Positive

MARGINS

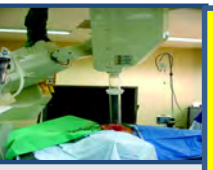


ELIOT TRIAL

Margins	Total	%	ERT	%	ELIOT	%
Negative	1228	94.9	610	94.3	618	95.5
Close to the margins	52	4.0	27	4.2	15	3.8
Positive	12	0.9	9	1.4	3	0.5
Not evaluable	2	0.2	1	0.2	1	0.2

1 out of 3 Relapsed ($p<0.05$)

Negative margin: ≥ 1mm



ELIOT out TRIAL

Variable	Ipsilateral breast tumor recurrence		Regional lymph node failure		Distant metastases	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Margins						
Negative	1.00		1.00		1.00	
Close	1.70 (0.54–5.41)	0.37	–	–	1.19 (0.16–8.72)	0.86
Positive	4.53 (0.63–32.6)	0.13	–	–		

ELSEVIER

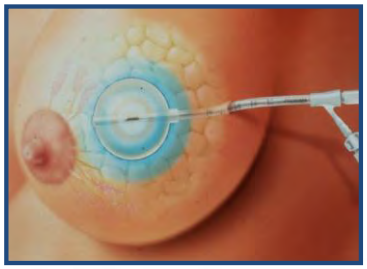
Brachytherapy 12 (2013) 91–98

BRACHYTHERAPY

Close margin : <2 mm

Impact of margin status on outcomes following accelerated partial breast irradiation using single-lumen balloon-based brachytherapy

Chirag Shah[1], J. Ben Wilkinson[2], Martin Keisch[3], Peter Beitsch[4], Douglas Arthur[5], Maureen Lyden[6], Frank A. Vicini[7,*]

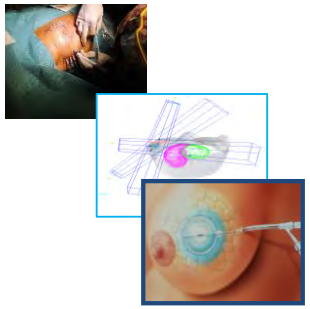


> 1400 patients

Six-year clinical outcomes by margin status

All patients	Negative, % (*N* = 1326)	Close, % (*N* = 110)	*p*-Value	Positive, % (*N* = 13)	*p*-Value	Close/positive, % (*N* = 123)	*p*-Value
Ipsilateral breast tumor recurrence	4.08	8.65	0.10	14.30	0.41	9.34	0.07
TR/MM failure	1.53	2.00	0.90	0	0.71	1.79	0.81
Elsewhere failure	2.59	6.79	0.04[a]	14.30	0.21	7.69	0.02[a]
Regional failure	0.76	0.95	0.75	0	0.78	0.85	0.83
Distant metastases	2.66	4.04	0.68	0	0.60	3.59	0.82
Disease-free survival	84.10	79.40	0.18	77.90	0.43	79.20	0.14
Overall survival	90.30	91.50	0.92	90.90	0.42	91.50	0.74
Cause-specific survival	98.20	99.00	0.57	100	0.65	99.10	0.50
Contralateral failure	2.57	1.06	0.41	0	0.60	0.95	0.34

DCIS



>2000 patients

gories (OR, 1.27; $P = .38$). ER negative receptor status (OR, 4.13; $P < .01$) and involved surgical margins (OR, 2.70; $P = .02$) were associated with elsewhere failures. No factors, however, were

Wilkinson 2013

		ASTRO GUIDELINES			GEC-ESTRO GUIDELINES		
		SUITABLE	CAUTIONARY	UNSUITABLE	GOOD	POSSIBLE	CONTRA-
LVI	IVP	No	Limited/focal	Extensive	Not allowed	Not allowed	Present

LVI

ABSENT

Limited or focal

Issues: different pathologic assessment
unreliable perioperative assesment

Ann Surg Oncol (2012) 19:553–559
DOI 10.1245/s10434-011-1941-7

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL

ORIGINAL ARTICLE – BREAST ONCOLOGY

A Single-Institution Review of Accelerated Partial Breast Irradiation in Patients Considered "Cautionary" by the American Society for Radiation Oncology

Tari S. Stull, MD[1], M. Catherine Goodwin, MD[1], Edward J. Gracely, PhD[2], Michael R. Chernick, PhD[3], Richard J. Carella, MD[4], Thomas G. Frazier, MD[1], and Andrea V. Barrio, MD[1]

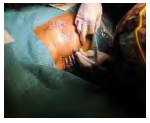
TABLE 2 Correlation of cautionary criteria with risk of recurrence at any site in patient cohort ($n = 109$)

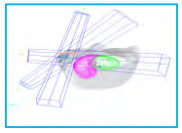
Variable	Hazard ratio [95% CI]	*P*
Age 50–59 years	0.57 [0.06–5.11]	0.61
Tumor size 2.1–3.0 cm[a]	–	0.48
Close margins	2.69 [0.45–16.16]	0.28
Focal LVI	3.94 [0.44–35.35]	0.22
ER-negative	2.87 [0.48–17.18]	0.25
ILC[a]	–	0.43
DCIS[a]	–	0.041

Impact of Lymphovascular Space Invasion, Extensive Intraductal Component, and Multifocality on Outcomes Following Accelerated Partial Breast Irradiation

M.S. Jawad, J.B. Wilkinson, C. Shah, J. Wobb, B. Stone, A. Fowler, C.K. Mitchell, M. Wallace, P.Y. Chen, and I.S. Grills; *William Beaumont Hospital, Royal Oak, MI*

Materials/Methods: Between 1993 and 2011, 692 patients with early-stage breast cancer were treated with APBI at a single institution, receiving either interstitial brachytherapy (n = 195), balloon-based brachytherapy (n = 292), or 3D-CRT (n = 205) as part of breast conserving therapy.





	LVI absent	LVI present	p
LR	1.8%	3.7%	0.10
RR	0%	4%	0.001
DM	1.9%	8.7%	0.005

ELIOT TRIAL

	LVI absent	LVI present	p
LR	4.2%	5.4%	0.89

ELIOT out TRIAL

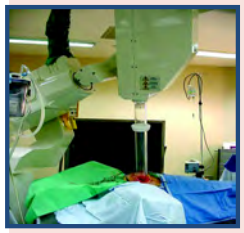
ltivariate analysis of clinical outcomes for patients with breast cancer treated with full-dose intraoperative radiotherapy categorized according to the American Society for Radiation Oncology (ASTRO) consensus statements

Variable	Ipsilateral breast tumor recurrence		Regional lymph node failure		Distant metastases	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
LVI						
Absent	1.00		1.00		1.00	
Focal	1.49 (0.75–2.96)	0.25	1.61 (0.44–5.86)	0.47	1.71 (0.62–4.75)	0.30
Diffuse	2.03 (1.03–3.99)	0.04	0.83 (0.10–7.32)	0.87	2.31 (0.86–6.25)	0.10

		ASTRO GUIDELINES			GEC-ESTRO GUIDELINES		
Grade	G	Any	Any	Any	Any	Any	Any

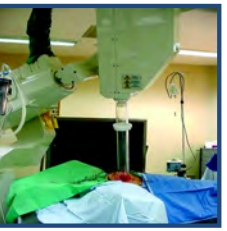
GRADE

Any



ELIOT TRIAL

	Patients (n/N)	IBTR 5-year event rate (95% CI)	Log-rank p value*
Tumour grade			
G1	5/196	1·1% (0·0–2·7)	..
G2	15/305	3·8% (1·5–6·1)	..
G3	15/129	11·9% (5·7–18·2)	0·0003



. University of Verona recurrences after APBI compared to ASTRO/ESTRO low-risk women

Factor	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	55	62	68	75
Histology	IDC	IDC	IDC	IDC
Tumor size, cm	2.0	2.8	1.5	1.8
Grade	G2	G2	G3	G3
Nodal status	pN0	pN0	pN0	pN0
ER status	positive	positive	positive	negative
PR status	positive	positive	positive	negative
HER2 status	negative	unknown	negative	unknown
LVI status	absent	absent	absent	present
Margin status	negative	negative	negative	negative
Adjuvant HT/CT	HT	HT	HT	none[a]
Time to relapse, months	28	36	40	60
Salvage	mastectomy	mastectomy	mastectomy	mastectomy

THE CHRISTIE-HOSPITAL TRIAL 1982-1987

Ca				P
Gross complete excision				
No	69	0.2733	1.31	0.41 (NS)
Yes	566	0.0	1.00	
	635			
Pathology				
Invasive ductal	531	−0.2102	0.81	0.07 (NS)
Lobular	95	0.3896	1.48	
Other/NK	82	0.0	1.00	
	708			
Grade				
G1	91	0.0	1.00	0.009
G2	206	0.9456	2.57	
G3	214	1.4809	4.40	
Lobular	95	1.1659	3.21	
Other/NK	102	0.9724	2.64	
	708			
Lymphatic invasion				
No	595	0.0	1.00	0.03
Yes	97	0.5812	1.79	
	692			
NK	+16			
	708			

VOLUME 27 · NUMBER 30 · OCTOBER 20 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

From the Department of Radiation Oncology, the University of Pittsburgh Cancer Center, Pittsburgh, PA; Departments of Radiation Oncology and Pathology, The Netherlands Cancer Institute/Antoni Van Leeuwenhoekhuis, Amsterdam; Department of Radiation Oncology, Dr Bernard Verbeeten Instituut, Tilburg; Department of Radiation Oncology, University Medical Centre, Leiden; Department of Radiation Oncology, Maastricht Radiation Oncology Clinic, Maastricht; Department of Radiation Oncology, Radboud University Medical Centre, Nijmegen; Department of Radiation Oncology, University Medical Centre, Utre-

Impact of Pathological Characteristics on Local Relapse After Breast-Conserving Therapy: A Subgroup Analysis of the EORTC Boost Versus No Boost Trial

Heather A. Jones, Ninja Antonini, Augustinus A.M. Hart, Johannes L. Peterse,† Jean-Claude Horiot, Françoise Collin, Philip M. Poortmans, S. Bing Oei, Laurence Collette, Henk Struikmans, Walter F. Van den Bogaert, Alain Fourquet, Jos J. Jager, Dominic A.X. Schinagl, Carla C. Wárlám-Rodenhuis, and Harry Bartelink

Contrast by Factor	P	Hazard Ratio	95% CI
Age > 50, yes *v* no	< .0001	0.40	0.28 to 0.57
N+ according to local pathology, N+ *v* N−	.2585	0.77	0.48 to 1.22
Systemic treatment (chemotherapy or tamoxifen), yes *v* no	.0088	0.57	0.38 to 0.87
Volume of excision biopsy specimen, cm^3	.1068	1.00	1.00 to 1.00
Treatment, no boost *v* boost 16 Gy	.0008	1.86	1.29 to 2.68
Vascular invasion, yes *v* no	.9715	0.99	0.65 to 1.50
Extensive intraductal component, yes *v* no	.8975	1.04	0.57 to 1.90
Histology			
Lobular *v* ductal	.4451	0.72	0.32 to 1.66
Mixed pattern *v* ductal	.3184	0.72	0.37 to 1.38
Other *v* ductal	.6439	0.88	0.50 to 1.54
Histologic grade			
Intermediate *v* high	.0320	0.60	0.37 to 0.96
Low *v* high	.0003	0.46	0.31 to 0.70

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

	Number allocated BCS+RT/BCS	10-year risk of a locoregional or distant recurrence (%)			Test for trend/h reduction
		BCS+RT	BCS	Absolute reduction with RT (95% CI)	2p unadjusted*
(b) Tumour grade					<0·00001
Low	750/757	11·0	22·4	11·4 (6·3 to 16·5)	
Intermediate	816/843	16·4	31·6	15·3 (10·4 to 20·2)	
High	448/431	28·6	53·3	24·7 (17·6 to 31·8)	

ASTRO "Suitable"
1.5% at 5-y

ESTRO "Good"
1.9% at 5-y

ELIOT out –trial patients	ASTRO consensus statement						
	Suitable		Cautionary		Unsuitable		
Patients	294		691		812		
5-year outcome	Even	Rate (%)	Even	Rate (%)	Even	Rate (%)	Log-rank P
Ipsilateral breast tumor recurrence	3	1.5	21	4.4	50	8.8	0.0003

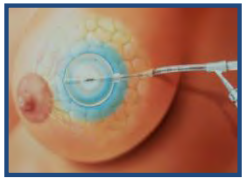
ELIOT out –trial patients	GEC-ESTRO consensus statement						
	Good		Possible		Contraindicat		
Patients	573		468		767		
5 -year outcome	Events	Rate* (%)	Even	Rate* (%)	Even	Rate* (%)	Log-rank P
In breast tumor recurrence	7	1.9	22	7.4	46	7.7	0.001

		ASTRO GUIDELINES			GEC-ESTRO GUIDELINES		
		SUITABLE	CAUTIONARY	UNSUITABLE	GOOD CANDIDATES	POSSIBLE CANDIDATES	CONTRA-INDICATION
Patient factors							
ER status	ERP	Positive	Negative	Any	Any	-	-

ER STATUS

(Beitsch 2010)

Univariate analyisis LR in Mammosite Registry trial	Invasive cases (n = 1,255) IBTR
Age (continuous)	NS
<50 vs. ≥50	NS
Tumor size	NS
ASTRO 'U' group	NS
Nodal status	NS
Overall stage	NS
Margins	NS
ER status	0002
Grade	NS
Chemotherapy use	NS
Hormone use	NS
EIC	NS

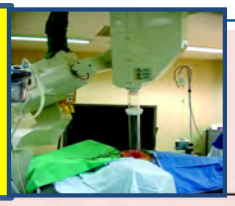


Wilkinson 2013

Table 3 Univariate analysis of IBTR

Variable	ASBS (*n* = 1,449) OR (95% CI)	*p* value	WBH (*n* = 529) OR (95% CI)	*p* value	Pooled (*n* = 1,978) OR (95% CI)	*p* value
Age at diagnosis <50 years vs. ≥50	1.40 (0.59–3.36)	0.45	3.16 (0.98–10.16)	0.05*	1.80 (0.90–3.58)	0.10
Age (continuous variable)	0.99 (0.97–1.02)	0.87	0.94 (0.90–0.99)	0.02*	0.99 (0.96–1.00)	0.20
Tumor stage T1 vs. T2	0.69 (0.16–2.90)	0.61	1.64 (0.21–12.76)	0.64	0.95 (0.53–1.71)	0.87
Tumor size ≤20 mm vs. >20 mm	1.61 (0.39–6.74)	0.51	1.13 (0.15–8.82)	0.91	1.45 (0.45–4.70)	0.53
Tumor size (continuous variable)	0.98 (0.93–1.04)	0.51	1.01 (0.93–1.10)	0.79	0.99 (0.95–1.04)	0.68
Estrogen receptor status (negative vs. positive)	3.61 (1.85–7.04)	<0.001*	1.11 (0.25–5.06)	0.89	2.82 (1.55–5.13)	<0.001*
Margin status (positive/close vs. negative)	2.13 (0.98–4.64)	0.06	0.97 (0.27–3.48)	0.97	1.60 (0.82–3.10)	0.16
Nodal status (positive vs. negative)	0.79 (0.11–5.88)	0.82	0.72 (0.09–5.60)	0.75	0.75 (0.18–3.15)	0.70
ASTRO consensus (suitable/cautionary vs. unsuitable)	0.95 (0.46–1.95)	0.88	0.37 (0.13–1.03)	0.06	0.71 (0.39–1.28)	0.25
ASTRO consensus (suitable vs. cautionary/unsuitable)	0.63 (0.32–1.24)	0.18	0.95 (0.34–2.65)	0.92	0.71 (0.40–1.25)	0.23

ELIOT TRIAL



	Patients (n/N)	IBTR 5-year event rate (95% CI)	Log-rank p value*
Oestrogen receptor			
Absent	8/63	14·9% (5·2–24·5)	..
Present	21/583	3·3% (1·8–4·9)	0·004
Overall p value	..	..	

	Variable DB ELIOT-OUT	ASTRO GUIDELINES			GEC-ESTRO GUIDELINES		
		SUITABLE	CAUTIONARY	UNSUITABLE	GOOD CANDIDATES	POSSIBLE CANDIDATES	CONTRA-INDICATION
Patient factors							
Histology	ID_istologia	Inv. Ductal*	Inv. lobular	Any	Inv. Ductal*	Inv. lobular	Any

HISTOLOGY

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 4, pp. e547–e551, 2011
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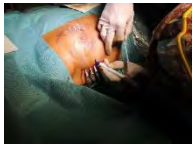
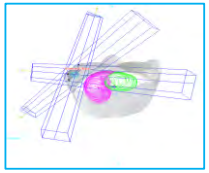
0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2011.04.050

CLINICAL INVESTIGATION Breast

CLINICAL OUTCOMES USING ACCELERATED PARTIAL BREAST IRRADIATION IN PATIENTS WITH INVASIVE LOBULAR CARCINOMA

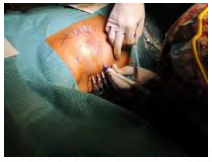
Chirag Shah, M.D., J. Ben Wilkinson, M.D., Simona Shaitelman, M.D., Inga Grills, M.D., Michelle Wallace, R.N., Christina Mitchell, R.N., and Frank Vicini, M.D.





Five-year outcomes between IDC and ILC patients

5-year actuarial	IDC ($n = 16$)	ILC ($n = 410$)	p value
LR	0%	2.5%	0.59
RR	0%	0.7%	0.80
DFS	100%	94%	0.43
DM	0%	3.5%	0.54
CSS	100%	97%	0.59
OS	92%	89%	0.88



Int. J. Radiation Oncology Biol. Phys., Vol. 80, No. 1, pp. 17–24, 2011
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0360-3016/$–see front matter
doi:10.1016/j.ijrobp.2010.01.020

CLINICAL INVESTIGATION Breast

ACCELERATED PARTIAL BREAST IRRADIATION: 5-YEAR RESULTS OF THE GERMAN-AUSTRIAN MULTICENTER PHASE II TRIAL USING INTERSTITIAL MULTICATHETER BRACHYTHERAPY ALONE AFTER BREAST-CONSERVING SURGERY

Vratislav Strnad, M.D.,* Guido Hildebrandt, M.D.,†‡ Richard Pötter, M.D.,§ Josef Hammer, M.D.,¶ Marion Hindemith, M.D.,† Alexandra Resch, M.D.,§ Kurt Spiegl, M.D.,¶ Michael Lotter, Ph.D.,* Wolfgang Uter, M.D.,‖ Mayada Bani,** Rolf-Dieter Kortmann, M.D.,† Matthias W. Beckmann, M.D.,** Rainer Fietkau, M.D.,* and Oliver J. Ott, M.D.*

ELSEVIER

Christie Hospital

Radiotherapy and Oncology 39 (1996) 223–227

RADIOTHERAPY & ONCOLOGY

Prognostic factors for breast recurrence after conservative breast surgery and radiotherapy: results from a randomised trial

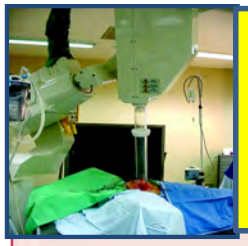
B. Magee*, R. Swindell, M. Harris, S.S. Banerjee

Christie Hospital, Manchester, UK

ILC vs IDC: no difference

ILC vs.IDC : 42% v.s 17%, p 0.07

LOBULAR HISTOLOGY



ELIOT TRIAL

	Patients (n/N)	IBTR 5-year event rate (95% CI)	Log-rank p value*
Histology			
Ductal	28/524	4·5% (2·6–6·5)	..
Lobular	3/53	4·6% (0·0–10·8)	..
Ductal and lobular	2/17	6·3% (0·0–18·1)	..
Other	2/53	2·1% (0·0– 6·1)	0·69

Table 5 Multivariate analysis of clinical outcomes for patients with breast cancer treated with full-dose intraoperative radiotherapy with electrons categorized according to the American Society for Radiation Oncology (ASTRO) consensus statements

ELIOT OUT TRIAL

Variable	Ipsilateral breast tumor recurrence		Regional lymph node failure		Distant metastases	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Histology						
Ductal	1.00		1.00			
Lobular	1.97 (1.00–3.90)	0.05	–	–	1.58 (0.45–5.55)	0.48
Other histologies	0.79 (0.25–2.50)	0.69	–	–	0.92 (0.16–5.21)	0.92

No difference when cone size> 4cm

	Variable DB ELIOT-OUT	ASTRO GUIDELINES			GEC-ESTRO GUIDELINES		
		SUITABLE	CAUTIONARY	UNSUITABLE	GOOD CANDIDATES	POSSIBLE CANDIDATES	CONTRA-INDICATION
Patient factors							
Pure DCIS	ID_istologia	Not allowed	≤3 cm	>3 cm	Not allowed	Allowed	-

DCIS

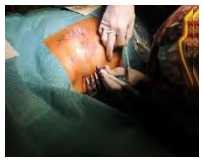
Ann Surg Oncol (2013) 20:1275–1281
DOI 10.1245/s10434-012-2694-7

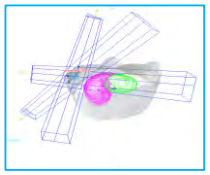
Annals of SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Should Ductal Carcinoma-in-situ (DCIS) Be Removed from the ASTRO Consensus Panel Cautionary Group for Off-protocol Use of Accelerated Partial Breast Irradiation (APBI)? A Pooled Analysis of Outcomes for 300 Patients with DCIS Treated with APBI

Frank Vicini, MD[1], Chira;
Maureen Lyden, MS[6]





580 patients

Series evaluating APBI in patients with DCIS

Study	Patients	Follow-up (mo)	IBTR (%)
University of Wisconsin[13]	32	60	0
Bryn Mawr[12]	46	36	0
WBH[9]	53	36	2
MammoSite Registry Trial, phase II[15]	100	9.5	2
Georgia Breast Center[14]	126	24	2.4
ASBS Registry[10]	194	60	3.4
ASBrS registry WBH Pooled	300	56.6	2.6
Total	604	9.5–60	0–3.4

5- y pooled LR rate: 2.6%

Study	N	F/U yrs	Med Age	Med Size (cm)	Grade	Margin Width	In-Breast Recurrence (%) 5-yr	7 yr	10 yr
Surgery alone **ECOG 5194** ≤2.5 cm, ≥3 mm margin	565	6.2	60	0.6	Low-intermediate grade	3 mm	**6.1%**	**10.5%**	-
<1cm, , ≥3 mm margin	105	6.7	59	0.5	High grade		**15.3%**	**18%**	-
APBI According to ECOG 5194 low-risk	65	3	60	< 2.5	I/II	NA	**2%**	 **Overall 5-y LR 1.4% (99 pts)**	
APBI according to ECOG 5194 High-risk	10	3	60	< 1	III	NA	**0%**		

Goyal 2010
White 2013. Shah 2012

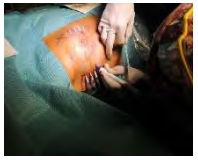
		ASTRO GUIDELINES			GEC-ESTRO GUIDELINES		
		SUITABLE	CAUTIONARY	UNSUITABLE	GOOD CANDIDATES	POSSIBLE CANDIDATES	CONTRA-INDICATION
Patient factors							
EIC (is)	Componente in	Not allowed	≤3 cm	>3 cm	Not allowed	Not allowed	Present

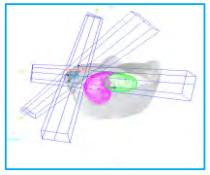
EIC

Impact of Lymphovascular Space Invasion, Extensive Intraductal Component, and Multifocality on Outcomes Following Accelerated Partial Breast Irradiation

M.S. Jawad, J.B. Wilkinson, C. Shah, J. Wobb, B. Stone, A. Fowler, C.K. Mitchell, M. Wallace, P.Y. Chen, and I.S. Grills; *William Beaumont Hospital, Royal Oak, MI*

Materials/Methods: Between 1993 and 2011, 692 patients with early-stage breast cancer were treated with APBI at a single institution, receiving either interstitial brachytherapy (n = 195), balloon-based brachytherapy (n = 292), or 3D-CRT (n = 205) as part of breast conserving therapy.



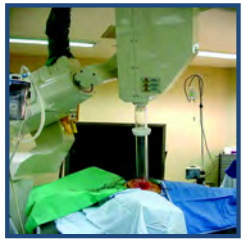


	EIC absent	EIC present	p
LR	0%	0%	-
RR	0.6%	5.3%	0.008
DM	2.7%	10.8%	0.10

ELIOT TRIAL

	EIC absent	EIC present	p
LR	2%	4.9%	0.21

ELIOT out TRIAL



Multivariate analysis of clinical outcomes for patients with breast cancer treated with full-dose intraoperative radiotherapy with electrons categorized according to the American Society for Radiation Oncology (ASTRO) consensus statements

Variable	Ipsilateral breast tumor recurrence		Regional lymph node failure		Distant metastases	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
EIC						
Absent/focal	1.00		1.00		1.00	
Extensive	0.59 (0.31–1.14)	0.11	0.68 (0.15–2.99)	0.61	0.78 (0.30–2.07)	0.62

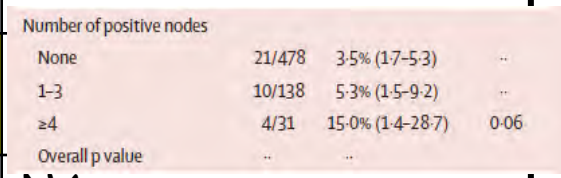
		ASTRO GUIDELINES			GEC-ESTRO GUIDELINES		
		SUITABLE	CAUTIONARY	UNSUITABLE	GOOD CANDIDATES	POSSIBLE CANDIDATES	CONTRA-INDICATION

N STAGE

Nodal factors							
N stage	PNnew N__se_dissez	pN0 (i^-,i^+)	pN0 (i^-,i^+)	pN1,pN2,pN3	pN0	pN1mi pN1a (by ALND)	pNx; ≥pN2a (≥4 positive nodes)
Nodal surgery	ID_Tipo interv Ntot	SNB or ALND	SNB or ALND	Not performed	SNB or ALND	SNB or ALND	Not performed

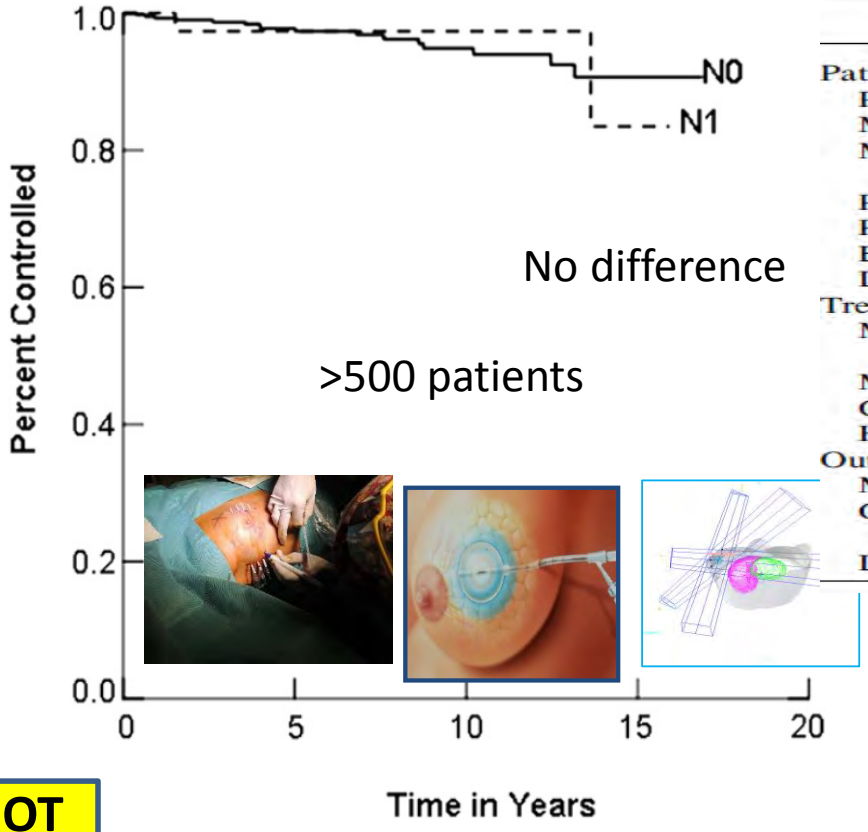
pN0/pN0(i_+)/pN1mi

Trial	PBI technique	Eligible N	pN	Impact on LR
TARGIT	Intraop photons	cN+	pN1: 15% pN2: 4%	NA (followed by EXRT)
ELIOT	Intraop electr	cN0	pN1: 21% pN2: 5%	
GEC-ESTRO	HDR/PDR BRT	pN0/pN1	pN1mi: 1%	NA
Florence Univ.	IMRT	pN0/pN1	pN1: 7.3%	None
NSABPB- 39 RTOG-413	HDR BRT/MammoSite BT/3D CRT	pN0/pN1	NA	NA
RAPID	3D CRT	pN0	NA	-
IMPORT LOW	IMRT	pN0/pN1	NA	NA
IRMA	3D CRT	pN0 /pN1	ongoing	ongoing
SHARE	3D CRT	pN0/pN0(i+)	ongoing	ongoing
HUNGARIAN	HDR BT/ext e-	pN0/ pNimi	pN1mi: 2.3%	None
Trento	Intraop electron	cN0	pN0	-
Verona Univ.	Intraop electron	cN0	pN1a: 22.1%	None
Udine	Intraop electron	cN0	pN1mi: 4.1%	None
Montpellier	Intraop electron	cN0	pN0	-



Number of positive nodes			
None	21/478	3·5% (1·7–5·3)	..
1–3	10/138	5·3% (1·5–9·2)	..
≥4	4/31	15·0% (1·4–28·7)	0·06
Overall p value	..	..	

Shah 2012



No difference

>500 patients

Table 1. Patient characteristics sorted by risk category

Characteristic	Low-risk group	High-risk group
Patient/tumor related		
Patients (*n*)	183	90
Median age (y)	63	47
Median pathologic size (mm)	11	14
Patients <50 y	0 (0)	70 (78)
Positive lymph nodes	0 (0)	16 (18)
Estrogen receptor negative	0 (0)	21 (23)
DCIS	28 (15)	8 (9)
Treatment related		
Multicatheter brachytherapy	162 (89)	85 (94)
MammoSite	21 (11)	5 (6)
Chemotherapy	20 (11)	48 (53)
Hormonal therapy	104 (57)	45 (50)
Outcome related		
Median follow-up (mo)	47.9	49.7
Crude ipsilateral breast recurrence	4 (2.2)	4 (4.4)
Death from any cause	8 (4.4)	5 (5.6)

RAPID COMMUNICATION

CLINICAL OUTCOME ANALYSIS IN "HIGH-RISK" VERSUS "LOW-RISK" PATIENTS ELIGIBLE FOR NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL B-39/ RADIATION THERAPY ONCOLOGY GROUP 0413 TRIAL: FIVE-YEAR RESULTS

Rakesh R. Patel, M.D., Michael E. Christensen, B.S., C. Wesley Hodge, M.D., Jarrod B. Adkison, M.D., and Rupak K. Das, Ph.D.

ELIOT Out TRIAL

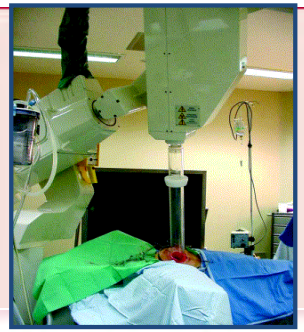
Multivariate analysis of clinical outcomes for patients with breast cancer treated with full-dose intraoperative radiotherapy ns categorized according to the American Society for Radiation Oncology (ASTRO) consensus statements

Variable	Ipsilateral breast tumor recurrence		Regional lymph node failure		Distant metastases	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Lymph node status						
Negative	1.00		1.00		1.00	
pN1mi or pN1a (by ALND)	1.29 (0.69–2.40)	0.43	0.32 (0.07–1.50)	0.15	2.05 (0.79–5.36)	0.14
pNx; ≥pN2a (≥4 positive nodes)	1.80 (1.01–3.22)	0.047	0.57 (0.15–2.17)	0.41	3.92 (1.71–8.97)	0.001

Something is missing……

San Gallen 2013

Luminal A	**ER+ and/or PR+, HER2−, and low Ki67 (<20%)**
Luminal B	**ER+ and/or PR+ and HER2+ (luminal-HER2 group)** **ER+ and/or PR+, HER2−, and high Ki67 (>20%)**
HER2	**ER−, PR−, and HER2+**
Basal-like	**ER−, PR−, HER2−, and CK5/6 and/or EGFR+**



ELIOT TRIAL

	Patients (n/N)	IBTR 5-year event rate (95% CI)	Log-rank p value*	
Molecular subtype				
Luminal A	7/256	1·4% (0·0–3·0)	..	
Luminal B	20/327	4·9% (2·4–7·4)		True and elsewhere
HER2-positive (non-luminal)	1/20	5·9% (0·0–17·1)		True ..
Triple negative	7/43	18·9% (6·1–31·7)	0·001	True and elsewhere

	Patients (n/N)	IBTR 5-year event rate (95% CI)	Log-rank p value*
Proliferative index (Ki-67)			
<14%	8/263	1·8% (0·0–3·5)	..
14–20%	5/138	1·5% (0·0–3·6)	..
>20%	22/244	9·1% (5·1–13·1)	0·002

IEO Arc

Factors	Suitability for IORT
AGE	50 Y
BRCA 1/2 mutation	No data (only indirect: >70% elsewhere LR)
Tumor size (pT)	≤ 2cm
Margins	Negative/ (if close , no DCIS)
Grade	any
LVI	Absent/limited
ER status	positive
Multicentricity/multifocality	Not allowed
Histology	Any (if IORT, use large cone)
Pure DCIS	G1/G2
EIC (is)	any
N stage	N0/N0 (i+)/N1mi
Nodal surgery	SN Biopsy/dissection
Neoadjuvant CT	No data

Let's consider the whole picture!

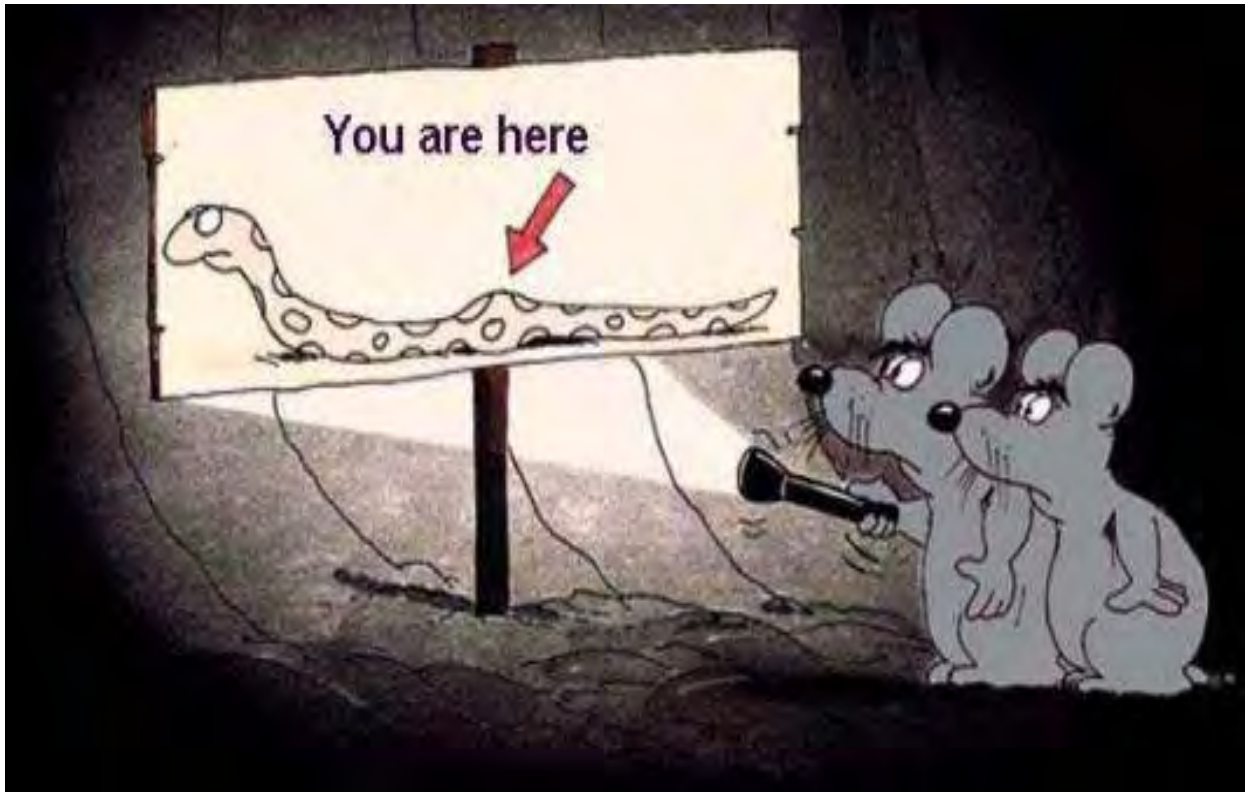
Wobb 2013

Five-year outcomes by number of cautionary + unsuitable risk factors (n = 692)

Outcome	0 (n = 240)	1 (n = 264)	2 (n = 143)	3+ (n = 44)	*P*
IBTR	1.9	0.9	0	9.9	<.01
CLTR	1.3	1.8	2.3	0	.56
RR	0	0	0	6.2	<.01
DM	0.6	2	6.1	6	.01
DFS	97.5	97	94	87.5	<.01
CSS	99	98.5	96	93	.16
OS	92	90	93	87	.28

- **the higher the number of high-risk factors the higher the risk of treatment failure**

Thank you for the attention



Update of Results from the ELIOT trial

Roberto Orecchia

Chair of Radiation Therapy, University of Milan,
Scientific Director at the European Institute of Oncology, Milan &
National Center of Oncological Hadrontherapy, CNAO, Pavia

roberto.orecchia@ieo.it

9 th ISIORT

Novara, 24th June 2016

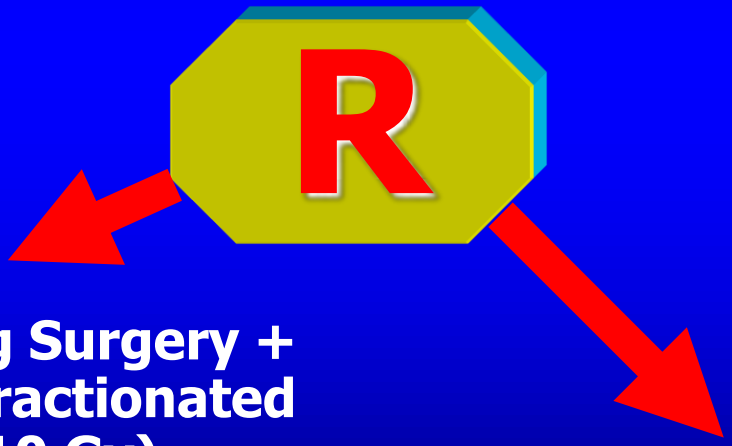
IEO
Arc Advanced Radiotherapy Center

ELIOT TRIAL IEO

November 2000 – December 2007

ClinicalTrials.gov Identifier NCT01849133

Tumor diameter up to 25 mm
Aged 48 to 75 years
Suitable for BCS



Breast Conserving Surgery +
Conventionally Fractionated
WBI (50 + 10 Gy)

Breast Conserving Surgery +
ELectron Intra Operative Therapy
ELIOT (21 Gy)

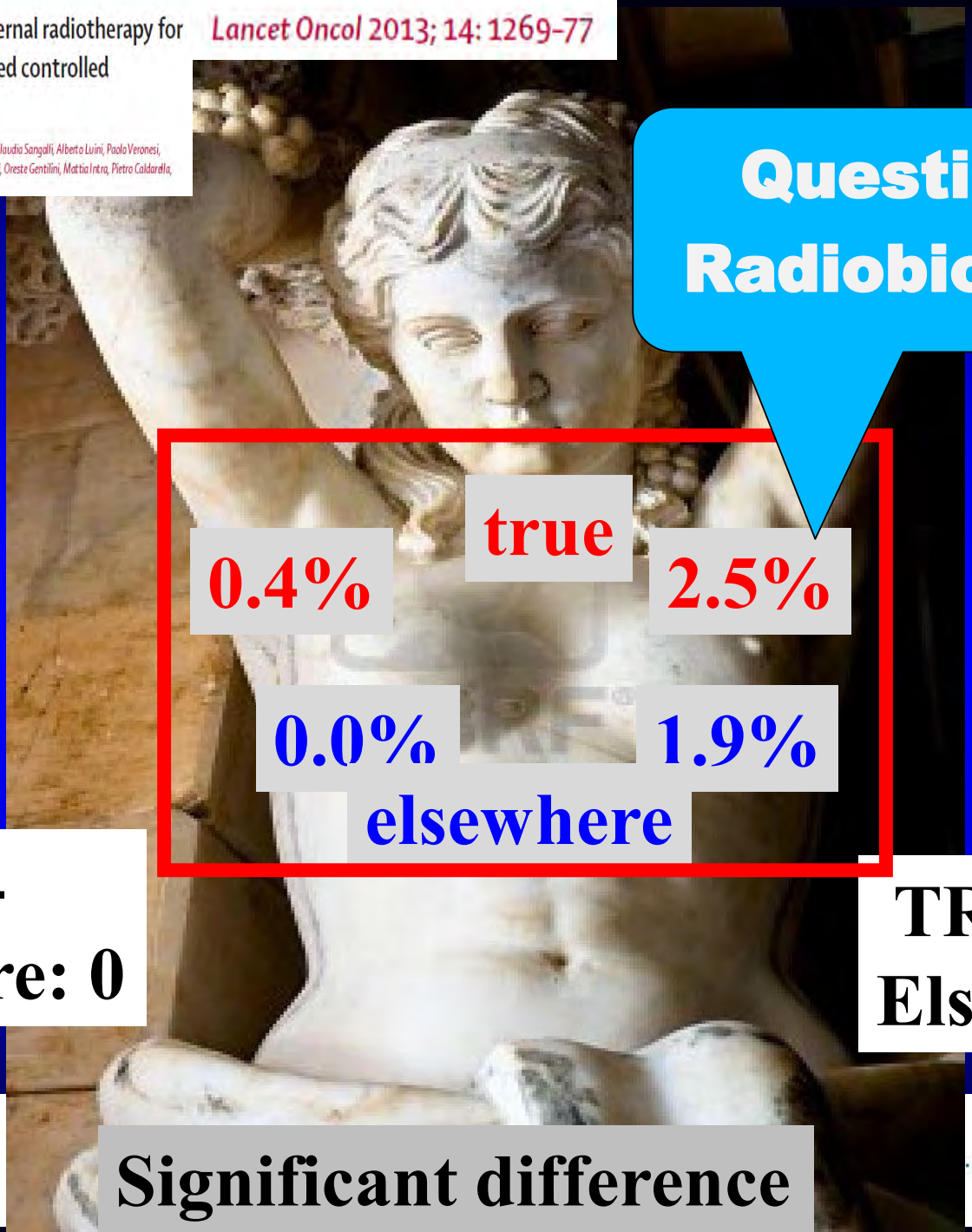
U Veronesi & R Orecchia,
Lancet Oncol, November 2013

	External RT (n=654)		ELIOT (n=651)		
Person-years until last visit	3,920		3,716		
Person-years until last contact	4,107		3,997		
Events	*Events*	*5-year event rate (95% confidence interval)*	*Events*	*5-year event rate (95% confidence interval)*	*Log-rank P value*
IBRT	**4**	**0.4% (0.0-1.0%)**	**35**	**4.4% (2.7-6.1%)**	**<0.0001**
True Local relapse	4	0.4% (0.0-1.0%)	21	2.5% (1.2-3.8%)	0.0003
New Ipsilateral Breast Tumour	0	0.0% (0.0-0.0%)	14	1.9% (0.8-3.1%)	0.0001
Axillary/Regional LN metastasis	2	0.3% (0.0-0.8%)	9	1.0% (0.2-1.9%)	0.03
Contralateral breast tumour	13	1.7% (0.6-2.7%)	8	1.1% (0.2-2.1%)	0.34

Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial

Umberto Veronesi, Roberto Orecchia, Patrick Maisonneuve, Giuseppe Viale, Nicole Rotmensz, Claudia Sangalli, Alberto Luini, Paola Veronesi, Viviana Galimberti, Stefano Zurrida, Maria Cristina Leonardi, Roberta Lazzari, Federica Cattani, Oreste Gentilini, Mattia Intra, Pietro Caldarella, Bettina Ballardini

Lancet Oncol 2013; 14: 1269-77



Question for Radiobiologists

WBI arm

5-year LR 0.4%

TRUE: 4
Elsewhere: 0

true

0.4% **2.5%**

0.0% **1.9%**

elsewhere

ELIOT arm

5-year LR 4.4%

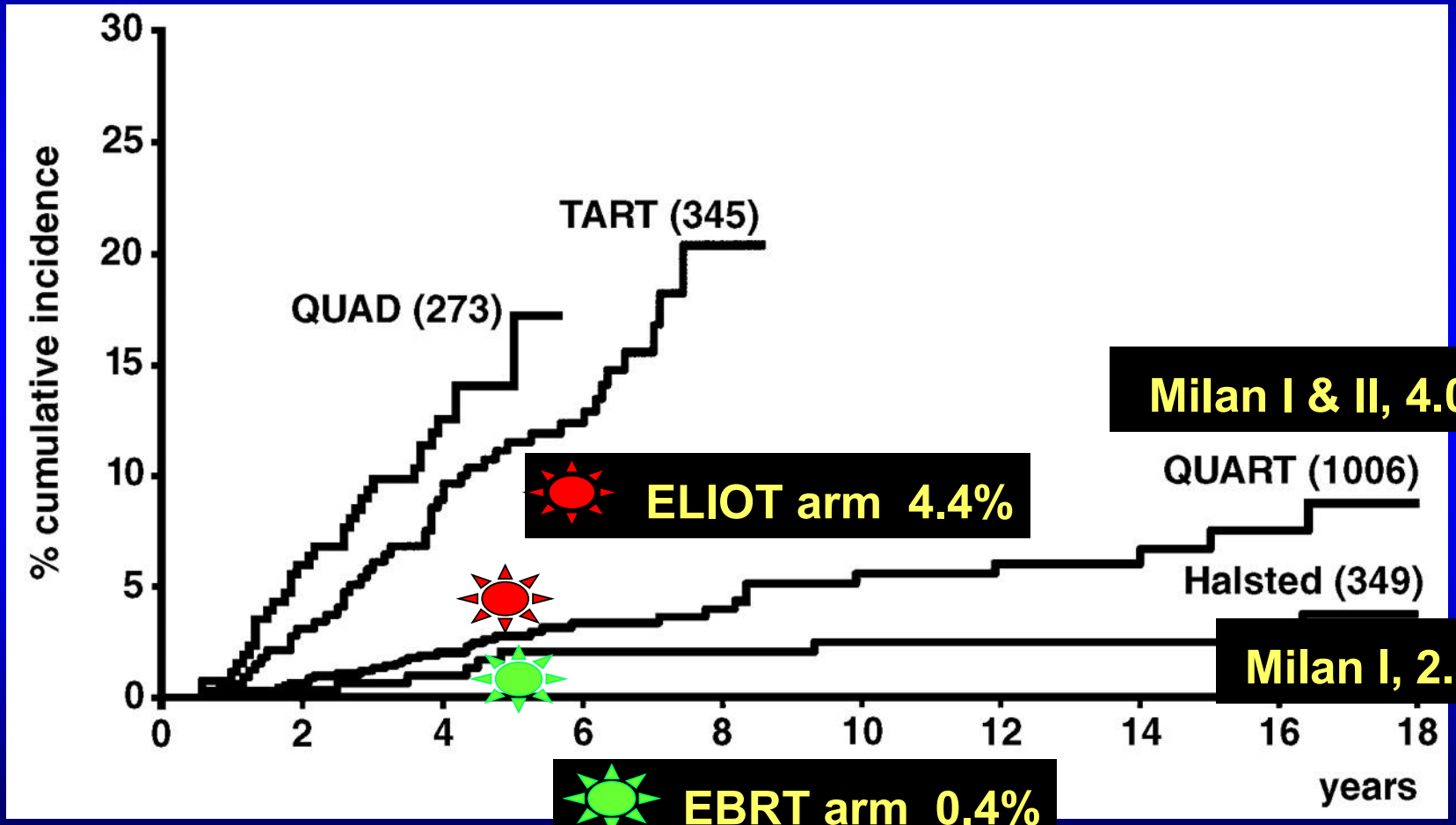
TRUE: 21
Elsewhere: 14

Significant difference

IEO Arc

IEO Istituto Europeo di Oncologia

5-year incidence of LR according to treatment in the 3 Milan trials (I, II, and III), and ELIOT trial



And now,
a new standard
for PBI?

LOCAL CONTROL at 5-y

APBI Brachytherapy:	**1.44%**
APBI ELIOT:	**4.4%**
APBI Targit:	**3.3% ***

WBI Brachitherapy:	**0.92%**
WBI ELIOT:	**0.4%**
WBI Targit:	**1.3% ***

Age <60 years old

APBI Brachytherapy: 44%

APBI ELIOT: 51%

APBI Targit: 40% (64y)

ELIOT trial. Impact of age

	Total	N. events	5-year event rate	P value
48-49	44	0	0.0%	
50-59	286	21	5.6%	0.11
60-69	259	10	3.1%	
70+	62	4	7.2%	

Positive Axillary Nodes

APBI Brachytherapy: 0%

APBI ELIOT: 21% N+1-3

6% 4 N+ or more

APBI Targit: 15% N+1-3

4% 4 N+ or more

ELIOT trial. Impact of N status

	Total	N. events	5-year event rate	P value
None	44	21	3.5%	
1-3 N+	286	10	5.3%	0.06
4 or more N+	31	4	15.0%	

Grade 3 tumors

APBI Brachytherapy:	**9%**
APBI ELIOT:	**20%**
APBI Targit:	**15%**

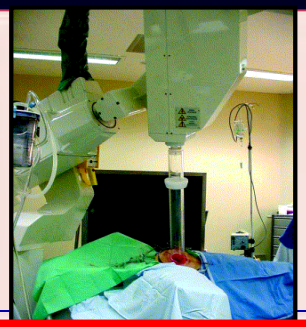
ELIOT trial. Impact of T Grade

	Total	N. events	5-year event rate	P value
G1	196	5	1.1%	
G2	305	15	3.8%	0.0003
G3	129	15	11.9%	

ELIOT trial. Impact of other factors

		5-year event rate	P value
pT size	Up to 2 cm vs >2 cm	1.9-4.7% vs 10.9%	0.006
ER status	ER+ vs ER-	3.3% 14.9%	0.004
Ki-67	Up to 20% vs >20%	1.5-1.8% vs 9.1%	0.002
Molecular subtype	Luminal A vs others	1.4% vs 4.9-18.9%	0.001

Low risk group	N	5-year event rate (95% confidence intervals)	Log-rank *P value*
Characteristics suggesting NO subsequent WBI			
			<0.0001
tumour ≤ 2.0 cm and 1-3 positive nodes and grade 1-2 Luminal A	**199**	**1.5% (0.3- 2.7%)**	
Other	**452**	**11.3% (6.4-16.1%)**	



ELIOT TRIAL

	Patients (n/N)	IBTR 5-year event rate (95% CI)	Log-rank p value*
Molecular subtype			
Luminal A	7/256	1·4% (0·0–3·0)	..
Luminal B	20/327	4·9% (2·4–7·4)	..
HER2-positive (non-luminal)	1/20	5·9% (0·0–17·1)	..
Triple negative	7/43	18·9% (6·1–31·7)	0·001

	Patients (n/N)	IBTR 5-year event rate (95% CI)	Log-rank p value*
Proliferative index (Ki-67)			
<14%	8/263	1·8% (0·0–3·5)	..
14–20%	5/138	1·5% (0·0–3·6)	..
>20%	22/244	9·1% (5·1–13·1)	0·002

IEO Arc

Breast Cancer Res Treat (2010) 124:141–151
DOI 10.1007/s10549-010-1115-5

CLINICAL TRIAL

Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons

Umberto Veronesi · Roberto Orecchia · Alberto Luini · Viviana Galimberti · Stefano Zurrida · Mattia Intra · Paolo Veronesi · Paolo Arnone · Maria Cristina Leonardi · Mario Ciocca · Roberta Lazzari · Pietro Caldarella · Nicole Rotmensz · Claudia Sangalli · Daniele Sances · Patrick Maisonneuve

ELIOT out trial

	All patients	True local recurrences			Second ipsilateral cancer		
	N	*N*	%	Annual rate (%)	*N*	%	Annual rate (%)
Molecular subtype[a]							
Luminal A	648	3	0.46	0.15	4	0.62	0.20
Luminal B	977	28	2.87	0.96	16	1.64	0.55
Cerb+++	53	6	11.32	3.88	0	–	–
Basal	137	5	3.65	1.19	4	2.92	0.95

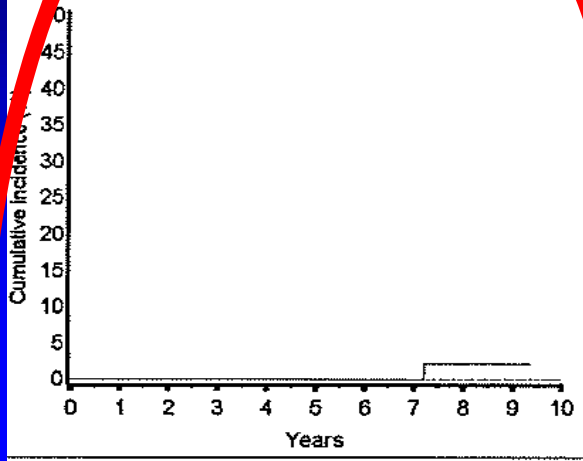
Luminal A: 1.08%
No- Luminal A: 4.51-11.32%

IEO Arc

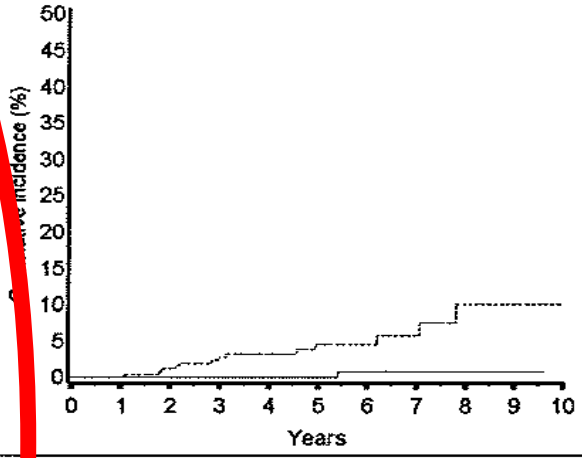
IEO Istituto Europeo di Oncologia

LOCAL RELAPSES

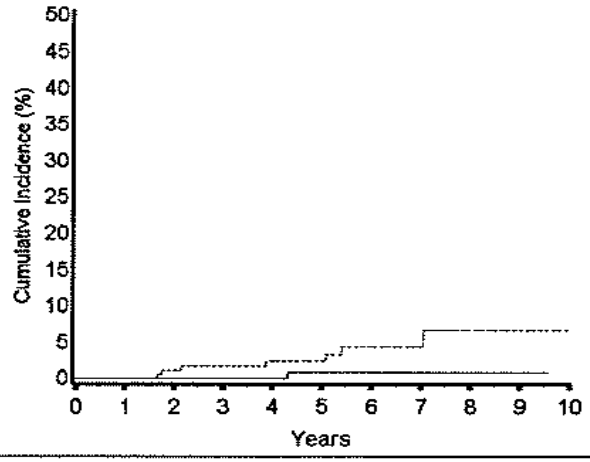
SUITABLE (n=269)
1/0
Log-rank p=0.42



CAUTIONARY (n=528)
1/13
Log-rank p=0.001

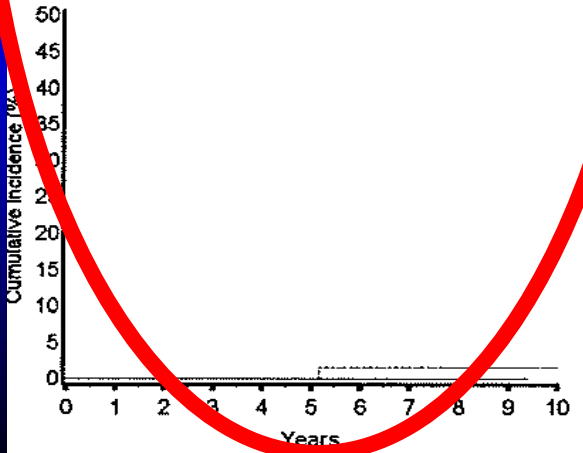


UNSUITABLE (n=387)
1/7
Log-rank p=0.04

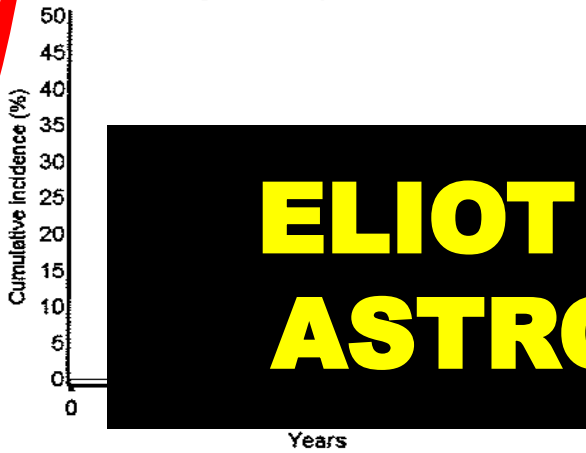


IPSILATERAL BREAST CANCER

SUITABLE (n=269)
0/1
Log-rank p=0.24



CAUTIONARY (n=528)
0/4
Log-rank p=0.04



UNSUITABLE (n=387)
1/5
Log-rank p=0.10

ELIOT Random/ ASTRO Groups

	All	ASTRO GUIDELINES Suitable	Cautionary	Unsuitable	Not assessable	Ext-RT IEO (Botteri)
Patients	1822	295 (16%)	690 (38%)	812 (45%)	25 (1%)	
Person-year-DFS	6364	1016	2409	2837	101	
Person-year-OS	6977	1091	2613	3157	116	
Local						
5-year		3	21	50	2	
		1.5%	4.4%	8.8%	9.9%	
Lumin						
Patients		118	271	251	8	733
Person-year-DFS	2330	436	948	916	30	
Loco-regional relapses	8	2	3	3	0	3
5-year rate*	1.7%	2.3%	1.6%	1.6%	-	0.31
Luminal B						
Patients	977	176	318	474	9	1127
Person-year-DFS	3371	576	1101	1650	44	
Loco-regional relapses	50	1	10	38	1	15
5-year rate*	7.4	0.9%	4.5%	11.5%	11.4	1.13
HER2						
Patients	53	-	25	28	0	118
Person-year-DFS	176	-	82	94	-	
Loco-regional relapses	6	-	3	3	-	6
5-year rate*	17.0	-	18.3%	16.0%		5.69
Triple negative						
Patients	137	-	74	58	5	208
Person-year-DFS	469	-	276	175	17	

"Suitable"
1.5% at 5-y

Milan ELIOT out-trial on 1822 patients
Stratification according to ASTRO groups
(IJROBP, Leonardi & Orecchia, 2012)

	External RT (n=654)		ELIOT (n=651)		
Person-years until last visit	3,920		3,716		
Person-years until last contact	4,107		3,997		
Events	*Events*	*5-year event rate (95% confidence interval)*	*Events*	*5-year event rate (95% confidence interval)*	*Log-rank P value*
IBRT	**4**	**0.4% (0.0-1.0%)**	**35**	**4.4% (2.7-6.1%)**	**<0.0001**
True Local relapse	4	0.4% (0.0-1.0%)	21	2.5% (1.2-3.8%)	0.0003
New Ipsilateral Breast Tumour	0	0.0% (0.0-0.0%)	14	1.9% (0.8-3.1%)	0.0001
Axillary/Regional LN metastasis	2	0.3% (0.0-0.8%)	9	1.0% (0.2-1.9%)	0.03
Contralateral breast tumour	13	1.7% (0.6-2.7%)	8	1.1% (0.2-2.1%)	0.34

R. Orecchia et al. Br J Radiol 2005 Jan;78(925):51-4.

Irradiation with standard tangential breast fields in patients treated with conservative surgery and sentinel node biopsy: using a 3-D tool to evaluate the first level coverage of the axillary nodes.

Dosimetric analysis of first axillary level coverage in standard irradiation of breast-cancer patients treated with quadrantectomy and SN biopsy.

The maximum dose mean ranged from 5% to 80% of the prescribed dose (mean value 48.7%). The mean total dose received by the volume of interest was lower than 40 Gy in all but one patient. No patient had total irradiation of first nodal level; only one patient had 35% of the volume enclosed in the 100% isodose.

Our analysis lead to the conclusion that therapeutic doses are not really delivered to first level axillary level nodes by a standard tangential field technique, and that specific treatment planning and beam arrangement are required when adequate coverage is necessary.

					p
Axillary/Regional LRR	2	0.3% (0.0-0.8%)	9	1.0% (0.2-1.9%)	0.03

Ipsilateral axillary recurrence A comparison between WBI and ELIOT

IEO Data (2016, ready for submission)

- 4,129 consecutive patients (T≤2cm, SNb-)
- 1997-2007 (median follow-up 8.3 years)
- BCS and WBI (2,939) or ELIOT (1,190)
- More patients in the WBI group for:
  - young age (54.0 vs 59.1)
  - Extensive In situ Component
  - Er negative status
  - HER 2 overexpression

Sensitivity analysis (2016, ready for submission)

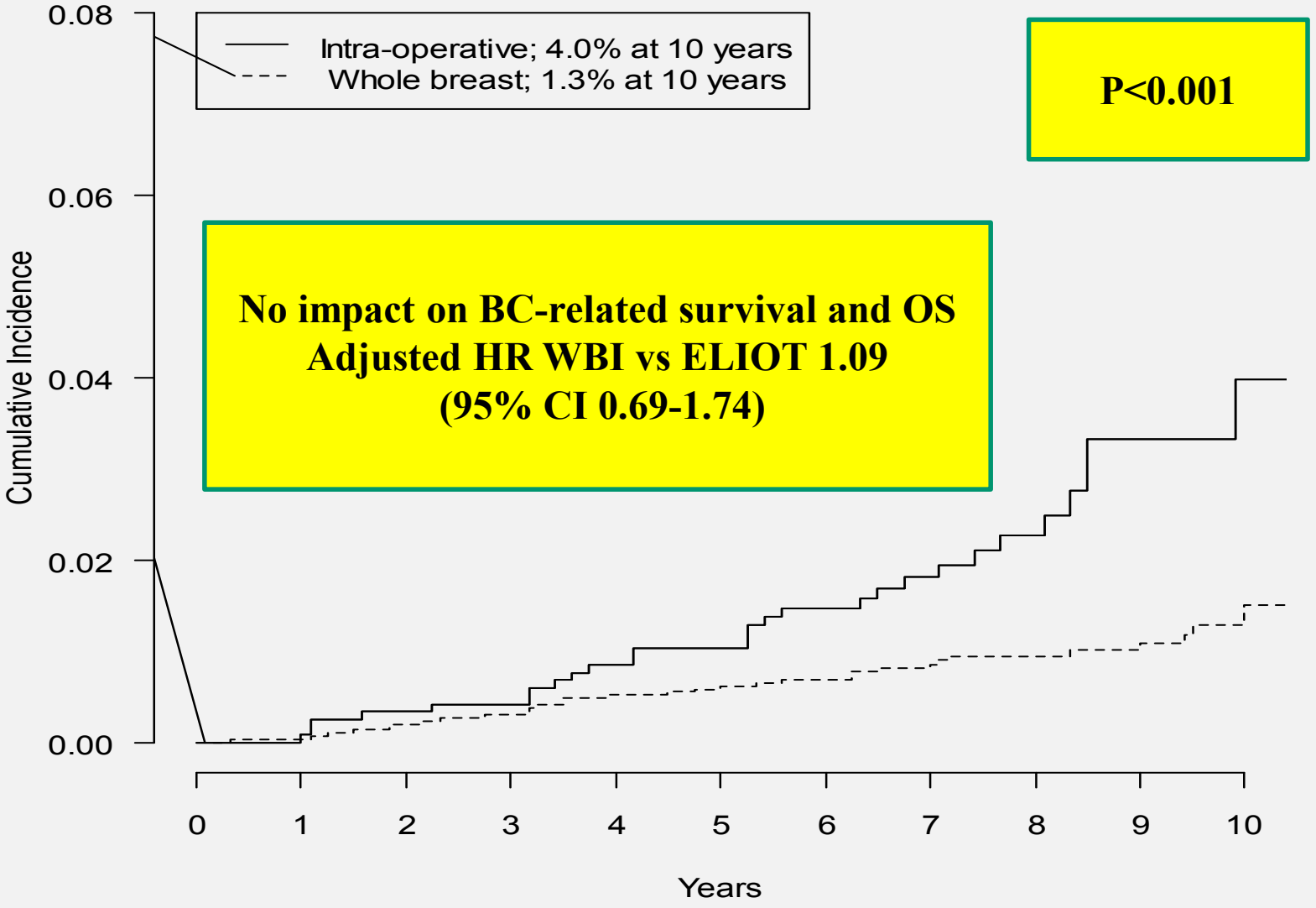
- 1:1 matched design study
- Matched for:
  - year of surgery
  - age
  - pT-stage

- 1,165 patients in WBI arm,
  1,165 in ELIOT arm

Multivariate analysis

		Axillary recurrence ± ipsilateral breast recurrence HR (95% CI)	Axillary recurrence without ipsilateral breast recurrence HR (95% CI)
Age (years)	One unit increase	0.98 (0.95-1.00)	0.99 (0.96-1.02)
Histotype	Ductal vs. others	2.53 (1.07-5.97)	1.89 (0.65-5.48)
Tumor size (cm)	> 1 vs ≤ 1	1.42 (0.83-2.45)	1.85 (0.86-4.01)
Multifocality/ Multicentriciry	Present vs Absent	2.56 (1.26-5.18)	2.70 (1.08-6.76)
Molecular subtype	Lum B (High Ki67) vs. Lum A	4.38 (1.58-12.2)	5.42 (1.03-28.5)
	Lum B (HER2+) vs. Lum A	2.49 (1.03-5.99)	5.89 (1.73-20.1)
	HER2+ vs. Lum A	1.64 (0.89-3.04)	3.35 (1.24-9.05)
	Triple - vs. Lum A	0.66 (0.15-2.90)	2.04 (0.39-10.8)
Peritumoral vascular invasion	Present vs absent	1.69 (0.89-3.19)	1.66 (0.74-3.77)
Type of radiotherapy	WBI vs. ELIOT	0.30 (0.17-0.51)	0.34 (0.17-0.71)

Risk of axillary recurrence



ELIOT. Toxicity

- **Overall, side effects showed a significant difference in favour of the ELIOT arm (p=0.0002)**

- **Few skin side effects in the ELIOT arm, including erythema (p<0.0001), dryness (p=0.04), hyper-pigmentation (p=0.0004) or pruritus (p=0.002). No differences for mammary fibrosis, mammary retraction, pain or burning.**

- **A higher incidence of fat necrosis was observed in the ELIOT arm with an incidence of 12% (p<0.04), mostly not symptomatic.**

- **A subgroup of 178 volunteers (95 from the ELIOT arm and 83 from the external RT arm) accepted to undergo a follow-up spiral CT-scan. Pulmonary fibrosis was diagnosed in 42 (23.6%) of the patients examined: 4 (10%) had received ELIOT and 38 (90%) external RT (p <0.0001). Twenty-six of these were grade 1 (1 in the ELIOT arm), 15 grade 2 (3 in the ELIOT arm) and one was grade 3 in the external RT arm.**

	External RT (n=654)		ELIOT (n=651)		
Person-years until last visit	3,920		3,716		
Person-years until last contact	4,107		3,997		
Other events	*Events*	*5-year event rate (95% confidence interval)*	*Events*	*5-year event rate (95% confidence interval)*	*Log-rank P value*
Distant metastasis*	35	4.8% (3.1-6.5%)	33	5.1% (3.3-6.9%)	0.94
Other primary cancer	22	3.2% (1.8-4.7%)	20	2.5% (1.2-3.8%)	0.88
Death as first event	7	0.9% (0.1-1.7%)	8	1.0% (0.1-2.0%)	0.69
Total deaths	31	3.1% (1.7-4.5%)	34	3.2% (1.7-4.7%)	0.59
Breast cancer	20	2.0% (0.9-3.2%)	23	2.1% (0.9-3.3%)	0.56
Other cause	11	1.1% (0.2-2.0%)	11	1.1% (0.2-2.0%)	0.93

Conclusions

- **ELIOT studies allowed to identify a low risk group suitable for PBI techniques, with no significant difference in terms of LRR**
- **T-size, N-status, Tumor Grade and Molecular Subtypes are the most important predictive factors**
- **The absolute risk of LR and RR remains in any case low, with no impact on survival at 10 years**

Thank you very much for your attention !!!

roberto.orecchia@ieo.it

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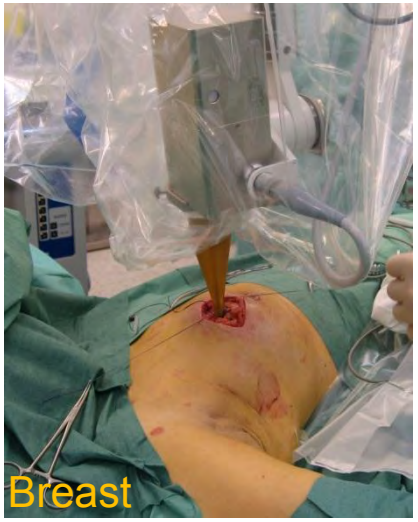
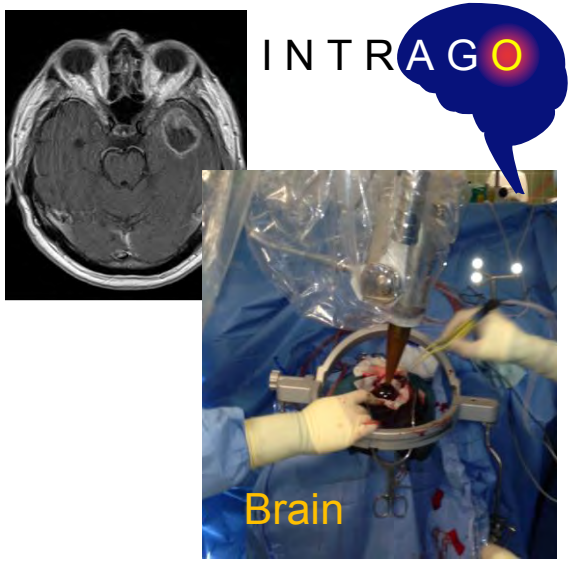
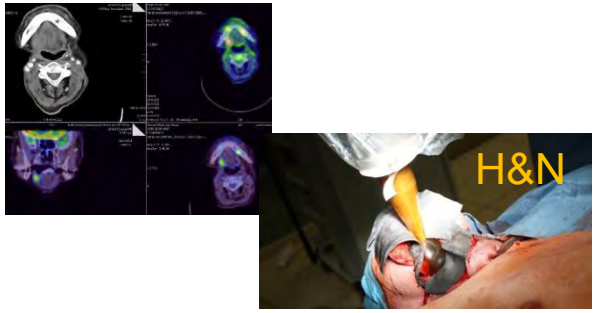
IORT with kV X-rays - Physical aspects

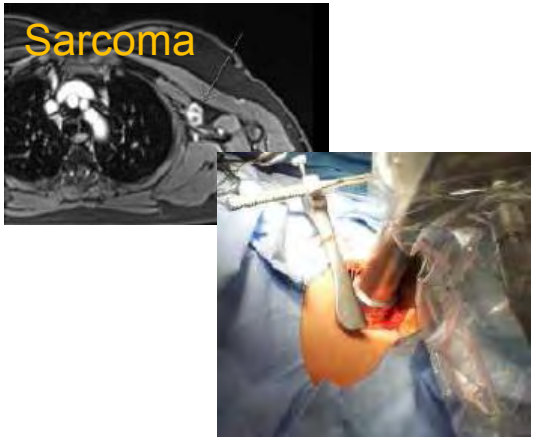
Dr. sc. hum. Frank Schneider

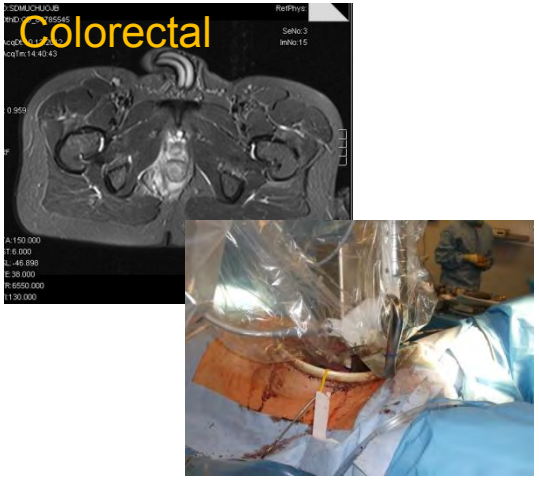
Clinical applications of kV IORT

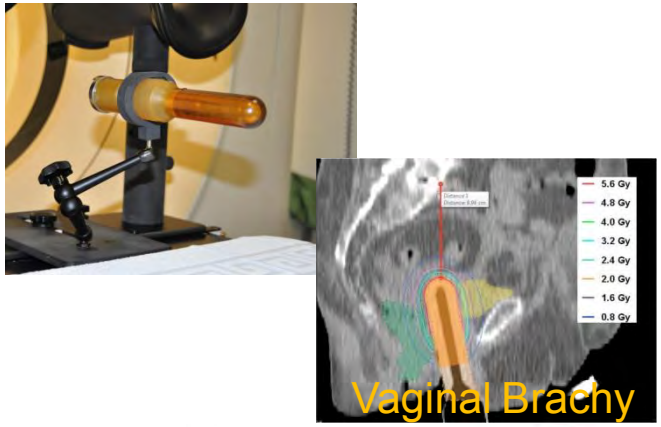












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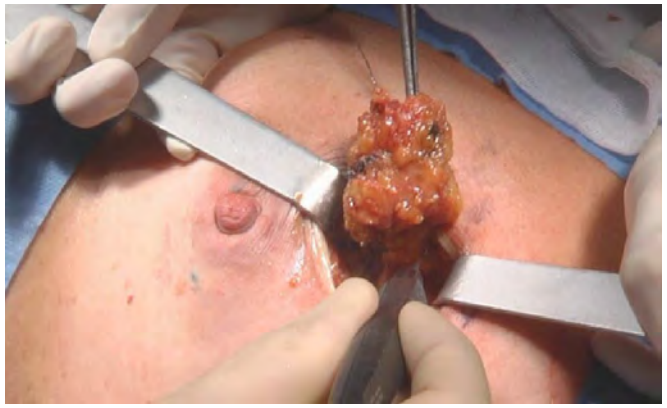
Clinical way of doing kV IORT

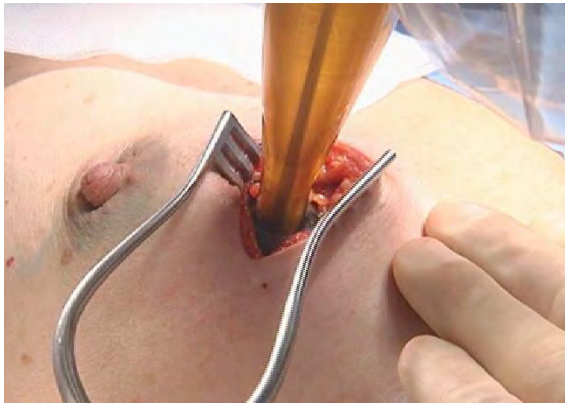
See no evil,

Hear no evil,

Speak no evil.

Evil = Physics





Articles

Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial

www.thelancet.com Published online June 5, 2010 DOI:10.1016/S0140-6736(10)60837-9

THE LANCET

"For selected patients with early breast cancer, a single dose of radiotherapy delivered at the time of surgery by use of targeted intraoperative radiotherapy should be considered as an alternative to external beam radiotherapy delivered over several weeks."

It works!

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INTRABEAM® : Main System Components

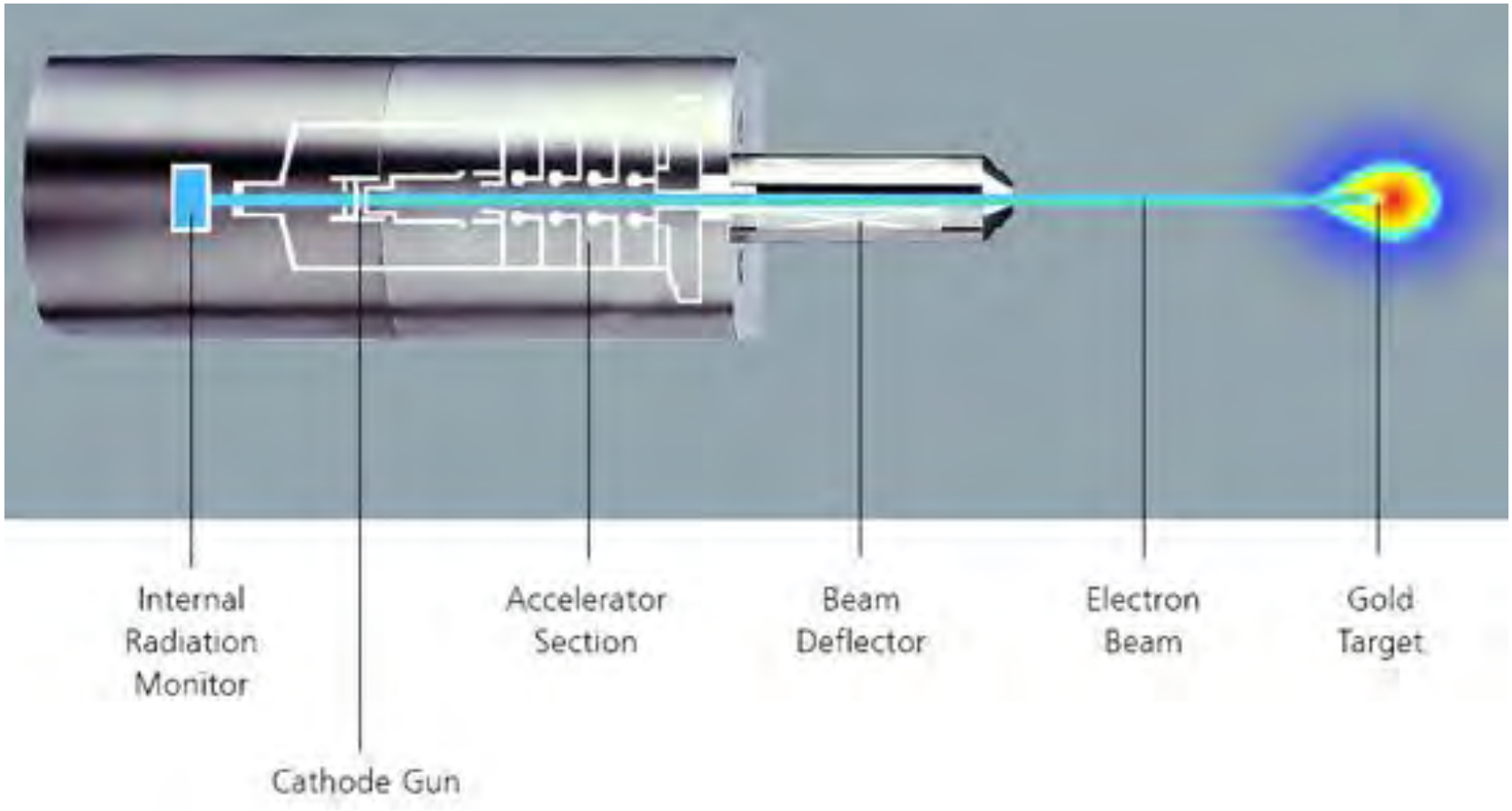
X-ray source with IRM

Control Console

User Terminal with

INTRABEAM® Software

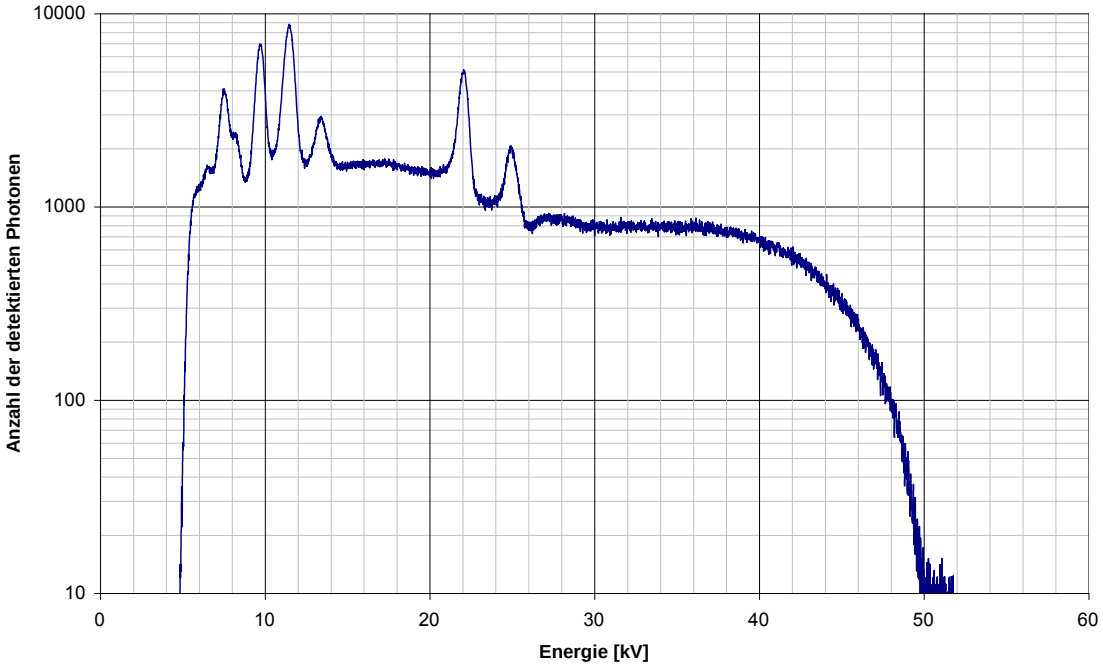
X-ray source - XRS 4

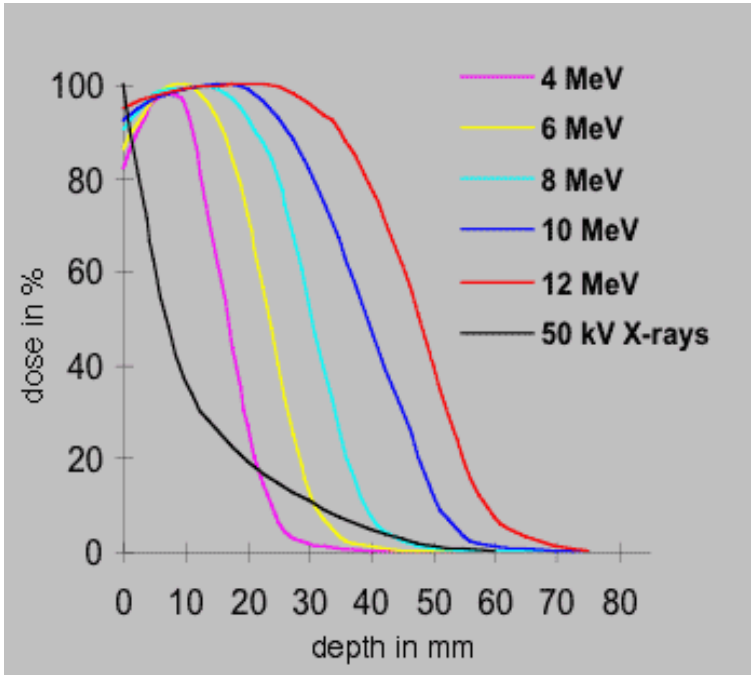


Spectrum and Depth Dose

50kVp spectrum

- ➔ max energy 50kV
- ➔ effective energy ~20kV (probe only)
- ➔ beam hardening with applicator





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Courtesy by Zeiss

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“Targit dose”

Depth doses

- measured in Zeiss factory using water tank
- dose rate with depth for probe only
- Dose rate calculation based on PTW chamber calibration factor for **exposure**

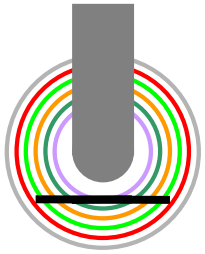
IC: PTW Type 23342

Courtesy by Zeiss

“Non-Targit dose”

Depth doses

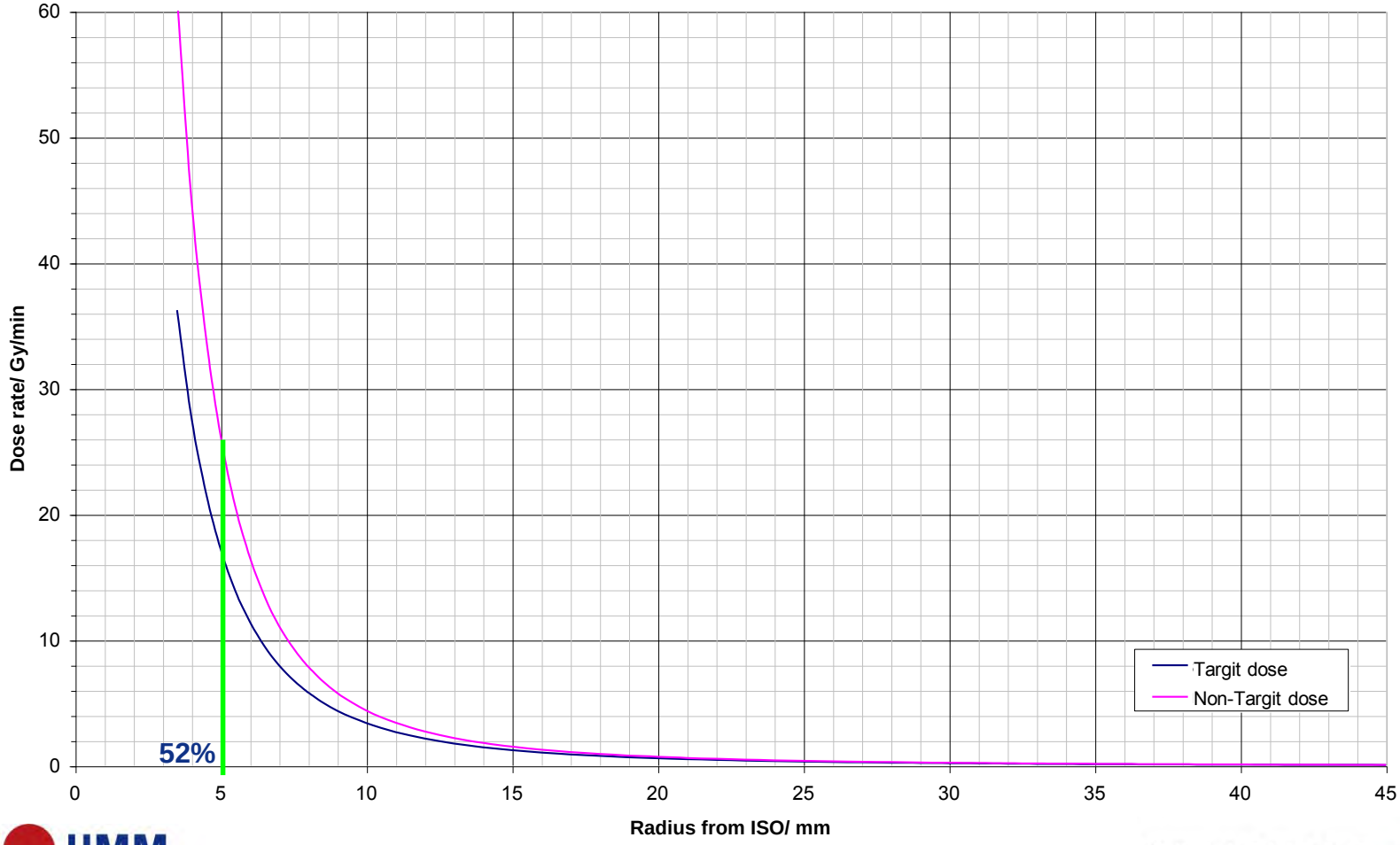
- measured in Zeiss factory using water tank
- dose rate with depth for probe only
- Dose rate calculation based on PTW chamber calibration factor for **air kerma** (recommended by AAPM TG61and IAEA TRS 398)



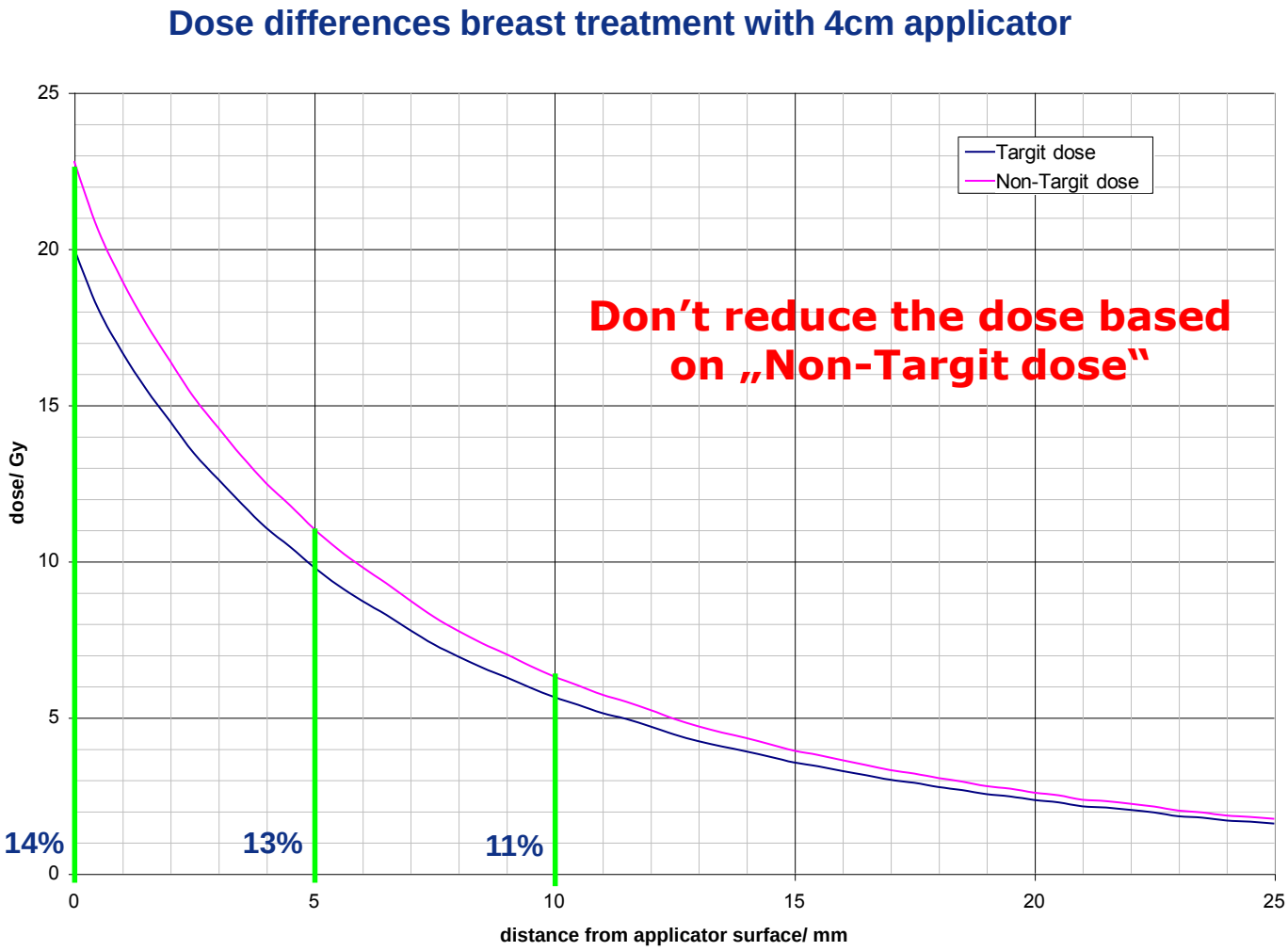
IC: PTW Type 34013

Why “Non-Targit dose”?

- State of the art !
- More precise dose (dose rate) in the near field of the probe



How does this affect the breast treatments?



Calibration Certificate

Carl Zeiss Surgical GmbH
Quality Management
73446 Oberkochen
Germany

ZEISS CARL ZEISS MEDITEC

Calibration Certificate

System:	**XRS**
Manufacturer:	Carl Zeiss Surgical GmbH
Type:	304534-7000-001
Serial No.:	507155
Work order No.:	1022778574

This certificate verifies that said object maintained its specified values during calibration. Calibration was carried out using calibration tools/working standards that are directly or indirectly based on recognized calibration methods traceable to national standards.

The calibration system is specified in the Carl Zeiss QA manual as per DIN/ISO 9001 or EN 29001.

Date of Calibration: 7. Jun. 10

Responsible person: CG-QM 12

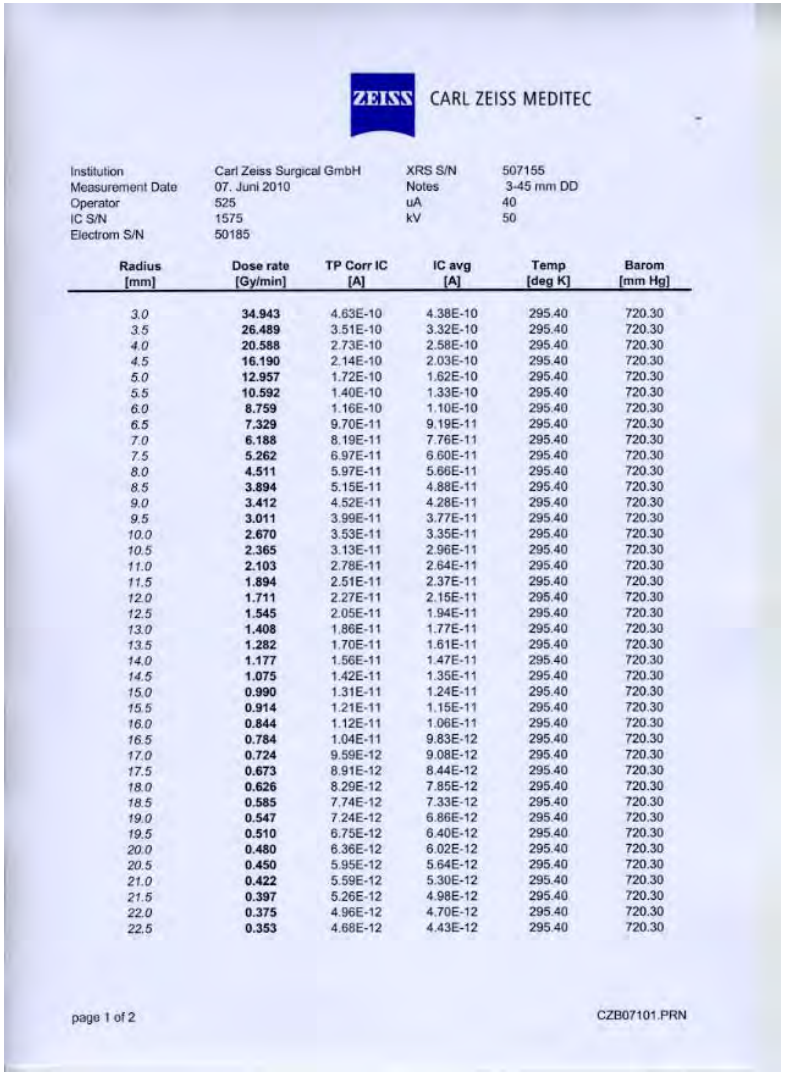
Person in charge: CG 525

Due date for next Calibration: 7. Jun. 11

The customer is responsible to check for different calibration due date according to national regulations or standards.

Carl Zeiss Surgical GmbH CGR-E

Calibration Certificate



ZEISS CARL ZEISS MEDITEC

Institution	Carl Zeiss Surgical GmbH	XRS S/N	507155
Measurement Date	07. Juni 2010	Notes	3-45 mm DD
Operator	525	uA	40
IC S/N	1575	kV	50
Electrom S/N	50185		

Radius [mm]	Dose rate [Gy/min]	TP Corr IC [A]	IC avg [A]	Temp [deg K]	Barom [mm Hg]
3.0	**34.943**	4.63E-10	4.38E-10	295.40	720.30
3.5	**26.489**	3.51E-10	3.32E-10	295.40	720.30
4.0	**20.588**	2.73E-10	2.58E-10	295.40	720.30
4.5	**16.190**	2.14E-10	2.03E-10	295.40	720.30
5.0	**12.957**	1.72E-10	1.62E-10	295.40	720.30
5.5	**10.592**	1.40E-10	1.33E-10	295.40	720.30
6.0	**8.759**	1.16E-10	1.10E-10	295.40	720.30
6.5	**7.329**	9.70E-11	9.19E-11	295.40	720.30
7.0	**6.188**	8.19E-11	7.76E-11	295.40	720.30
7.5	**5.262**	6.97E-11	6.60E-11	295.40	720.30
8.0	**4.511**	5.97E-11	5.66E-11	295.40	720.30
8.5	**3.894**	5.15E-11	4.88E-11	295.40	720.30
9.0	**3.412**	4.52E-11	4.28E-11	295.40	720.30
9.5	**3.011**	3.99E-11	3.77E-11	295.40	720.30
10.0	**2.670**	3.53E-11	3.35E-11	295.40	720.30
10.5	**2.365**	3.13E-11	2.96E-11	295.40	720.30
11.0	**2.103**	2.78E-11	2.64E-11	295.40	720.30
11.5	**1.894**	2.51E-11	2.37E-11	295.40	720.30
12.0	**1.711**	2.27E-11	2.15E-11	295.40	720.30
12.5	**1.545**	2.05E-11	1.94E-11	295.40	720.30
13.0	**1.408**	1.86E-11	1.77E-11	295.40	720.30
13.5	**1.282**	1.70E-11	1.61E-11	295.40	720.30
14.0	**1.177**	1.56E-11	1.47E-11	295.40	720.30
14.5	**1.075**	1.42E-11	1.35E-11	295.40	720.30
15.0	**0.990**	1.31E-11	1.24E-11	295.40	720.30
15.5	**0.914**	1.21E-11	1.15E-11	295.40	720.30
16.0	**0.844**	1.12E-11	1.06E-11	295.40	720.30
16.5	**0.784**	1.04E-11	9.83E-12	295.40	720.30
17.0	**0.724**	9.59E-12	9.08E-12	295.40	720.30
17.5	**0.673**	8.91E-12	8.44E-12	295.40	720.30
18.0	**0.626**	8.29E-12	7.85E-12	295.40	720.30
18.5	**0.585**	7.74E-12	7.33E-12	295.40	720.30
19.0	**0.547**	7.24E-12	6.86E-12	295.40	720.30
19.5	**0.510**	6.75E-12	6.40E-12	295.40	720.30
20.0	**0.480**	6.36E-12	6.02E-12	295.40	720.30
20.5	**0.450**	5.95E-12	5.64E-12	295.40	720.30
21.0	**0.422**	5.59E-12	5.30E-12	295.40	720.30
21.5	**0.397**	5.26E-12	4.98E-12	295.40	720.30
22.0	**0.375**	4.96E-12	4.70E-12	295.40	720.30
22.5	**0.353**	4.68E-12	4.43E-12	295.40	720.30

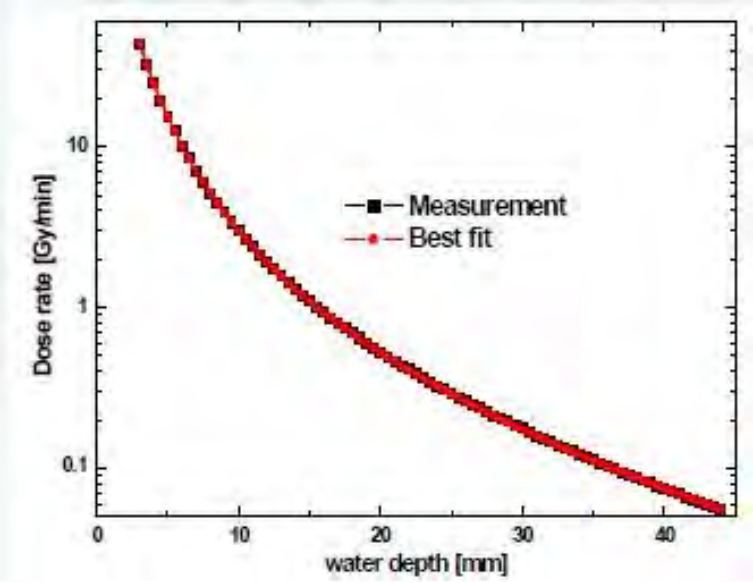
page 1 of 2

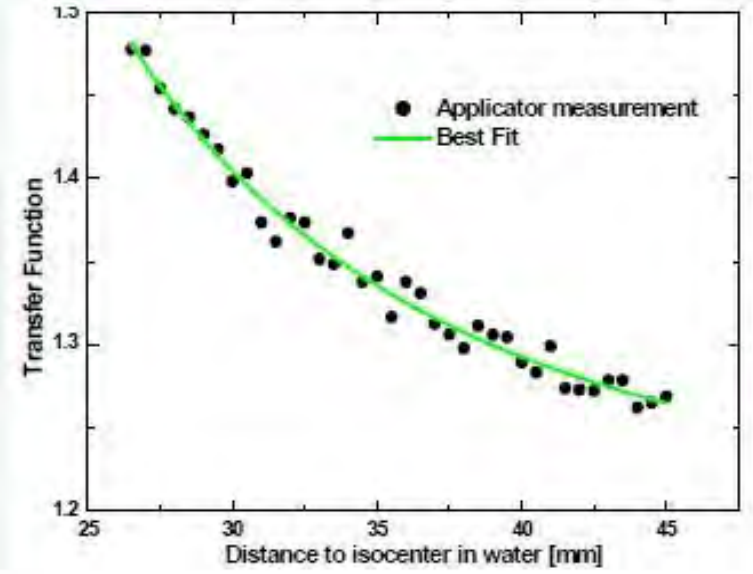
CZB07101.PRN

Calculation of treatment time

➔ Time = $\frac{\text{Prescribed dose}}{\text{Dose rate x output difference (QA)}}$

➔ Dose rate = Dose rate (bare probe, depth) x transfer function (applicator depth)

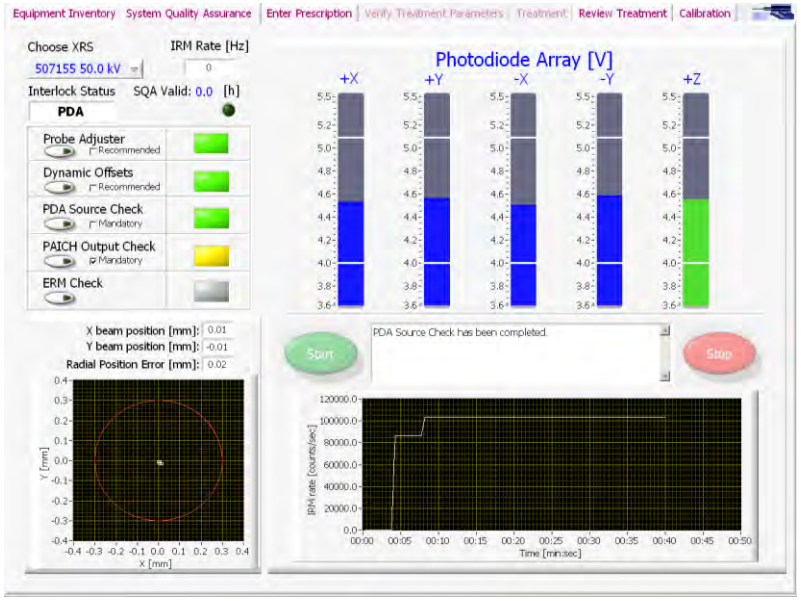




➔ Calibration files contain best fit (extrapolated to surface)

Onboard quality assurance

Equipment for constancy check of dose rate, isotropy and mechanical straightness



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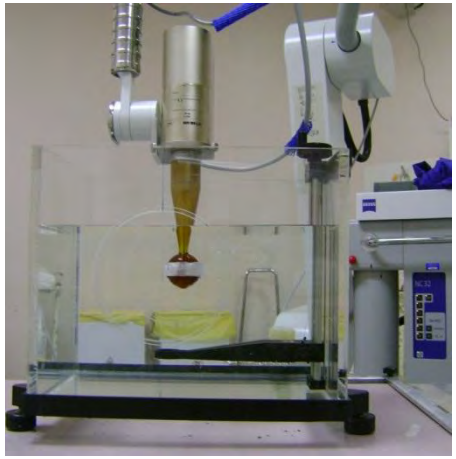
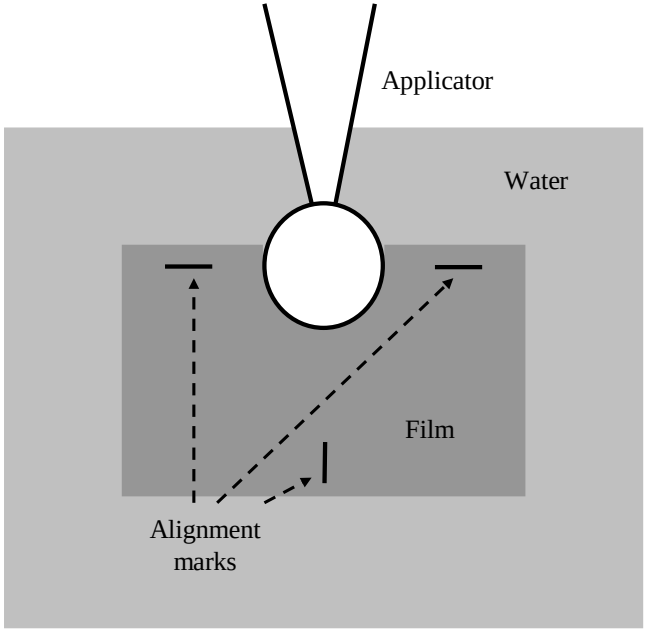
Independent quality assurance

IC in water tank

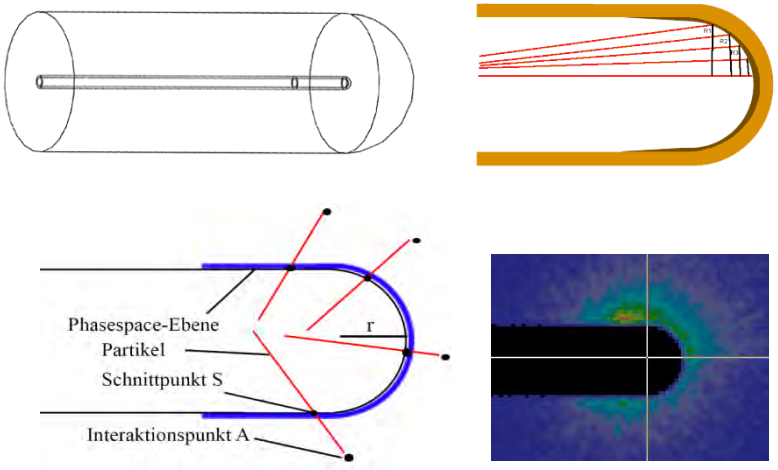


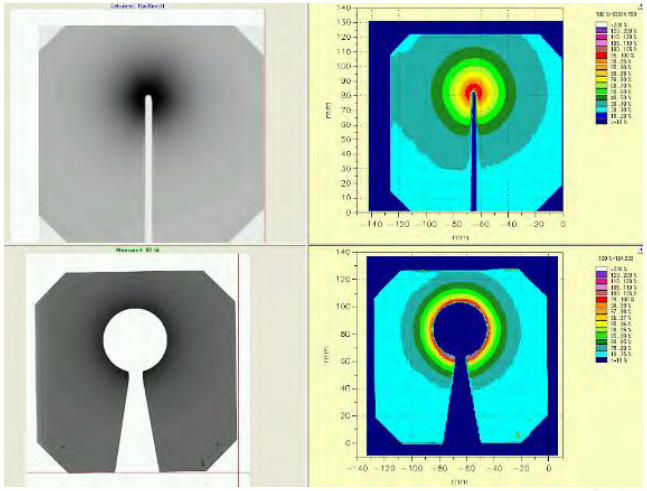
TLD measurements



Film dosimetry

Monte Carlo simulations





Clausen et al. Strahlenther Onkol 2009: 185/S1; 51

Eaton and Duck Phys Med Biol 2010: 55; N359-69

Avanzo et al. Med Phys. 2012: 39(5); 2359-6

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radiation protection

Radiation protection measurement in OR

Figure 1: measurement setup

All values
in μSv/hr

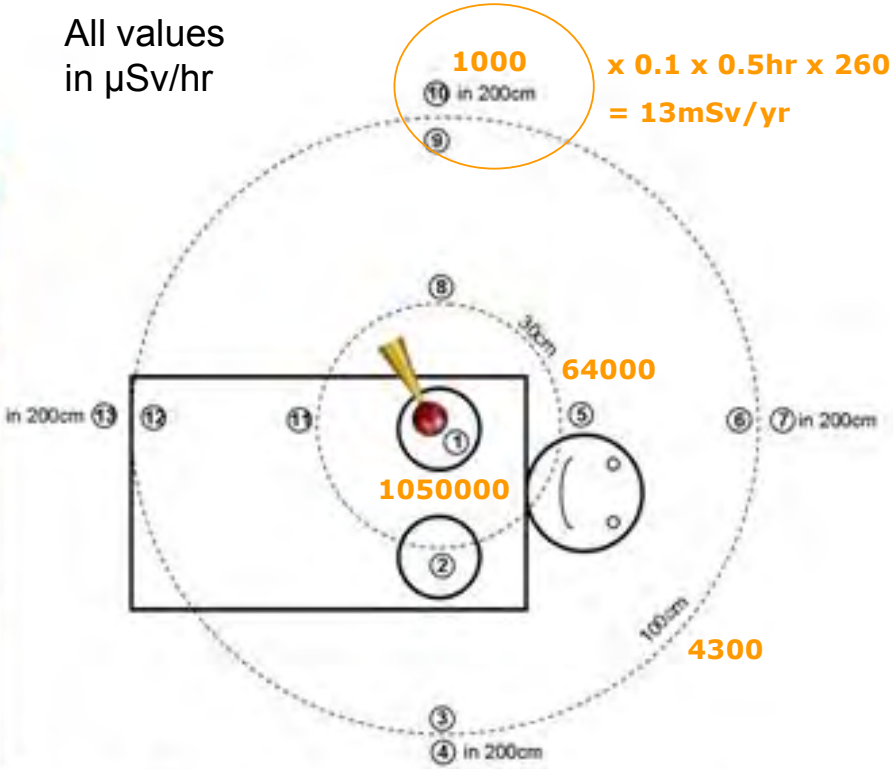
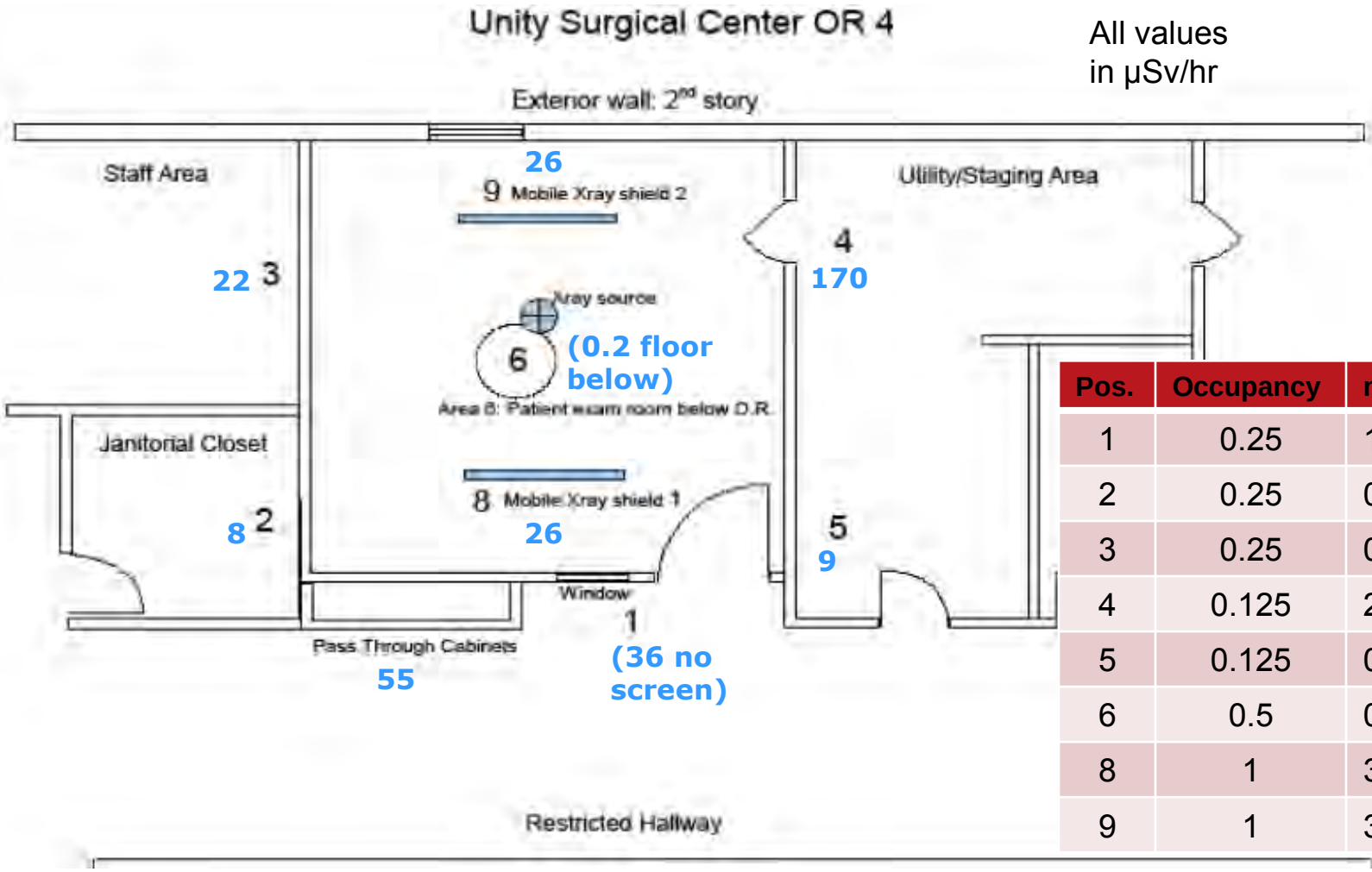


Figure 2: Points of dose rate measurements

Theatre is controlled area

Radiation protection measurement outside OR

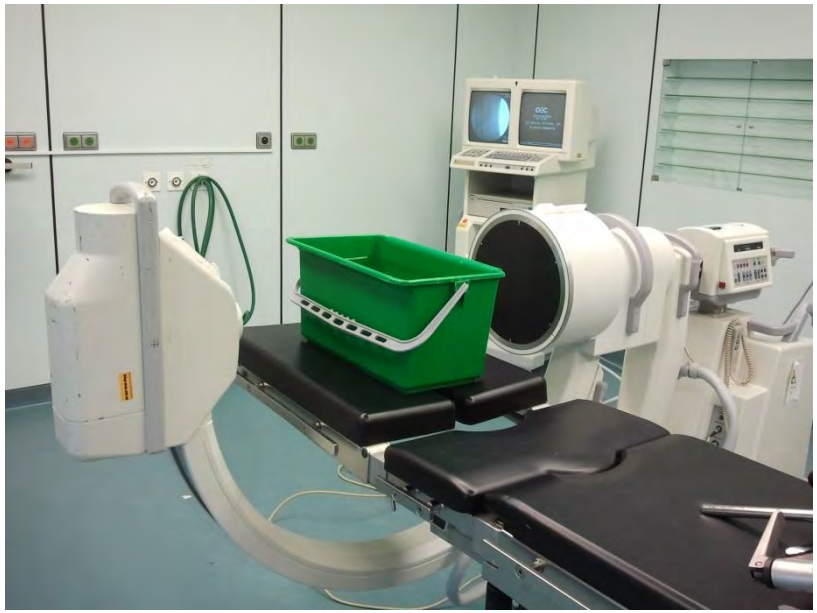


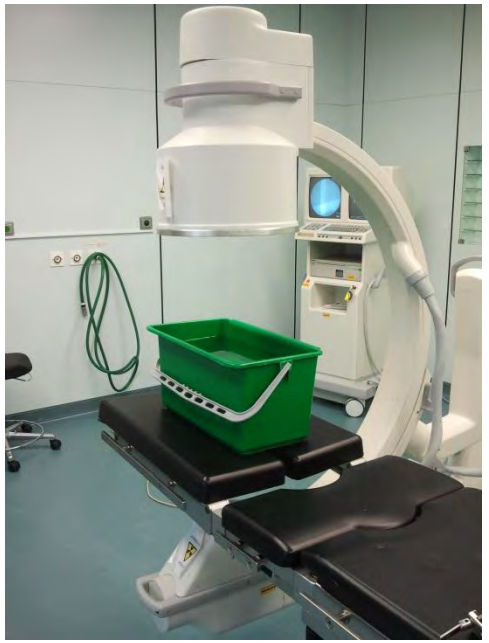
All values in µSv/hr

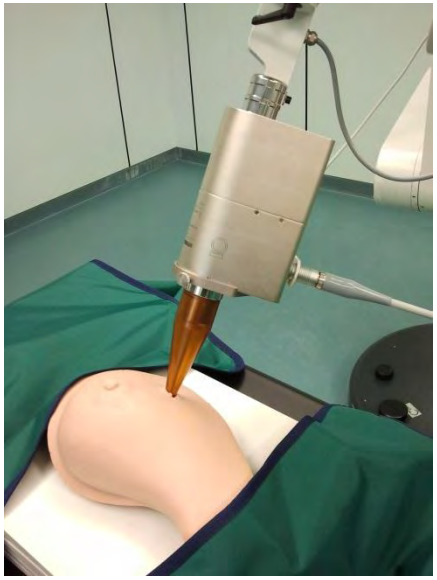
Pos.	Occupancy	mSv/year
1	0.25	1.788
2	0.25	0.260
3	0.25	0.715
4	0.125	2.763
5	0.125	0.146
6	0.5	0.013
8	1	3.38
9	1	3.38

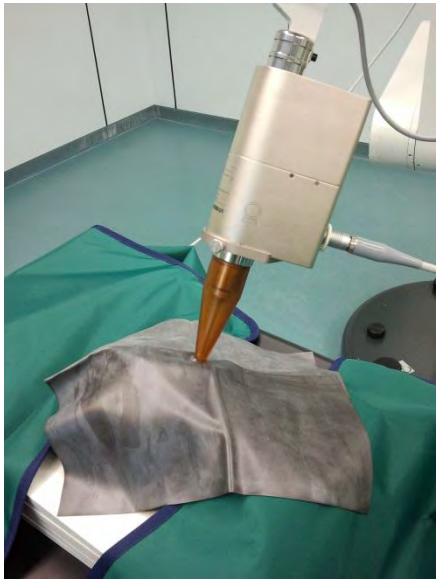
Other rooms not controlled areas

Radiation protection measurement – IORT vs. C-arm









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Radiation protection measurement – IORT vs. C-arm

Yearly dose in 2 m distance
(example: 1 per day; 5 per week; 52 weeks = 260 treatments):

C-arm fluoroscopy (varying positions):

- Average simulated treatment: 56 – 467 µSv/h
- Average patient treatment: 95 µSv/h x 260 x 0.25 h = **6.2 mSv**

Kypho-IORT (varying treatment depth):

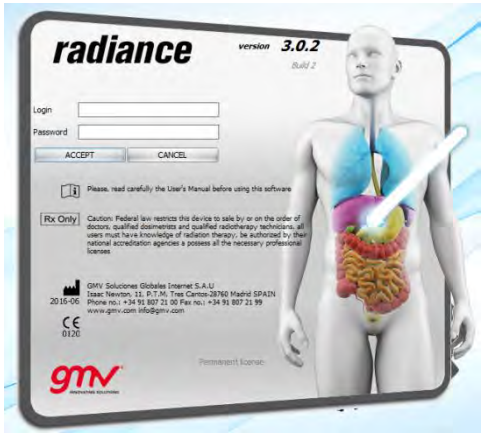
- Average simulated treatment: 66 – 141 µSv/h
- Average patient treatment: 131 µSv/h x 260 x 0.1 h = **3.4 mSv**

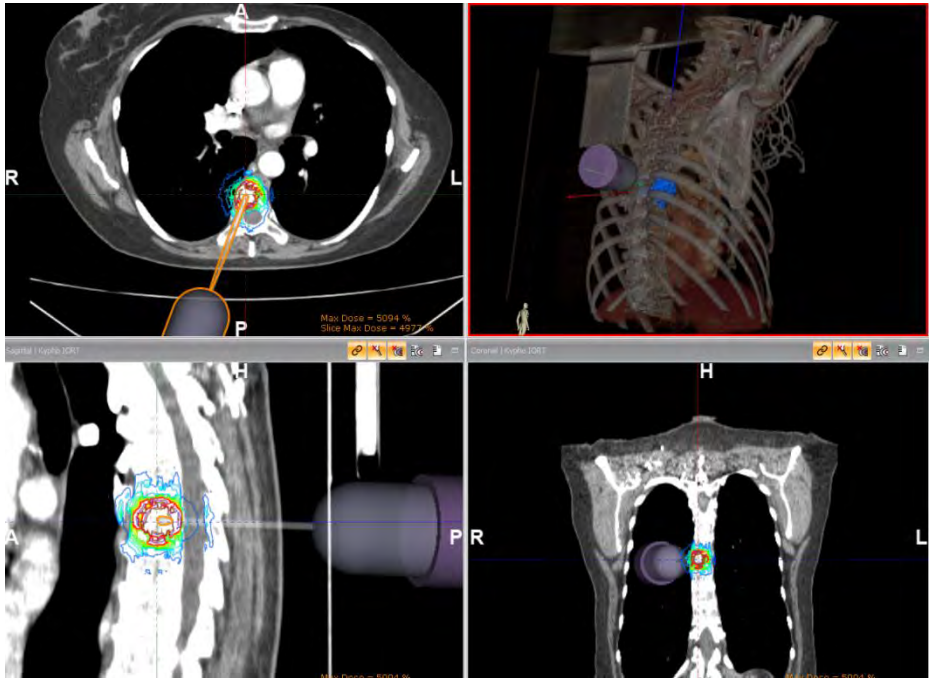
Breast-IORT (with Pb 0.175 mm tungsten rubber):

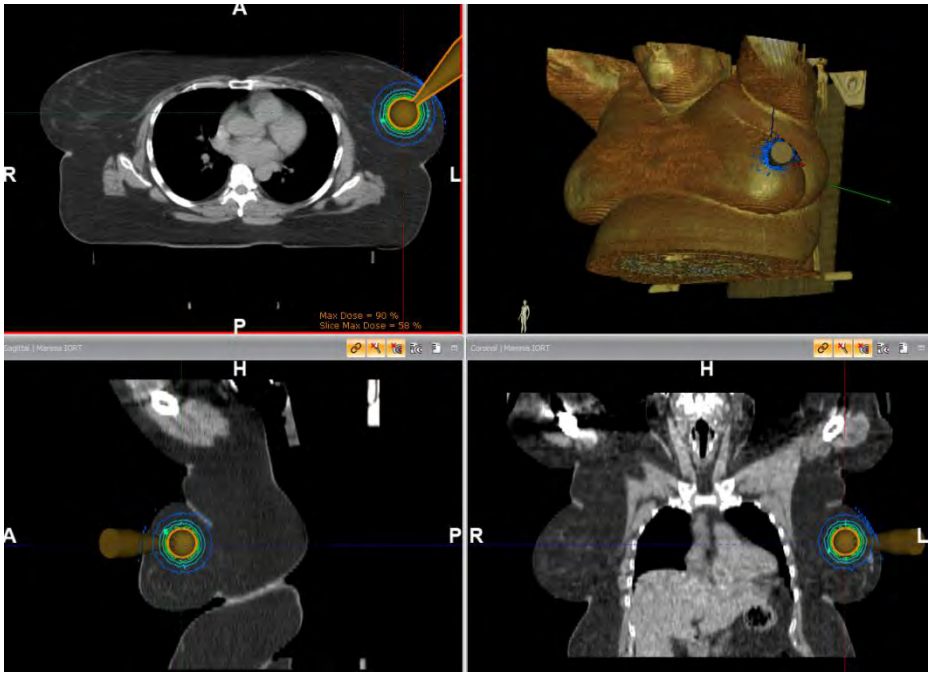
- Average simulated treatment: 27 µSv/h
- Average patient treatment: 46 µSv/h x 260 x 0.5 h = **6.0 mSv**

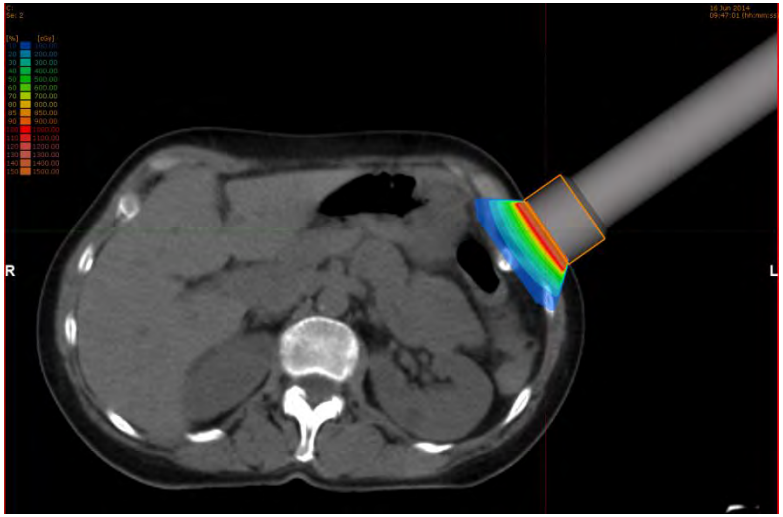
Next step forward

Treatment planning









future

Bob Ross – The Joy of Painting

Wikipedia, YouTube

Mannheim's Joy of "Ray Painting"

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FORSCHUNGS CAMPUS M²OLIE

RoRaTh

Robotic Radiation Therapy

Robotic RayPainting

Sven Clausen, Andreas Rothfuss, Frank Schneider
Department of Radiation Oncology
University Medical Center Mannheim
University of Heidelberg

KUKA

Fraunhofer IPA

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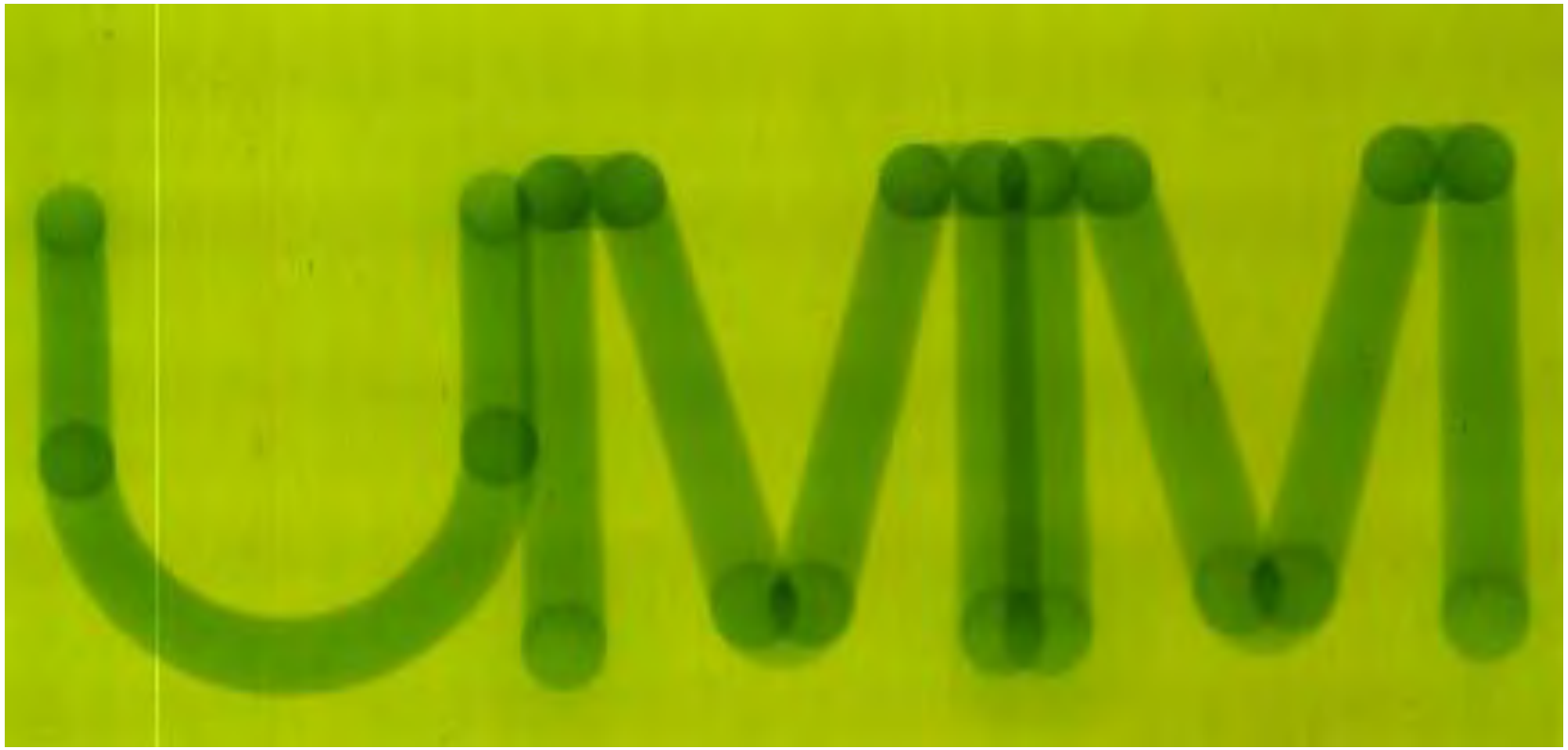
Courtesy by Dr. Clausen

Take home points

- ➔ Radiation protection is straight forward
- ➔ Flexible clinical use (different applicators, no fixed treatment rooms)
- ➔ Treatment planning will open a wide new field in kV IORT
- ➔ kV IORT is a huge playground for medical physicists; there is always something to investigate



Thank you for your attention

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Update of results of randomized trials– TARGIT

Elena Sperk, MD
Department of Radiation Oncology Mannheim

Übersicht

1. INTRABEAM ® System
2. Pubmed research IORT and breast cancer (2015 – June 2016)
    1. IORT with electrons
    2. IORT with low energy kV x-rays n
    3. Reviews
    4. Conclusion Pubmed research
3. Prospective trials
    1. TARGIT A
    2. TARGIT A: Mannheim cohort
    3. TARGIT E
    4. TARGIT C
    5. TARGIT B(oost)
4. Meta-Analysis: Electrons, low energy kV x-rays, Brachytherapy
5. Conclusion
6. What `s next?
7. Recommendations

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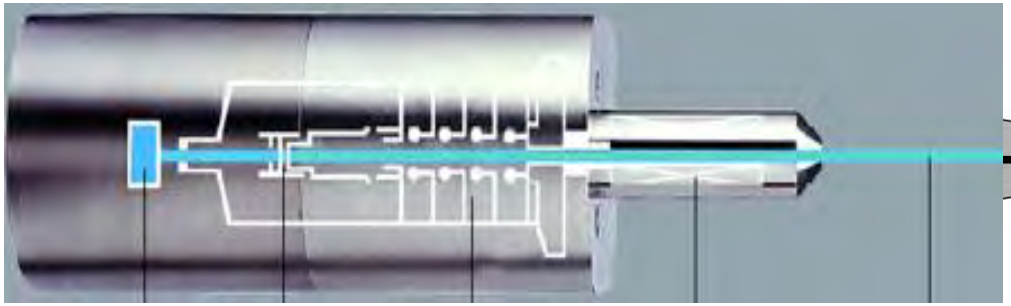
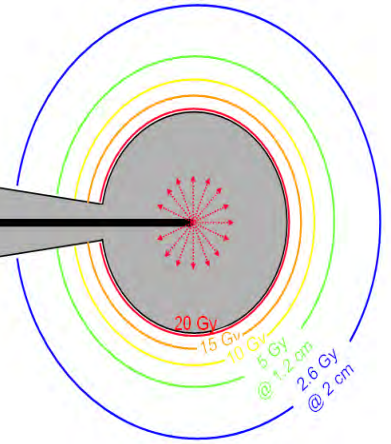
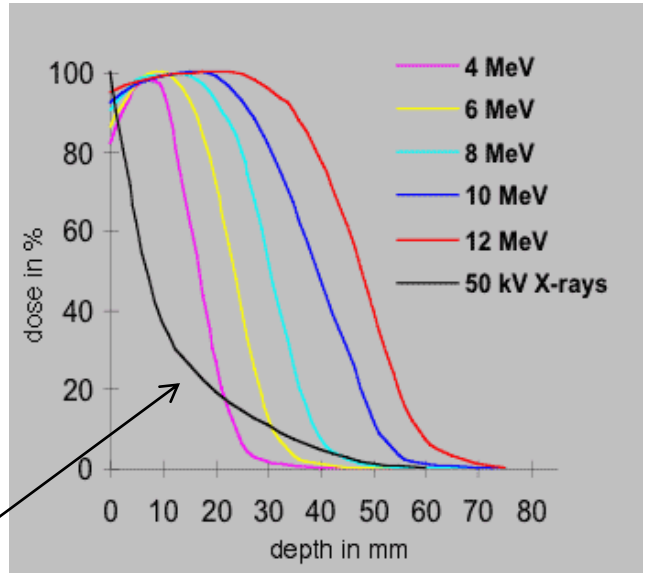
1 INTRABEAM System





Applicators:
1.5 – 5.0 cm



Steep dose
fall off

Spherical dose distribution (4 cm applicator) for 20 Gy prescribed dose at the applicator surface

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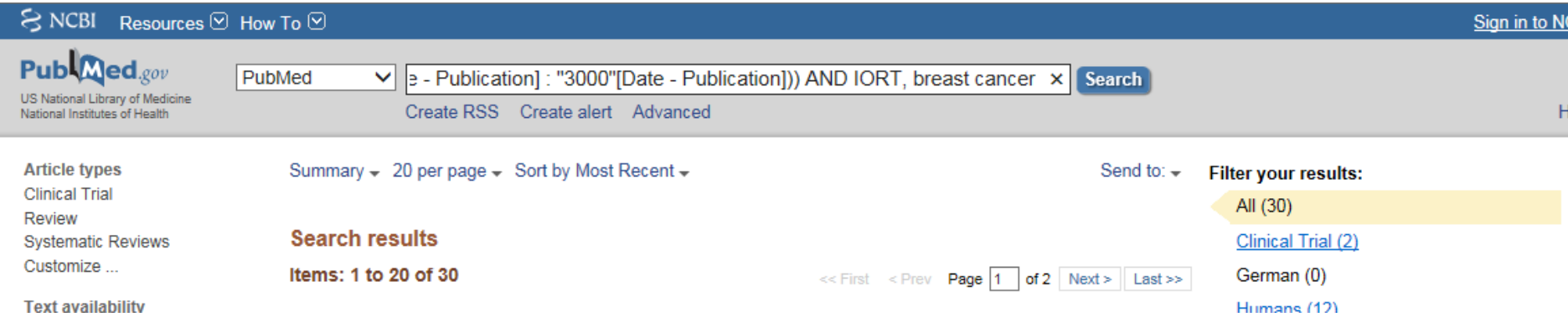
2. Pubmed research– Year 2015 – 2016

14.06.2016



IORT, breast cancer 30 hits	prospective	retrospective	Review
IORT with electrons	3	2	8
IORT with low energy kV x-rays	4	6	

All = 23
Not included: French Publication, Rectum IORT, Double Review, Response, Brachytherapy, Axxent, Review Chinese Paper

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2.1 Pubmed research – IORT with electrons

Author	Journal	Year	Topic	Design	N=	F/U	Result
Electrons				R=Retrospective, P=Prospective			
Wang X	Oncotarget	2015	IOERT in Chinese Han population	R	50	Median 51.8 months	IOERT is safe and reliable, very acceptable cosmetic results (Mobetron)
Kawamura M	Radiat Oncol	2015	Phase I/II trial 19,20,21Gy	P	32	Median 6 years	IOERT well tolerated in Asian population, no recurrence, 24% hypertrophic scarring
Massa M	Plast Reconstr Surg Glob Open	2015	Aesthetic evaluation in oncoplastic BCS	P	96	35-62 months	Excellent cosmetic results and high patient satisfaction
Cracco S	Breast J	2015	Cosmesis, acute complications after oncoplastic BCS	R	192	Mean 17 months	IOERT safe, fast, feasible, no difference in cosmesis
Robatjazi M	Phys Med	2015	Gafchromic EBT2 films	Physics	10	n/a	EBT2 films can be used for patient-specific QA in vivo for IOERT

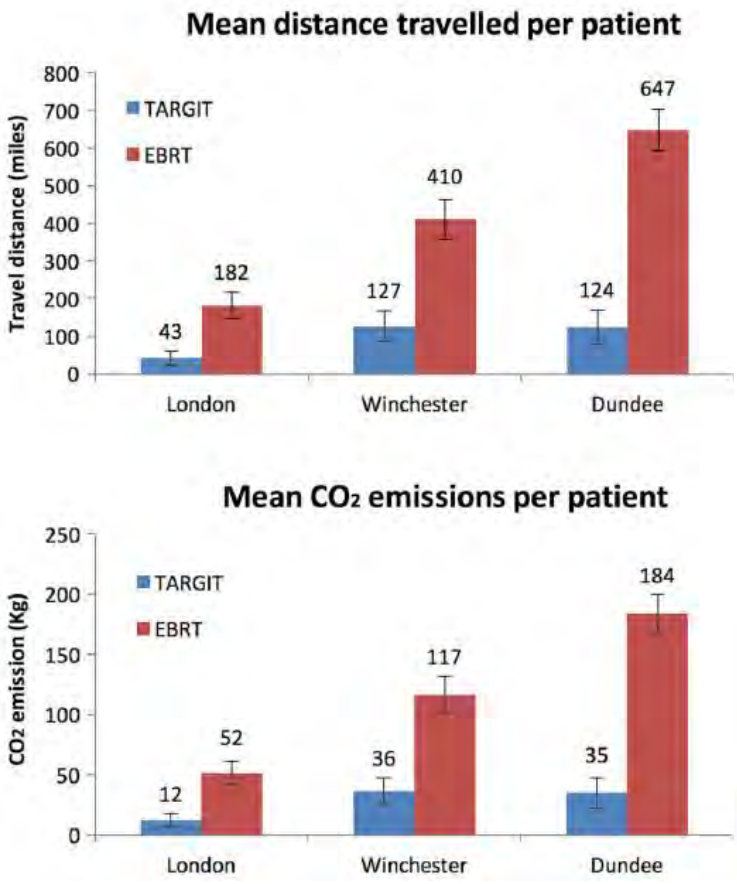
2.2 Pubmed research – IORT with kV x-rays

Author	Journal	Year	Topic	Design	N=	F/U	Result
kV x-rays				R=Retrospective, P=Prospective			
Ebner F	Arch Gynecol Obstet	2016	IORT Boost: Seroma production	R	152	Acute toxicity	No increased seroma production after IORT
Coombs NJ	BMJ Open	2016	Social benefits	R	485	n/a	TARGIT reduces travel time/has environmental benefits
Valente SA	Ann Surg Oncol	2016	Consolidation of data in the US	R	822	Median 23.3 months	In breast recurrence 2.3%, rising use of IORT
Ebert MA	Radiat Res	2016	Radiation dama repair	Biology	n/a	n/a	Uncertainties of ex vivo samples
Fabris L	Oncogene	2016	miR-223, EGF pathway	Biology	29	n/a	Up-reg miR-223 decreases EGF pathway and impairs proliferation of breast cancer cells
Zur M	J Surg Oncol	2016	Acute toxictiy	P	395	Tox within 1y	IORT is safe (grade III-IV complications in 5%)
Rivera R	Breast J	2016	TARGIT for DCIS	P	35	36 months	Local recurrence 5.7%, Overall Survival 100%
Jalaguier-Coudray A	Eur J Radiol	2015	Radialogic findings	Radiology	271	6 months	Atypical calcifications = BIRADS 2, corresponded on tungsten deposits
Abbott AM	Am J Surg	2015	IORT >/< 70 years	R	100	24 months	Local recurrence 2%, low wound infection rates, no age difference
Wuu CS	Radiat Prot Dosimetry	2015	RBE, dosimetry	Biology	n/a	n/a	Low-dose RBE and clinically relevant RBE are presented, RBE of IORT ranges between 1.38 – 2.29

Social and economical aspects

Coombs et al 2016 BMJ Open

Environmental and social benefits of the targeted intraoperative radiotherapy for breast cancer: data from UK TARGIT-A trial centres and two UK NHS hospitals offering TARGIT IORT



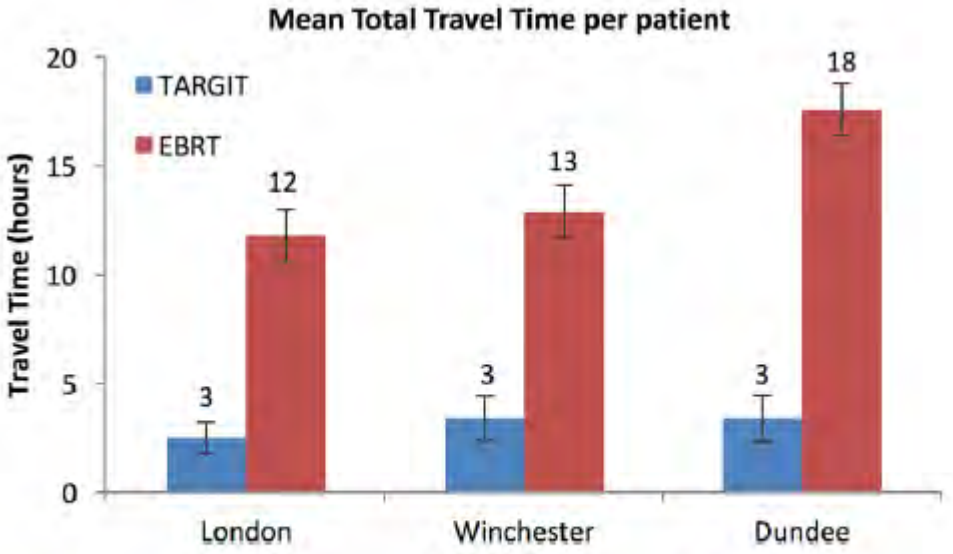


Figure 3 Mean time travelled by a patient for each allocated treatment. EBRT, external beam whole breast radiotherapy.

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2.3 Pubmed research – Reviews IORT

Author	Journal	Year	Topic	Design	N=	Result
Reviews						
Esposito E	Int J Surg	2016	IORT in elderly patients	Review		IORT is an option
Najafipour F	Med J Isalm Repub Iran	2015	Safety, effectiveness, economic evaluation	Review		IORT is safe and cost-effective
Wenz F	Breast Care	2015	APBI in clinical practice	Review		15-25% of BCS patients may qualify for APBI, different consensus statements
Zhang L	Medicine (Baltimore)	2015	IORT vs. EBRT	Syst. Review, Meta-Analysis	5415	IORT with sign. higher risk for local relapse, prudent selection of low risk patients is imperative
Trifiletti DM	Future Oncol	2015	Techniques for IORT	Review		Future techniques with in-room imaging and rapid treatment planning are shown additionally
Esposito E	Br J Surg	2015	TARGIT A, ELIOT	Review		More specific guidelines for IORT for inclusion criteria would assist clinicians, IORT is an alternative to EBRT
Holmes D	Breast J	2015	TARGIT A, ELIOT	Review		Patient selection important
Hanna GG	Br J Radiol	2015	Current IORT techniques	Review		Mature F/U needed

2.4 Conclusion Pubmed research

- Rising evidence for
  - Cosmesis
  - Acute toxicity
  - Dosimetry/QA
  - Radiobiology
- New aspects
  - Social and environmental benefits
- No data regarding long term toxicity
- Many Reviews und Discussion about TARGIT A / ELIOT

(Vaidya JS, Int J Radiat Oncol Biol Phys, 2015:Pride, Prejudice or Science….)

- No randomized controlled trials!

3.1 Prospective trials – TARGIT A (2014)

Published Online
November 11, 2013
http://dx.doi.org/10.1016/
S0140-6736(13)61950-9

Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial

33 centers
Med. FU 2.5 y n=3451
Med. FU 5 y n=1222

3451 Patients (TARGIT n=1721, EBRT n=1730)

Jayant S Vaidya, Frederik Wenz, Max Bulsara, Jeffrey S Tobias, David J Joseph, Mohammed Keshtgar, Henrik L Flyger, Samuele Massarut, Michael Alvarado, Christobel Saunders, Wolfgang Eiermann, Marinos Metaxas, Elena Sperk, Marc Sütterlin, Douglas Brown, Laura Esserman, Mario Roncadin, Alastair Thompson, John A Dewar, Helle M R Holtveg, Steffi Pigorsch, Mary Falzon, Eleanor Harris, April Matthews, Chris Brew-Graves, Ingrid Potyka, Tammy Corica, Norman R Williams, Michael Baum, on behalf of the TARGIT trialists' group

	Events; 5-year cumulative risk (95%CI)		Absolute difference*
	TARGIT	EBRT	
All patients			
Local recurrence (n=3375)	23; 3·3% (2·1–5·1)	11; 1·3% (0·7–2·5)	12 (2·0%)
Any other recurrence (n=3375)	46; 4·9% (3·5–6·9)	37; 4·4% (3·0–6·4)	9 (0·5%)
Death (n=3451)	37; 3·9% (2·7–5·8)	51; 5·3%(3·9–7·3)	−14 (−1·4%)

Non-inferiority margin 2,5%
(GEC ESTRO 3%)

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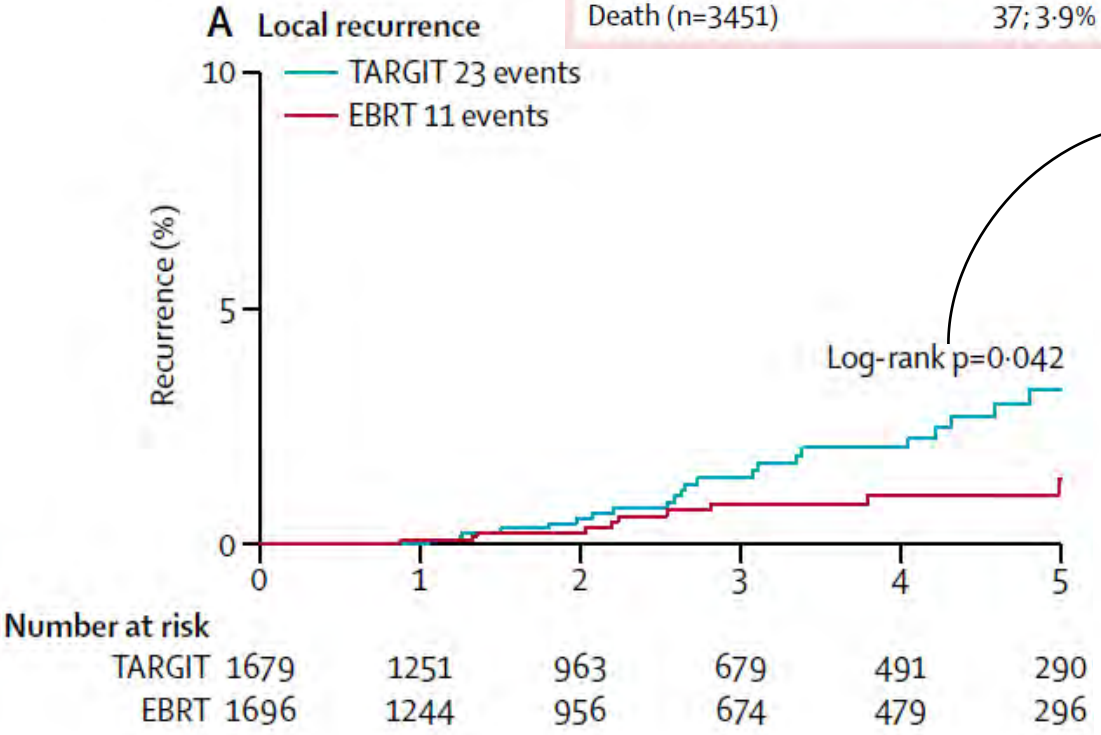
Lancet 2014; 383: 603–13

3.1 TARGIT A: Details LR

	Events; 5-year cumulative risk (95%CI)		Absolute difference*
	TARGIT	EBRT	
All patients			
Local recurrence (n=3375)	23; 3·3% (2·1–5·1)	11; 1·3% (0·7–2·5)	12 (2·0%)
Any other recurrence (n=3375)	46; 4·9% (3·5–6·9)	37; 4·4% (3·0–6·4)	9 (0·5%)
Death (n=3451)	37; 3·9% (2·7–5·8)	51; 5·3%(3·9–7·3)	–14 (–1·4%)



Authors' reply

Furthermore, we had prespecified that the significant p value for difference for the log-rank test would be less than 0·01 for local recurrence—as this was the second such analysis. So the 2% difference was not only within the non-inferiority margin but also, since the p value was 0·04, strictly speaking, it was not statistically significant.

www.thelancet.com Vol 383 May 17, 2014

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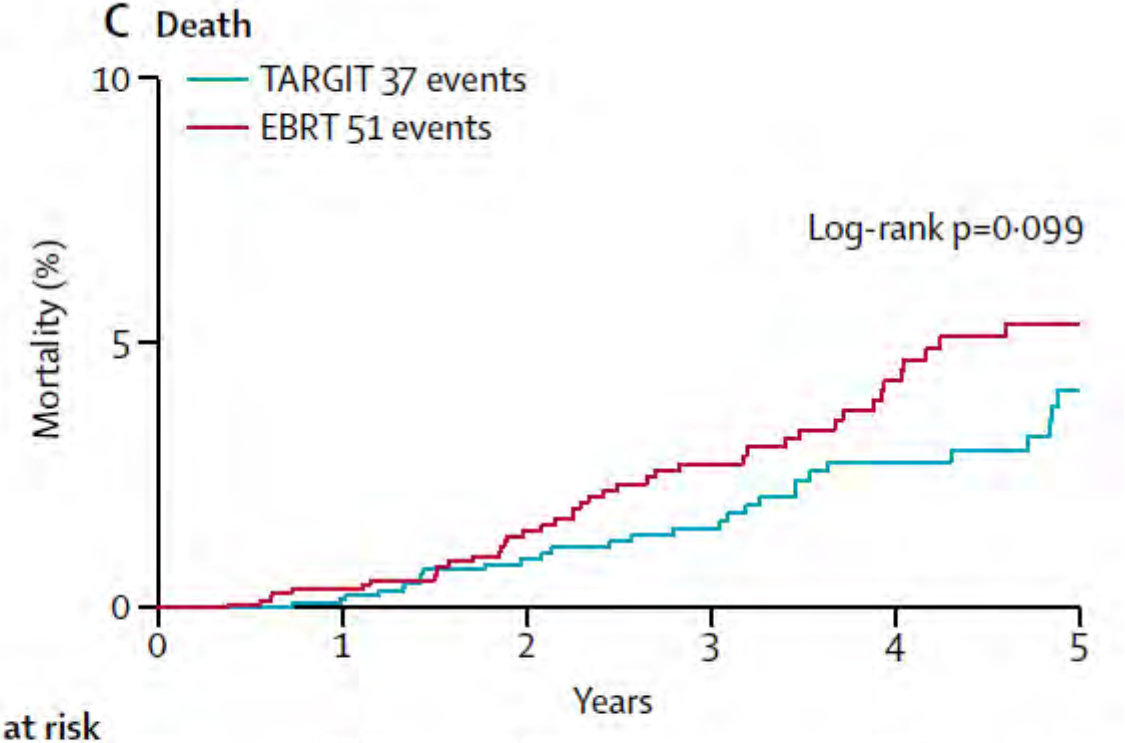
Lancet 2014; 383: 603–13

3.1 TARGIT A: Details OS

	Events; 5-year cumulative risk (95%CI)		Absolute difference*
	TARGIT	EBRT	
All patients			
Local recurrence (n=3375)	23; 3·3% (2·1–5·1)	11; 1·3% (0·7–2·5)	12 (2·0%)
Any other recurrence (n=3375)	46; 4·9% (3·5–6·9)	37; 4·4% (3·0–6·4)	9 (0·5%)
Death (n=3451)	37; 3·9% (2·7–5·8)	51; 5·3%(3·9–7·3)	−14 (−1·4%)



Number at risk

TARGIT	1721	1285	997	706	514	309
EBRT	1730	1272	978	693	496	302

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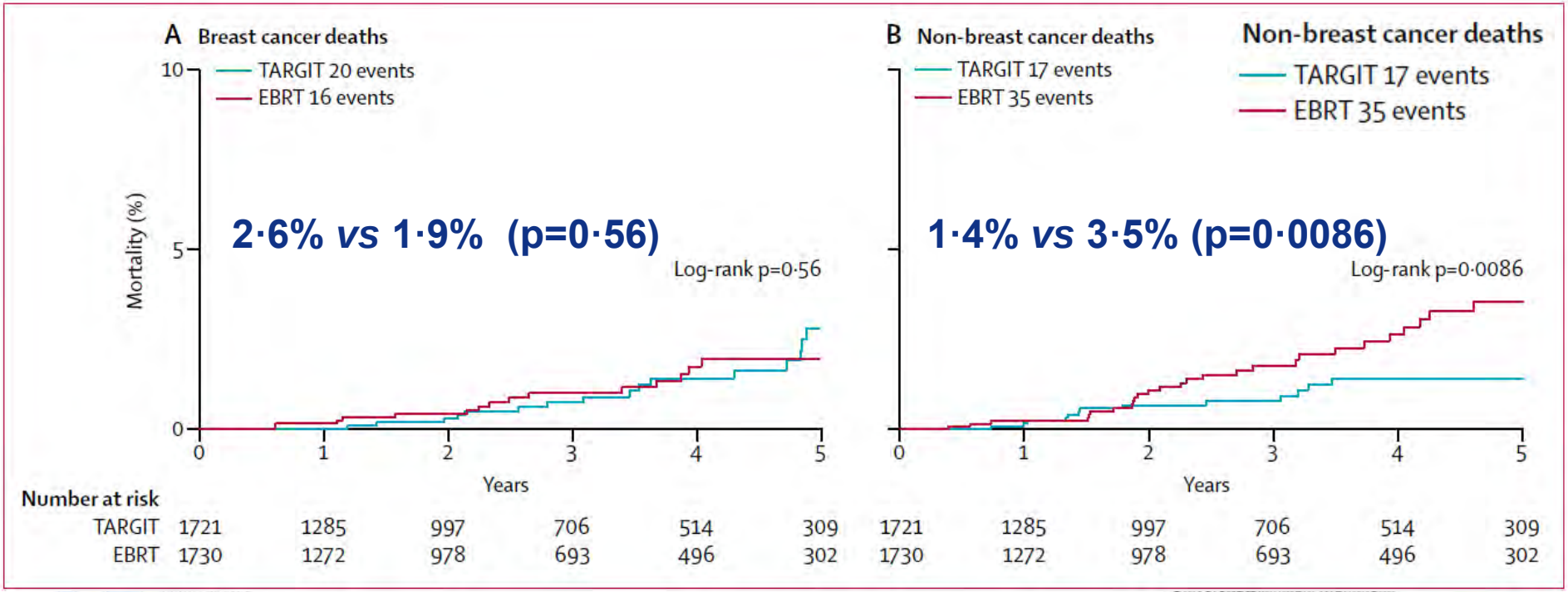
Lancet 2014; 383: 603–13

3.1 TARGIT A: Breast cancer vs. Non breast cancer deaths

	TARGIT	EBRT
Other cancers	8	16
Cardiovascular causes		
Cardiac*	2	8
Stroke	0	2
Ischaemic bowel	0	1
Old age or unknown†	1	5
Other‡	6	4
Total	17	35

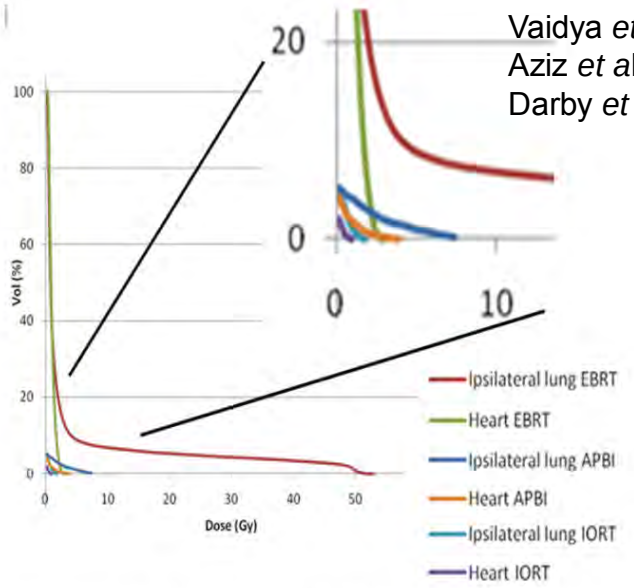


3.1 TARGIT A: Early cardiac effects after RT?

	TARGIT	EBRT
Other cancers	8	16
Cardiovascular causes		
Cardiac*	2	8
Stroke	0	2
Ischaemic bowel	0	1
Other†	7	8
Total	17	35

5-year risk 1·4% for TARGIT versus 3·5% for EBRT; log-rank p=0·0086. TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy. *Included one "sudden death at home" in EBRT group. †TARGIT: two diabetes, one renal failure, one liver failure, one sepsis, one Alzheimer's disease, one unknown; EBRT: one myelopathy, one perforated bowel, one pneumonia, one old age, four unknown.

Table 2: Causes of death other than breast cancer in all patients



Cumulative DVH for ipsilateral lung and heart for IORT, APBI and EBRT.

Vaidya *et al.* Lancet 2014
Aziz *et al* Radiat Oncol 2011
Darby *et al.* NEJM 2013

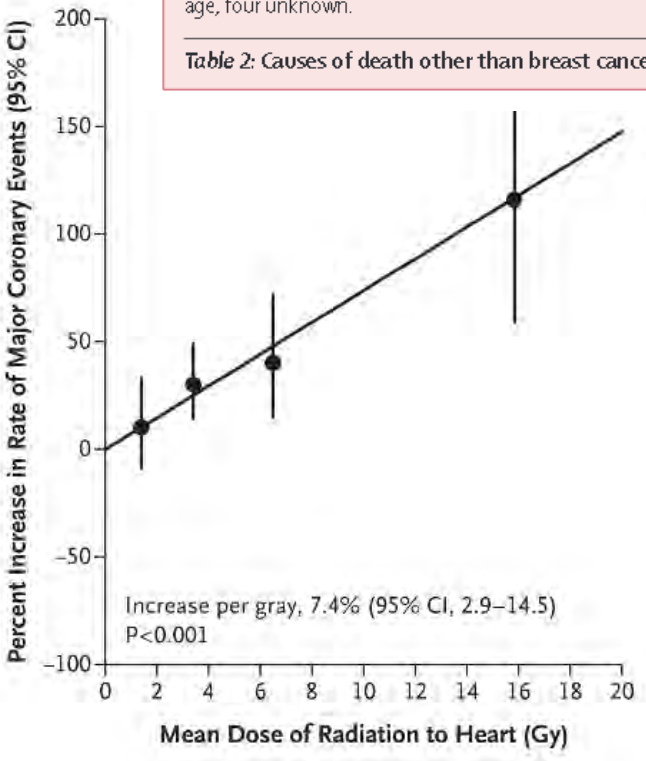


Table 3. Percentage Increase in the Rate of Major Coronary Events per Gray, According to Time since Radiotherapy.

Time since Radiotherapy*	No. of Case Patients	No. of Controls	Increase in Rate of Major Coronary Events (95% CI)†
			% increase/Gy
0 to 4 yr	206	328	16.3 (3.0 to 64.3)
5 to 9 yr	216	296	15.5 (2.5 to 63.3)
10 to 19 yr	323	388	1.2 (−2.2 to 8.5)
≥20 yr	218	193	8.2 (0.4 to 26.6)
0 to ≥20 yr	963	1205	7.4 (2.9 to 14.5)

3.2 TARGIT A: Mannheim cohort

n = 183

Median age 64.4 years

Median Follow-Up 74 months

TARGIT A - Mannheim	5 year Overall Survival	5 year local relapse free survival
Arm A IORT +/- WBRT	**94.9%**	**100% (0)**
Arm B WBRT	**92.7%**	**98.8% (1)**

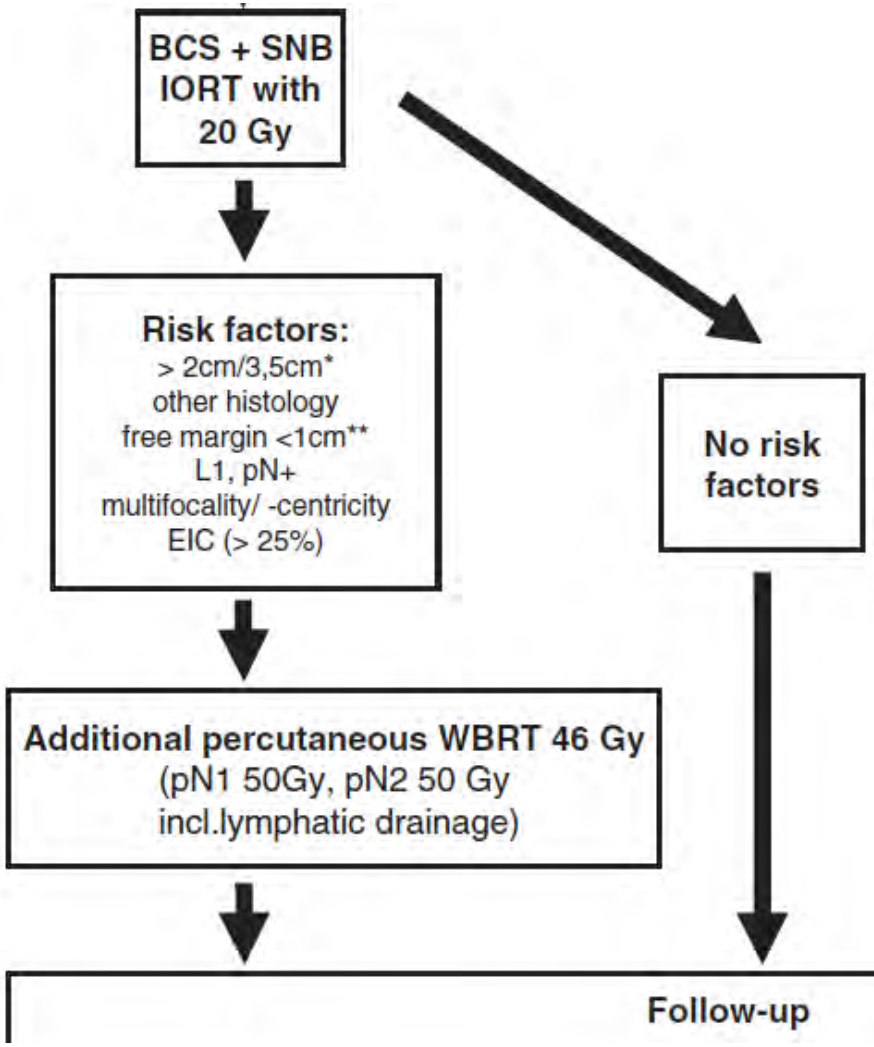
Y. Abou-Madyan et al.
Presented at the DEGRO 2016,
Poster ASTRO 2016

3.3 TARGIT E(lderly)

TARGIT-E(lderly)—Prospective phase II study of intraoperative radiotherapy (IORT) in elderly patients with small breast cancer

Christian Neumaier[1*], Sperk Elena[1], Welzel Grit[1], Abo-Madyan Yasser[1,2], Kraus-Tiefenbacher Uta[1], Keller Anke[1], Gerhardt Axel[3], Sütterlin Marc[3] and Wenz Frederik[1]

≥ 70 years
mammo-/ultrasonography/biopsy
invasive ductal
cT1 and small T2 (≤3,5cm)
cN0 cM0
no risk factors:
no mulitfocality/ -centricity
no EIC (biopsy)
No L1 (biopsy)



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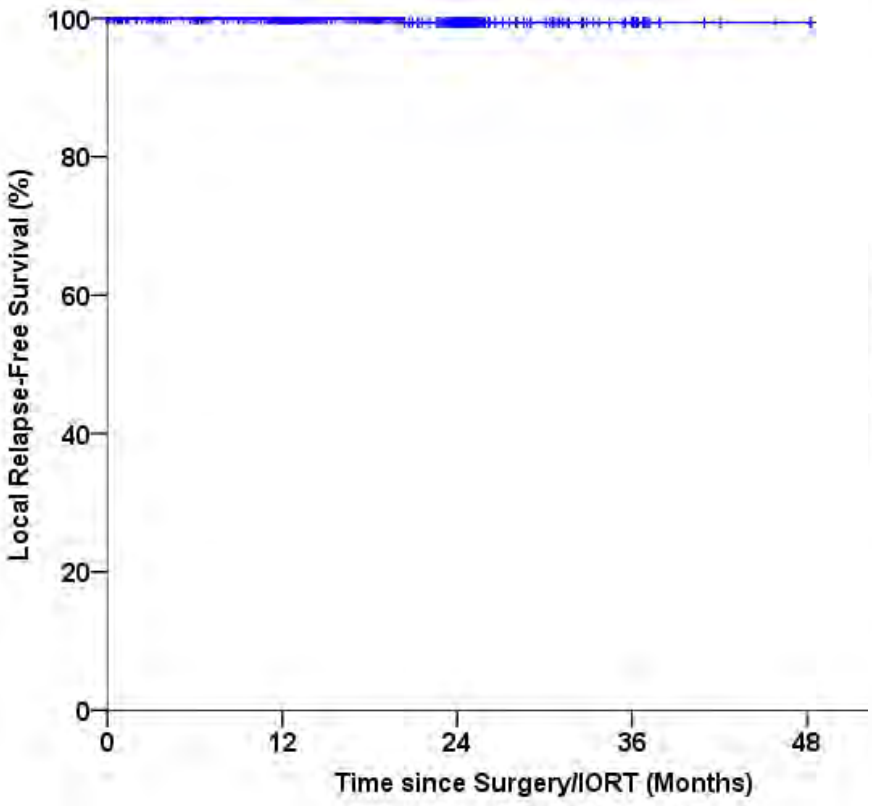
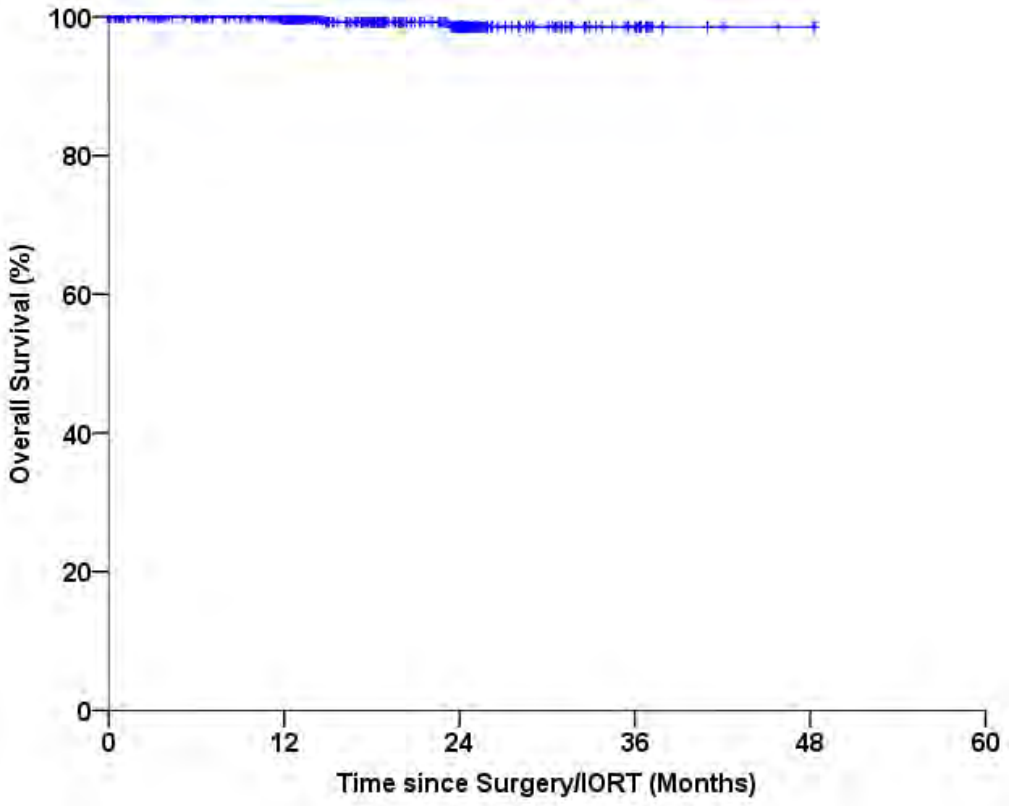
3.3 TARGIT E(elderly)

TARGIT E	30 months OS	30 months local recurrence free survival
Safety analysis	**98.6%** **3 Deaths (11, 14, 23 months after IORT)**	**99.4%** **1 local recurrence (20 months after IORT)**





Wenz et al.
Presented at the ASCO 2016, DEGRO 2016

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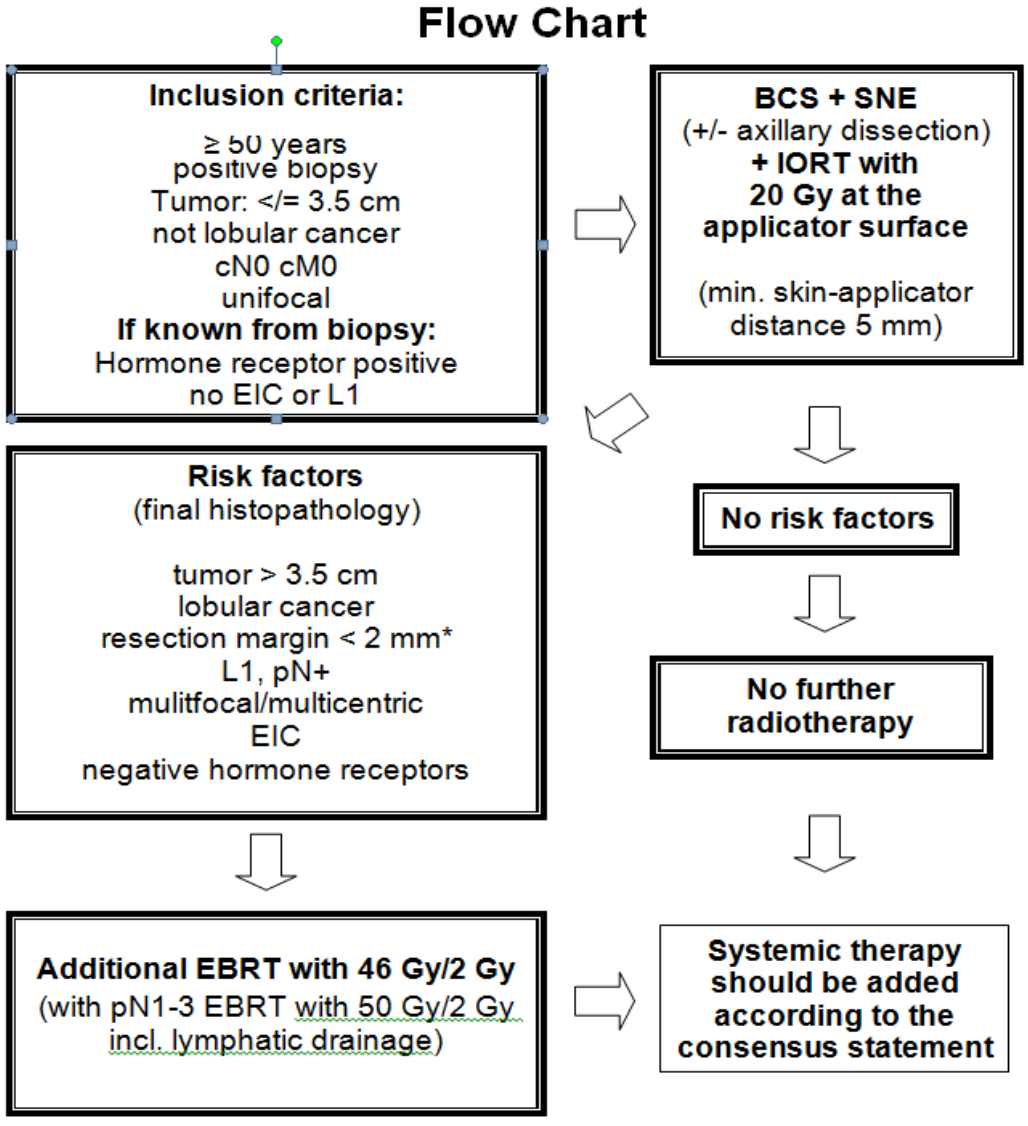
3.4 TARGIT C(onsolidation)

TARGIT-C(Consolidation) Prospective Phase IV Study of IORT in Patients With Small Breast Cancer (TARGIT-C)



ClinicalTrials.gov Identifier:
NCT02290782

- N = 386
- Primary Outcome: Local control
- Open, France will start in late summer

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3.5 TARGIT B(oost)

A Comparison of Intra-operative Radiotherapy Boost With External Beam Radiotherapy Boost in Early Breast Cancer. (TARGIT-B)

This study is currently recruiting participants. (see Contacts and Locations)

Verified October 2015 by University College, London

ClinicalTrials.gov Identifier:
NCT01792726

Estimated Enrollment:	1796
Study Start Date:	June 2013
Estimated Study Completion Date:	April 2022
Estimated Primary Completion Date:	January 2022 (Final data collection date for primary outcome measure)

- Prospective randomized trial
- Primary outcome: local control

Inclusion Criteria:

At least one of these criteria must be satisfied:

- < 46 years of age, > 45 years of age, but with one of the following poor prognostic factors: lymphovascular invasion, gross nodal involvement (not micrometastasis), more than one tumour in the breast but still suitable for breast conserving surgery through a single specimen
- > 45 years of age, but with at least two of the following poor prognostic factors: ER and/or PgR negative, grade 3 histology, positive margins at first excision, those patients with large tumours which have responded to neo-adjuvant chemo- or hormone therapy in an attempt to shrink the tumour and are suitable for breast conserving surgery as a result, lobular carcinoma or Extensive Intraductal Component (EIC)

Exclusion Criteria:

- Bilateral breast cancer at the time of diagnosis.
- Patients with any severe concomitant disease that may limit their life expectancy
- Previous history of malignant disease does not preclude entry if the expectation of relapse-free survival at 10 years is 90% or greater (e.g., non-melanoma skin cancer, CIN, etc).

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4. Meta-Analysis APBI: kV x-rays, Brachytherapy

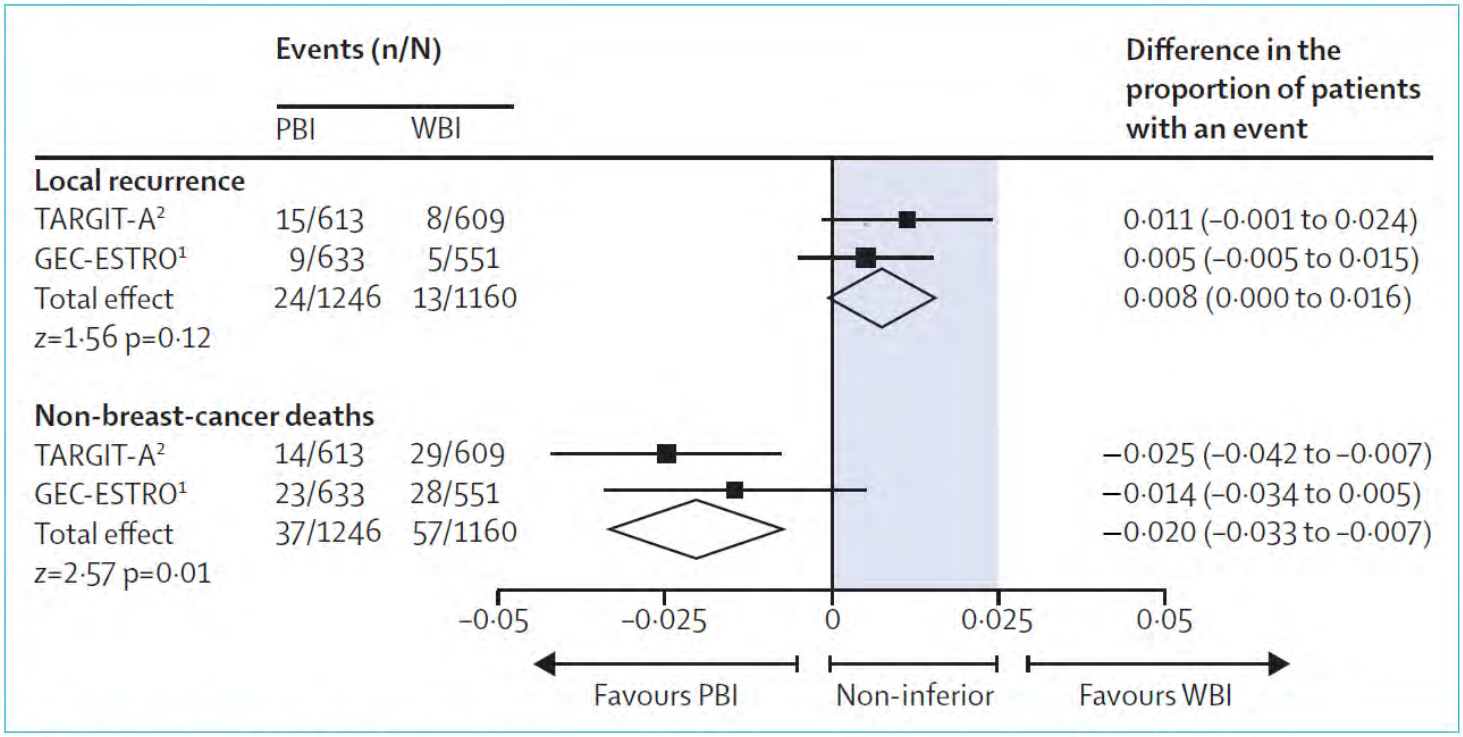
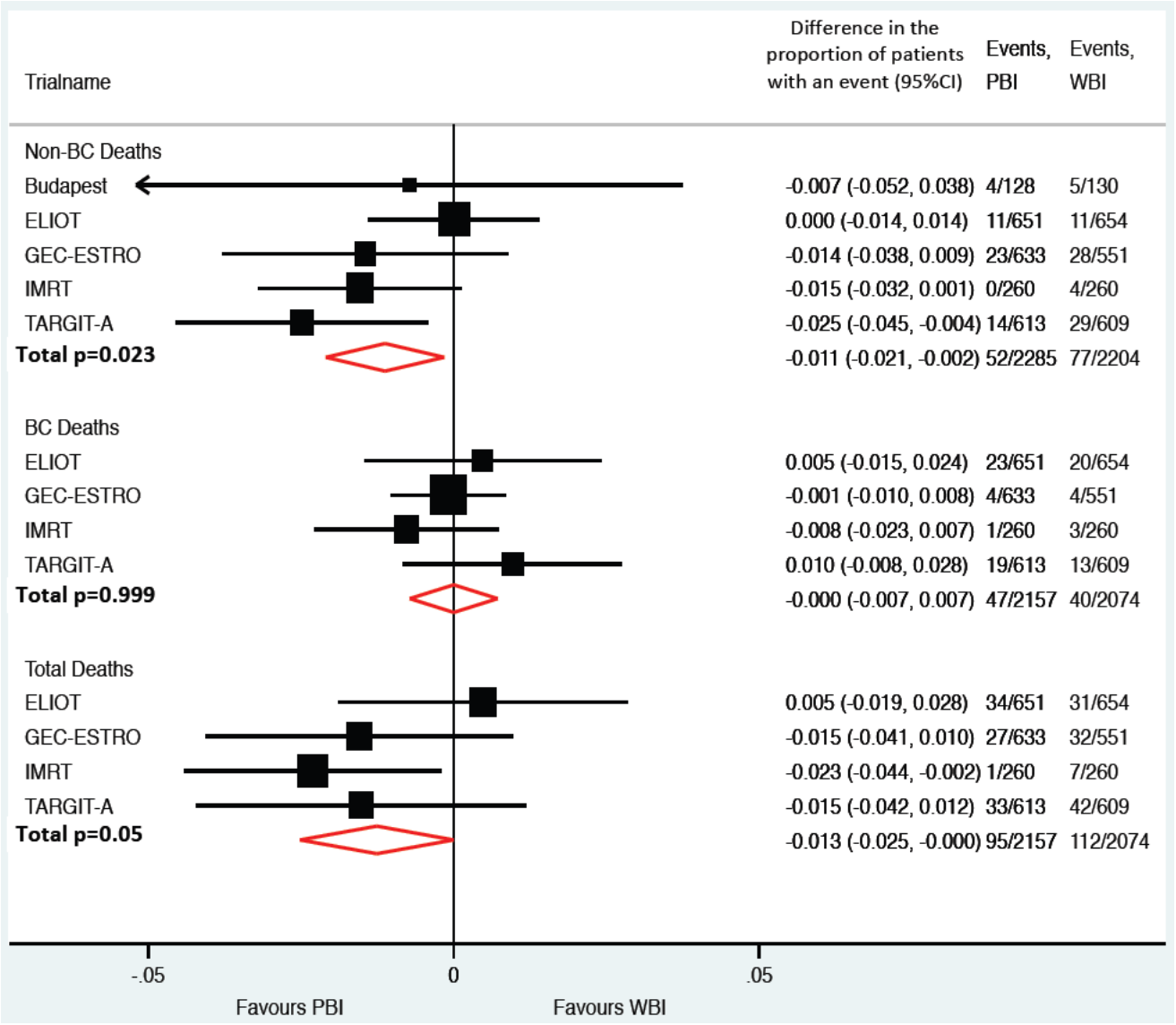


Figure 1: **Meta-analysis of the outcomes of local recurrence and non-breast-cancer mortality**
Values are numbers of patients with an event (n/N) and absolute differences in the proportion of patients who had an event in each of the randomised groups (not hazard ratios). The shaded area shows the more stringent non-inferiority margin (2·5%) for the TARGIT-A trial, rather than the margin for the GEC-ESTRO trial (3%). There was no heterogeneity between the TARGIT-A and GEC-ESTRO trial results (p=0·521 for local recurrence and p=0·515 for non-breast-cancer mortality). PBI=partial breast irradiation. WBI=whole breast irradiation.

Vaidya, Bulsara, Wenz et al.
Lancet Correspondence April 2016

4. Meta-Analysis APBI: Electrons, kV x-rays, Brachytherapy



Polgar J Surg Oncol 2002
Veronesi Lancet Oncol 2013
Strnad Lancet 2015
Livi Eur J Cancer 2015
Vaidya Lancet 2014

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Vaidya, Bulsara, Wenz et al. in press

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5. Conclusion

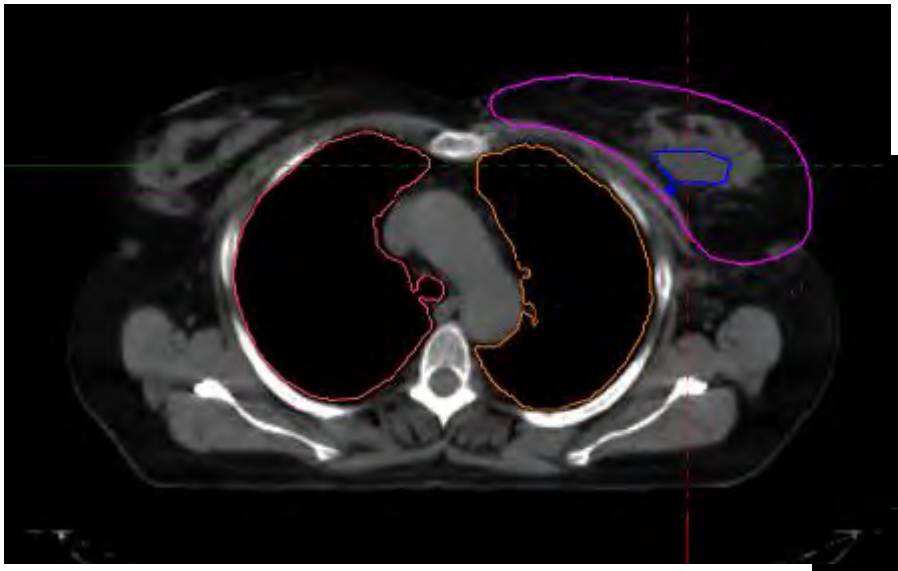
- ✓ Rising evidence for IORT in many different fields
- ✓ More and more IORT user worldwide
- ✓ Positive social and environmental benefits after IORT
- ✓ APBI, intraoperatively with electrons or kV x-rays or as brachytherapy is a safe and effective method for breast cancer
- ✓ A lot of discussion about how IORT works/radiobiology

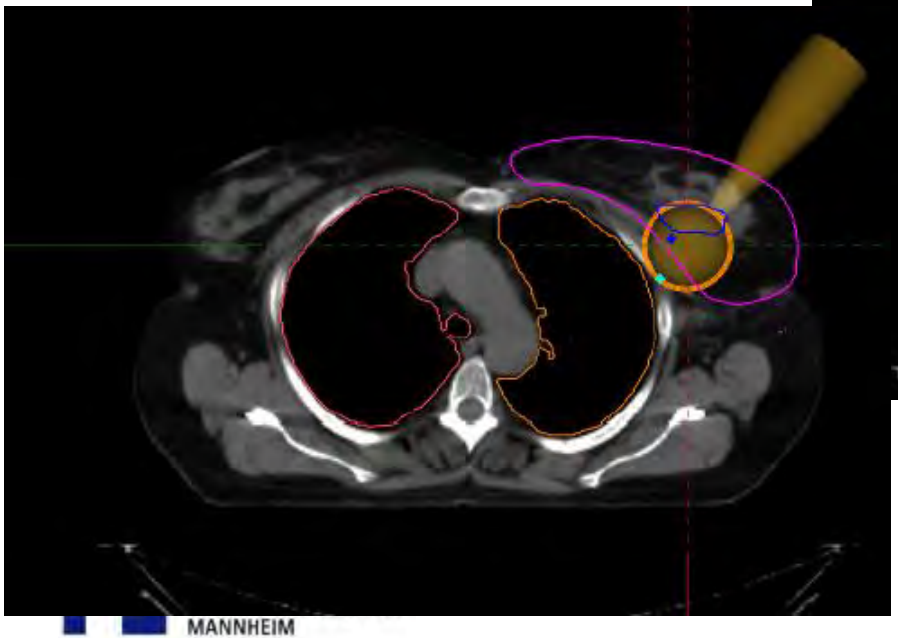
→ Update for TARGIT A whole cohort is not published, yet

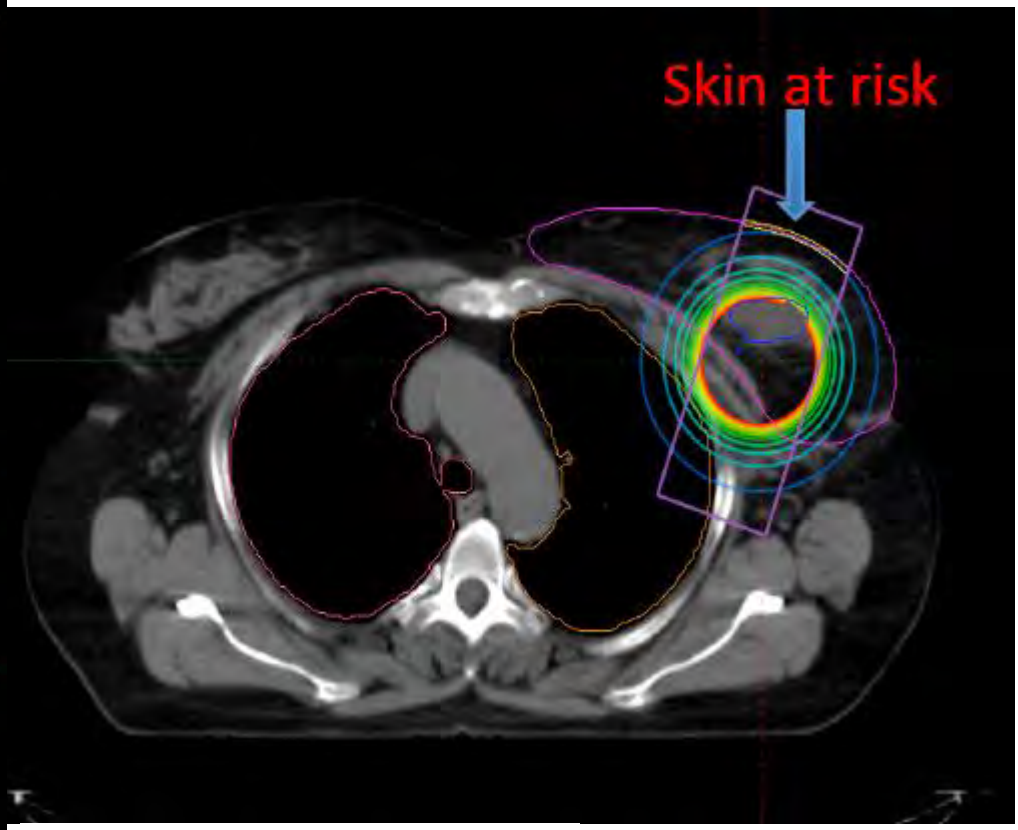
→ TARGIT A Mannheim: in preparation

→ TARGIT E: in preparation

6. What`s next: postoperative dose reconstruction

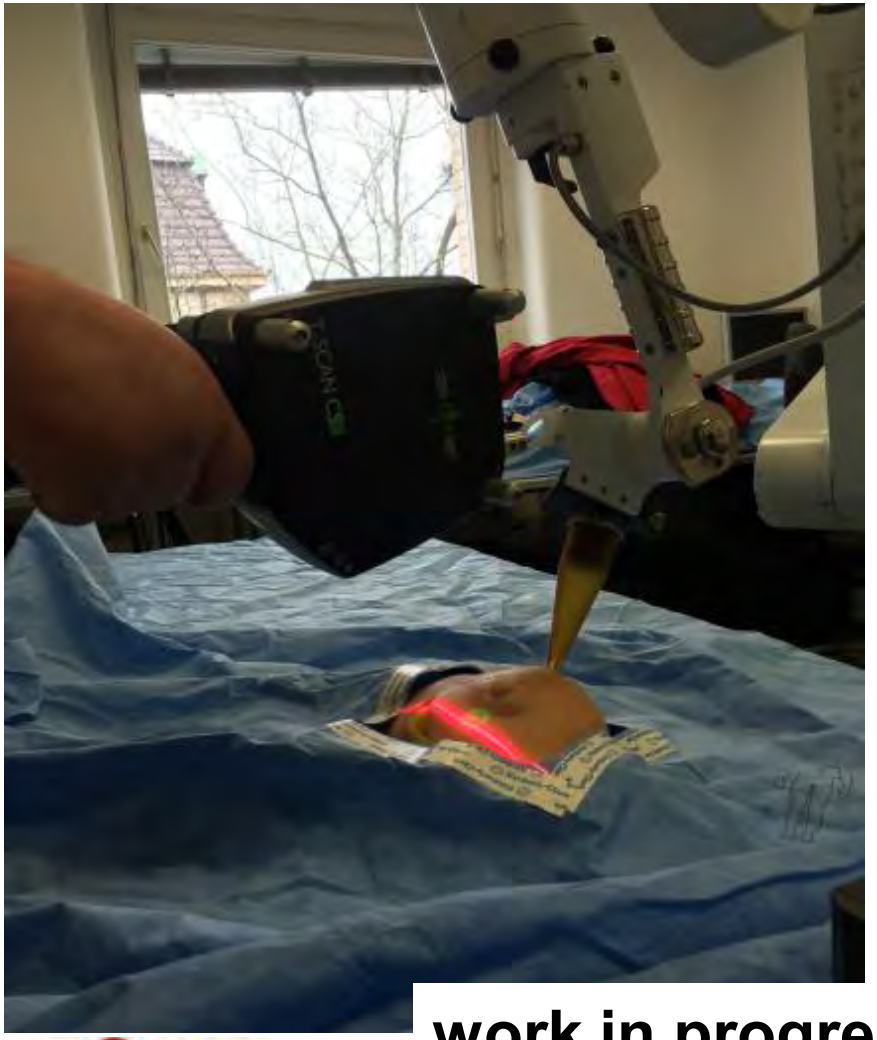


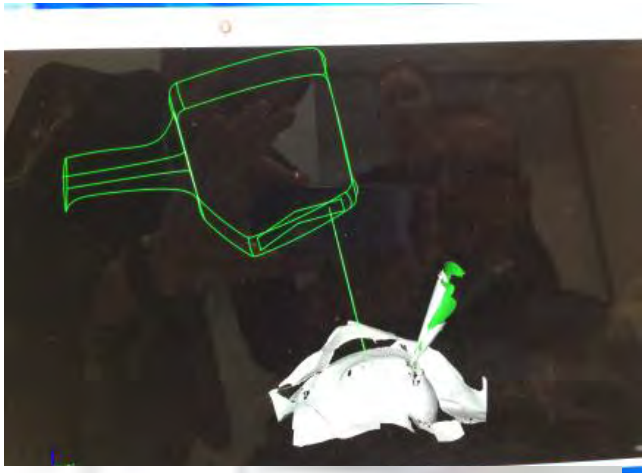


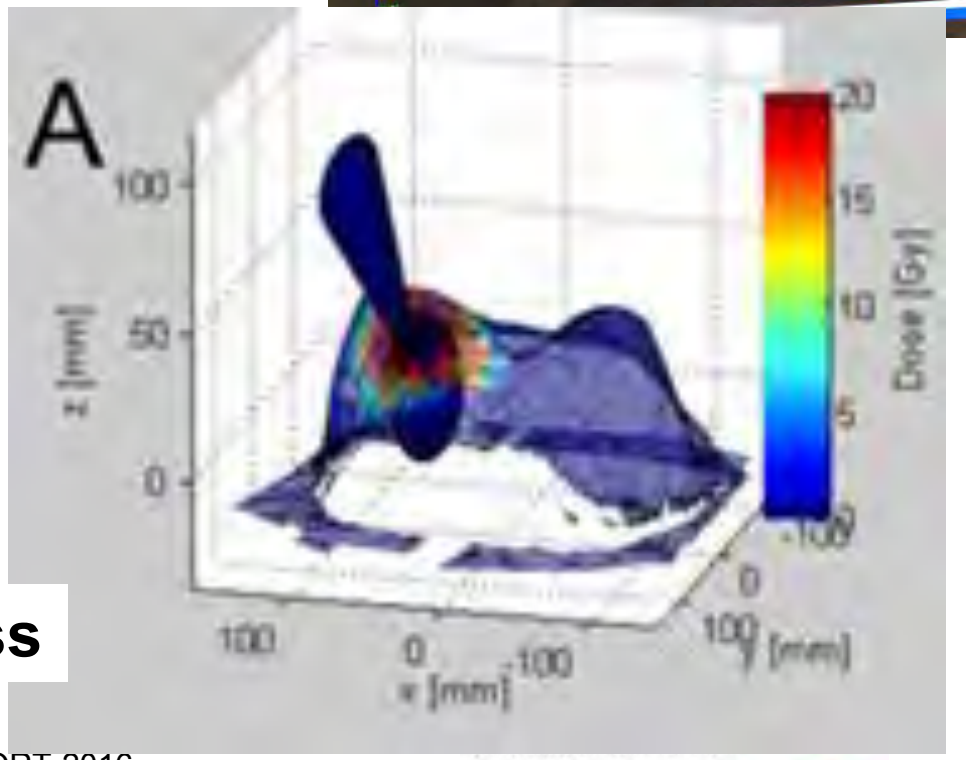


work in progress

6. What`s next: intraoperative dose reconstruction







work in progress

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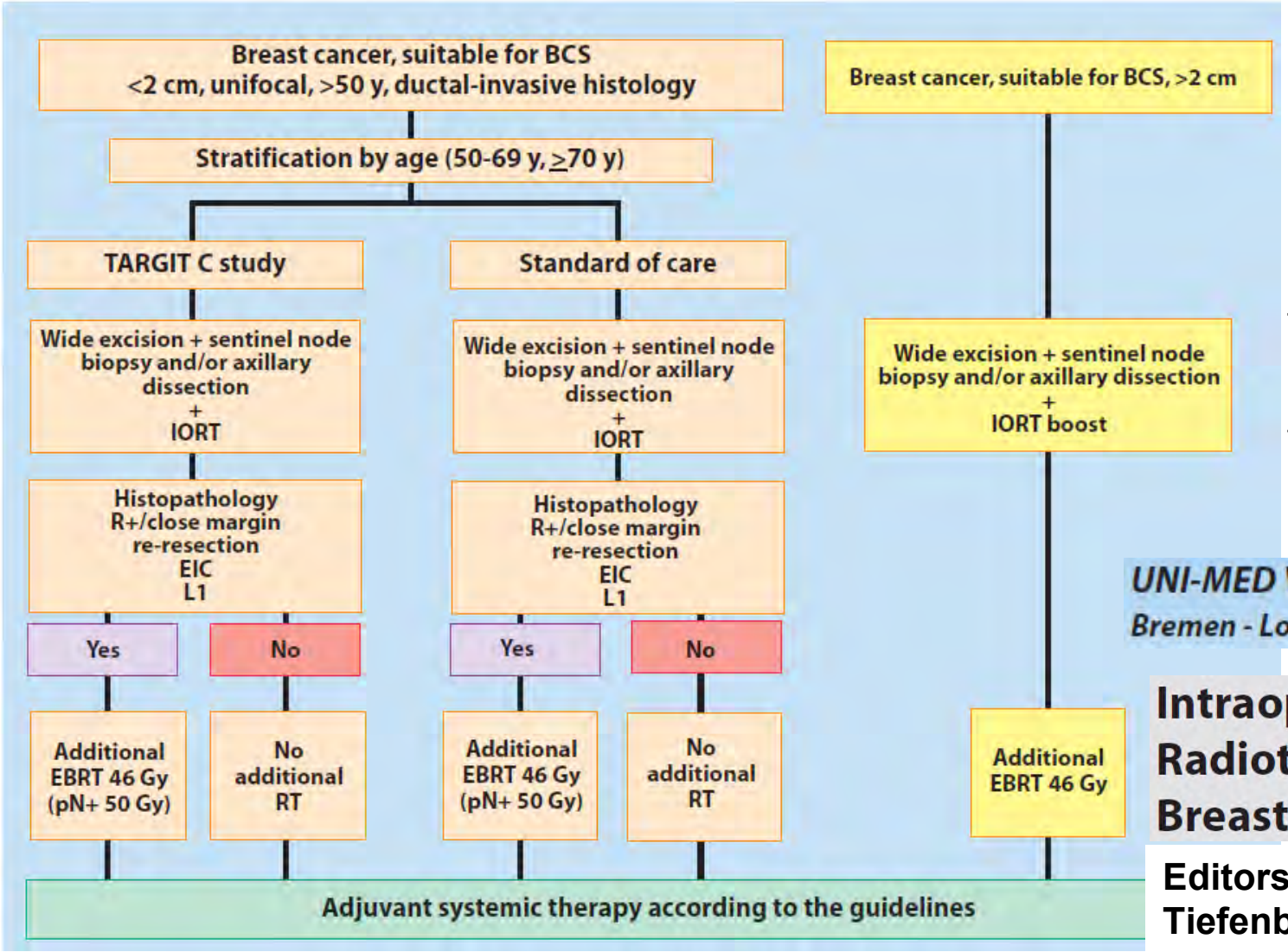
7. Recommendations for IORT kV x-rays



TARGIT BQR (Boost Quality Registry), TARGIT B(oost)

UNI-MED Verlag AG
Bremen - London - Boston

Intraoperative Radiotherapy for Breast Cancer

Editors Wenz, Kraus-Tiefenbacher

***S3 Guideline 2012/Statement 5.3.1:**

c. Bei brusterhaltender Operation sollte die Möglichkeit einer Re-Bestrahlung (Teilbrustbestrahlung) geprüft werden.

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A cohort analysis to identify eligible patients for intraoperative radiotherapy (IORT) of early breast cancer

Radiation Oncology 2014, **9**:154

Elena Sperk[1*], Daniela Astor[1], Anke Keller[1], Grit Welzel[1], Axel Gerhardt[2], Benjamin Tuschy[2], Marc Sütterlin[2] and Frederik Wenz[1]

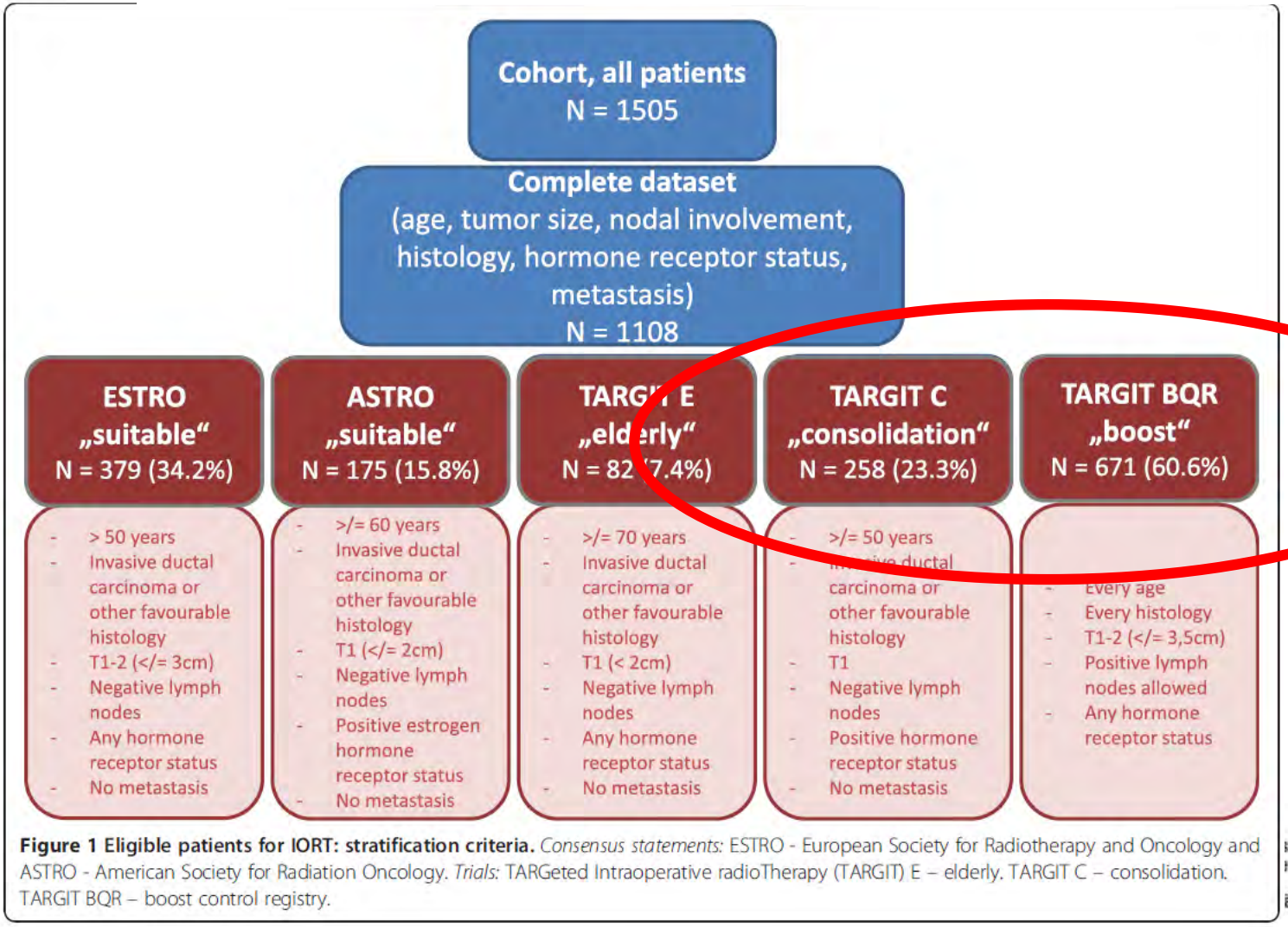

Figure 1 Eligible patients for IORT: stratification criteria. *Consensus statements:* ESTRO - European Society for Radiotherapy and Oncology and ASTRO - American Society for Radiation Oncology. *Trials:* TARGeted Intraoperative radioTherapy (TARGIT) E – elderly. TARGIT C – consolidation. TARGIT BQR – boost control registry.

IORT with low energy kV x-rays worldwide

Thank you for your attention!

elena.sperk@umm.de

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der Universität Heidelberg

Universitätsklinikum Mannheim

IORT with low energy X-rays in breast cancer –

The view of a surgeon

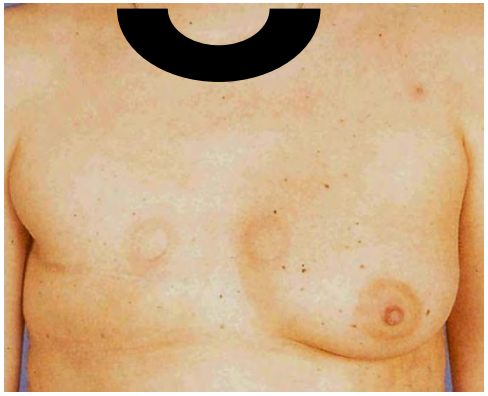
Prof. Dr. med. Marc W. Sütterlin

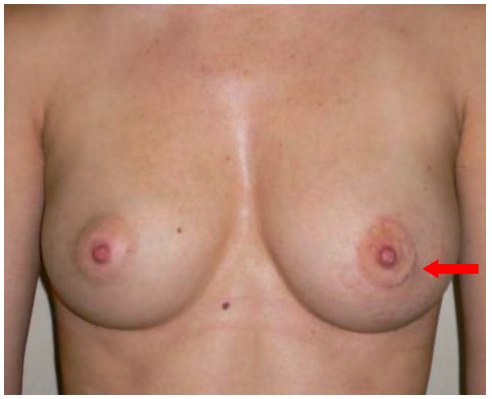
Director of the Dept. of Obstetrics, Gynecology and Reproductive Medicine, University Medical Center Mannheim

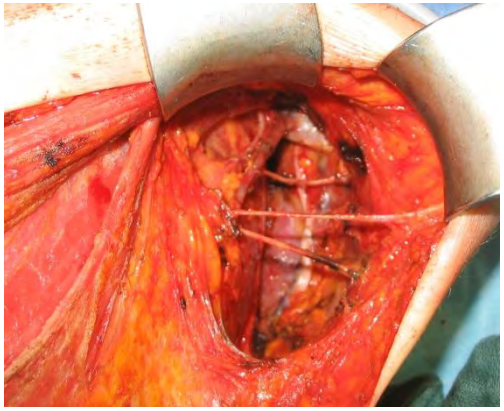
Head of the Breast and Gynecologic Cancer Center

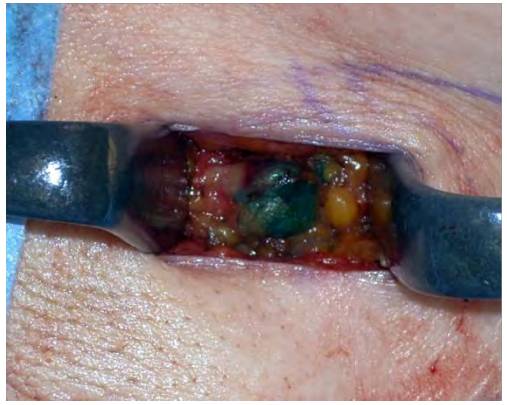
Professor for Gynecology and Obstetrics, Medical Faculty Mannheim, Heidelberg University / Germany

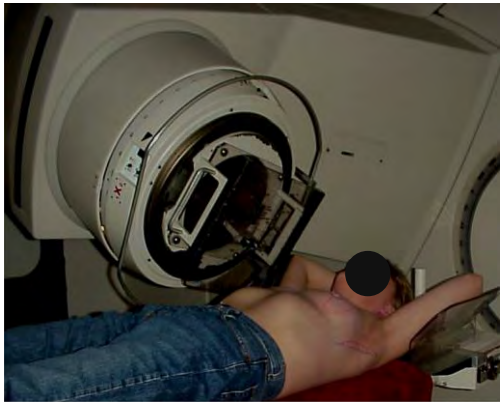
Development of risk adapted breast cancer treatment

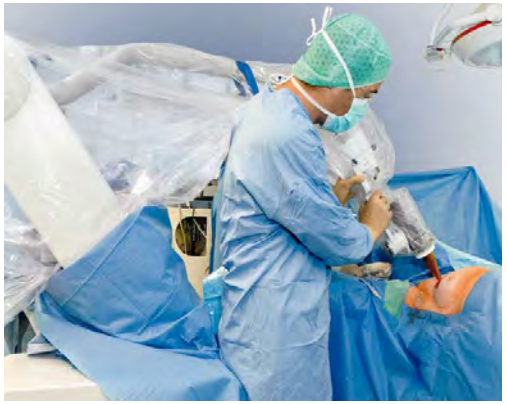






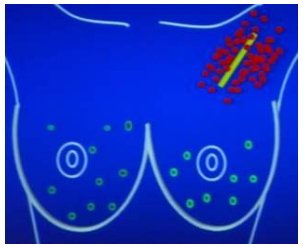






IORT: Clinical applications

- Tumor bed boost (instead of external boost)
- APBI as a single dose TARGIT Targeted Intra-operative Radiation Therapy



- BCT after previous EBRT of the breast
  - in-breast-recurrence after BCT for BC
  - primary BC after EBRT for other reasons (e.g. lymphoma)

IORT: Pro

- reduction of postoperative radiation time

- immediate radiotherapy after tumor excision (no temporal miss)

- no geographical miss

- smaller treatment volume

- skin-sparing

IORT: Contra

- prolonged operation time

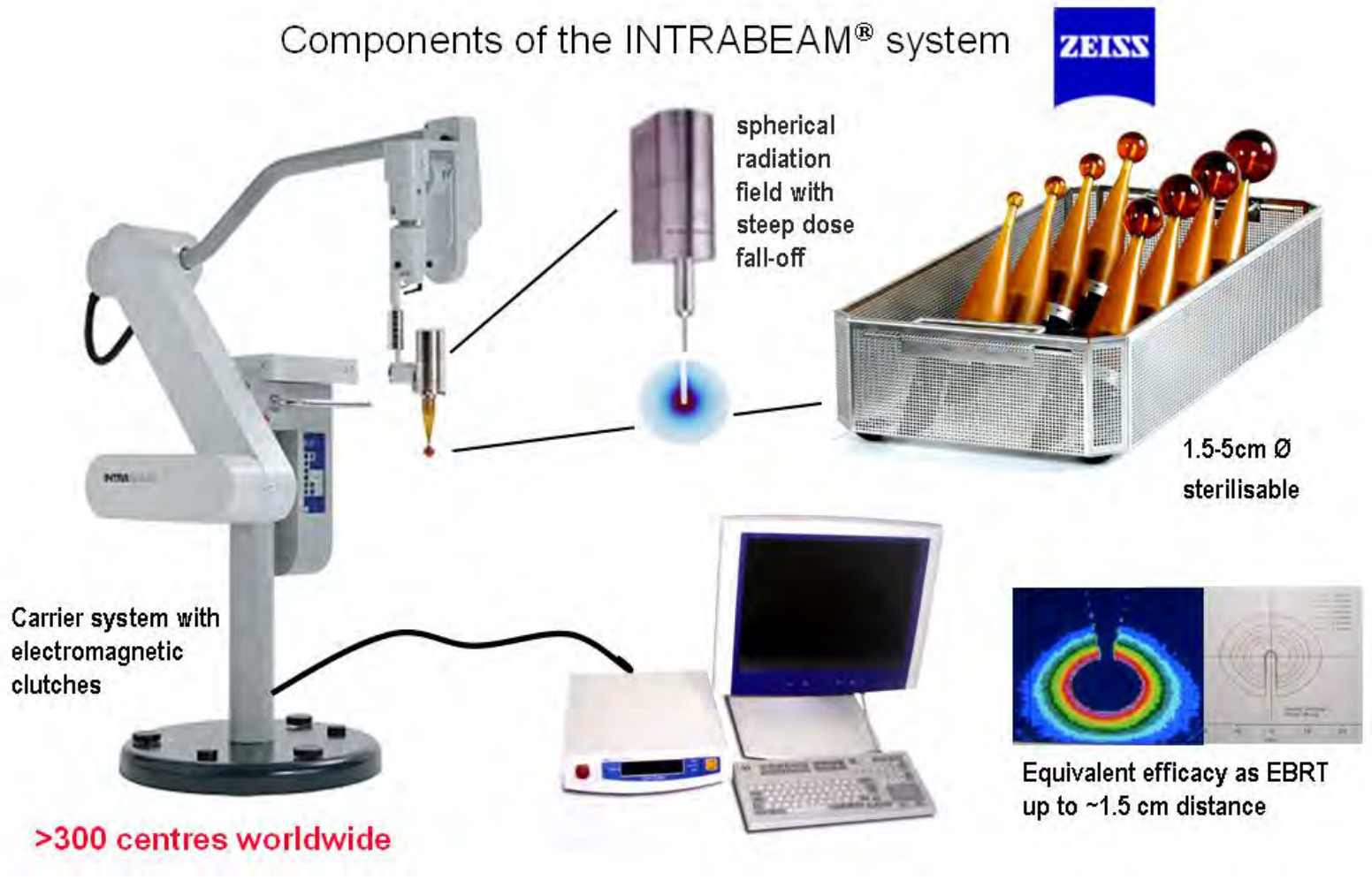
- not suitable for all BC patients (e.g. large wound cavity)

- final histological result at time of IORT not known

- limited data (in comparison to EBRT)

Intraoperative Radiotherapy (IORT) with Low Energy X-rays (max. 50 kV)

Experience in Mannheim: > 500 pts. since 2002



Irradiation time: ~20 (2.5 cm applicator)-**50 min** (5 cm applicator)

IORT with low energy X-rays: Patient selection

Clinical criteria for the use of IORT as the only radiotherapy in combination with BCS within the scope of a risk-adapted concept for early breast cancer

- ≥50 years
- positive biopsy
- unifocal tumour ≤3.5 cm
- NST (not lobular cancer)
- HR+ (positive hormone receptors)
- no EIC or L1
- cN0 cM0
- resection margin >2mm
- prepathology concept

TARGIT-C(onsolidation) trial
Prospective phase IV study

If additional risk factor in final histopathology => EBRT

IORT as a boost with subsequent EBRT: whenever technically possible

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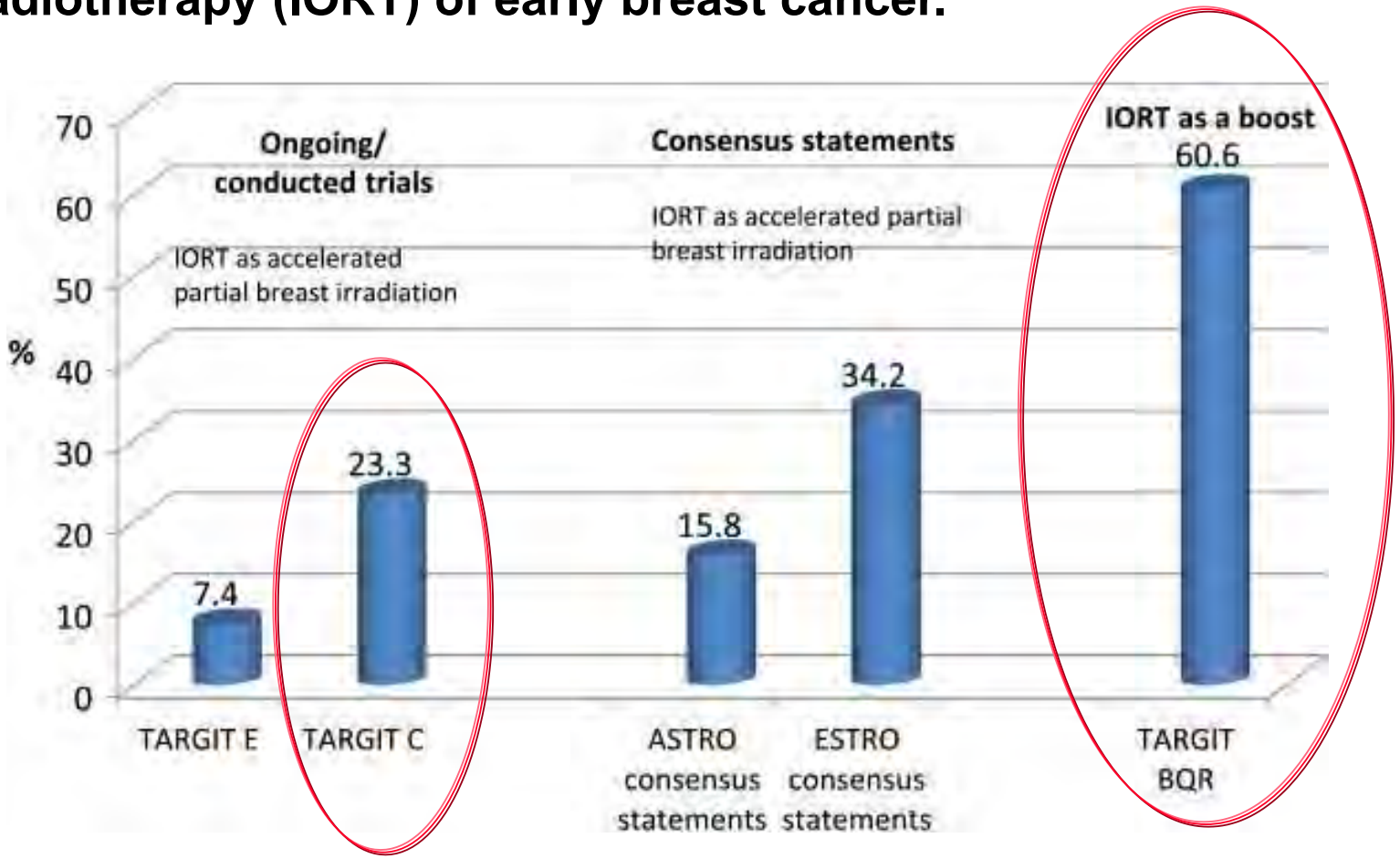
A cohort analysis to identify eligible patients for intraoperative radiotherapy (IORT) of early breast cancer.

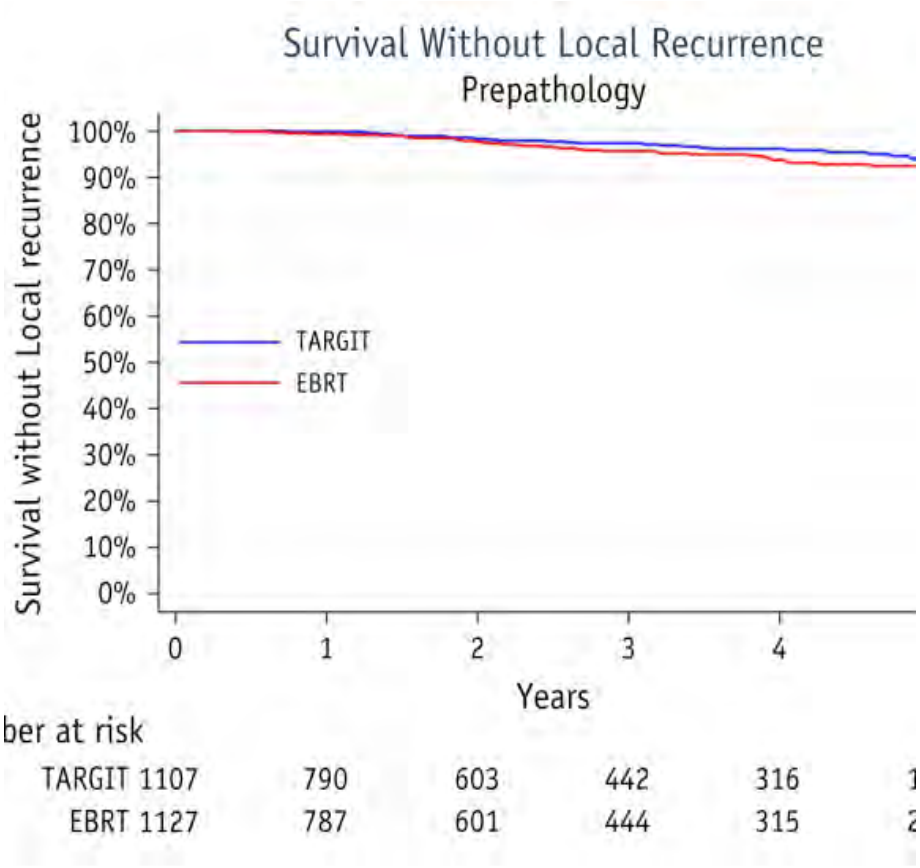


Eligible patients for IORT as accelerated partial breast irradiation and for IORT as a boost.
Consensus statements: ESTRO - European Society for Radiotherapy and Oncology and ASTRO - American Society for Radiation Oncology. *Trials:* TARGeted Intraoperative radioTherapy (TARGIT) E – elderly. TARGIT C – consolidation. TARGIT BQR – boost control registry. APBI – accelerated partial breast irradiation.

Sperk E et al., Radiat Oncol 2014 Jul 12;9:154. doi: 10.1186/1748-717X-9-154

IORT with low energy X-rays: Efficacy & Toxicity

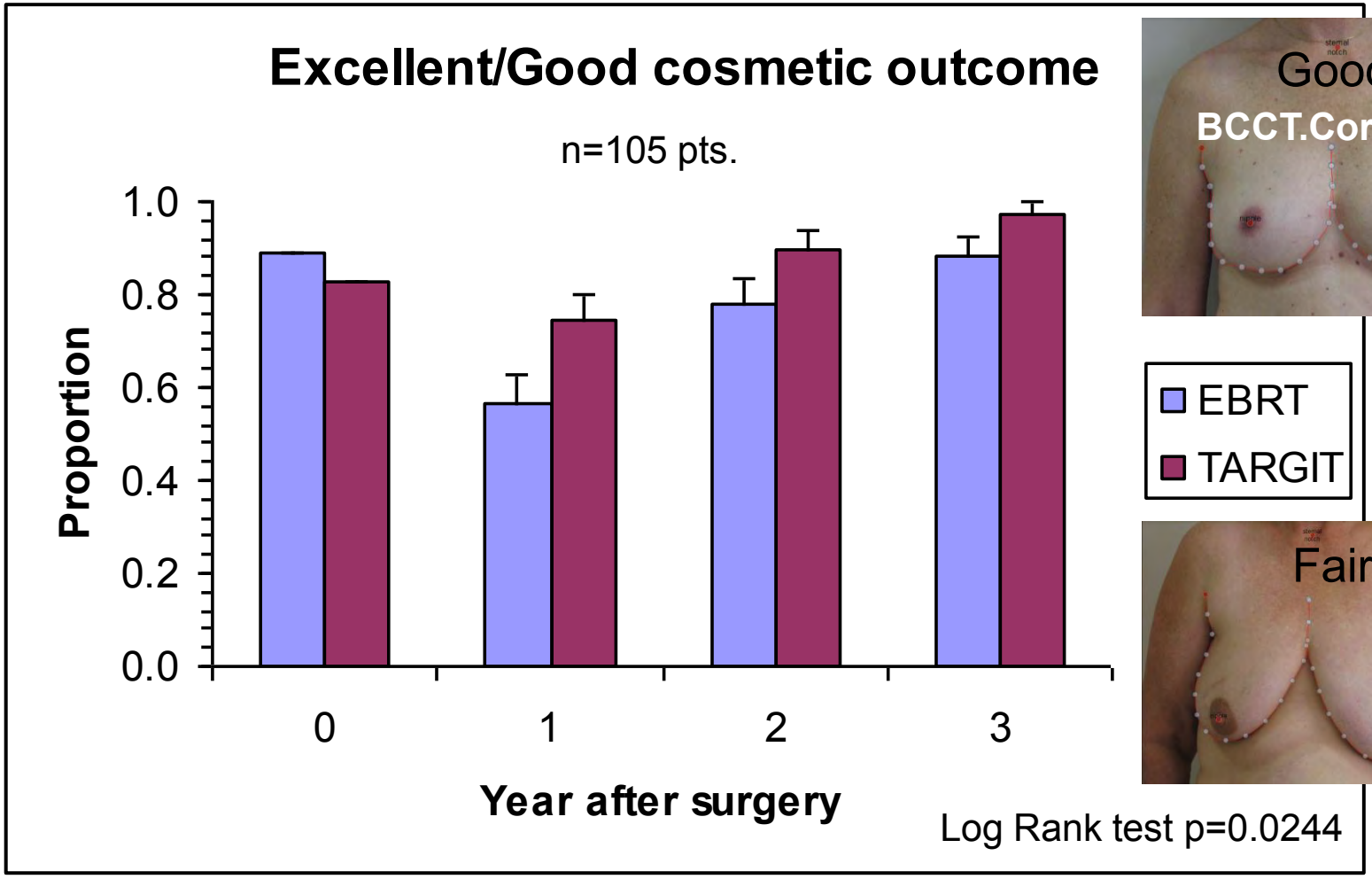
Pride, Prejudice, or Science: Attitudes Towards the Results of the TARGIT-A Trial of Targeted Intraoperative Radiation Therapy for Breast Cancer
Vaidya et al.
International Journal of Radiation Oncology, Biology, Physics 2015; 92(3): 491–497.



Complications 6 months after randomisation

Radiotherapy related complications	
Radiation Therapy Oncology Group (RTOG) Grade 3 or 4 radiotherapy toxicity	
4 (0.2%)	13 (0.8%)
p=0.029	

IORT & Cosmetic results

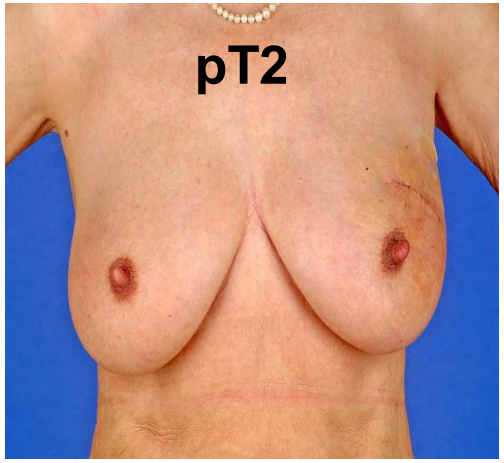


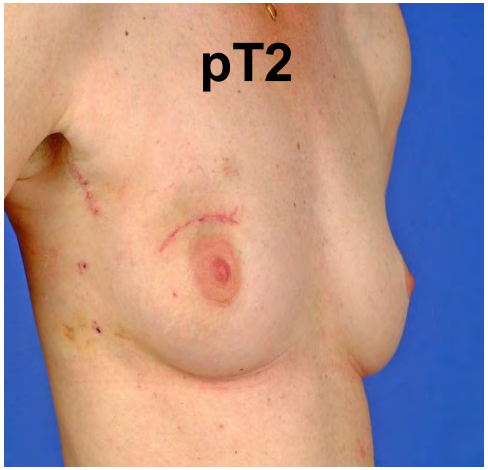
1st year: More patients randomised to IORT had excellent or good cosmetic outcome, compared with those randomised to EBRT (76.7% versus 60.3%)

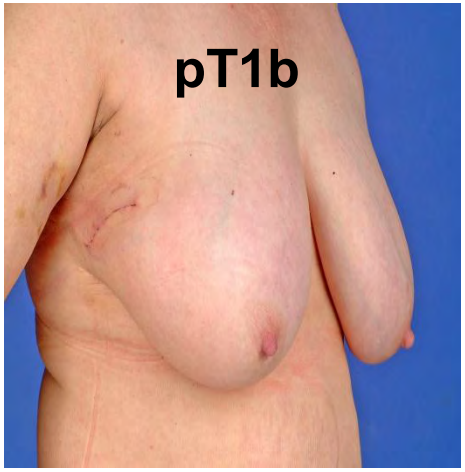
Keshtgar et al, Society of Surgical Oncology, 63rd Annual Cancer Symposium, 3-7 March 2010, St Louis, USA

Intrabeam IORT: Cosmetic Results

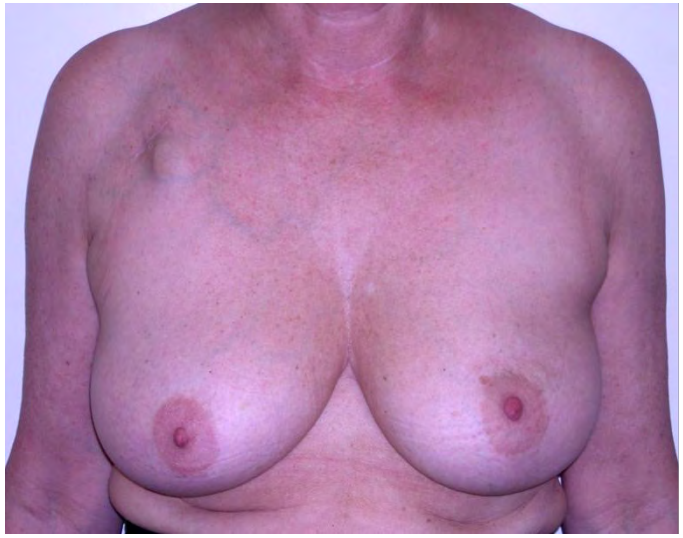
1 week postop.

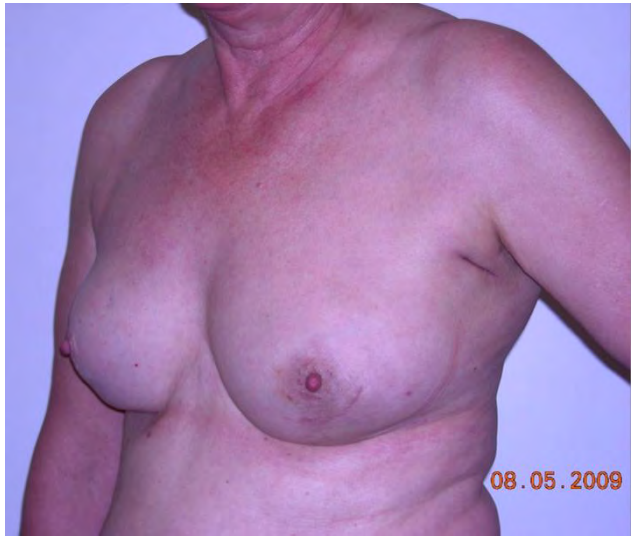






1 year postop.



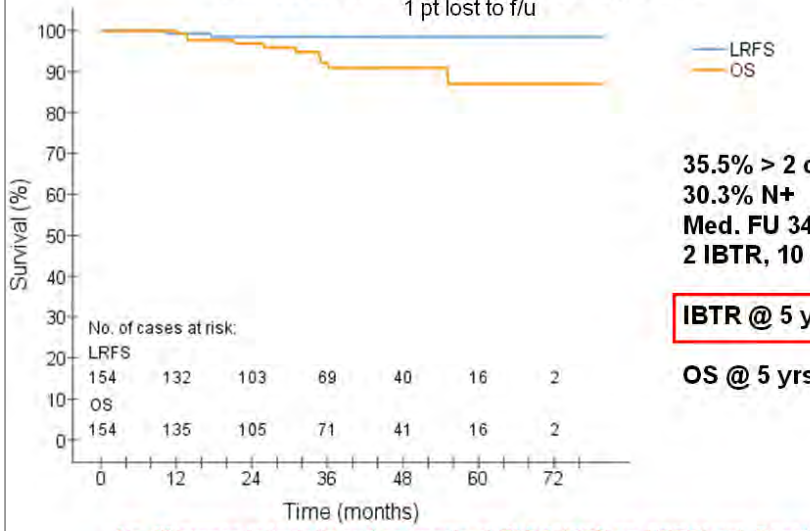


IORT Boost: Efficacy & Toxicity

IORT as a boost: Mannheim 2002 – 2007

n = 154: 20 Gy IORT + 46-50 Gy EBRT

1 pt lost to f/u



35.5% > 2 cm
30.3% N+
Med. FU 34 mon.
2 IBTR, 10 †, 8 FM

IBTR @ 5 yrs 1.5%

OS @ 5 yrs 87%

No difference in toxicity and cosmesis of EBRT+IORT vs. EBRT+ ext. Boost:
Tumor bed fibrosis after 3 years 5%, teleangiectasia or hyperpigmentation in 6%

Intraoperative radiotherapy (IORT) as a boost during breast conserving surgery (BCS) using low kV X-rays – the first five years of experience with a novel approach. Wenz F, Welzel G, Blank E, Hermann B, Steil V, Sütterlin M, Kraus-Tiefenbacher U; International Journal of Radiation Oncology, Biology, Physics 2010

5-year-local recurrence rate < 2%

IORT as a boost: Internat. Multicentre Study

LONG-TERM RESULTS OF TARGETED INTRAOPERATIVE RADIOTHERAPY (TARGIT) BOOST DURING BREAST-CONSERVING SURGERY

Median Follow up: 60.5 months

Table 2B. High-risk factors compared with EORTC and START-B trial

High-risk factors	EORTC boost	START-B trial	Targit n=299 boost
Young age	33% were ≤50	21% were <50	32% were ≤50
% >1 cm	75%	86%	78%
% Grade 3	Not available	23%	29%
% Node +	21%	23.6%	29%
Recurrence rate at 5 years	4.3%	2.8%	1.73%

Abbreviations: EORTC = european organization for research and treatment of cancer; START-B = standardisation of breast radiotherapy study.

Vaidya et al., Int. J. Radiation Oncology Biol. Phys., 2011, Vol. 81, No. 4, 1091–7

No difference in toxicity & cosmesis of EBRT+IORT vs. EBRT+ ext. Boost:
Tumor bed fibrosis after 3 years 5%, teleangiectasia or hyperpigmentation in 6%

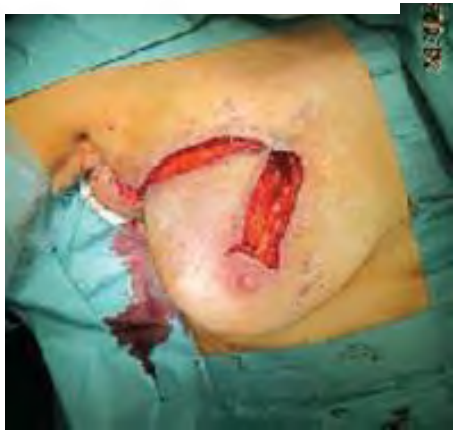
Intrabeam IORT & Oncoplastic Breast Surgery

Intraoperative Boost Radiotherapy during Targeted Oncoplastic Breast Surgery: Overview and Single Center Experiences

Wolfram Malter,[1] Verena Kirn,[1,2] Lisa Richters,[1,2] Claudius Fridrich,[1,2] Birgid Markiefka,[3] Rudolf Bongartz,[4] Robert Semrau,[4] Peter Mallmann,[2] and Stefan Kraemer[1]

[1] *Breast Center, University Hospital of Cologne, Kerpenerstrasse 34, 50931 Cologne, Germany*

Targeted oncoplastic breast surgery principles	
Glandular rotation	109
Dermoglandular rotation	29
Tumor-adapted reduction mammoplasty	11



„We describe our experiences with IORT boost (50 kV energy X-rays; 20Gy) in combination with targeted oncoplastic breast surgery in a routine clinical setting. Our experiences demonstrate the **applicability and reliability of combining IORT boost with targeted oncoplastic breast surgery** in breast-conserving therapy of early breast cancer.“

International Journal of Breast Cancer 2014

Intrabeam IORT & Neoadjuvant Chemotherapy

- increasing use of neoadjuvant CT

- very limited data for combination of nCT and IORT

- so far no evidence for increased toxicity

- intraoperative pathological assessment of margins difficult

- increased risk for re-excision => loss of irradiated tissue

Initial experience of intraoperative radiotherapy as tumour bed boost after neoadjuvant chemotherapy in breast cancer patients.
Spaich S, Tuschy B, Sperk E, Wenz F, Sütterlin M;
submitted

Indications of intraoperative radiotherapy with low energy x-rays in breast cancer?

Tumor Bed Boost (followed by WBRT): **++**

APBI (single dose TARGIT): **+** (in selected pts. with risk adaption)

BCT after EBRT: **((+))** very limited data !

WBRT: whole breast radiotherapy

APBI: accelerated partial breast irradiation

BCT: breast conserving therapy

EBRT: external breast radiotherapy

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Thank you!


10. INTRABEAM User Meeting
30.6.-1.7.2016, Mannheim
Further information: Tel. 0049-621-383-4493
Mannheim

Results of the TARGIT A-trial in context

5-year-Local Recurrence-rates:

TARGIT A Prepathology Stratum (2,298 pts): IORT 2.1% vs. EBRT 1.1%

NSABP B32 (5,611 pts): SNB 0.7% vs. SNB+ALND 0.4%*

ACOSOG Z0011 (n=891): Ø ALND 1.3% vs. ALND 0.7%* (after pos. SNB)

AMAROS (n=1,425): ax. Rad. 1.03% vs. ALND 0.54%* (after pos. SNB)

* ax. recurrence

Intrabeam Applicator Selection & Fibrosis

Elena Sperk, Xuerui Li, Frank Schneider, Sven Clausen, Christel Weiß, Frederik Wenz

Background:
- Fibrosis is the most frequent adverse event after IORT Boost in combination with EBRT
- Interval >5 weeks between IORT and EBRT reduces risk of higher grade fibrosis

=> Evaluation of dosimetric risk factors for fibrosis using a simulated irradiation plan

IORT cases between **2002 – 2008, Follow up ≥ 3 Jahre**

Collectives

•Group A: Cases with fibrosis ° II-III, n=14

•Group B: Cases without fibrosis , n=28

- Significantly increased rate of fibrosis ° II-III due to larger applicatiors and 50% dose volume
- Multivariate analysis: Applicator size is an independent risk factor for fibrosis ° II-III

→ **For each cm of applicator diameter the risks of fibrosis increases by factor 3.85**

The applicator size is an independent risk factor for the development of clinically relevant fibrosis after IORT boost

Omission of planned Intrabeam-IORT

UMM: 2002 until 2/2009

57 cases (19%) with omission of planned IORT (∑ 299)
(7 Targit cases)

Most frequent reasons (80% of all reasons)

- Insufficient distance from tumor to skin
- Large wound cavity
- Tumor size

IORT for patients where EBRT is not an option

IORT in breast cancer (relapse) after EBRT

BMC Cancer 2007, 7:178

BioMed Central

Research article

Open Access

Intraoperative radiotherapy (IORT) is an option for patients with localized breast recurrences after previous external-beam radiotherapy

Uta Kraus-Tiefenbacher[1], Lelia Bauer[2], Antonella Scheda[1], Carola Schoeber[3], Joerg Schaefer[1], Volker Steil[1] and Frederik Wenz*[1]

- 15 pts. with local relapse., 2 pts. after EBRT due to Hodgkin's disease
- Intrabeam IORT with a single dose of 14.7-20 Gy during BCS
- No LR after 26 months med. FU, 14/17 pts. disease free

[after med. FU of 40 months (12 pts. >36 months.): 1 IBTR with 21 months, 3 Met.]

- Low acute toxicity, no grade III/IV°
- Cosmetic results: 7 excellent, 7 good, 3 acceptable

Published case numer extremely limited

So far no toxicity > grade II

So far only few LR

TARGIT in Special Circumstances

UCL

Reason for IORT	N	Age	FUP (IQR) months	LRs
Previous EBRT - Previous Breast Cancer - Hodgkin's Disease	22	51 (47-57)	42 (35-44)	0
Collagen Vascular Disease	5	63 (58-64)	23 (23-24)	0
Clinical reasons including Co-morbidities	23	75 (64-84)	31 (19-48)	1
Compelling personal reasons	26	66 (53-76)	37 (24-56)	1
Total	***81***	***66 (56-75)***	***27 (24-56)***	***2***

Intrabeam IORT: Imaging during Follow up

High incidence (up to 60%) **of seroma and oil cysts**

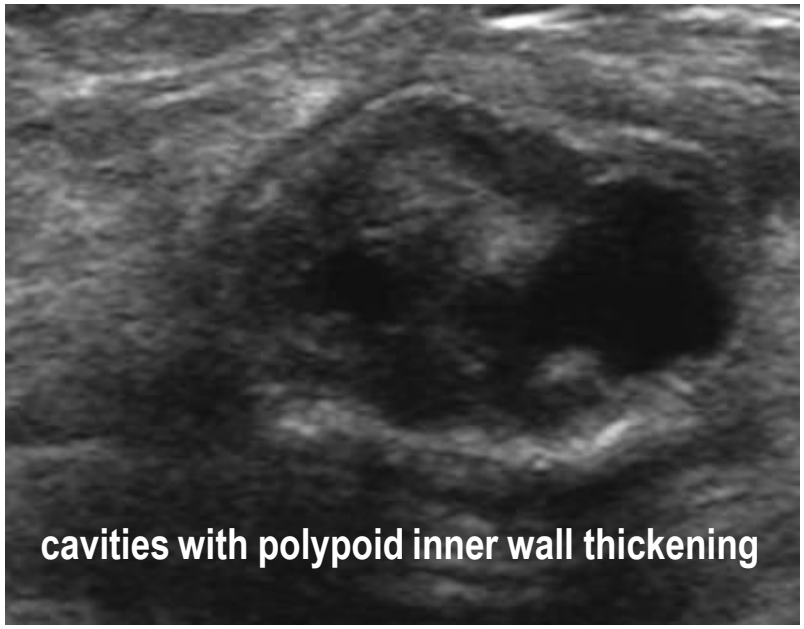
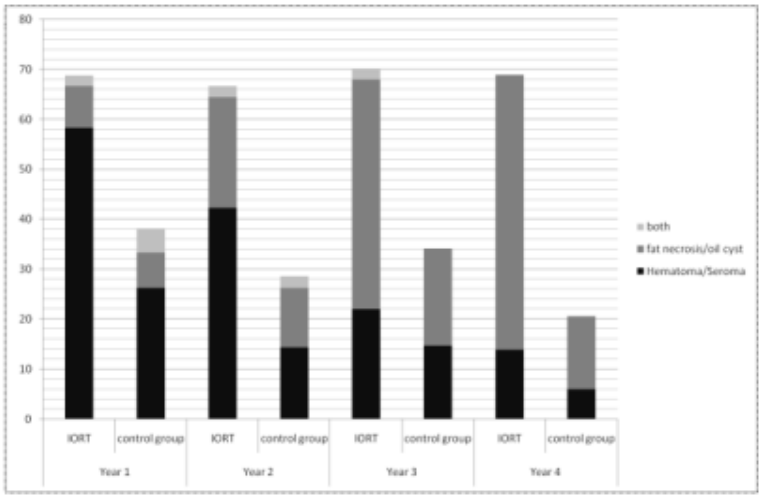
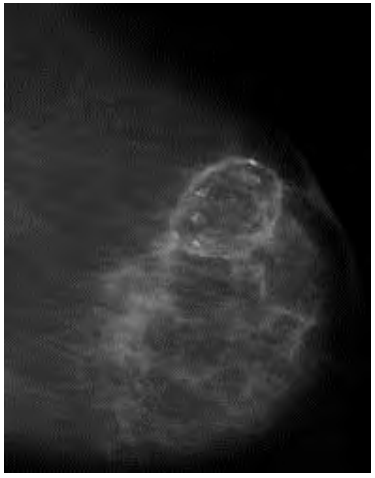
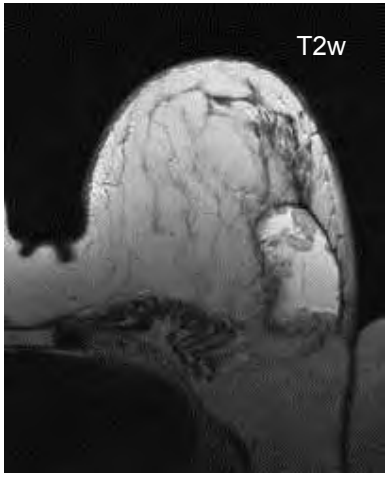


Figure 3: Process of circumscribed sonographic findings over 4 years after treatment, IORT vs. control group



Number of patients IORT/Control: Year 1: 48/42, Year 2: 45/42, Year 3: 50/41, Year 4: 29/34





Long-term follow-up-findings in mammography and ultrasound after intraoperative radiotherapy (IORT) for breast cancer. Breast 2009;18(5):327-34; Ruch et al.

Postoperative seroma formation after intraoperative radiotherapy using low-kilovoltage x-rays given during breast-conserving surgery.
IJROBP 2010; 77: 1140-1145; Kraus-Tiefenbacher et al.

Do structural changes at the tumor bed after intraoperative radiotherapy (IORT) of breast cancer complicate the evaluation of follow-up mammograms?
Eur J Radiol 2012; 81 (3): e255-259; Wasser et al.

First description of MR mammographic findings in the tumor bed after intraoperative radiotherapy (IORT) of breast cancer. Clin Imaging 2012; 36 (3): 176-184; Wasser et al.

Are mammographic follow-up findings indeed more pronounced after intraoperative radiotherapy for breast cancer? Subgroup analysis from a randomized trial (TARGIT A).
The Breast Journal (submitted) Engel et al.

Intrabeam IORT: Imaging during Follow up

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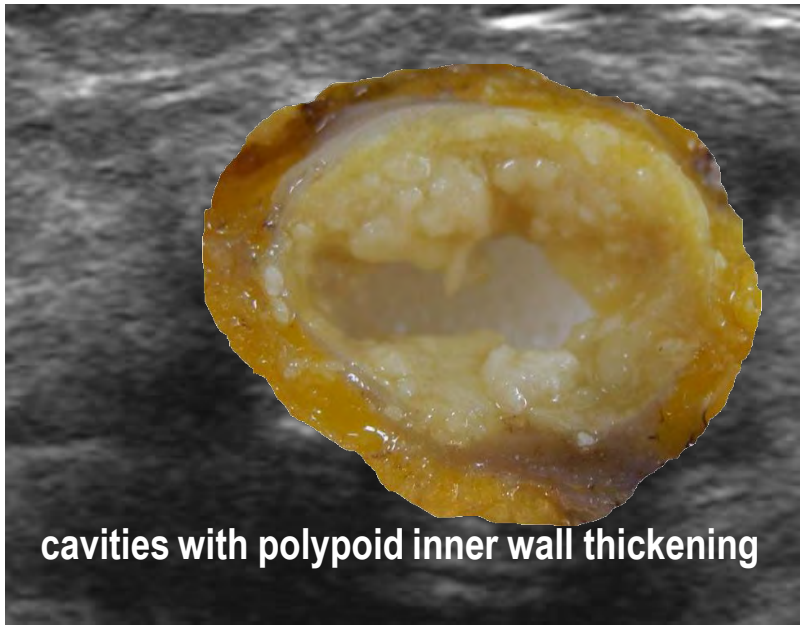

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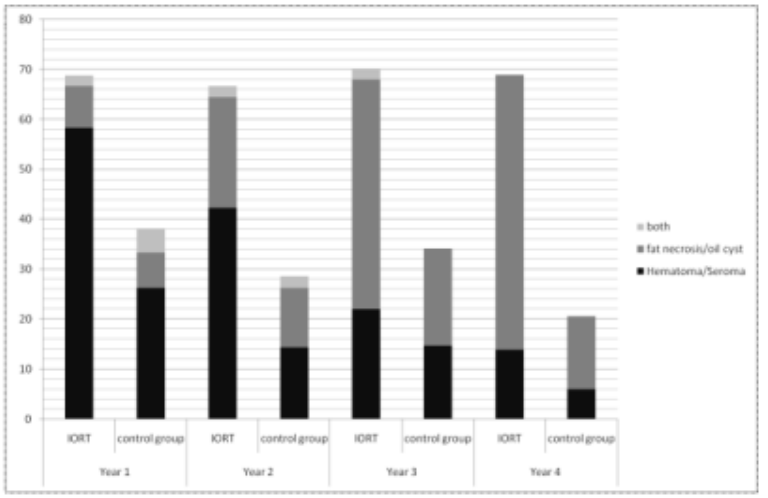

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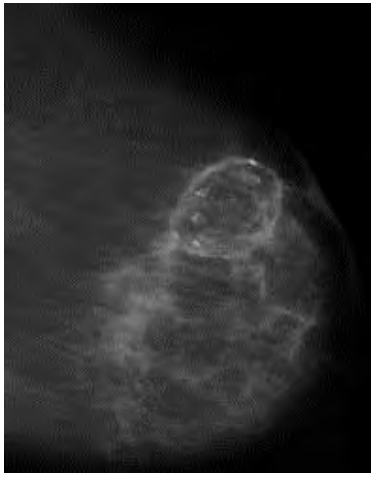

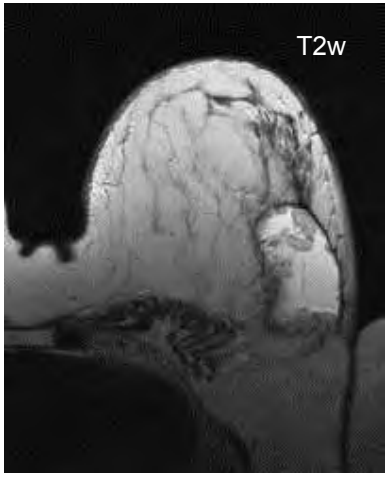

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EBM Evidence-Based Medicine

9th International ISIORT Conference

June 24/25th 2016
Novara, Italy

Evidence Based Medicine and IORT: BREAST CANCER

Antonella Ciabattoni MD

U.O.C. Radioterapia

Ospedale S. Filippo Neri, Roma

SISTEMA SANITARIO REGIONALE ASL ROMA 1

REGIONE LAZIO

Thanks to A. Spera MD for literature search

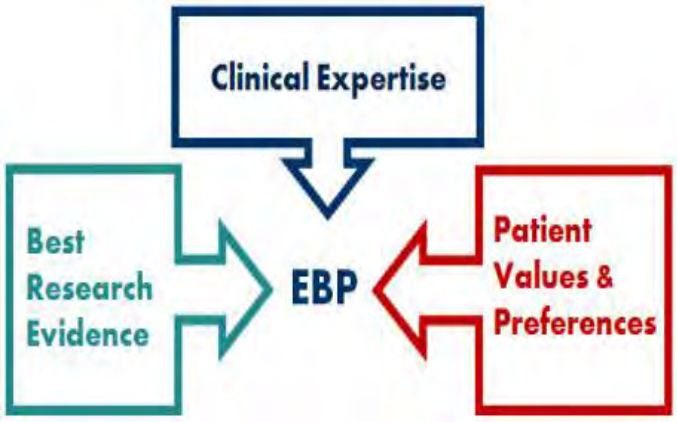
Time-poor clinician suffering from information overload

Evidence-Based Medicine

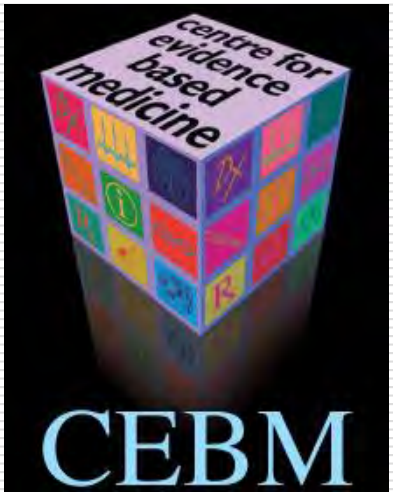
EBM is ...”the conscientious, explicit and judicious use of current best evidence in making decisions about the care of an individual patient.

It means integrating individual clinical expertise with the best available external clinical evidence from systematic research”

(Sackett, D. BMJ 1996;312:71-72)



EBM Evidence-Based Medicine



9th International ISIORT Conference
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Novara, Italy

www.cebm.net

UNIVERSITY OF OXFORD

Evidence-Based Medicine

The Evidence Pyramid is a guideline to the hierarchy of study design

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening Intervention
I [4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6]	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6]	All or none	All or none	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial[9] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study[10] ▪ Interrupted time series without a parallel control group	Diagnostic case-control study[6]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Assessment of study quality
Grades of Recommendations

1. The evidence base, in terms of the number of studies, **level of evidence** and quality of studies (risk of bias).
2. The consistency of the study results.
3. The potential clinical impact of the proposed recommendation.
4. The generalisability of the body of evidence to the target population for the guideline.
5. The applicability of the body of evidence to the healthcare context.

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

What is the purpose of EBM in IORT?

- Patient care
- Public health
- Research

➢ *Improving the quality of patients' lives…*

Evidence Based Medicine and IORT: BREAST CANCER

Clinical question

- Population — Breast cancer pts
- Intervention — IORT
- Comparator — EBRT
- Outcome/s — **

The PICO method

**

- Is the rate of local cancer recurrence, disease-free survival rates and/or overall survival rates the same or lower for IORT treated patients compared to those treated by standard breast conservation therapy? LR
- Are there the same number or fewer perioperative complications, short-term and long-term postoperative complications associated with the IORT patients compared to those treated by standard breast conservation therapy? TOX
- Is cosmesis (both surgeon and patient-rated cosmesis) the same or better with the IORT patients compared to those treated by standard breast conservation thera COSMESIS

Finding Evidence-based Answers

- PubMed Clinical Queries (www.pubmed.gov)
- Trip Database (http://www.tripdatabase.com/)
- Database of Abstracts of Reviews of Effectiveness (http://www.crd.york.ac.uk/crdweb/)
- DynaMed (http://www.dynamicmedical.com/)
  - **Subscription required.*
- Essential Evidence Plus (http://www.essentialevidenceplus.com/)
  - **Subscription required.*
- Cochrane Library (http://www.cochrane.org/)
  - **Subscription for full access, abstracts free.*
- FPIN (http://www.fpin.org/)
  - **Subscription required.*
- Clinical Evidence (www.clinicalevidence.com/)
  - **Subscription required.*

Intraoperative radiotherapy/breast: 548 total

Year

2016: 1 review (elderly)
4 clinical studies

2015: 3 systematic reviews
13 clinical studies

2014: 5 systematic reviews
30 clinical studies

2013: 4 systematic reviews
27 clinical studies

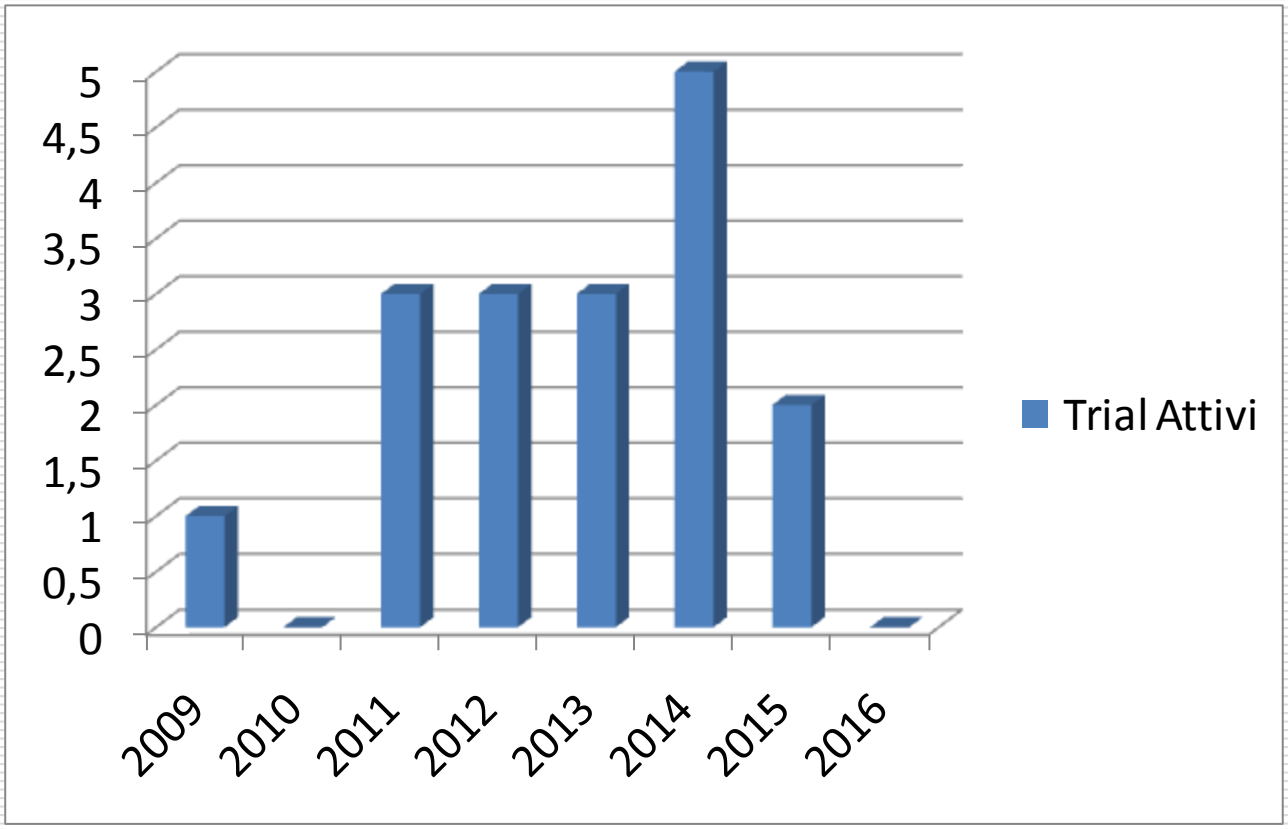
MeSH

MeSH (Medical Subject Headings) is the NLM controlled vocabulary thesaurus used for indexing articles for PubMed.

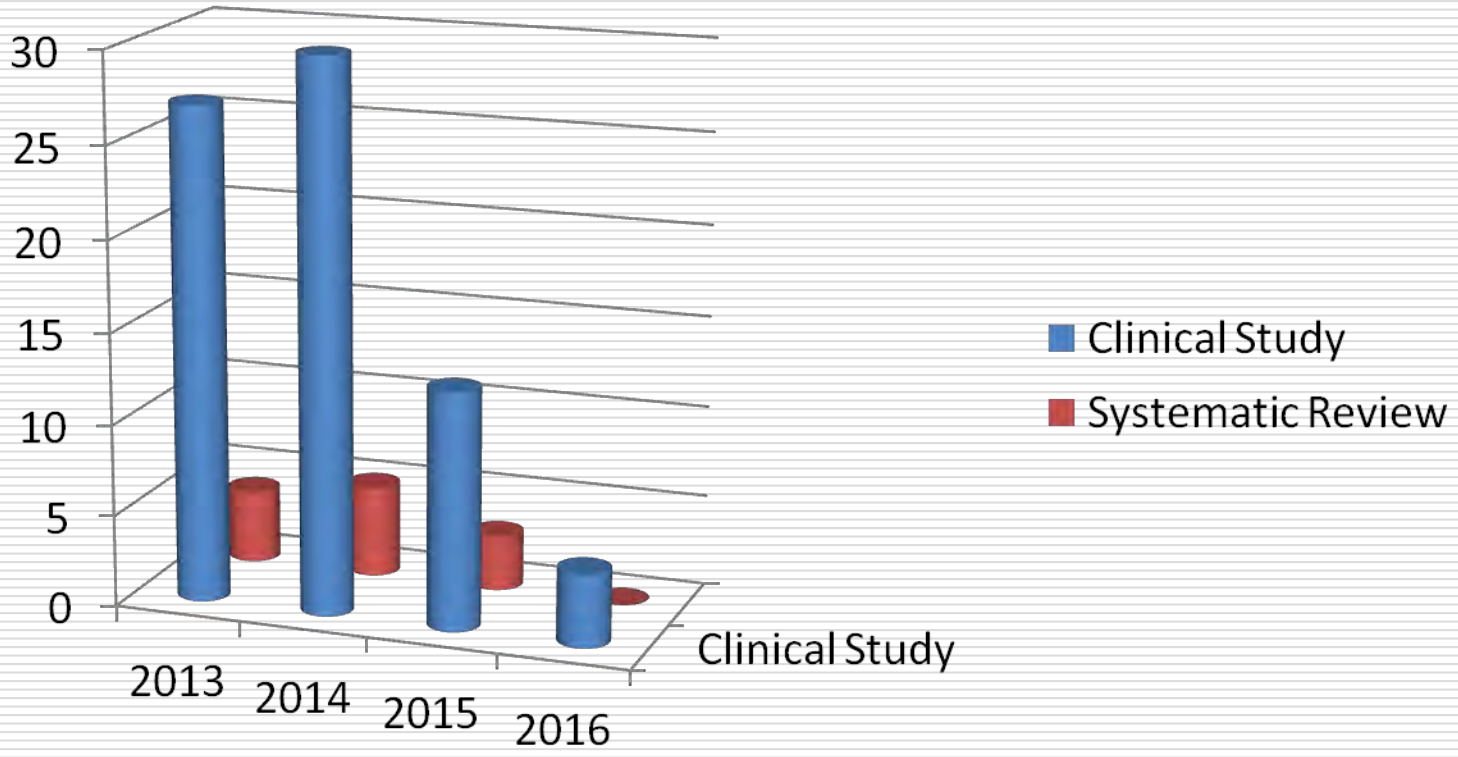
Intraoperative radiotherapy/breast: 656 total

Year	
2016:	4 papers, all primary research
2015:	3 systematic reviews
	2 evidence based synopses
	9 primary research
	29 clinical trials
2014:	2 systematic reviews
	2 evidence based synopses
	16 primary research
	60 clinical trials

ONGOING TRIALS



TYPES OF PUBLICATIONS



Evidence Based Medicine and IORT: BREAST CANCER

Meta-Analysis

Randomized Controlled Trial

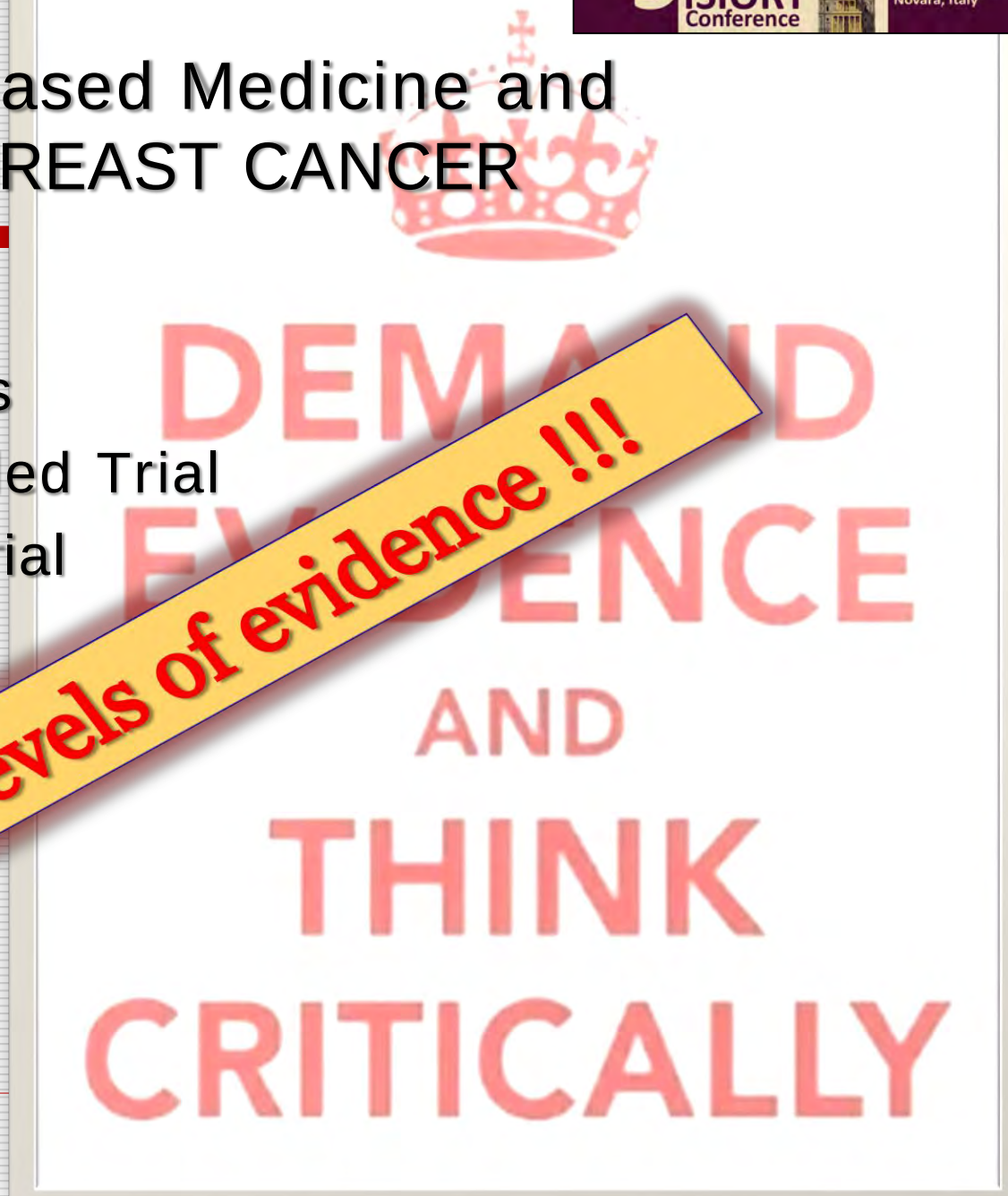
Uncontrolled Trial

Case Series

Anecdote

More s… …tic obse… …n ▶ better evidence

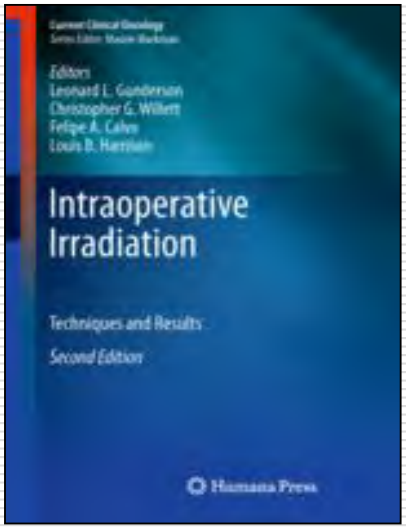
but...no levels of evidence !!!



Evidence Based Medicine and IORT: BREAST CANCER

The certainties…

IORT as strategy for improvement of local control



"… The final goal of IORT being enhanced locoregional tumor control……"

Gunderson, L.L., Willett, C.G., Calvo, F.A., Harrison, L.B. (Eds.) 1999 , 2nd ed. 2011

Evidence Based Medicine and IORT: BREAST CANCER

The "old good documents"...

A Systematic Review of Intraoperative Radiotherapy in Early Stage Breast Cancer

ASERNIP/S

Australian Safety and Efficacy Register of New Interventional Procedures-Surgical

ASERNIP-S REPORT NO. 27

October 2002

Objective

The objective of this review was to assess the safety and efficacy of intraoperative radiotherapy (IORT) in comparison with the current standard treatment for early breast cancer of breast conserving surgery with postoperative radiotherapy (BCT).

3.4 Literature Search Strategies

- Ovid PreMEDLINE and MEDLINE from 1984 to January Week 4, 2002
- Current Contents from 1993 to Week 9, 2002
- Cochrane Library's Cochrane Controlled Trials Register and Cochrane Database of Systematic Reviews, DARE and NHS-EED up to March 11, 2002
- EMBASE from 1988 to Week 10, 2002
- UK National Research Register
- NIH ClinicalTrials.Gov Database
- PubMed Database
- HTA Assessment Database (NHS R&D HTA website)

Table 3: Total Numbers of Articles Retrieved from Database Searches

Procedure	# Retrieved	# Initially Included	# Studies Finally Included
New IORT Procedure	230 papers	25 papers	8 studies (9 papers)
Comparator BCT Procedure	3393 papers	138 papers	8 studies (16 papers)

Study	Yr	Level of Evidence	N	Stage or Histology (n)	IORT/RT Delivered	IORT Device

Table 6 –Level of Evidence Distribution -IORT Studies

Level of Evidence	Number of IORT Studies
I	0
II	1
III-1	0
III-2	1
III-3	0
IV	6

Conclusion

The evidence currently available on the use of IORT in early breast cancer is poor. Therefore, both the relative safety and efficacy of the IORT in comparison with BCT cannot be determined. In view of this, the ASERNIP-S review group has recommended that IORT in early breast cancer should only be used in Australasia under the auspices of a randomised controlled trial. Further national and international research should focus on several issues that also require more clarification. The subgroups of early breast cancer patients most suited to IORT should be clearly identified and the differing roles that IORT may play in both "high" and "low" risk tumours needs further exploration.

Evidence Based Medicine and IORT: BREAST CANCER

The "old good documents"...

Associazione Italiana di Radioterapia Oncologica
Gruppo di Studio
Sulla Radioterapia Intraoperatoria (IORT)

INDICAZIONI ALL'USO DELLA IORT

SECONDO

LA MEDICINA BASATA SULLE EVIDENZE

Report 04/01 (approvato dal C. D. A.I.R.O. in data 03/12/04)

ISTITUTO SUPERIORE DI SANITÀ

Guidelines for quality assurance in intra-operative radiation therapy
English version

Edited by Antonella Rosi and Vincenza Viti
Laboratorio di Fisica

Rapporti ISTISAN
03/1 EN

EBM and IORT: Materials and Methods

In 2005 a structured questionnaire was mailed to all the Italian Radiation Oncology centres known to perform (or being in the process of implementing) IORT and it was updated at the end of 2007. Indication of treatment modality, use of dedicated or multi-purpose facilities, treatment sites, participation in clinical studies, as well as adherence to EBM as defined in the national guidelines were acquired

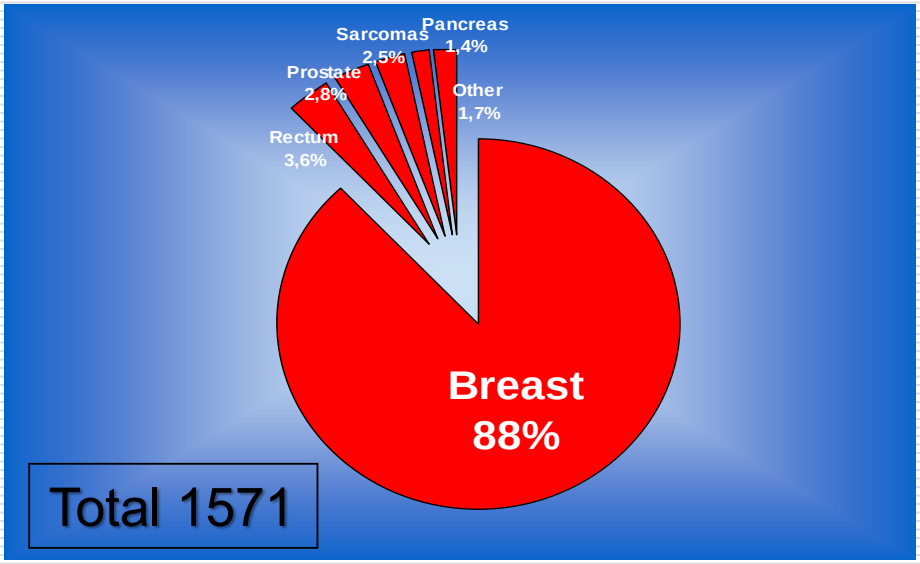
EBM and IORT

The analysis of the data received provided the consent of the Centers on 4 sites of disease in which IORT was considered an evidence-based treatment:

- locally advanced rectal cancer
- recurrence of rectal cancer
- soft tissue sarcomas
- pancreatic neoplasms

NO BREAST CANCERS !!!

EBM	50%
Clinical Trials	45%
Individual	5%



Radiotherapy and Oncology 104 (2012) 139–142

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

2012

Special commentary

Has partial breast irradiation by IORT or brachytherapy been prematurely introduced into the clinic?

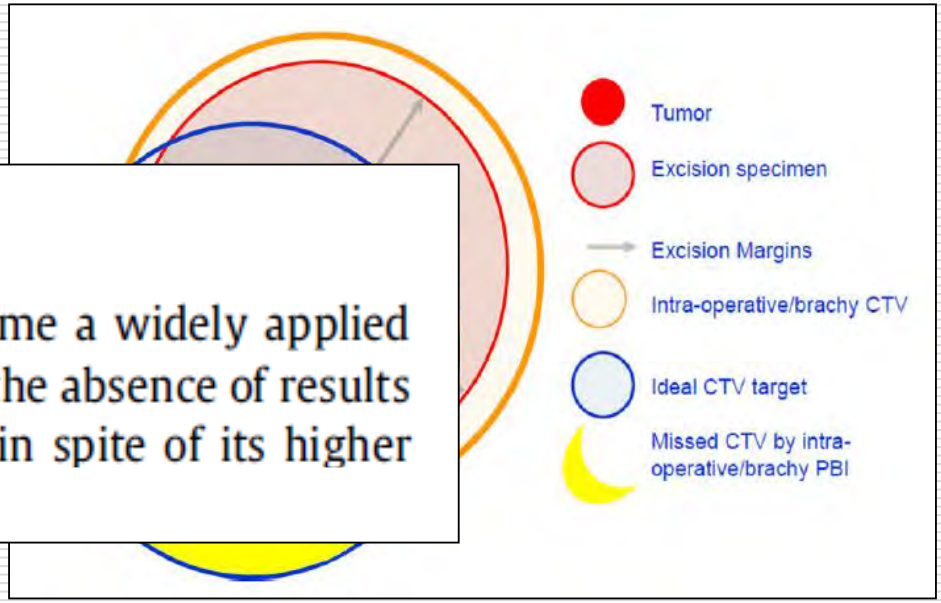
Harry Bartelink [a,*], Celine Bourgier [b], Paula Elkhuizen [a]

[a] Netherlands Cancer Institute, The Netherlands; [b] Institut Gustave Roussy, France

Evidence based medicine – local control after APBI?

- ✓ No publication of large randomized clinical trials with sufficient follow up is available
- ✓ Some syudies have imited numbers of patients per treatment arm and are underpowered
- ✓ One of the main limitations of brachy PBI or IORT is the absence of pathology information during the procedures

Evidence based medicine – APBI target volumes?



Conclusions

PBI with brachytherapy or IORT has become a widely applied treatment also outside clinical trials, even in the absence of results from the ongoing major phase III trials and in spite of its higher cost.

EBM Evidence-Based Medicine

Evidence Based Medicine and IORT: BREAST CANCER

Evidence Based Medicine and IORT: BREAST CANCER

Breast Care

Review Article · Übersichtsarbeit

Breast Care 2013;8:102–109
DOI: 10.1159/000351193

Published online

St. Gallen 2013: Brief Preliminary Sum… of the Consensus Discussion

Nadia Harbeck[a] Christoph Thomssen[b] Michae…

[a]Breast Center, Department of Obstetrics and Gynecology…
[b]Department of Gynecology, Martin Luther Universit…
[c]Department of Surgery and Comprehensive C…

…nes"…

…py

Whereas the evidence for brachytherapy is more solid, there is still little information regarding the effectiveness of PBI with EBRT or IORT, which should preferably be investigated within trials.
The Panel could not reach a majority view regarding the current acceptability of the various techniques for PBI as definitive treatment.

Par… without… was not endor… was considered an … tumor pathology (49% YES, 22… vote on intra-operative radiotherapy…

DEGRO practical guidelines: radiotherapy of breast cancer I

Radiotherapy following breast conserving therapy for invasive breast cancer

F. Sedlmayer[1] · M.-L. Sautter-Bihl[2] · W. Budach[3] · J. Dunst[4] · G. Fastner[1] · P. Feyer[5] · R. Fietkau[6] · W. Haase[7] · W. Harms[8] · R. Souchon[9] · F. Wenz[10] · R. Sauer[11]
Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO)

The "Guidelines"…

Strahlentherapie und Onkologie 10 · 2013

Intraoperative Radiotherapy: Summary

The German guidelines still do not recommend APBI outside clinical studies. Radiotherapy restricted to parts of the affected breast (PBI) as sole radiation treatment including sole intraoperative radiotherapy (IORT) represents no treatment standard.

The "Guidelines"...

2013

I primi risultati degli studi prospettici (36,37) mostrano che il trattamento con IORT in dose unica, in pazienti selezionate a basso rischio di recidiva locale, è sicuro e ben tollerato, anche se il follow-up è ancora breve. Sebbene tali risultati sembrino promettenti, essi confermano l'opportunità di procedere al trattamento con IORT solo dopo appropriata e corretta selezione delle pazienti che tenga conto di tutti i criteri di rischio ASTRO ed ESTRO (14,15), di cui è possibile disporre prima dell'intervento chirurgico.

The "Guidelines"...

Taccuino IORT Mammella

Istruzioni operative

2014

Coordinatori: Dott. L. Tomio e Dott. M Guenzi

Estensori:

Dott. A. Venturini (UO Radioterapia Ospedale Infermi - AUSL Rimini);

Dott. A. Baldissera (UO Radioterapia Ospedale Bellaria - Bologna);

Dott. A Ciabattoni (UO Radioterapia oncologica, Osp. San Filippo Neri-Roma);

Dott. M. Guenzi (UOC Oncologia radioterapica - Azienda Osp. Univ. IRCCS San Martino-IST-Genova)

A. Fozza (SCDU Radioterapia, A.O. Città della Salute e della Scienza, Torino);

Dott. S. Fissi (Breast Unit IRCCS Fondazione S. Maugeri - Pavia);

Dott. L. Tomio (UO Radioterapia oncologica - Osp. S. Chiara - Trento);

Dott. M. Roncadin (SOC Oncologia radioterapica CRO - Aviano);

Dott. S. Massarut (SOC Oncologia radioterapica CRO - Aviano);

Dott. F. Cavagnetto (Fisica Medica - Azienda Osp. Univ. IRCCS san Martino-IST-Genova);

Dott. G. Sartor (Fisica medica CRO - Aviano)

Indicazioni

IORT esclusiva, anche al di fuori di studi clinici.

La Radioterapia intraoperatoria (IORT) è una modalita' di **irradiazione parziale** e si ritiene indicata come **trattamento esclusivo** in un sottogruppo di Pazienti operate conservativamente e considerate **a basso rischio di recidiva locale**.

IORT con elettroni con finalità di Boost anticipato.

Le **indicazioni**, al di fuori di studi clinici, sono le **stesse della IORT esclusiva** per quanto riguarda le caratteristiche di T (dimensioni, unifocalità, ecc.) mentre le Pazienti possono avere **un'età ≤ 50 anni e stato premenopausale.**

Patient Selection for APBI

Table 5 Patient Selection Criteria for the Use of APBI

Organization	Patient Age (y)	Tumor Size (cm)	Histology	Lymph Node Status	Margin Status
ABS	≥50	≤3	Infiltrating ductal carcinoma	Negative (by sentinel lymph node or axillary dissection)	Negative (at inked margin)
American Society of Breast Surgeons	≥45	≤2	Invasive ductal carcinoma or ductal carcinoma in situ	Negative (by sentinel lymph node or axillary dissection)	Negative (>2 mm)
NSABP B-39/RTOG- 0413	≥18	≤3	Invasive ductal carcinoma and ductal carcinoma in situ	Allows for 0-3 nodes involved (with negative sentinel lymph node or >6 nodes sampled)	Negative (at inked margin)
ASTRO ("suitable" patients outside of a clinical trial)	≥60	≤2	Invasive ductal carcinoma or other favorable subtypes (mucinous, tubular, and colloid)	Negative (by sentinel lymph node or axillary dissection)	Negative (>2 mm)
GEC-ESTRO ("low risk" patients outside of a clinical trial)	≥50	≤3	Invasive ductal carcinoma or other favorable subtypes (mucinous, tubular, and colloid)	Negative (by sentinel lymph node or axillary dissection)	Negative (>2 mm)

Abbreviations: ABS, American Brachytherapy Society; ASBS, American Society of Breast Surgeons; NSABP, National Surgical Adjuvant Breast and Bowel Project; ASTRO, American Society for Radiation Oncology; GEC-ESTRO, Groupe Européen de Curiethérapie—European Society for Therapeutic Radiology and Oncology.

The "Guidelines"...

Table 2 American Society for Radiation Oncology and GEC-ESTRO recommendations on patient selection criteria for Accelerated Partial Breast Irradiation

Factor	ASTRO Suitable	GEC-ESTRO Low-risk	ASTRO Cautionary	GEC-ESTRO Intermediate-risk	ASTRO Unsuitable	GEC-ESTRO High-risk
Patient factors						
Age (yr)	≥ 60	> 50	50-59	40-50	< 50	< 40
BRCA1/2 mutation	Not present	Not defined	Not present	Not defined	Present	Not defined
Pathologic factors						
Tumor size (cm)	≤ 2	≤ 3	2.1-3.0	≤ 3	> 3	> 3
T stage	T1	T1-2	T0 or T2	T1-2	T3-4	T2 (> 3 cm), T3-4
Histology	IDC or other favorable subtypes	IDC, mucinous, tubular, medullary and colloid carcinoma	ILC allowed	ILC allowed	Any	Any
Grade	Any	Any	Any	Any	Any	Any
Pure DCIS	Not allowed	Not allowed	≤ 3 cm	Allowed	> 3 cm	Any
EIC	Not allowed	Not allowed	≤ 3 cm	Not allowed	> 3 cm	Allowed
Associated LCIS	Allowed	Allowed	Allowed	Allowed	Allowed	Allowed
Multicentricity	Unicentric	Unicentric	Unicentric	Unicentric	Multicentric	Multicentric
Multifocality	Clinically unifocal ≤ 2 cm	Unifocal	Clinically unifocal 2.1-3 cm	Multifocal (limited within 2 cm of the index lesion)	Clinically multifocal, > 3 cm	Multifocal (> 2 cm from the index lesion)
LVSI	No	Not allowed	Limited/focal	Not allowed	Extensive	Allowed
ER status	Positive	Any	Negative	Any	Any	Any
Surgical margins	≥ 2 mm	≥ 2 mm	< 2 mm	< 2 mm	Positive	Positive
Nodal factors						
N stage	pN0 (i-, i+)	pN0	pN0 (i-, i+)	pN1mi, pN1a	≥ pN1	pNx, ≥ pN2a
Nodal surgery	SN biopsy or ALND				None performed	
Neoadjuvant therapy	Not allowed	Not allowed	Not allowed	Not allowed	If used	If used

DCIS: Ductal carcinoma in situ; EIC: Extensive intraductal component; LCIS: Lobular carcinoma *in situ*; ASTRO: American Society for Radiation Oncology.

EBM Evidence-Based Medicine

BreastCare

Review Article

Breast Care 2015;10:247–252
DOI: 10.1159/000437194

Published online: July 15, 2015

2015

Accelerated Partial Breast Irradiation in Clinical Practice

Frederik Wenz[a] Felix Sedlmayer[b] Carsten Herskind[a] Grit Welzel[a] Elena Sperk[a]
Christian Neumaier[a] Benjamin Gauter-Fleckenstein[a] Jayant S. Vaidya[c] Marc Sütterlin[d]

Results from Clinical Studies

- HUNGARIAN "multicatheter"
- TARGIT A
- ELIOT
- TARGIT E
- TARGIT C

Ongoing Clinical Studies with APBI as Single Modality

- NSABP B-39/ RTOG 0413
- GEC-ESTRO

Ongoing Clinical Studies on APBI Combined with External-Beam WBRT

- TARGIT B
- HIOB

BreastCare

Review Article

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Conclusion and Future Directions

STRONG LEVEL OF EVIDENCE

APBI has been [illegible] investigation for more than 15 years. The [illegible] the underlying biology, optimal technical [illegible] ent selection criteria, and imaging changes [illegible] up has increased enormously. After the completion [illegible] phase III trials with long-term follow-up [39], APBI is [illegible] currently increasingly used either in phase IV studies, in registries, stud[illegible] 41]. One may expect that 15–25% of the patients undergoing BCS may qualify for APBI alone, and up to 60% for APBI as a boost followed by WBRT [9].

A cohort analysis to identify eligible patients for intraoperative radiotherapy (IORT) of early breast cancer

Sperk *et al.*

2014

Cohort, all patients
N = 1505

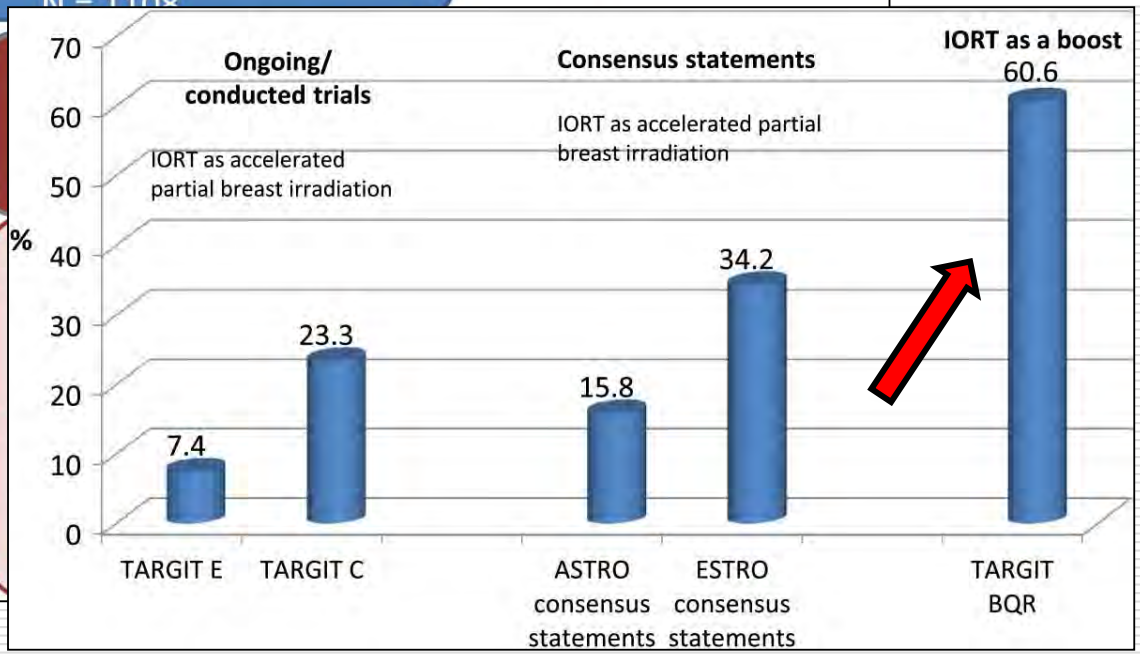
Complete dataset
(age, tumor size, nodal involvement, histology, hormone receptor status, metastasis)
N = 1108

ESTRO „suitable“
N = 379 (34.2%)

- > 50 years
- Invasive ductal carcinoma or other favourable histology
- T1-2 (</= 3cm)
- Negative lymph nodes
- Any hormone receptor status
- No metastasis

ASTRO „suitable“
N = 175 (15.8%)

- >/= 60 years
- Invasive ductal carcinoma or other favourable histology
- T1 (</= 2cm)
- Negative lymph nodes
- Positive estrogen hormone receptor status
- No metastasis



QUERY *"IORT/breast cancer"* if you set the filter for relevance

Medicine
SYSTEMATIC REVIEW AND META-ANALYSIS
OPEN
Medicine • Volume 94, Number 27, July 2015

Intraoperative Radiotherapy Versus Whole-Breast External Beam Radiotherapy in Early-Stage Breast Cancer

...uo, MD

METHODS

Literature Search

We searched the MEDLINE, EMBASE, the Web of Science, Cochrane Library (CENTRAL, Issue 8 of 12, Oct 2014) and ClinicalTrials.gov databases us... phrases: "breast cancer," "radiotherapy," ... radiotherapy," "IORT," "intrabeam," and ... radiotherapy." MeSH terms and free terms ... electronic search. There were no restrictions ... The references of the included studies were also reviewed to identify potentially eligible article... Z.Z.) conducted the literature sear...

Total 2189 records identified through electronic search

2 additional records identified through other sources

Study Characteristics

The 4 included studies, consisting of 2 RCTs[12,13,25] (the ELIOT and TARGIT trials) and 2 non-RCTs,[23,24] included 5415 patients: 2702 patients in the IORT arm and 2713 in the EBRT arm. The baseline characteristics of each study were balanced

Quality Assessment

Overall, the methodological quality of the 2 RCTs was good. Both the 2 RCTs had a score of 8 points. Points were lost because the patients and investigators were not blinded. The MINORS' scores of the other 2 non-RCTs were both 20 and were acceptable.

TABLE 1. The Main Characteristics and the Quality Assessment Results of the Included Studies

Author Year	Dates of Accrual	Study Design	Patient Characteristics	Sample Size	Arms			Outcome	Quality assessment: PEDro scale	Quality assessment: MINORS
Veronesi et al 2013 (ELIOT)	2000–2007	RCT	48–75 years old;	1305	IORT (N = 65		5.8 years	Ipsilateral breast	8	/
Vaidya et al 2014(TARGIT)	2000–2014	RCT								
Vanoni et al 2014	2000–20									
Zhou et al 2012	2007–2011	Non-RCT	tumor size ≤ 2.5 cm		EBRT (N = 71)	12MeV electrons Whole breast irradiation		Cosmetic evaluation; Local relapses; Death		

In conclusi… significantly higher risk of IBTR with IORT … whole-breast EBRT for women with early … ancer and breast-conserving surgery, due to … rogeneity, the results should be interpreted with … Overall mortality did not differ significantly between … groups. Identifying appropriate patients with a low risk of local recurrence is very important. For carefully selected patients who have a low risk of local recurrence, IORT should be a feasible choice.

GOOD LEVEL OF EVIDENCE

METHODOLOGICAL INDEX FOR NON-RANDOMIZED STUDIES (MINORS), 2003

Accepted Manuscript

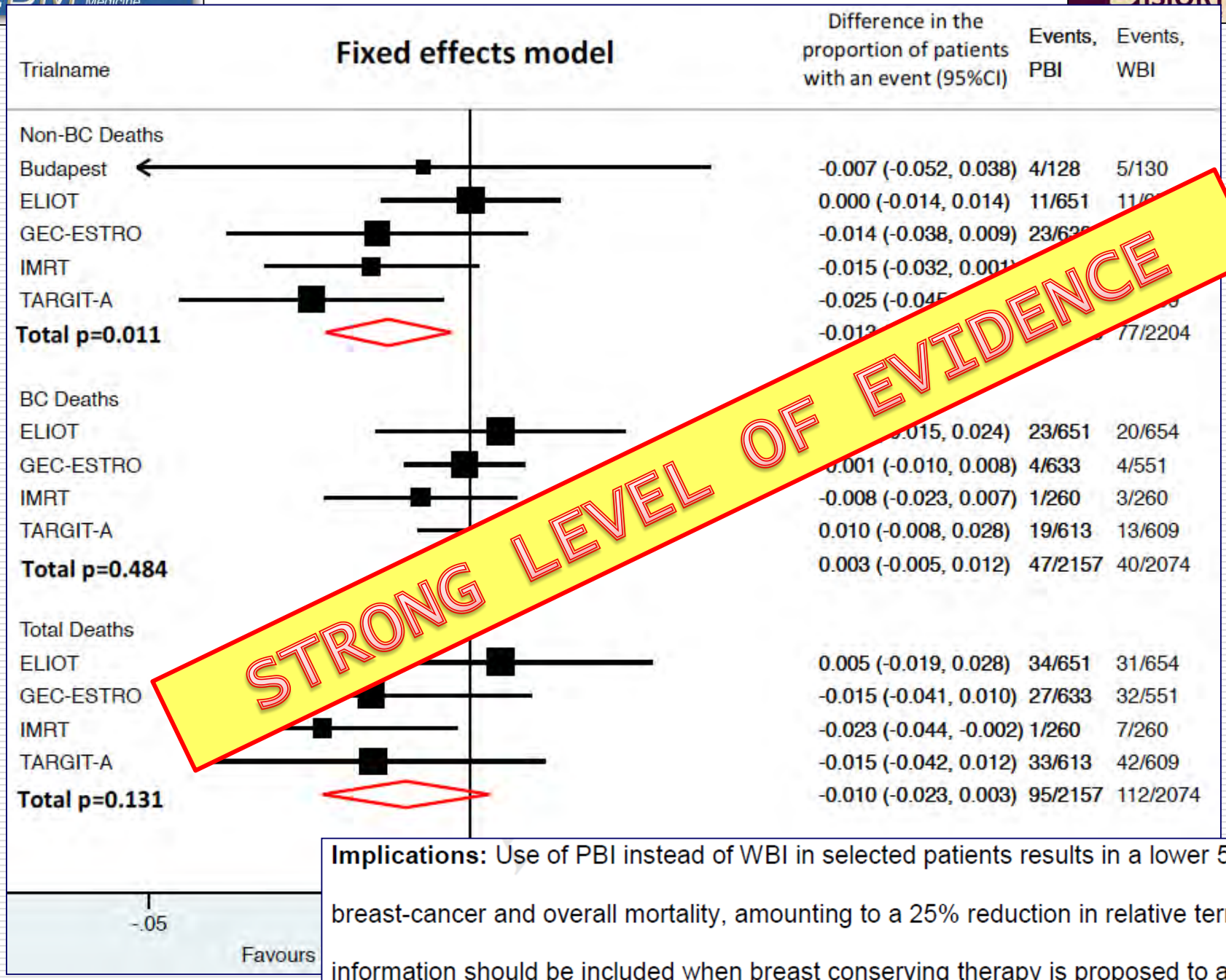
Reduced mortality with partial breast irradiation for early breast cancer – a meta-analysis of randomised trials

Professor Jayant S. Vaidya, Professor of Surgery and Oncology, Professor Max Bulsara, Professor of Biostatistics, Professor Frederik Wenz, Professor of Radiation Oncology, Mr Nathan Coombs, Consultant Surgeon, Dr Julian Singer, Consultant Clinical Oncologist, Mr Stephen Ebbs, Consultant Surgeon, Dr Samuele Massarut, Head of Breast Services, Professor Christobel Saunders, Professor of Surgery, Professor Michael Douek, Professor of Surgical Oncology, Dr Norman Williams, Reader, Professor David Joseph, Professor of Radiation Oncology, Professor Jeffrey S. Tobias, Professor of Cancer Medicine, Professor Michael Baum, Emeritus Professor of Surgery

DOI: 10.1016/j.ijrobp.2016.05.008

A meta-analysis of 5-year data from 9 published randomized trials of PBI vs WBI, found no difference in breast cancer mortality (n=4489,difference 0.000%(95%CI -0.7 to +0.7),p=0.972).

PBI was better than WBI for non-breast cancer mortality (n=4231,difference 1.1% (95%CI -2.1% to -0.2%),p=0.023),and total mortality (difference 1.3% (95%CI -2.5% – 0.0%),p=0.05), leading to a 25% relative risk reduction.



STRONG LEVEL OF EVIDENCE

Implications: Use of PBI instead of WBI in selected patients results in a lower 5-year non-breast-cancer and overall mortality, amounting to a 25% reduction in relative terms. This information should be included when breast conserving therapy is proposed to a patient.

Evidence Based Medicine and IORT: BREAST CANCER

QUERY *"IORT/breast cancer/boost"*

if you set the filter for relevance

Hindawi Publishing Corporation
International Journal of Breast Cancer
Volume 2014, Article ID 472516, 6 pages
http://dx.doi.org/10.1155/2014/472516

2014

Hindawi

International Journal of Breast Cancer

Review Article

Boost IORT in Breast Cancer: Body of Evidence

Felix Sedlmayer,[1,2] Roland Reitsamer,[3] C
Franz Zehentmayr,[1,2] Heinz Deutschman

BreastCare

Editorial

Breast Care 2015;10:237–238
DOI: 10.1159/000439009
Published online: August 19, 2015

2015

Romancing the Boost – the Higher, the Better?

Strahlenther Onkol
DOI 10.1007/s00066-015-0895-2

ORIGINAL ARTICLE

Jan 2016

Survival and local control rates of triple-negative breast cancer patients treated with boost-IOERT during breast-conserving surgery

Gerd Fastner · Cornelia Hauser-Kronberger · Angelika Moder · Roland Reitsamer · Franz Zehentmayr · Peter Kopp · Christoph Fussl · Thorsten Fischer · Heinrich Deutschmann · Felix Sedlmayer

EBM Evidence-Based Medicine

Hindawi Publishing Corporation
International Journal of Breast Cancer
Volume 2014, Article ID 472516, 6 pages
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International Journal of Breast Cancer

Review Article

Boost IORT in Breast Cancer: Body of Evidence

Felix Sedlmayer,[1,2] Roland Reitsamer,[3] Christoph Fussl,[1] Ingrid Ziegler,[1]
Franz Zehentmayr,[1,2] Heinz Deutschmann,[1,2] Peter Kopp,[1] and Gerd Fastner[1]

9th International ISIORT Conference
June 24/25th 2016
Novara, Italy

5. Clinical Results

The ISIORT Europe Pooled Analysis (BIO-Boost)
Radiotherapy and Oncology, vol. 108, pp. 279–286, 2013.

The Boost IORT with Low-Kilovoltage X-Rays.
International Journal of Radiation Oncology Biology Physics, vol. 81, no. 4, pp. 1091–1097, 2011.

Boost IOERT after Primary Systemic (Neoadjuvant) Treatment.
International Journal of Cancer, 2014.

The Salzburg Experience
Strahlentherapie und Onkologie, vol. 188, p. 189, 2012.

HIOB Trial
Radiotherapy & Oncology, vol. 111, Supplement 1, pp. 201–202, 2014.

AND….

Targit B: Trial Design

High risk Breast cancer suitable for conservation

R

Study Arm	Control Arm
Intraoperative BOOST with IntraBeam + EBRT	External tumor bed BOOST (16 Gy) + EBRT

STRONG LEVEL OF EVIDENCE

- Activated: in 2014
- SUPERIORITY trial:
- Total accrual: **1900** pts

By courtesy of M. Roncadin

CRO AVIANO

Review Article

Intraoperative radiotherapy for breast cancer

Gland Surgery 2014;3(2):109-119

Norman R. Williams[1], Katharine H. Pigott[2], Chris Brew-Graves[1], Mohammed R. S. Keshtgar[3]

[1]Clinical Trials Group, Division of Surgery & Interventional Science, Faculty of Medical Sciences, University College London, London, W1W 7EJ, UK; [2]Radiotherapy Department, [3]The Breast Unit, Royal Free London Foundation Trust, University College London, Hampstead NW3 2QG, UK

Correspondence to: Professor Mohammed R. S. Keshtgar, BSc, FRCSI, FRCS (Gen), PhD. Professor of Cancer Surgery and Surgical Oncology; Royal Free London Foundation Trust, University College London, The Breast Unit, Pond Street, Hampstead, London, NW3 2QG, UK. Email: m.keshtgar@ucl.ac.uk

Supported by level-one evidence

ELIOT and TARGIT are supported by strong evidence if patients are valuated according to ESTRO and ASTRO criteria

Risk-adaptive technique

It should be pointed out that IORT cannot always be given, even in women who meet the eligibility criteria.

…for insufficient tumor-skin distance, oversized wound cavity or a combination of both

Reduced irradiation of normal tissues

In addition to the avoidance of irradiation of skin, the rapid attenuation of IORT X-rays means there is much less radiation exposure to normal tissues.

The estimated risk for secondary cancer was considerably lower after IORT and/or APBI as compared to EBRT (23).

Better cosmetic outcome

Objective and Subjective valuation

Review Article

Intraoperative radiotherapy for breast cancer

Gland Surgery 2014;3(2):109-119

Norman R. Williams[1], Katharine H. Pigott[2], Chris Brew-Graves[1], Mohammed R. S. Keshtgar[3]

[1]Clinical Trials Group, Division of Surgery & Interventional Science, Faculty of Medical Sciences, University College London, London, W1W 7EJ, UK; [2]Radiotherapy Department, [3]The Breast Unit, Royal Free London Foundation Trust, University College London, Hampstead NW3 2QG, UK

Correspondence to: Professor Mohammed R. S. Keshtgar, BSc, FRCSI, FRCS (Gen), PhD. Professor of Cancer Surgery and Surgical Oncology; Royal Free London Foundation Trust, University College London, The Breast Unit, Pond Street, Hampstead, London, NW3 2QG, UK. Email: m.keshtgar@ucl.ac.uk

Economically viable

The institutional perspective

Much cheaper than LINAC
No shieldings
Alternative method of delivering dose
Depending on the level of remboursement
Saved time in Radiotherapy Dept.
Procedure in the meantime of surgery

Societal perspective

Total treatment time
Travel time
Time off work (patient and family).

Excellent patient preference and satisfaction

The majority of women with breast cancer will accept a small increment of local risk for a simpler delivery of radiation.

Better quality of life

A review of 227 studies for aesthetic in breast surgery found only one that was validated

Pusic AL, Plast Reconstr Surg 2007

IORT patients (TARGIT) presented less general pain,fewer breast and arm symptoms, and better role functioning than EBRT patients (P<0.01)

Welzel G, Radiat Oncol 2013

Review Article

Gland Surgery 2014;3(2):109-119

Intraoperative radiotherapy for breast cancer

Norman R. Williams[1], Katharine H. Pigott[2], Chris Brew-Graves[1], Mohammed R. S. Keshtgar[3]

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IORT can be given to a previously irradiated breast

IORT can be given to women who would not be given EBRT

Frail patients and elderly
Parkinson's Disease
Cardiac pacemaker
Collagen and vascular disease
Motor neuron disease
Obesity
Cardiovascular disease
Severe respiratory disease

Editorial

Is current clinical practice modified about intraoperative breast irradiation?

Michela Massa[1], Simonetta Franchelli[2], Renzo Panizza[1], Tiberio Massa[3]

[1]Plastic and Reconstructive Surgery, SS. Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy; [2]Plastic and Reconstructive Surgery, IRCCS AOU San Martino-IST, National Institute of Cancer Research, L.go Rosanna Benzi 10, 16132, Genoa, Italy; [3]Diagnostic Mammography Department, IRCCS AOU San Martino-IST, National Institute of Cancer Research, L.go Rosanna Benzi 10, 16132, Genoa, Italy

Correspondence to: Michela Massa, MD. Plastic and Reconstructive Surgery, A.O. SS. Antonio e Biagio e Cesare Arrigo, Via Venezia 16, 15100 Alessandria, Italy. Email: michelamassa01@gmail.com.

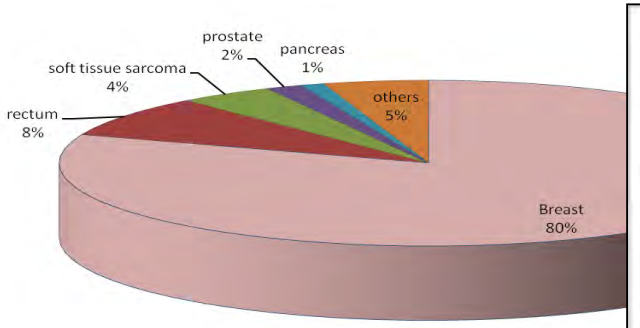
Chinese Journal of Cancer Research, Vol 28, No 2 April 2016

Therefore in the clinical cases of lower risk of recurrence and respecting the strict selection criteria, IORT should be taken into account, considering also the advantage of a good quality of life and the less chronic skin toxicities especially after IORT alone identified in IORT patients (20).

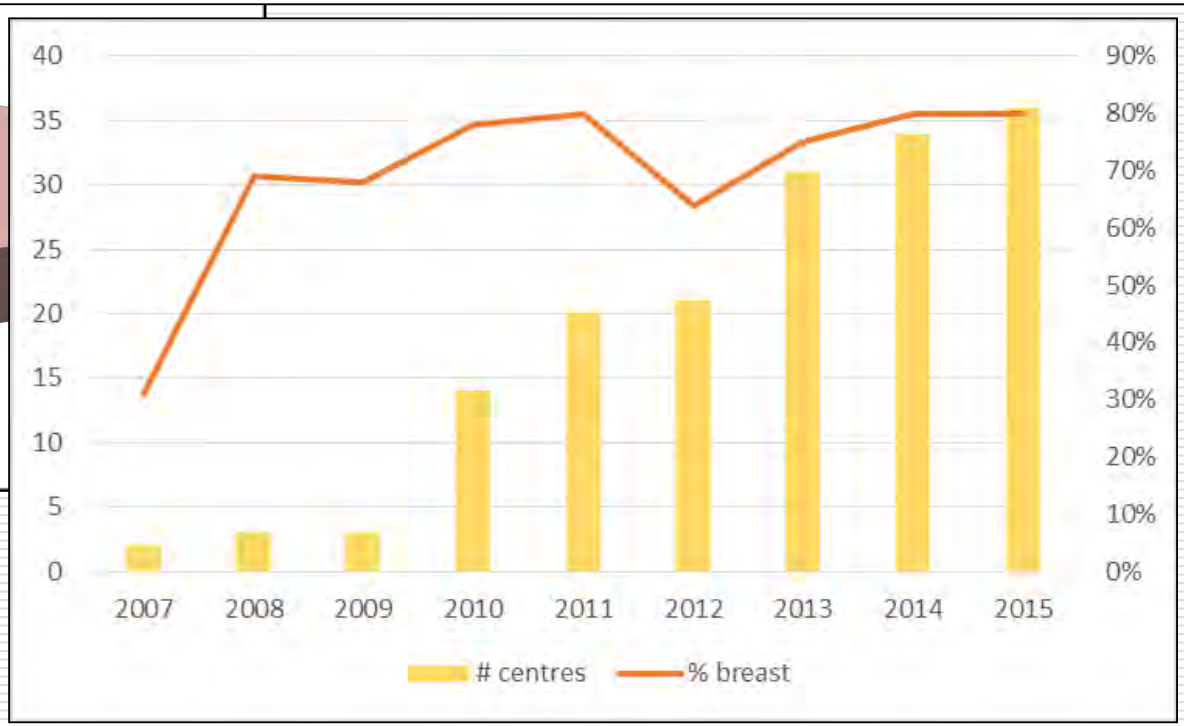
The complexity in surgical techniques and oncologic treatment involves a multidisciplinary team and require a continuous dynamic communication between oncologic surgeon, plastic surgeon and radiotherapist to carry out a successful breast cancer treatment that satisfy the patient and ensure an adequate local control of the tumor.

EBM and IORT: Clinical Practice

Tumour types



Percentage of breast IORT out of all IORT

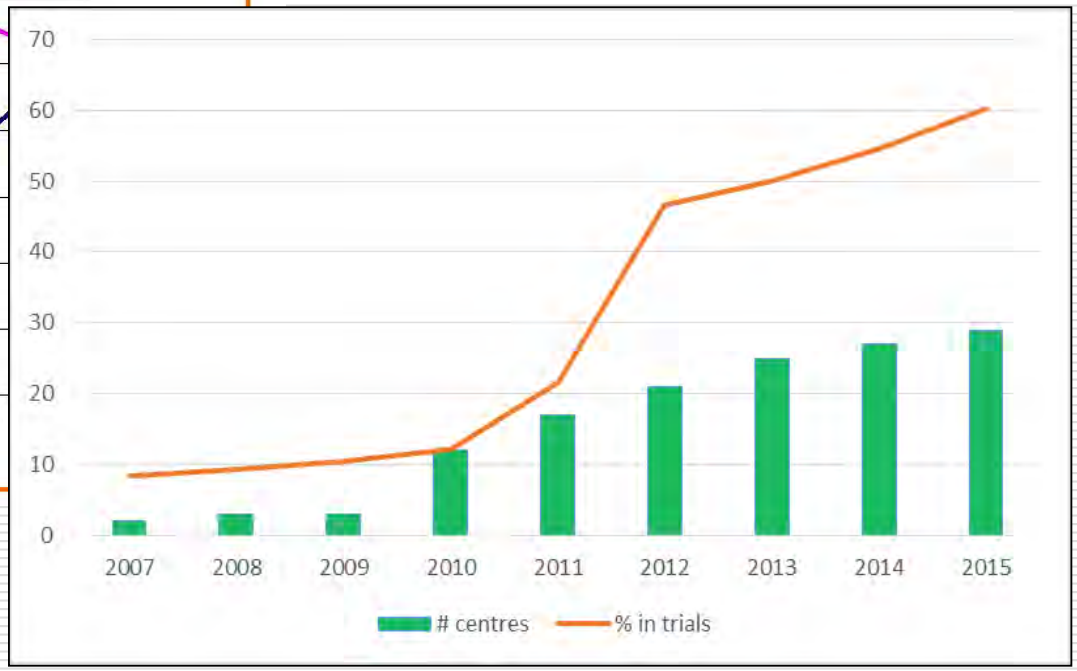


By courtesy of M. Krengli, 2016

EBM and IORT: Clinical Practice

Single Shot vs. Boost

N. of centres and % of breast cancer patients included in clinical trials



By courtesy of M. Krengli, 2016

TAKE HOME MESSAGE

- OPTIMAL SINGLE DOSE IN SELECTED PATIENTS: Level A (younger pts for BOOST)
- RISK ADAPTED TECHNIQUE is the best FOR SINGLE DOSE: Level A
- LOW ACUTE TOX AND GOOD COSMESIS: Level A
- POSSIBLE IN PREVIOUSLY IRRADIATED PTS: Level C
- POSSIBLE IN PTS WHO WOULD NOT BE GIVEN ERT: Level C
- LARGE DATA BASE

(TARGIT) Registry database; [about 2 screens]. Available online: http://www.controlled-trials.com/ISRCTN91179875/targit

ISIORT INTERNATIONAL SOCIETY of INTRAOPERATIVE RADIATION THERAPY

ISIORT – EUROPE Data Registry
8,763 cases from 36 centres

TARGIT Targeted Intra-operative Radiation Therapy

TAKE HOME MESSAGE

About 1/2 of 'valid' evidence today will be out of date in 5 years

About 1/2 of valid evidence is not implemented

RCT and metanalysis are necessary

"...and, as you go out into the world, I predict that you will, gradually and imperceptibly, forget all you ever learned at this university."

ScienceCartoonsPlus.com

TAKE HOME MESSAGE

"τι μπορούμε να μάθουμε να μάθουν τη λήψη"

"That which we have to learn to do, we learn by doing it"

"Aristotle"

IORT for Gastrointestinal Malignancies

Michael G. Haddock, MD

Mayo Clinic

ISIORT 2016

IORT History

Comas C., Prio A. Irradiation roentgen intra-abdominale ,après intervention chirurgicale dans un cas de cancer de l'uterus, Congres International d'Electrologie .Imprenta Francesca Badia,Barcelona,pp 5-14, 1907

IORT History

THE TREATMENT OF SOME ABDOMINAL CANCERS BY IRRADIATION THROUGH THE OPEN ABDOMEN COMBINED WITH CAUTERY EXCISION

LEO ELOESSER, M.D.

SAN FRANCISCO, CALIF.

FROM THE DIVISION OF SURGERY, STANFORD UNIVERSITY MEDICAL SCHOOL AT THE SAN FRANCISCO HOSPITAL

Annals of Surgery, 1937

IORT History
Stanford, 1937

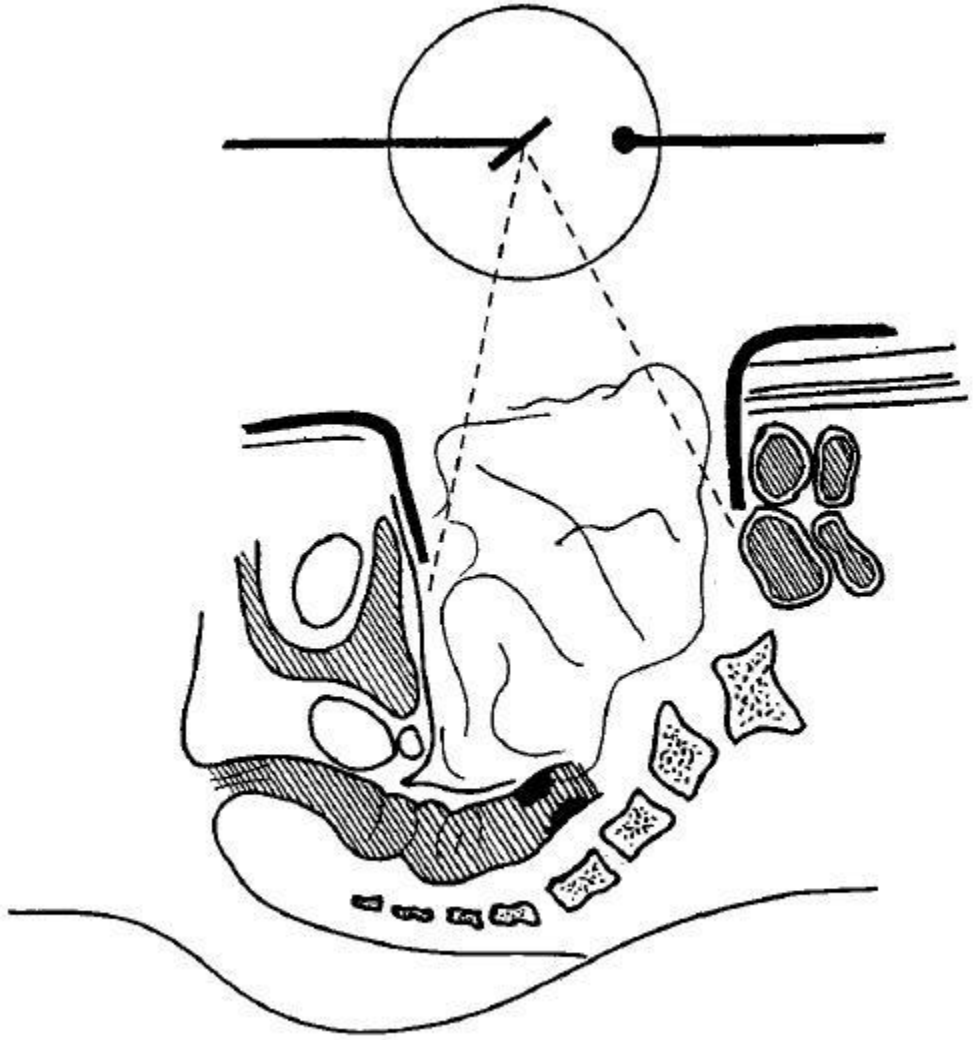


FIG. 1.—Irradiation of cancer of sigmoid (abdominal approach).

IORT History
Stanford, 1937

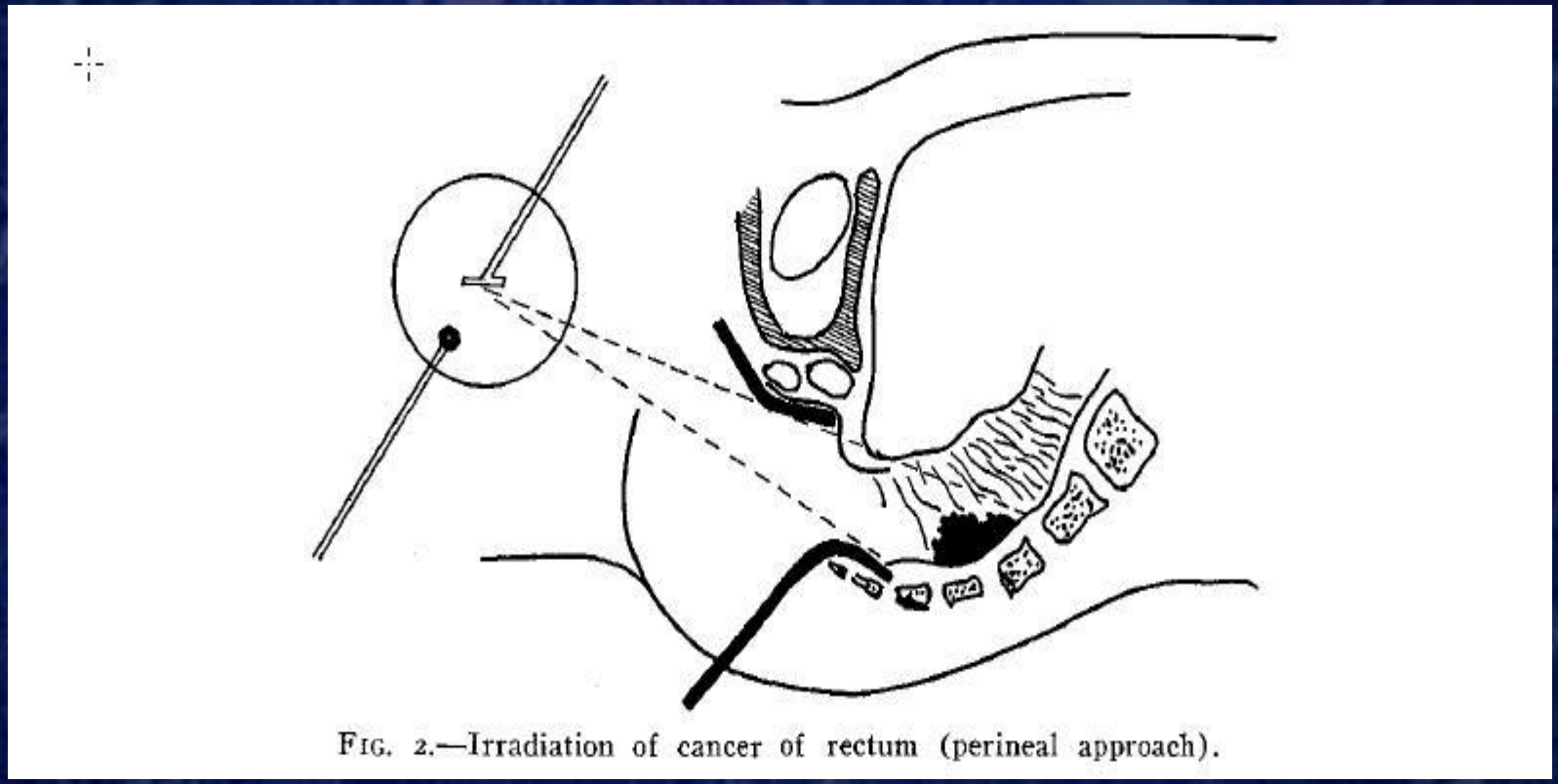


FIG. 2.—Irradiation of cancer of rectum (perineal approach).

Vol. XLII - Nº EXTRAORDINARIO 1998

REVISTA DE MEDICINA

UNIVERSIDAD DE NAVARRA

ISIORT'98

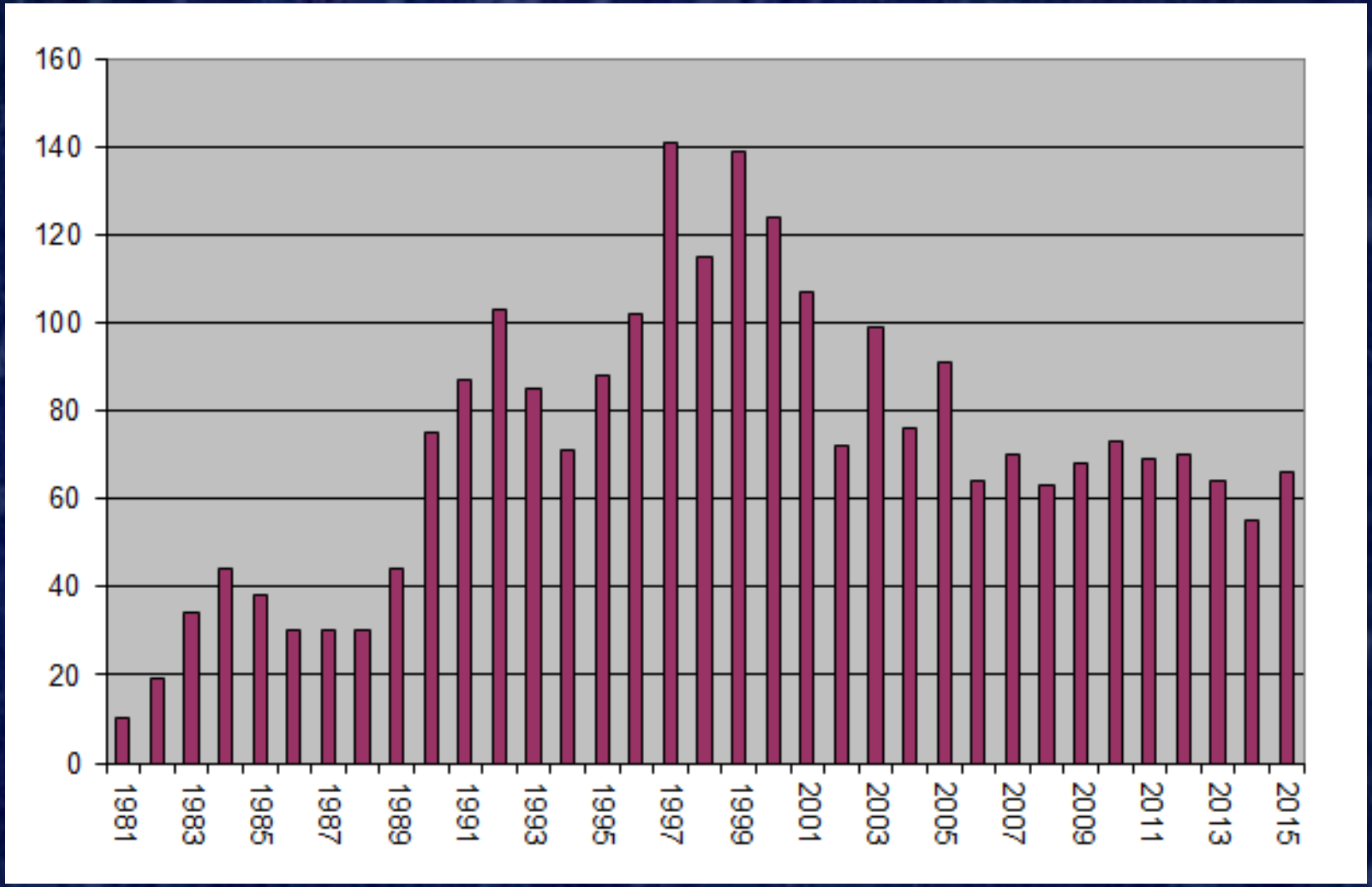
I[RST] CONGRESS

OF THE INTERNATIONAL SOCIETY

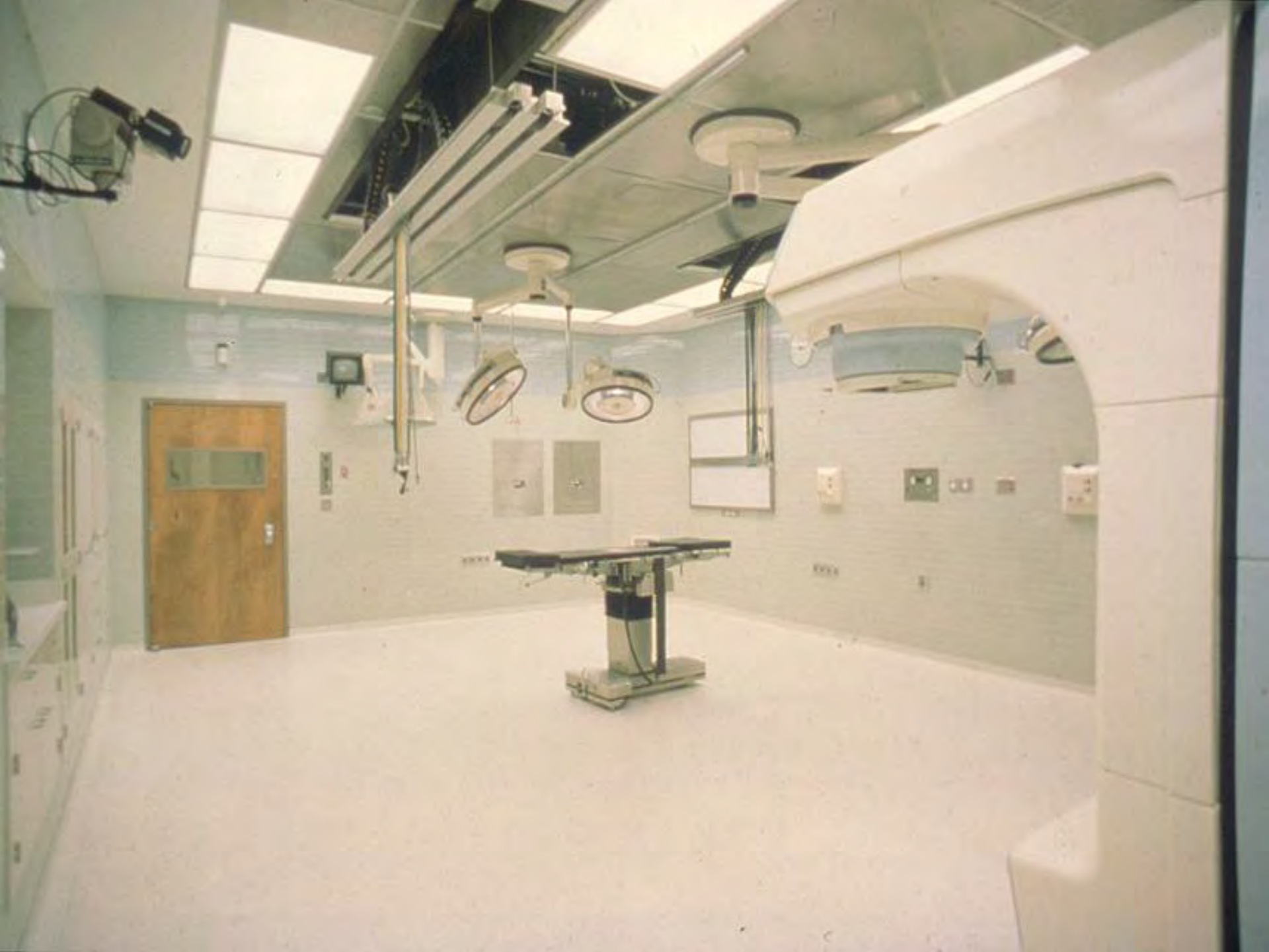
OF INTRAOPERATIVE RADIATION THERAPY

September 6 - 9, 1998
Auditorium
School of Medicine
University of Navarra
Pamplona, Spain

IORT Cases per year, Mayo Rochester




37° F
© 2012 OxBlue



IOERT Cases – Mayo Rochester
April 1981 – May 6, 2016

Site	Primary	Recurrent	Total
GI	418	865	1283
Soft tissue/bone	504	261	765
GYN	39	207	246
GU	14	63	77
Head and Neck	23	50	73
Miscellaneous	13	28	41
Total	1011	1474	2485

IOERT Cases – Mayo Rochester
April 1981 – May 6, 2016

Site	Primary	Recurrent	Total
Esophagus	26	7	33
Stomach	17	10	27
Hepatobiliary	26	6	32
Pancreas	123	12	135
Small bowel	8	7	15
Colon	49	223	272
Rectum	156	567	723
Anus	13	33	46
Total	418	865	1283

IORT Rationale

Tumor control probability
Radiobiologic Axioms

- Surviving fraction of tumor cells is a function of radiation dose
- Functional radiation effects in normal tissues is related to dose
- The dose needed to obtain tumor control may exceed normal tissue tolerance

Radiation Tolerance Doses

Organ	Injury at 5 yrs	1-5% $TD_{5/5}$	25-50% $TD_{5/5}$	Volume or length
Esophagus	Ulcer, stricture	60-65 Gy	75 Gy	75 cm^3
Stomach	Ulcer,perforation	45-50 Gy	55 Gy	100 cm^3
Intestine	Ulcer, stricture	45-50 Gy	55 Gy	100 cm^3
Colon	Ulcer, stricture	55-60 Gy	75 Gy	100 cm^3
Rectum	Ulcer, stricture	55-60 Gy	75 Gy	100 cm^3
Anus	Ulcer, stricture	60-65 Gy	75 Gy	Whole
Liver	Liver failure	35 Gy	75 Gy	Whole
Bile Ducts	Stricture	50 Gy	70 Gy	--

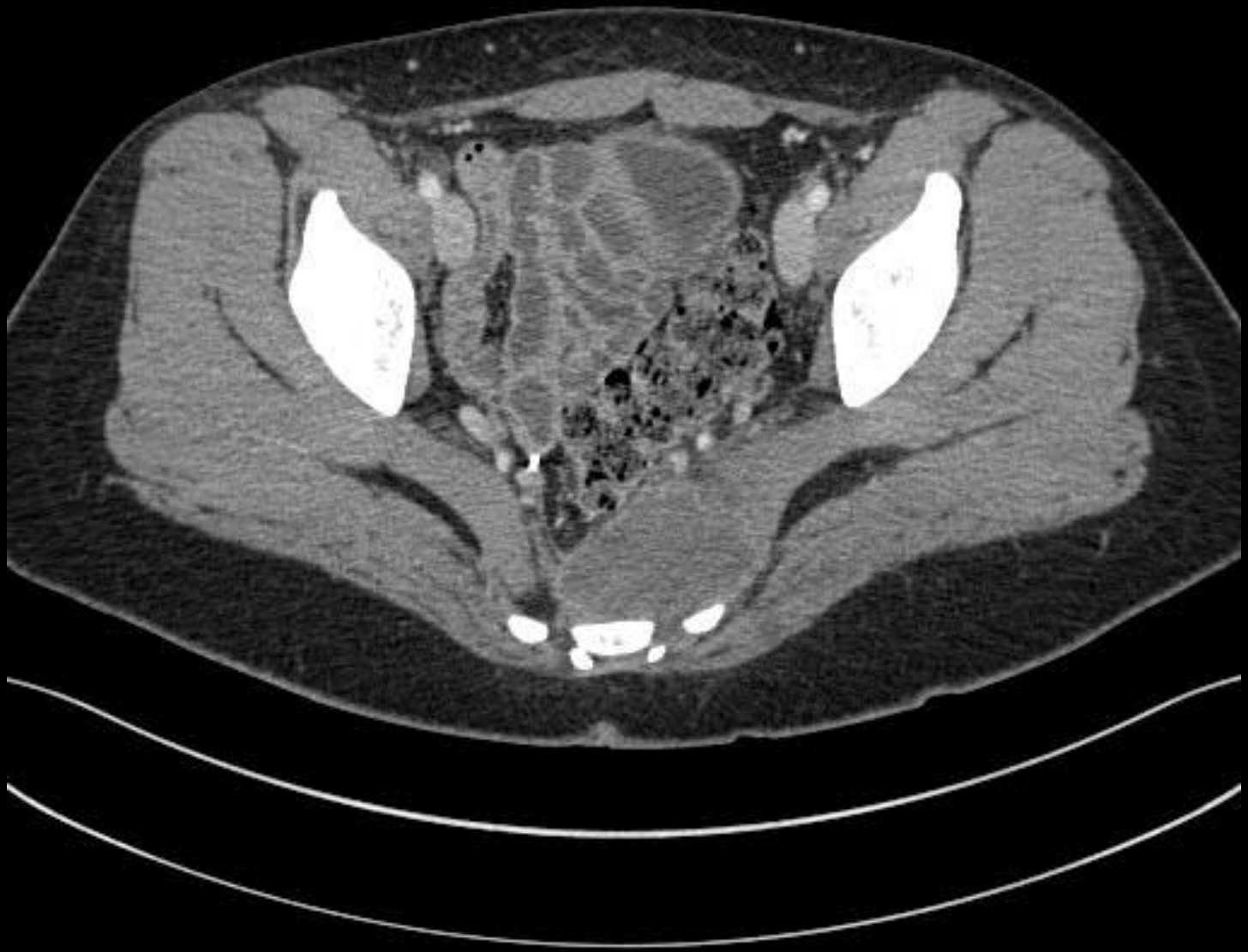
Gunderson and Martenson, Front Radiat Ther Oncol 23:277, 1988

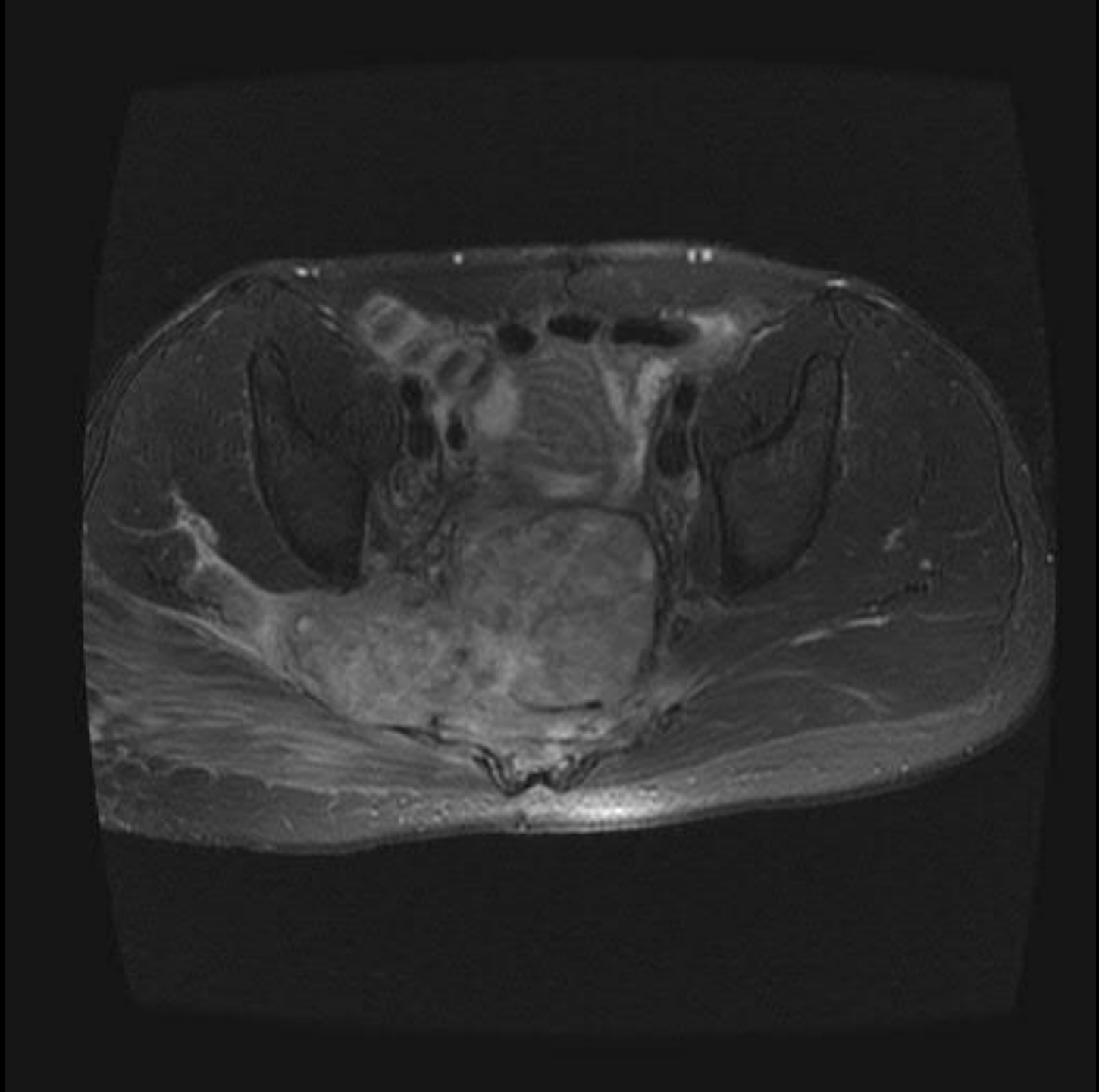
IORT
General Rationale

- able to treat small volume of tissue within IORT boost field
- can limit dose to sensitive normal organs such as small bowel
- can increase effective radiation dose – IORT is dose escalation tool

Patient Selection Criteria
IOERT

- Surgery alone unacceptable local control
- External beam dose > 60 - 70 Gy for curative attempt
- IOERT at time of planned operative procedure
- IOERT + EBRT would theoretically result in a more favorable therapeutic ratio between cure and complications
- No evidence of distant disease or distant disease treatable for cure





IORT for GI Malignancies
Potential IORT Sites

- Esophageal Cancer
- Gastric Cancer
- Biliary Cancer
- Pancreas Cancer
- Colorectal Cancer
- Anal Cancer

Esophageal Cancer
IORT

- Lower esophageal cancer > 6 cm
  - 45 pts IORT
  - 30 pts no IORT
- 20-30 Gy IORT to upper abd nodes
- 68% received EBRT
- 60% received chemotherapy

Tamaki, J Rad Research 53:882-891, 2012

Esophageal Cancer
IORT

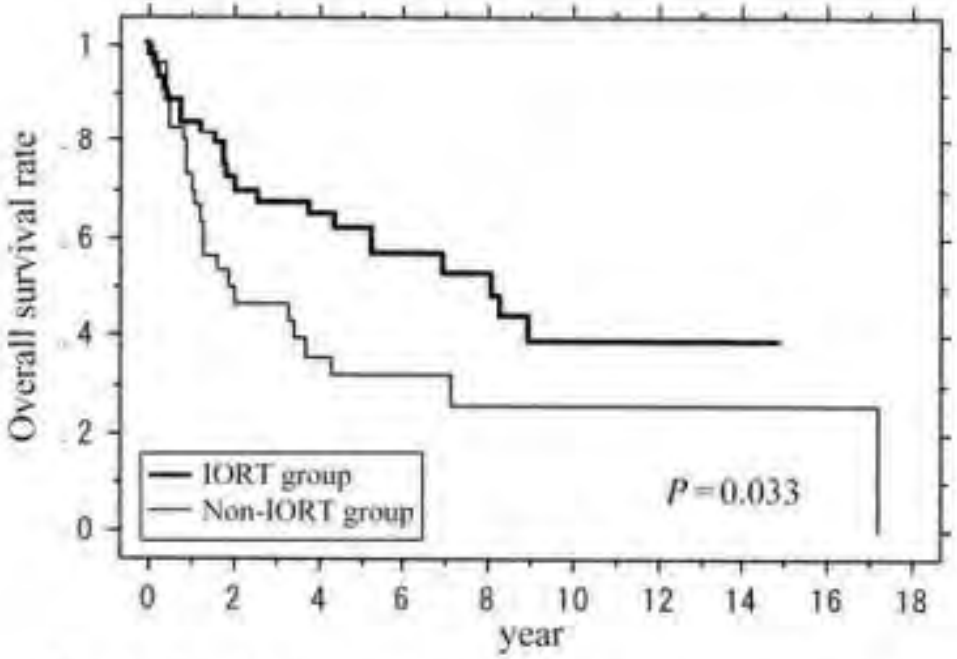
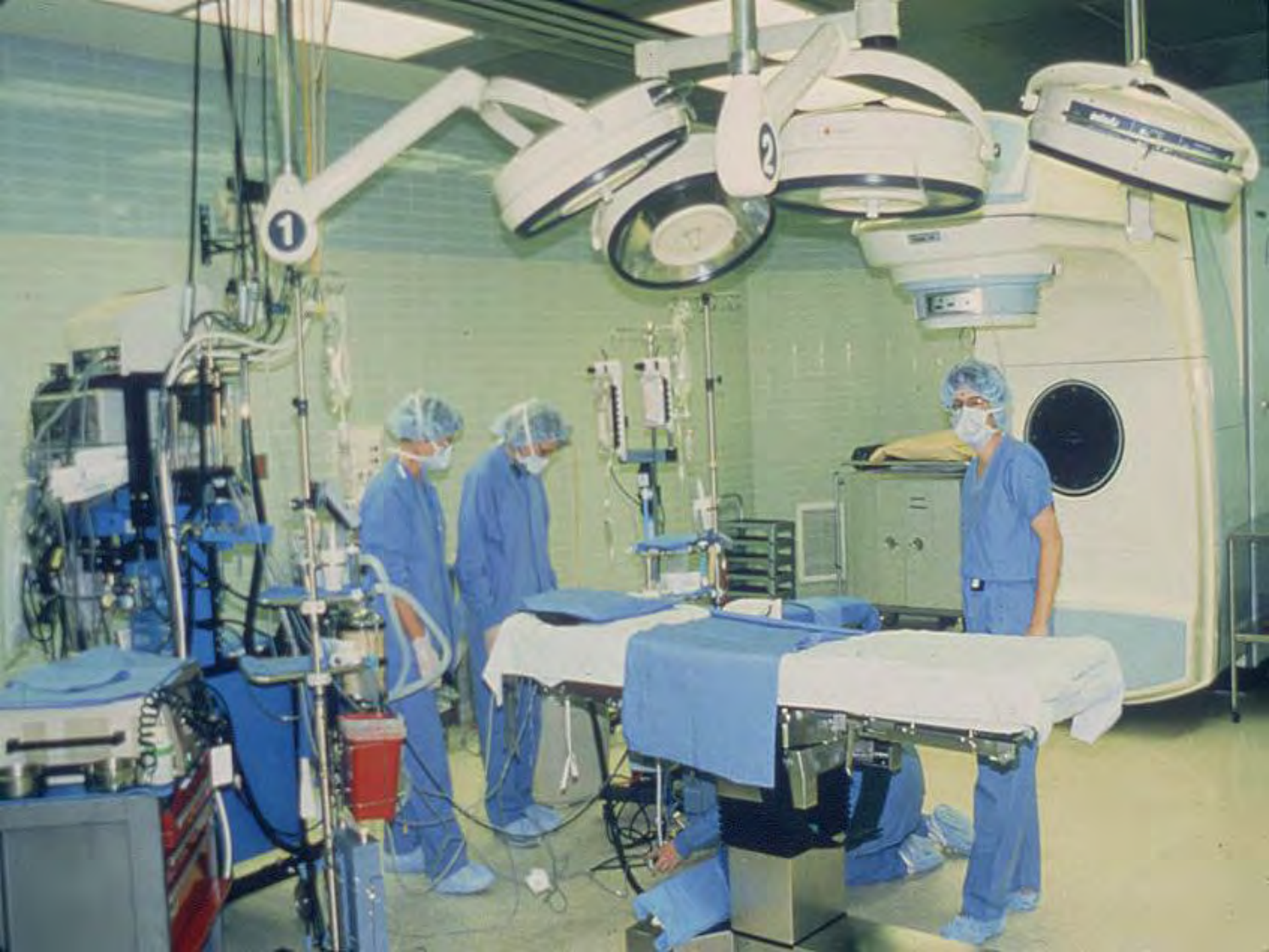


Fig. 3. Kaplan-Meier analysis of overall survival rate in the IORT group ($n = 45$) and non-IORT group ($n = 30$) within the subgroup of patients whose primary lesion was located in the lower thoracic or abdominal part of the esophagus or measured >6 cm in length.

Abdominal control
89% vs 63%
P = 0.01

Tamaki, J Rad Research 53:882-891, 2012


1
2

IORT for GI Malignancies
Potential IORT Sites

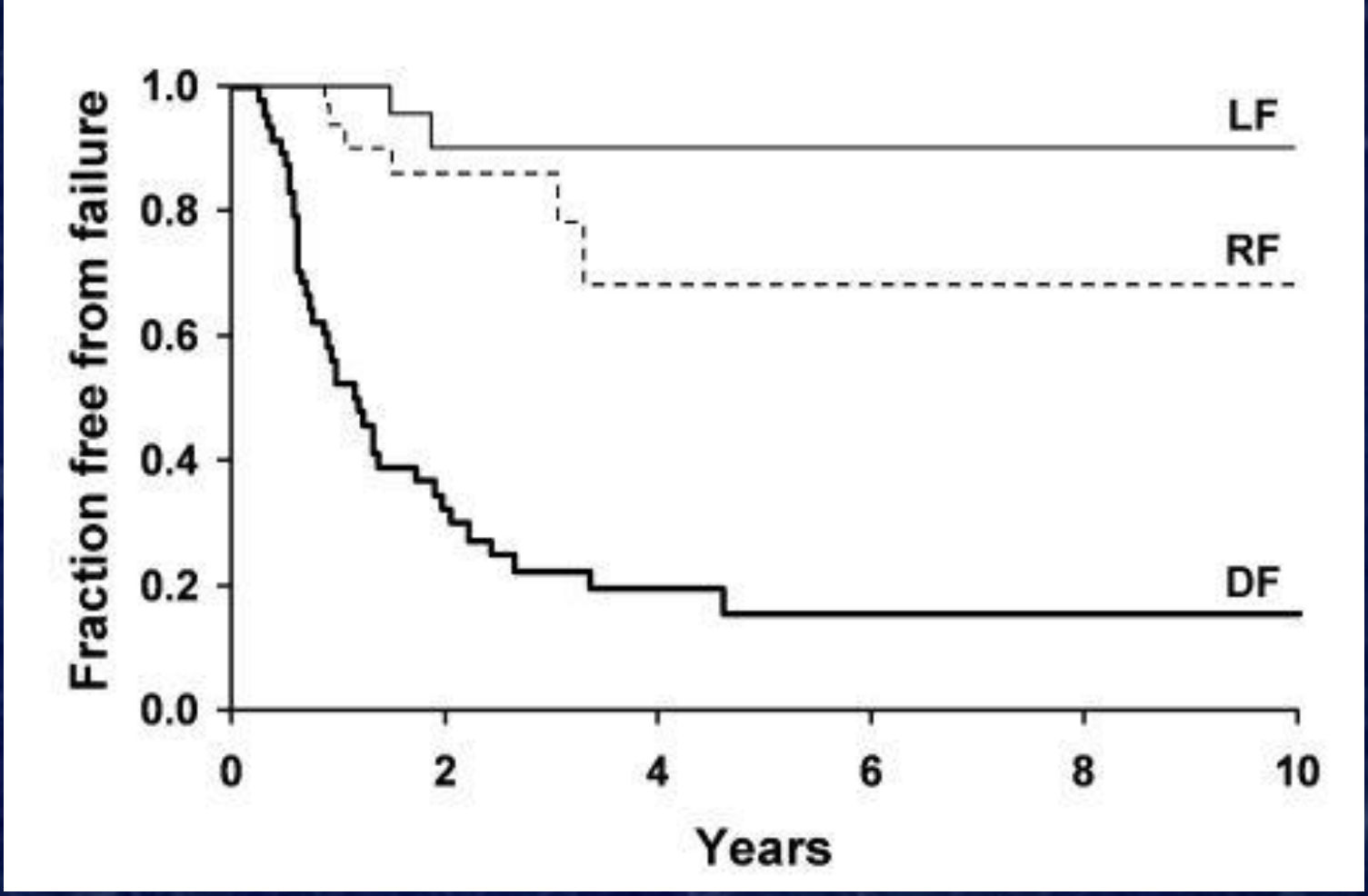
- Esophageal Cancer
- Gastric Cancer
- Biliary Cancer
- Pancreas Cancer
- Colorectal Cancer
- Anal Cancer

Esophagogastric Cancer
IORT

- 50 pts 1984 – 2001
  - 37 primary
  - 13 recurrent
- IORT: 10-25 Gy
- 48/50 EBRT, 92% chemo with EBRT
- R0 42%, R1 46%, R2 12%
- 3-yr S 27%

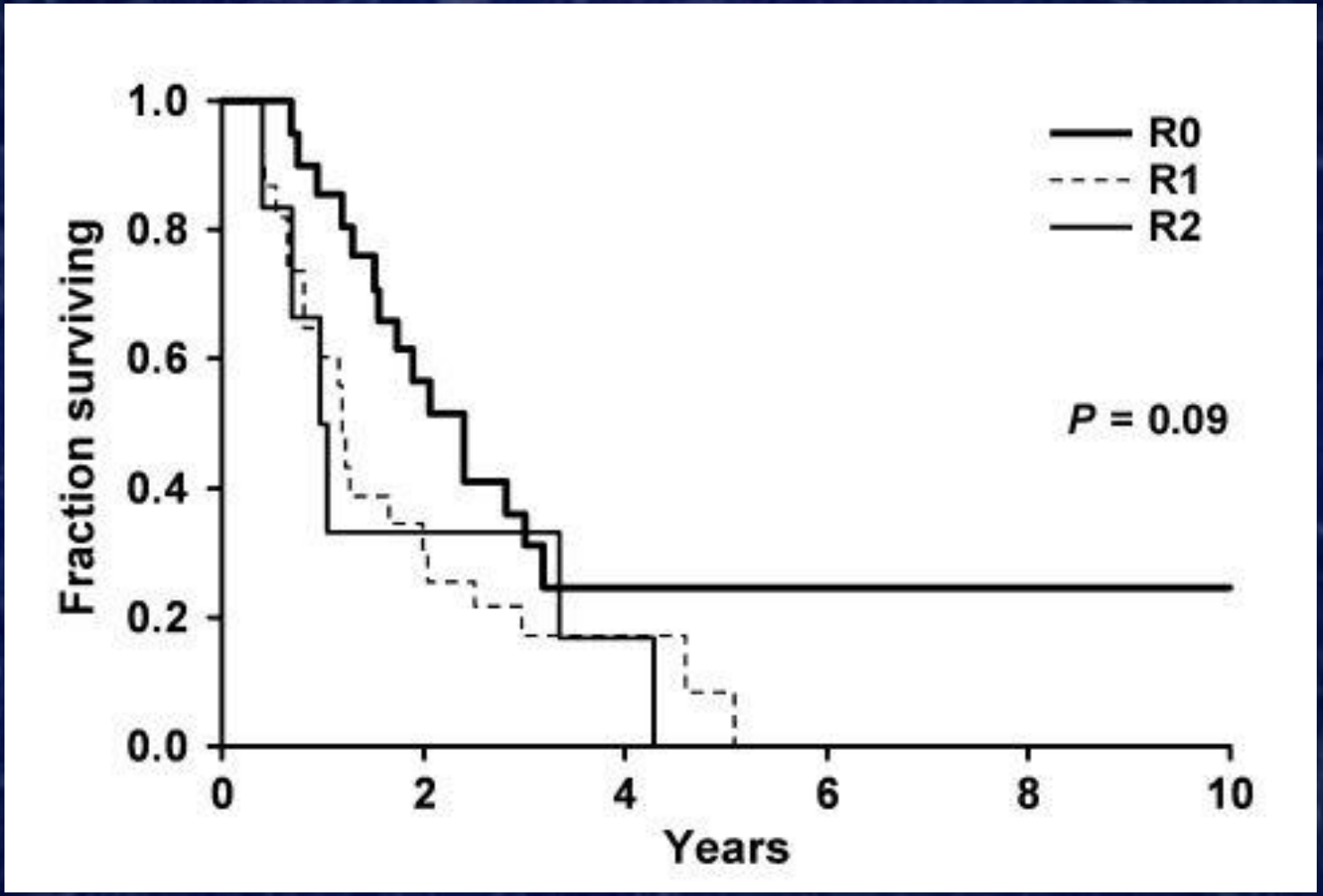
Miller, Disease Esophagus 19:487-495, 2006

Esophagogastric Cancer
IORT



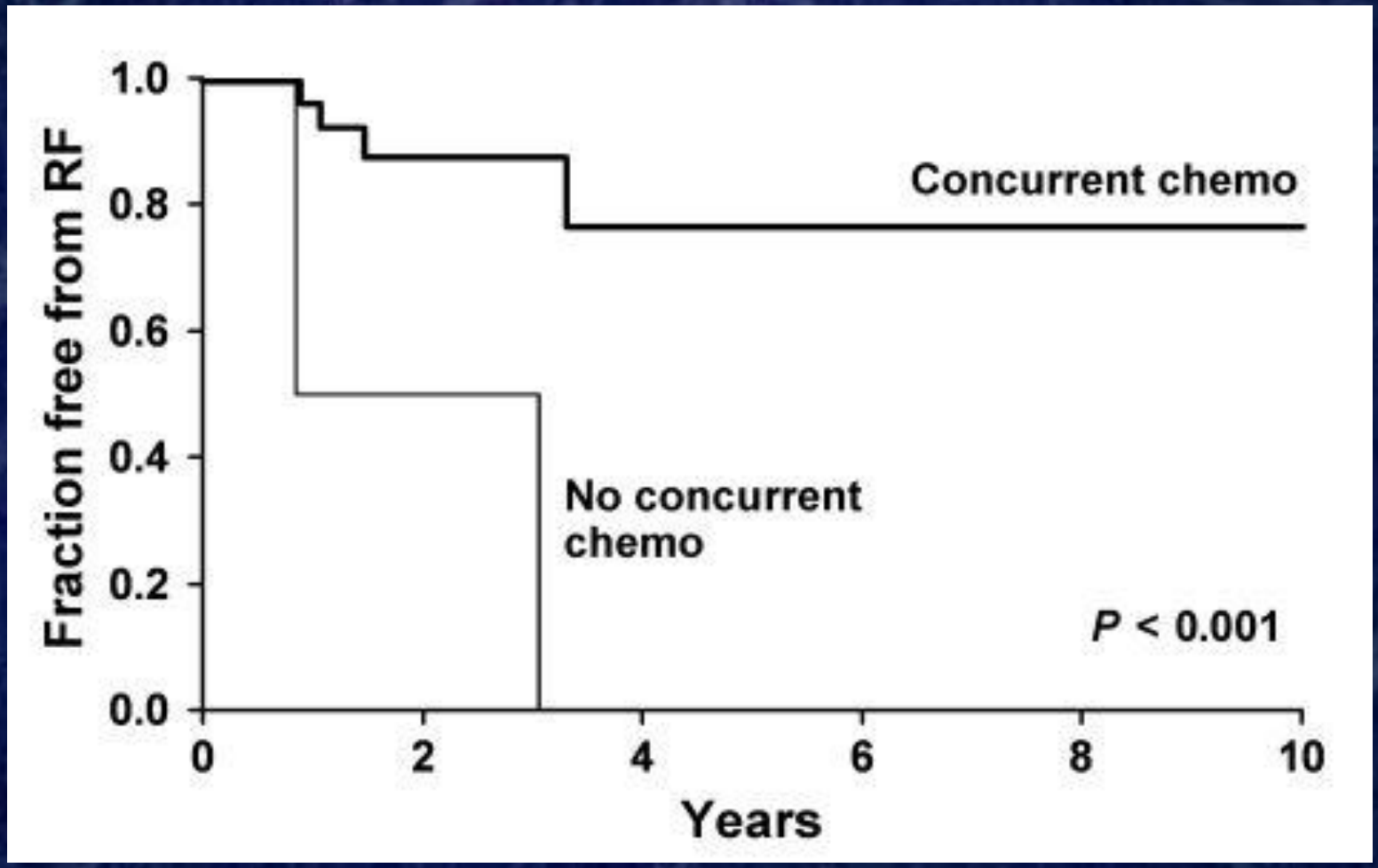
Miller, Disease Esophagus 19:487-495, 2006

Esophagogastric Cancer
IORT



Miller, Disease Esophagus 19:487-495, 2006

Esophagogastric Cancer
IORT



Miller, Disease Esophagus 19:487-495, 2006

Gastric Cancer
IORT Meta-analysis

Author (Refs.)	Year	Years of accrual	Study design	Nodal dissection	N pts	Endpoints reported
Drognitz *et al* (9)	2008	February 1991 to July 2001	S + IORT (6-15 MeV, 15-25 Gy) S	D2	122	OS
Zhang *et al* (8)	2012	March 2003 to October 2005	S + IORT (9-16 MeV, 12-15 Gy) + EBRT + CT S + EBRT + CT	D2	97	OS Locoregional control
Martinez Monge *et al* (11)	1997	October 1982 to March 1993	S + IORT (9-20 MeV, 10-17 Gy) + EBRT S + EBRT	D2	62	OS Locoregional control
Sindelar *et al* (24)	1993	No reported	S + IORT (11-15 MeV, 20 Gy)+ EBRT S + EBRT	No reported	41	OS Locoregional control
Santoro *et al* (10)	1998	July 1976 to July 1993	S + IORT (27-30 Gy) S	D2	59	Locoregional control
Qin *et al* (21)	2006	1992 to 1998	S + IORT (6-16 MeV, 10-30 Gy) S	D2 or D3	292	OS (stage III)
Ogata *et al* (22)	1995	August 1983 to July 1992	S + IORT (12 MeV, 28-30 Gy) S	D2	47	OS (stage III)
Abe *et al* (23)	1995	No reported	S + IORT (28-35 Gy) S	No reported	77	OS (stage III)

Yu, Molecular and Clinical Oncology 3:185-189, 2015

Gastric Cancer
IORT Meta-analysis

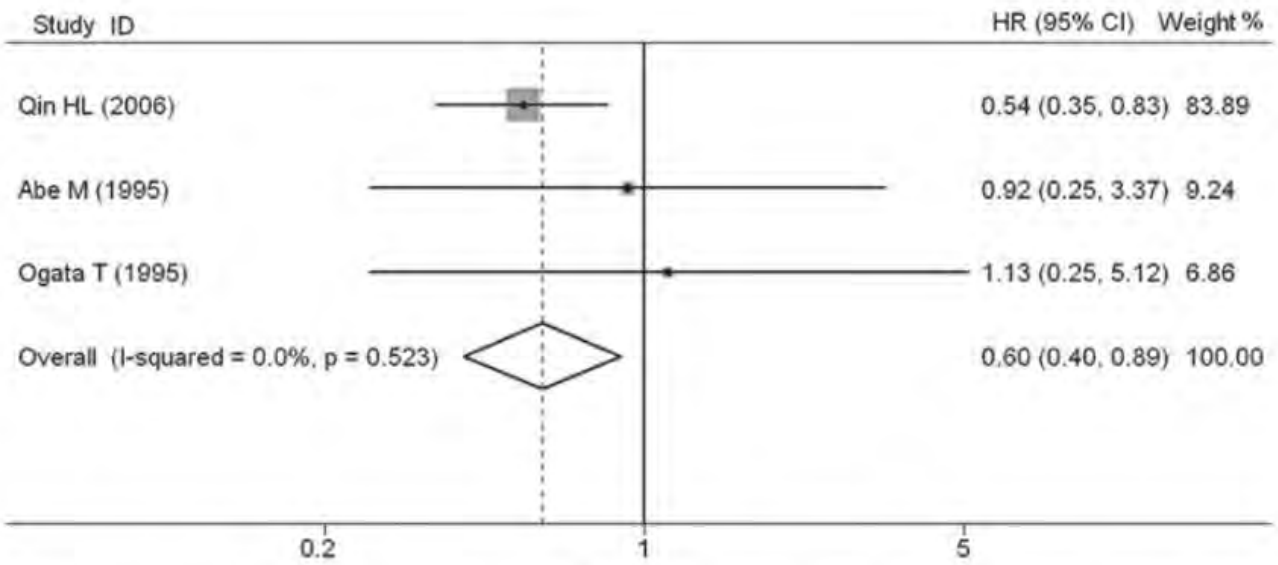


Figure 3. Fixed-effects meta-analysis of the impact of adjuvant IORT on the overall survival rate for the subgroup of patients with stage III disease in three eligible studies. HR, hazard ratio; CI, confidence interval; IORT, intraoperative radiotherapy; S, surgery.

Yu, Molecular and Clinical Oncology 3:185-189, 2015

Gastric Cancer
IORT Meta-analysis

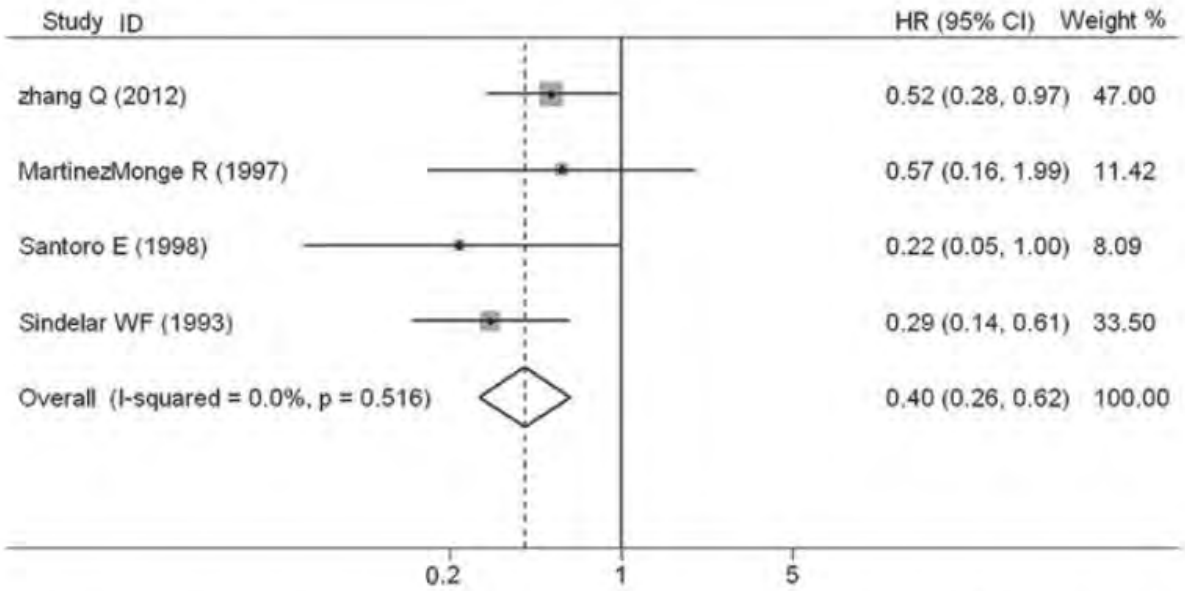
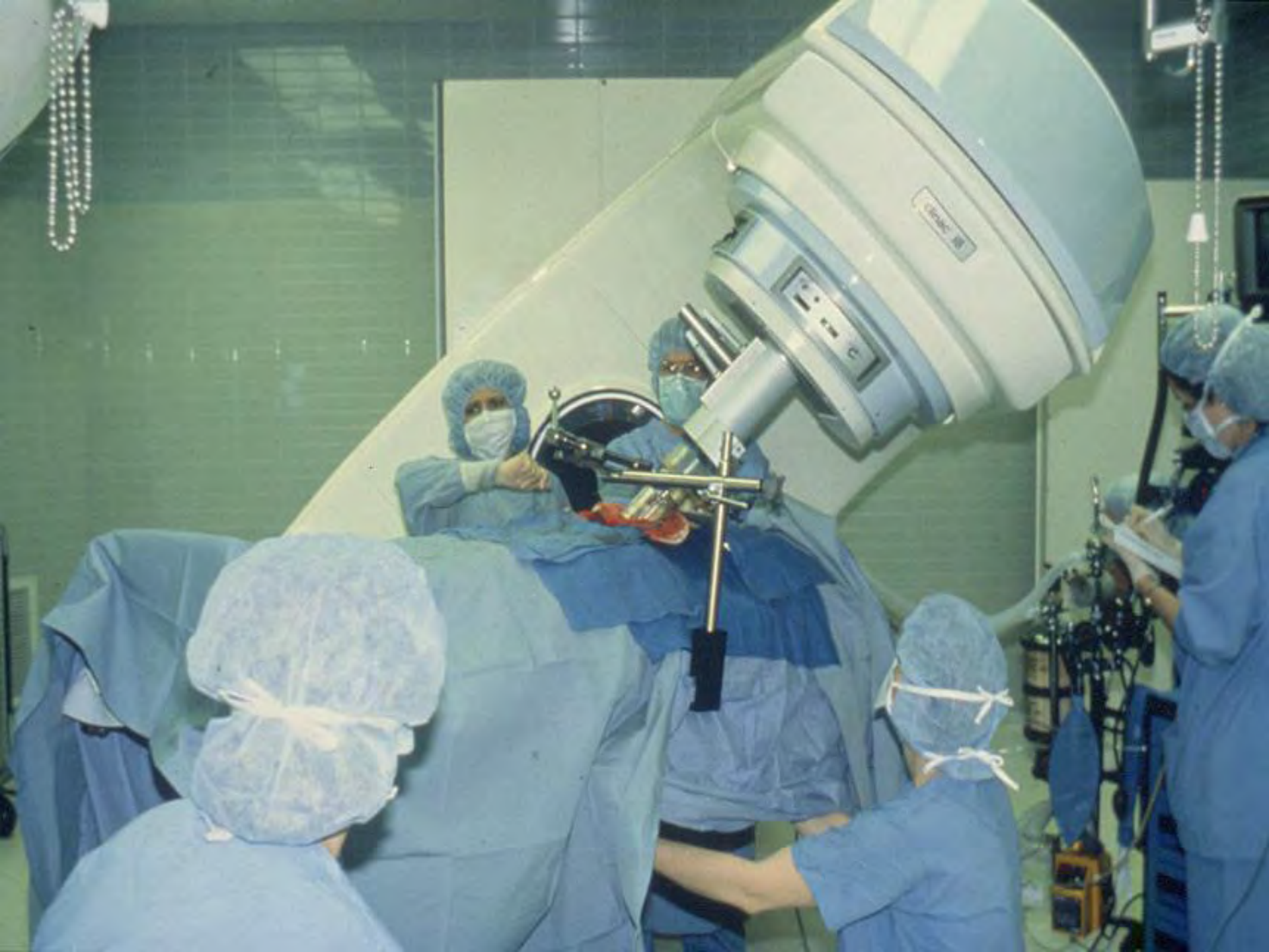


Figure 4. Fixed-effects meta-analysis of the impact of adjuvant IORT on the locoregional control rate. HR, hazard ratio; CI, confidence interval; IORT, intraoperative radiotherapy; EBRT, external-beam radiotherapy; CRT, chemoradiation; S, surgery.

Yu, Molecular and Clinical Oncology 3:185-189, 2015



IORT for GI Malignancies
Potential IORT Sites

- Esophageal Cancer
- Gastric Cancer
- Biliary Cancer
- Pancreas Cancer
- Colorectal Cancer
- Anal Cancer

Unresectable Cholangiocarcinoma
IORT

Series	Treatment	# pts	Median S (mo)	2-yr S	5-yr S
TJU	EBRT (> 55 Gy)/5FU/brachy	15	24	48%	
Pittsburgh	EBRT + 5-FU	38	14	20%	0
Iwasaki	R1-2 resection + IORT	13		15%	
	R1-2 resection alone	13		8%	
Todoroki	R1 resection + IORT	8			21%
	R1 resection + EBRT + IORT	27			59%
Essen	Laparotomy + IORT	9	23	42%	
	Laparotomy alone	9	9	0	
Mayo	EBRT + 5-FU	11	12	0	0
	EBRT + 5-FU + brachy	9	13	22%	22%
	EBRT + 5-FU + IORT	14	18.5	29%	7%

IORT for GI Malignancies
Potential IORT Sites

- Esophageal Cancer
- Gastric Cancer
- Biliary Cancer
- Pancreas Cancer
- Colorectal Cancer
- Anal Cancer

Resectable Pancreatic Cancer
Local Relapse

Study	Local Relapse
GITSG	47%
EORTC	51%
ESPAC-1	63%
CONKO-001	37%
RTOG 9704 5-FU	28%
RTOG 9704 Gem	23%

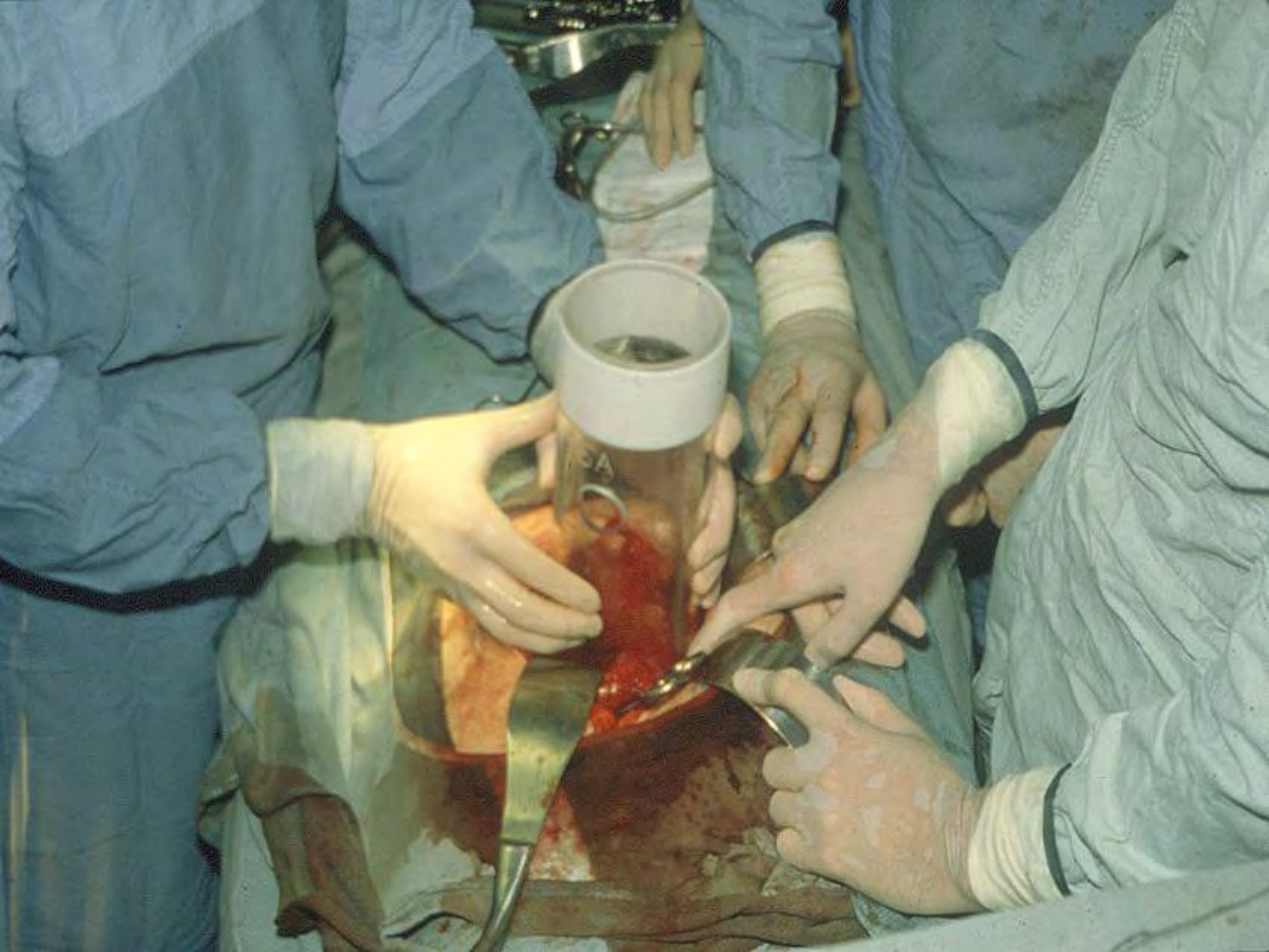
Resectable Pancreatic Cancer
IORT Results

STUDY	Treatment	# Pts	IORT dose	Local relapse	Overall survival
Sindelar, NCI	S + EBRT	12	0	100%	12 mo med
	S + EBRT + IORT	12	20 Gy	33%	18 mo med
Alfieri, Rome	S alone	20	0	70%	5.5%
	S + IORT +/- EBRT	26	10 Gy	42%	16%
Reni, Milan	S alone	76	0	60%	6%
	S + IORT +/- EBRT	127	10-25 Gy	27%	22%
Valentini,ISIORT	Preop EBRT + IORT	63	7.5-25 Gy	26%	37%
	IORT + postop EBRT	106	7.5-25 Gy	81%	19%
	S + IORT	95	7.5-25 Gy	100%	6%
Ogawa, Japan	S+ IORT +/- EBRT	210	20-30 Gy	16%	~17%

Resectable Pancreatic Cancer
Effect of Margins and IORT Dose

- Multi-institution Japanese survey
- IORT 20-30 Gy +/- EBRT
- Local relapse at 2 years:
  - R0 resection 13%
  - R1 resection 25%
  - IORT dose < 25 Gy 22%
  - IORT dose ≥ 25 Gy 14%

Ogawa, Red Journal 77:734, 2010



Locally Advanced Pancreas ACA

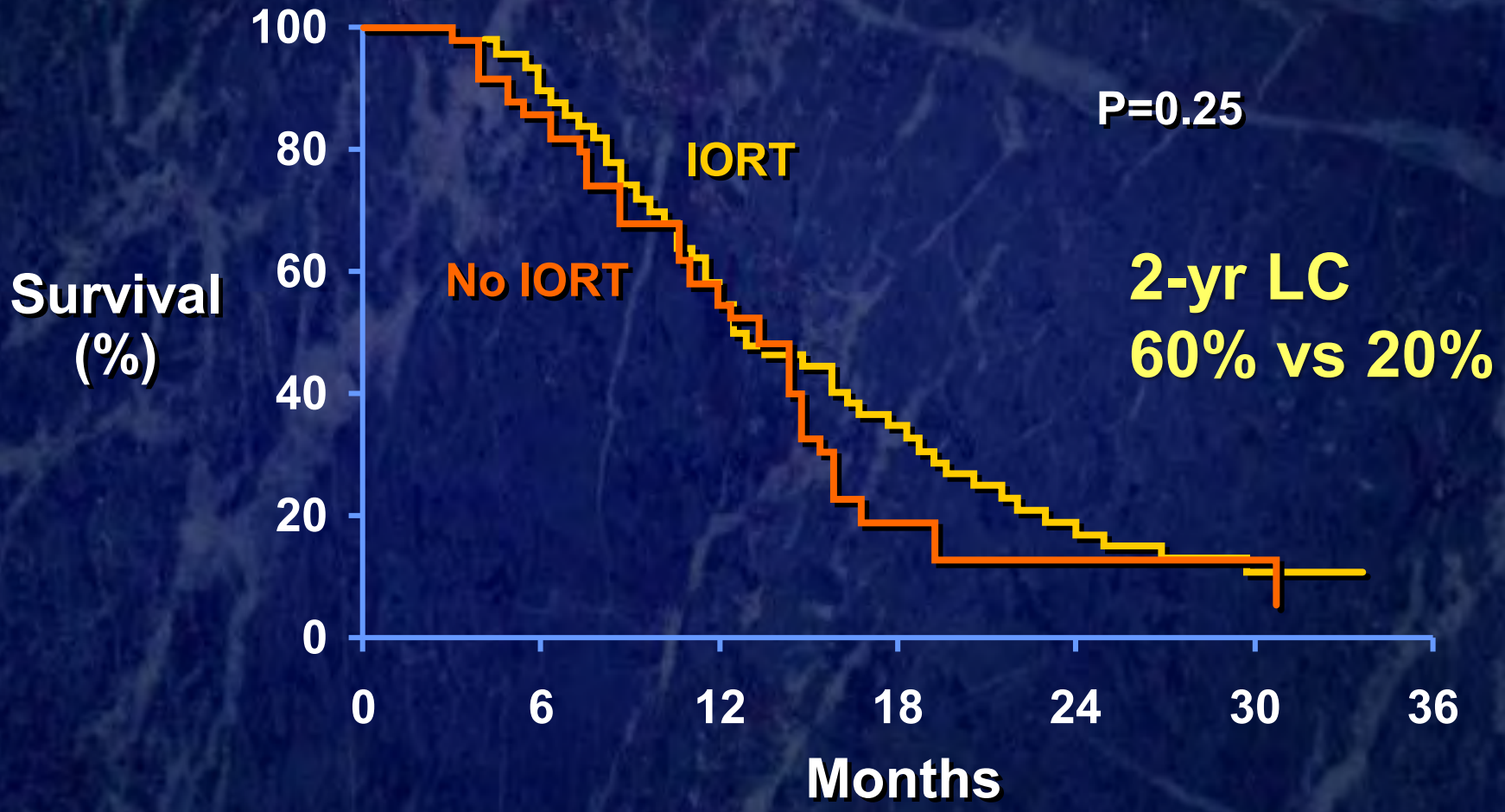
Mayo IORT

- 52 pt, 45-50 Gy + 1750-2000 cGy
- Local failure 7%
- Median survival 12 mo
- Distant mets 48%
- Peritoneal spread 28%

Gunderson: IJROBP 13:319, 1987

Locally Advanced Pancreas ACA

Mayo IORT



MAYO CLINIC

Adapted from: Roldan et al: Cancer 61:1110, 1988

Locally Advanced Pancreas ACA
IOERT Series

Series	#pts	EBRT Gy	IOERT Gy	Med mo	Survival 1-yr %	2-yr %	5-yr %	LC %
MGH	150	50	15-20	13	54	15	4	
RTOG	51	50.4	20	9	33	-	-	
TJU	49	40-55	10-20	16	58	22	7*	69
Mayo pre	27	50-54	20	15	60	28	7	78
Mayo post	56	45-54	20	10.5	42	6	0	

*4 yr survival

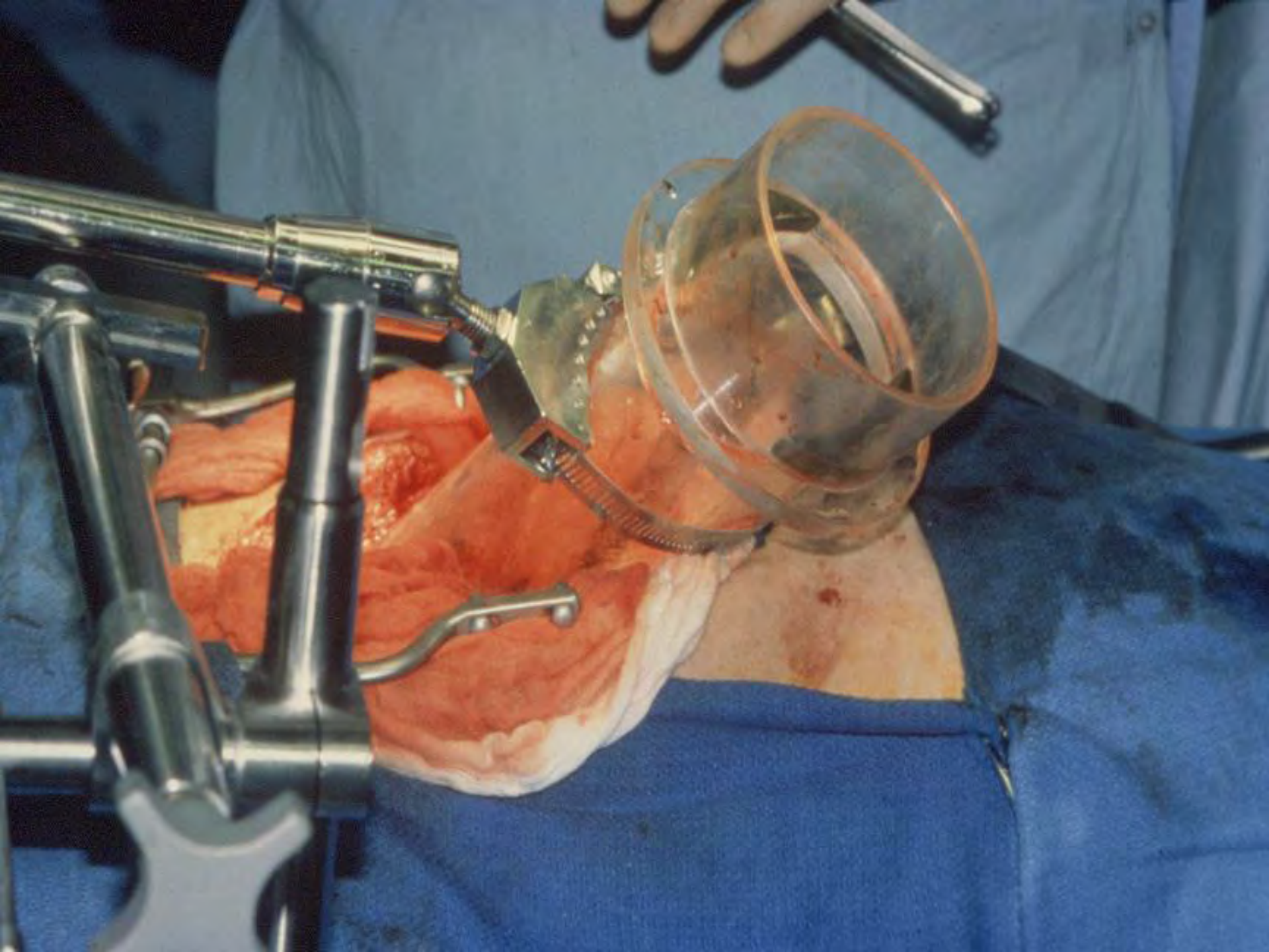
Locally Advanced Pancreas ACA
Effect of Treatment Sequence
Mayo Clinic

Sequence	#pts	EBRT Gy	IOERT Gy	Survival 2-yr %	Survival 5-yr %	2-yr LC %
Preop	27	50-54	20	27	7	81
Postop	56	45-54	20	6	0	65

Garton, Red journal 27(5): 1153-1157, 1993

Unresectable Pancreas Cancer
IORT

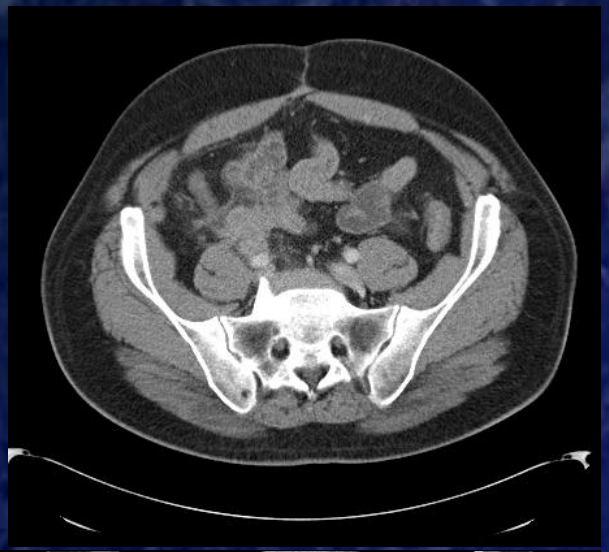
- Pain relief: complete relief in 75-90%
- Improved quality of life
- Prolonged local control
- Effect on survival not proven
- IORT not yet studied in modern chemotherapy era

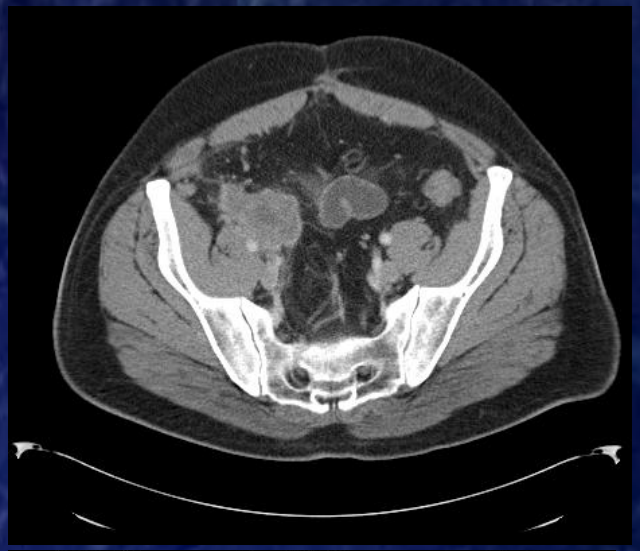


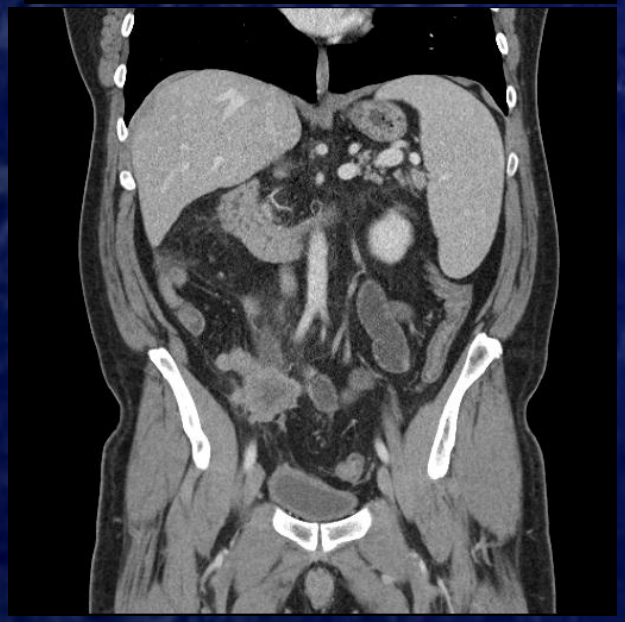
IORT for GI Malignancies
Potential IORT Sites

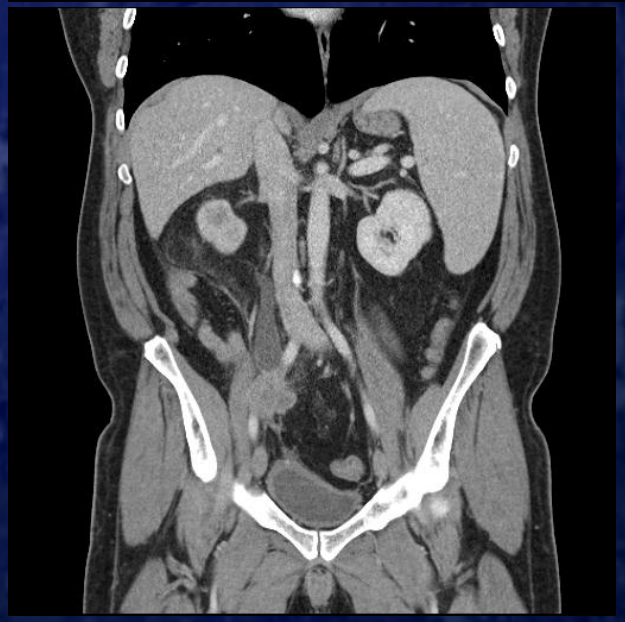
- Esophageal Cancer
- Gastric Cancer
- Biliary Cancer
- Pancreas Cancer
- Colorectal Cancer
- Anal Cancer

Advanced Primary Colon Cancer









Locally Advanced Colon Cancer
Mayo Clinic Results

Group	# Patients	5-year LR	5-year DM	5-year OS
R0 resection	50	10%	~30%	66%
R1 resection	18	54%	~57%	47%
R2 resection	35	79%	~68%	23%
		$p < 0.0001$	$p = 0.002$	$p = 0.0009$
EBRT > 50 Gy	73	36%	-	50%
EBRT ≤ 50 Gy	30	50%	-	45%
		$p = 0.18$		$p = 0.16$
R1-2 + IOERT	9	11%	~12%	76%
R1-2, no IOERT	44	82%	~76%	26%
		$p = 0.02$	$p = 0.01$	$p = 0.04$

Schild, Red Journal 37:51-58,1997

Primary Colon Cancer
IOERT for subtotal resection

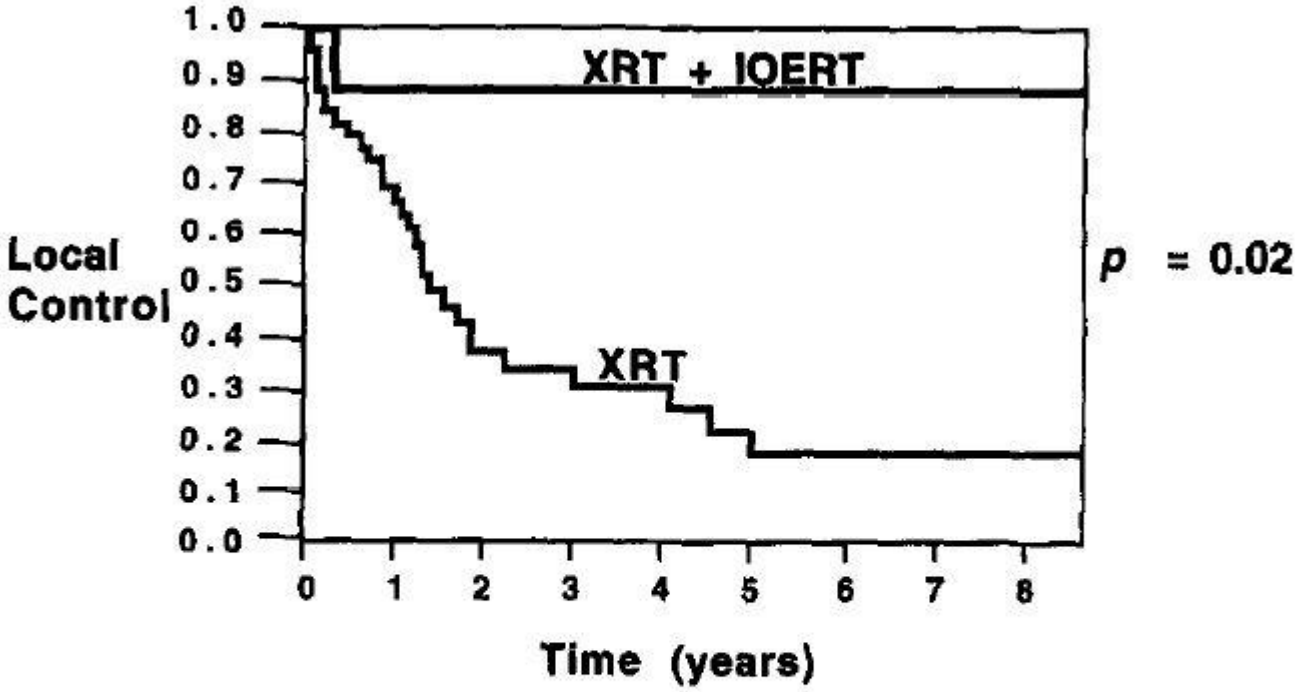
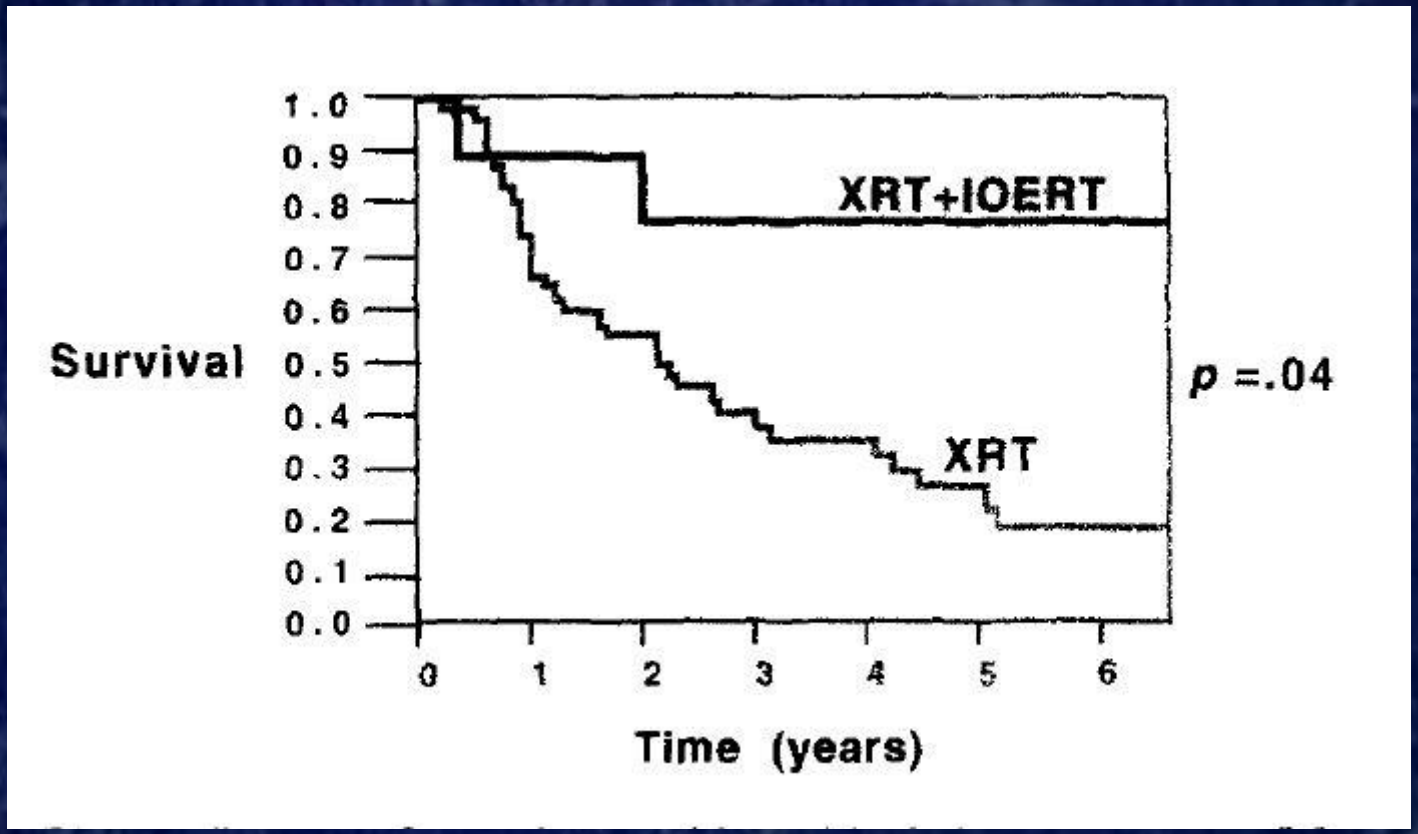


Fig. 2. Local control rate for patients with residual disease present following resection according to whether intraoperative electron irradiation (IOERT) was administered in addition to external beam radiotherapy (XRT).

Schild, Red journal 37:51, 1997

Primary Colon Cancer
IOERT for subtotal resection



Schild, Red journal 37:51, 1997

Locally Advanced Rectal Cancer
Selected Series with Control Group

		IORT						No IORT				
Study	Margin	EBRT Dose Gy	# Pts	IORT dose Gy	5-yr LC	5-yr DM	5-yr OS	# Pts	EBRT Dose Gy	5-yr LC	5-yr DM	5-yr OS
MGH	R0	50.4	20	10-20	88%		53%**	18	50.4	67%		53%**
Japan	NS	20	99	15-25	98%	20%	79%	68	0	84%	20%	58%
Rome	R0	45-55	29	10-15	100%	-	-	49	45 - 55	81%	-	
Dutch	R1	45-50	31	10	84%	-	-	17	45-50	41%	-	-
Shanghai	R0-1	45-50.4	71	10-20	90%	54%	75%	77	45-50.4	79%	56%	66%
French	R0-1	40	72	18	92%	26%	70%	68	40	93%	30%	75%

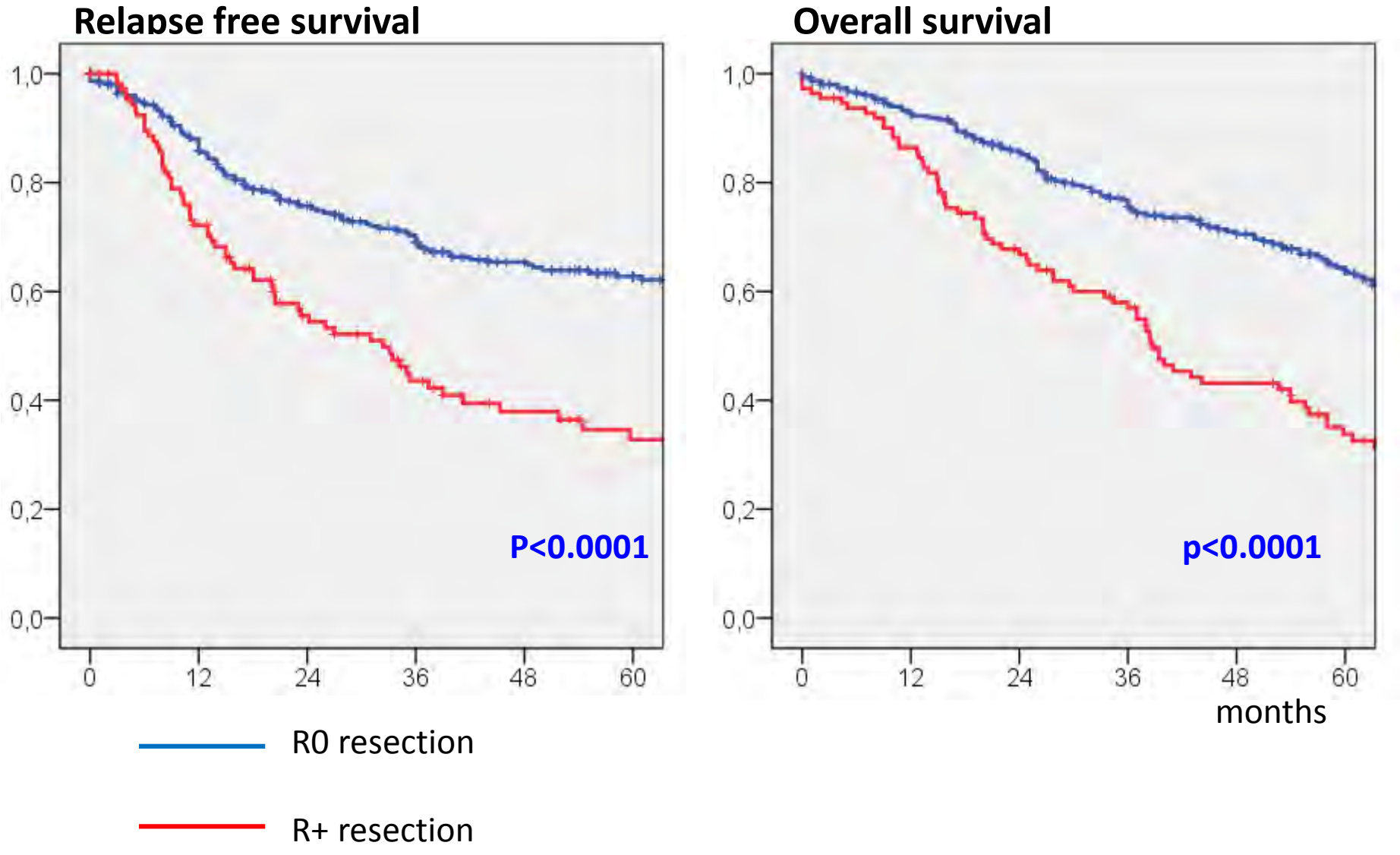
** Disease-free survival

Locally Advanced Rectal Cancer
Selected Series

Study	# Pts	Years	EBRT , Gy	Margins	IORT , Gy	5-yr LC	5-yr DM	5-yr OS
Willett, MGH[25]	20	1978-1989	50.4	R0	10-20	88%	-	53%*
Valentini, Rome[26]	29	1991-2006	45-55	R0	10-15	100%	-	-
Alberda, Rotterdam[27]	31	1996-2012	45-50**	R1	10^	84%	-	-
Zhang, Shanghai[28]	71	1994-2007	45-50.4	R0-1	10-20	90%	54%	75%
Sadahiro, Japan[29]	99	1991-2001	20	ns	15-25	98%	20%	79%
Mathis, Mayo Clinic[20]	106	1981-2007	50.4	R0-2	7.5-25	86%^^	49%^^	49%
Roeder, Heidelberg[30]	243	1991-2004	41.4	R0-2	10-15	92%	-	-
Sole, Madrid[31]	335	1995-2010	45-50.4	R0-1	10-15	92%	25%***	75%
Kusters, European pooled[32]	605	to 2005	45-50.4	R0-2	10-12.5	88%	29%	67%

T4 Rectal CA – IOERT Pooled Analysis, MCR-CHE

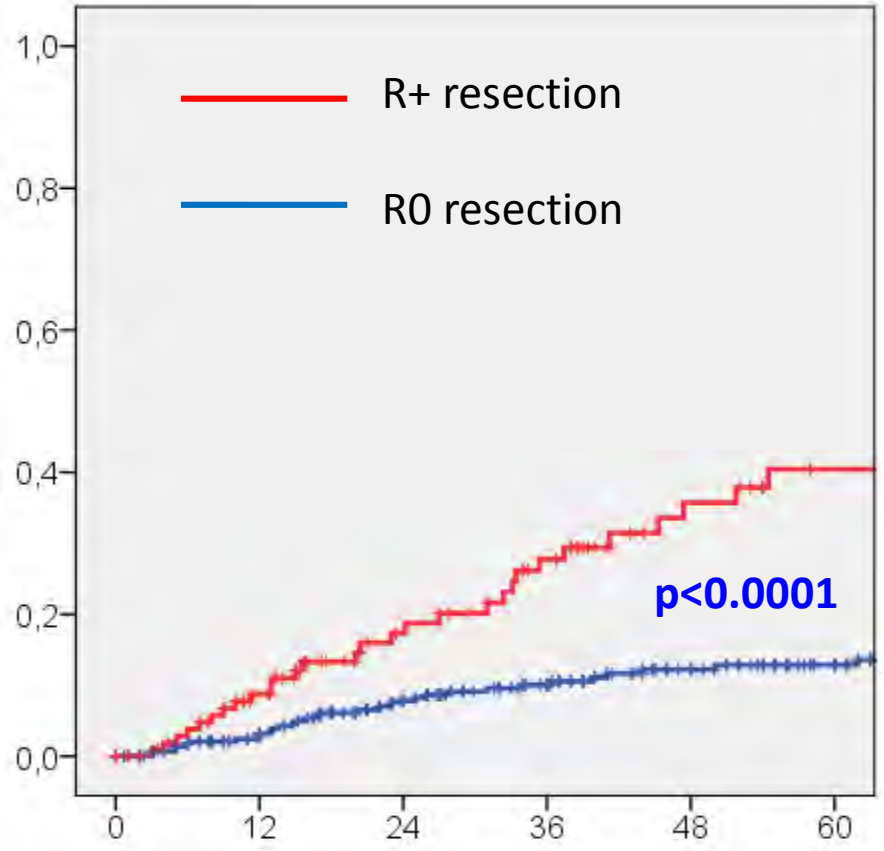
Survival Outcomes vs Radicality of Resection-417 pts



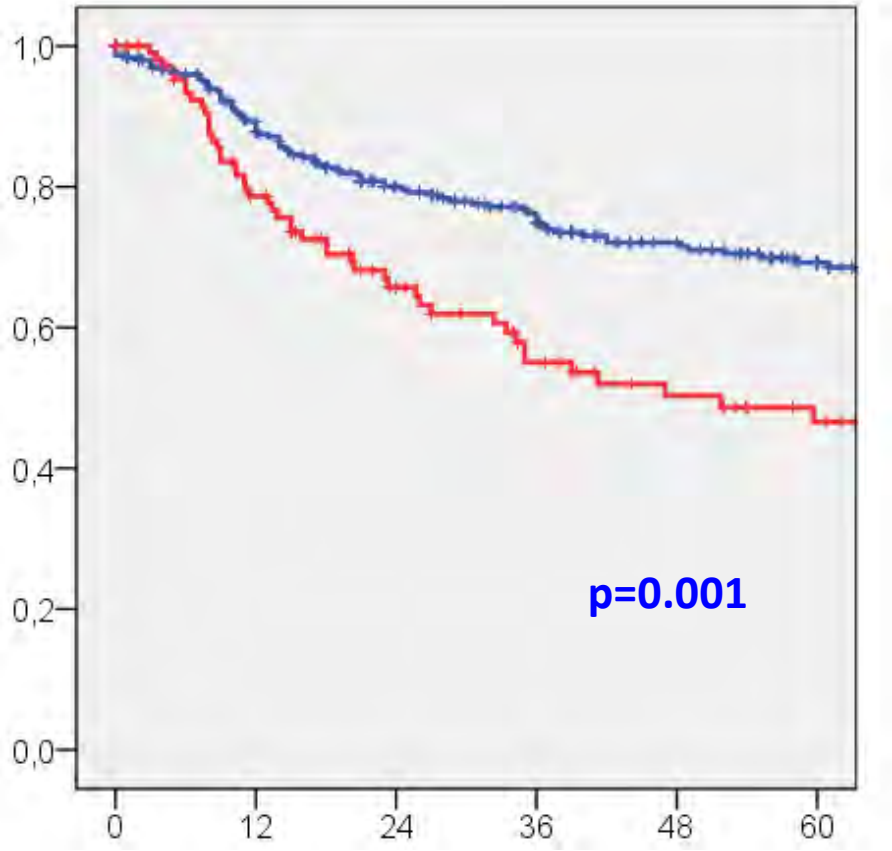
T4 Rectal CA – IOERT Pooled Analysis, MCR-CHE

Relapse Outcomes vs Radicality of Resection – 417 pts

Local recurrence rate



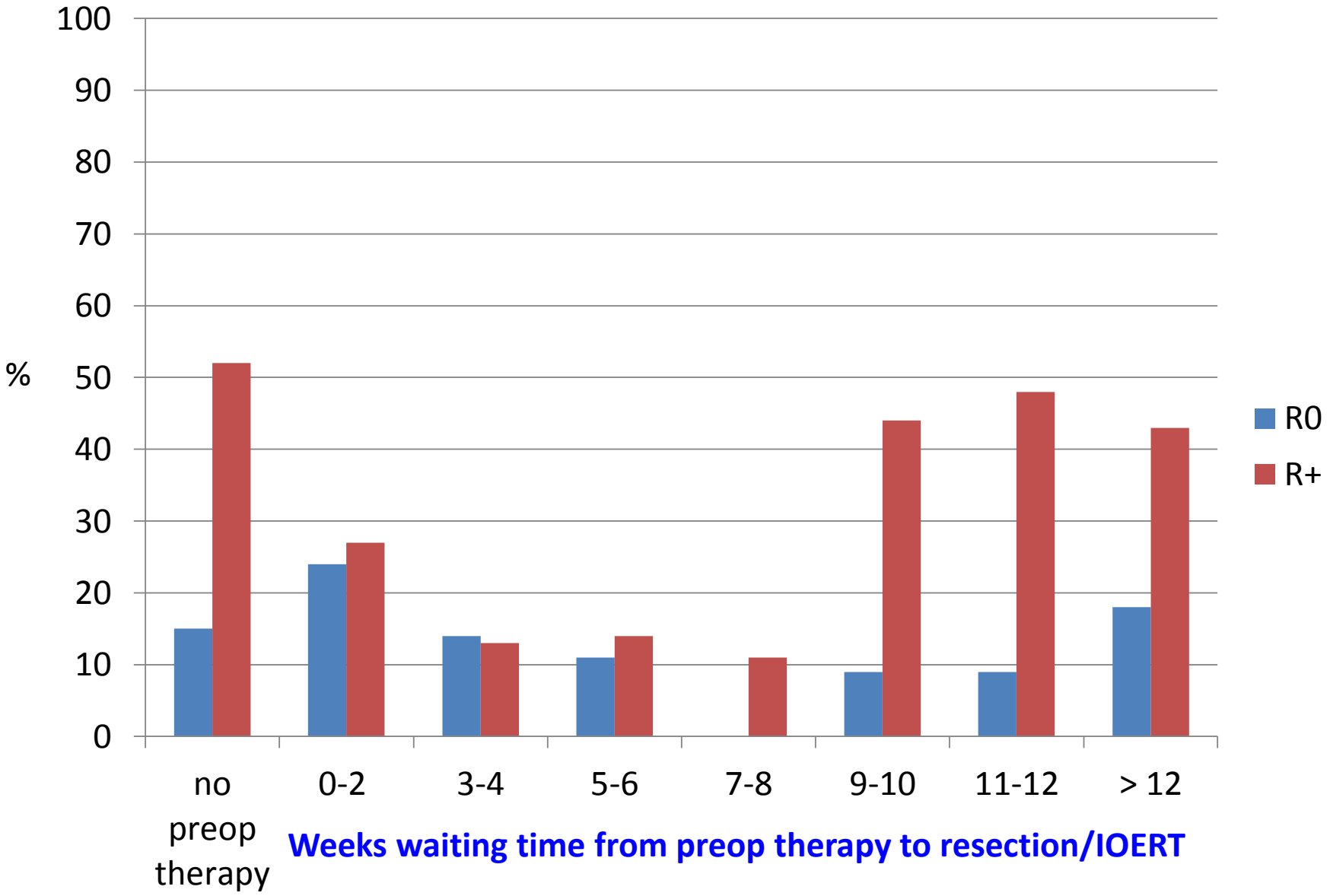
Metastasis free survival rate



months

T4 Rectal CA, IOERT Pooled Analysis, MCR-CHE

3-year Local Relapse vs Waiting Times, R0/R+ Resection



Locally Recurrent Colorectal Cancer
Results of monotherapy for salvage

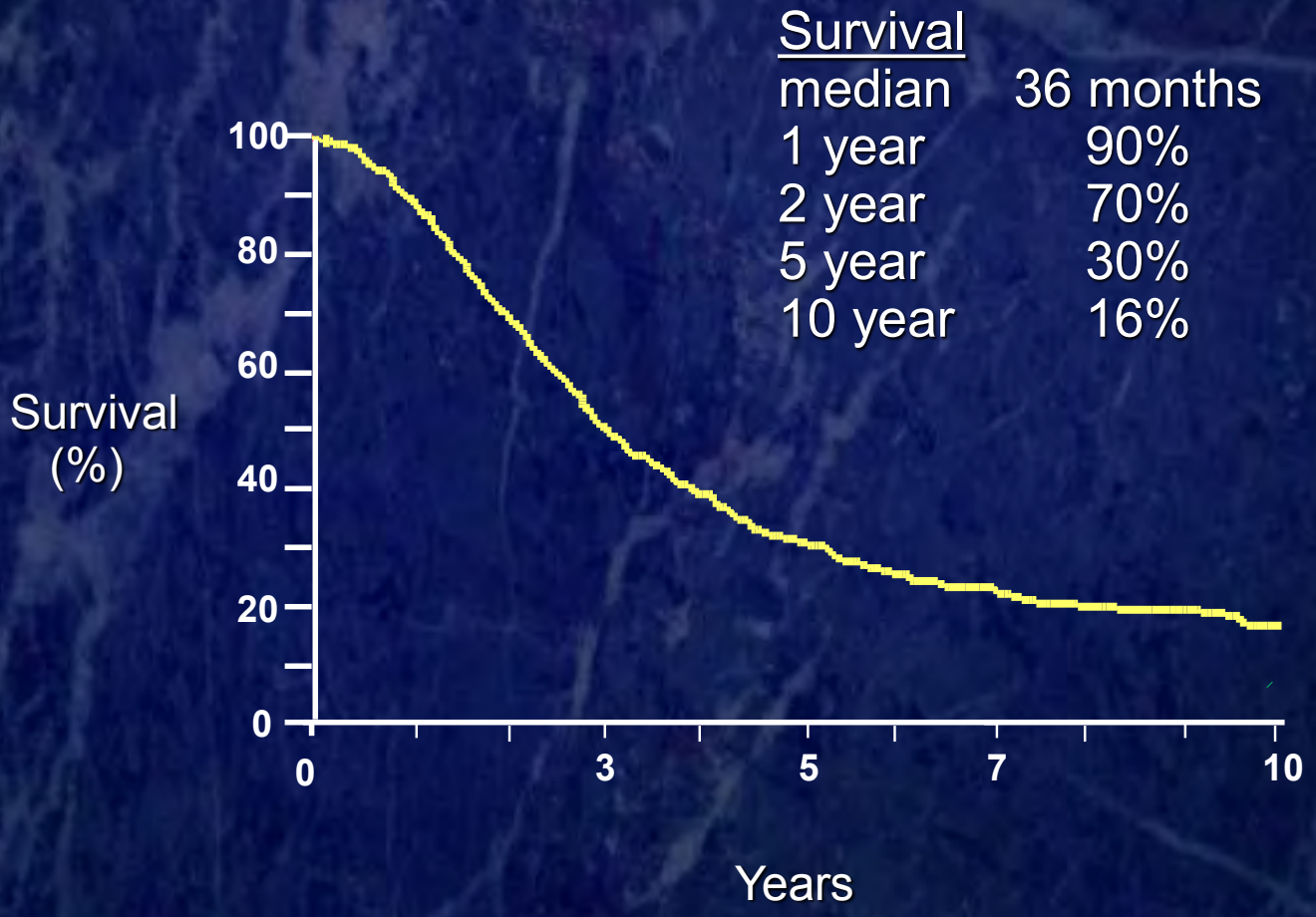
- Surgical resection alone:
  - anastomotic recurrence without fixation: long term survival in 50%
  - subtotal resection for locally advanced disease: 0-5% long term survival
- Radiotherapy +/- chemotherapy
  - pain relief in 75%, median duration 6-9 months
  - long term survival 0-10%
  - local control 20-30%

Recurrent Colorectal Cancer
Survival and Local Control

Series	#Pts	EBRT	Med S (mos)	5-yr S (%)	LR (%)
Lybeert	76	Y	14	5	68
(Neth, 1992)	-	< 50 Gy	12	0	
	-	≥ 50 Gy	20	10	
Guiney					
(Aus 1997)	16	low pall.	9	0	94
	80	45/15	15	4	94
	39	50-60 Gy	18	9	82
Suzuki	64	50 Gy	17	7	84
(Mayo 1995)					

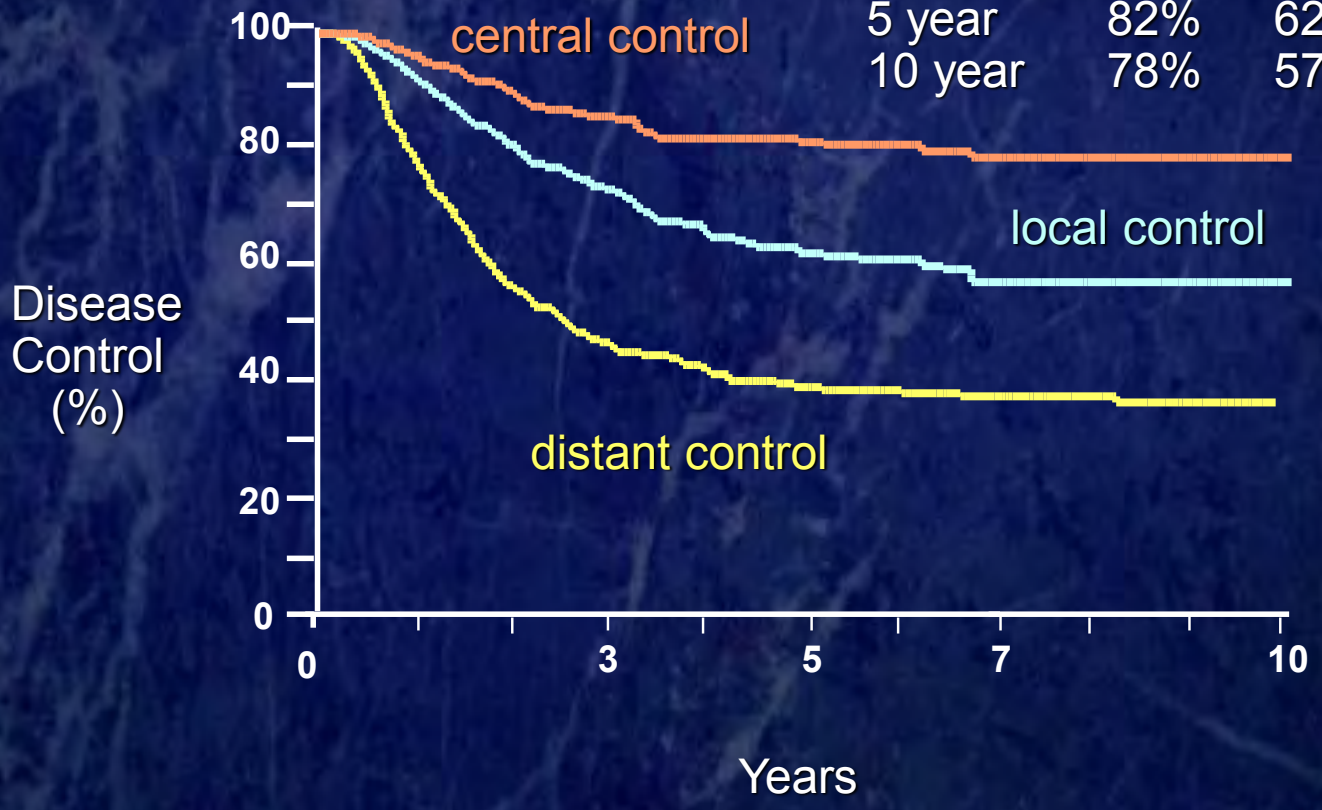
Overall Survival

Recurrent Colorectal IOERT



Disease Control - Recurrent Colorectal Ca

Endpoint	CC	LC	DC
crude	87%	74%	51%
1 year	96%	92%	78%
2 year	90%	80%	56%
5 year	82%	62%	38%
10 year	78%	57%	36%



IORT Results
R0 resection

Series	#Pts	EBRT (Gy)	IORT (Gy)	5-yr S (%)	LR (%)
Vermaas 2005	17	50	10	45 (3yr)	65
Alektiar 2000	53	45-50	10-18	36	57
Abuchaibe 2000	8	40-50	15	29	50
Dresen 2008	84	30-50	10	59 (3yr)	25
Lindel 2001	25	50	10-15	40	44
Eble 1998	14	41.4	12-20	71(4yr)	21
Wiig 2002	18	46-50	15	60	30
Valentini 1999	11	45-47	10-15	41	20
Haddock 2010	236	30-50	12.5	46	28

IORT Results
R1 resection

Study	# Pts	EBRT dose, Gy	IORT dose, Gy	IORT technique	5-year LC	5-yr DM	5-yr OS
Alektiar, MSKCC	21	50.4*	10-18	IOHDR	26%	-	11%
Wiig, Norway	29	46-50	15-20	IOERT	50%	-	20%
Eble, Heidelberg**	9	41.4	10-20	IOERT	67%	33%	33%^
Dresen, Eindhoven***	34	50.4^^	12.5	IOERT	29%	69%	27%
Haddock, Mayo Clinic	224	50.4^^^	15	IOERT	56%	62%	27%

***50.4 in patients with no prior EBRT; no EBRT in patients with prior radiation**
****4-year results**
^4-year relapse free survival^^30.6 Gy in previously irradiated patients
^^^5-39.6 Gy in previously irradiated patients
*****3-year results**

IORT Results
R2 resection

Study	# Pts	EBRT dose, Gy	IORT dose, Gy	5-year LC	5-yr DM	5-yr OS
Lindel, MGH	15	50.4*	15-20	12%	-	13%
Eble, Heidelberg**	8	41.4	10-20	60%	75%	25%^
Dresen, Eindhoven	29	50.4^^	15-17.5	29%	71%	24%
Haddock, Mayo Clinic	156	50.4^^^	20	49%	73%	16%

*20-50 Gy in previously irradiated patients
**4-year results
^4-year relapse free survival
^^30.6 Gy in previously irradiated patients
^^^5-39.6 Gy in previously irradiated patients

Survival- Multivariate Analysis
Recurrent Colorectal IOERT

Group	Multivariate P value
• R0 vs R1 vs R2	< 0.0001
• No prior Chemo	0.0004
• Treatment after 3/3/97	0.012
• Colon vs. rectum	0.065
• Systemic chemo	0.075
• Age < 61.5	0.122
• CT with EBRT	0.400
• Prior EBRT	0.897

IOERT Related Neuropathy

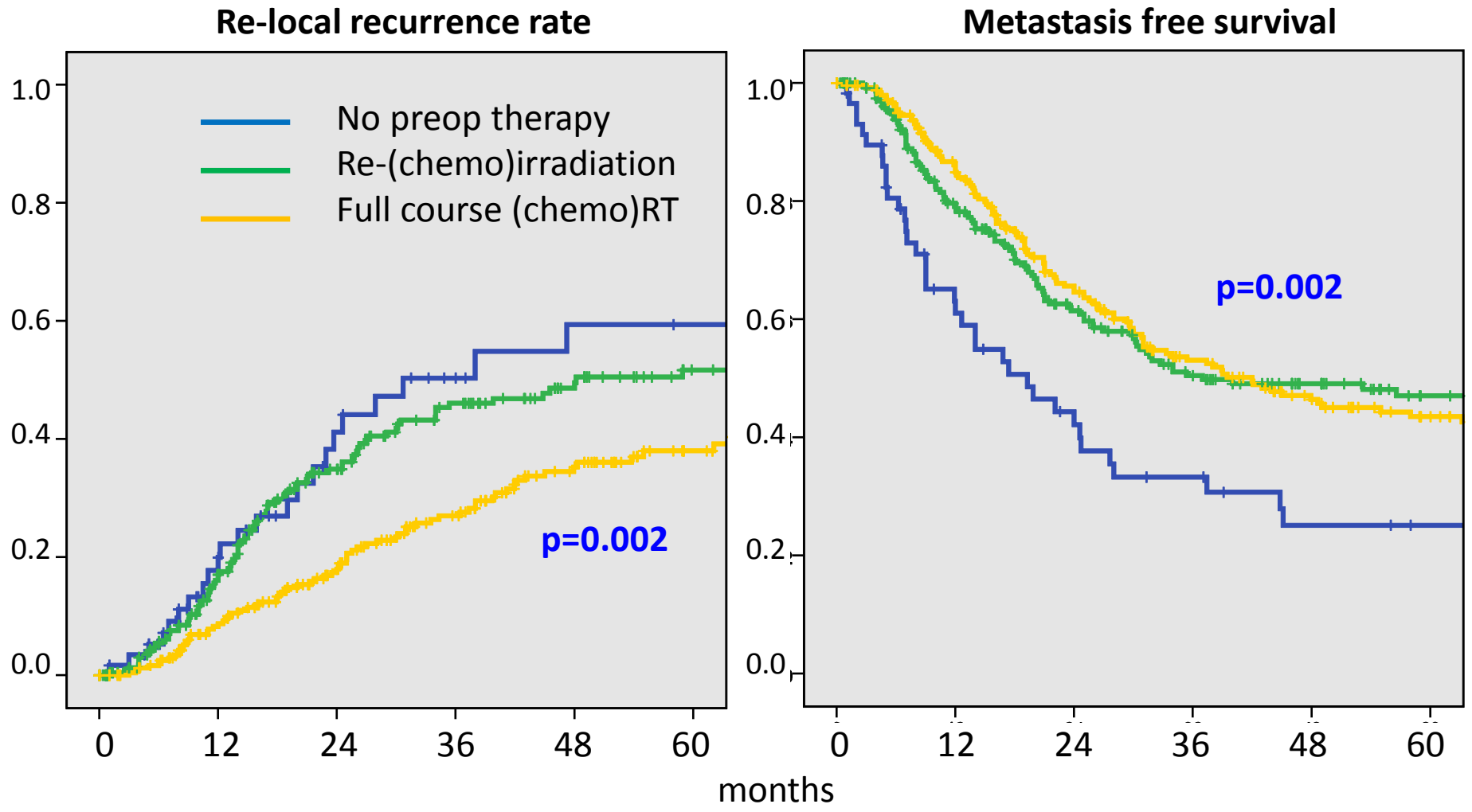
Recurrent Colorectal Cancer

	IOERT Dose	
	≤ 1250 cGy	> 1250 cGy
any neuropathy	9%	21%
Grade 1	3%	7%
Grade 2	4%	10%
Grade 3	1%	4%

P = 0.0003

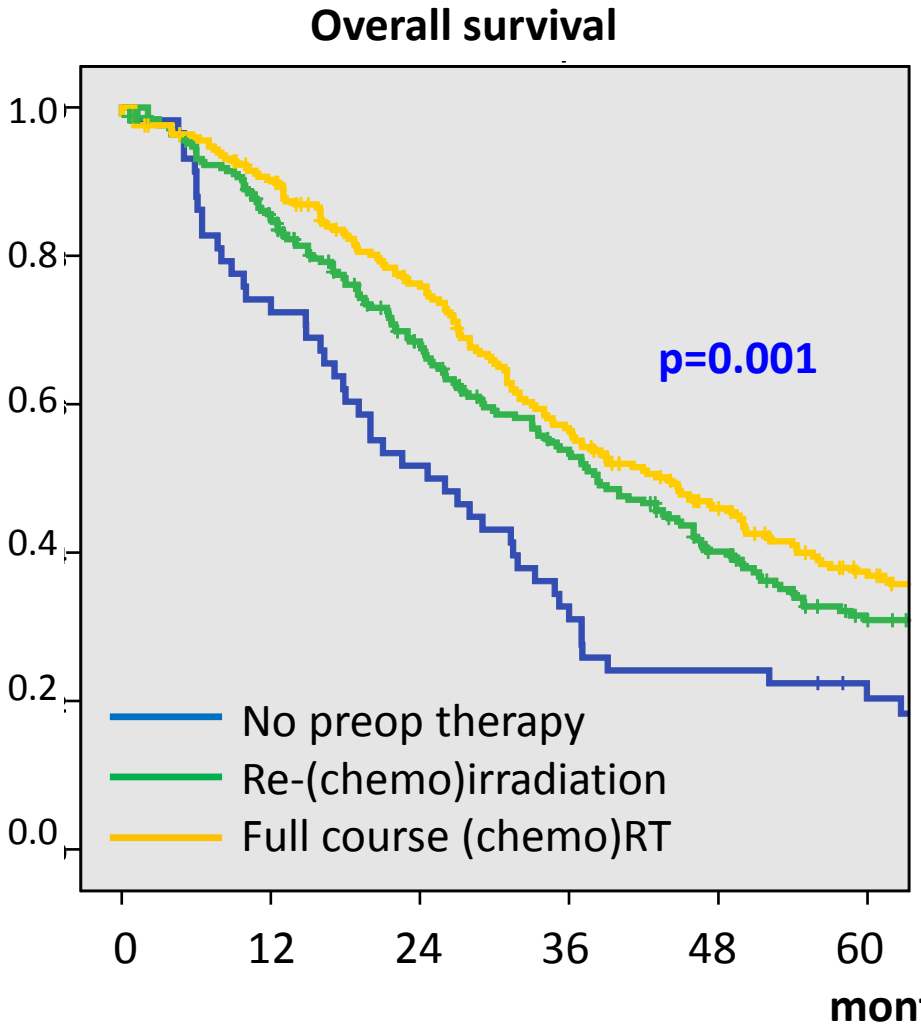
LRRC – IOERT Pooled Analysis, MCR-CHE, 565 pts

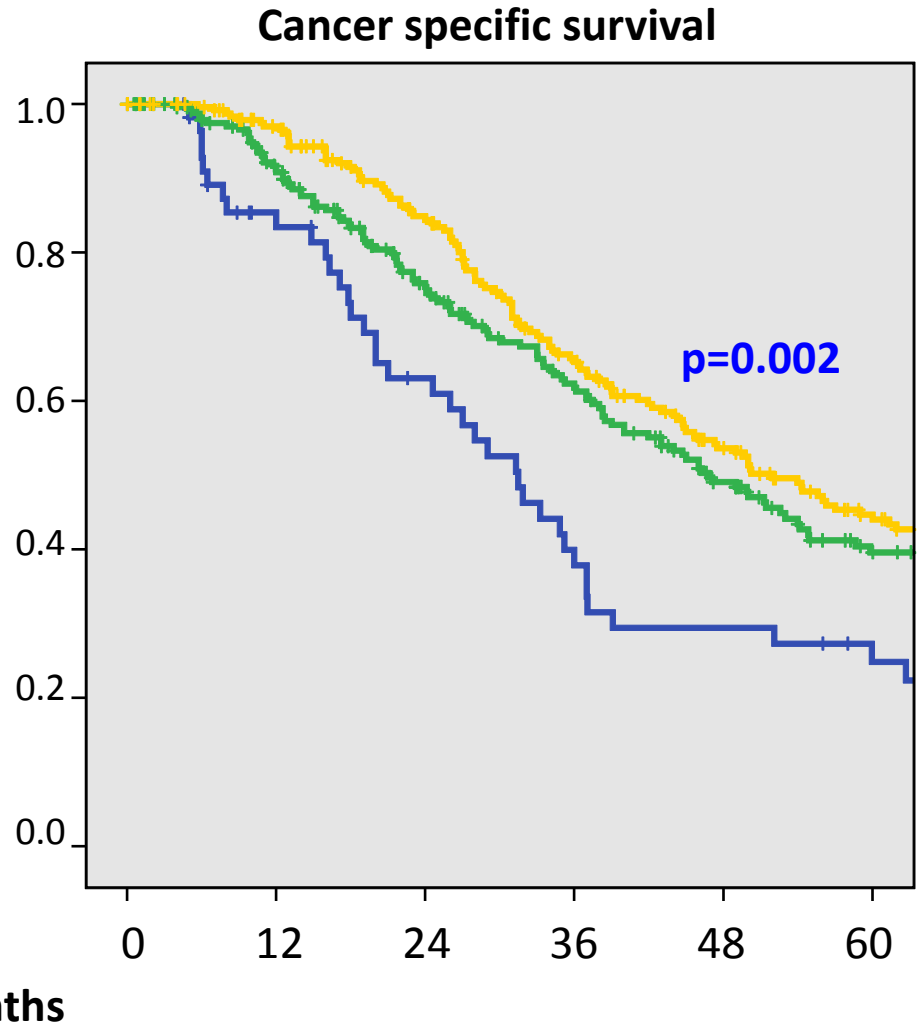
Relapse Outcomes vs Preoperative Treatment



LRRC – IOERT Pooled Analysis, MCR-CHE, 565 pts

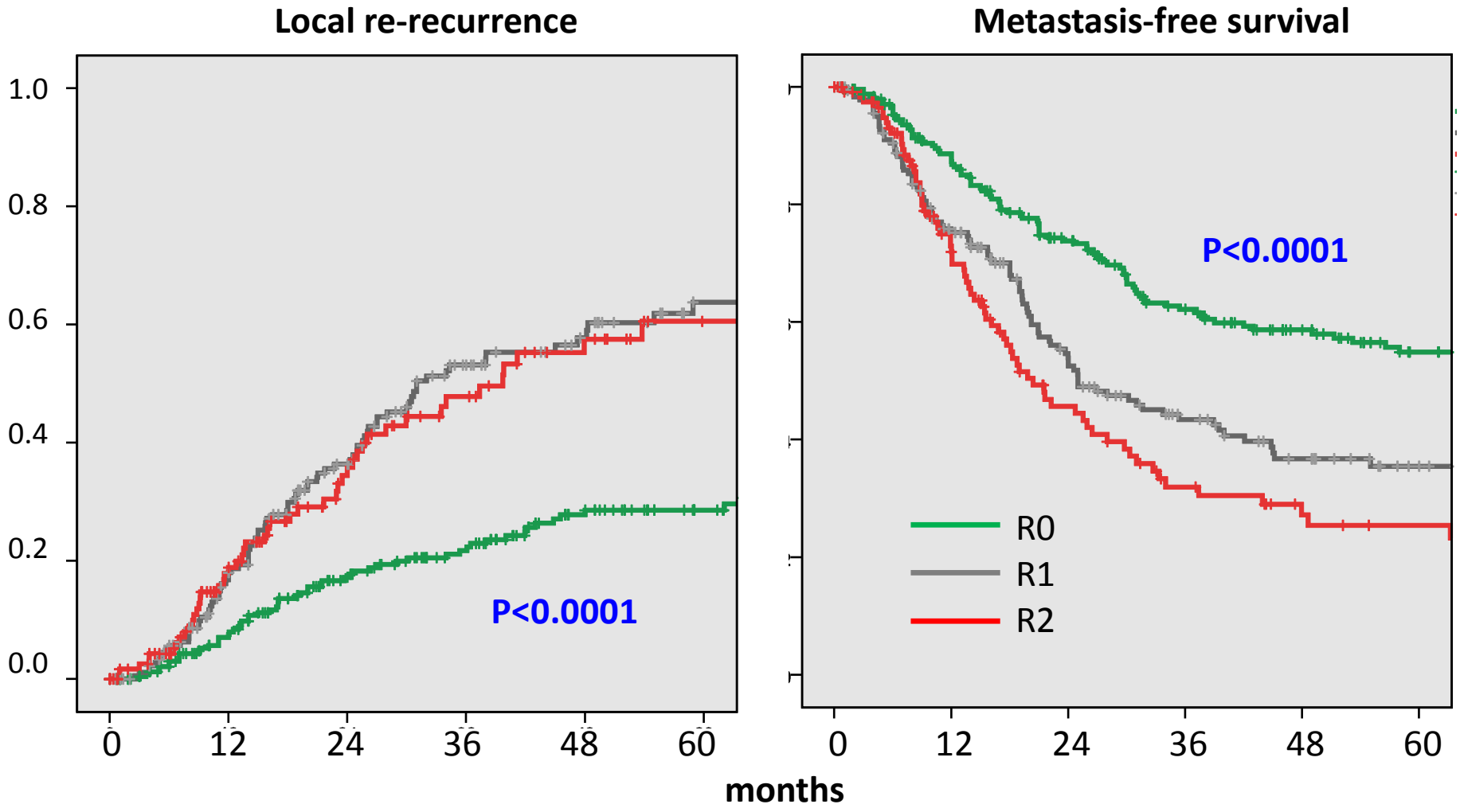
Survival Outcomes vs Preoperative Treatment





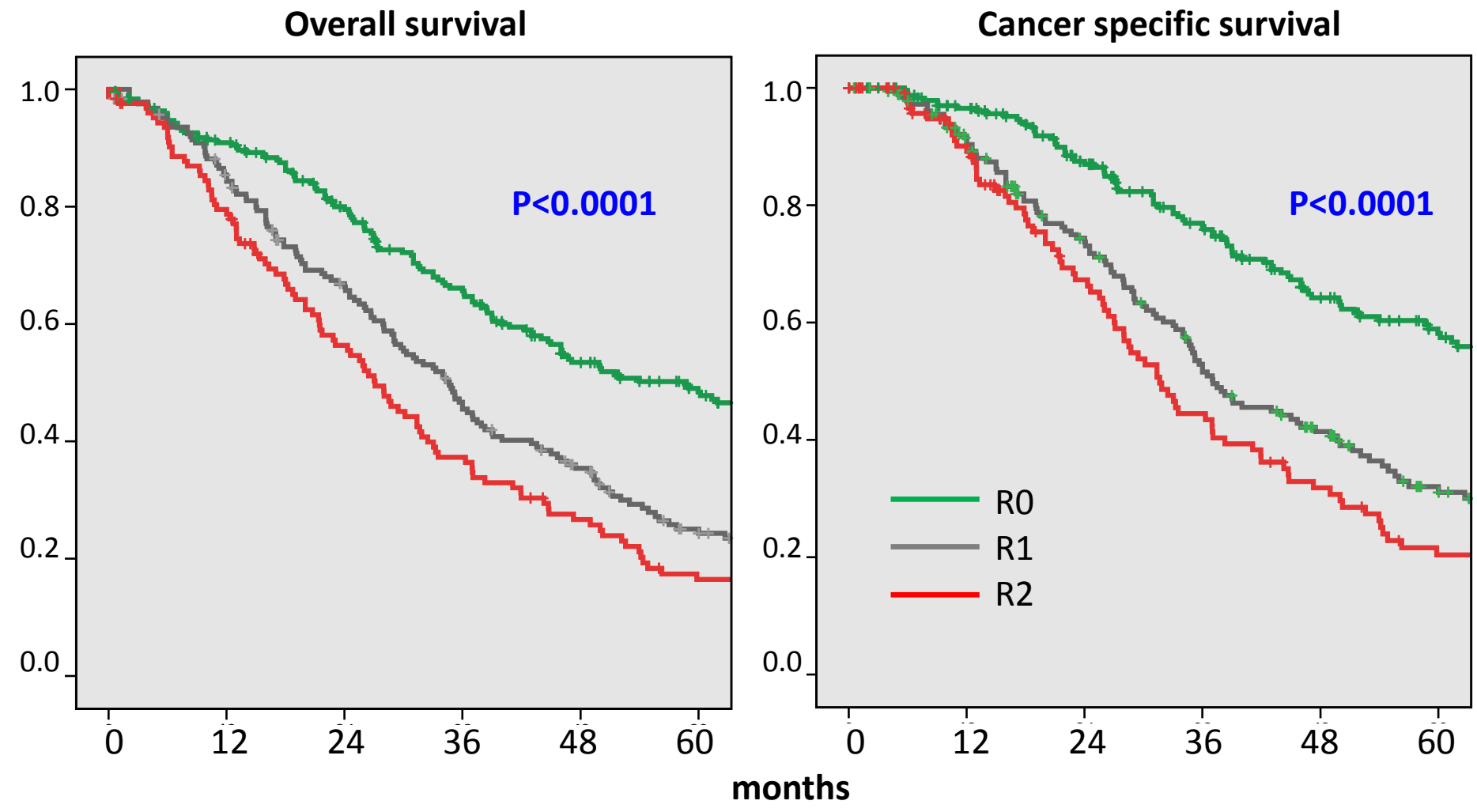
LRRC – IOERT Pooled Analysis, MCR-CHE, 565 pts

Relapse Outcomes vs Radicality of Resection



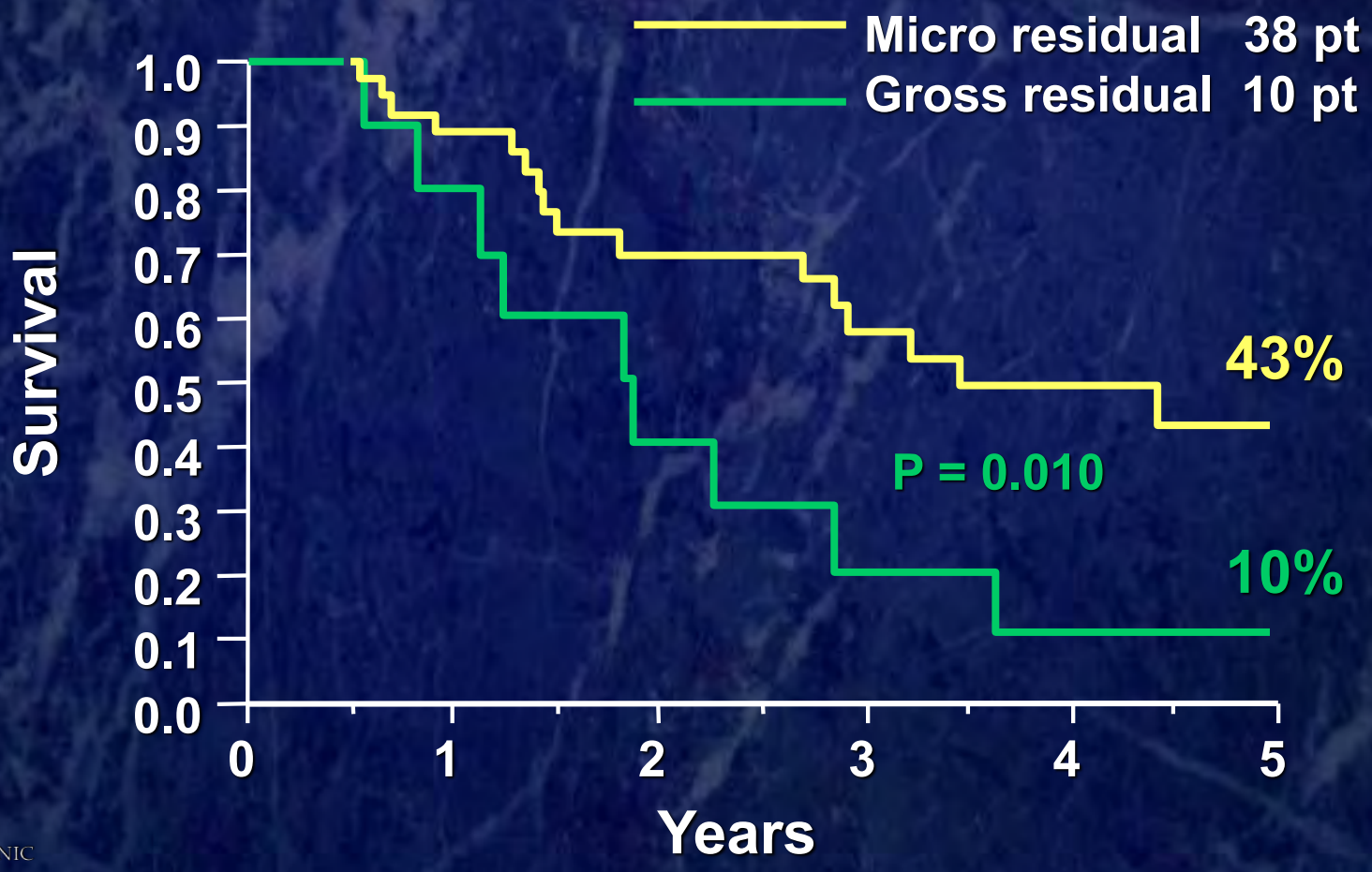
LRRC – IOERT Pooled Analysis, MCR-CHE, 565 pts

Survival Outcomes vs Radicality of Resection



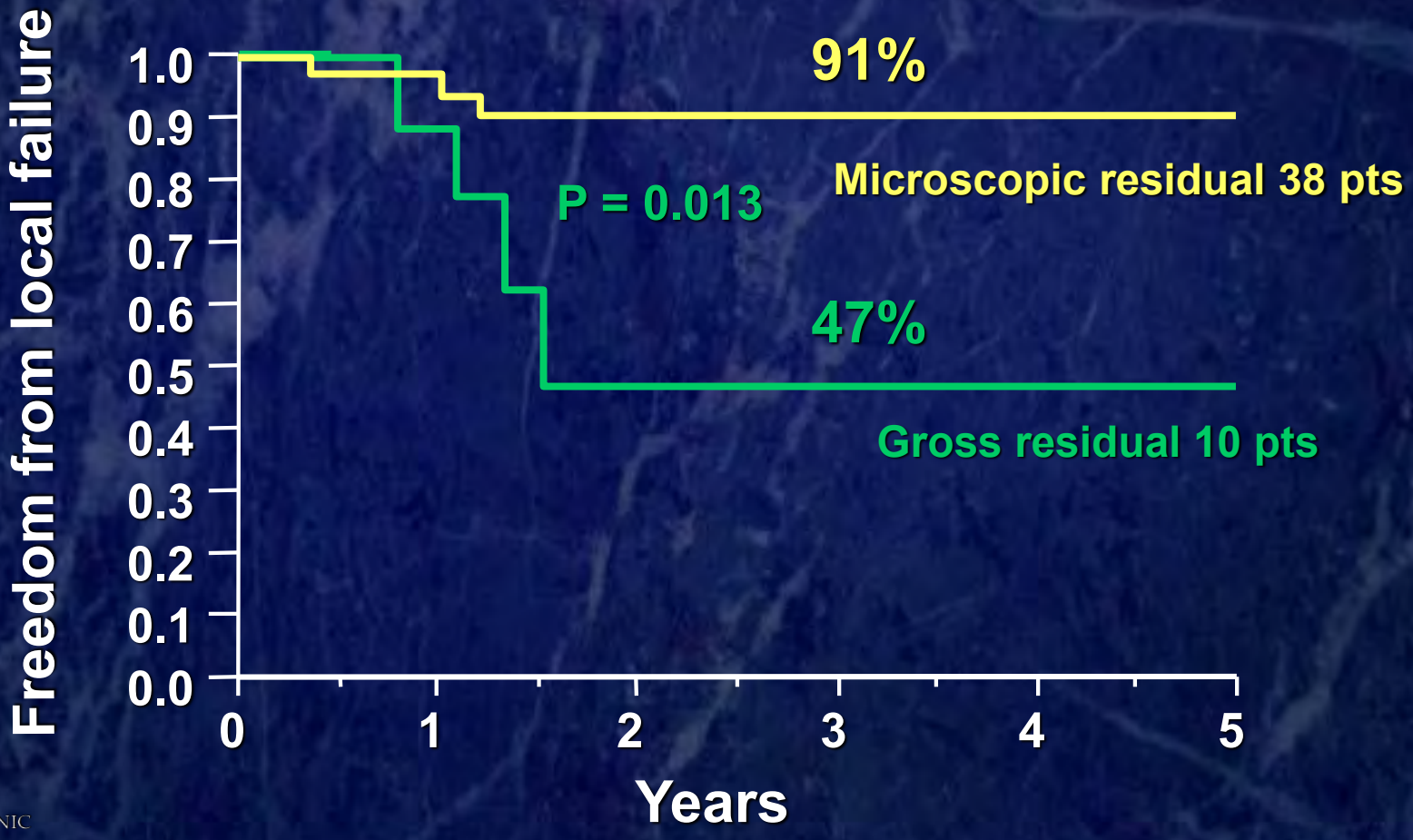
IOERT for Colorectal Nodal Mets

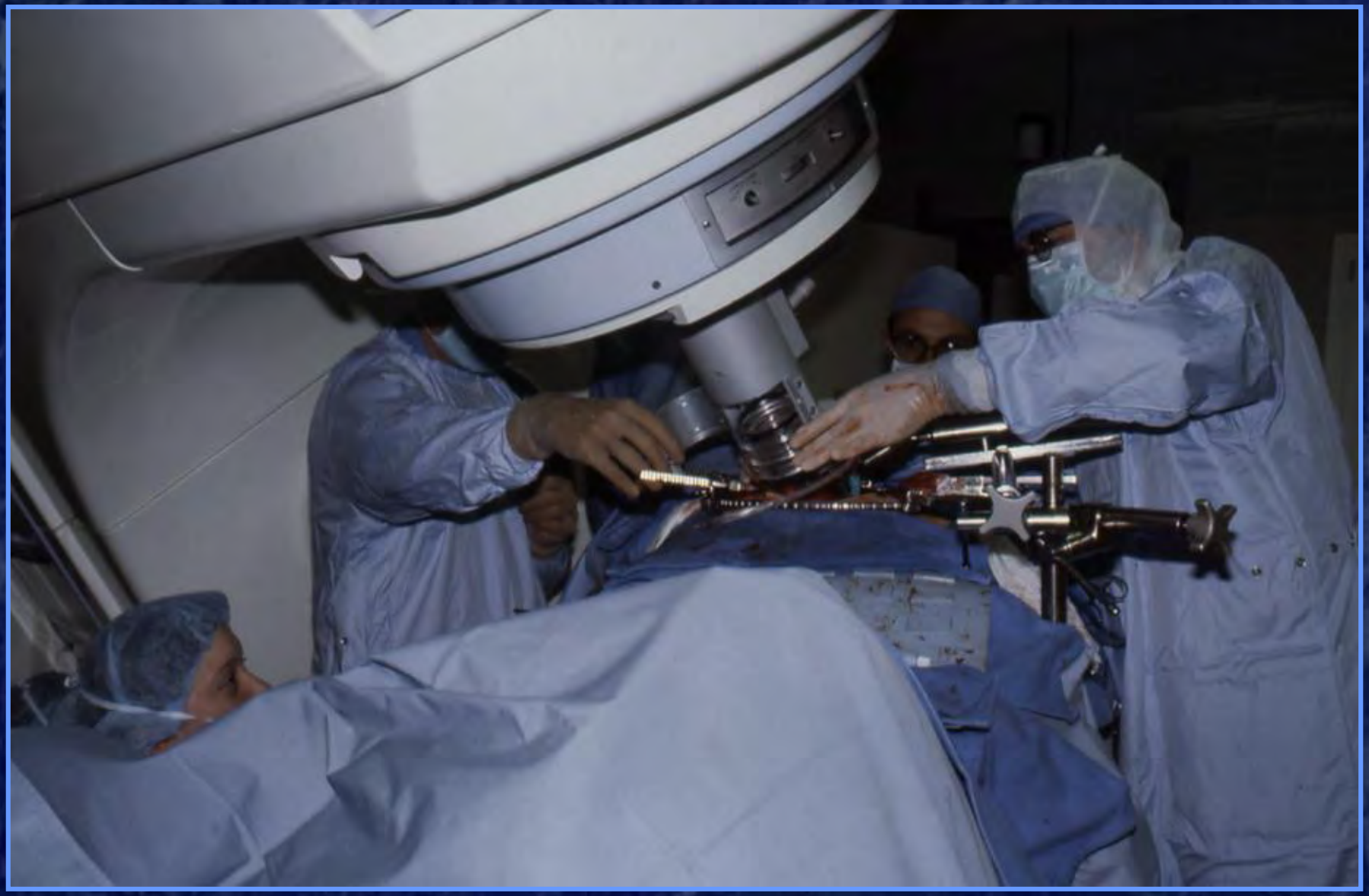
Survival by amount of residual



IOERT for Colorectal Nodal Mets

Local control by residual





IORT for GI Malignancies
Potential IORT Sites

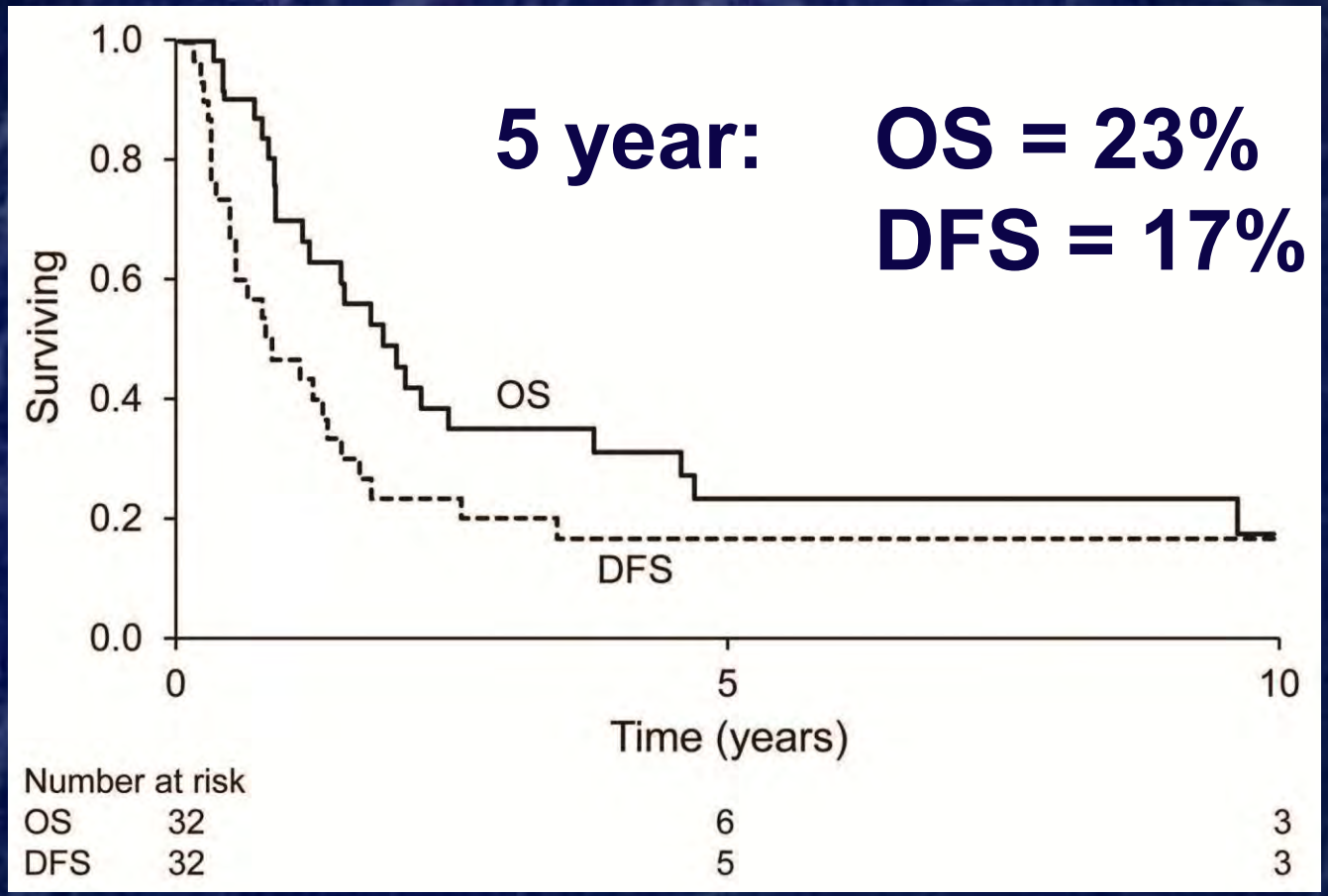
- Esophageal Cancer
- Gastric Cancer
- Biliary Cancer
- Pancreas Cancer
- Colorectal Cancer
- Anal Cancer

Anal Cancer
IORT: Mayo series

- 32 patients: 9 residual, 23 recurrent
- EBRT: 30 Gy/15 + 5-FU
- IORT: 12.5 Gy
- Surgery: R0 – 16, R1 – 13, R2 – 3
- 5-yr S 23%
- 5-yr relapse:
  - Central: 21%
  - Locoregional: 51%
  - Distant: 40%

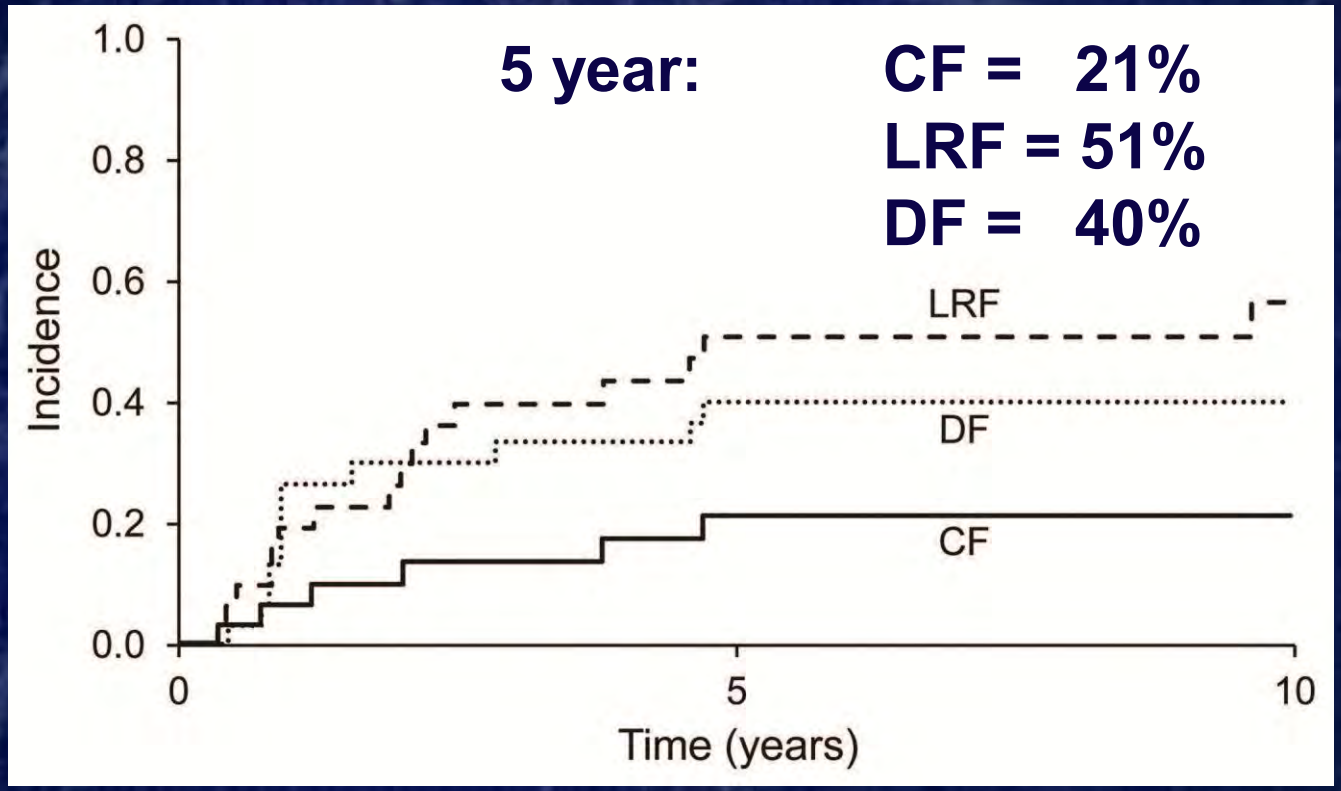
Hallemeier, Dis Colon Rectum 57:442-8, 2014

Anal Cancer
IORT: Mayo series



Hallemeier, Dis Colon Rectum 57:442-8, 2014

Anal Cancer
IORT: Mayo series



Hallemeier, Dis Colon Rectum 57:442-8, 2014

IORT for GI Malignancies
Conclusions

- IORT is an important component of an intensive multidisciplinary effort
- IORT associated with improved local control and survival in locally advanced primary and recurrent disease
  - Esophagogastric cancer
  - Biliary cancer
  - Pancreatic cancer
  - Colorectal cancer
- Gross total resection is key prognostic factor

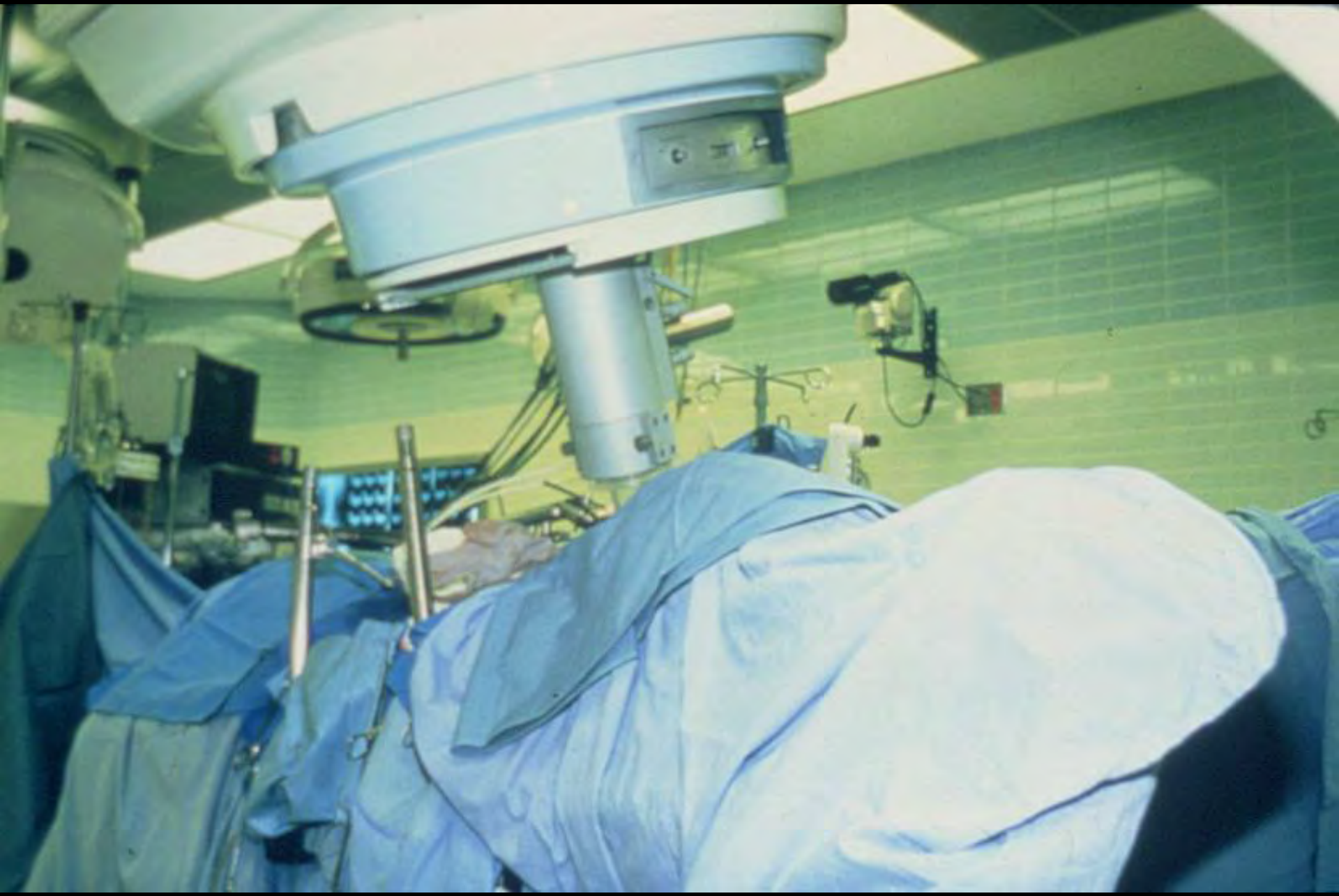
IORT for GI Malignancies
Conclusions

- Distant relapse is main pattern of failure for most GI sites
- Nerve is dose limiting for IOERT
  - Higher frequency and severity with IOERT dose > 1250 cGy
- Multimodality curative intent approach is appropriate for selected patients


1
3
4

The End

Grazie mille!



Which factors contribute to early tumor control failure after APBI/IOERT for elderly breast cancer patients ?

RCWEST
RADIOTHERAPIECENTRUM WEST

P.Koper, radiation oncologist

H.Struikmans, M.Mast, U Fisscher, A.Pethoukhova; radiotherapy, MCHaaglanden/Bronovo
A.Marinelli, J.vander Sijp; surgery MCHaaglanden/Bronovo
JH.Franssen, G.Speijer, F.Gescher radiotherapy Haga ziekenhuis
J.Merkus, I.Jannink; surgery Haga ziekenhuis
E.Roeloffzen, A.Zwanenburg; radiotherapy Isala kliniek
AB.Francken; surgery Isala kliniek

Breast conserving therapy using APBI in Elderly Patients; a feasibility study. METC ZuidWest Holland 10-042

Elderly breast cancer patients ≥ 60 years

T1 cN0 SN0 (perop.) any grade, any ER, any HER2
T2 cN0 up to 30 mm SN0 (perop.), ER+, HER2 neg. excl. triple Neg. (grade 3, after ELIOT publication)

IOERT/ELIOT	APBI ext beam
1*23.3 Gy (100%) / 1 day	10*3.85 Gy (ICRU) / 2 weeks
Number needed 179; LR < 5%/ 5yr ; closed at 311	Number needed 179; LR < 5%/ 5yr ; active at 255

A comparative non-randomized study

practical study: having IORT in MCH/Bronovo and no IORT in collaborating (other NL) hospitals

Randomisation illusion; practically ….. and efficacy (assumption IORT=APBI)

Regular follow up Mammography, tumour control etc.	**Regular follow up** Mammography, tumour control etc.
QOL; EORTC C30 / Br 23	**QOL;** EORTC C30 / Br 23
Cosmetic Q (patient / doctor)	**Cosmetic Q** (patient / doctor)
Colour pictures (BCCT at 3 yr)	**Colour pictures** (BCCT at 3 yr)
Geriatric Q; GFI/VES13/G8	**Geriatric Q;** GFI/VES13/G8

RCWEST
RADIOTHERAPIECENTRUM WEST

Kaplan Meier analysis 2 year actuarial overall survival and TLR (first event)

Factors that contribute to early tumor failure after APBI/IOERT for elderly breast cancer patients

Actuarial 2 year	IORT Med fu 24.1 M	APBI Med fu 18.3 M
TLR first event	0.5%	0%
TLR all	1.2%	0%
IBTR first event	1.2%	0%
IBTR all	1.9%	0%
®Death (breast)	4(0)	2(0)
Bleeding *	1%	2.5%
Wounddehisc. *	4%	1%
Seroma *	1.4%	1%
Infection **	5%	3%

NS

® up till now IORT 9(1) and APBI 2(0)

* serious/surgery; ** antibiotics/surg

RCWEST
RADIOTHERAPIECENTRUM WEST

Possible risk factors that might explain difference?

	IORT		APBI
ER-	6%		6%
Her2+	6%	X	5%
Triple neg	6%		4%
Age (median)	69	X	68
No syst ther	59%		62%
Adj horm ther	34%	X	29%
Adj chemo ther	2%		3%
Adj both	5%		5%

RCWEST
RADIOTHERAPIECENTRUM WEST

Possible risk factors that might explain difference?

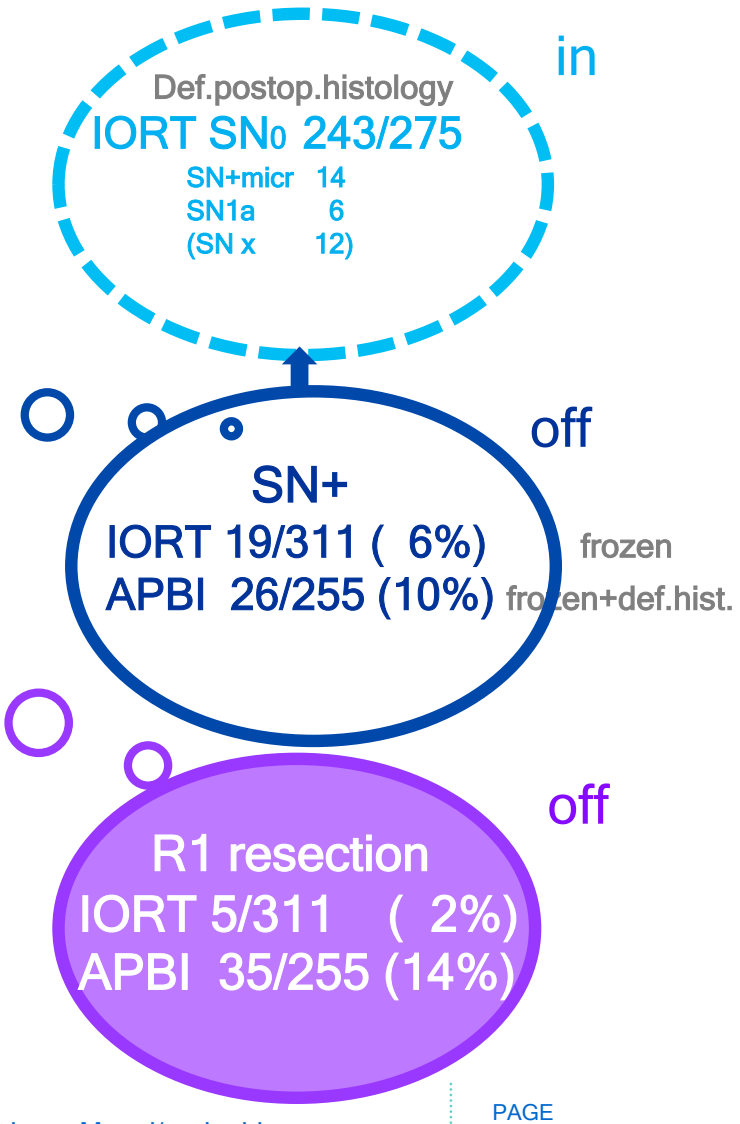
Grade 3 ? DCIS ?

	IORT	APBI
Invas gr3 + DCIS gr3	21%+2%	14%+8%
DCIS gr1,2 + DCIS gr3	8%+3%	14%+8%
	=11%	=22% !!!
Invas 0mm	8%	14%
Invas <10mm	33%	25%
Invas 10-20mm	49%	49%
Invas >20mm	10%	13%
Invas+DCIS 0mm	1%	0%
Invas+DCIS <10mm	33%	28%
Invas+DCIS 10-20mm	53%	55%
Invas+DCIS >20mm	13%	16%

Possible risk factors that might explain difference?

Reasons off study

	IORT	APBI
Informed consent	311	255
SN+	16	20
SN+/other *	1	2
SN+/R1	2	4
R1	3	23
R1/other **	-	3
Tight margin	-	5
Other	19	21
Off study	41	78
On study	251	170



* bone M and/or double tumor
** primary tumour too large

Possible risk factors that might explain difference?

"new phenomenon" !!??

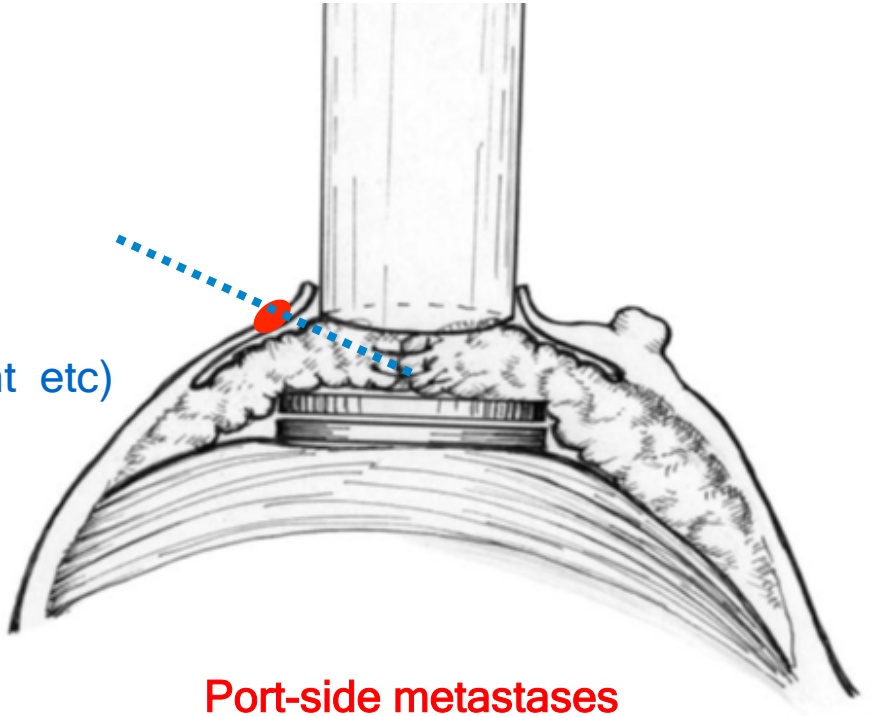
25% of (TLR) IBTR

port-side metastases

=biopsy tract spill (histological identical ; first event etc)

15% uncertain

1. in combination with distant M
2. still unclear (histology) but "looks like"



Port-side metastases

IBTR / metastases in reconstructed path of (mammography/sterotactic) biopsy

HOW ?

Your radiologist is trying to help you !?!

Review article; "Therapeutic potential of Breast Lesion Excision System:is it feasible to completely excise small solid carcinomas?"

Not completely New. Has been reported in skin sparing mastectomy

WHEN?

Grade 3 !! Although not exclusively

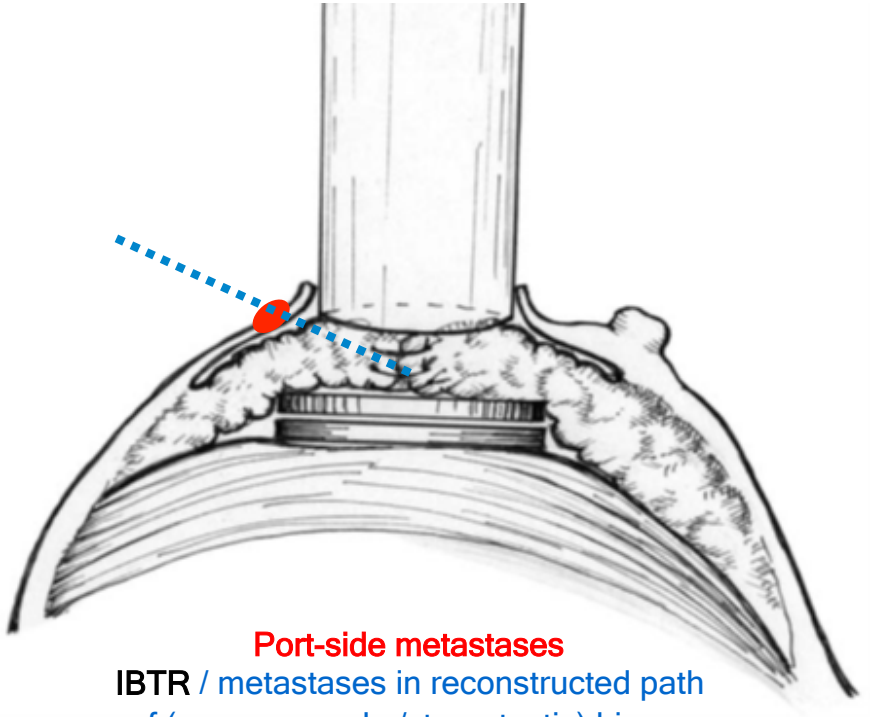
T2 gr 3, 25 mm, margin 3 mm, ER+PR-HER-; tamoxifen
T1c gr 3,17 mm + DCIS gr 3, margin 1mm, ER-PR-HER+++; no adj syst.
T1c gr 2, 12 mm + DCIS gr 2, margin 3 mm, ER+PR-HER-; no adj syst.

Grade 3 > 4% ; Grade 2 = 0.5%

Adjustment of surgical protocol:

Colour picture and ink marking (patient) of biopsy site

Surgical removal of biopsy site at lumpectomy / SN



Port-side metastases
IBTR / metastases in reconstructed path of (mammography/stereotactic) biopsy

TLR?
Out Q recurrence?

Factors that contribute to early tumor failure after APBI/IOERT for elderly breast cancer patients

Conclusions part 1 / take home message

There is more than IORT for a “successful IORT treatment”!

Port side recurrence / biopsy tract spill

Biopsy procedure (be aware of efforts to completely excise small tumours)
Unsuspected biopsy direction

Addendum surgical protocol: mark biopsy and remove

Surgical protocol (we expected more R1 for IORT, but found less!)
Immediate pathology check / specimen mammography is important

Factors that contribute to early tumor failure after APBI/IOERT for elderly breast cancer patients

RCWEST
RADIOTHERAPIECENTRUM WEST

Conclusions part 2

Lessons learned from IORT vs APBI comparison

Surgical protocol (we expected more R1 for IORT, but found less!)
Immediate pathology check / specimen mammography is important

APBI can (more easily) select favourable patients (exclude unfavourable ?)
Treatment bias?

DCIS favourable? DCIS registration study
grade 3 unfavourable for TLR / port side metastases ? IBTR ?

These are early results …..Longer follow up needed !!!

Act. 2 year IORT TLR 0.5 / 1.2% (IBTR all 1.9%); APBI TLR 0% / 0% (IBTR all 0%)

Thanks for your attention

Peter

9th International ISIORT Conference

June 24/25th 2016
Novara, Italy

BREAST CONSERVING SURGERY:

INTRAOPERATIVE RADIOTHERAPY USING NOVAC 7, EXPERIENCE WITH 703 CASES AT CITTÀ DI CASTELLO HOSPITAL (ITALY).

USL Umbria 1

Marina Alessandro

Radiation Oncology Department

Città di Castello Hospital

RATIONALE

In the last years there has been growing interest to experience less extensive treatments for selected patients at low risk of locoregional and systemic recurrence of breast cancer

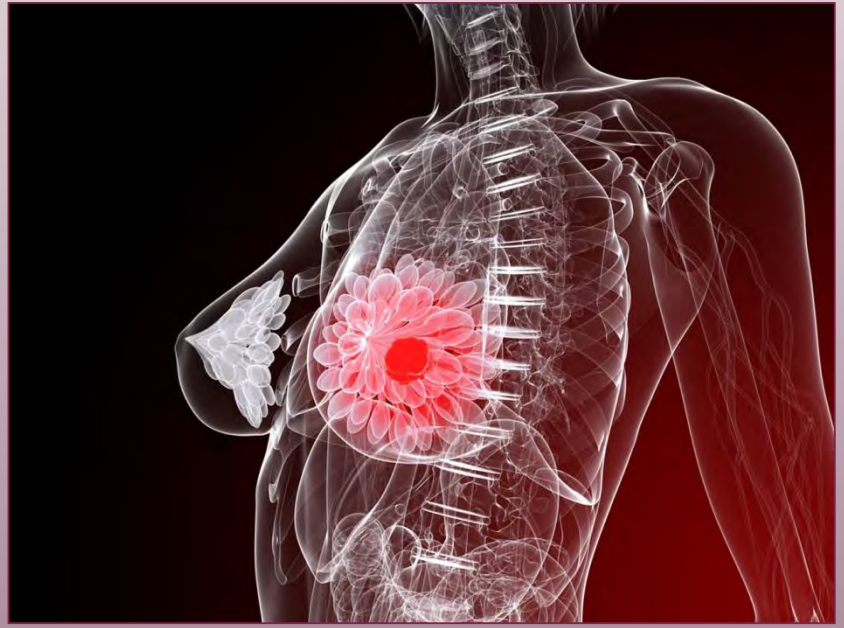
Personalised management is considered the future of cancer care: medicine aiming at giving patients the best treatment according to

- their personal medical history,
- their physiological status
- and the molecular characteristics of their tumours.

RATIONALE

The whole breast irradiation is not always the most convenient treatment for age, comorbidity, logistical and socio-economic reasons.

To reduce the radiation treatment time and to control tumor disease in breast area with the higher risk of relapse, was proposed Partial Breast Irradiation (PBI).



9th International ISIORT Conference June 24/25th 2016 Novara, Italy

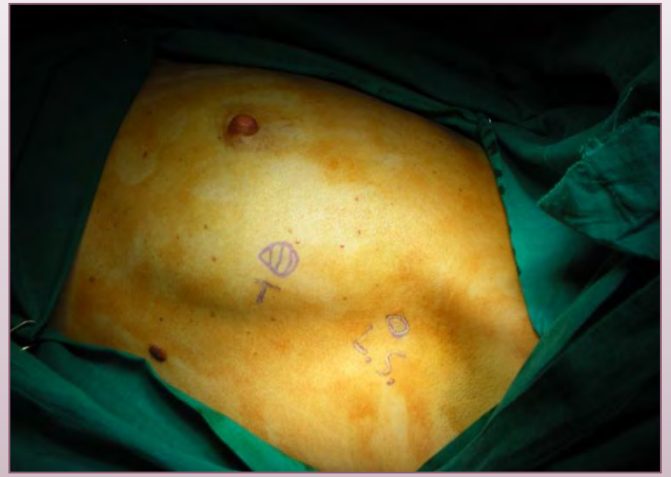
IOERT: EXPERIENCE

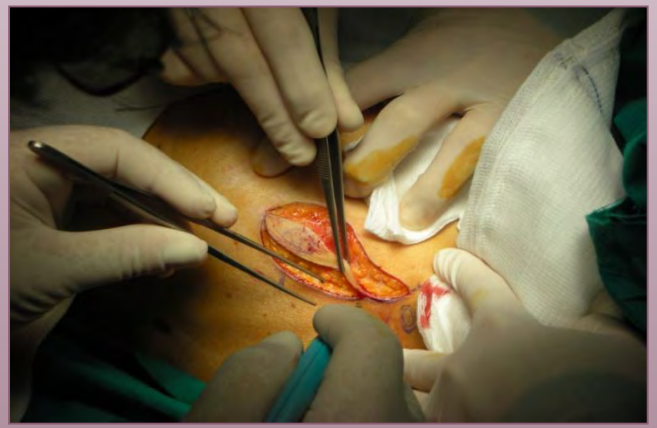
In our center we use a mobile linear accelerator, the NOVAC 7, as approach to deliver partial breast irradiation or as tumor bed boost for the breast cancer (electron beam energy from 3 to 9 MeV)

From february 2005 to april 2016

703 cases of breast cancer received IOERT immediately after breast resection with

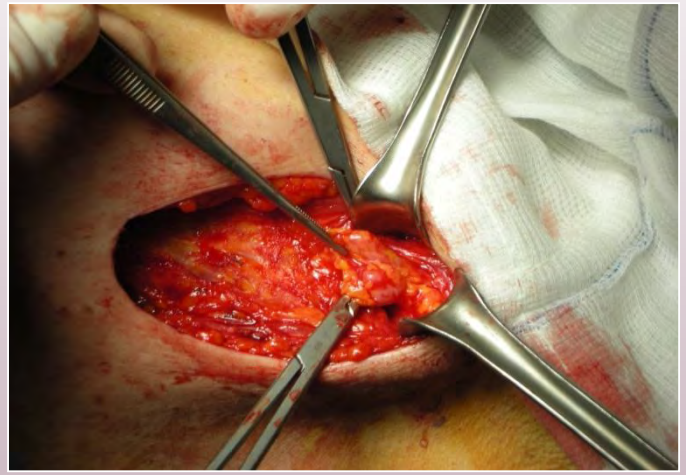
SINGLE DOSE	BOOST
21 Gy	10 Gy

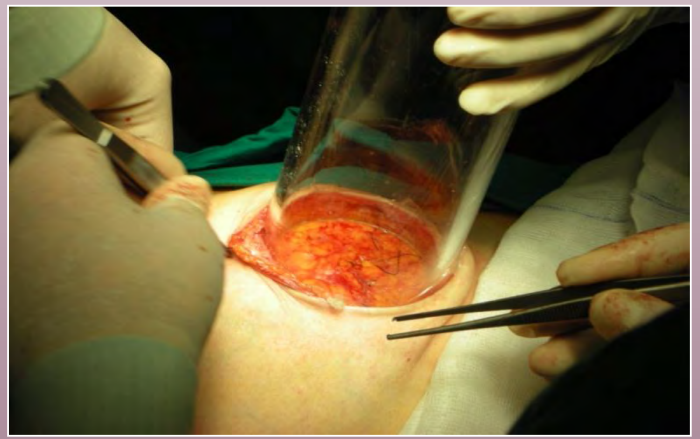




IORT: ADVANTAGES

- Direct visualisation excludes the danger of geographical miss
- Exposes the area with a higher risk to a highly effective single dose
- Shortening total treatment irradiation time
- Sparing the skin in order to have a better cosmesis

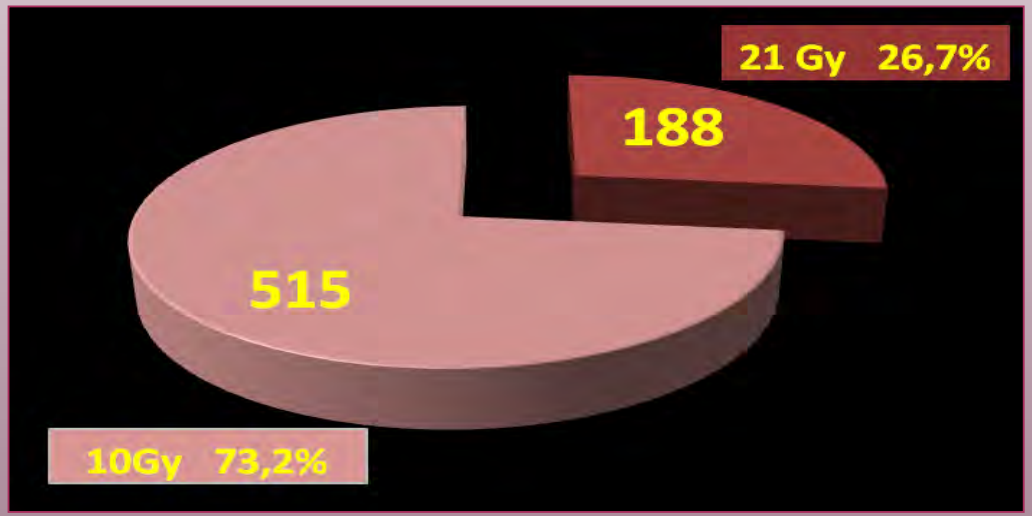


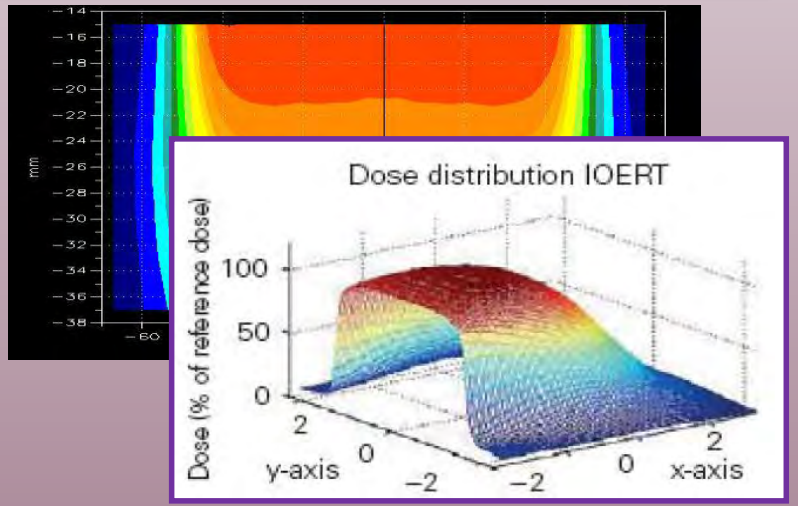


IOERT: EXPERIENCE

188 patients
were treated with a
Single dose IOERT
of 21 Gy

515 patients
were treated with dose
of 10 Gy, as anticipated
boost, followed by 44-50 Gy
whole-breast
external-beam radiotherapy



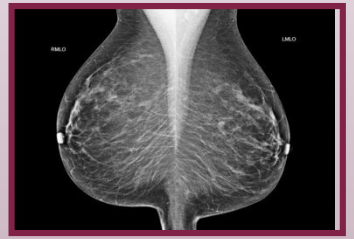


IOERT: EXPERIENCE

All cases are evaluated by multidisciplinary team made up of surgeon, radiologist, radiation oncologist, medical oncologist, pathologist, nurses and radiographers

Usually preoperative diagnosis is histological with predictive parameters:

type
grading
ER
PR
Ki-67
HER 2



IOERT: EXPERIENCE

We evaluated 635 pts with a follow-up >12 months:
456 treated with IOERT as anticipated boost and 179 treated with IOERT single dose.
The median follow-up was 54 months for boost group and 70 months for the IOERT single dose group.

IOERT BOOST: Patients characteristics

Patients: 456

IDC = 367 pts

ILC = 53 pts

DCIS = 36 pts

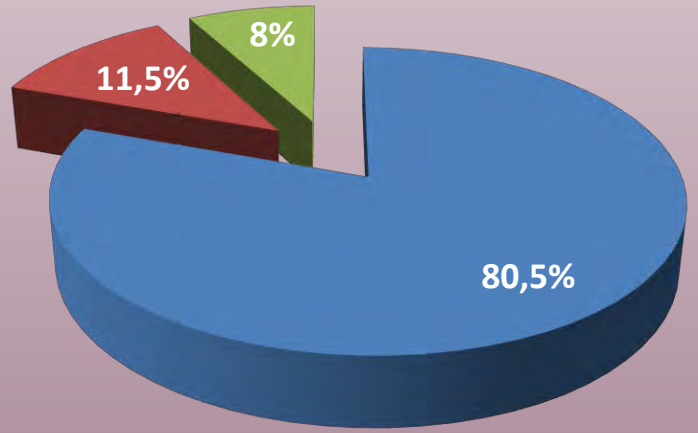
Median age: 56 (range 21 to 74 yrs)

Tumor stage : T1 : 384 pts

T2 : 36 pts

N+ : 81 pts

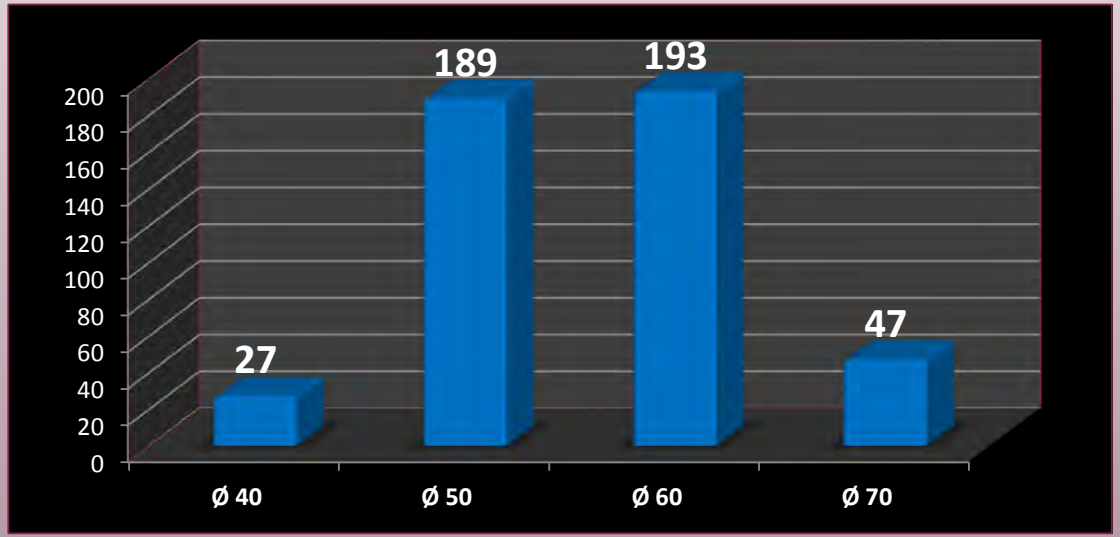
GRADING G3: 82 pts



IOERT BOOST: Treatments characteristics

Patients: 456

- Electron energy: 7 – 9 MeV
- Dose: 10 Gy, reference isodose 90%
- Diameter applicators: 5 - 6 cm (from 4 to 7 cm)



PTV = GTV + 2 cm WBRT = 44-50 Gy / 16-25 fr

IORT: EXPERIENCE

In the last year we included
11 patients in the HIOB trial

Centri	Referente	N° Pazienti/3 anni
Bari	Liocе	20
Bologna	Frezza	30
Caglairi	Lay	30
Cuneo	Fillini	20
Ferrara	Stefanelli	20
Foligno- Castello	Alessandro	40
L'Aquila	Bonfili	20
Novara	Krengli	15
Pavia	Ivaldi	15
Reggio Emilia	Palmieri	10
Rimini	Venturini	30
Rio Nero in Vult.	Fusco	Operativo 20
Roma	Ciabattoni	From 2014 Aug
Torino	Ricardi	Operativo ???
Trento	Tomio	20
Treviso	Gava	Operativo 20
Trieste	Vidali	40
Verona	Gabbani	30
Vicenza	Baiocchi	20
TOTAL		390

Own insurance

LANDESKRANKENHAUS SALZBURG
UNIVERSITÄTSKLINIKUM
DER PARACELSUS MEDIZINISCHEN PRIVATUNIVERSITÄT

Hypofractionated Whole-Breast Irradiation preceded by Intra-Operative Radiotherapy with Electrons as anticipated Boost

HIOB

A new Option in Breast-Conserving Treatment for Operated Breast Cancer Stages I and II

Prospective one-armed multi-center-trial

ISIORT 01

ClinicalTrials.gov Identifier: NCT01343459

5.5. HIOB Trial

Hypofractionated Whole-Breast Irradiation following Intra-Operative Electron Boost. (http://www.clinicaltrials.gov/ct2/show/NCT01343459?term=hiob&rank=1).

In an attempt to further reduce overall treatment duration without compromising local control rates, the multicentre HIOB trial was started in January 2011 as an ISIORT investigator initiated study. In this trial, Boost IOERT of 10 Gy is combined with hypofractionated WBI (15 × 2.7 Gy) for stage I/II breast cancer. A similar concept of IOERT plus short-term WBRT was tested in a phase II design by the Milano Group [38]. The HIOB trial design follows a sequential probability ratio test (SPRT), defining annual in-breast recurrence rates as benchmarks for successful treatment. Superiority of the intervention is defined by falling below the best published evidence in non-IORT cohorts. Beside tumor-related endpoints, major emphasis is made on cosmetic outcome, where a first analysis on early results is available [44].

IOERT SINGLE DOSE: Patients characteristics

Patients: 179

IDC: 166 pts

ILC : 10 pts

DCIS : 3 pts

Median age = 73 (range 50 – 88 years)

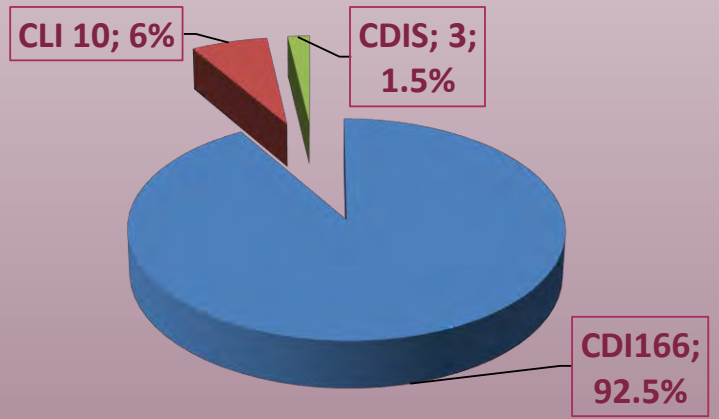
T<2cm :158 pts

N+ : 15 pts

ER+ : 169 pts

High grade (G3) : 14 pts

Close margins : 6 pts



CONSENSUS STATEMENT

Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 4, pp. 987–1001, 2009

ACCELERATED PARTIAL BREAST IRRADIATION CONSENSUS STATEMENT FROM THE AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)

BENJAMIN D. SMITH, M.D.,*† DOUGLAS W. ARTHUR, M.D.,‡ THOMAS A. BUCHHOLZ, M.D.,†

Table 2. Patien

***Patients "suitable" for PBI** if all criteria are present*

Factor	Criterion
Patient factors	
Age	≥60 y
BRCA1/2 mutation	Not present
Pathologic factors	
Tumor size	≤2 cm*
T stage	T1
Margins	Negative by at least 2 mm
Grade	Any
LVSI	No†
ER status	Positive
Multicentricity	Unicentric only
Multifocality	Clinically unifocal with total size ≤2.0 cm†
Histology	Invasive ductal or other favorable subtypes§
Pure DCIS	Not allowed
EIC	Not allowed
Associated LCIS	Allowed
Nodal factors	
N stage	pN0 (i^-, i^+)
Nodal surgery	SN Bx or ALND‖
Treatment factors	
Neoadjuvant therapy	Not allowed

Taccuino IORT Mammella

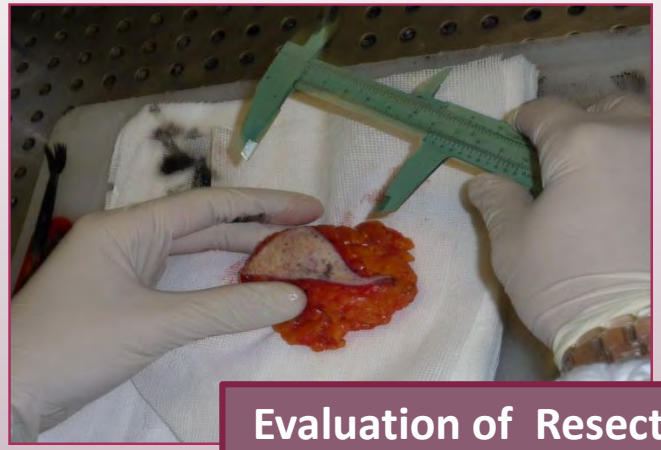
Istruzioni operative

Coordinatori: Dott. L. Tomio e Dott. M Guenzi

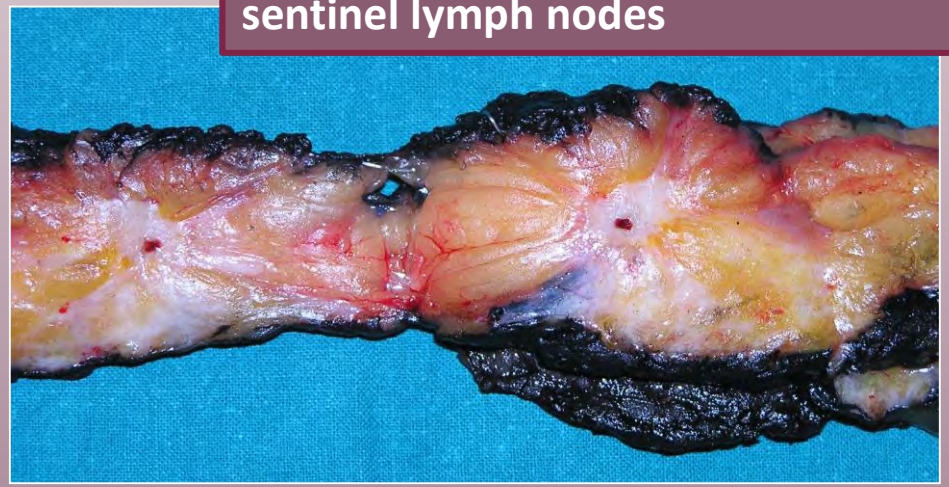
Associazione Italiana di Radioterapia Oncologica

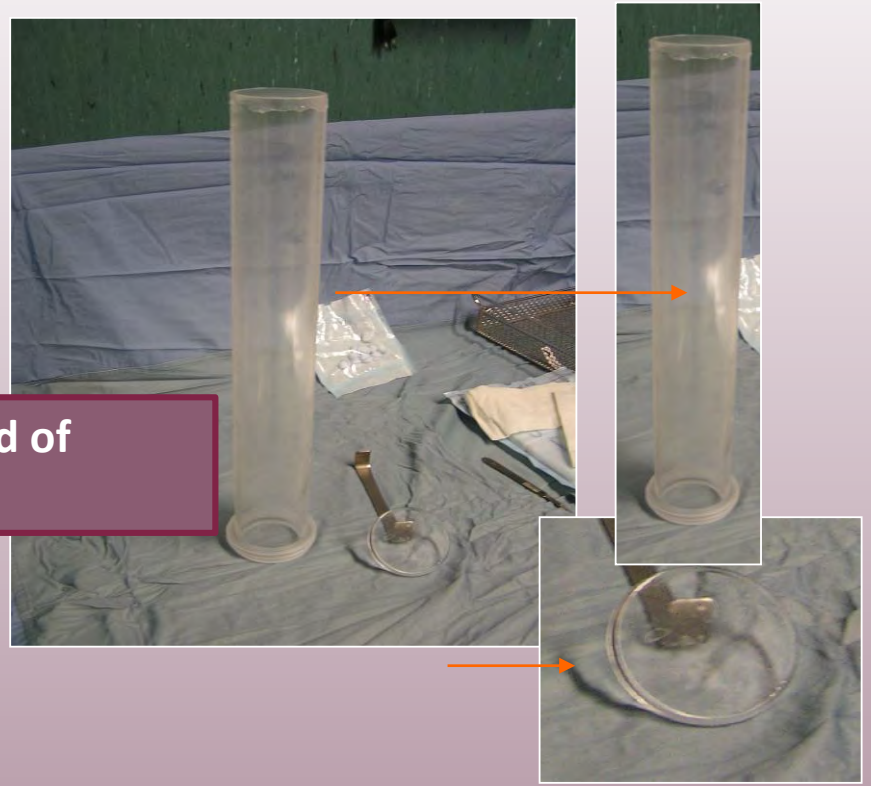
From 2010 we considered ASTRO parameters to select patients suitable for the single dose

IORT: EXPERIENCE



Evaluation of Resection Margins and of sentinel lymph nodes





PTV : GTV + 2 or 3 cm

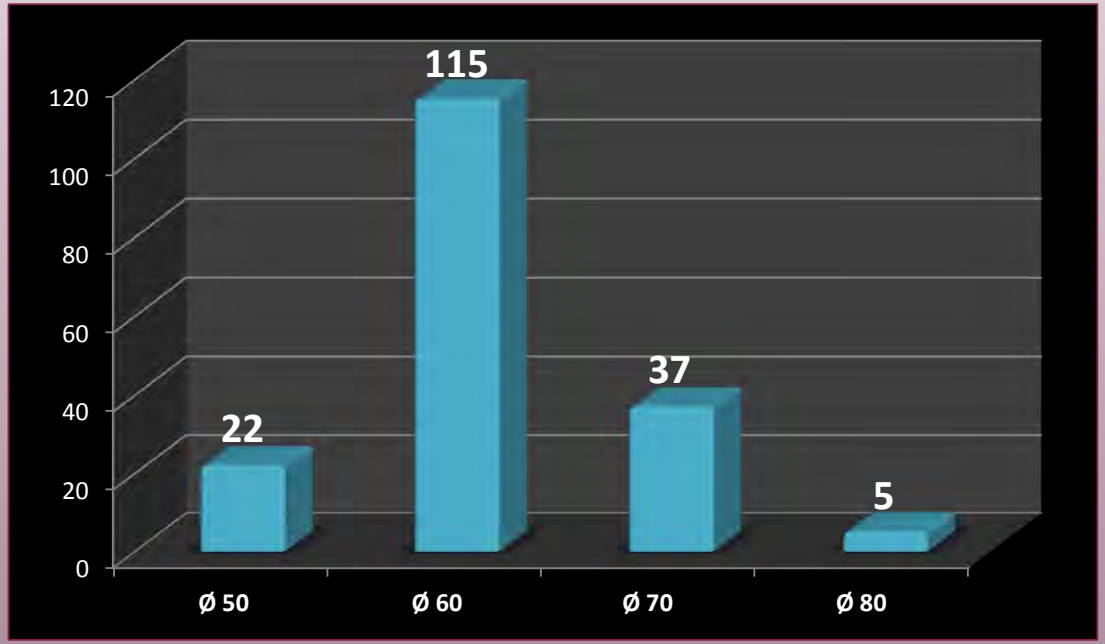
IOERT SINGLE DOSE: Treatments characteristics

Patients: 179

Electron energy: 7 – 9 MeV

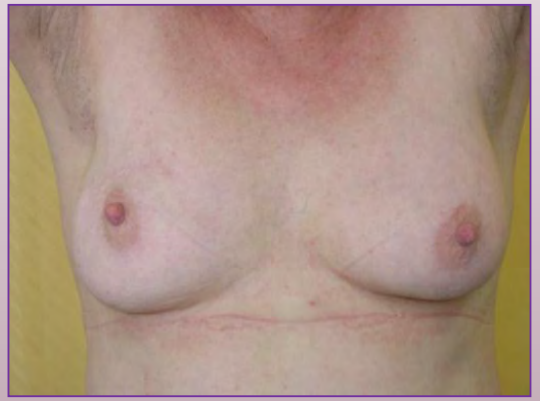
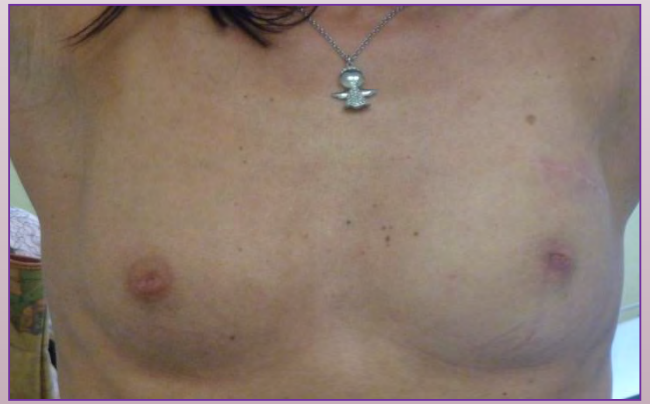
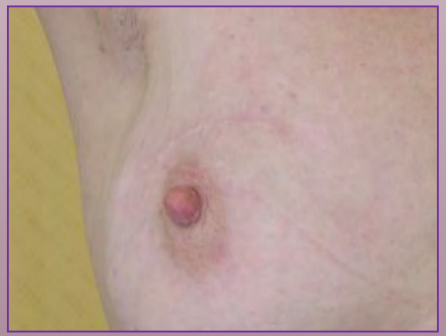
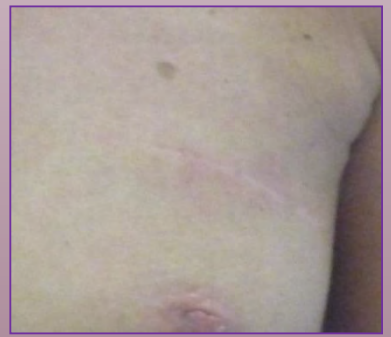
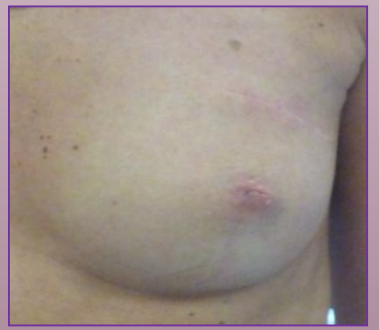
Dose: 21 Gy, reference isodose 90%

Diameter applicators: 6 cm (from 5 to 8 cm)



RESULTS 1

- **No** surgical or radiation **complications** have been observed.
- The **compliance** to treatment has been **very good**.
- The cosmetic results are generally good

RESULTS 2

To date we observed:

- **4 local recurrences** in the first group (**boost**)
- **6 recurrences out of** the primary tumor quadrant in the second (**single dose**)

2 patients developed a lymphnode recurrence:

- the first in the boost group
- the second in the single dose group

4 of the 6 patients, who have been treated with IOERT single dose did not meet the ASTRO parameters according to grading, tumor size and state of the sentinel nodes.

RESULTS 3

37 pts developed distance metastasis:

- 32 pts in the boost group
- 5 pts in the single dose group

17 pts died for cancer:

- 13 boost group
- 4 single dose

25 pts died for other reasons

28 pts were lost during the follow-up

9th International ISIORT Conference June 24/25th 2016 Novara, Italy

CONCLUSION 1

IOERT should be now considered as an alternative to EBRT for specifically selected and well-informed patients

IOERT with a single dose is feasible, well tollerated and very well accepted by patients not suffering a long cycle of radiotherapy

In our experience it resulted an appropriate technique for the PBI, providing direct localization of the tumor bed and minimizing the damage to normal tissues.

CONCLUSION 2

One of the main limitations in the use of IORT is the lack of histological information.

A careful selection of patients who may benefit from a partial breast irradiation is needed.

We believe that the core-biopsy examination can be very predictive and therefore mandatory before an exclusive treatment.

The close and constant collaboration with the surgeon and the pathologist has been essential in the improvement of the entire procedure.

CONCLUSION 3

Our data suggest that the **anticipated boost is associated with a low incidence of local recurrence** and can be considered equivalent to the external boost in terms of acute and late toxicity.

IOERT as a boost could be an **alternative to post-operative boost** with a more accurate dose distribution, allowing smaller volumes of the treatment and reducing post-operative radiotherapy time.

9th International ISIORT Conference

June 24/25th 2016
Novara, Italy

Thank you very much !

Marina Alessandro

9th International ISIORT Conference

June 24/25th 2016
Novara, Italy

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Bologna

INTRAOPERATIVE RADIOTHERAPY FOR EARLY BREAST CANCER:

A MONOCENTRIC EXPERIENCE

A. Baldissera

Preliminary results of patients treated with IORT at Bellaria Hospital, Bologna, Italy.

Radiotherapy Unit, Dr. G. Frezza

Breast Surgery Unit, Dr.ssa M.C. Cucchi

INTRODUCTION

- Single-dose intraoperative radiotherapy (IORT) is an alternative treatment for selected cases of early stage breast cancer.

- Intraoperative radiotherapy should be part of discussions to decide a personalised treatment regimen.

Veronesi U. et al. ELIOT Trial. Lancet Oncol. 2013;14:1269-77

- Risk-adapted approach should be considered as an option for eligible patients with breast cancer carefully selected.

Vaidya JS et al. TARGIT-A randomised trial. Lancet. 2014;383:603-13

METHODS
-Outcome measures-

- Histopathology
- Adjuvant treatment
- Clinical tolerability
- Local recurrences
- Overall survivor (OS)

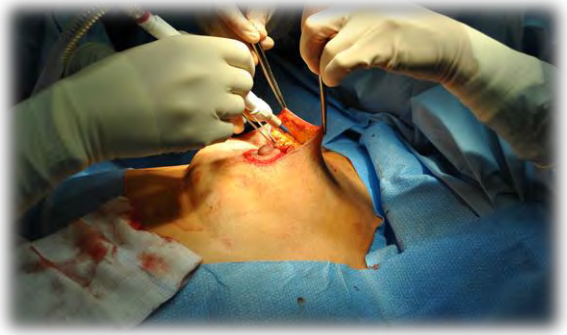
24 JUNE 2016 NOVARA, ITALY

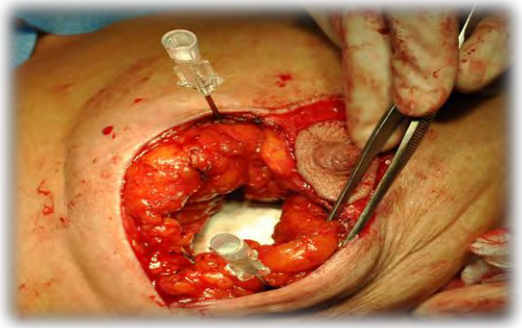
METHODS
-Selection Criteria

- We analysed data of 108 women who underwent conservative surgery and IORT with primary intent, from January 2011 to December 2015.

- Early breast cancer

- Age ≥ 60 y





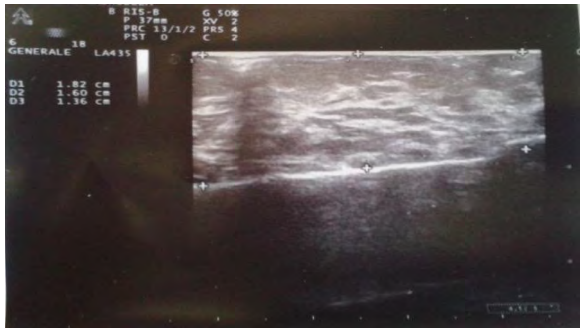
SURGERY

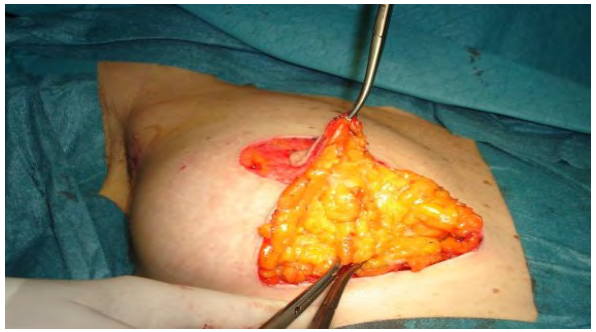
- Surgery was performed in the operating IORT room
- Surgical technique for IORT: quadrantectomy and evaluation of sentinel node
- Residual mammary gland preparation as described by Veronesi et al.
- Margin of resection evaluated by macroscopic assessment with frozen section on specific sites.

IORT

- Dedicated mobile electron accelerator (LIAC)
- 21 Gy were prescribed at 90% isodose

- Energy beam: 4-6-8-10 MeV electron beam ; energies according to the tissue thickness measured by ultrasonography of the breast portion to be irradiated





- Collimation by hard-docking system
- Applicators diameter: 4 5-6-7-8 cm
- Bevel Angle (degree): 0°-15°

PTS CHARACTERISTICS

		Study population (n = 108)
Median Age, years (range)		72 (49-85)
Cancer Stage according to TNM, n (%)		
	T1a	2 (1.9)
	T1b	25 (23.1)
	T1c	62 (57.5)
	2	19 (16.7)
	N0	100 (92.6)
	N1a	2 (2.8)
	N1mic	2 (2.8)
	N2	1 (0.9)
Tumor grading, n (%)		
	Grade 1	15 (13)
	Grade 2	62 (57.4)
	Grade 3	29 (26.9)

		Study population (n = 108)
Histology		
	Ductal	71 (65.7)
	Lobular	22 (20.4)
	Other histologies	13 (13.9)
Adjuvant therapy		
	None	14 (13)
	Hormonotherapy	81 (75)
	Chemotherapy+ Hormonotherapy	12 (11.1)
	Chemotherapy	1 (0.9)

- 1) Multiple Sclerosis: IDC G1 (pT1b sN0) F.U. 4 year NED
- 2) Pacemaker near the breast area: IDC G2 (pT2 sN0) 15 months NED

Our treatment settings

Energy					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	4	5	4,6	4,6	4,6
	6	54	50,0	50,0	54,6
	8	38	35,2	35,2	89,8
	10	11	10,2	10,2	100,0
	Total	108	100,0	100,0	

Diameter					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	5	18	16,7	16,7	16,7
	6	33	30,6	30,6	47,2
	7	43	39,8	39,8	87,0
	8	14	13,0	13,0	100,0
	Total	108	100,0	100,0	

Angle					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	100	92,6	92,6	92,6
	7	1	,9	,9	93,5
	15	7	6,5	6,5	100,0
	Total	108	100,0	100,0	

RESULTS

Median follow-up: 26 months (range 2-52)

- **ONE** patient had a **local relapse** in a different quadrant after 18 months;
- **ONE** patient had an **axillary lymph node recurrence** after 12 months;
- **ONE** patient developed **liver metastases** after 20 months;
- **ONE** patient **died** from progressive disease after 34 months.

RESULTS

- **Local relapse: D.A. 81 years Diagnosis 10/2014**: QSE +IORT (Coll 7 cm , 8 MeV) + HT

  IDC G3 pT2 (2,3 cm) snN0 (ER 90%; PRg neg; Ki67 40%; HER2 neg)

  April 2016 *Relapse QIE*

  Mastectomy : IDC 3,4 cm ER 90%; PRg 40%, Ki67 30%, HER2 2+ (FISH not ampli). HT

NED May 2016

- **Axillary lymph node recurrence** : **S.P. 74 years Diagnosis 10/2013:** QSE +IORT +HT

  IDC (mucinous) pT1c sN0 ER 90%; PRg 30%; Ki67 5%; HER 2 neg

  November 2014:

  Axillary nodes dissection: metastases in 6/20 node ;ER 90%, PRg neg, Ki67 5%, HER-2 2+ (FISH not amplificated)

  Adjuvant chemotherapy and RT infraclavear nodes.

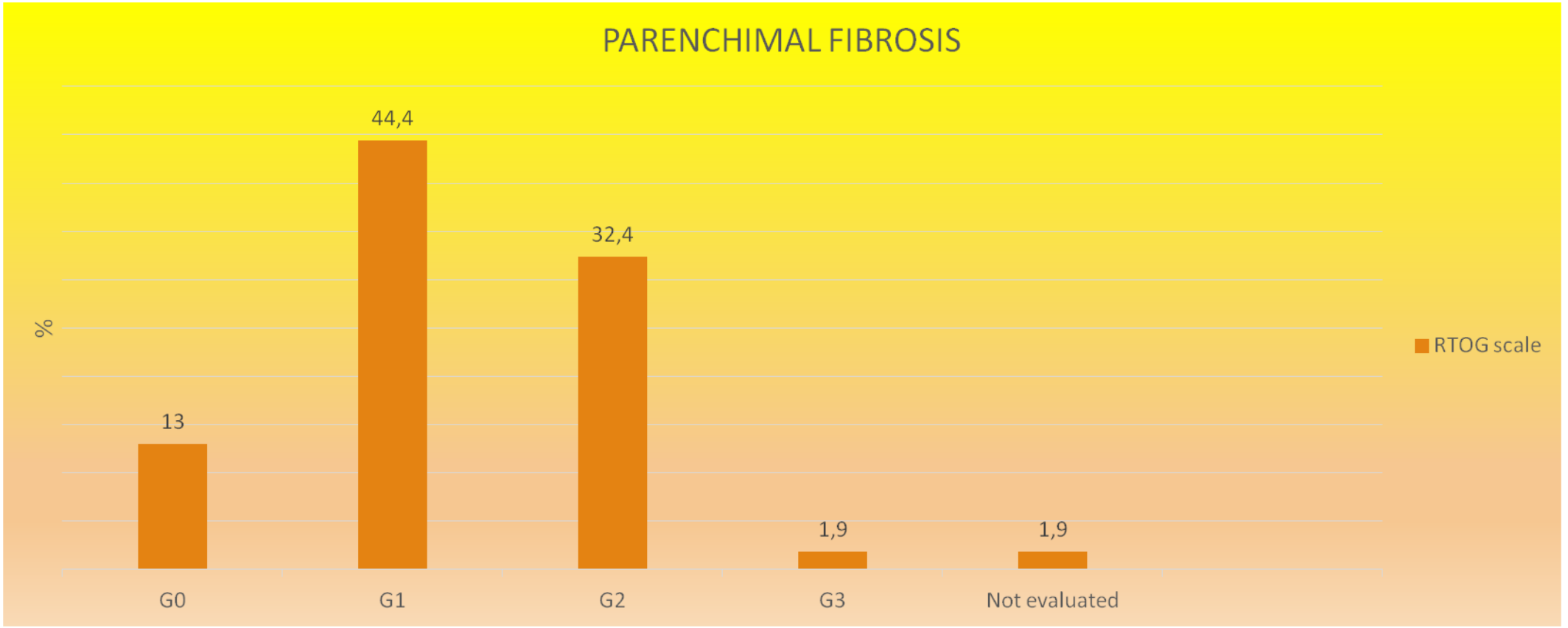
NED april 2016

RESULTS

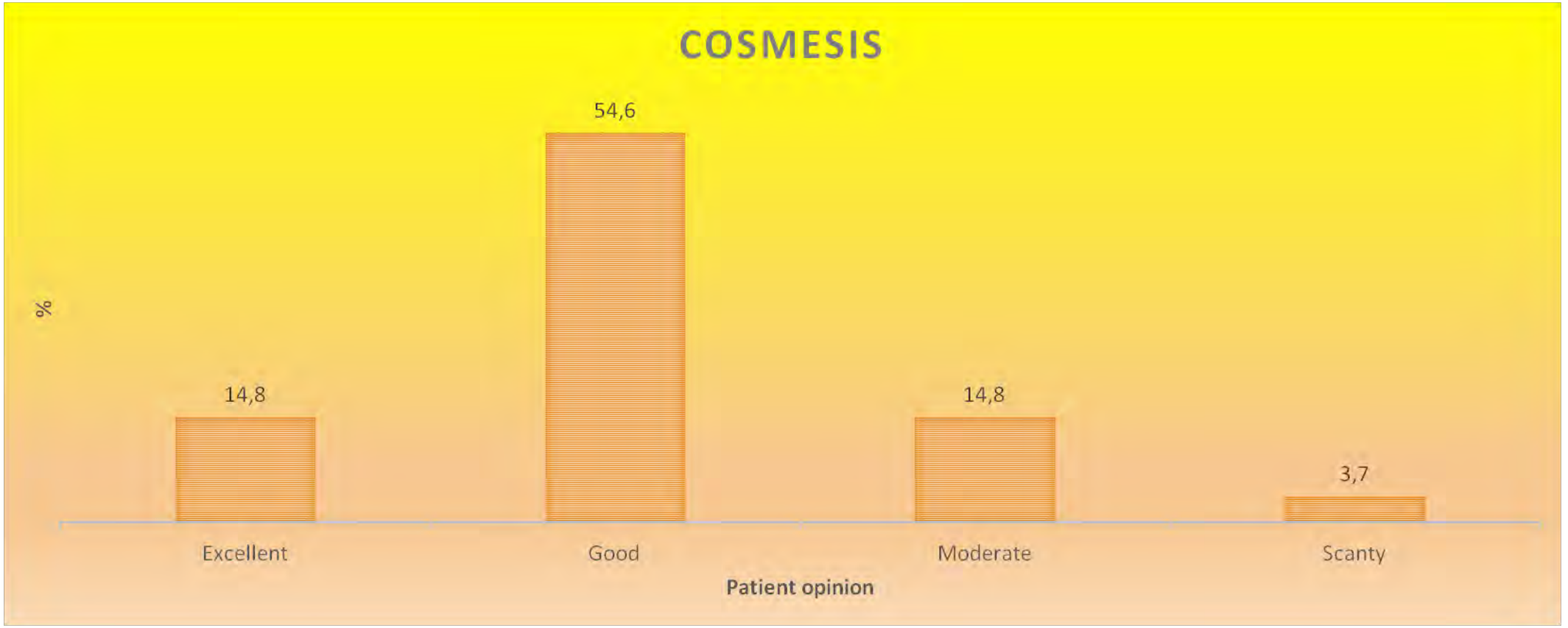
➢**ONE** patient underwent mastectomy after five months because of **chronic fistula** in the irradiated area;

Wound related complications	N. of patients
Seroma requiring more than 3 aspirations or surgery	3
Wound infection	2
Skin breakdown	2

RESULTS
late toxicity



COSMETICS RESULTS



CONCLUSIONS

- IORT represents a safe and effective alternative treatment option in selected patients with early breast cancer
- Low complications rate with good clinical and cosmetic outcomes support IORT as a treatment option for selected women.
- The short follow-up, for about half patients, does not allow an accurate analysis of DSF and OS

Intraoperative Radiotherapy of Breast Cancer: Analyses of Data from 3 centers in Turkey

Bese N., Altinok A., Alan O., Dizdar N., Caglar H., Ince U., Uras C.

Acibadem University Breast Health Center-Istanbul
Medipol University Hospital-Istanbul
Okmeydani Research and Education Hospital-Istanbul

IORT Facilities in Turkey

- 6 centers with IORT facilities in Turkey
- 4 in Istanbul, 2 in Ankara
- 3 low-energy X rays and 3 electrons (1 LIAC and 2 Mobetron machines)
- LIAC installed Acibadem Maslak hospital in September 2012

Aim of this study

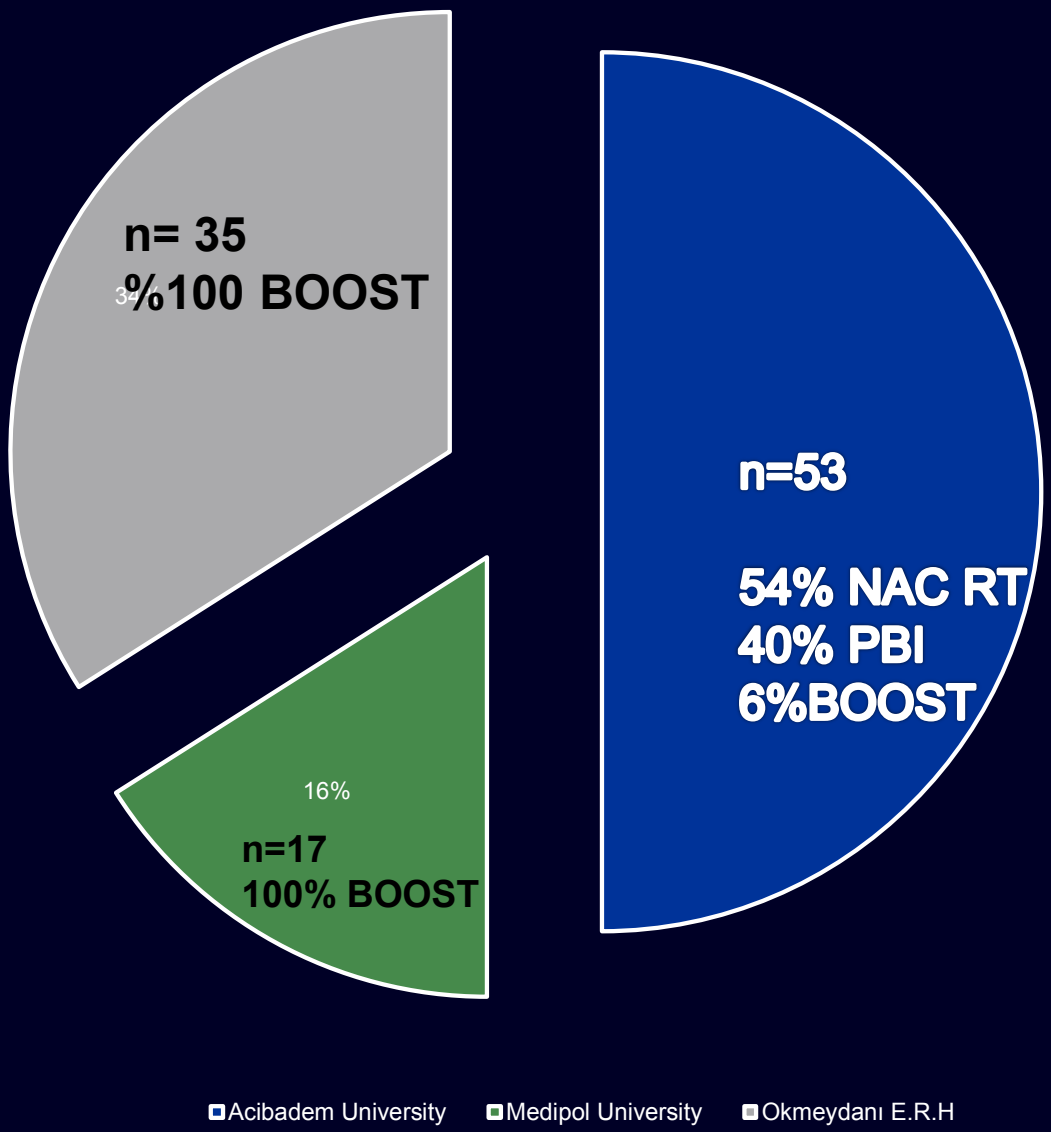
- Analyze of IOBRT data collected from 3 different centers located in Istanbul, Turkey.

Data of 126 patients from 3 centers treated between the years October 2012-December 2015 were submitted to ISIORT Registry

83% of all, were breast cancer and characteristics of 105 breast cancer patients are presented

Treatment Characteristics	
Beam energy units	
Electron	88 (84%)
Low energy X rays	17 (16%)
Surgery	
BCS	76 (72%)
NAC sparing mastectomy	29 (28%)
IORT	
PBI (21Gy-e)	21 (20%)
Boost (10-12Gy –e, 20Gy- KV)	55 (52%)
NAC irradiation (16Gy-e)	29 (28%)
Energy	
PBI (8-12MeV-e)	Median 12MeV
Boost (6-10MeV-50KV n=17)	Median 6MeV for e
NAC irradiation (8-10MeV-e)	Median 10MeV
RT + EBRT (n=56)	
EBRT conventional (46-50Gy)	48(86%)
EBRT hypofractionation (39-42Gy)	8 (14%)
Systemic treatment	
Chemotherapy	46 (44%)
PBI	2 (4%)
Boost	41 (90%)
NAC irradiation	3 (7%)

Patient characteristics	All patients (n=105)	PBI (n=21)	Boost (n=55)	NAC RT (n=29)
Median age (years)	52 (26-80)	60 (41-78)	53 (30-80)	43 (26-56)
Pathologic subtype IDC	74 (71%)	11 (53%)	52 (95%)	11 (38%)
ILC	4 (4%)	1 (5%)	1 (2%)	2 (7%)
Mixt type	2 (2%)	-	2 (3%)	-
Tubuler	5 (4%)	3 (14%)	-	2 (7%)
DCIS	20 (19%)	6 (29%)	-	14 (48%)
T stage T1	55 (52%)	13 (62%)	29 (53%)	13 (45%)
T2	30 (29%)	2 (10%)	26 (47%)	2 (7%)
Tis	20 (19%)	6 (28%)	-	14 (48%)
Nstage N0	77 (73%)	19 (90%)	30 (55%)	28 (97%)
Ni	2 (2%)	1 (1%)	1 (2%)	-
Nmicro	6 (6%)	1(1%)	5 (9%)	-
N1	14 (13%)	-	13 (24%)	1(3%)
N2	4 (4%)	-	4 (7%)	-
N3	2 (2%)	-	2 (3%)	-


n= 35
%100 BOOST
n=53
54% NAC RT
40% PBI
6%BOOST
16%
n=17
100% BOOST
Acibadem University
Medipol University
Okmeydanı E.R.H

Conclusions

- Total number of patients underwent IORT is less than expected.

  - Reimbursement procedures by the government and private insurance companies

  -Selection of patients for PBI with IORT; needs a comprehensive work-up

  -NAC sparing surgery is also performed in centers dedicated to breast cancer treatment and selection of patients for EBRT, NAC RT or without any RT needs expertise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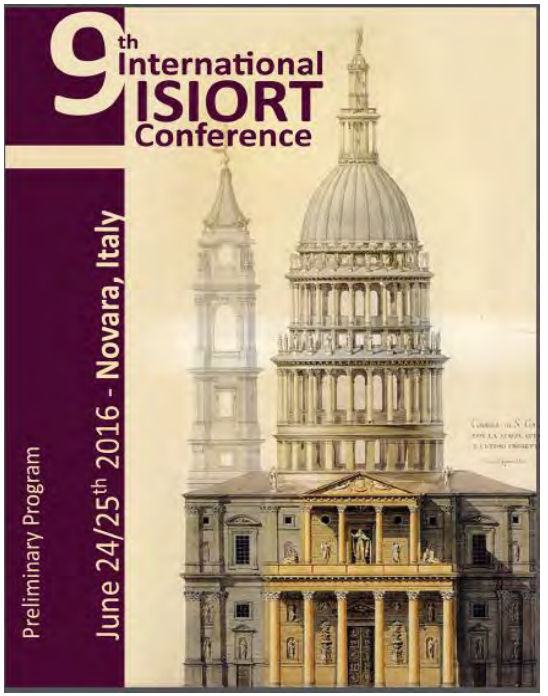
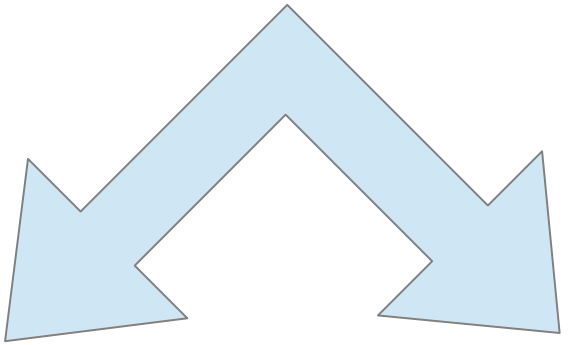
AZIENDA ULSS 9 TREVISO



MD MARJANA LEKAJ
MD MARIA GIOVANNA CESARO
RADIATION ONCOLOGY DEP. TREVISO HOSPITAL
Chief. MD ALESSANDRO GAVA

SINGLE CENTRE RETROSPECTIVE CASE-CONTROL STUDY



IORT EBRT

EARLY STAGE BREAST CANCER

INDICATIONS for IORT

- From 2004 to December 2014, 212 patients with Stage I-II breast cancer were treated with IORT
- Until 2009 the patients were included in“REGINA ELENA randomized study»
- From 2009 we adopted the **ESTRO guidelines** and at the same time we selected, as control group with similar characteristics, who received external beam whole breast radiotherapy (EBRT).

“REGINA ELENA STUDY” CRITERIA

Disegno dello Studio

Sesso □48 anni □75 anni

Stato Ormonale Menopausa

Diagnosi Cr Mammario unicentrico, □ □ 2,5 cm

Nessuna Terapia Precedente

Nessun II Tumore eccetto □ Ano

□ Basocellulare della cute

□ Portio

Nessuna Malattia in Atto o Psicosi

Crireri di Esclusione: – Non Carcinoma

– Cr Duttale/Lobulare in situ

– Cr Paget

– Cr in prossimità della cute/sul prolungamento ascellare

– Multicentricità

– Margini □

- Dimensioni mammella (spessore)

– Non adesione al programma di Follow-Up

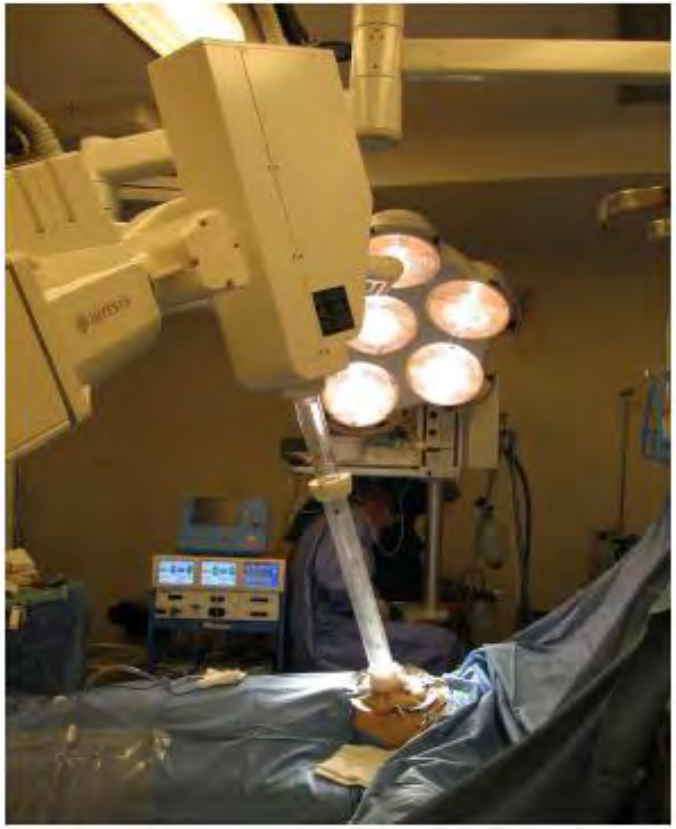
– Controindicazioni a radioterapia

CHIR □ EI. Estemporaneo IORT 21 Gy all’isodose 90%

RTE 50 Cy □ Boost 10 Gy

Suitable/good	ESTRO
age	>50 years
BRCA1/2mutation	
histology	IDC , mucin, tubular, medullary, colloid
ILC	Not allowed
Associated LCIS	Allowed
DCIS	Not allowed
HG	Any
Tumor size	pT1-2 (≤30 mm)
Surgical margin	Negative (≥2mm)
Multicentricity	Unicentric
Multifocality	Unifocal
EIC	Not allowed
LVI	Not allowed
ER, PR status	Any
Nodal status	pN0 (SN bx or ALND)
Neoadjuvant CT	Not allowed

CHARACTERISTICS OF NOVAC 7



Characteristics:

Linear Accelerator electrons releasing.

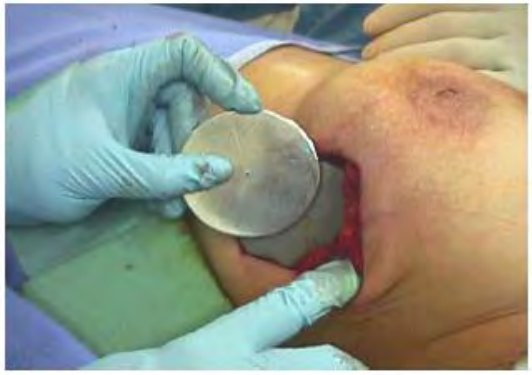
4 different energetic levels: (3, 5, 7, 9 MeV)

High dose rate

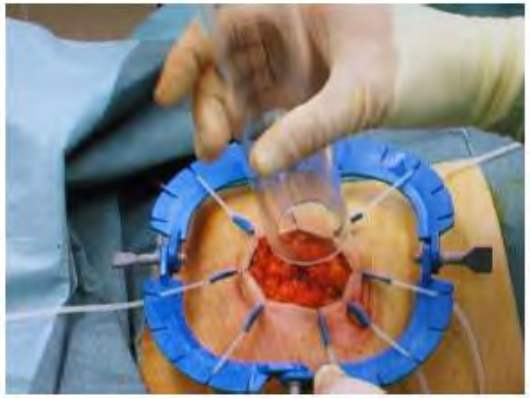
Variable dedicated applicator from 4 to 10 cm diameter

IORT: MODALITY OF EXECUTION

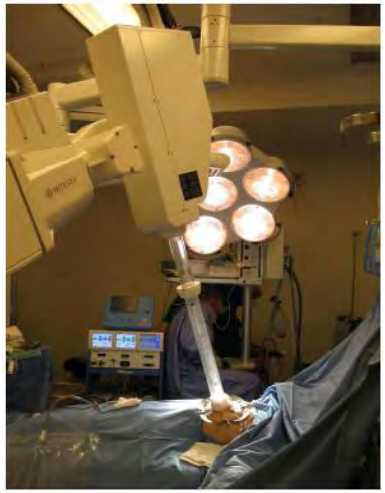
- QUADRANTECTOMY sec. Veronesi and sentinel lymph node biopsy
- According to the dimensions of the lesions and to the histologic results from the extemporaneous biopsy we established the dimensions of collimator (from 4 to 8 cm).
- Delivered Energy 9 MeV
- The prescribed dose was 21 Gy, isodose at 90% in one fraction
- Time of irradiation 60 sec



Attenuator disk is placed between the pectoralis muscle and the residual gland



Perspex Collimator is introduced through the skin and placed directly in contact with the breast target

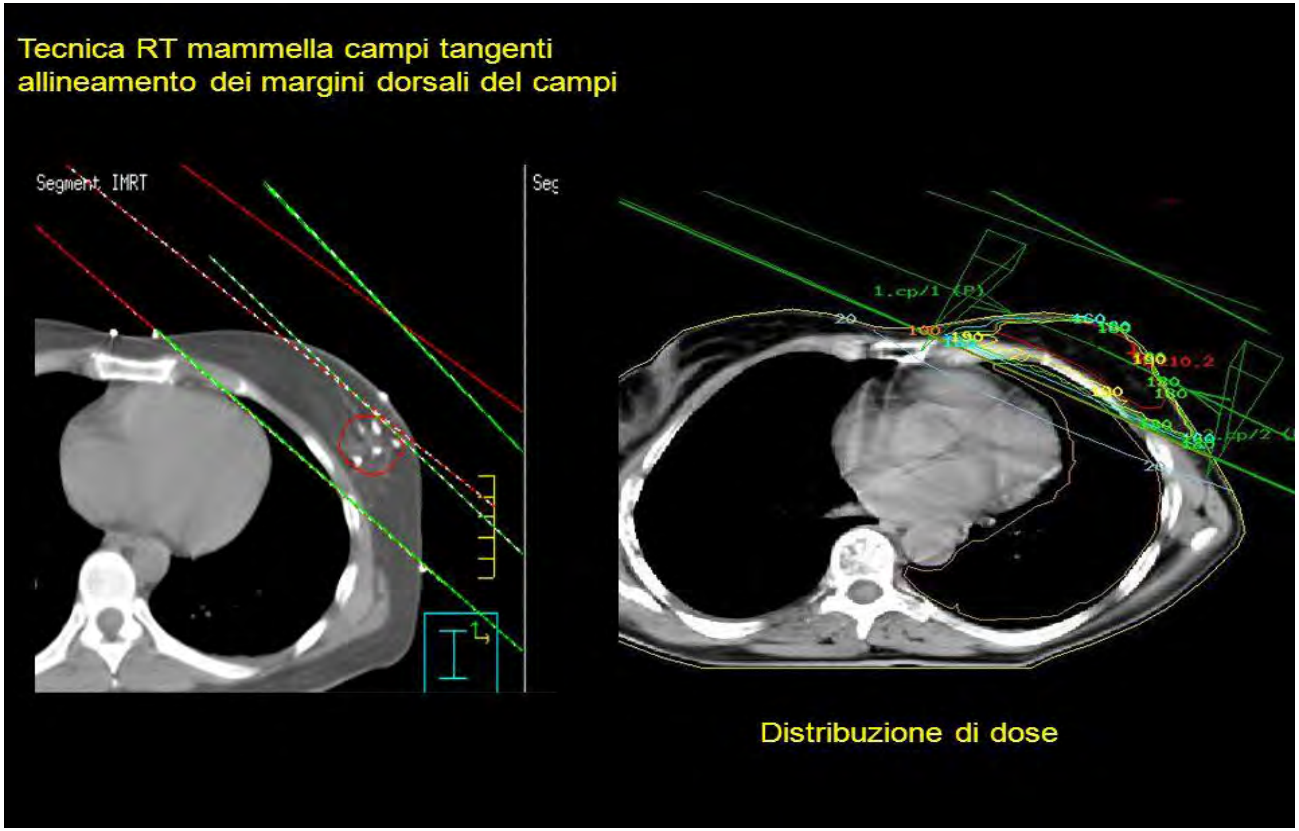


NOVAC sterile applicator in the operating theatre

EBRT

EBRT was performed through 3D conformational technique by LINAC ONCOR

The dose delivered was 50 Gy in 25 fractions to whole breast with boost tumour bed 10 Gy in 5 fractions or 42,56 Gy in 16 fractions with boost 10 Gy in 5 fractions.



CHARACTERISTICS OF PATIENTS

		IORT: 212 patients		EBRT: 212 patients	
		freq.	%	freq	%
T (dimensions)	< 10 mm	97	45,8	76	35,9
	10 – 20 mm	104	49	104	49,3
	> 20 mm	11	5,2	32	14,8

		IORT: 212 patients		EBRT: 212 patients	
		freq	%	freq	%
GRADING	G1	77	35,8	38	17.9
	G2	98	45,8	167	78,8
	G3	37	17,5	7	3,3

		IORT: 212 patients		EBRT: 212 patients	
		freq	%	freq.	%
MARGINS	Negative	204	96.2	167	78.8
	Closed	8	3.8	38	17.9
	Invasion	0	0	7	3,3

CHARACTERISTICS OF PATIENTS

		IORT: 212 patients		EBRT: 212 patients	
		freq.	%	freq	%
HISTOTYPE	Invasive ductal carcinoma	187	88,3	163	76,9
	Invasive lobular carcinoma	11	5,2	15	7
	others	14	6,5	34	16,1

		IORT: 212 patients		EBRT: 212 patients	
		freq.	%	freq.	%
INTRADUCTAL COMPONENT	absent	137	65	97	45,8
	present	75	35	115	54,2

		IORT: 212 patients		EBRT: 212 patients	
		freq.	%	freq.	%
MULTIFOCAL	yes	2	0,9	14	6,6

		IORT: 212 patients		EBRT: 212 patients	
		freq.	%	freq.	%
POSITIVE NODES	N0	169	79,7	179	84,4
	N1	42	18,8	33	15,6
	N2	1	0,5	-	-

CHARACTERISTIC OF PATIENTS

		IORT		EBRT	
		frequency	%	frequency	%
ER	positive	11	5,2	11	5,2
	negative	201	94,8	201	94,8
PR	positive	165	77,8	166	78,3
	negative	47	22,2	46	21,7
Ki67	< 20 %	183	86,7	185	87,3
	> 20 %	29	13,3	27	12,7
HER2 NEU	positive	13	6,1	8	3,8
	negative	199	98,4	204	96,2

CHARACTERISTICS OF PATIENTS

		IORT: 212 patients		EBRT: 212 patients	
		freq.	%	freq	%
ADJUVANT CHEMOTHERAPY	no	168	79,2	173	81,6
	yes	44	20,8	39	18,4

		freq.	%	freq	%
HORMONE THERAPY	no	53	25	23	10,8
	yes	159	75	189	89,2

RESULTS

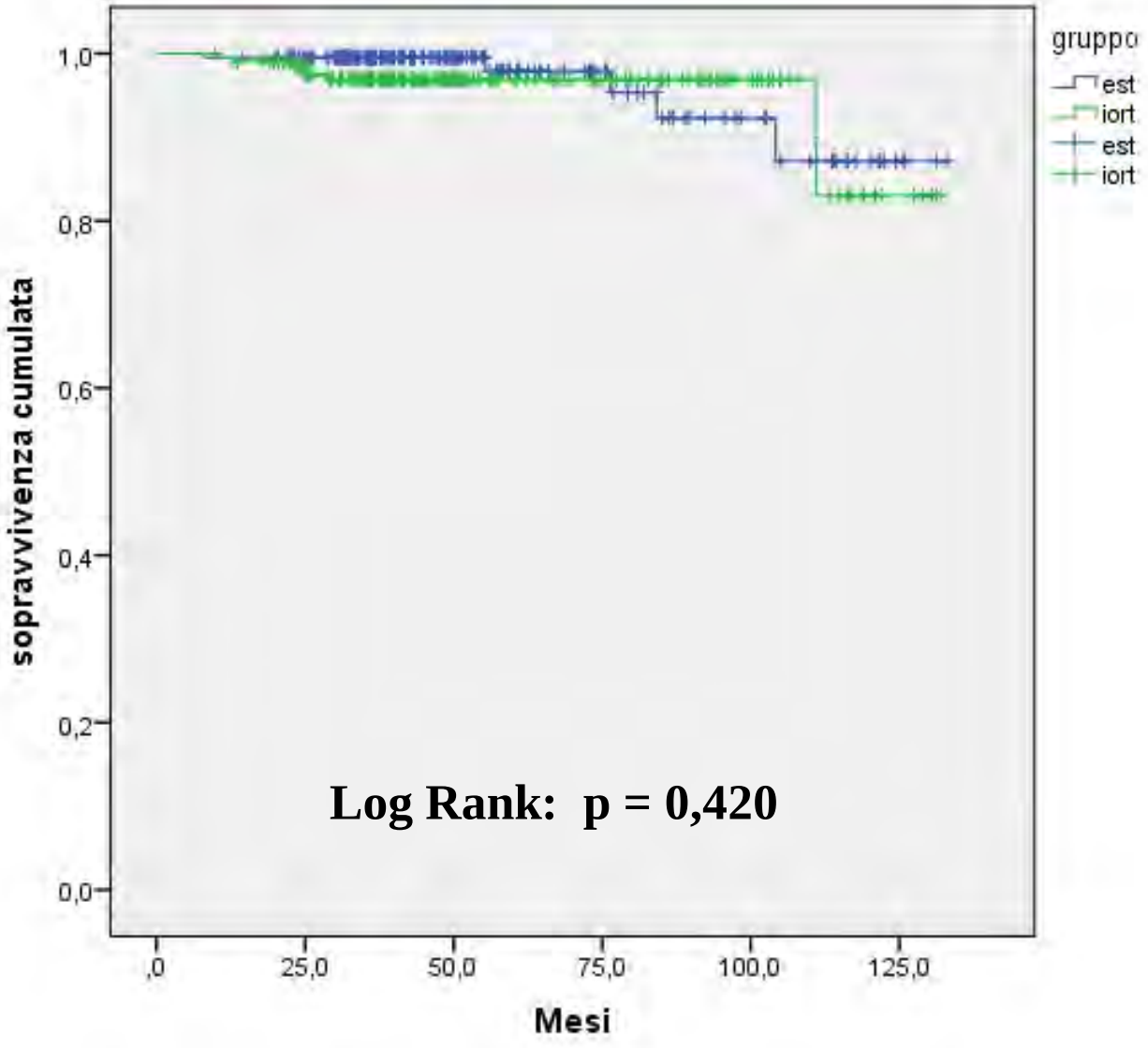
- RECURRENCE:
  - LOCAL
  - REGIONAL NODES
  - DISTANT METASTASIS
- OVERALL SURVIVAL
- DISEASE FREE SURVIVAL
- COSMETIC RESULTS

RESULTS: RECURRENCES

IORT		***EBRT***
total: 11 pt		total: 9 pt
8 pt	**LOCAL**	5 pt
3 pt	**REGIONAL NODE**	1 pt
4 pt	**DISTANT METASTASIS**	4 pt

Median follow up is 47 months in IORT group
and 43 months in control group

LOCAL RELAPSES



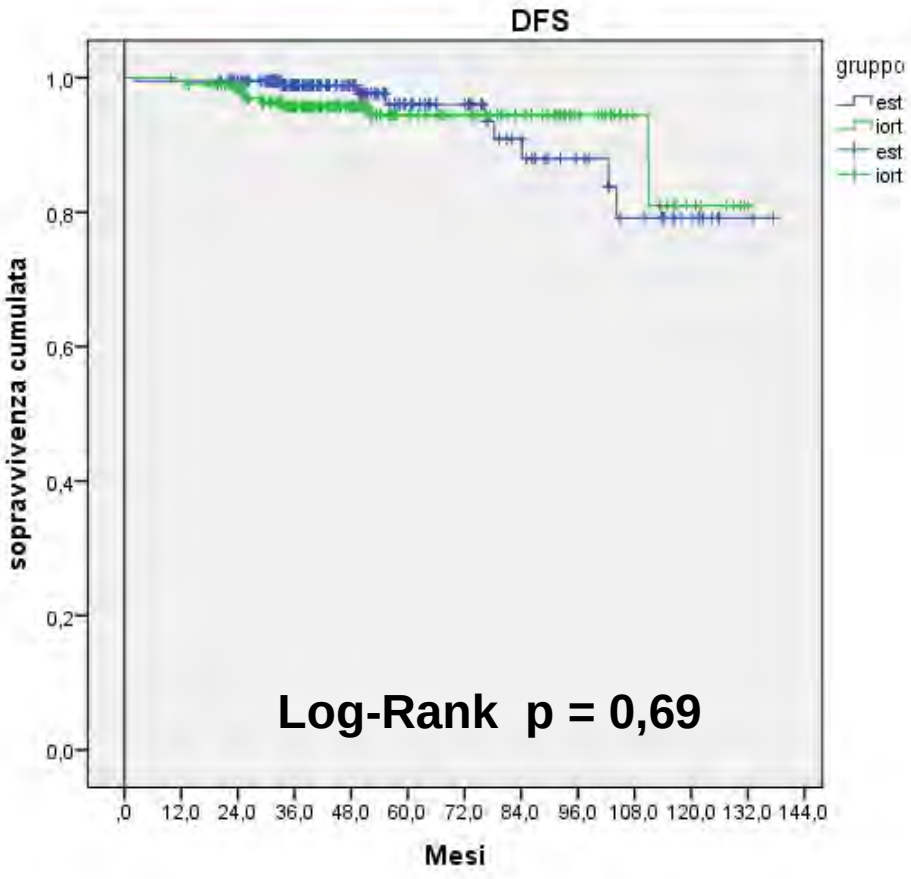
CHARACTERISTICS of PATIENTS with RECURRENCES in IORT

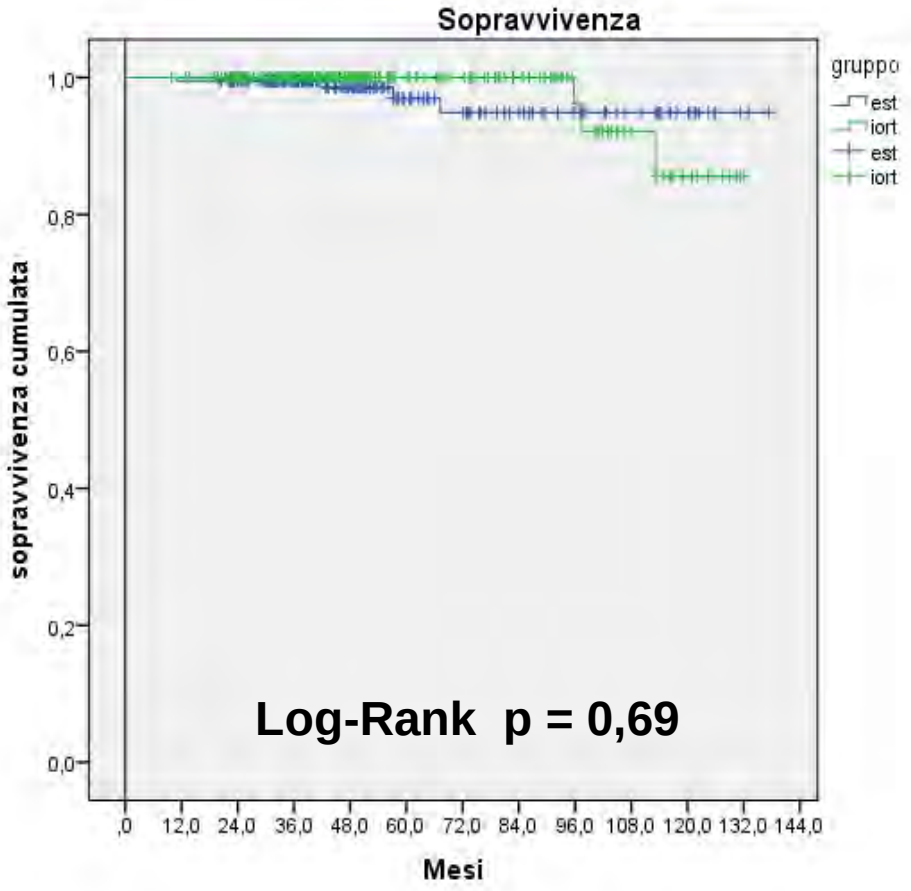
AGE	Dimension (mm)	MARGIN	G	ER	PR	Ki67	HER2	LYMPH SENT.	STAGE	LOCAL	LYMPH NODE	METASTASIS
74	12	-	G1	+	+	10	-	-	T1cN0M0	+		
61	22	-	G2	+	+	5	-	+	T2N1aM0	+		
61	12	-	G3	+	-	40	-	-	T1cN0M0		+	+
69	12	-	G2	+	+	10	-	-	T1cN0M0			+
86	20	-	G2	+	+	8	-	-	T1cN0M0	+	+	+
69	19	-	G2	+	+	20	-	-	T1cN0M0	+	+	+
63	20	-	G1	+	+	20	+	-	T1cN0M0	+		
68	11	-	G1	+	+	10	-	-	T1cN0M0	+		
65	15	-	G2	+	-	18	-	-	T1cN0M0		+	
62	16	-	G2	+	+	15	-	-	T1cN0M0	+	+	
52	12	-	G2	+	+	12	-	-	T1cN0M0	+		

CHARACTERISTICS of PATIENTS WITH RECURRENCES IN EBRT

Age	Dimension (mm)	MARGIN	G	ER	PR	Ki67	HER 2	SENT. LYMPH	STAGE	LOCAL	LYMPH.	METASTASIS
64	20	+	G2	+	+	10	-	-	T1cM0M0	+		
65	20	-	G3	+	+	50	-	-	T1cN0M0			+
64	11	-	G2	+	+	7	-	+	T1cN1aM0	+		
54	18	close	G3	+	+	10	-	-	T1cN0M0	+		
57	25	close	G2	+	+	15	-	-	T2N0M0		+	
64	19	-	G2	+	+	15	-	+	T1cN1aM0	+		
51	15	-	G2	+	+	15	-	-	T1cN0M0	+		+
66	14	close	G2	+	-	10	-	-	T1cN0M0			+
73	20	-	G1	+	-	10	-	-	T2nN0M0		+	

OVERALL SURVIVAL
DISEASE FREE SURVIVAL





DFS after 10 yrs EBRT: 80.9%
DFS after 10 yrs IORT: 79.1%

OVS after 10 yrs EBRT: 94.9%
OVS after 10 yrs IORT: 85.6%

COSMETIC RESULTS

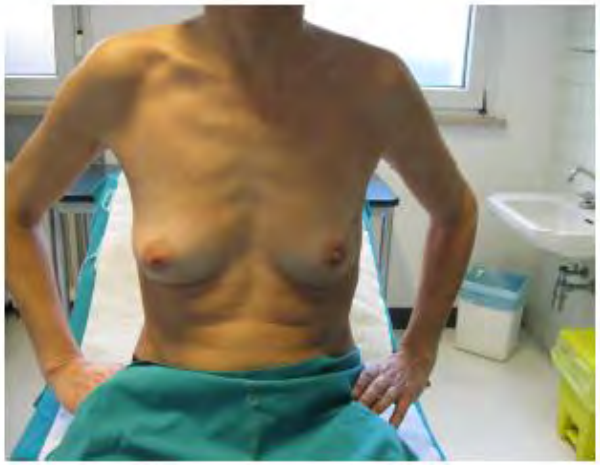
- The evalutation of cosmetic result is based on the following parameters:
  - Simmetry and shape of the breast
  - Surgical wound
  - Cutaneus pigmentation

  } 12 months after IORT

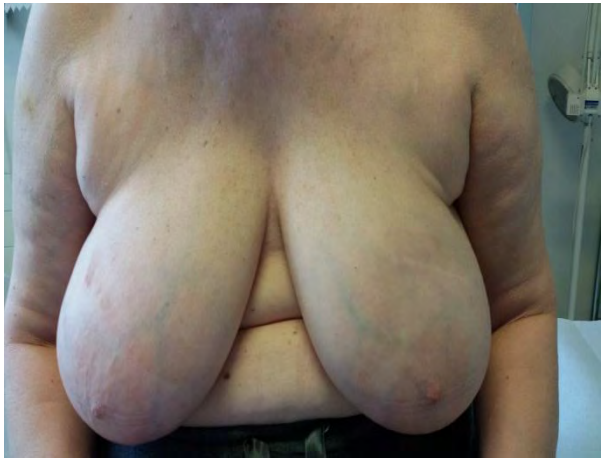
- Combining them we established this cosmetic scale:
  - Excellent
  - Good
  - Fair
  - Poor

COSMETIC RESULTS

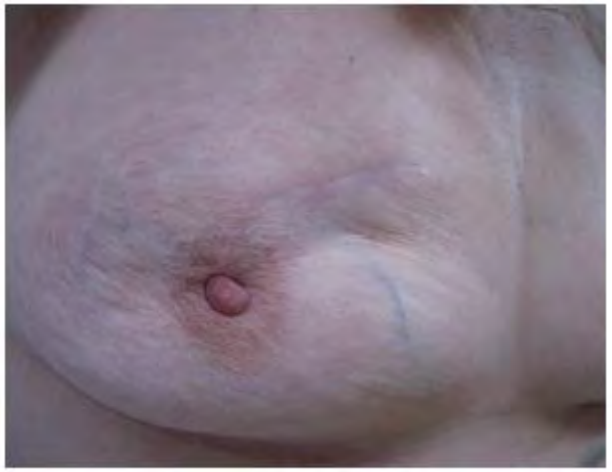
	IORT		EBRT	
	frequency	%	frequency	%
EXCELLENT	7	3,3	37	17,5
GOOD	182	85,8	127	59,9
FAIR	14	6,6	41	19,3
MEDIOCRE	-	-	1	5
POOR	8	3,8	6	2,8
ASYMMETRY	1	5	-	-



EXCELLENT



GOOD



POOR

CONCLUSIONS

No statistically significant difference between IORT and EBRT group concerning local relapses.

Therefore IORT seems to be valid alternative to EBRT in selected patients with low risk disease, providing an effective local control of the neoplasia

Furthermore:

- Cosmetic results are satisfactory
- Low cost and easy logistic management
- No interferences with CT
- Performed directly during surgical session

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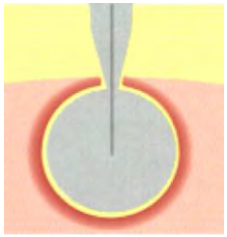


Medizinische Fakultät Mannheim
der Universität Heidelberg

Universitätsklinikum Mannheim

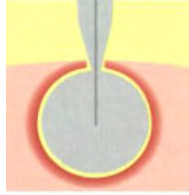
TARGIT-E(lderly):

- interim (safety) analysis (n = 80)
- first outcome analysis (n = 447, med f/u 14 mon)

for the TARGIT E Trialists

Elena Sperk, MD
Department of Radiation Oncology Mannheim

TARGIT E(lderly)



- Risk-adapted, multicentric, international, single arm, **phase II trial** (ClinicalTrials.gov: NCT01299987)
- Based on **TARGIT-A protocol** (experimental arm)
- Set up to test the efficacy of a single dose of IORT in a **well-selected group of elderly patients with small breast cancer** with no risk factors

Neumaier C et al. BMC Cancer 2012, 12:171
http://www.biomedcentral.com/1471-2407/12/171

BMC Cancer

STUDY PROTOCOL Open Access

TARGIT-E(lderly)—Prospective phase II study of intraoperative radiotherapy (IORT) in elderly patients with small breast cancer

Christian Neumaier[1*], Sperk Elena[1], Welzel Grit[1], Abo-Madyan Yasser[1,2], Kraus-Tiefenbacher Uta[1], Keller Anke[1], Gerhardt Axel[3], Sütterlin Marc[3] and Wenz Frederik[1]

Abstract

Background: Patients ≥ 70 years with small, low-risk breast cancer who are operated but not irradiated how local relapse rates around 4% after 4 years. With adjuvant whole breast radiotherapy (WBRT) the local relapse rate drops to 1% after 4 years under Tamoxifen. It has been demonstrated that the efficacy of radiotherapy of the tumor bed only in a selected group can be non-inferior to WBRT.

Methods/Design: This prospective, multicentric single arm phase II study is based on the protocol of the international TARGIT-A study. The TARGIT-E study should confirm the efficacy of a single dose of intraoperative radiotherapy (IORT) in a well selected group of elderly patients with small breast cancer and absence of risk factors. Patients will receive IORT (20 Gy with Intrabeam system/Carl Zeiss) during breast conserving surgery. In presence of risk factors postoperative WBRT will be added to complete the radiotherapeutic treatment according to international guidelines. Endpoints are

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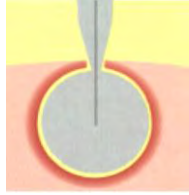
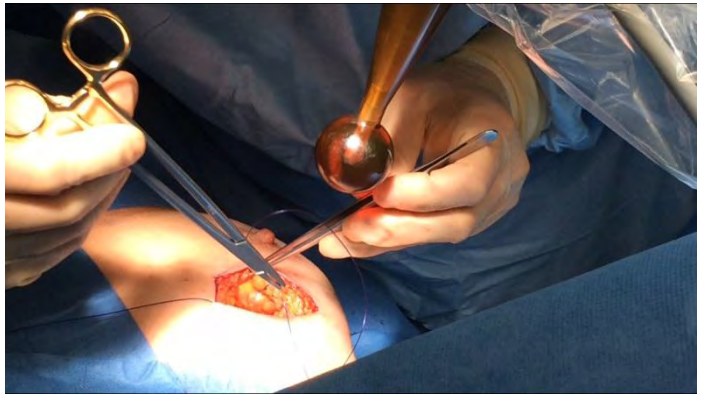
Study design



Elderly pts with small breast cancer (≥ 70yrs)

cT1 (≤ 3.5 cm)
cN0 cM0
ductal-invasive histology
no risk factors:
multifocality/- centricity
EIC (biopsy)
L1 (biopsy)



BCS+SNE
IORT
20 Gy

no risk factors

observation

Risk factors in final path
Tumor > 2cm (>3.5cm international)
Other histology
Margins < 1cm (< 2 mm international)
pN+, L1
mulitfocality/-centricity
EIC

Adjuvant/postop WBRT 46 Gy
(pN1: 50 Gy; pN2: 50 Gy + RNI)

Patient characteristics

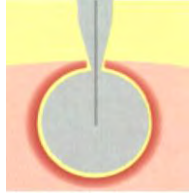
International (n = 8)	German (n = 20)	
Herlev DK	Mannheim UKL	Meiningen
Montpellier F	Berlin DRK	Magdeburg UKL
Marseille F	Hamburg Agaplesion	Cologne UKL
Leon Berard F	Cologne Mehrheim	Hannover UKL
Bordeaux F	LMU Munich	Nuremberg Nord
Nantes F	Westerstede	Homburg UKL
Dijon F	Regensburg UKL	Essen UKL
Frauenfeld CH	Munich DRK	Ludwigsburg
	Bottrop	Hamburg UKL
	Hamburg Jerusalem	Hamm

Patient characteristics

	International (n = 447)	German (n = 232)
med age	74 yrs	74 yrs
70 - 80 yrs [%]	84	85
1-10/11-20/>20 mm	35/46/10	28/52/13
G1/G2/G3 [%]	35/47/9	28/52/11
LVI [%]	9	11
pN+ [%]	13	17
ER+ [%]	87	85
Her2neu +++ [%]	5	7
chemo [%]	6	8
hormone therapy [%]	74	75
EBRT +/- IORT [%]	21	29

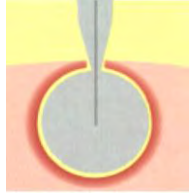
may not add to 100% due to missing values

Study design



- **α=0.05; β= 0.1** estimated drop-out rate/loss to follow-up of 20%
- anticipated LRR **0.5 / 1 / 1.5%** at **2.5 / 5 / 7.5** years
- Stopping rules: LRR > **3 / 4 / 6** at **2.5 / 5 / 7.5** years
- **planned safety analysis after 80 treated patients**

Safety analysis



100 patients

14 centers
02/2011 FPI

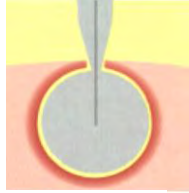
9 Screening failures
(cT2, histology, bilateral BC, EIC in biopsy)

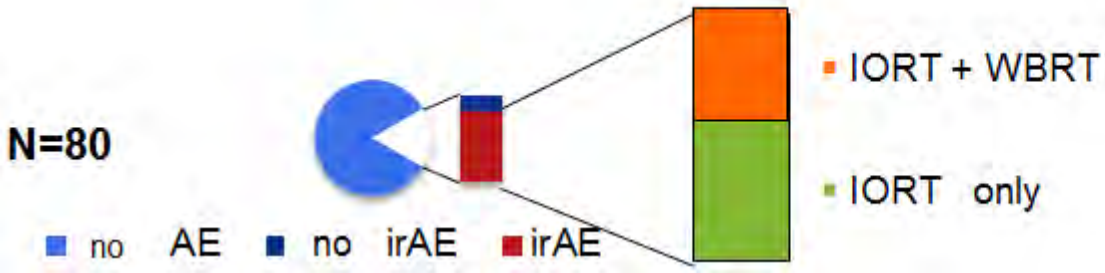
10 Drop outs
(no OP, patient withdrawl after surgery, refusal of WBRT without IORT, investigator withdrawl)

1 LtFU (IORT no FU)

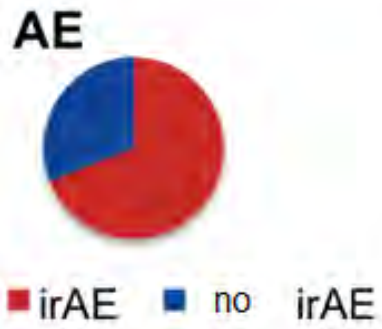
→ **80 patients**

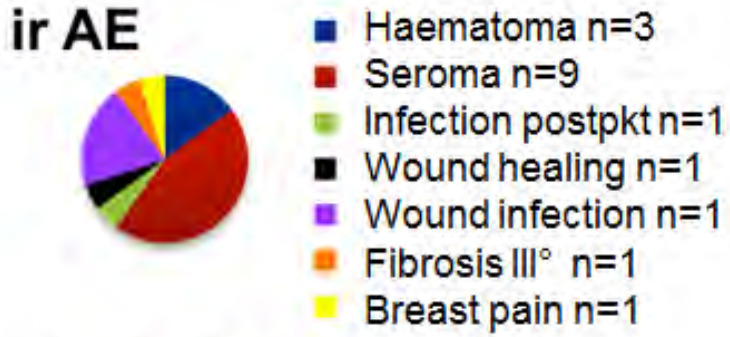
Safety



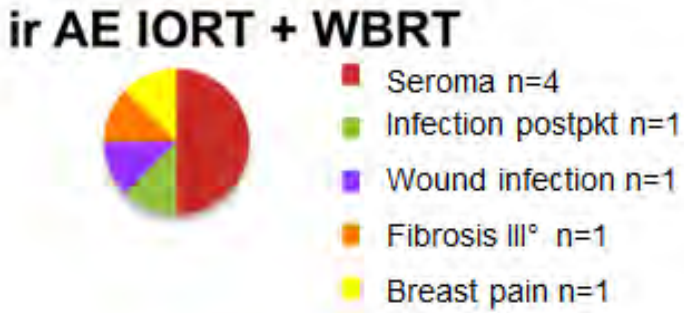

N=80
no AE
no irAE
irAE
IORT + WBRT
IORT only


AE related to patient received certain treatment
IORT only
IORT + WBRT


AE
irAE
no irAE


ir AE
Haematoma n=3
Seroma n=9
Infection postpkt n=1
Wound healing n=1
Wound infection n=1
Fibrosis III° n=1
Breast pain n=1


ir AE IORT
Haematoma n=3
Seroma=5
Wound healing n=1
Wound infection n=3


ir AE IORT + WBRT
Seroma n=4
Infection postpkt n=1
Wound infection n=1
Fibrosis III° n=1
Breast pain n=1

Update 01/2016

interim analysis (n = 80): no LRR, no stopping rule violated

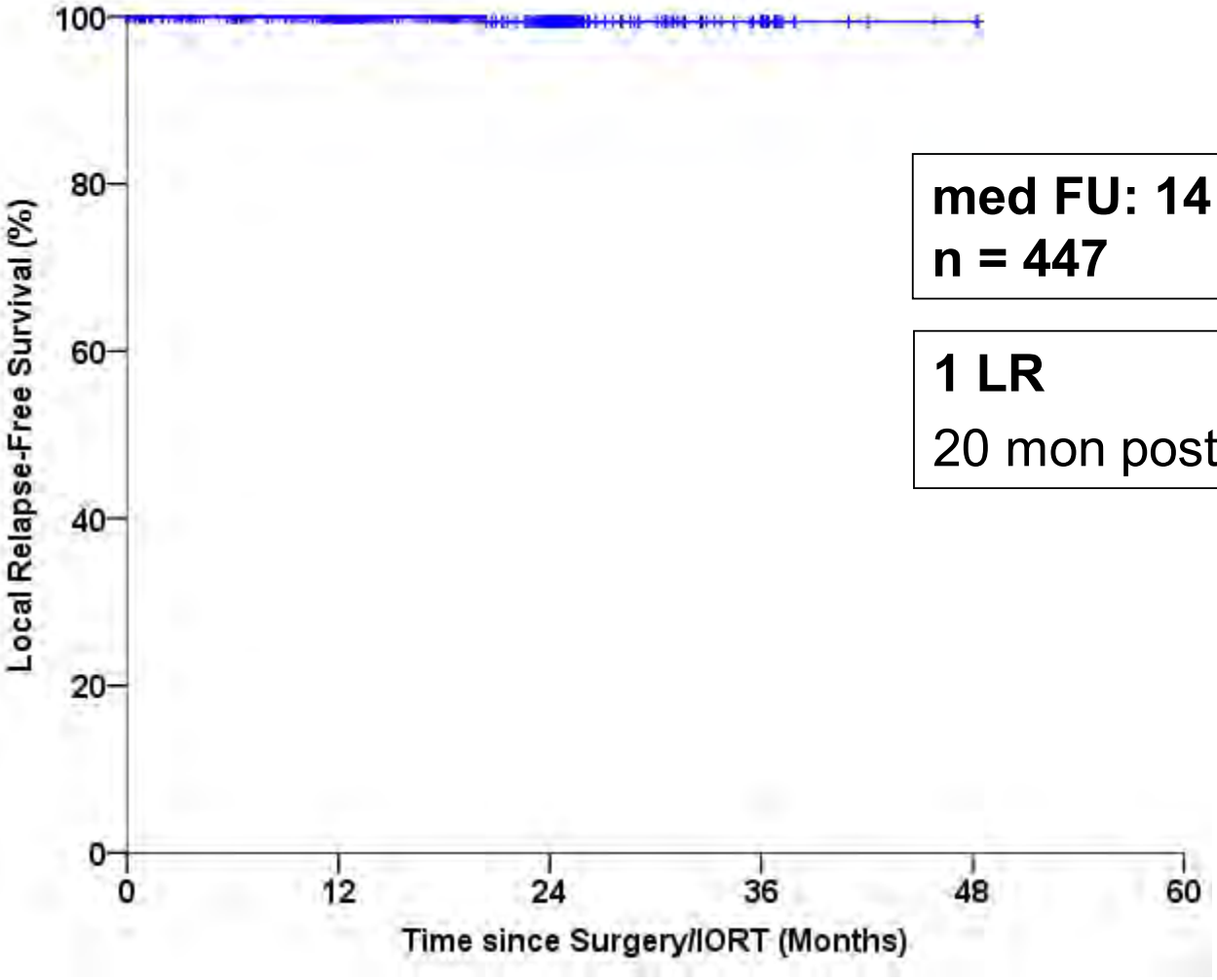
Update 1/2016

- trial closed
- n = 538 enrolled
- 50% Germany (20 centers)
- 50% DK, CH, F (8 centers)

FU available for n = 447

- med FU 14 mon

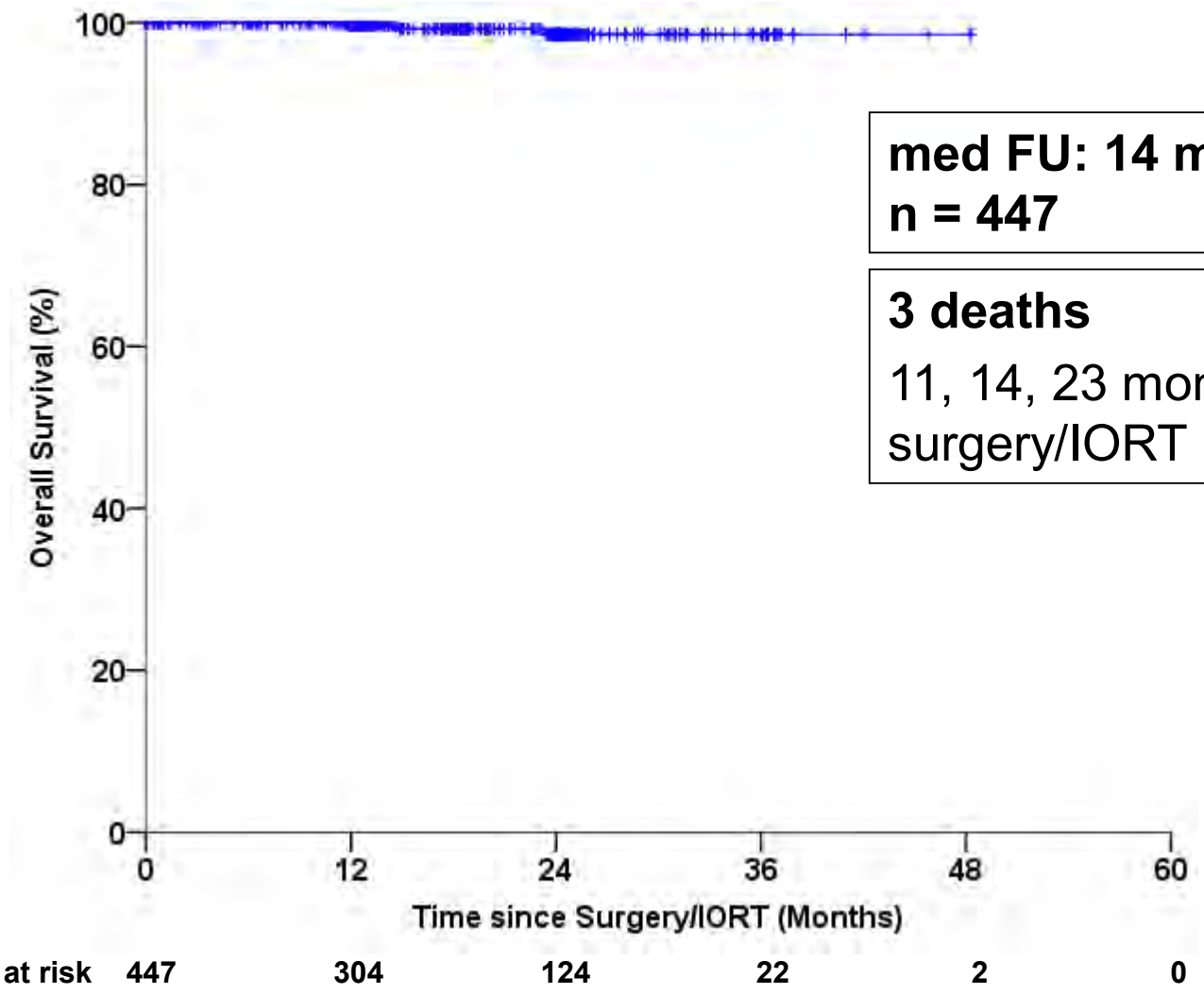
01/2016: Local relapse-free survival



med FU: 14 mon [0-48 mon]
n = 447

1 LR
20 mon post surgery/IORT

01/2016: Overall survival

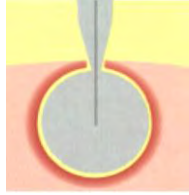


med FU: 14 mon [0-48 mon]
n = 447

3 deaths

11, 14, 23 mon post surgery/IORT

Summary



- TARGIT-E(lderly) is a risk-adapted, multicentric, international, phase II trial based on the TARGIT-A protocol
- Safety analysis after inclusion of 80 pts reveals an AE profile similar to TARGIT-A
- **Efficacy update 1/2016:**

❖ n = 447 pts, median FU 14 mon

❖ **very low LRR (1/447; 0.2%)**

❖ **very good OS (3/447; 0.7%)**

A cohort analysis to identify eligible patients for intraoperative radiotherapy (IORT) of early breast cancer

Radiation Oncology 2014, 9:154

Elena Sperk[1*], Daniela Astor[1], Anke Keller[1], Grit Welzel[1], Axel Gerhardt[2], Benjamin Tuschy[2], Marc Sütterlin[2] and Frederik Wenz[1]

***S3 Guideline 2012/ Statement 5.3.1:**

Re-RT (partial breast RT) should be considered during re-BCS

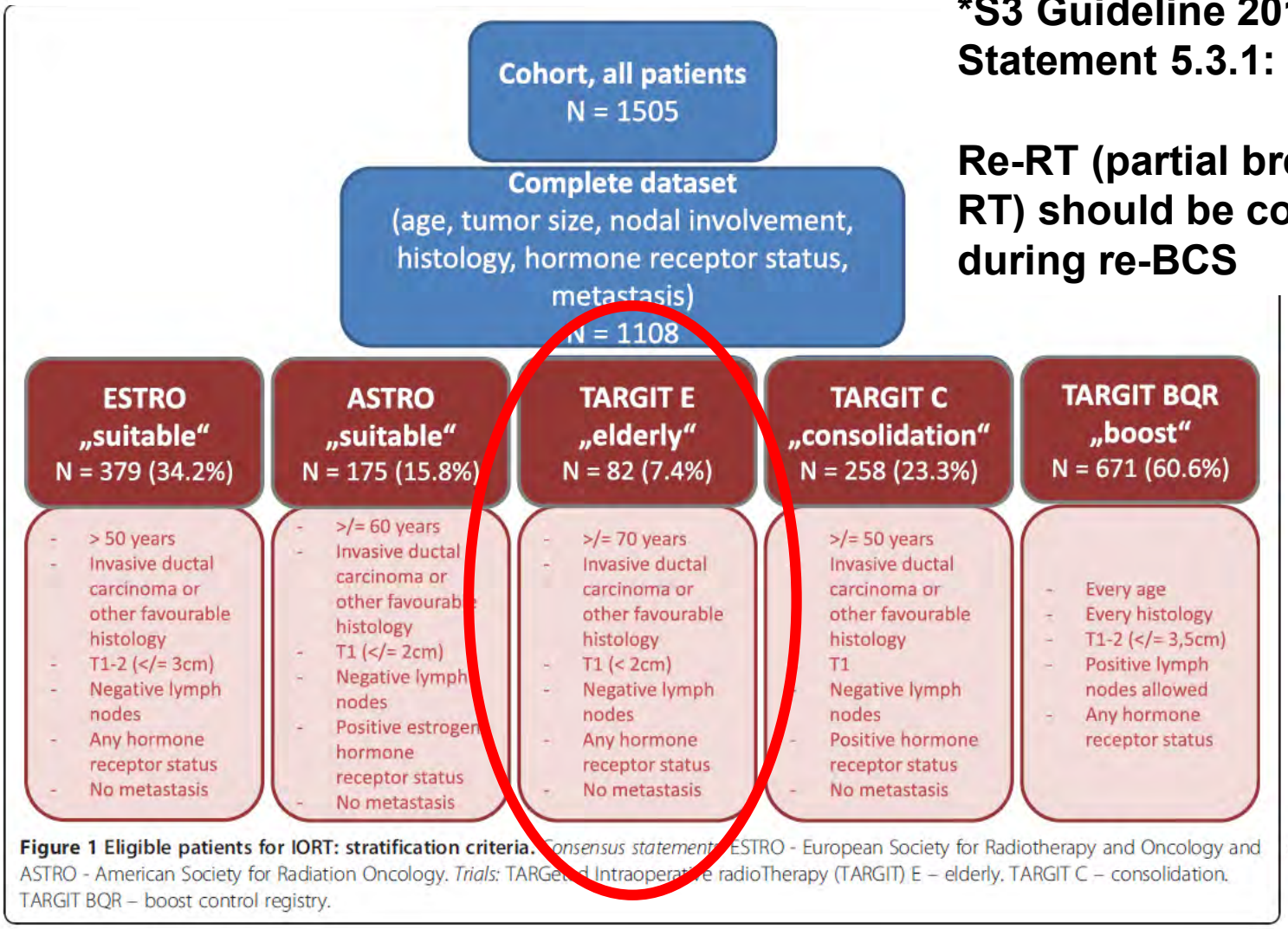


Figure 1 Eligible patients for IORT: stratification criteria. *Consensus statement:* ESTRO - European Society for Radiotherapy and Oncology and ASTRO - American Society for Radiation Oncology. *Trials:* TARGeted Intraoperative radioTherapy (TARGIT) E – elderly. TARGIT C – consolidation. TARGIT BQR – boost control registry.

IORT with low energy kV x-rays worldwide

Thank you for your attention!

elena.sperk@umm.de

9th International ISIORT Conference
June 24/25th 2016
Novara, Italy

PARTIAL BREAST WITH ELECTRONS:PRELIMINARY RESULTS OF THE MULTICENTER GROUP EMILIA ROMAGNA REGION ITALY

Stefanelli A.,Zini G.,[1] Baldissera A.,Frezza G.,[2]Iotti C.,[3] Venturini A.,Perini F.[4]

1 Department of Radiation Oncology, University Hospital "S. Anna", Ferrara, Italy

2 Department of Radiation Oncology, Bellaria Hospital ,Bologna ,Italy.

3 Department of Radiation Oncology, S. Maria Nuova Hospital Reggio Emilia Italy.

4 Department of Radiation Oncology, Infermi Hospital Rimini Italy.

IORT TEAM

RADIONCOLOGIST

SURGEON

ANESTHETIST

MEDICAL PHYCIST

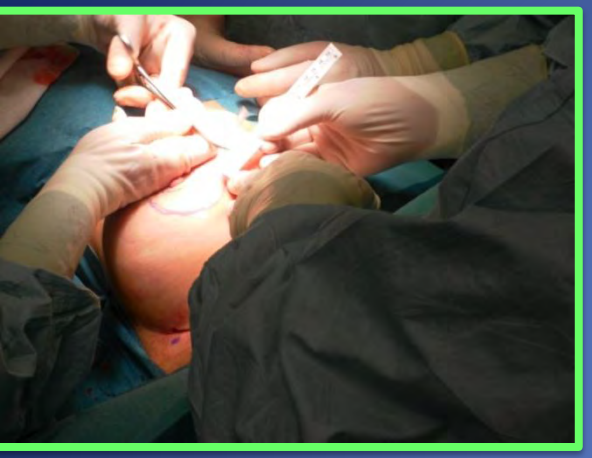
RADIOLOGY TECHNICIAN

NURSE

LIAC
SORDINA COMPANY

Electrons beams
4,6,8,10 Mev

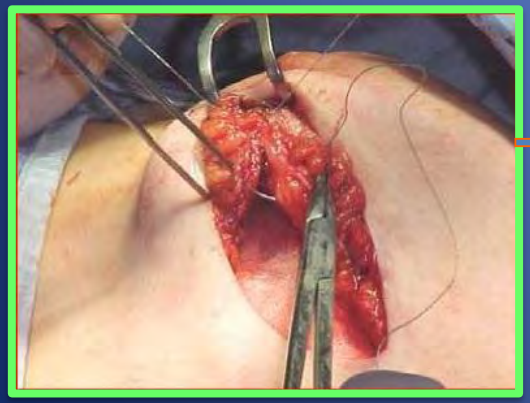
IORT STEPS



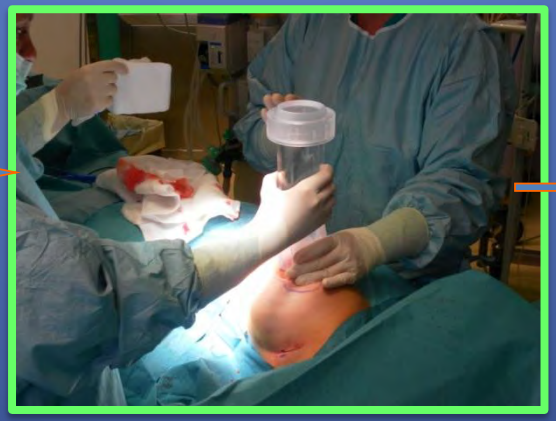
Conserving surgery

insertion protection disc

Temporary suture and thickness measurement



Distal collimator placement



Docking done

Methods

From 2009 to May 2016 we were treated with intraoperative radiotherapy (IORT) as a radical treatment of 498 patients with breast carcinoma after conservative surgery

Methods

Until December 2013, the enrollment of patients was done according to the protocol of the Emilia Romagna Region IRMA 3 .

From 2014 in accordance with the guidelines Italian Association of Radiation Oncology (AIRO) for breast IORT

IRMA3 inclusion criteria:

Until December 2013

.cytological or histological preoperative or intraoperative invasive non lobular carcinoma

* Age ≥ 50 years female

* Performance status: 0-2 ECOG

* life expectancy of at least 5 years

* cT 1-2 (<2.5 cm in diameter) CN0 M0 according to the TNM classification, candidates for conservative surgery

* negative intra or preoperative sentinel lymph node

* No microcalcifications peritumoral for DCIS on mammography

*Unifocal disease

*informed consent

AIRO criteria:

from january 2014

- Age ≥ 50 years female
- Unifocal disease
- histological preoperative invasive non lobular carcinoma
- T ≤ 2 cm
- favorable biological profile disease (LUMINAL A ER+ RPg+ Her2- Mib1 < 20% G2)
- N0
- Negative margins

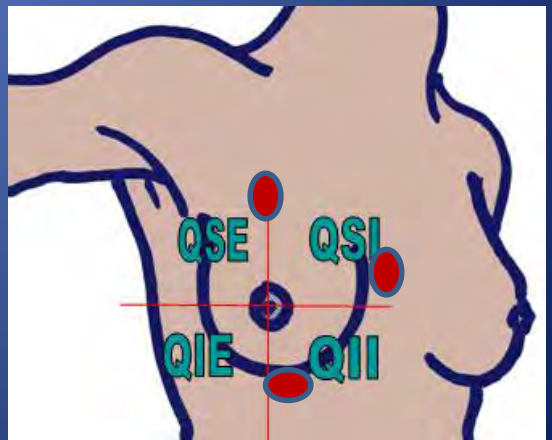
All patients received a dose of 21 Gy isodose of 90% with energy as a function of the thickness of the breast volume.

Results (Only local recurrence analyzed)

- Three of the 498 patients (0.6%) had a local recurrence of the disease. One patient had an axillary lymph node recurrence, one patient had recurrence in the same quadrant and one patient in a different quadrant.

Conclusion

- The preliminary results of our experience confirms the feasibility of intraoperative treatment in terms of local control in the subset of low-risk patients in line with the most recent trials. It is however necessary a longer follow-up and a more accurate analysis of the data.
- Also in the selection of patients it is important to assess the location of the disease and the volume of the gland (thickness) for the feasibility of the treatment



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FULL-DOSE 21 Gy INTRAOPERATIVE ELECTRON RADIOTHERAPY IN EARLY BREAST CANCER: RESULTS AFTER A MEDIAN 5.2 -YEARS FOLLOW UP IN 758 PATIENTS FROM A SINGLE ITALIAN INSTITUTION

Silvia Takanen
Department Radiation Oncology

No interests to disclose

9° International ISIORT Conference
Novara 24 June 2016

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INTRODUCTION AND PURPOSE

To individuate most important prognostic factors

in selecting patients with early breast cancer eligible for IORT,

resulted from our retrospective study after a median follow up

of 5.2 years

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METHODS

From February 2006 to January 2016

Papa Giovanni XXIII Hospital (Bergamo, Italy)

early breast cancer

(AJCC TNM 7th edition)

758 patients

Median age 64 (range 48-84)

- **Histology according to WHO classification**
- **Tumor grading according to NGS**
- **LVI focal or diffuse (Rosen's criteria)**
- **EIC absent, present <25% or >25%**
- **ER and PR positive or negative (<10%)**
- **Her2 neu negative or positive (3+ FISH)**
- **Ki67 positive (>20%) or negative (≤20%)**
- **Surgical margins negative, close, positive**

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METHODS

Breast conserving surgery

772 ELIOT procedures

10 pts synchronous BC
3 pts contralateral metachronous BC
1 pt ispilateral metachronous BC

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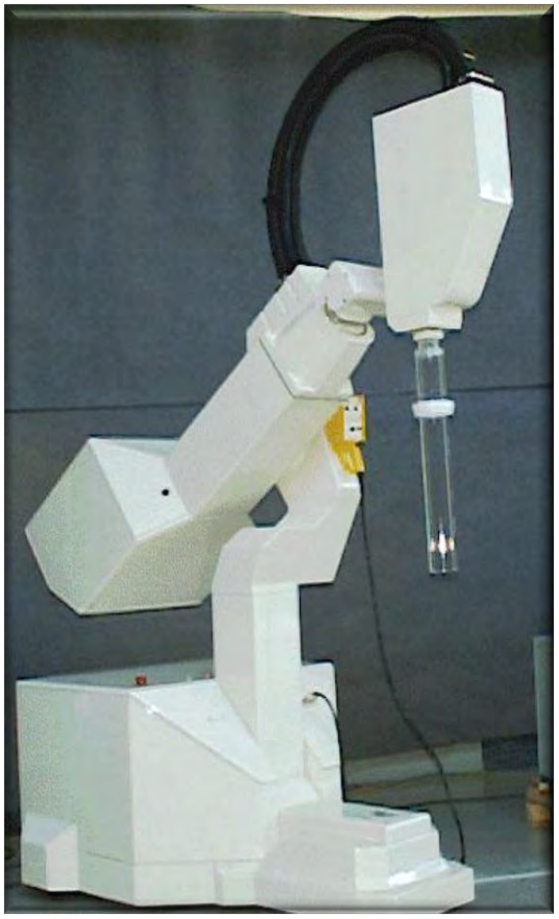
METHODS

ELIOT

- NOVAC 7 HITESYS, NRT, Italy
- 21 Gy at 90% isodose
- Energy 9 MeV
- Collimators diameters 4-6 cm
- In-vivo dosimetry



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METHODS

Patients analysis according to GEC-ESTRO and ASTRO recommendations for APBI

Categories	GEC-ESTRO / ASTRO *Polgar, Rad Onc 2010 / Smith, IJROBP 2009*	
	Patients n	
Low risk/Suitable	350	116
Intermediate risk/Cautionary	185	381
High risk/Unsuitable	237	275

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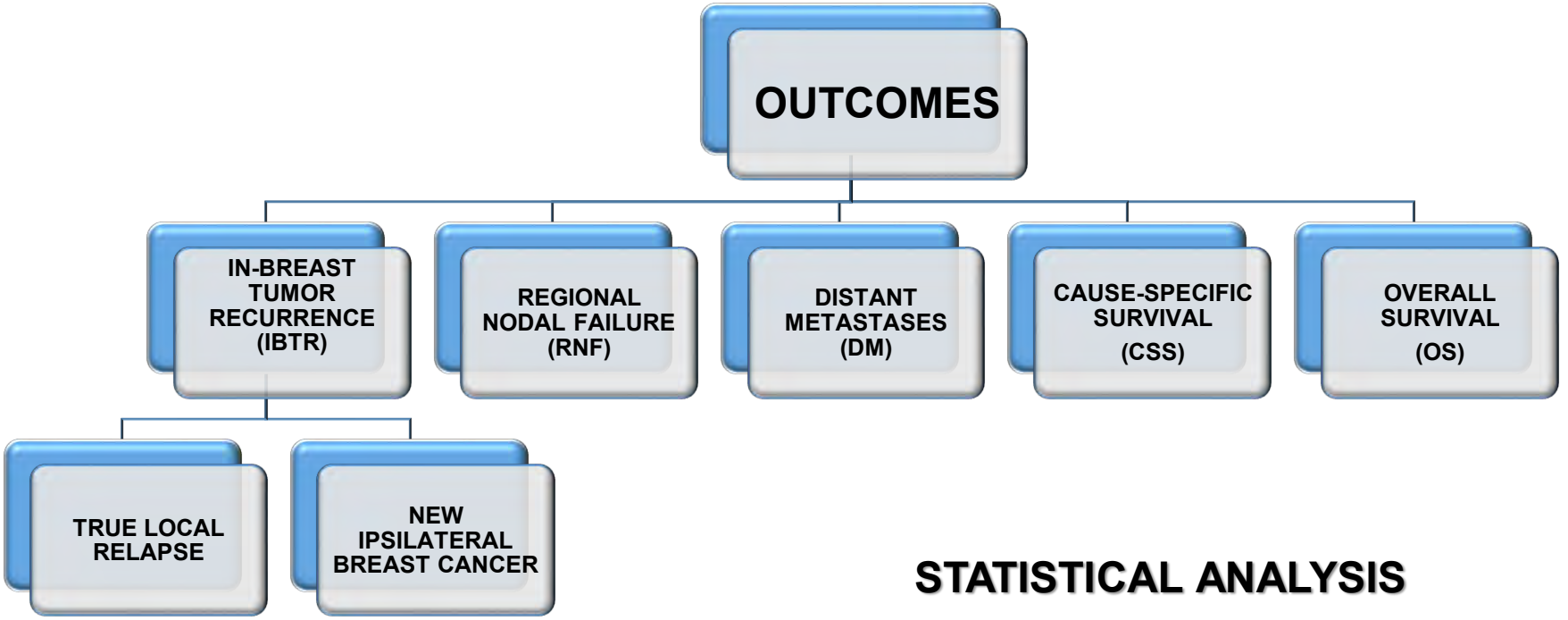
METHODS



STATISTICAL ANALYSIS

- ❑ Kaplan-Meier 5 years ratio (CI 95%)
- ❑ Log Rank Test (p value < 0.05)
- ❑ Cox proportional hazard regression analysis

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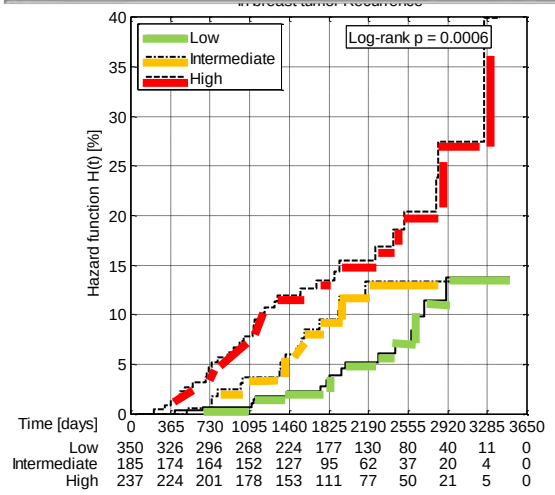
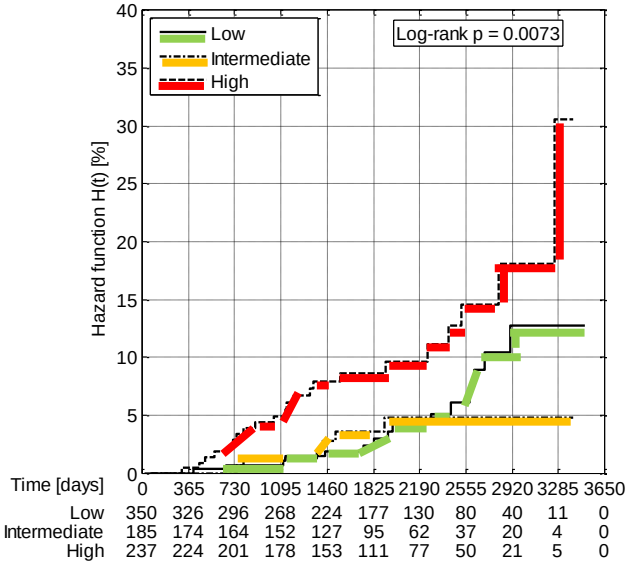
RESULTS

Significant outcomes for groups categorized according **GEC-ESTRO**

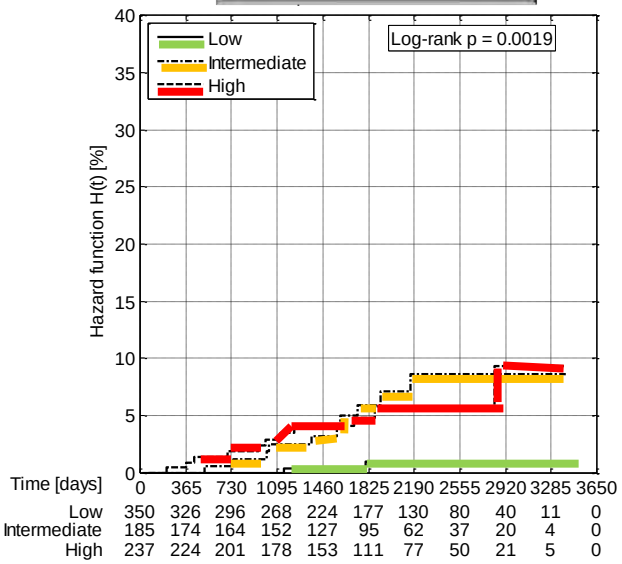
In-breast Tumor Recurrence (p<0.006)



True local relapse (p<0.0073)



New ipsilateral BC (p<0.0019)



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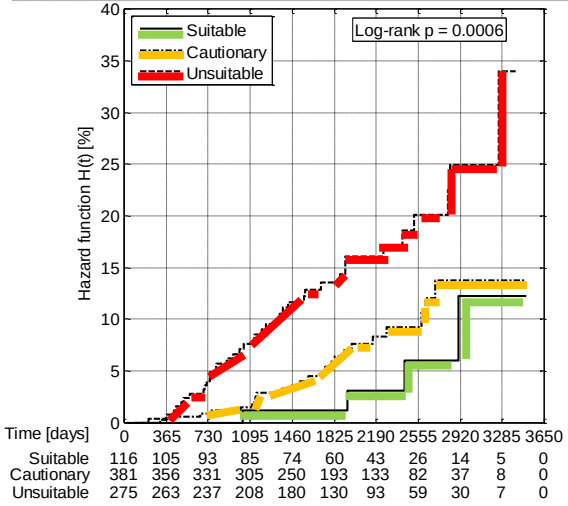
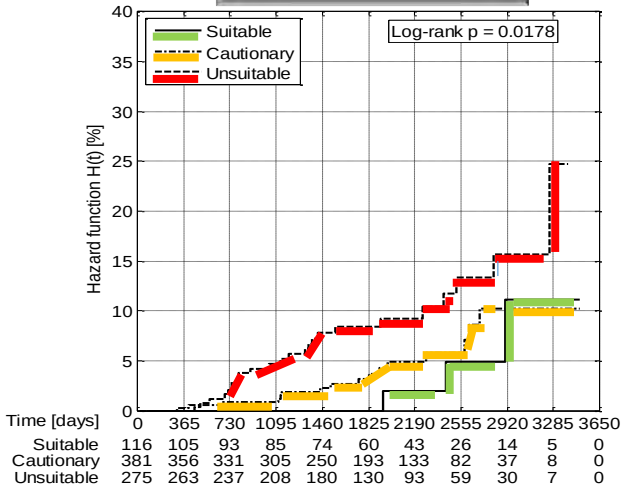
RESULTS

Significant outcomes for groups categorized according to **ASTRO**

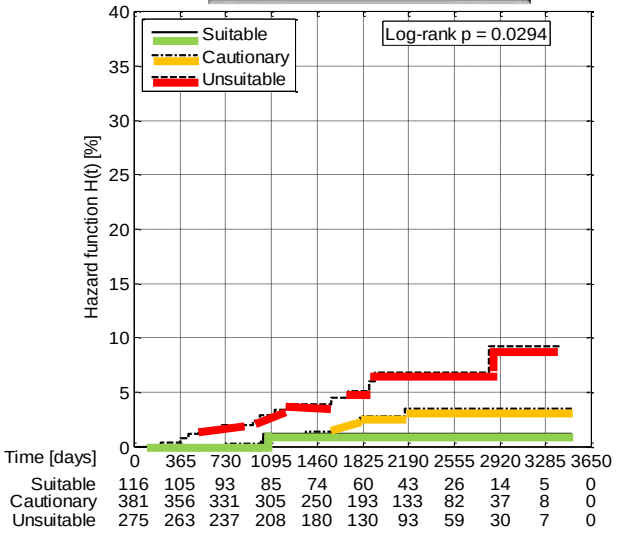
In-breast Tumor Recurrence (p<0.0006)



True local relapse (p<0.0178)



New ipsilateral BC (p<0.0204)



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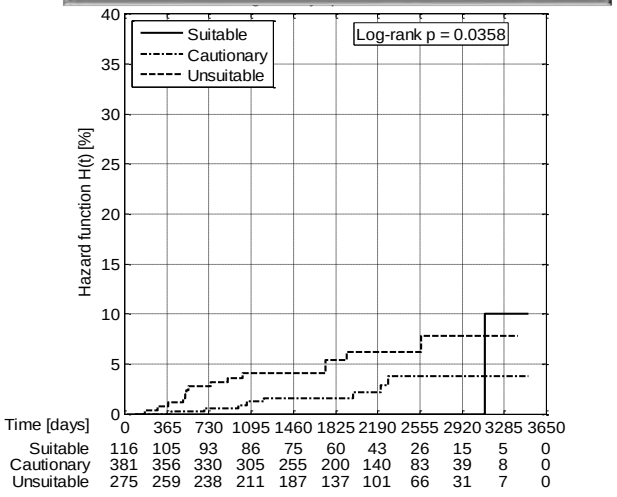
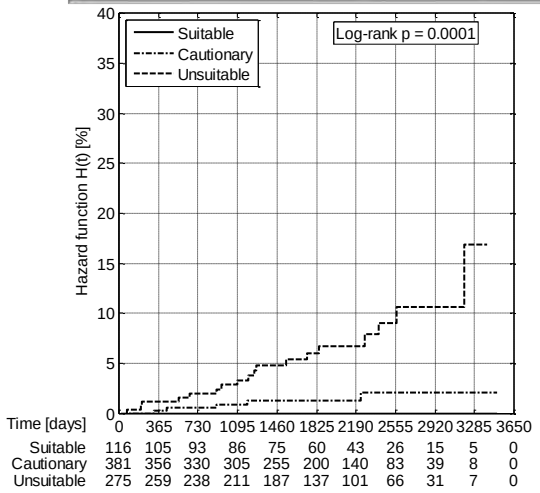
RESULTS

Significant outcomes for groups categorized according to **ASTRO**

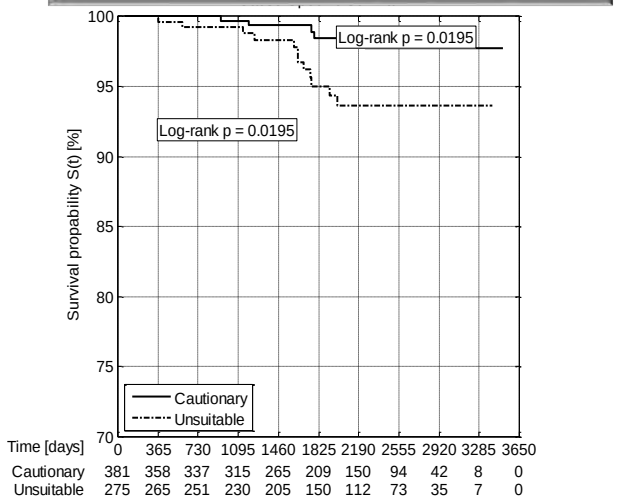
Regional Nodal Failure(p<0.0006)



Distant Metastases(p<0.0001)



Cause-Specific Survival(p<0.0195)



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RESULTS

Significant prognostic factors for every outcome based on **univariate analysis**

Predictive risk factors			True Local recurrence				Ipsilateral breast cancer				In breast tumor recurrence				Regional lymph node faliure				Distant metastases				Cause-specific survival				Overall survival			
		Number at risk	HR	CI 95%		p-value	HR	CI 95%		p-value	HR	CI 95%		p-value	HR	CI 95%		p-value	HR	CI 95%		p-value	HR	CI 95%		p-value	HR	CI 95%		p-value
AGE	> 60	522	1,00								1,00				1,00				1,00				1,00				1,00			
	51-60	231	1,81	0,96	3,40	0,06					1,63	0,99	2,70	0,06	2,10	0,91	4,84	0,08	1,13	0,45	2,84	0,79	1,25	0,46	3,45	0,66	0,66	0,32	1,34	0,25
	≤ 50	19	7,79	2,63	23,03	0,00					4,40	1,55	12,46	0,01	3,14	0,40	24,54	0,28	7,64	2,15	27,11	0,00	2,84	0,36	22,21	0,32	0,95	0,13	6,94	0,96
HISTOL	Ductal + other	668	1,00								1,00				1,00								1,00				1,00			
	Lobular + mixed	104	0,31	0,07	1,27	0,10	3,20	1,36	7,56	0,01	1,11	0,57	2,17	0,77	2,21	0,87	5,63	0,10					0,82	0,19	3,57	0,79	0,65	0,23	1,81	0,41
T size	≤ 1.5	498	1,00								1,00				1,00				1,00				1,00				1,00			
	1.6-2	151	1,88	0,90	3,92	0,09	1,10	0,39	3,08	0,86	1,55	0,86	2,81	0,15	2,58	0,94	7,14	0,07	2,58	0,93	7,12	0,07	1,22	0,37	3,96	0,74	1,06	0,51	2,19	0,88
	> 2.0	122	2,21	1,08	4,51	0,03	1,24	0,44	3,48	0,69	1,81	1,01	3,23	0,05	3,15	1,18	8,44	0,02	3,22	1,21	8,62	0,02	1,27	0,39	4,15	0,69	0,81	0,35	1,87	0,62
Lymph node status	pN0 + pN1mic	654	1,00								1,00				1,00				1,00				1,00				1,00			
	pN1a	84	0,95	0,37	2,43	0,92	1,61	0,54	4,79	0,39	1,17	0,57	2,37	0,67	0,74	0,17	3,16	0,68	3,97	1,56	10,08	0,00	2,56	0,81	8,04	0,11	1,25	0,52	2,97	0,62
	≥ pN2a	33	1,22	0,37	3,99	0,74	1,91	0,44	8,27	0,39	1,43	0,57	3,59	0,45	1,70	0,39	7,36	0,48	5,80	1,86	18,06	0,00	2,70	0,60	12,20	0,20	1,37	0,42	4,46	0,61
Grading	I, II	597	1,00								1,00				1,00				1,00				1,00				1,00			
	III	175	3,01	1,65	5,48	0,00	1,82	0,77	4,29	0,17	2,54	1,56	4,13	0,00	1,47	0,60	3,58	0,39	3,68	1,62	8,36	0,00	5,83	2,16	15,77	0,00	2,14	1,16	3,95	0,01
Ki67	Negative	530	1,00								1,00				1,00				1,00				1,00				1,00			
	Positive (>20%)	237	2,98	1,62	5,50	0,00	2,43	1,07	5,50	0,03	2,77	1,70	4,52	0,00	2,85	1,25	6,52	0,01	3,38	1,46	7,82	0,00	4,96	1,75	14,07	0,00	2,47	1,35	4,51	0,00
Triple negative	TN	716	1,00								1,00				1,00				1,00				1,00				1,00			
	non TN	50	2,77	1,23	6,25	0,01	4,19	1,56	11,30	0,00	3,23	1,73	6,06	0,00	1,96	0,58	6,61	0,28	1,92	0,57	6,48	0,29	3,92	1,28	12,02	0,02	2,48	1,10	5,57	0,03
LVI	Absent	657	1,00								1,00				1,00				1,00				1,00				1,00			
	Present	115	2,16	1,11	4,21	0,02	2,49	1,02	6,05	0,04	2,27	1,33	3,87	0,00	1,96	0,77	4,97	0,16	5,05	2,23	11,46	0,00	3,82	1,45	10,03	0,01	1,90	0,96	3,76	0,07

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HPG23 groups

Suitable for ELIOT

- Age>50 years
- Non lobular histology
- Tumour size ≤ 2 cm
- pN0 or pNmic
- ki67≤ 20%
- Non triple negative
- G1-G2

Unsuitable for ELIOT

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RESULTS

Differences for all the clinical outcomes between **"suitable" and "unsuitable"** for IORT from **HPG23** patients

		Number at risk	Numbers of events	Numbers censored	Ratio at 5 years	CI at 95%	p-value
In breast tumor Recurrence	Suitable	298	6	292	1,8%	(0.0%- 3,8%)	<0,005
	Unsuitable	474	60	414	11,6%	(8,1%- 15,1%)	
True local recurrence	Suitable	298	3	295	0,6%	(0,0%- 1,9%)	<0,005
	Unsuitable	474	40	434	6,9%	(4,2%- 9,6%)	
New Ipsilateral breast cancer	Suitable	298	3	295	1,1%	(0,0%- 2,7%)	<0,015
	Unsuitable	474	20	454	4,7%	(2,4%- 7,0%)	
Regional Lymph node failure	Suitable	298	2	296	0,4%	(0,0%- 1,3%)	<0,005
	Unsuitable	474	21	453	4,0%	(2%- 6,1%)	
Distant Metastates	Suitable	298	1	297	0,5%	(0,0%- 1,3%)	<0,005
	Unsuitable	474	22	452	4,1%	(2,1%- 6,2%)	
Cause Specific Survival	Suitable	298	1	297	99,4%	(98,2%- 100%)	0,110
	Unsuitable	474	16	458	96,3%	(94,3%- 98,3%)	
Overall Survival	Suitable	298	12	286	96,3%	(93,7%- 98,8%)	0,231
	Unsuitable	474	31	443	93,0%	(90,4%- 95,7)%	

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CONCLUSIONS

Preoperative selection

- Age > 50
- Non lobular histology
- Tumor size ≤ 2 cm
- cN0 and uN0

- Ki67 ≤ 20%
- NTN receptor status
- G1-G2

Thank you


بسم الله الرحمن الرحیم

Intra Operative Radiation Therapy

Physical & Clinical Review of Iranian Experience

9th International ISIORT Conference

2016

Novara, Italy

24 & 25 JUNE

Professor Mohammad E Akbari

Surgical Oncologist

Cancer Research Center

SBUMS, Tehran Iran, crc@sbmu.ac.ir

Cure Malignant Cases

Surgery	49%
Radiation Therapy alone or with Other	40%
Chemotherapy	11%

Atomic Energy Agency/UN

2013 ?

History of IORT

History

Transferring Patient for IORT from OR to RT department

History

INTRABEAM

Low KV-X Ray

Conventional/IORT comparison

Conventional(EBRT)

- Low Dose
- Fractionated
- Tissue Tolerance
- Delay to Treat

Time and frequencies

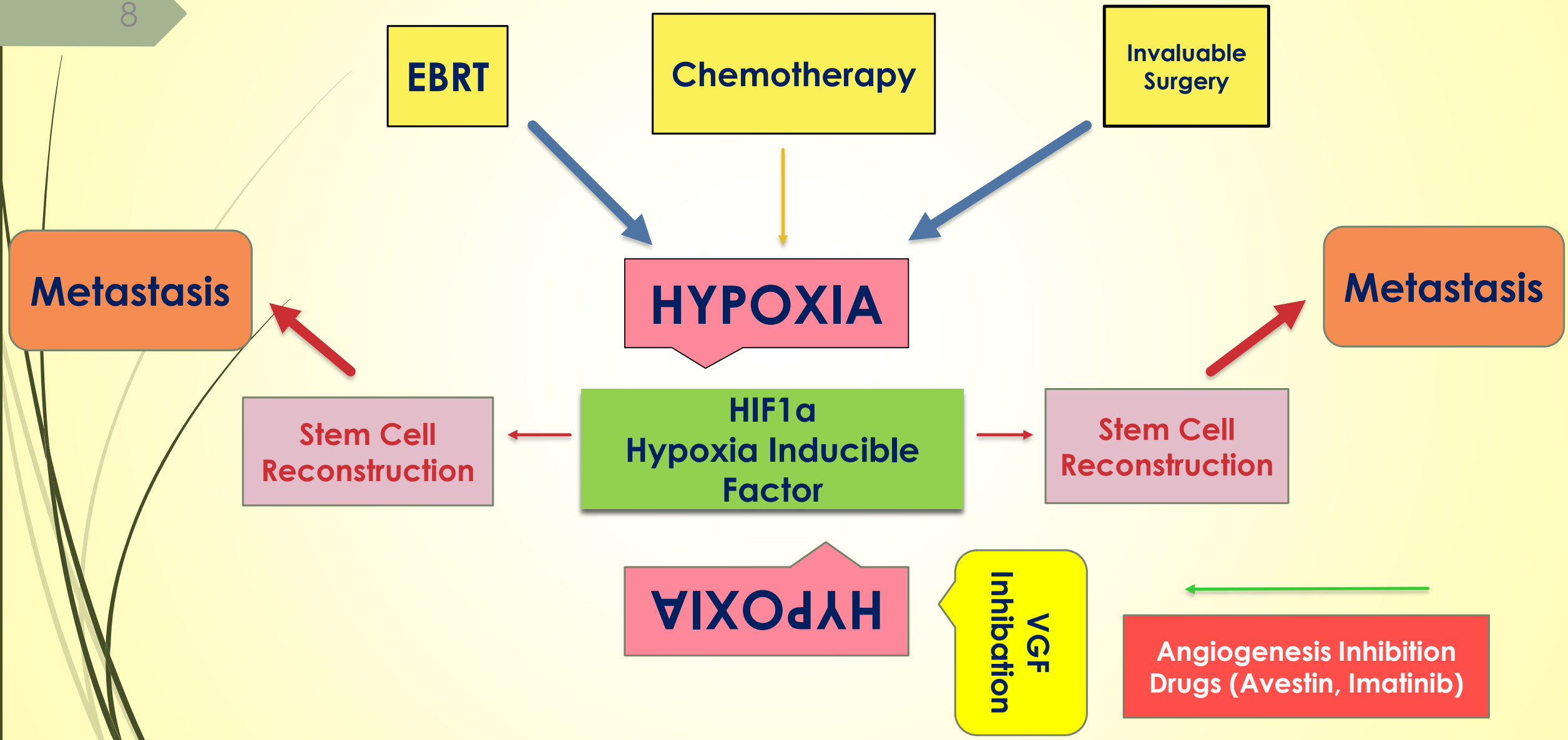
Site questionable irradiation

……

IORT

- Most tolerable Dose
- Exactly on Time
- Exactly on Site
- Neighbor Safety
- Economically profitable
- Very low complication(s)
- ……

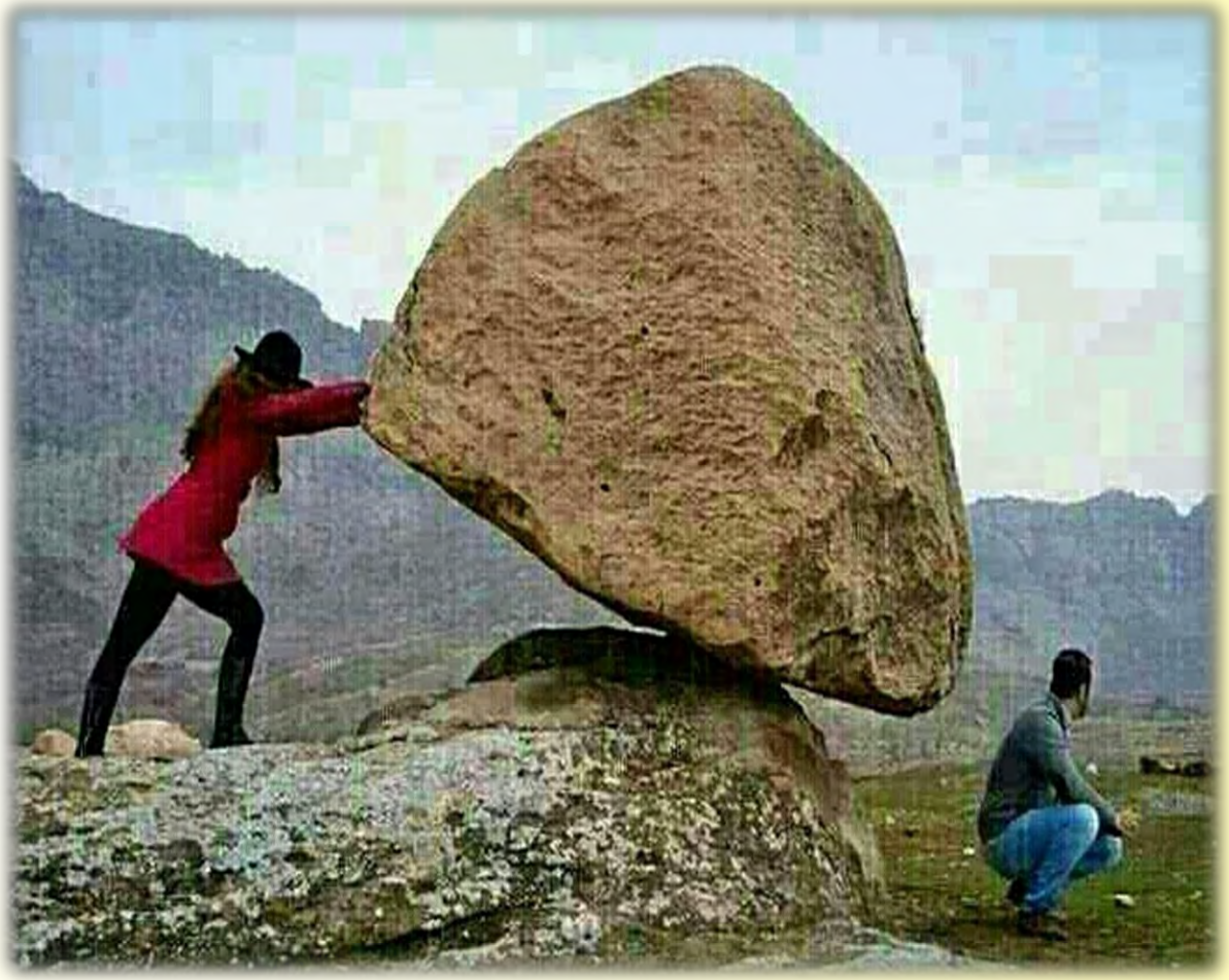
Are We do the Best for our Patients?



IORT

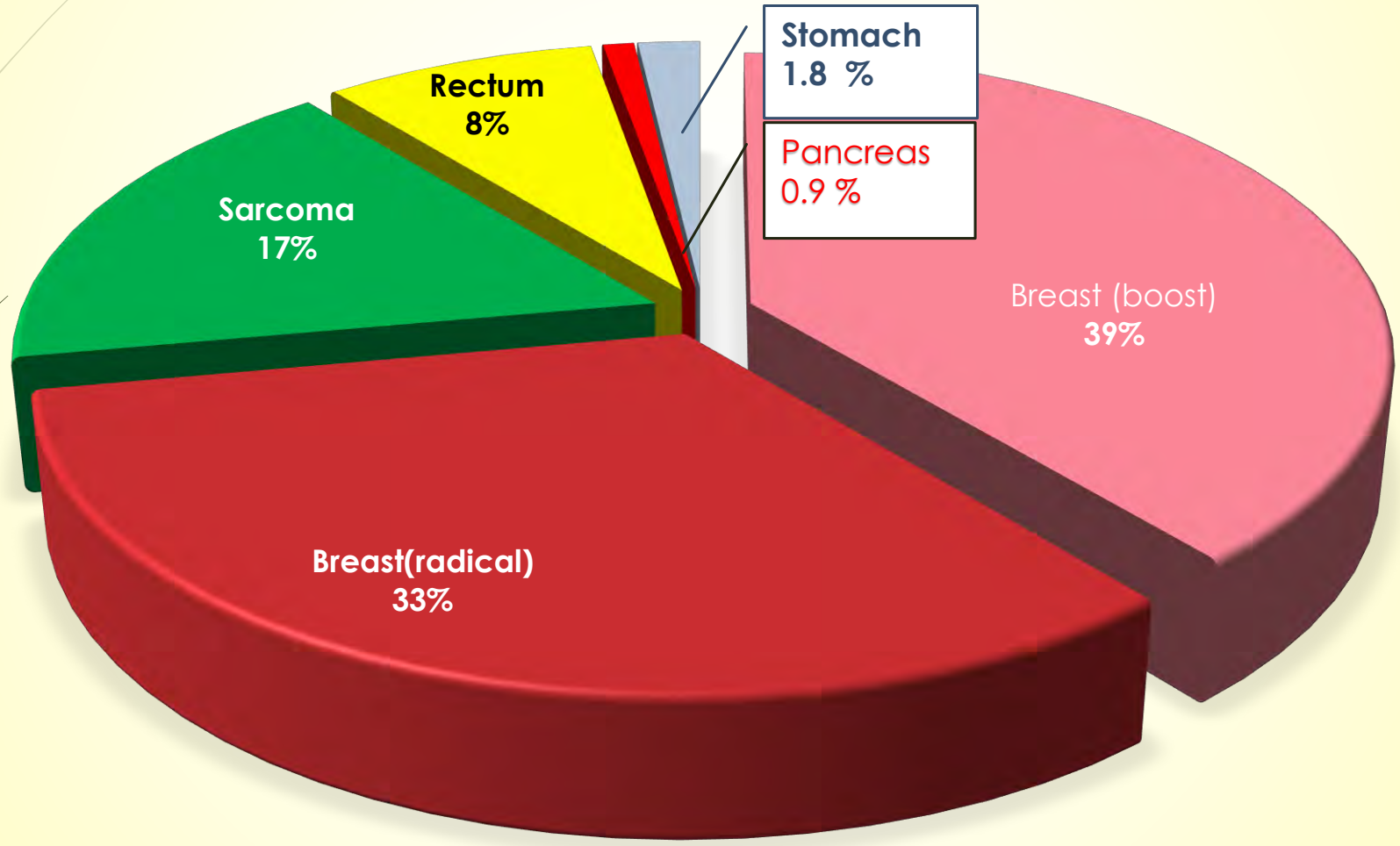
More Power

Less Time



More Effectiveness?

Share of IORT Cases

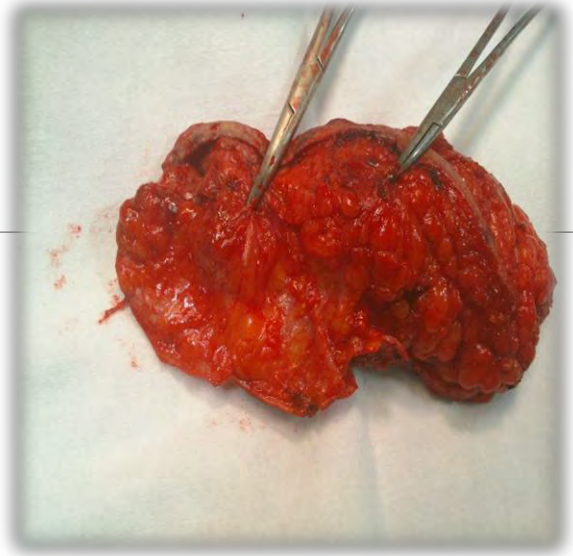


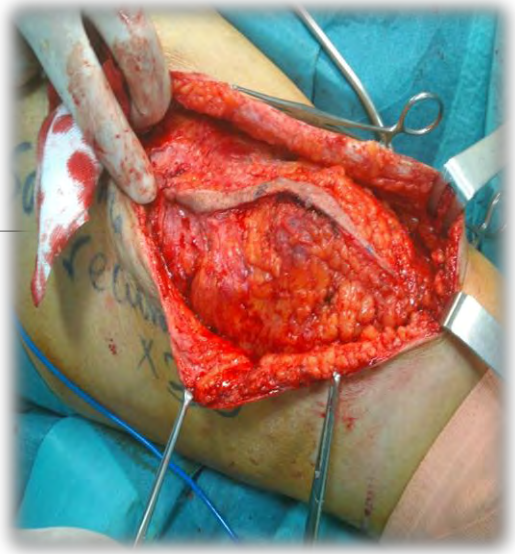
560 IORT Cases, Iran Experience

Row	Site	Linac	Low k v X-Ray	Percent
1	Breast	355	44	71.25
2	Brain	-	9	1.6
3	Sarcoma	90	3	16.6
4	Rectum	40	4	7.85
5	Stomach	10	-	1.8
6	Pancreas	5	-	0.9
	Total	500	60	100%
		560 Cases		

Case 2

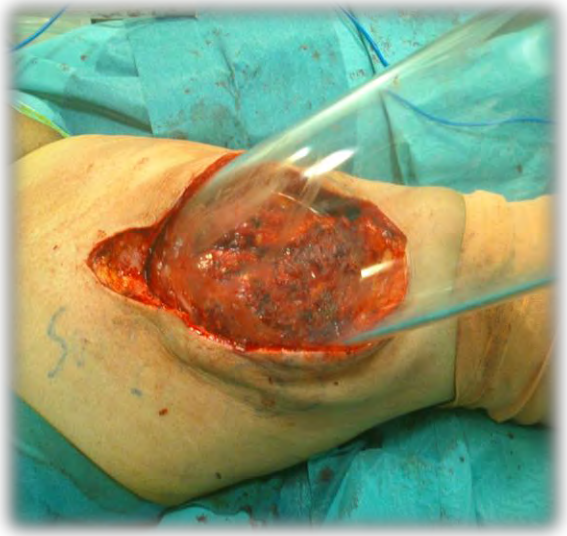
Age: 46 Sex: Female
Localization: Rt Thigh
Pathology: Sarcoma
Recurrence: yes
Previous Radiotherapy: yes
Size Tumor: 10 cm

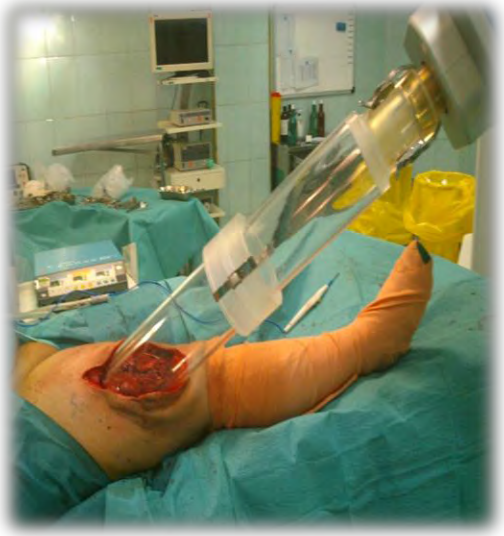




IORT Treatment

Type: Radical Radiotherapy
Applicator: 10 cm
Energy: 26 Mev
Dose: 23 Gy
Time: 1 min 4 Sec





IORT, Linac

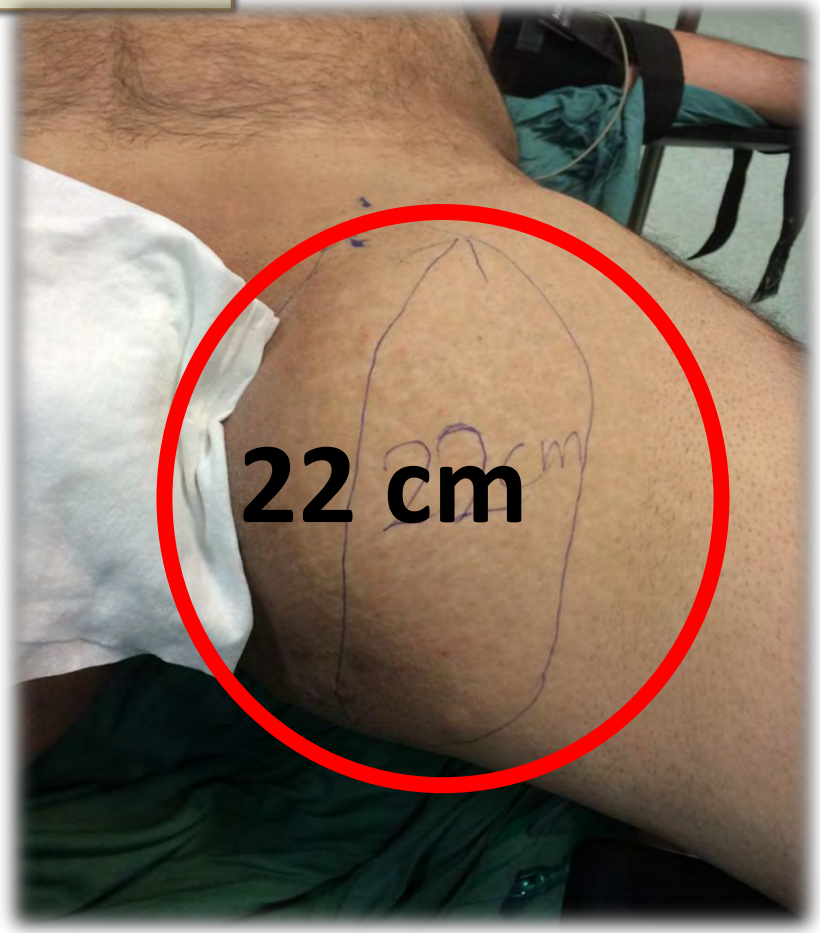
38 years old

Male

with big mass upper part of thigh

High Grade SARCOMA

originate from Obturator channel



IORT Linac

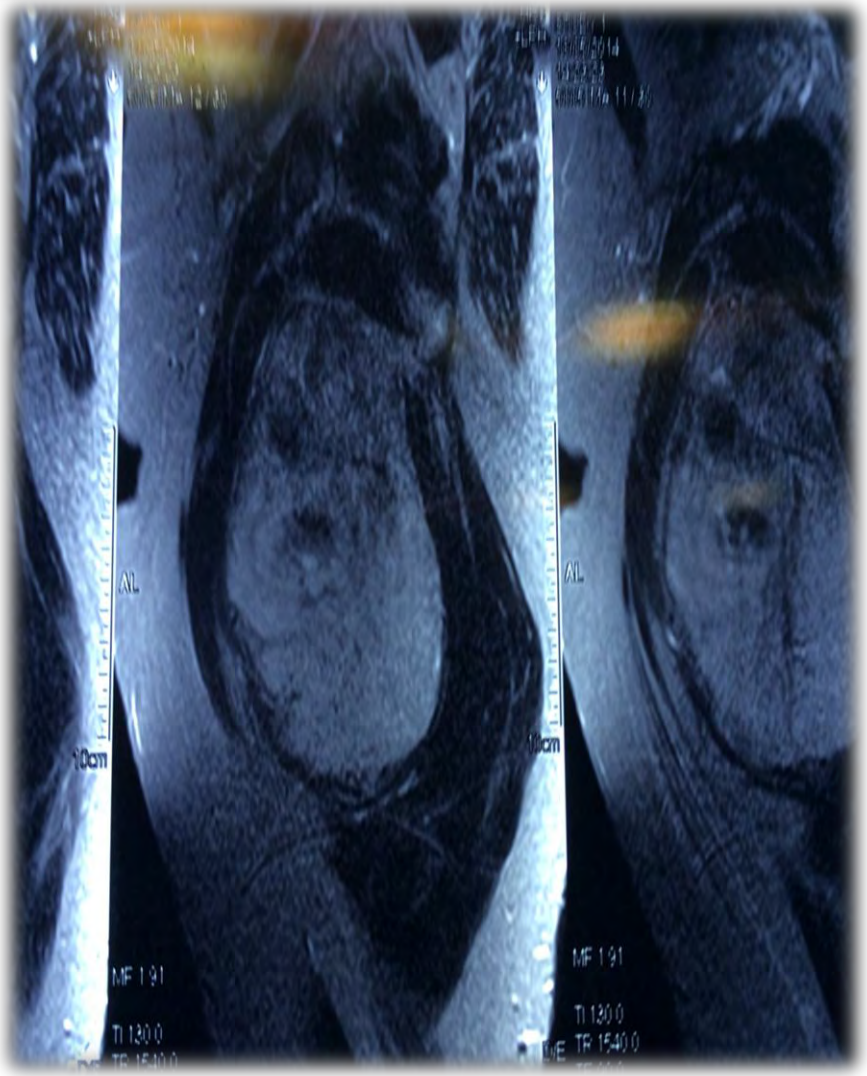
38 years old

Male

with big mass upper part of thigh

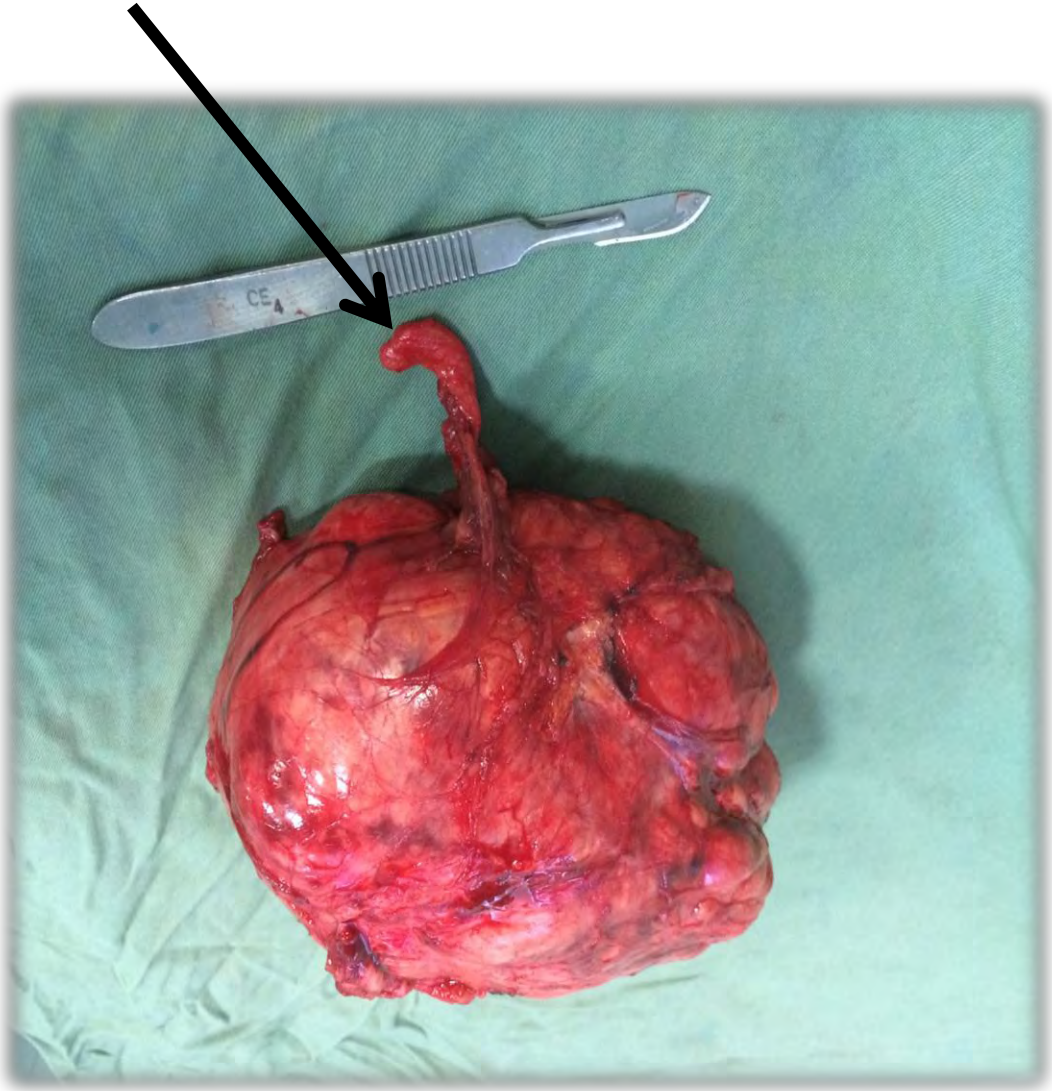
High Grade SARCOMA

originate from Obturator channel



IORT Linac

Obturator Canal



Mass Removed with free margin

IORT, Linac

Ready for IORT
18 GY each field
36 GY 2 fields

Case 3

Age: 50 Sex: Female

Localization: Para-arotic

Pathology: Para-arotic Lymph Adenopathy

Recurrence: yes

Previous Radiotherapy: yes

IORT Treatment

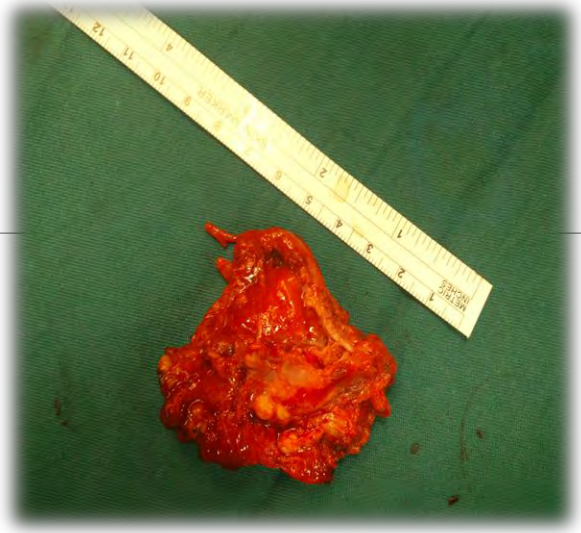
Type: Radical Radiotherapy

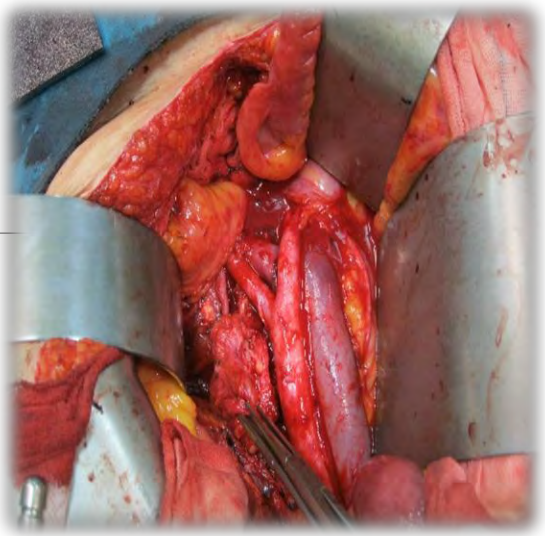
Applicator: 10 cm

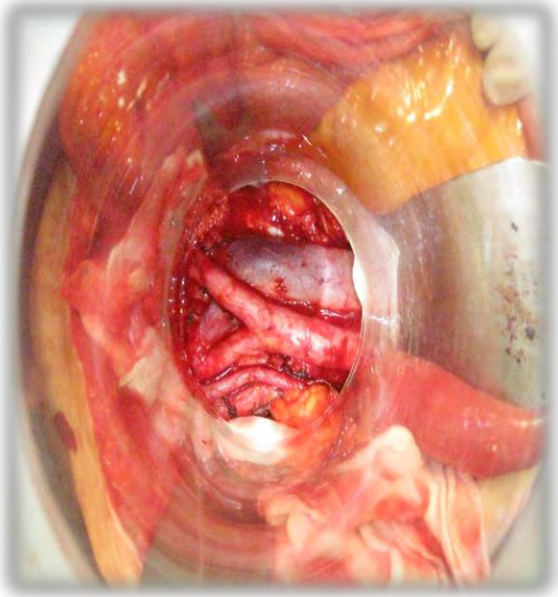
Energy: 6 Mev

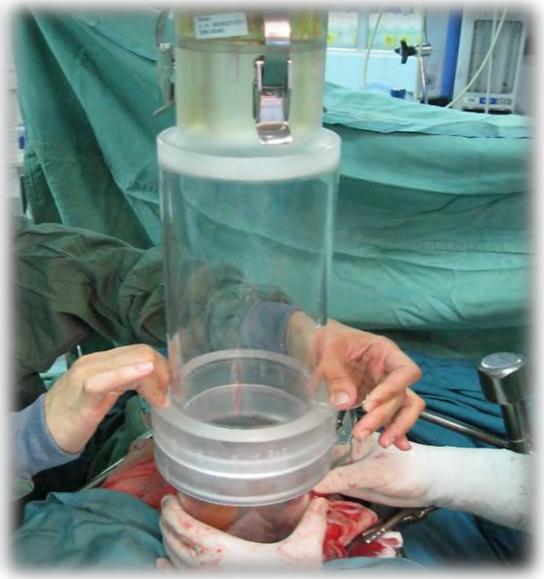
Dose: 21 Gy

Time: 1 min 59 Sec



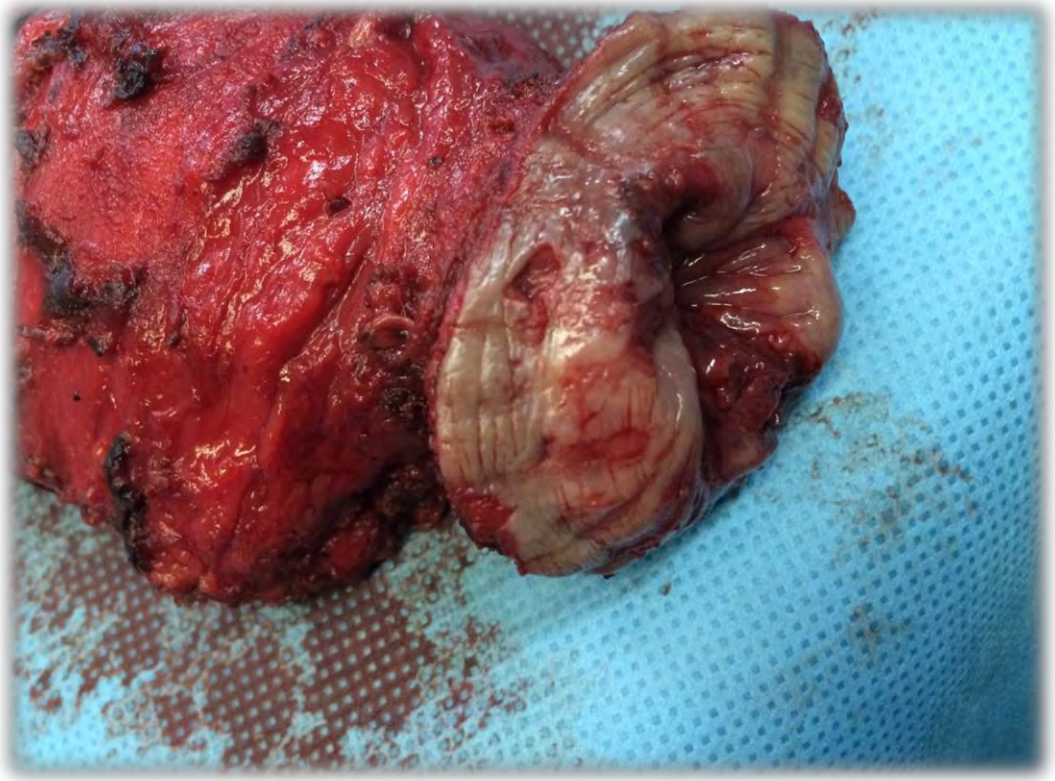






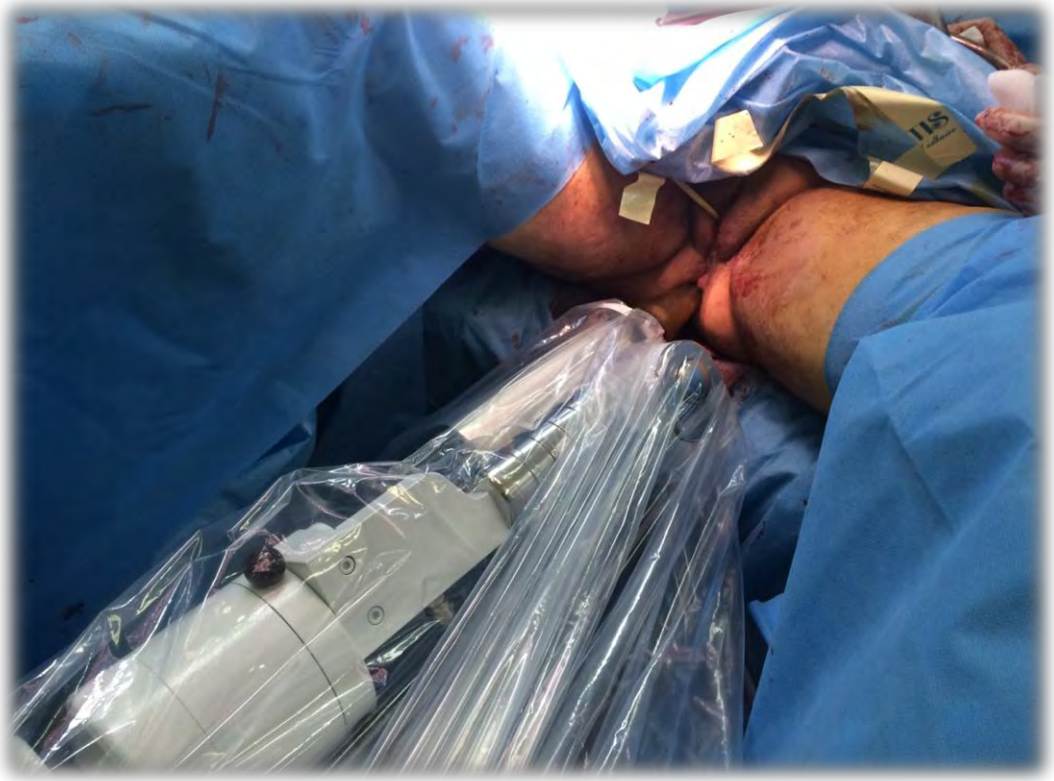
Rectal Ca

Female, 45 years old 2 cm from anal verge APR after Neo adjuvant Chemo Radiation



IORT, x- ray

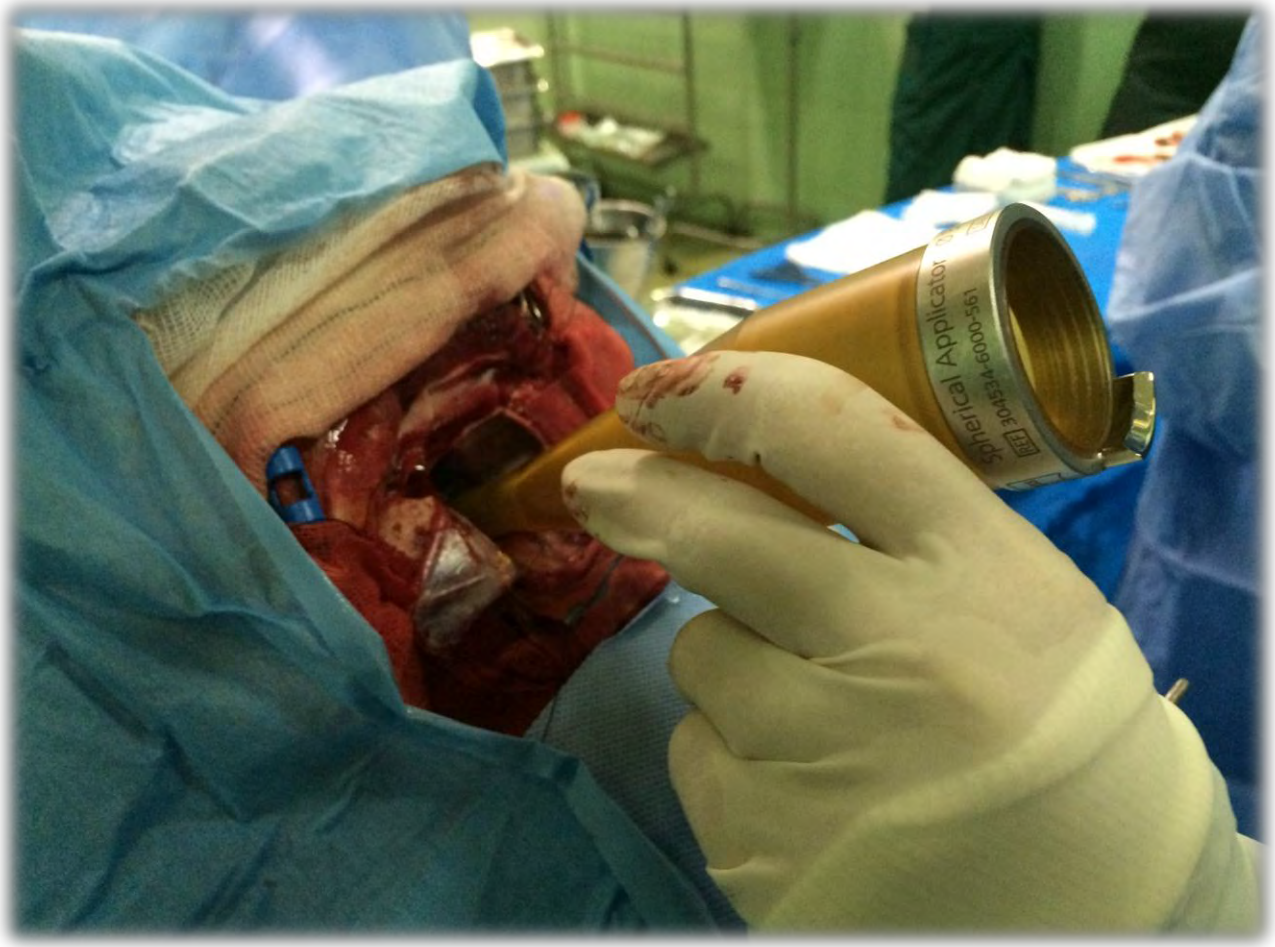
Ready for IORT with friendly movable intrabeam machine

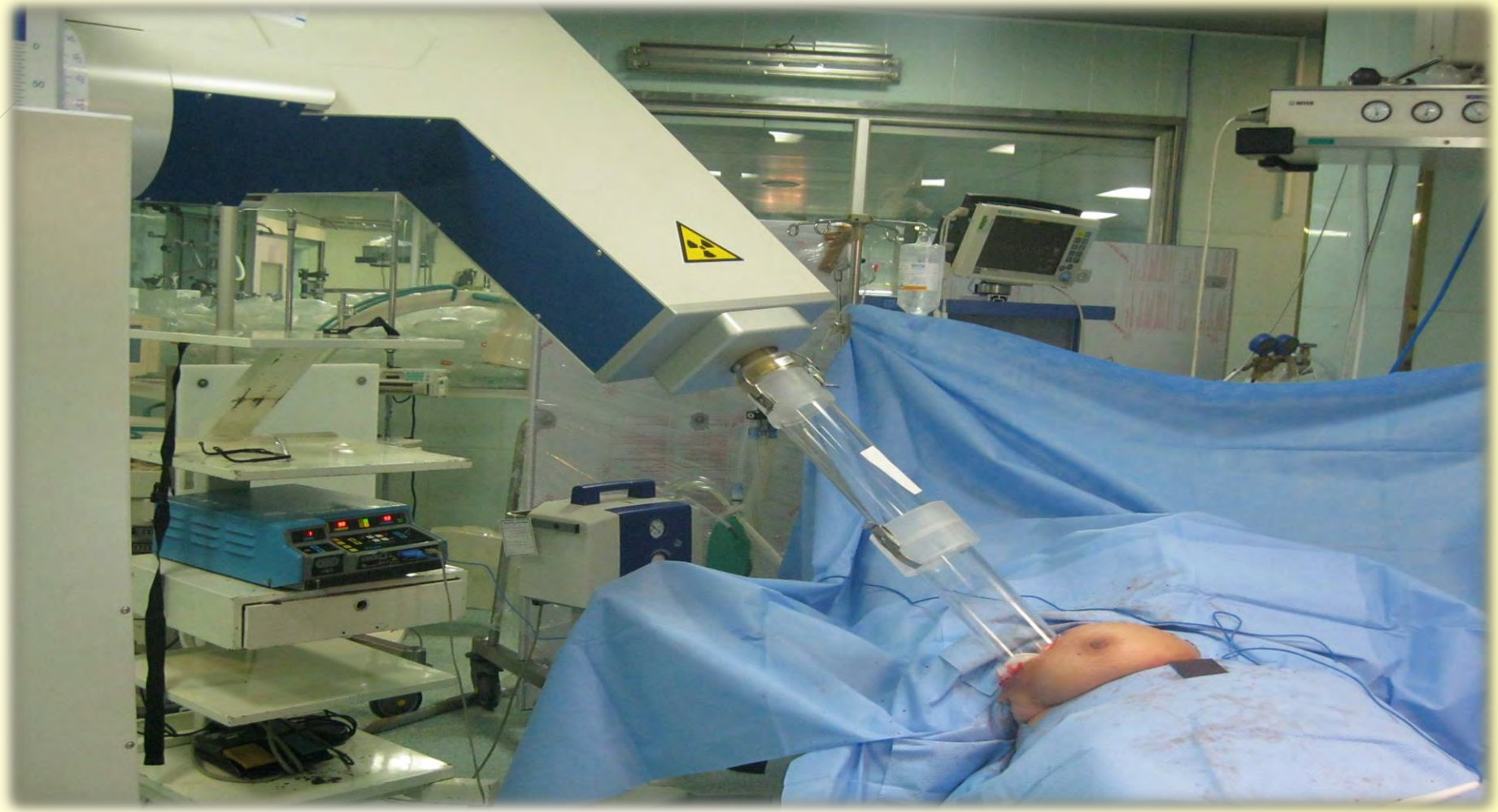


Brain IORT with Low KV X-Ray Machine

Applicator Insertion

Spherical type 3.5cm





Around 70 percent of our cases are Breast Cancer

IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

Lady 62 Years Old before surgery with dx of:

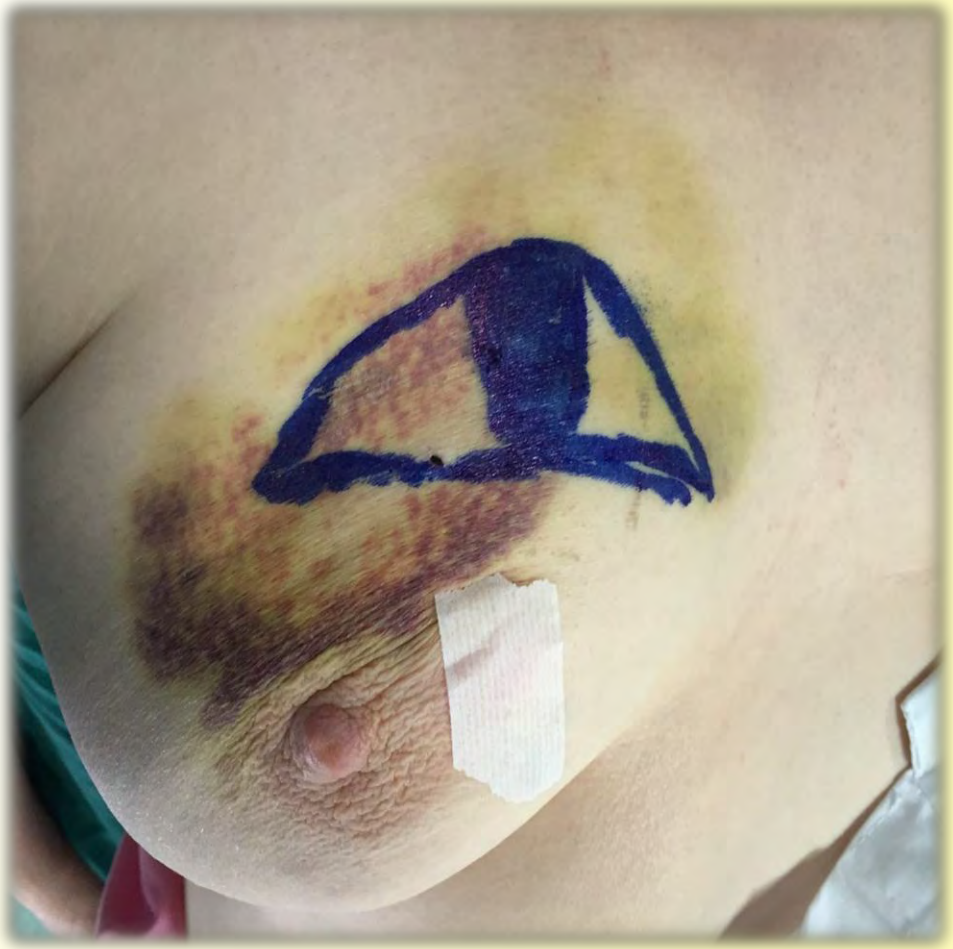
IDC

ER +

PR+

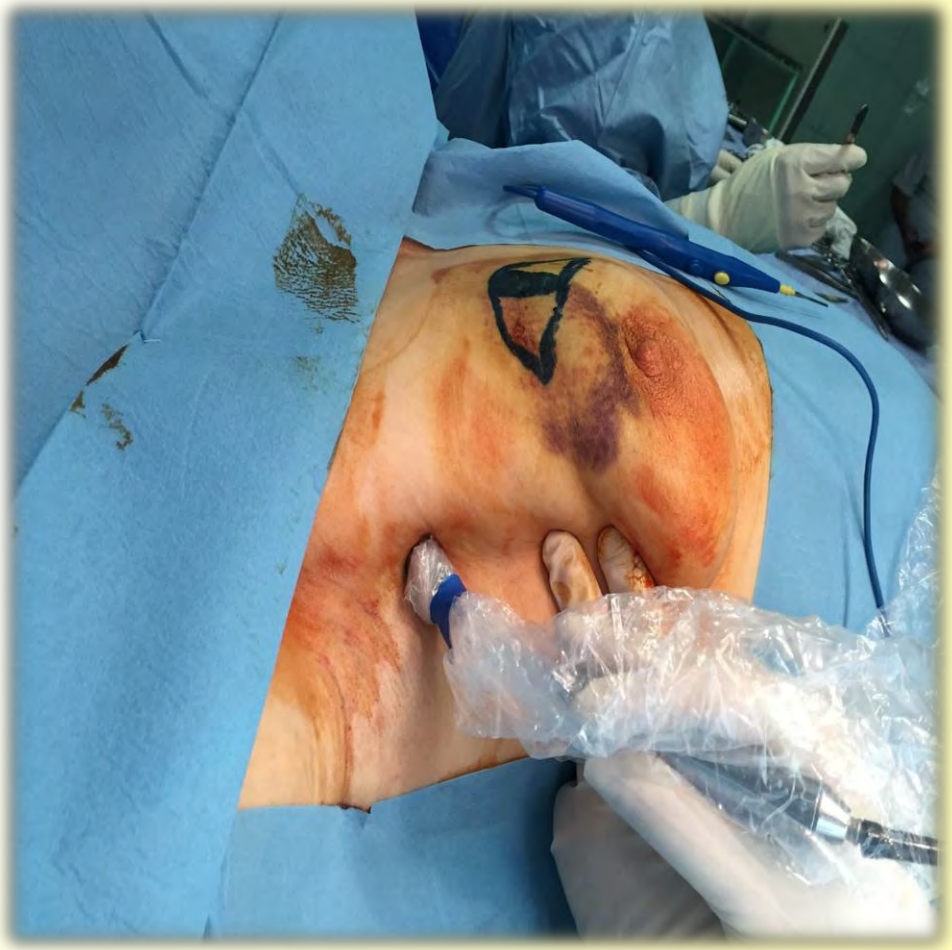
Her-2-

Eligible for SLNB and BCS



IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

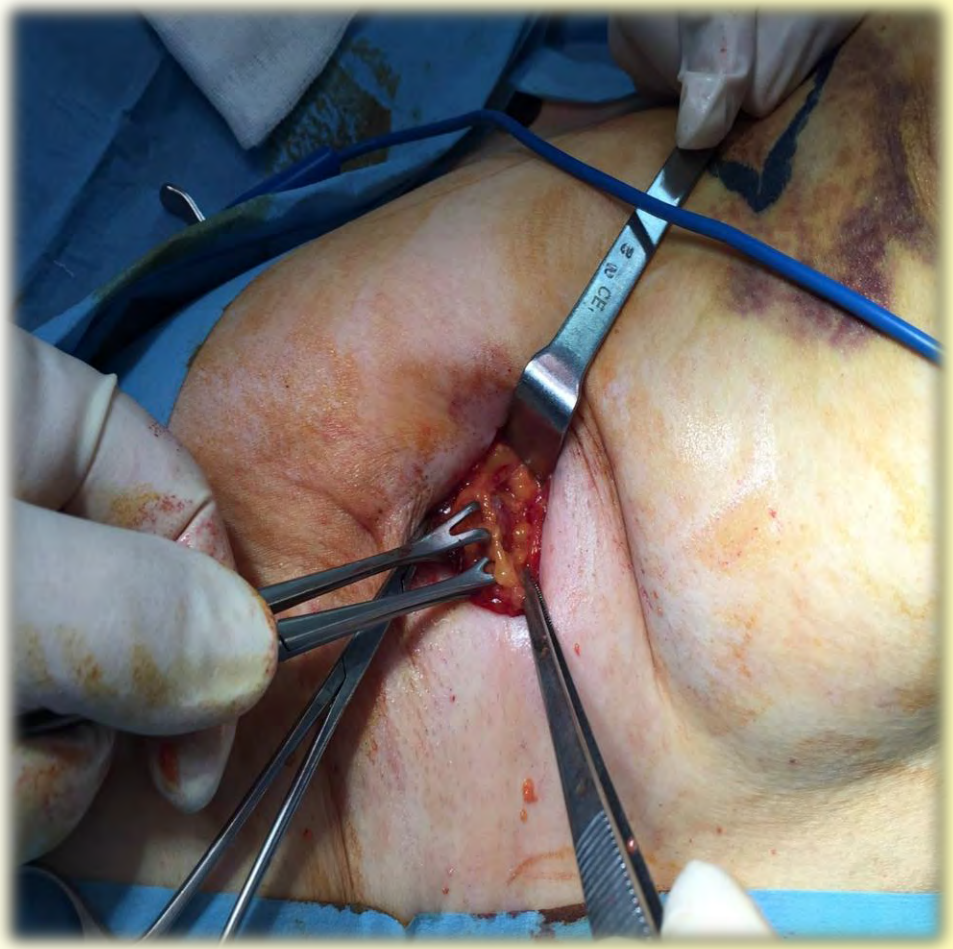
Searching for Sentinel Lymph Node



IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

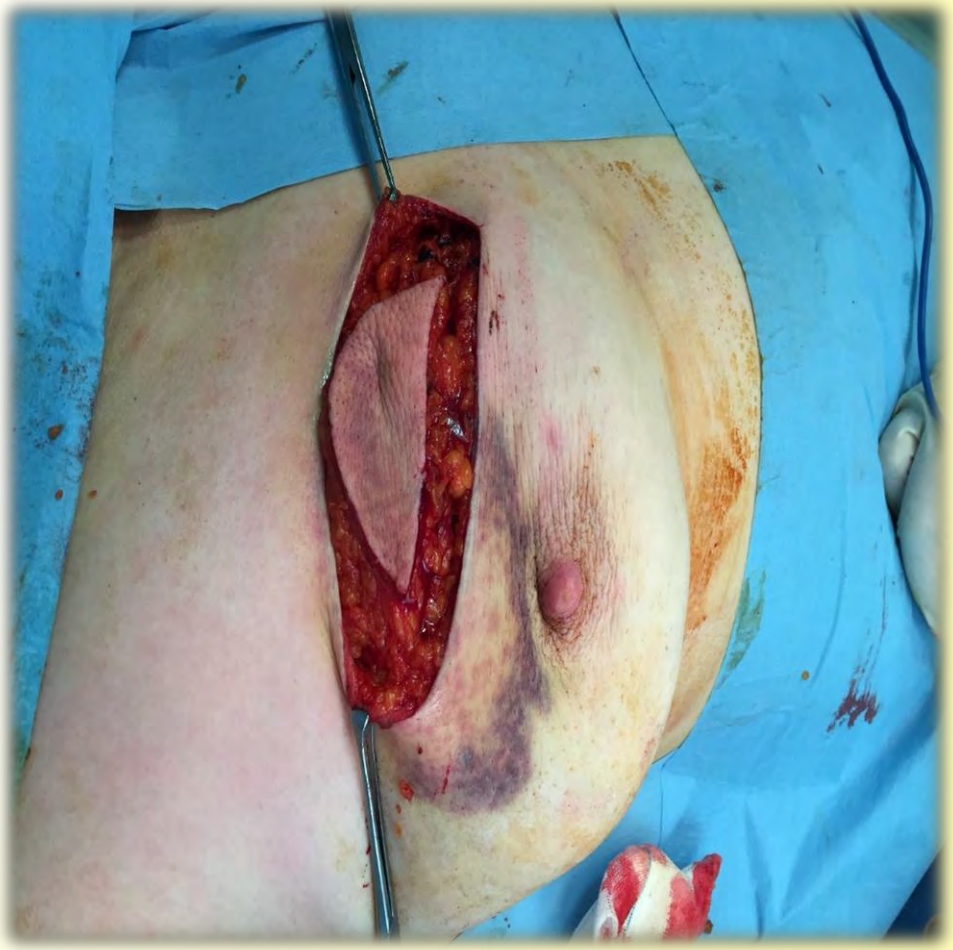
Searching for Sentinel Lymph Node

In this case it was negative



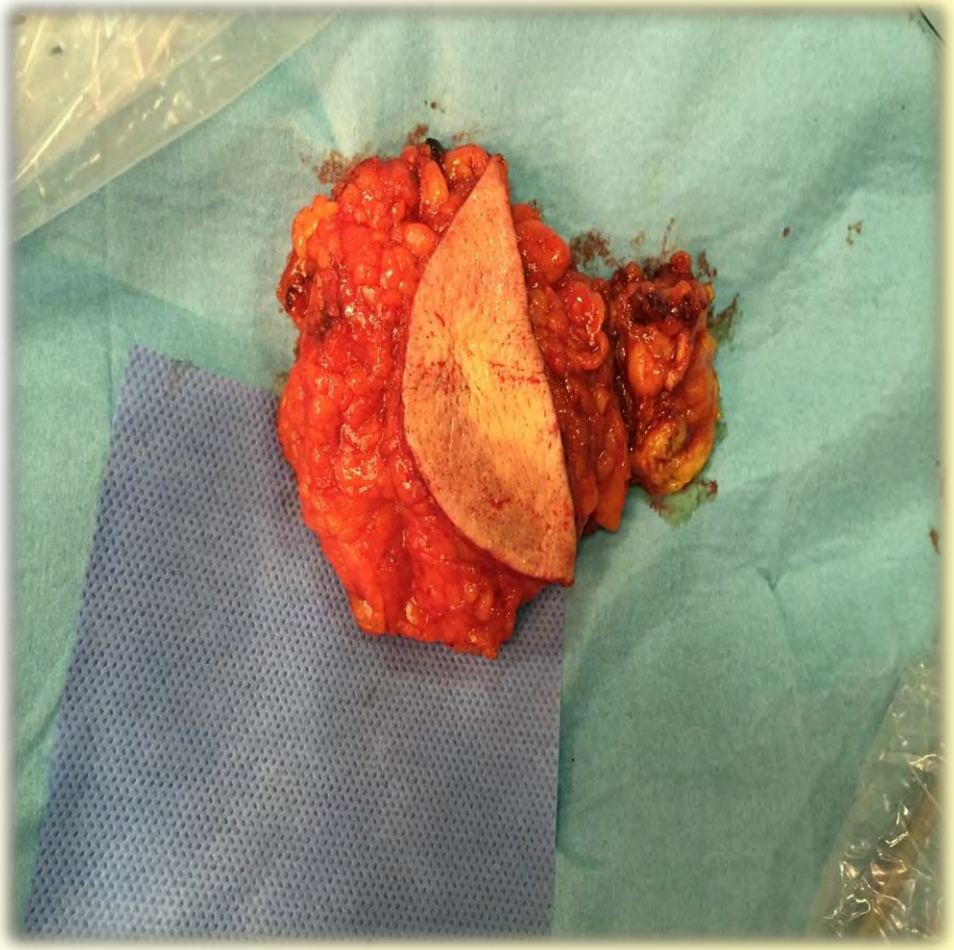
IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

Incision for removing the mass



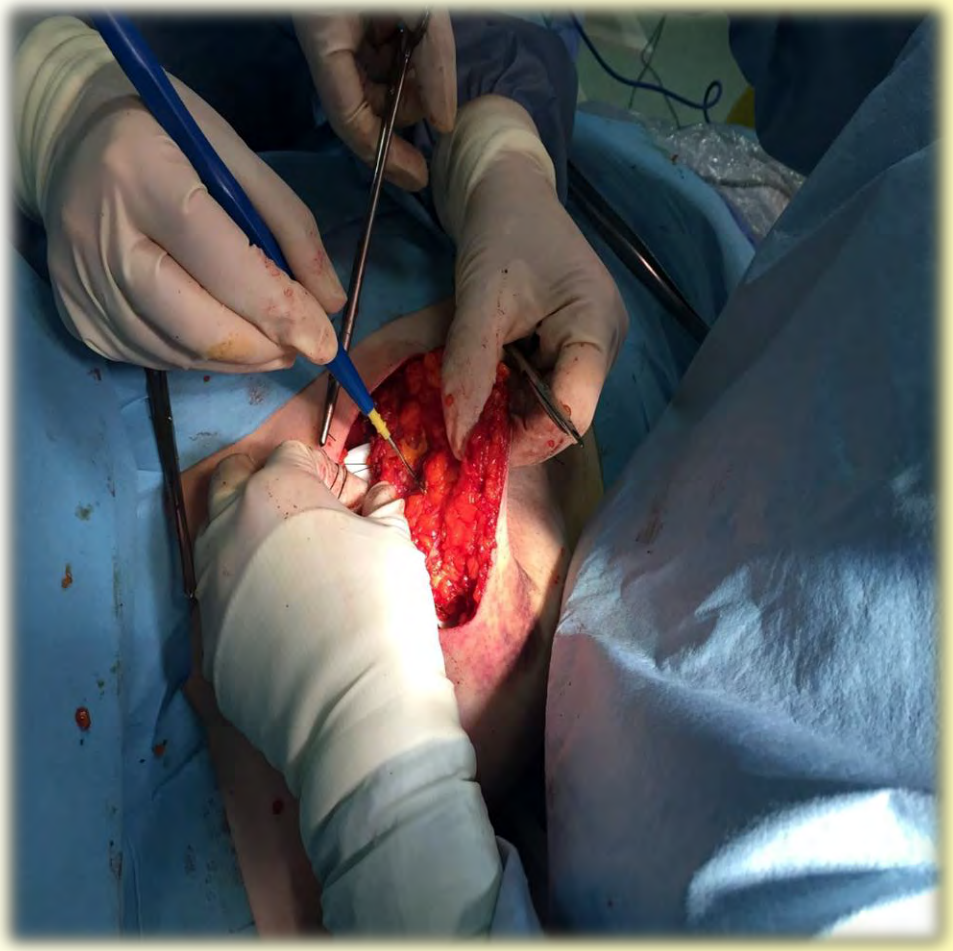
IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

Mass Removed



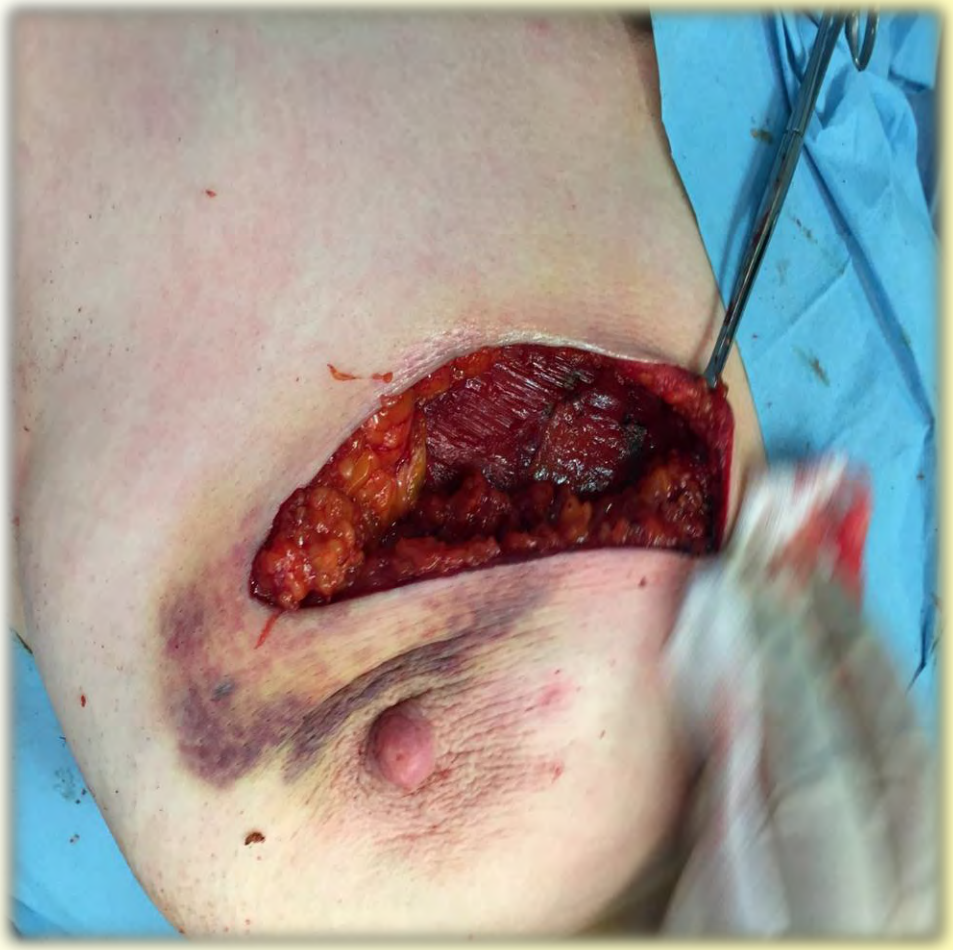
IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

Preparing the Marginal Flaps



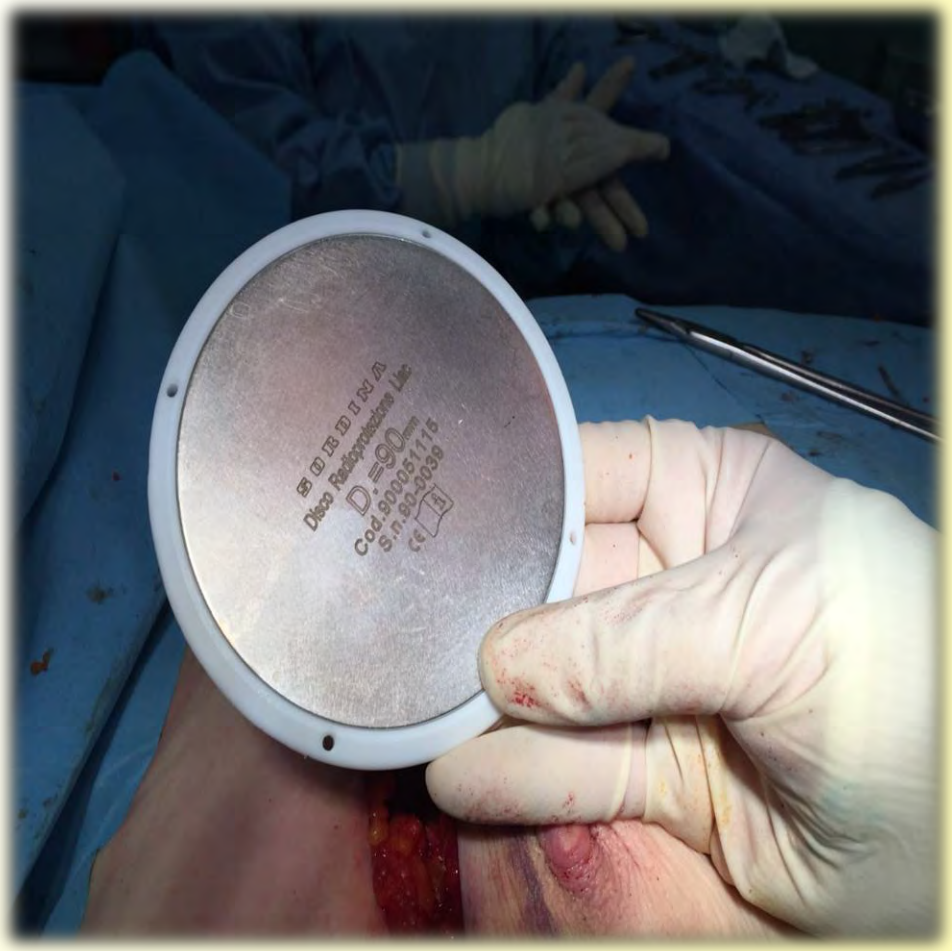
IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

Cavity is ready for DISK insertion



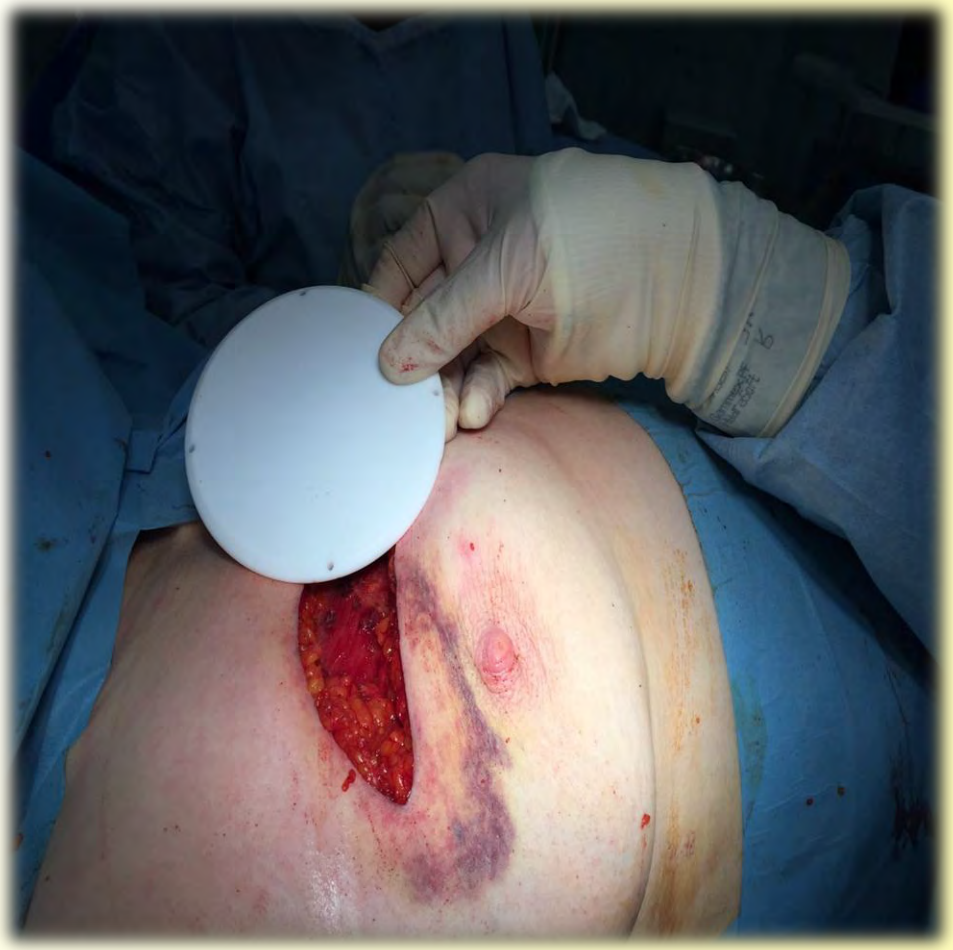
IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

The Back of Protective DISK which is built by a plate of LEAD



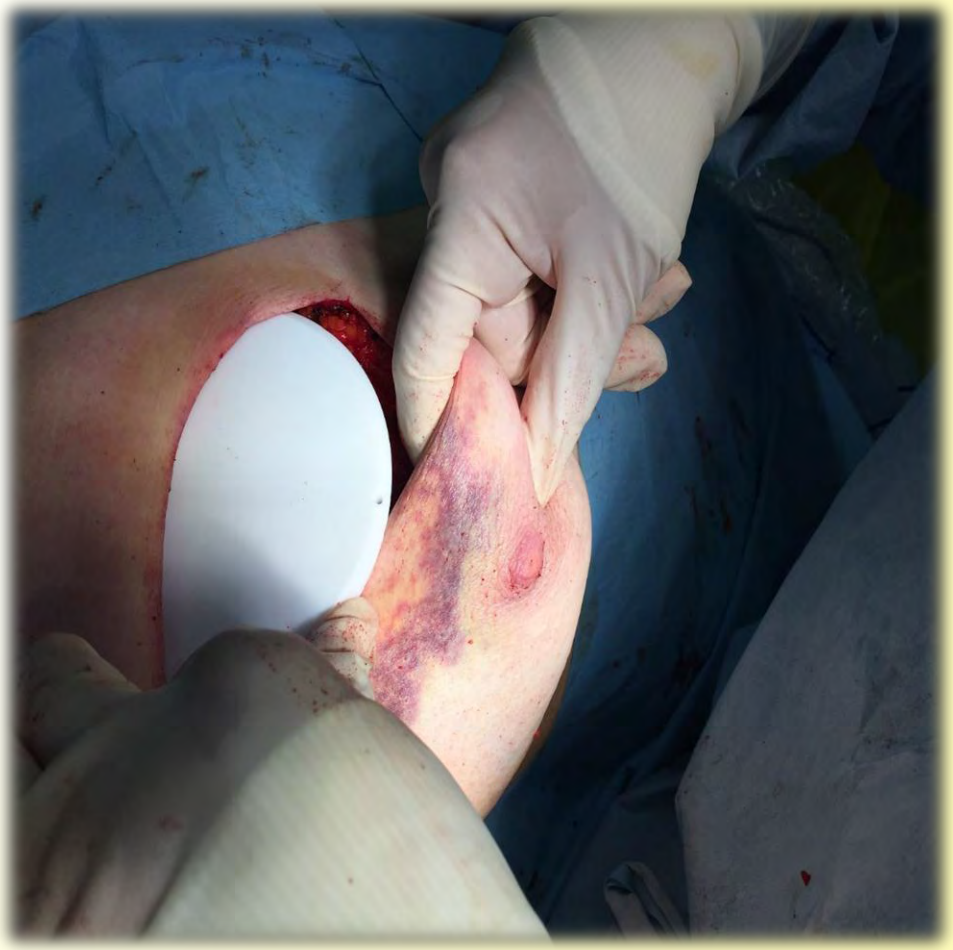
IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

The Surface of protective DISK which is built by PVC (Plastic)



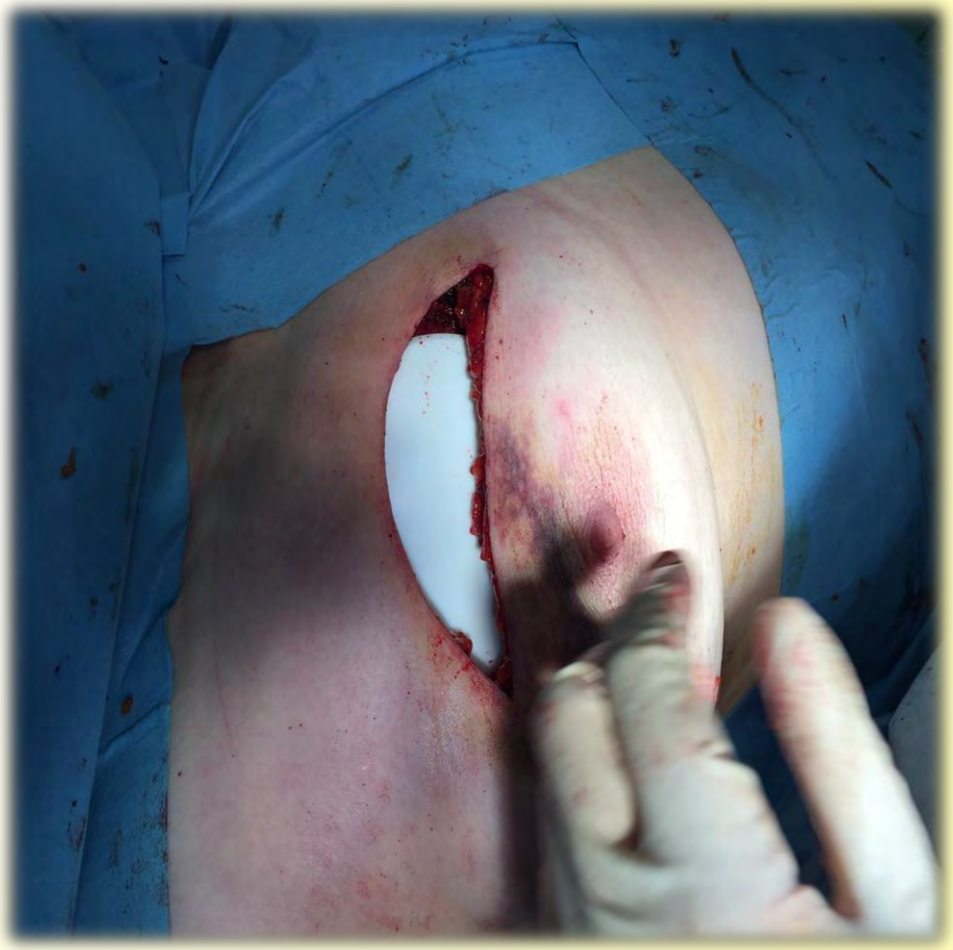
IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

Insertion of DISK beneath of breast tissue



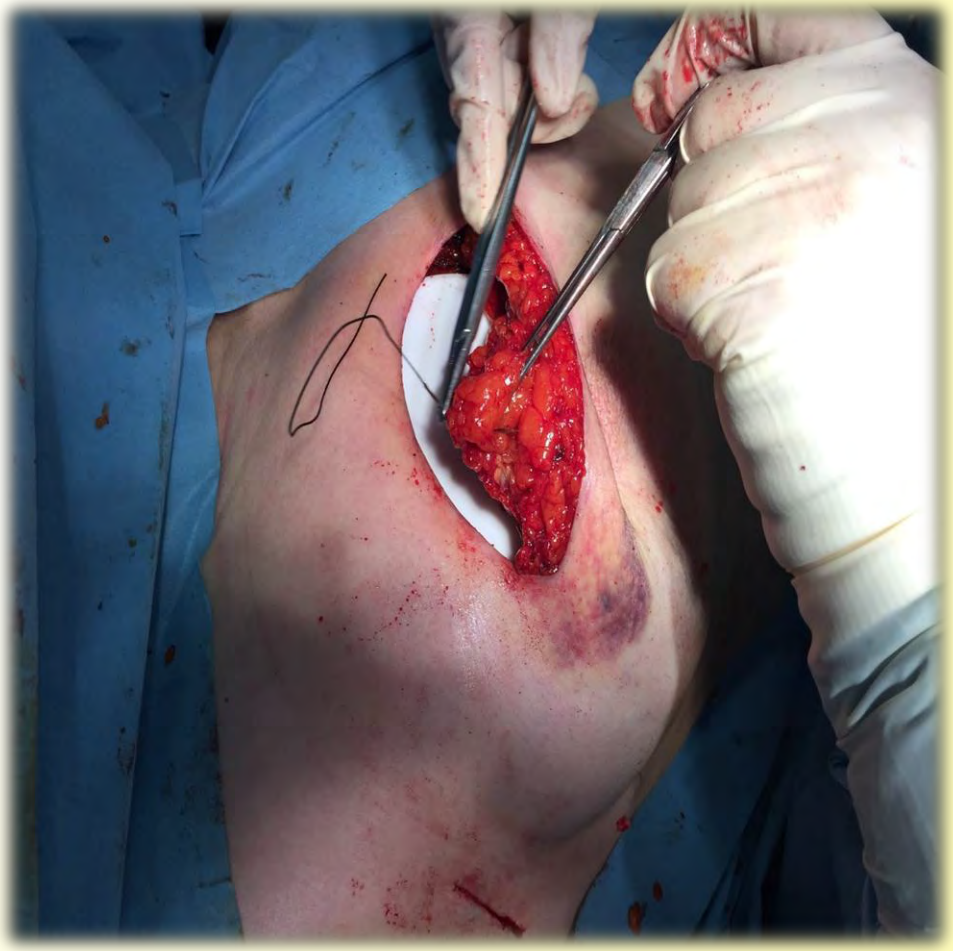
IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

Insertion of DISK beneath of breast tissue



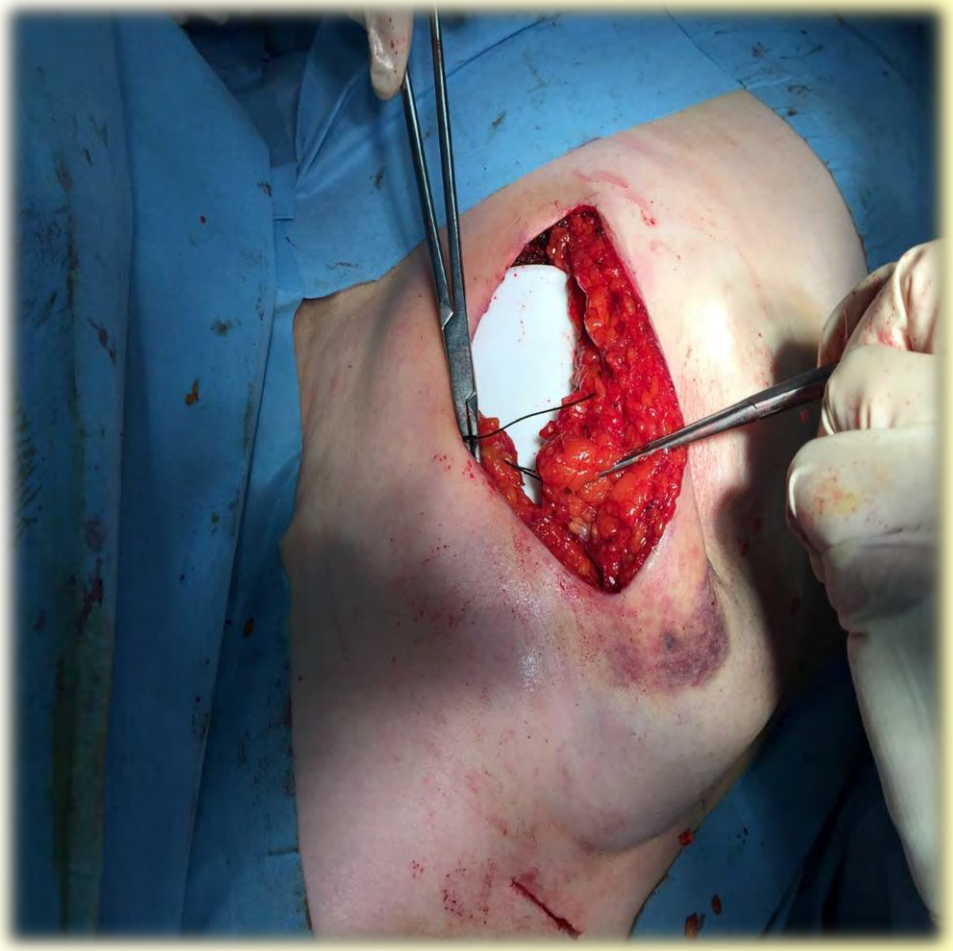
IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

Temporary suturing the flaps for covering the DISK by marginal flaps



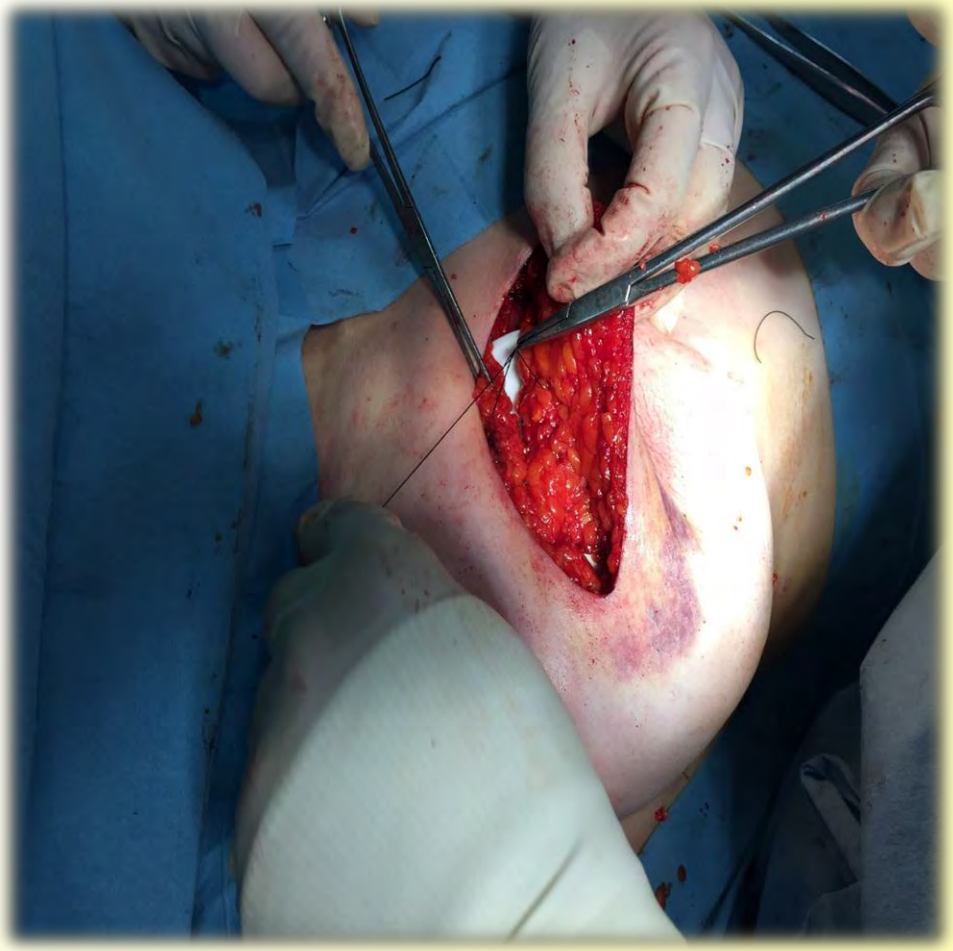
IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

Temporary suturing the flaps for covering the DISK by marginal flaps



IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

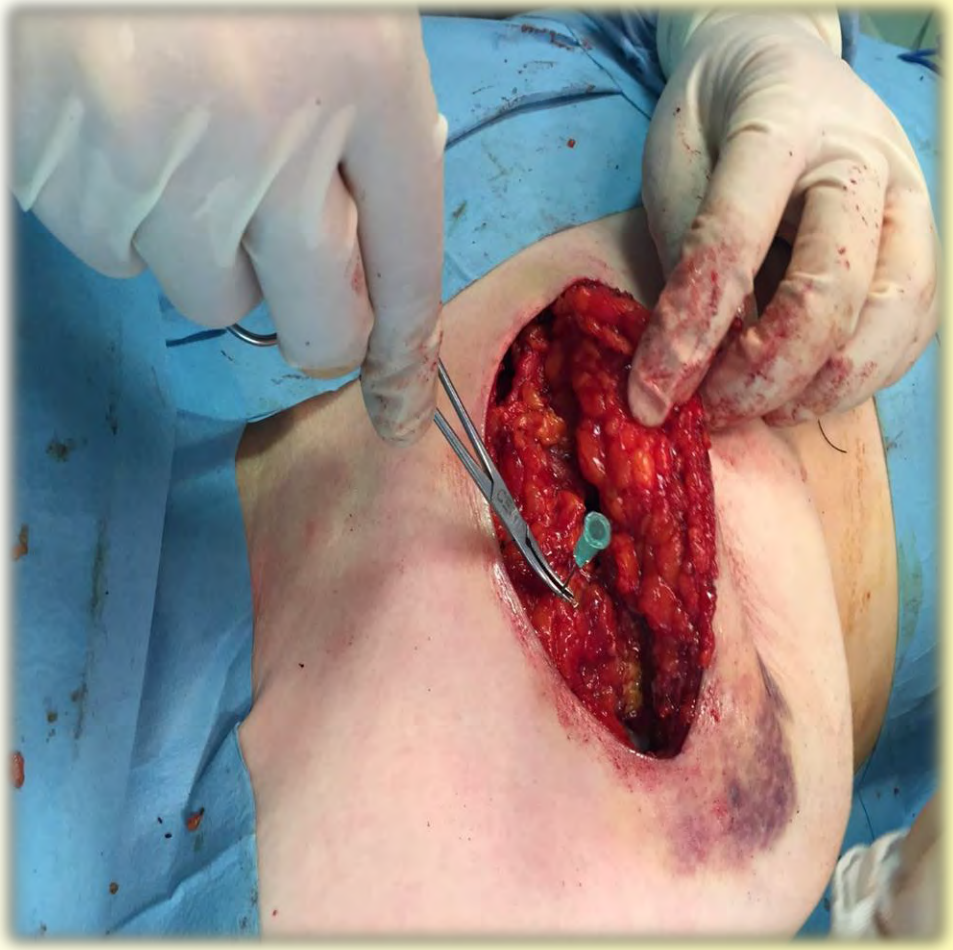
Temporary suturing the flaps for covering the DISK by marginal flaps



IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

Measuring the depth of marginal flaps that should be irradiated .

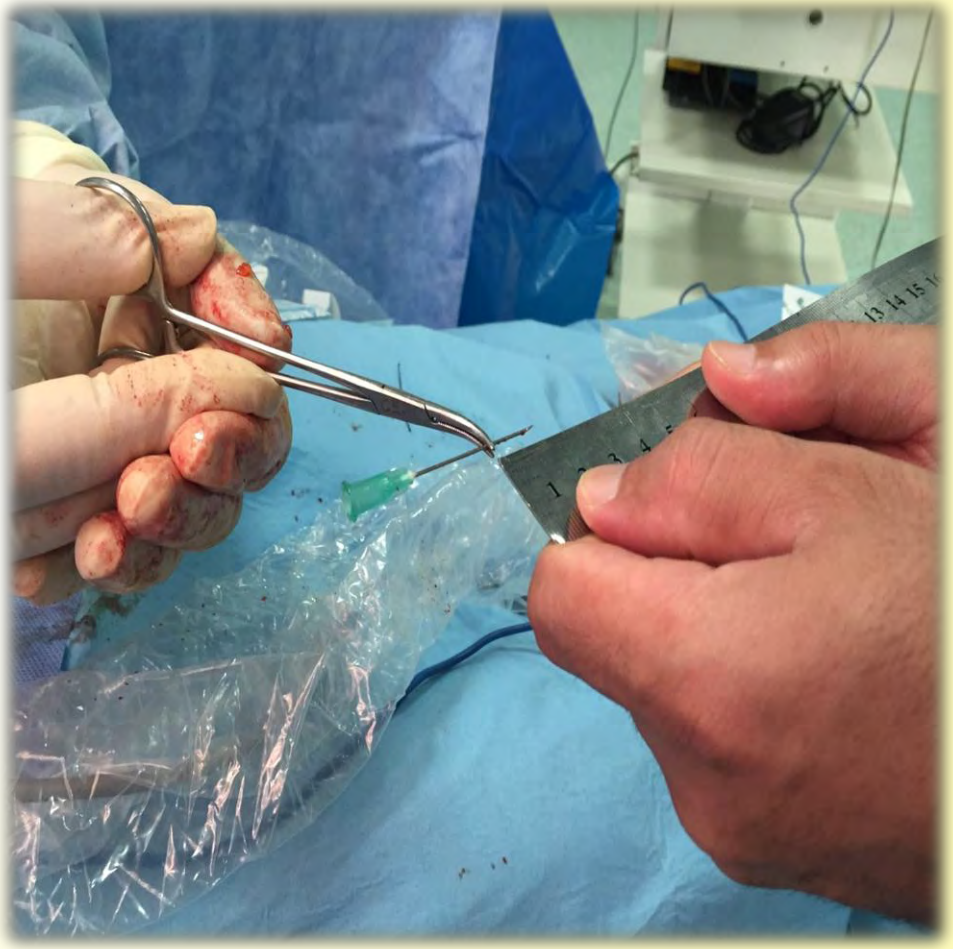
It is necessary for clearing the size of energy



IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

Measuring the depth of marginal flaps that should be irradiated .

It is necessary for clearing the size of energy

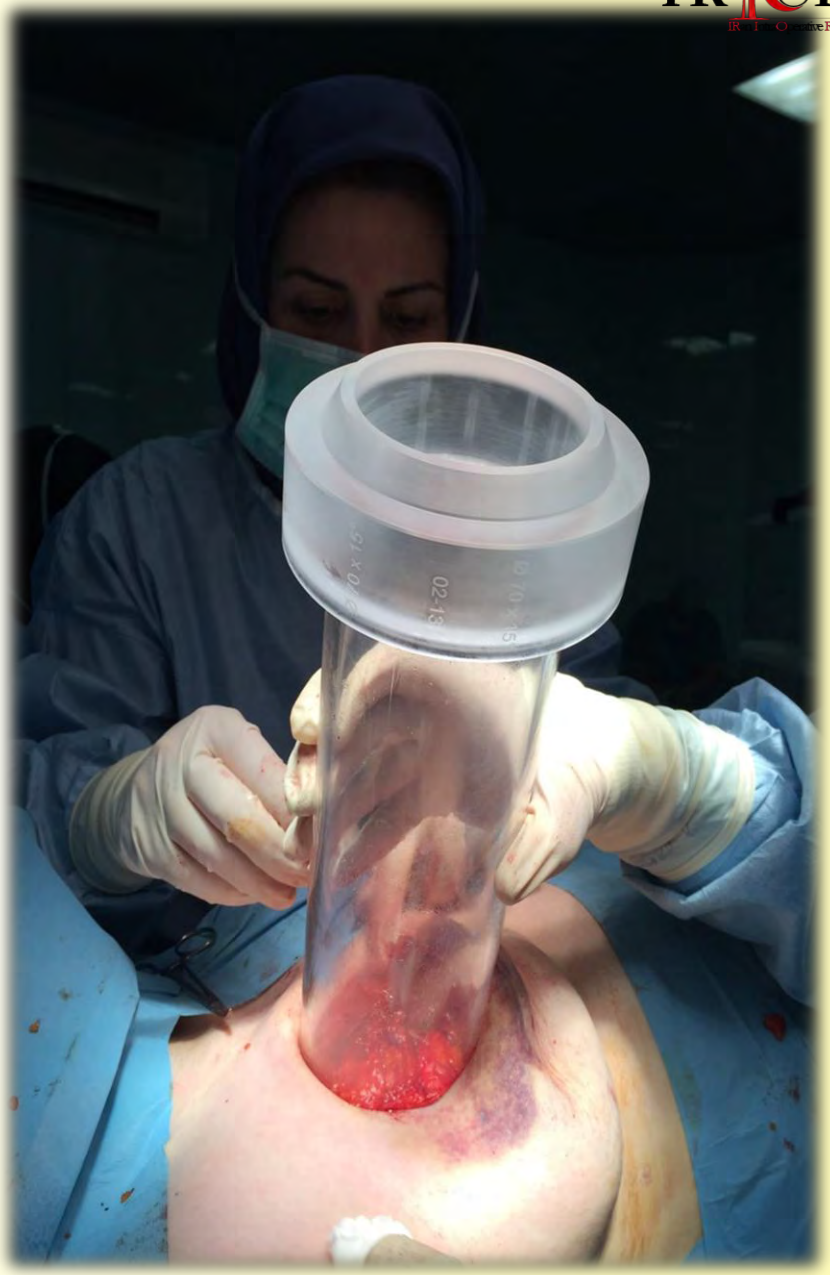


IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

Selecting the appropriate diameter of applicator

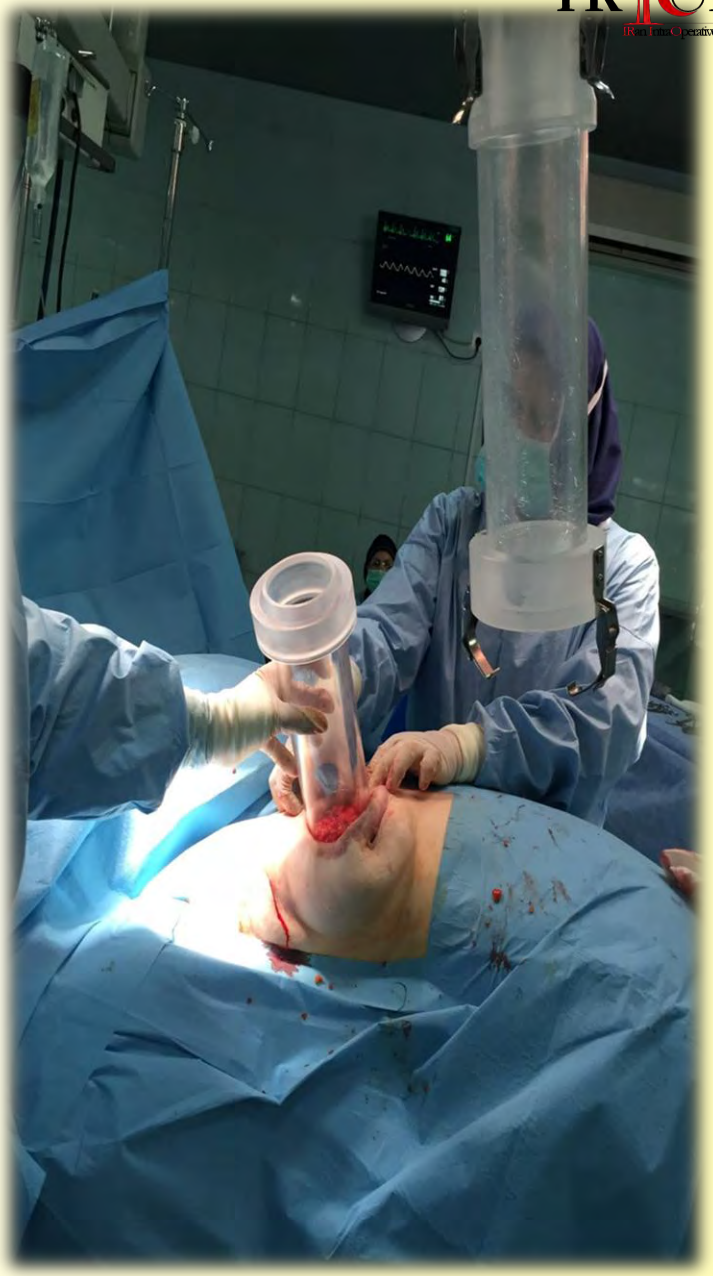
IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

Insertion the Applicator



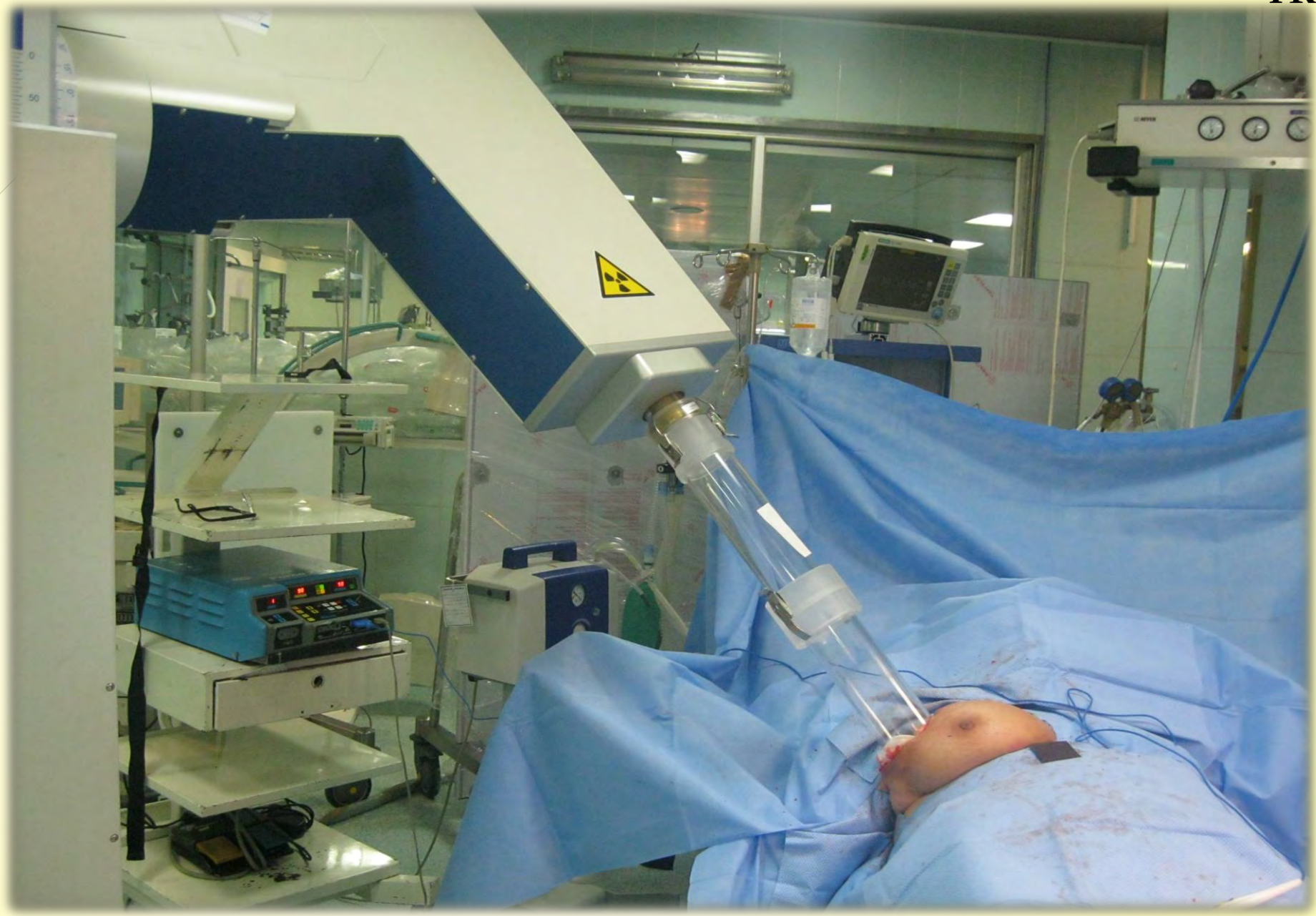
IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

Moving Machine with Applicator Holder toward Patient for Hard knocking



IORT in a case with 2cm mass in UIQ of Rt Breast with Linac

Finish Insertion the applicator, ready for IOERT

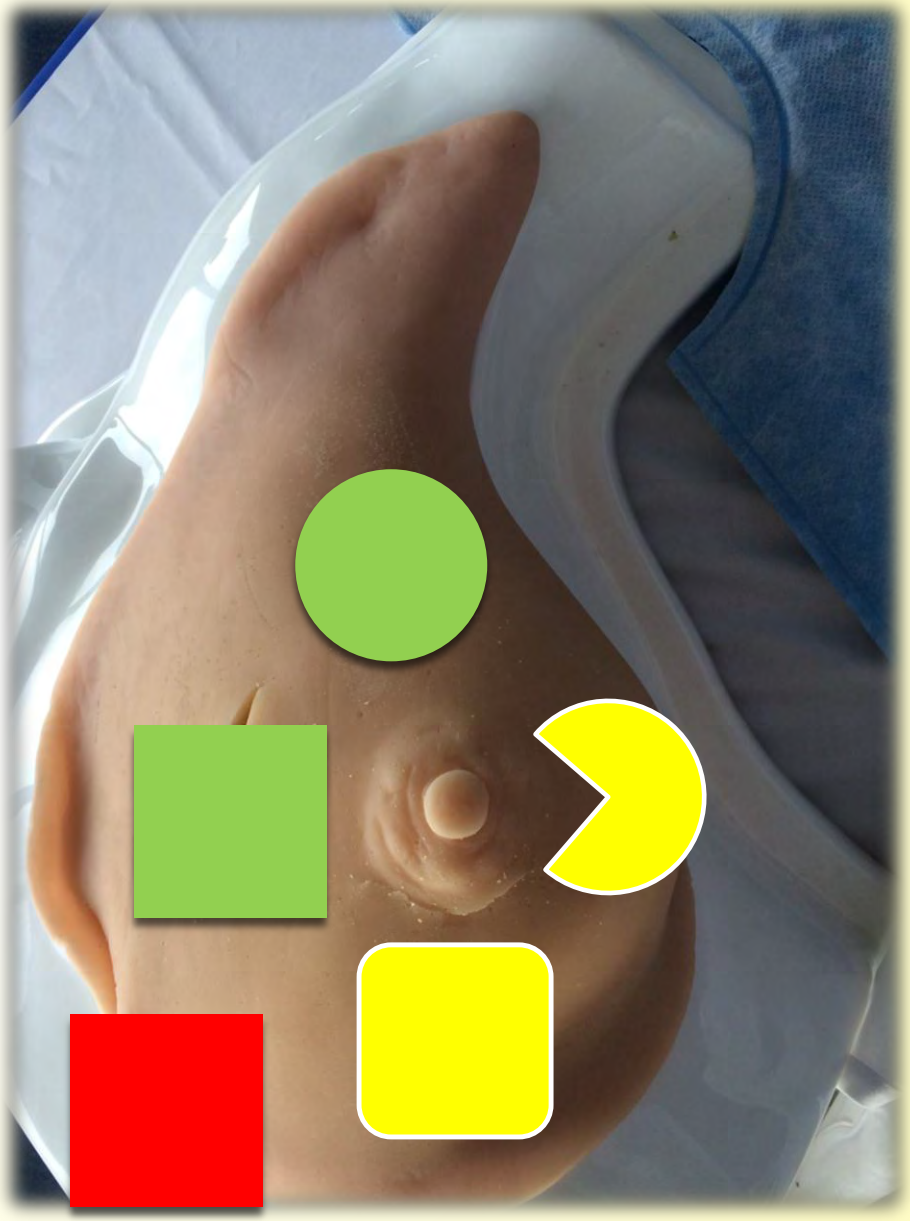


IORT, x-ray

Green=OK

Yellow=acceptable

Red=un acceptable



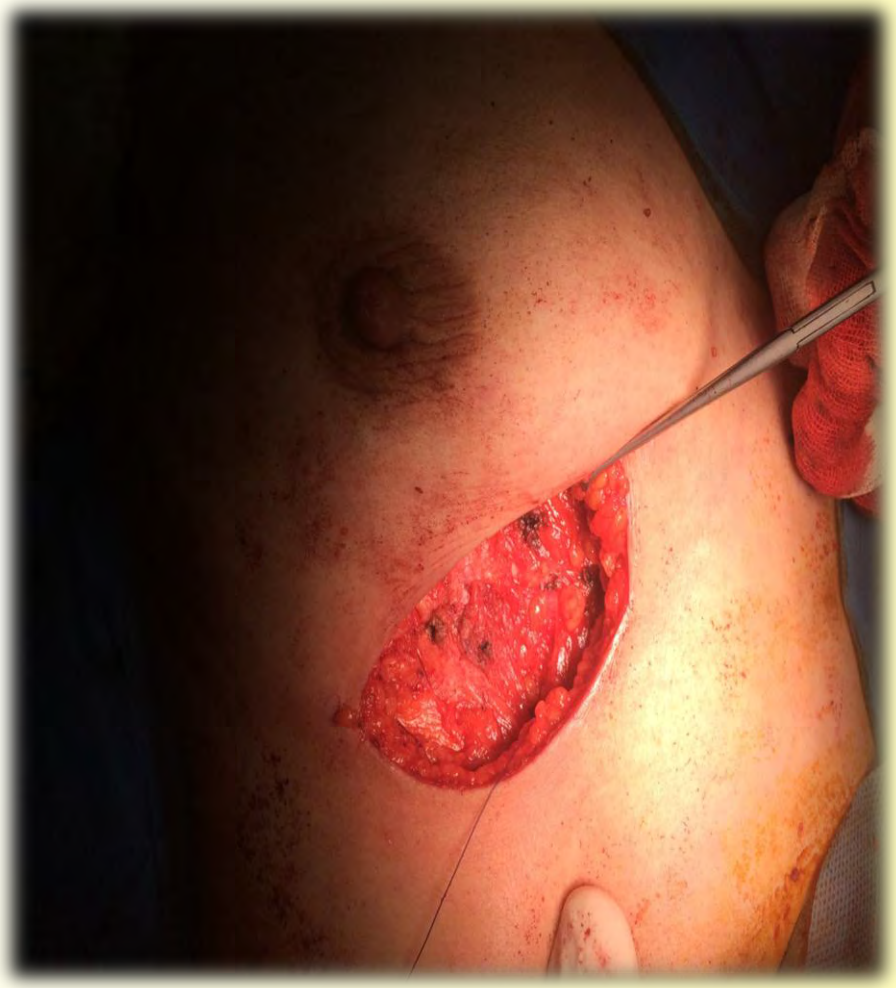
IORT, x-ray

Our Spherical Applicators from 1.5-5 cm

Sweet able for Breast, pelvic and more....

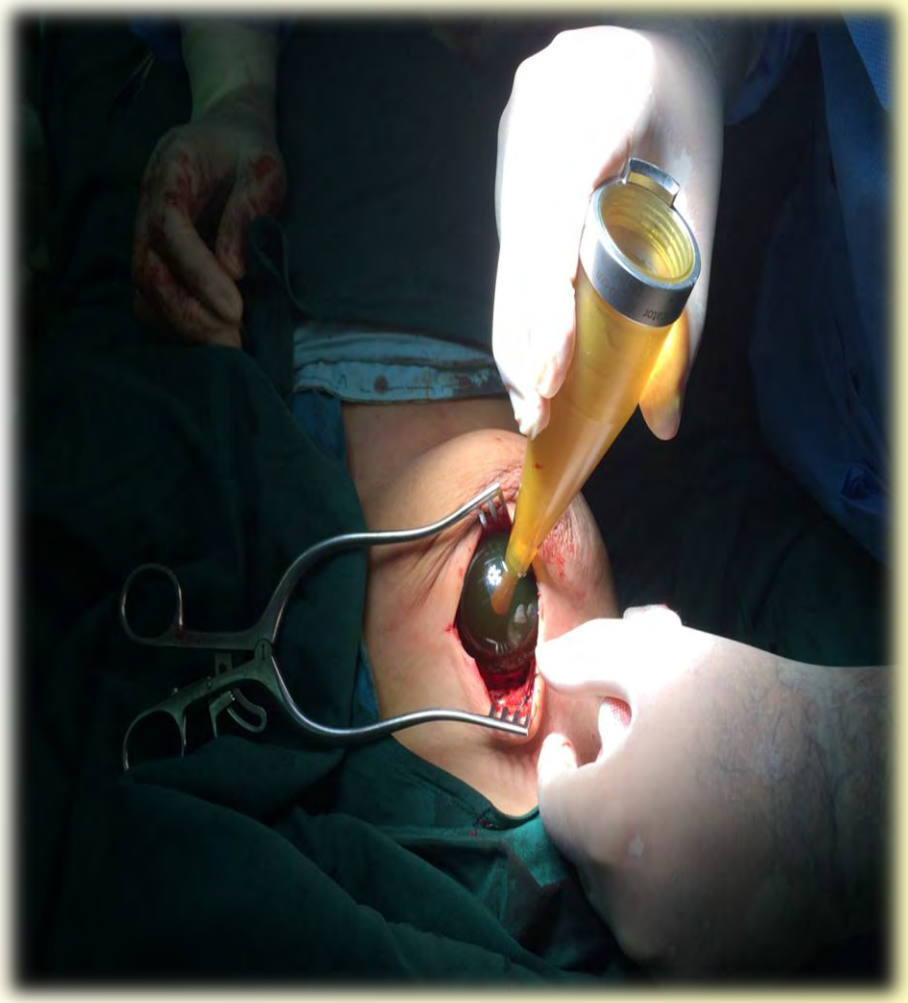
IORT, x-ray

Lower part and Margin of Breast not Sweet able for IORT



IORT, x-ray

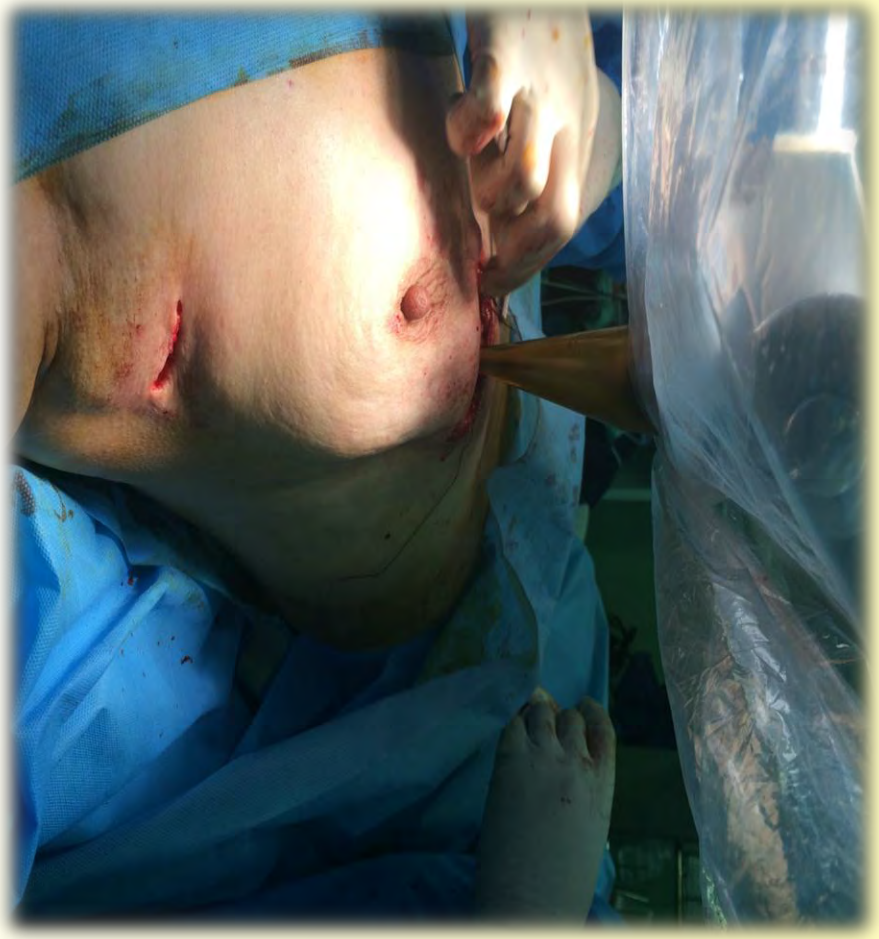
Insertion the appropriate Size Applicator



IORT, x-ray

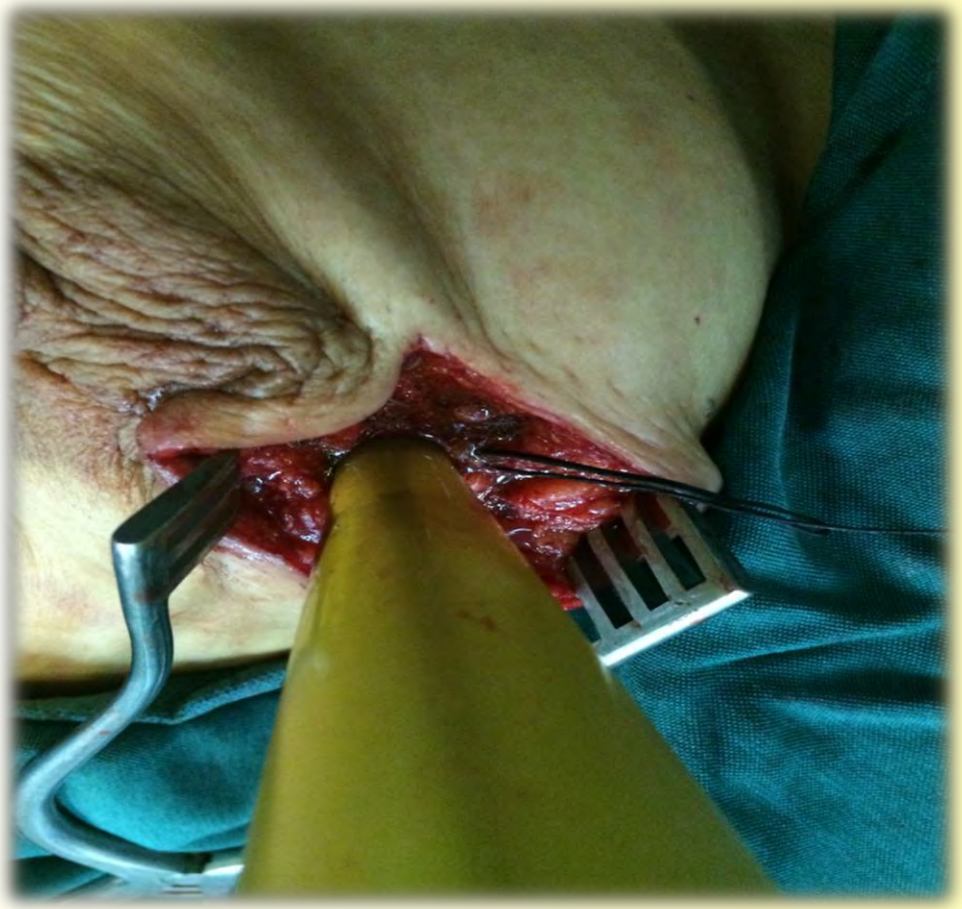
Ready for IORT

20 GY as Boost or Radical RT no need for EBRT



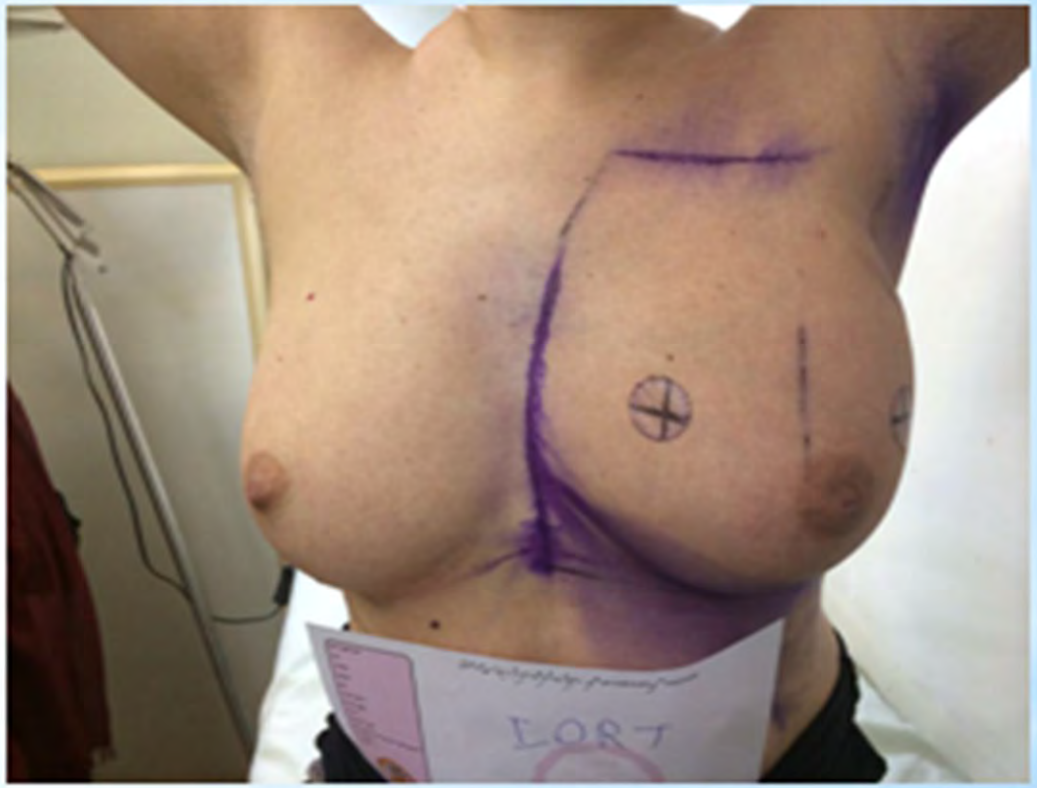
IORT, x-ray

There is some limitation on Tumor Size and depth Breast Tissue are pursed around the applicator , notice to the skin and tissue



IORT, Linac*

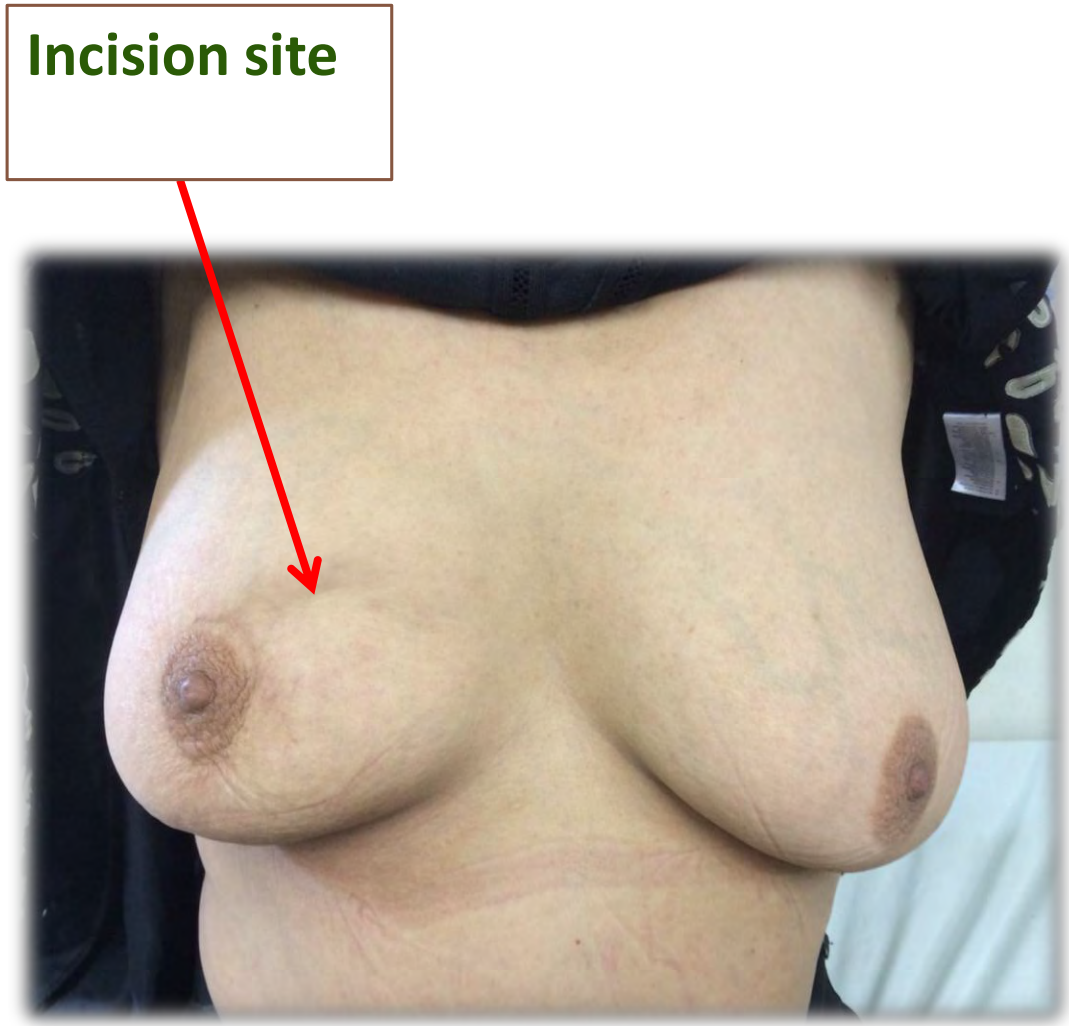
Five Months after Surgery



1

IORT, linac

26 months after IORT with Linac Machine



Outcome of Iran IORT Experiences Compare with EBRT

Items	IORT Low K V and Linac	EBRT
Cosmetic	++++	+++
Seroma	++++	++
Recurrence	+	+
Wound Healing	++	+
Patient Satisfaction	++++	+

UNIVERSITY HOSPITAL
UNIKLINIKUM
SALZBURG

IOERT as tumorbed Boost in breast cancer stages I-III: Updated 10-years results

Fastner G[1], Kaiser J[1], Kopp P[1], Kronberger C[4], Moder A[5], Wallner M[1], Reitsamer R[2,3], Fischer Th[2,3], Fussl C[1], Zehentmayr F[1], Sedlmayer F[1]

[1] UC Radiotherapy and Radio-Oncology, Landeskrankenhaus, Paracelsus Medical University, Salzburg, Austria

[2]UC for Gynecology, Landeskrankenhaus, Paracelsus Medical University, Salzburg, Austria

[3] UC for Special Gynecology (Breast Center), Landeskrankenhaus, Paracelsus Medical University, Salzburg, Austria

[4]Department of Pathology, Landeskrankenhaus,Paracelsus Medical University, Salzburg, Austria

[5]Intitute of Inborn Errors in Metabolism, Landeskrankenhaus, Paracelsus Medical University, Salzburg, Austria

IOERT Boost - clinical results

Author (yy)	Patients (n) (IORT/ext.)	T-Stage	med.-Dosage Gy IOERT/external	cum. Dosage Gy WBI/Dosis/fx	Med. FUP (Months) IOERT/ext.	LR % IOERT/ext.
Merrick (1997)	21	T1-2	10	45-50 (1.8-2)	71	0
Dubois (1997)	101 (51/50)	T1-2	10 / ns	45-50 (-2)	24	0/ns
Lemanski (2006)	50	T1-2	10	50 (2)	109	4
Ciabattoni (2004)	234 (122/112)	T1-2	10 / 5 x 2	50 (2)	n.s.	0 /1.7
Reitsamer 2006	378 (190/188)	T1-2	9 / 6 x 2	51-56 (1.7-1.8)	51/81	0 / 4.3
Ivaldi 2008	204	T1-3	12	37.05 (2.85)	8.9	ns
Fastner 2013 (pooled analysis)	1109	T1-4	10	50-54 (1.7-2)	72.4	0.8 crude 1.4
Fastner 2014 (PST plus IOERT)	107 (81/26)	T1-4	10 / 6x2	50-54 (1.7-2)	59/67.5	1.5 / 12 crude 2.5/7.7
Fastner 2015 (IOERT in TNBC)	71	T1-3	9.6	51-57.6 (1.6-1.85)	97	11 crude 7%

IOERT - BOOST : Results after 10 years FUP ?

Patients 1998 - 2005

Age	n
≥ 60	340
50-59	234
40-49	157
< 40	39
T-Stage	
1	536
≥ 2	219
x	2
0	10
is	3
N- Stage	
0	493
+	275
x	2
pCR	9
R-status	
R0	762
R1	0
Rx	8
Multifocality	
yes	111
no	659

Histology	n
IDC	533
ILC	73
mixed	77
andere	61
ns	1
EIC-status	
negativ	745
positiv	25
Grading	
G1	92
G2	486
G3	190
x	2
HER2-status	
neg	606
pos	74
ns	90
Subtypes	
Luminal A	422
Luminal B	182
Non Luminal	35
Triple negative	74
ns	57

N: 835; Eligible: 770

Age (y): med. 58 (22 – 89)

Median FUP (months): 121 (4 -200)

Higher Risk-selection:

Age < 50 y u/o **≥T2** u/o **Multifocality**
G3 u/o u/o **TNBC** u/o **Non-luminal**

n: 496 pts. (64 %)

Methods

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- IOERT-Dosage, Gy:

Med. [D_{max}] 10 (7-12)

Limit: 5, Rib surface

V 90 ml: Med. 7.5 (2.15-105)

- Electron energy, MeV:

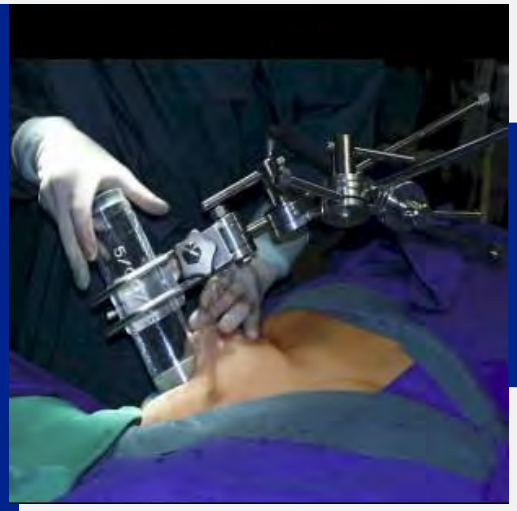
Med. 6 (4 – 18)

- Tube diameter, cm:

Med 6 (4 – 10)

- Postop. WBI-Dosage, Gy:

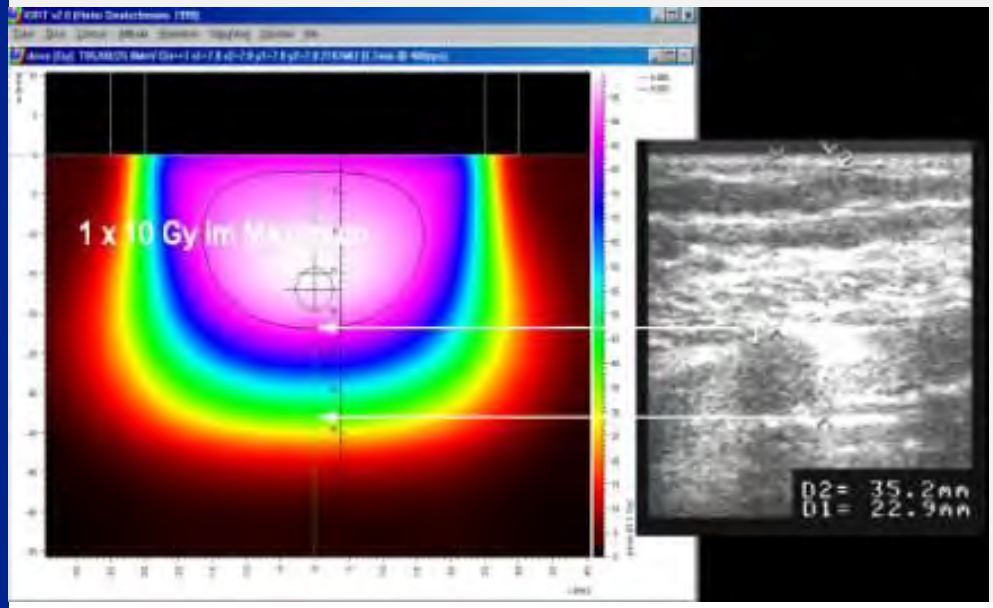
Med. 54 (51– 57); 1.7-2 /Fx



ZIEL: Target volume:

***min. 2 cm* in all directions calc. from macroscopic tumor edge**

Ref-Isodose: 90%



Methods

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RNI : n=122 (16%)

- SCL +/- mammaria int. : Mean 49 Gy (45-54)

Adj. CTX: n = 169 (22%)

Neoadj. CTX: n = 46 (6%); pCR: 19.5%

AHT: n = 622 (81%)

Results

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➢ **In Breast recurrences (IBR):**	**n= 21**
• Within the index quadrant (In-Q):	n = 12
• Outside the index quadrant (Out-Q):	n = 9
„observed“ recurrence rate:	**2.7%**
➢ Patients with metastases:	n= 106
„observed“ rate	**14%**
➢ Died patients:	n = 108
„Observed“ rate	**14%**
Died of disease:	n = 44 **(6%)**

Results

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- Reg. Recurrences: n= 5

„Obeserved“ reg. recurrence rate 0.65%

Time gap (months) IOERT – first occurence of IBR ?

- All: Med. 83 (19 - 185)
- In-Q: Med: 63 (36 – 123)
- Out-Q: Med. 84 (20 – 185)

- 10-J LC: **97.2 %**
- 10-J MFS: 86%
- 10-J BCSS: 93.2%
- 10-J OS: 85.7%

LC – all patients

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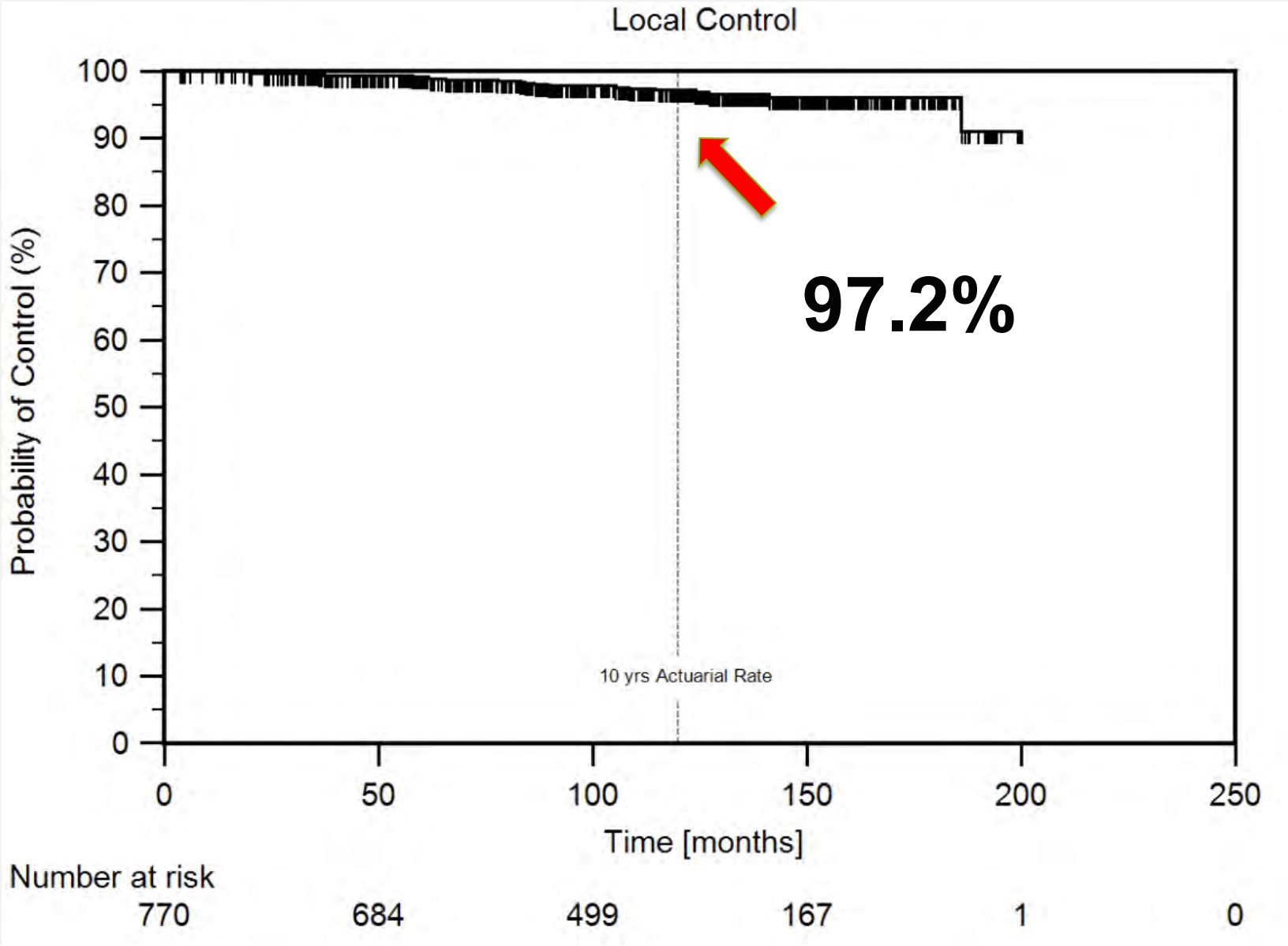

LC by age

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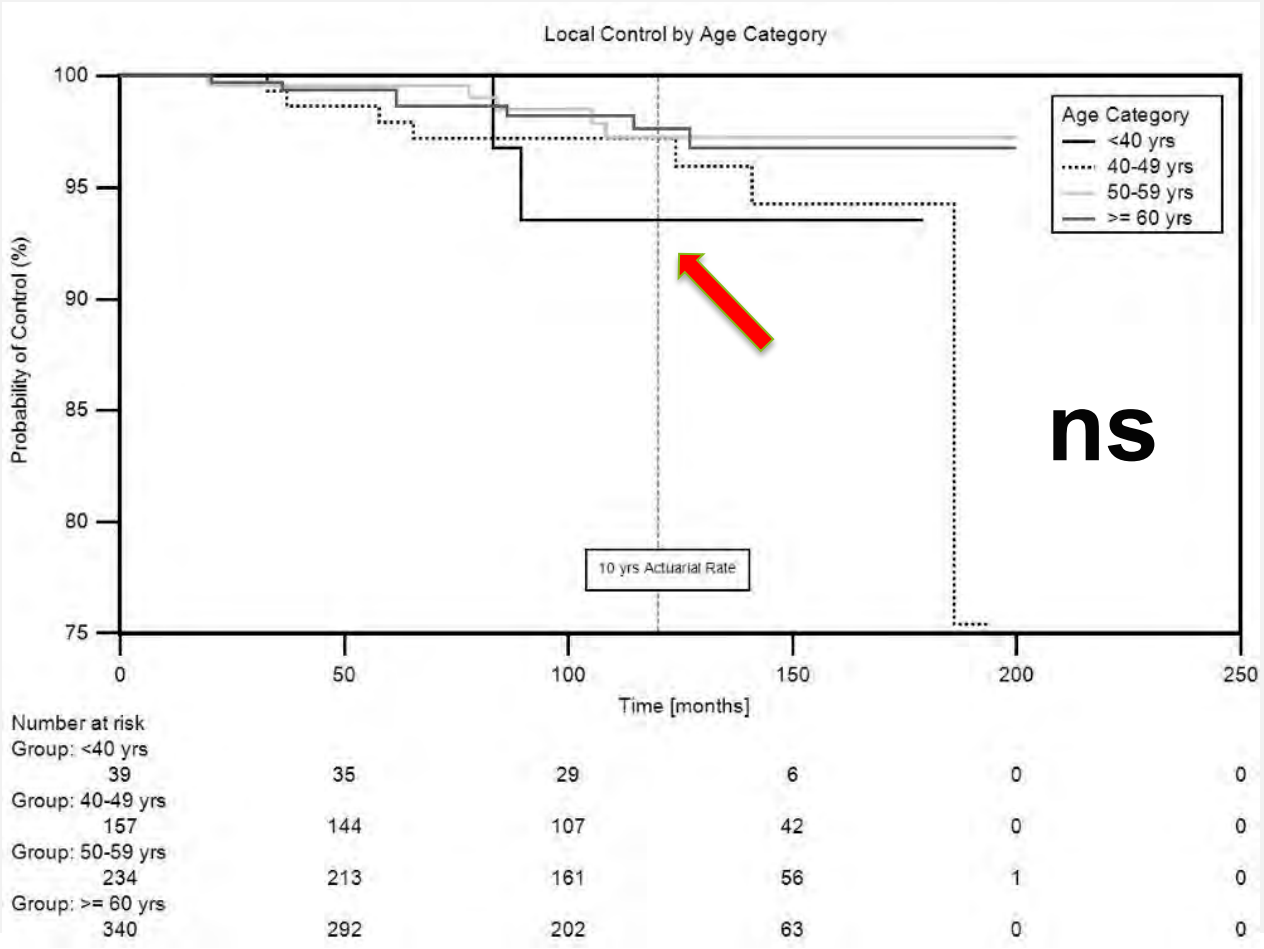
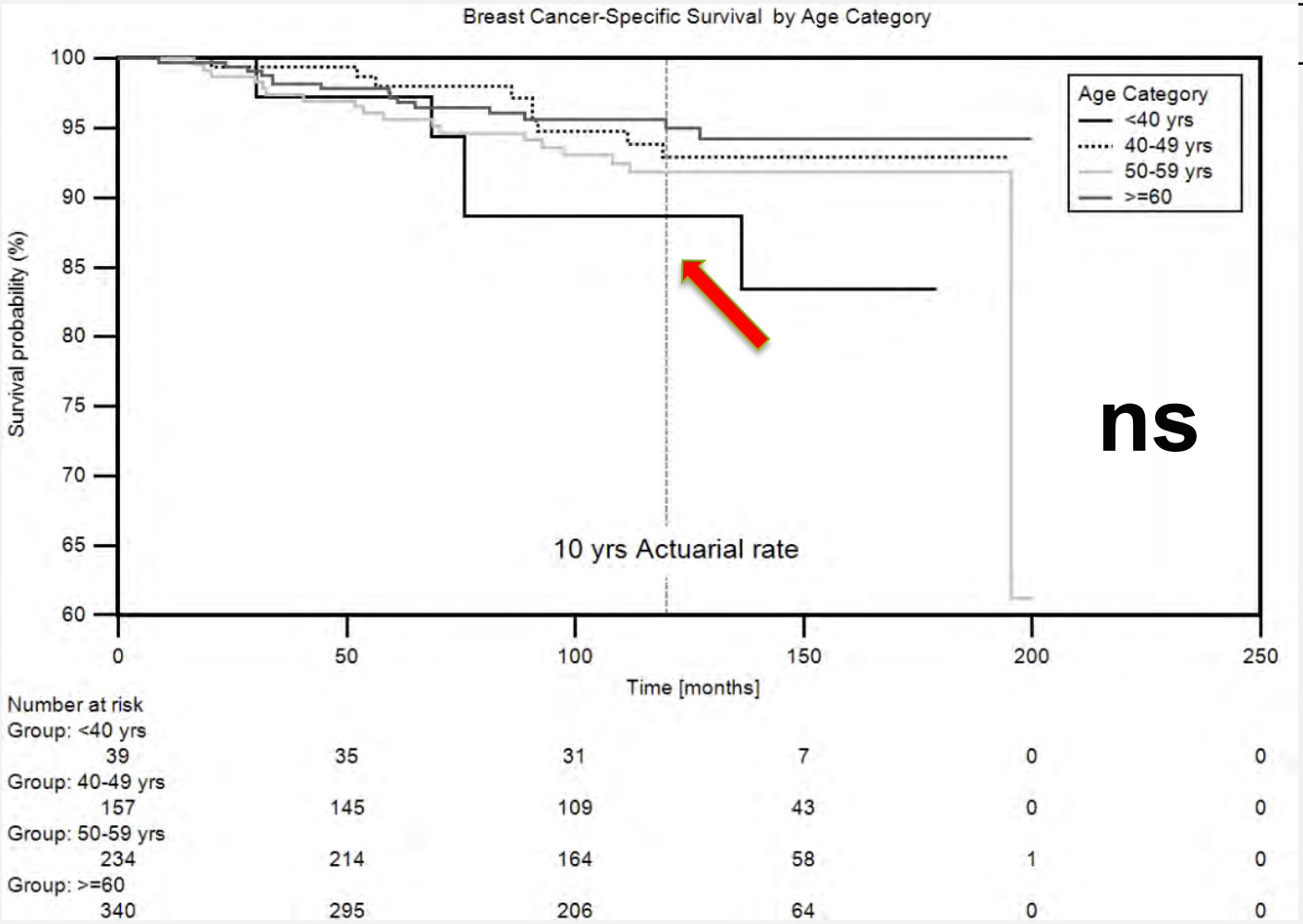
Age (J)	Patients (n) / %	LR: n / %	10Y-LC %
≥ 60	340 / 44.2	7 / 2.0	97.6
50 - 59	234 / 30.4	5 / 2.2	97.2
40-49	157 / 20.4	7 / 4.4	97.3
< 40	39 / 5	2 / 5.1	93.5



BCSS by age

UNIKLINIKUMSALZBURG



Age (J)	10Y-LC %
≥ 60	95.0
50 - 59	91.8
40-49	90.3
< 40	88.6

LC by subtypes

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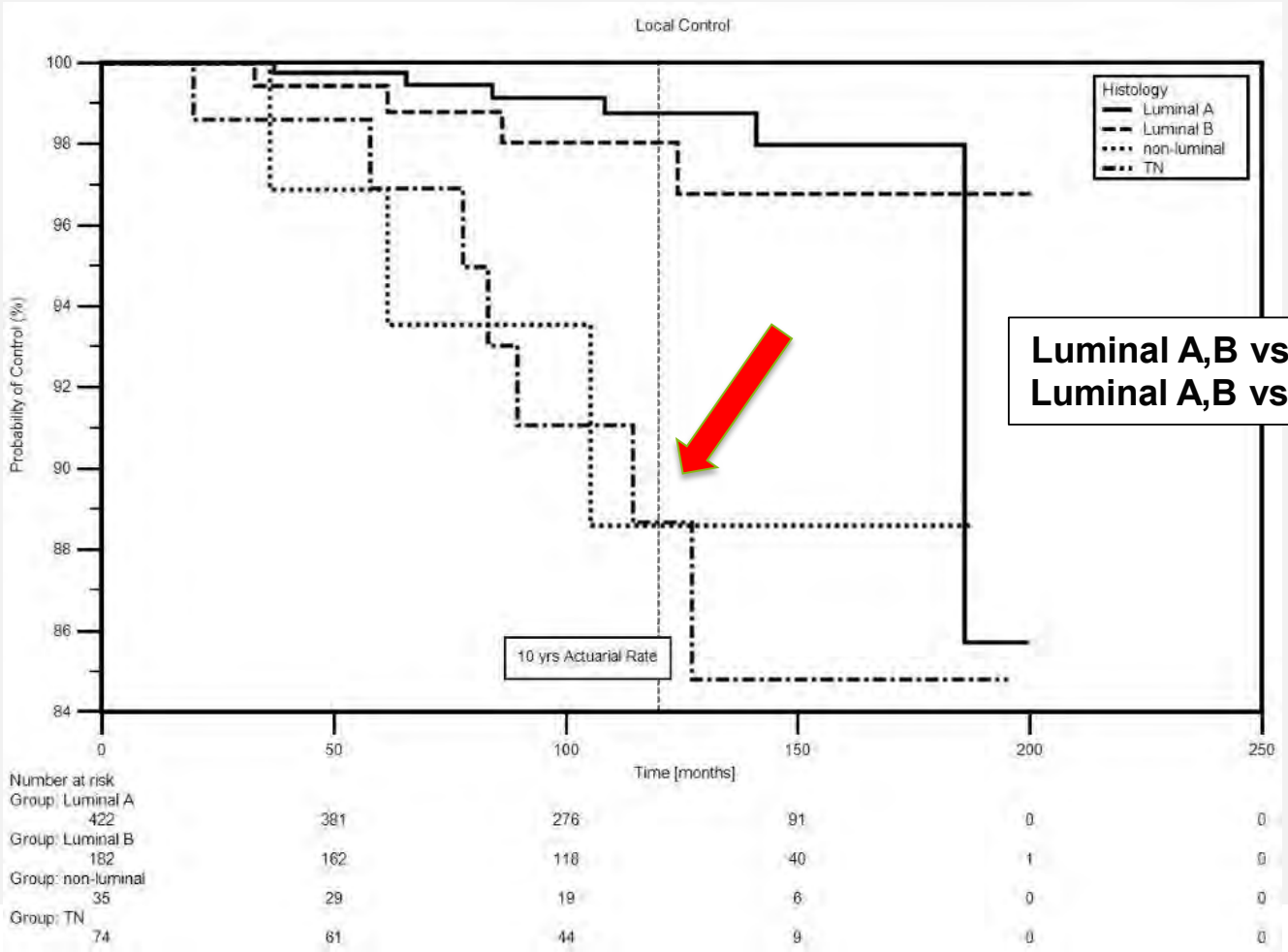
Subtype	Patients (n) / %	LR: n / %	10Y-LC %
Luminal A	422 / 55	6 / 1.4	98.7
Luminal B	182 / 23.6	4 / 2.2	98
non-luminal	35 / 4.5	3 / 8.5	88.6
TN	74 / 9.6	7 / 9.4	88.7



Luminal A,B vs. TN: p= 0.005
Luminal A,B vs. non-Lum.: p= ≤0.05

BCSS by subtypes

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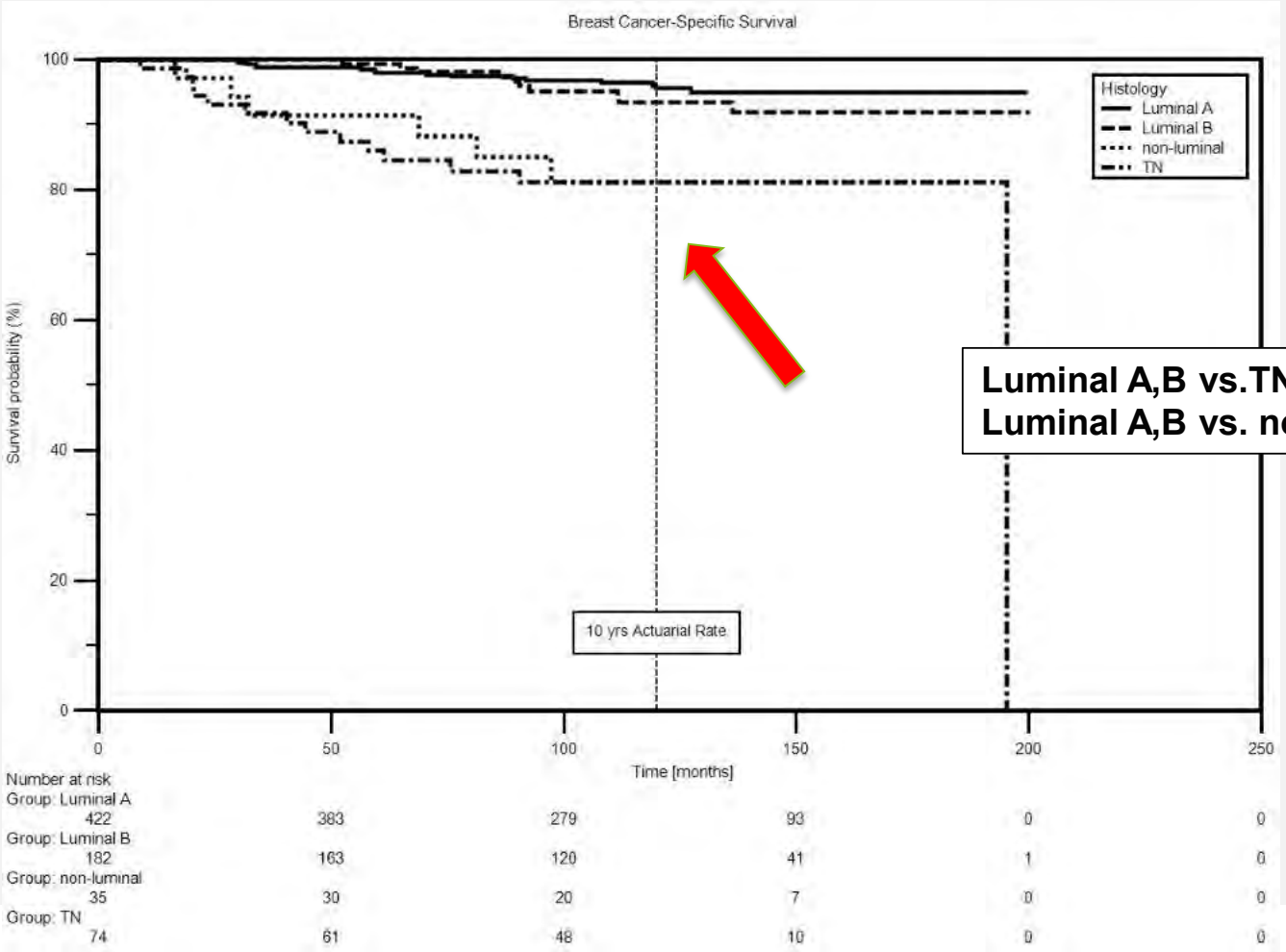
Subtype	10Y-BCSS %
Luminal A	95.5
Luminal B	93.4
non-luminal	81.2
TN	81.2



Luminal A,B vs.TN: p= 0.005
Luminal A,B vs. non-Lum.: p= ≤0.015

OS by subtypes

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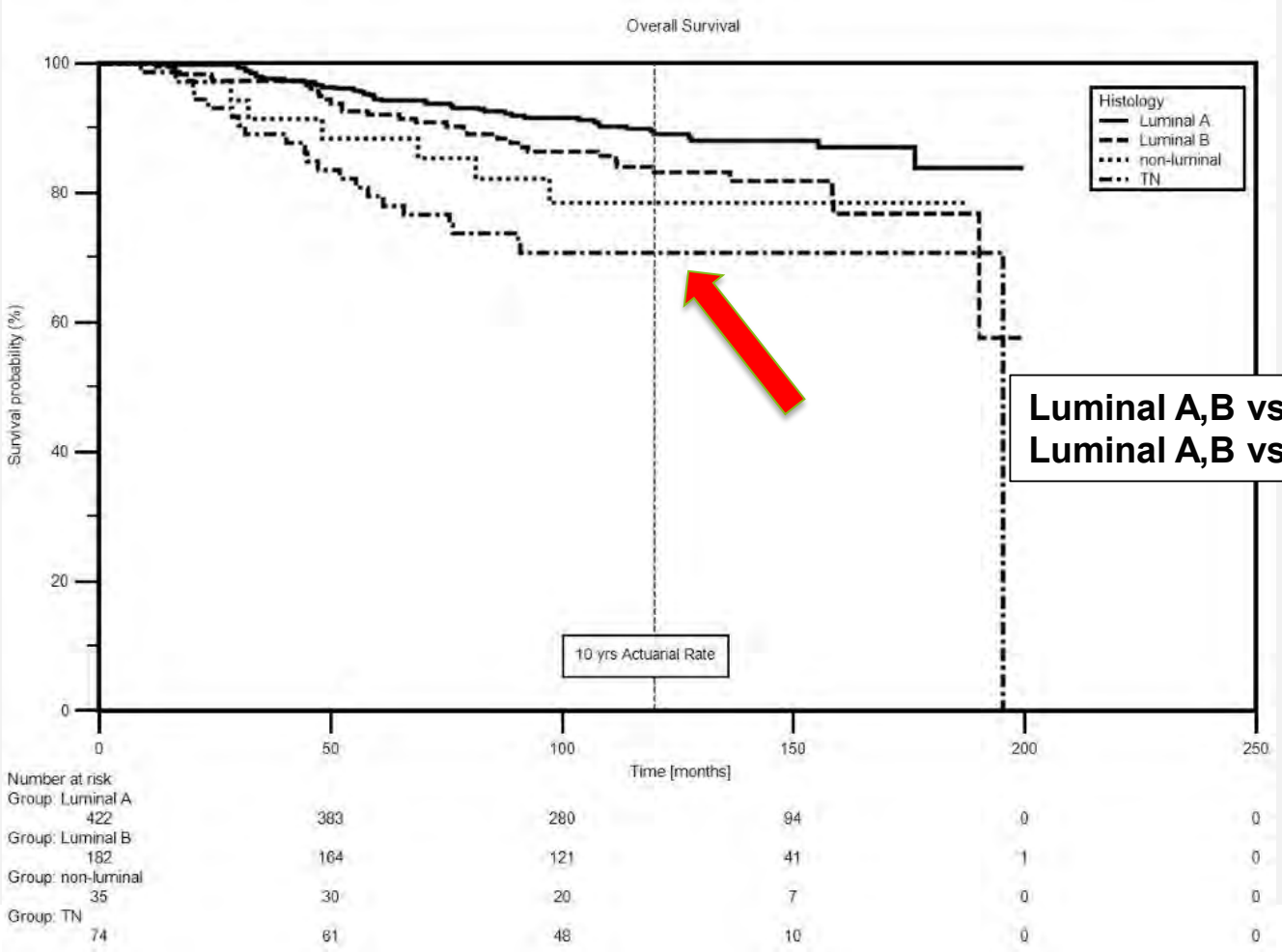
Subtype	10Y-OS %
Luminal A	89.2
Luminal B	83.2
non-luminal	78.5
TN	70.8



Luminal A,B vs.TN: p= < 0.05
Luminal A,B vs. non-Lum.: ns

IBR and risk factors ?

Factor	Patients (n) / %
G3	8 / 38
≥ T2	5 / 24
Non Luminal	3 / 14
Triple negative	7 / 33
< 50 Y	9 / 43
Multifocality	6 / 29
Tube < 6 cm	11 / 52

Time Gap IOERT – WBI (weeks)?

- All Patients: Med. 6 (3 – 37)
- All Recurrences: Med. 7 (4 – 30)
- In-Q: Med. 9 (5 – 30)
- Out-Q: Med. 7 (4 – 16)

Conclusion

➢ IOERT as a Boost:

- Enables *High Local control rate* in patients with an unselected risk profile after 10-years FUP
- First IBR were observed *median 7 years* after IOERT
- *Possible Risik factors:* G3, TNBC,non-luminal, <50 Y, multifocality, or tube diameters < 6 cm

INTRAOPERATIVE ELECTRON BOOST RADIOTHERAPY (IOERT) FOR EARLY BREAST CANCER: INSTITUTIONAL EXPERIENCE (2009-2015)

LEONARDO GUERRERO
Department of Radiation Oncology Gregorio Marañón General University Hospital

PURPOSE:

To assess feasibility, toxicity and cosmetic results of IOERT during breast conserving surgeries for early breast cancer.

Hospital General Universitario Gregorio Marañón
SaludMadrid
Comunidad de Madrid

Department of Radiation Oncology and Gynecology

PATIENTS AND METHODS:

<u>February 2009-May 2015</u>:

- 63p : Early BC → breast conserving surgery + IOERT.
- Adapted to results of sentinel lymph nodes biopsy.

35 = **21Gy** (single dose)

28 = **10Gy boost** + conventional regimen of external beam radiotherapy

9th International ISIORT Conference

Hospital General Universitario Gregorio Marañón

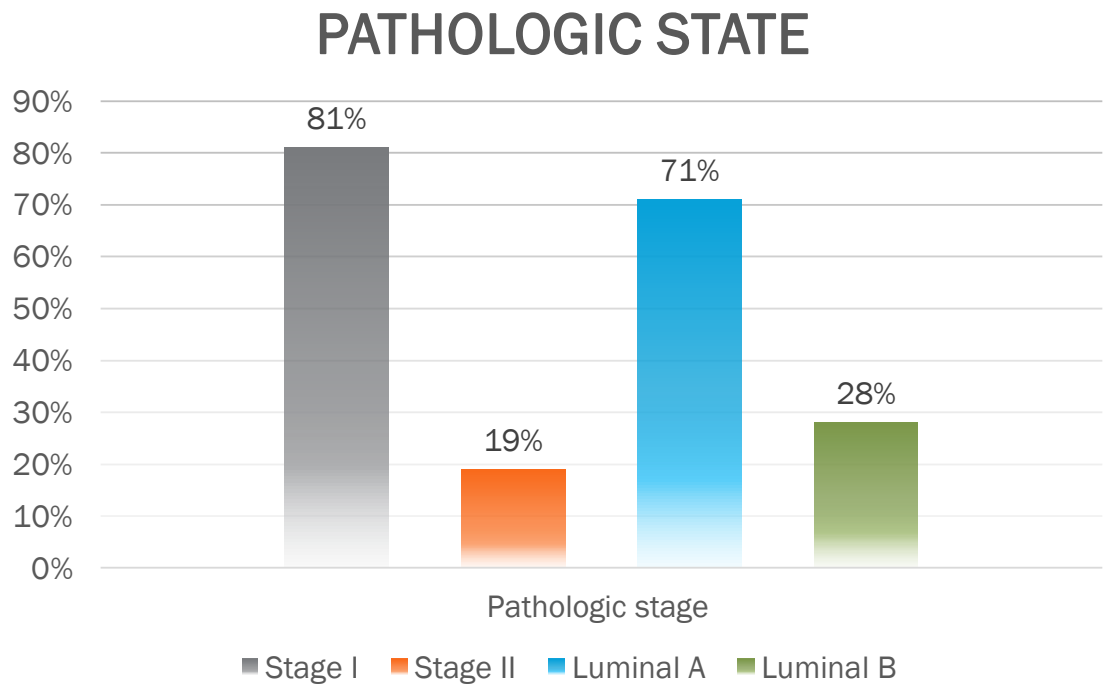
SaludMadrid

Comunidad de Madrid

Department of Radiation Oncology and Gynecology

RESULTS:

Median age: 69 year-old (43-91).
Median Follow up: 41 months (4-88).



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Comunidad de Madrid

Department of Radiation Oncology and Gynecology

RESULTS:

Electron energies: 6-12 MeV.

6 MeV 78%.

Applicator diameter: 5 cm (71%).

Beveled end of 0º, 15º, 30º were 43%, 33%, 24% respectively.

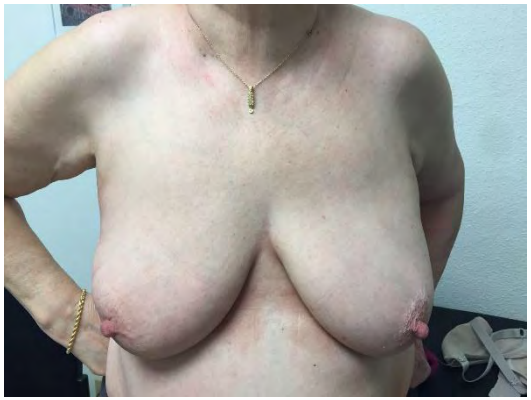
We used metallic internal patient-shielding in all procedures.

RESULTS:

Time for wound healing was ≤ 15 days in 95%.

Cosmetic results (NSABP/RTOG scale), were:

- Excellent 10 (18%).
- Good 38 (69%).
- Fair 7 (13%).



There was no local relapse.

5-yr Overall Survival (OS): 94% (Only two patients died for no tumor reasons).

CONCLUSIONS:

In selected population (based on ESTRO/ASTRO criteria) IOERT is an attractive accelerated partial breast irradiation technique, secure, repeatable, with low toxicity and good cosmetic results.

Hospital General Universitario Gregorio Marañón

SaludMadrid

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THANK YOU.

ISIORT

INTERNATIONAL SOCIETY of INTRAOPERATIVE RADIATION THERAPY

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Chairman: Prof. Dr. med. Frederik Wenz

Medizinische Fakultät Mannheim
der Universität Heidelberg

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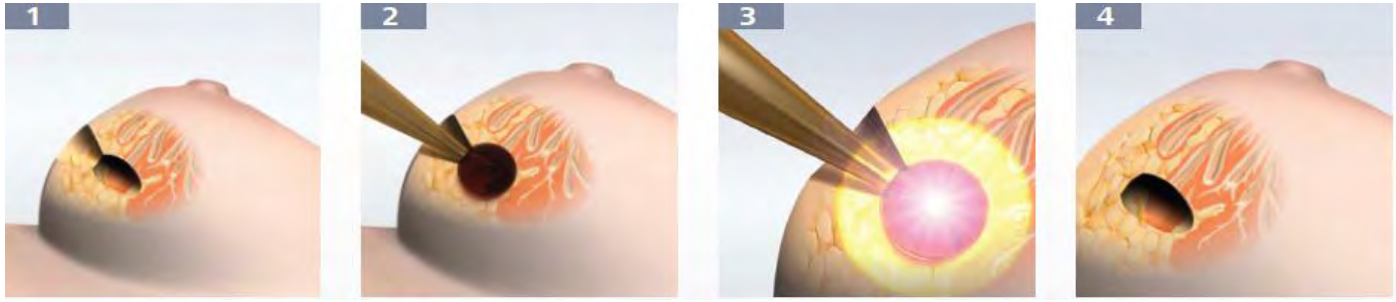
Risk factors for intramammary breast cancer recurrence after intraoperative radiotherapy (IORT)

Elena Sperk,

Philipp Teich, Christel Weiß, Marc Sütterlin, Frederik Wenz



Rationale

- There are known risk factors for recurrence after breast cancer with breast conserving therapy
- Up to date no special analysis of risk factors after intraoperative radiotherapy (IORT) for breast cancer are published.

Aims

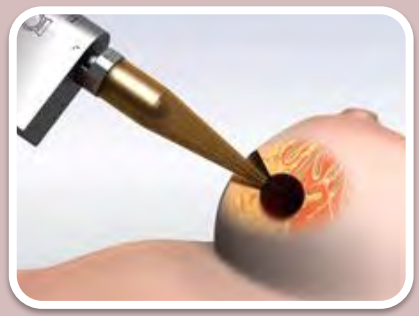
1) To identify risk factors for local, ipsilateral and contralateral recurrence
2) Create a risk classification.

Methods

02/2002-
08/2011

N = 398 patients

treated in breast cancer center Mannheim



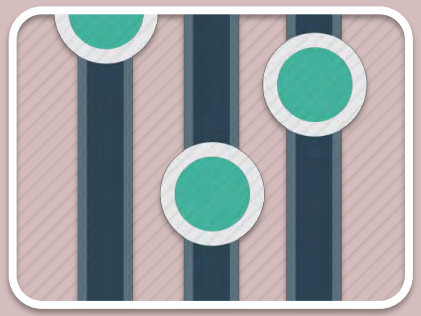
N = 285

IORT Boost

+ EBRT 46-50Gy

N = 113

IORT alone



Parameter:

age, TNM status, grading, histology (lobular vs. no special type), lymphovascular invasion, hormone receptor status, Luminal A/B/triple negative, uPA/PAI, number of resections, resection status, EIC, adjuvant therapy, localization of the tumor and recurrence

(univariate analysis):

1) local recurrence (< 2 cm of the tumorbed)

2) ipsilateral recurrence (> 2 cm of the tumorbed)

3) contralateral recurrence

4) control group with no recurrence

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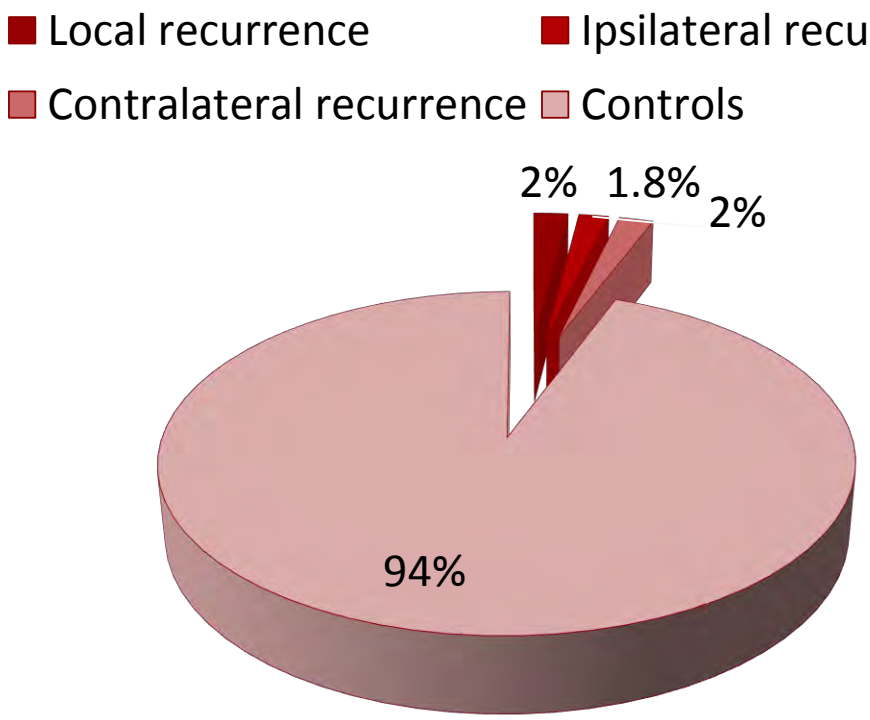
Patients

	Local recurrence	Ipsilateral recurrence	Contralateral recurrence	Controls
N =	8	7	8	380
Age (Median)	64.5 (46-95)	52.2 (39-74)	60.9 (46-78)	63.0 (30-90)
Death (n=)	4	1	1	35
EBRT (n=)	4	5	7	264
Days IORT-EBRT	79 (35-129)	79 (27-161)	60 (25-129)	77 (13-307)
Dose IORT	19.7 (18-20)	20	19.3 (15-20)	19,8 (6-20)
RT Time (Min)	34.9 (19-52)	27 (19-37)	39.2 (19-50)	31.6 (8-53)
Applicator size	4.3 (3.5-5.0)	3.8 (3.0-4.5)	5.0 (3.5-5.0)	4.1 (2.0-5.0)
Dose EBRT	46.0 (46-46)	46.9 (45.6-50)	47.1 (46-50)	47.1 (32-66)
Duration Radiother. (Days)	36.75 (33-40)	36.4 (31-41)	34.8 (31-40)	34.9 (16-62)
Tumor characteristics				
Tumor size (mm)	15 (1-24)	14.4 (8-24)	16 (11-23)	15.4 (0-45)
Localization				
left upper outer	3 (38%)	3 (42.9%)	0 (0.0%)	107 (29.0%)
left upper inner	3 (38%)	0 (0.0%)	0 (0.0%)	48 (13.0%)
left lower outer	0 (0.0%)	1 (14.3%)	0 (0.0%)	18 (4.9%)
left lower inner	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (4.34%)
right upper outer	1 (13%)	1 (14.3%)	4 (50.0%)	120 (32.5%)
right upper inner	0 (0.0%)	0 (0.0%)	1 (12.5%)	36 (9.8%)
right lower outer	0 (0.0%)	0 (0.0%)	2 (25.0%)	28 (7.6%)
right lower inner	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (4.3%)
central/ retromamillary	1 (12.5%)	2 (28.6%)	1 (12.5%)	14 (3.8%)
no information	0 (0.0%)	0 (0.0%)	0 (0.0%)	11(2.9%)
Histology				
Invasive-ductal	6 (7%)	3 (42.9%)	7 (87.5%)	252 (67.2%)
Invasive-lobular	1 (12.5%)	3 (42.9%)	1 (12.5%)	93 (24.8%)
Others	1 (12.5%)	1 (14,3%)	0 (0%)	30 (8%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (1.3%)
Tumor size				
<1 cm	1 (12.5%)	2 (28.6%)	0 (0,0%)	77 (20.5%)
1-<2 cm	4 (50.0%)	4 (57.1%)	6 (75.0%)	210 (55.9%)
≥2 cm	3 (37.4%)	1 (14.3%)	2 (25.0%)	89 (23.7%)

T				
0	0 (0.0%)	0 (0.0%)	0 (0.0%)	3
1	4 (50,00%)	6 (85,7%)	6 (75,0%)	283 (74,5%)
2	3 (37,5%)	1 (14,3%)	2 (25,0%)	88(23,2%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4a	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0,3)
X	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (2,2)
N				
0	6 (75,0%)	5 (71,4%)	6 (75,0%)	280 (73,7%)
1	2 (25%)	2 (28,6%)	2 (25,0%)	56 (14,7%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	16 (4,2%)
3	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (1,1%)
X	0 (0.0%)	0 (0.0%)	0 (0.0%)	21 (26,3%)
M				
0	8 (100,0%)	7 (100,0%)	8 (100,0%)	360 (94,7%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	12 (3,2%)
X	0 (0.0%)	0 (0.0%)	0 (0.0%)	8 (2,1%)
G				
1	0 (0.0%)	1 (14,3%)	0 (0.0%)	23 (6,0%)
2	5 (62,5%)	5 (71,4%)	3 (37,5%)	156 (41,1%)
3	2 (25,0%)	1 (14,3%)	4 (50,0%)	44 (11,6%)
X	1 (12,5%)	0 (0,0%)	1 (12,5%)	9 (2,4%)
L1	2(25%)	1(14%)	3(38%)	67(19%)
Bisphosphon.-therapy	1(12,5%)	2(28,6%)	2(25,0%)	19(5,0%)
Luminal type				
Luminal A	5(71,4%)	5(71,4%)	5(62,5%)	289(78,5%)
Luminal B	0(0,0%)	1(14,3%)	1(12,5%)	45(12,2%)
Triple negativ	2(28,6%)	1(14,3%)	2(25,0%)	34(9,2%)
Unknown	1	0 (0.0%)	0 (0.0%)	12
EIC/DCIS				
Positive	1 (14.3%)	1 (14.3%)	3 (37.5%)	76 (20.1%)
Negative	6 (85.7%)	6 (85.7%)	5 (62.5%)	302 (79.9%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.5%)

Results: Risk factors



- Age (mean) 63.8 years
- Median F/U 44.2 months

Risk factors for **contralateral recurrence**:
- **pN1 + L1**

Risk factors for **ipsilateral recurrence**:
- Triple-negative tumor
- Less number of intraoperative re-resections
- **pN1 + L1**

Risk factors for **local recurrence**:
- Young age
- Therapy with Bisphosphonates
- Medial Tumor localization
- Resection margin < 1mm
- Less number of intraoperative re-resections
- **pN1 + L1**

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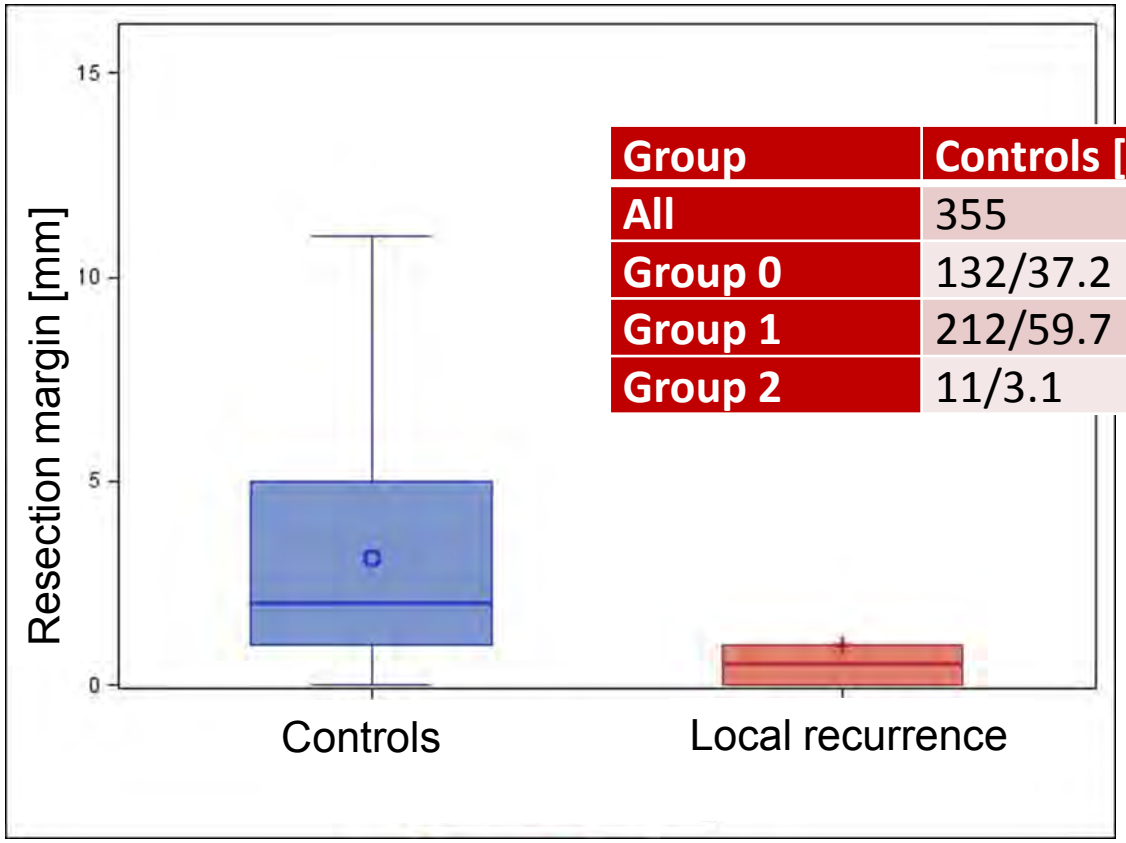
Results: Resection margin

Boxplot: minimal Resection margin in controls and local recurrence patients



Group	Controls [n/%]	LR [n/%]	p
All	355	13	0.06
Group 0	132/37.2	8/61.5	
Group 1	212/59.7	4/30.7	
Group 2	11/3.1	1/7.7	

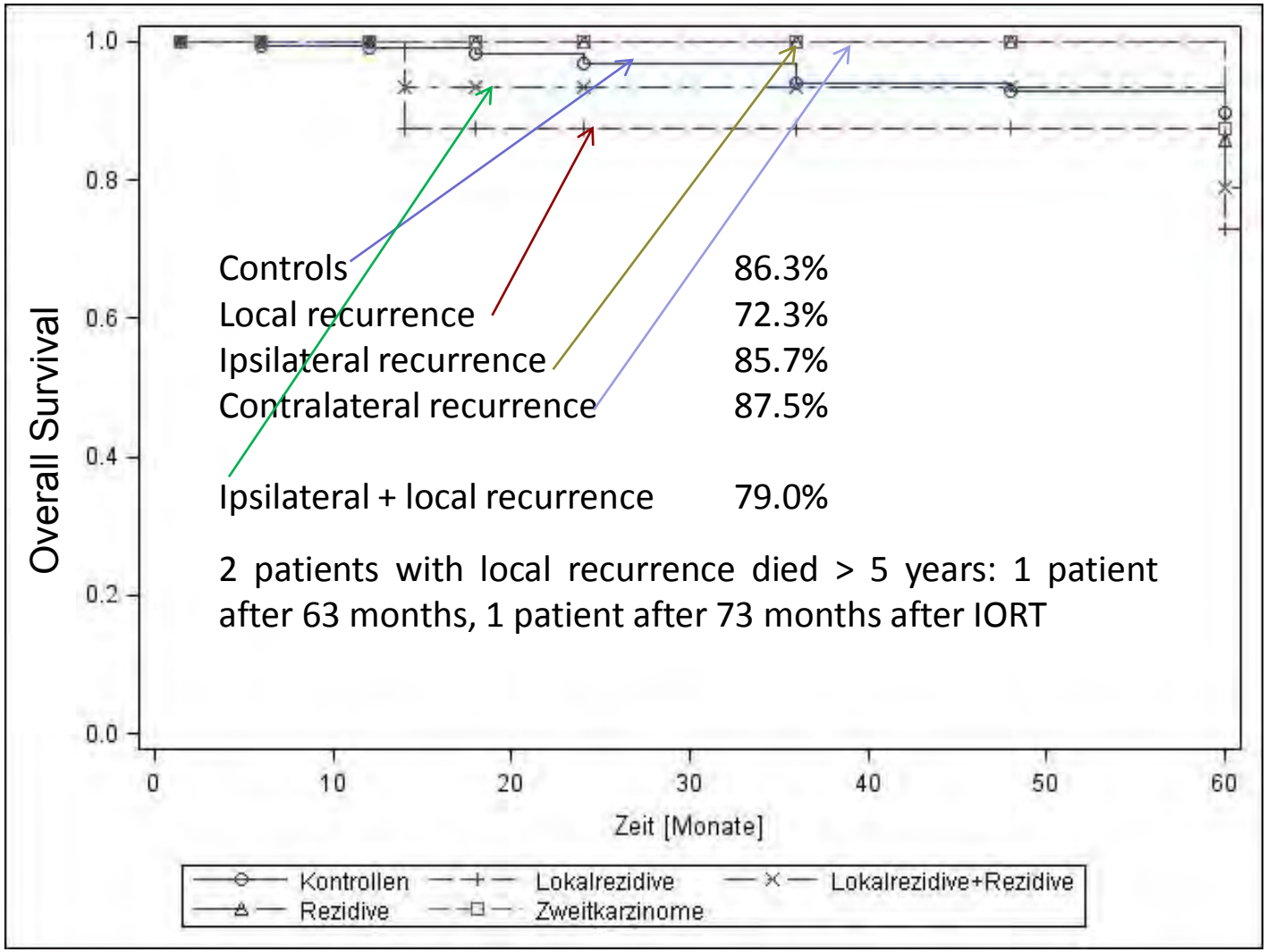
Group 0: ≤ 1 mm
Group 1: 1.1 - 9.9 mm
Group 2: ≥ 10 mm

Results: Risk constellation

Risk for intramammary recurrence after IORT
(Local recurrence, ipsilateral or contralateral recurrence)

Risk [%]	<5		5-10		>10	>15	
T	1-2	1-2	1-2	1-2	1-2	1-2	1-2
N	1	0	0	0	0	1	0
G	1-2	1-2	1-2	3	1-2	1-2	1-2
L+	-	-	-	-	+	+	-
Histology	Ductal	Lobular	Ductal	Ductal	Ductal	Ductal	Ductal
Triple-negative	-	-	-	-	-	-	+

5 Year Overall Survival



Controls	86.3%
Local recurrence	72.3%
Ipsilateral recurrence	85.7%
Contralateral recurrence	87.5%
Ipsilateral + local recurrence	79.0%

2 patients with local recurrence died > 5 years: 1 patient after 63 months, 1 patient after 73 months after IORT

Conclusion: Risk factors IORT

- ✓ Low recurrence rate after IORT regarding local, ipsilateral or contralateral recurrence. Good overall survival.
- ✓ Known risk factors: young age, lymphovascular invasion, medial tumor localization, neg. hormone receptors, resection margin < 2 mm.
- ✓ No risk factors: tumor size, positive lymph nodes, histological type (lobular vs. ductal)
- ✓ High risk constellation: Combination of positive lymph nodes and lymphovascular invasion and secondly triple negative tumors.

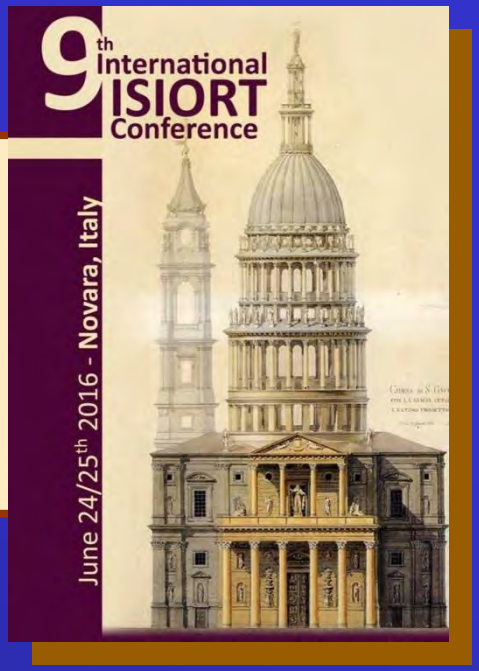
…. For your attention!

IORT Group Mannheim:

Dr. Y. Abo-Madyan, Dr. S. Clausen
Dr. F. Giordano, Prof. Dr. G. Glatting
Prof. C. Herskind, A. Keller
A. Kipke, Dr. C. Neumaier
Dr. C. Nwankwo, Dr. T. Reis
Dr. F. Schneider, Dr. E. Sperk
Prof. M. Veldwijk, G. Welzel

Prof. Dr. F. Wenz

Intraoperative Ultrasound role on breast Intraoperative Electron Radiation Therapy (B-IOERT) boost



Cristiana Vidali
S.C. Radioterapia
A.S.U.I. Trieste

IORT as anticipated boost: clinical rationale

To date, every interim analysis showed lower local recurrence rates than standard treatment schedules

ADVANTAGES:

- No topographic miss
- More favourable radiobiology of a single dose (α/β)
- Shorter radiation time (< 1–2 weeks)
- Good dose distribution
- Complete skin sparing
- Minimal toxicity in the long-term follow up

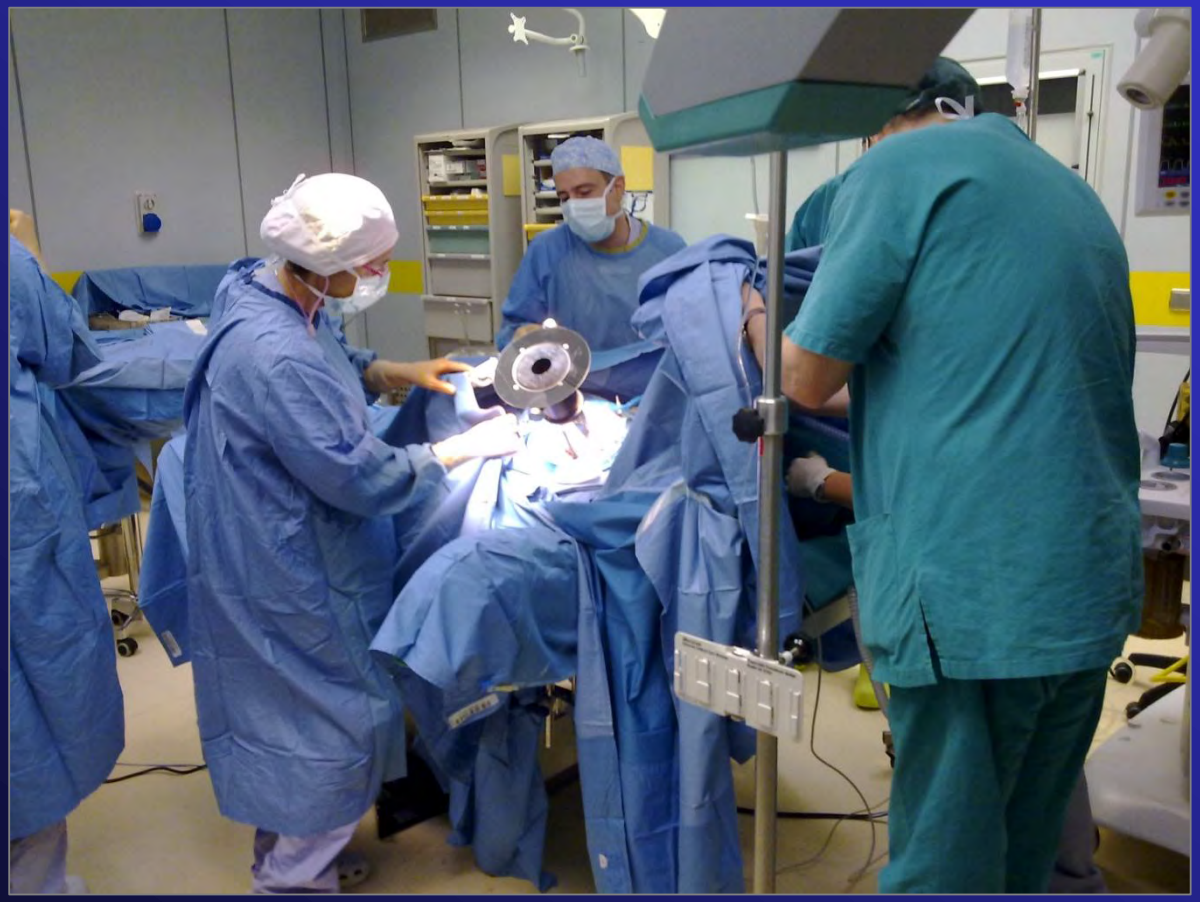
DRAWBACKS:

- Uncertainty of the final pathologic report
- Lack of definition of the resection margins

IOERT in Trieste

CASTELLO DI MIRAMARE. Veduta del porticciolo, riserva marina del WWF. © APT Trieste - ph.: Alessandro Savella.

The first case of IOERT in Trieste
June 22, 2012



IOERT Trieste Protocol

➢ IOERT as anticipated boost:

- 10 Gy (max. dose). The PTV should be encompassed by 90% of the prescribed dose (i.e. 9 Gy). Dose inhomogeneity: -10% within the target volume is allowed

➢ Standard WBI:

- 50 Gy – 2 Gy in 25 fr.
- Start:
  - ≤ 12 weeks from surgery without adjuvant CT
  - ≤ 35 days from the end of CT and < 6 months from surgery

LANDESKRANKENHAUS SALZBURG
UNIVERSITÄTSKLINIKUM
DER PARACELSUS MEDIZINISCHEN PRIVATUNIVERSITÄT

IORT

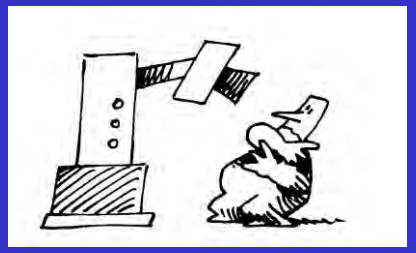
HIOB Protocol
Prospective one-armed multi-center-trial

- **IOERT as anticipated boost:** dose: 11.1 Gy (max. dose)
  + hypofractionated WBRT: total dose 40.5 Gy - 2.7 Gy/fr. in 15 fractions – 5 fr./week

- **Clinical rationale:** it combines the advantages of hypofractionated WBRT as well as IOERT-boost, which seems to be superior to other boost strategies in terms of local tumour control, with less acute toxicity and late toxicity equivalent to standard RT schedules

- **WBI must start :**
  - not before day 36 until day 56 postop. without adjuvant CT
  - ≤ 21 days from the end of CT and ≤ 9 months from surgery

IOERT:
the experience of Trieste

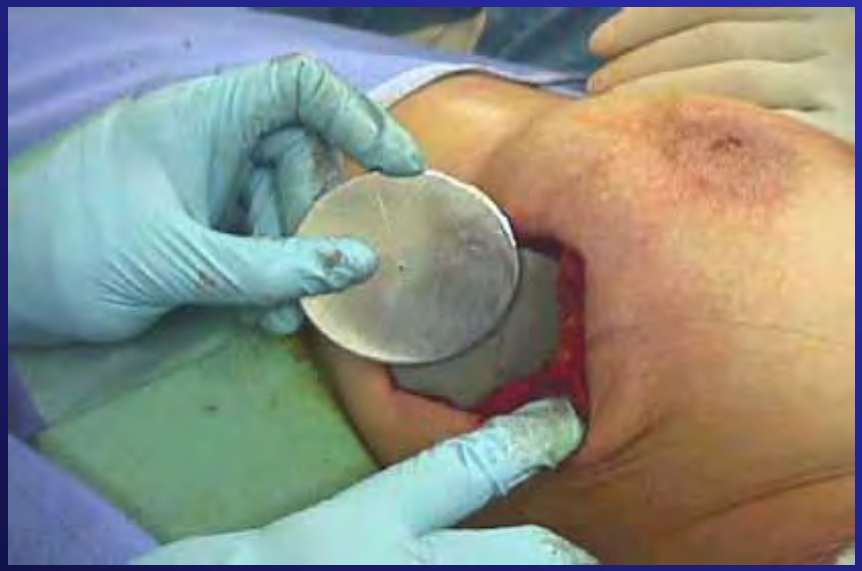


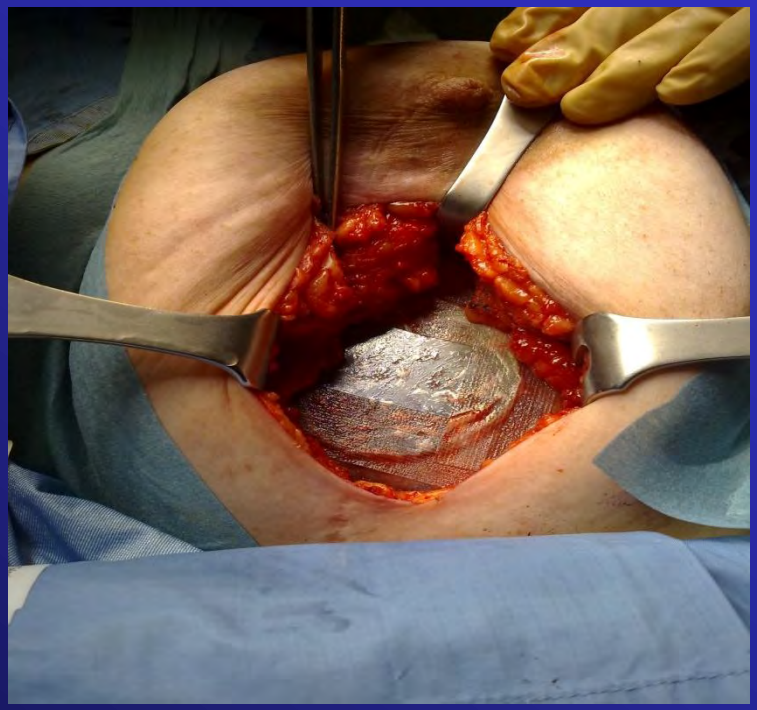
- From June 2012 to April 2016:
  75 cases (74 patients, one with synchronous bilateral cancer)
- ***Median age:*** 67 years (range:47-85)
- ***Median FU:*** 18 months (range: 1-38)
- ***Stage:***

  cT1a N0: 2
  cT1b Nx: 2
  cT1c N0: 35
  cT2 N0: 1
  cT1b N0: 32
  cT1b N1: 1
  cT1c Nx: 2

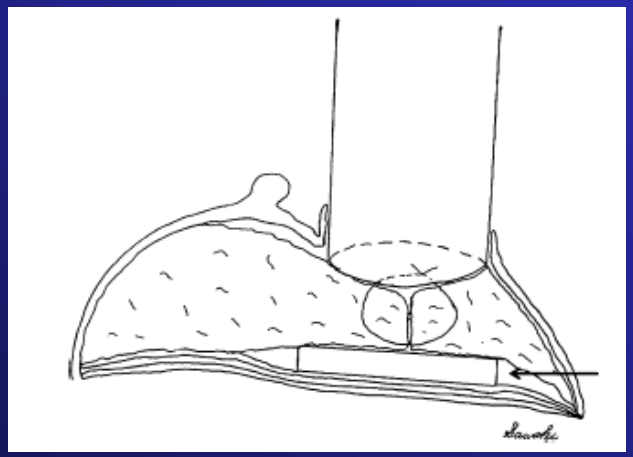
- **HIOB Protocol (since 14.11.2014)** ➡ 28 patients

Shielding disk positioned between the residual breast and the pectoralis fascia

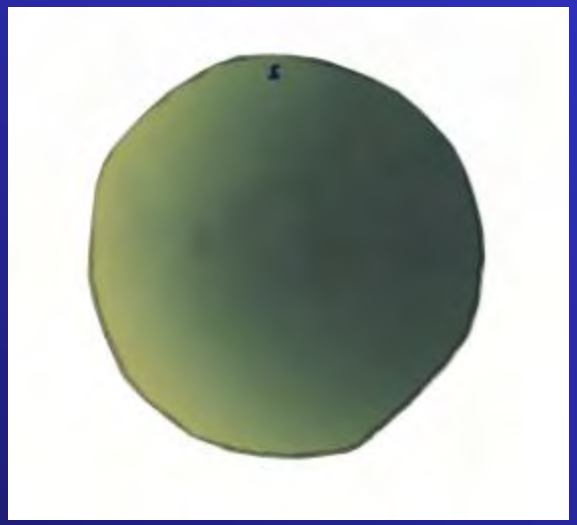




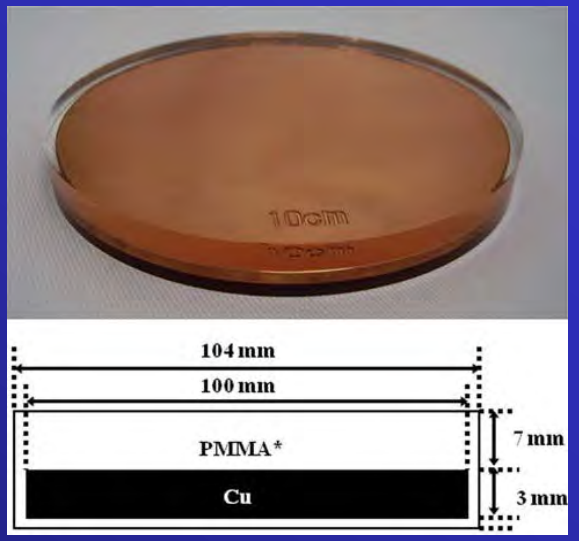
Characteristics of the shielding disk



Shielding disk size



«In vivo dosimetry» with EBT3 Gafchromic films



Shielding disk with PMMA and copper layers

IOERT and FMECA

(Failure Mode and Effects and Criticality Analysis)

Int J Radiat Oncol Biol Phys 82, 2: E305-311

- A prospective approach to fully assess and manage the risks of accidental exposures deriving from the use of innovative methodologies
- RPN (risk priority number): estimate of the criticality level of each step of the procedure

S = Severity

O = Occurrence

D = Detectability

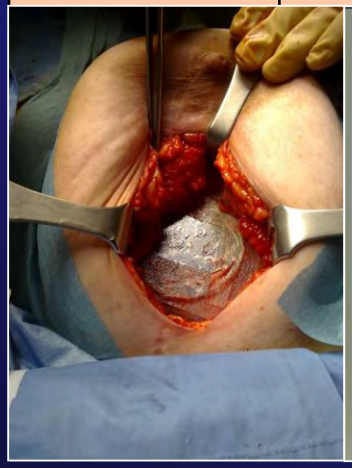
RPN = S x O x D

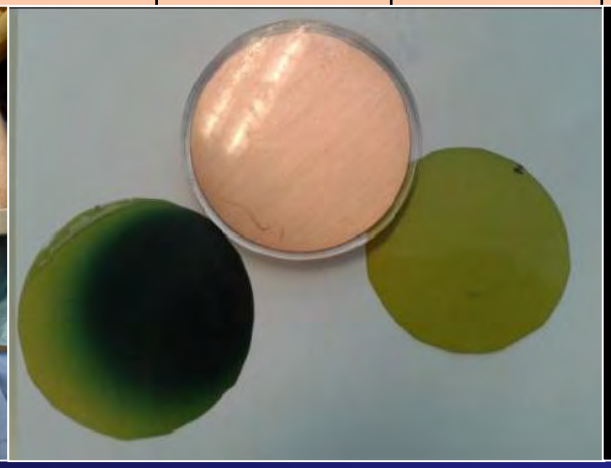
High risk :	Intermediate risk:	Low risk:
RPN > 60	30 < RPN < 60	RPN < 30

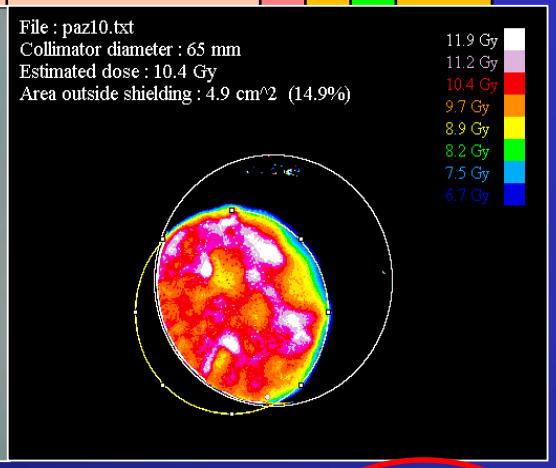
PROFESSIONAL FIGURES	PROCEDURE	FAILURE MODE	FAILURE EFFECTS	FAILURE CAUSES	INITIAL RISK RANKING 2012				CORRECTIVE ACTIONS 2012	REVISED RISK RANKING 2014			
Radiation Oncologist - Surgeon	Measure of the tumour bed thickness	Wrong measure	Incorrect prescription of the energy of the Electron beam	Wrong placement of the device used for the measurements	4	3	4	48	Increase in the n. of measurements and choice of the average value	4	2	3	24 (-50%)
Phisicist	Preparation of gafchromic film and placement on the perspex bolus	1) Inadequate placement 2) Wrong calibration, use, conservation of the gafchromic film	Wrong measure of the delivered dose	Erroneous observation of the "In vivo dosimetry" procedure	4	3	5	60	Careful observation of the "In vivo dosimetry" procedure	4	2	4	32 (-46.7%)
Radiation Oncologist - Surgeon	Applicator placement	Absent or incomplete adherence of the applicator to the tumour bed	Non-homogeneous irradiation	Air gap presence, blood accumulation, very sloping tumour bed	4	4	4	64	Accurate visual control, correct placement of the patient on the operating table	4	3	3	36 (-43.75%)
Radiation Oncologist - Surgeon	Alignment of the protective plate	Misalignment of the protective plate	Unintended normal tissues irradiation below the tumour bed	Low accuracy in the alignment	5	4	4	80	Selection of a plate much larger than the applicator size and new shielding set-up	5	3	4	60 (-25%)

The most critical phase

PROFESSIONAL FIGURES	PROCEDURE	FAILURE MODE	FAILURE EFFECTS	FAILURE CAUSES	INITIAL RISK RANKING 2012			
Radiation Oncologist – Surgeon	Alignment of the protective plate	Misalignment of the protective plate	Unintended normal tissues irradiation below the tumour bed	Low accuracy in the alignment	5	4	4	80



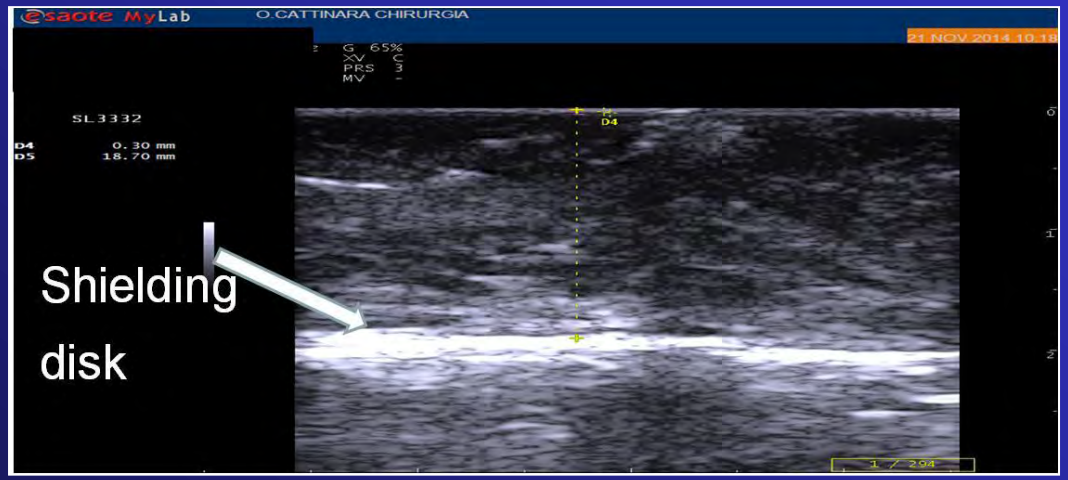




INITIAL RISK RANKING 2012				CORRECTIVE ACTIONS	REVISED RISK RANKING 2014			
5	4	4	80	Selection of a plate much larger than the applicator size and new shielding set-up	5	3	4	60 -(25%)

Intraoperative Ultrasound

Esaote
MyLab™One/Touch
Linear probe SL 3332



Comparison between needle and IOUS measures

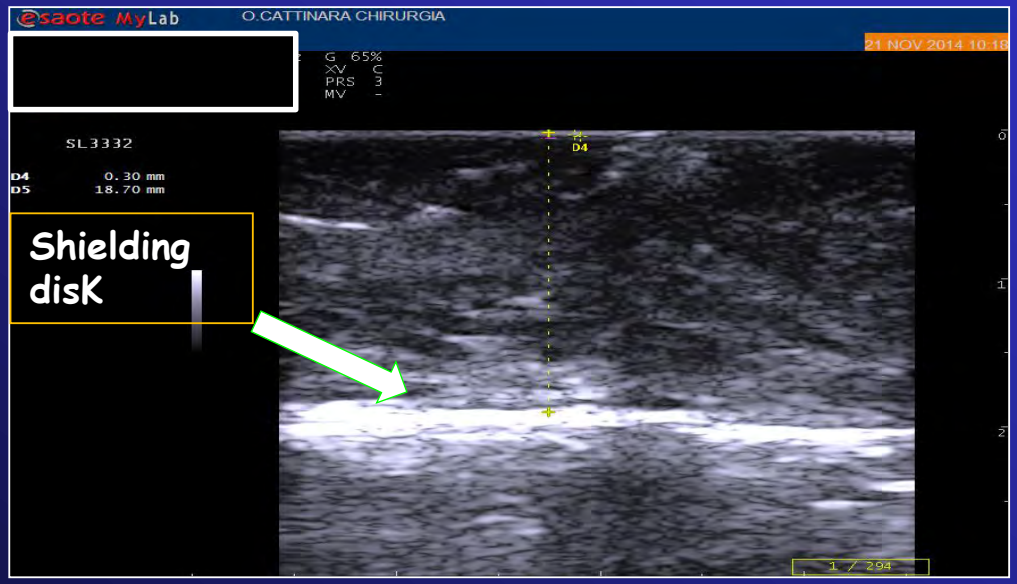
pt. N.	date	method	point 1 mm	point 2 mm	point 3 mm	point 4 mm	point 5 mm	avarage mm	STD	IOUS vs needle mm
44	21/11/14	needle	14,0	13,0	9,0	10,0	14,0	12,0	2,3	0,2
		IOUS	11,8	10,3			14,5	12,2	2,1	
45	05/12/14	needle	11,0	13,0	18,0	17,0		14,8	3,3	-0,3
		IOUS	10,3	14,0	16,9	16,6		14,4	3,1	
46	19/12/14	needle	7,0	11,0	6,0	10,0	13,0	9,4	2,9	-0,4
		IOUS	8,8	9,3	9,0	8,9		9,0	0,2	
47	09/01/15	needle	10,0	13,0	11,0	8,0	8,0	10,0	2,1	0,4
		IOUS	9,4	12,0	12,8	8,1	9,5	10,4	2,0	
48	16/01/15	needle	11,0	14,0	12,0	10,5	11,0	11,7	1,4	0,3
		IOUS	10,4	15,0	11,5	11,5	11,8	12,0	1,7	
49	23/01/15	needle	15,0	9,0	12,0	9,0	13,0	11,6	2,6	0,0
		IOUS	11,5	10,8	13,4	7,9	14,6	11,6	2,6	
50	29/01/15	needle	5,0	5,0	6,0	6,0	6,0	5,6	0,5	0,2
		IOUS	5,0	5,9	6,4	5,3	6,4	5,8	0,6	
51	29/02/15	needle	5,0	9,0	6,0	9,0	4,0	6,6	2,3	0,5
		IOUS	5,6	8,7	5,7	10,1	5,2	7,1	2,2	
52	05/03/15	needle	15,0	14,0	11,0	14,0	12,0	13,2	1,6	-0,8
		IOUS	13,4	14,0	10,9	13,5	10,3	12,4	1,7	
53	19/03/15	needle	15,0	14,0	20,0	15,0	18,0	16,4	2,5	-0,5
		IOUS	16,6	14,3	18,4	13,9	16,2	15,9	1,8	
54	23/04/15	needle	10,9	12,0	11,2	10,0	13,0	11,4	1,1	-0,4
		IOUS	10,0	12,0	12,0	9,0	12,0	11,0	1,4	
55	30/05/15	needle	11,0	6,0	13,0	15,0	9,0	10,8	3,5	-1,2
		IOUS	10,0	5,2	13,5	10,7	8,4	9,6	3,1	
56	07/05/15	needle	8,0	10,0	9,0	9,0	9,0	9,0	0,7	0,2
		IOUS	7,6	9,1	10,6	9,1	9,5	9,2	1,1	
57	14/05/15	needle	7,0	8,0	5,0	5,0	5,0	6,0	1,4	0,3
		IOUS	7,1	7,5	6,4	4,7	6,1	6,3	1,1	
58	28/05/15	needle	10,0	10,0	14,0	10,0	11,0	11,0	1,7	-0,4
		IOUS	10,9	9,0	14,5	9,0	9,5	10,6	2,3	
59	11/06/15	needle	13,0	9,0	9,0	15,0	8,0	10,8	3,0	-0,6
		IOUS	11,3	8,3	8,3	14,6	8,5	10,2	2,8	
60	18/06/15	needle	5,5	5,5	9,0	4,0		6,0	2,1	0,9
		IOUS	6,1	5,8	8,7	6,8		6,9	1,3	
61	08/10/15	needle	16,0	9,0	16,0	11,0	15,6	13,5	3,3	-0,1
		IOUS	16,0	8,7	15,5	12,0	14,7	13,4	3,0	
62	15/10/15	needle	10,0	10,0	9,0	5,0	9,0	8,6	2,1	-0,1
		IOUS	9,9	9,8	10,3	4,1	8,4	8,5	2,5	
63	29/10/15	needle	9,0	11,0	7,0	7,0	15,0	9,8	3,3	0,1
		IOUS	9,7	11,8	6,6	7,4	14,1	9,9	3,1	
70	25/02/16	needle	10,0	12,0	13,0	11,0		11,5	1,3	-0,5
		IOUS	9,9	11,3	11,6	11,2		11,0	0,8	
71	10/03/16	needle	11,0	16,0	6,0	10,0	9,5	10,5	3,6	-0,3
		IOUS	10,0	14,0	6,0	11,0	10,0	10,2	2,9	
73	01/04/16	needle	11,0	9,0	8,0	9,0	10,0	9,4	1,1	0,5
		IOUS	11,4	10,5	8,6	8,9	10,0	9,9	1,2	

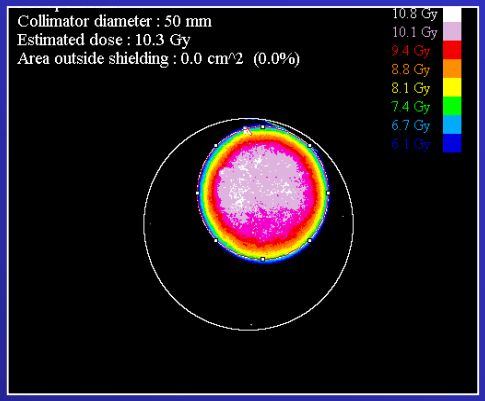
- ✓ Average difference calculated on 5 points in the tumour bed: 0.5 mm
- ✓ In vivo dosimetry confirmed that IOUS application reduced the misalignment, in terms of irradiated area outside the shielding disk from 5.6 cm^2 to 2.6 cm^2
- ✓ The percentage of patients in which the electron field was totally inside the shield moved from 23% to 68%

Final revision after the introduction of the IOUS probe

IOUS probe application:

- to measure the target thickness
- to check the position of the shielding disk





CORRECTIVE ACTIONS	*REVISED RISK RANKING 2014*				*CORRECTIVE ACTIONS*	*FINAL REVISED RISK RANKING 2015*			
Selection of a plate much larger than the applicator size and new shielding setup	*5*	*3*	*4*	*60*	*Selection of a plate much larger than the applicator size, new shielding setup and <u>check with the IOUS probe</u>*	*5*	*3*	*2*	*30 (-50%)*

PROFESSIONAL FIGURES	PROCEDURE	FAILURE MODE	FAILURE EFFECTS	FAILURE CAUSES	REVISED RISK RANKING 2014				CORRECTIVE ACTIONS 2012	FINAL REVISED RISK RANKING 2015			
Radiation Oncologist - Surgeon	Measure of the tumour bed thickness	Wrong measure	Incorrect prescription of the energy of the Electron beam	Wrong placement of the device used for the measurements	4	2	3	24	- Increase in the n. of measurements and choice of the average value - Use of the IOUS probe	4	1	1	4 (-83.3%)
Phisicist	Preparation of gafchromic film and placement on the perspex bolus	1) Inadequate placement 2) Wrong calibration, use, conservation of the gafchromic film	Wrong measure of the delivered dose	Erroneous observation of the "In vivo dosimetry" procedure	4	2	4	32	Observation of the "In vivo dosimetry" procedure, labelling of the gafchromic film and double check	4	1	1	4 (-87.5%)
Radiation Oncologist - Surgeon	Applicator placement	Absent or incomplete adherence of the applicator to the tumour bed	Non-homogeneous irradiation	Air gap presence, blood accumulation, very sloping tumour bed	4	3	3	36	Accurate visual control, correct placement of the patient on the operating table	4	3	3	36 (-0%)
Radiation Oncologist - Surgeon	Alignment of the protective plate	Misalignment of the protective plate	Unintended normal tissues irradiation below the tumour bed	Low accuracy in the alignment	5	3	4	60	New shielding set-up and check with the IOUS probe	5	3	2	30 (-50%)

IOERT + WBI: acute toxicity

	Needle (%)	IOUS (%)	Total (%)
Patients total N.	50	23	73
Erythema (grade I)	45 (90)	20 (87)	65 (89)
Erythema (grade II)	2 (4)	/	2 (2.7)
Edema	8 (16)	2 (8.7)	10 (13.7)
Hematoma	1 (2)	/	1 (1.4)
Seroma	1 (2)	1 (4.35)	2 (2.7)
Delayed wound healing	1 (2)	1 (4.35)	2 (2.7)
Pain	1 (2)	1 (4.35)	2 (2.7)
Hardening of the tumour bed	12 (24)	3 (13)	15 (20.6)
Overall acute toxicity	26 (52)	8 (34.75)	34 (46.5)

Conclusions

- IOUS proved to be accurate in evaluating the target depth
- After its introduction in the clinical practice very good results, in terms of the dose delivered and shielding alignment, have been obtained. The results show a significant reduction of the undesiderable dose and an important contribution in the optimization of patient safety
- Furthermore IOUS helped to reduce treatment related toxicity

Thanks to:
M. Severgnini, M. Bortul, G. Bellio,
M. Urbani, L. Toscano, M de Denaro, A.Beorchia

IOERT Trieste Protocol

➢ *Inclusion Criteria*

- Age: ≥ 18 years
- Surgery: QUAD + SLB or axillary dissection
- Preop. cytological and/or histological diagnosis of unifocal invasive carcinoma
- Stage: cT1-T2 (< 2.5 cm); cN0/N1; cM0
- All grades and receptor status (G1-G3, any HR and Her-2)
- R0 ≥ 2 mm
- Written informed consent of the patient

➢ *Exclusion Criteria*

- Age < 18 years
- LCIS, DCIS, Paget disease, non epithelial tumours
- Invasive multifocal or multicentric carcinoma or EIC
- Stage: cT2 (> 2,5 cm), T3, T4; cN > 1; cM1
- R1 or R0 < 2 mm
- Karnofsky Index < 70
- Neoadjuvant CT
- General contraindications to RT
- No written informed consent of the patient

HIOB Protocol

Inclusion Criteria

- Age: ≥ 35 years
- Histological diagnosis of unifocal or multifocal (max. distance < 5 cm) invasive carcinoma
- Stage: T1-T2; N0/N1; M0
- All grades and receptor status (G1-G3, any HR and Her-2)
- R0 no ink on tumors (invasive or in situ)
- Written informed consent of the patient
- Adjuvant and neoadjuvant CT: allowed

Exclusion Criteria

- Age < 35 years
- LCIS, DCIS
- Invasive multicentric or multi-focal (max. distance > 5 cm) carcinoma
- Stage: T3, T4; N > 1; M1 - R1
- Re-excision after IOERT or immediate secondary mastectomy
- Previous RT to the involved breast
- Breast size (PTV) > 2500 ml
- Karnofsky Index < 70
- General contraindications to RT
- No written informed consent of the patient

IMMUNOTHERAPY & POTENTIAL ROLE COMBINED WITH INTRAOPERATIVE RADIOTHERAPY

ISIORT 2016

John C. Grecula, M.D.
Professor, Ohio State Univ College of Medicine
Chief of Staff Elect, James Cancer Hospital

THE OHIO STATE UNIVERSITY JAMES CANCER HOSPITAL AND SOLOVE RESEARCH INSTITUTE

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

DISCLOSURES

I have no disclosures relevant to this lecture

ERA of Immunotherapy

Samir Khleif, M.D.

OUTLINE

1. **Review of Immune System**
2. Mechanisms of Check Point Inhibitors
3. Mechanisms of RT cell death
4. Combinations of RT & Immunotherapy

THE OHIO STATE UNIVERSITY JAMES CANCER HOSPITAL AND SOLOVE RESEARCH INSTITUTE

NCI CCC
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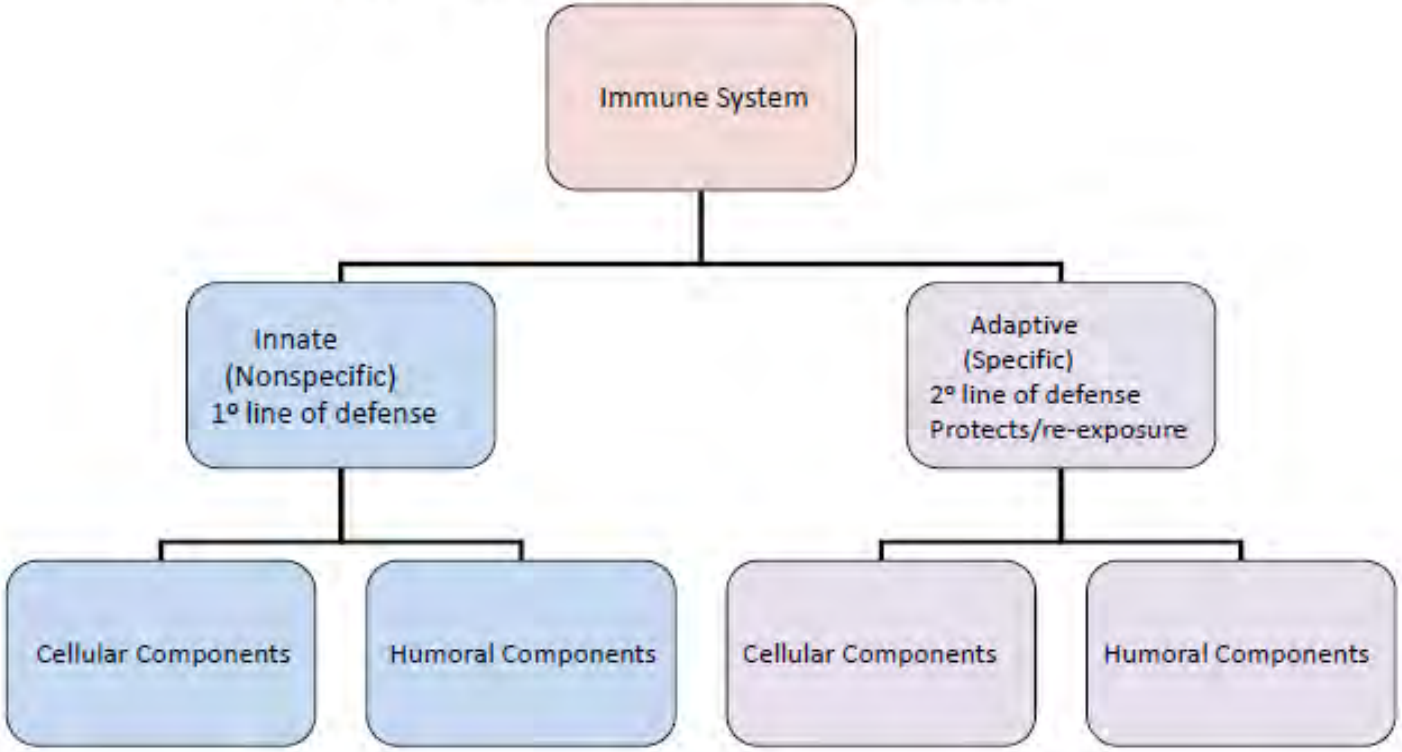
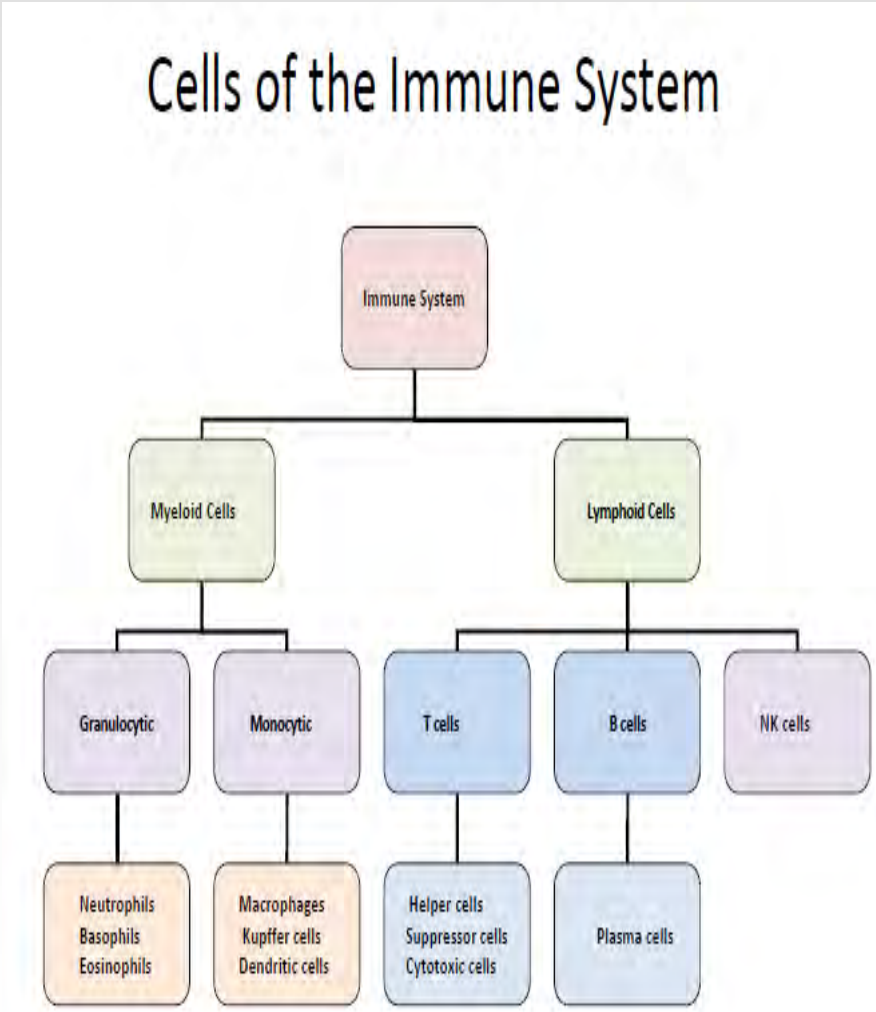
The Immune System

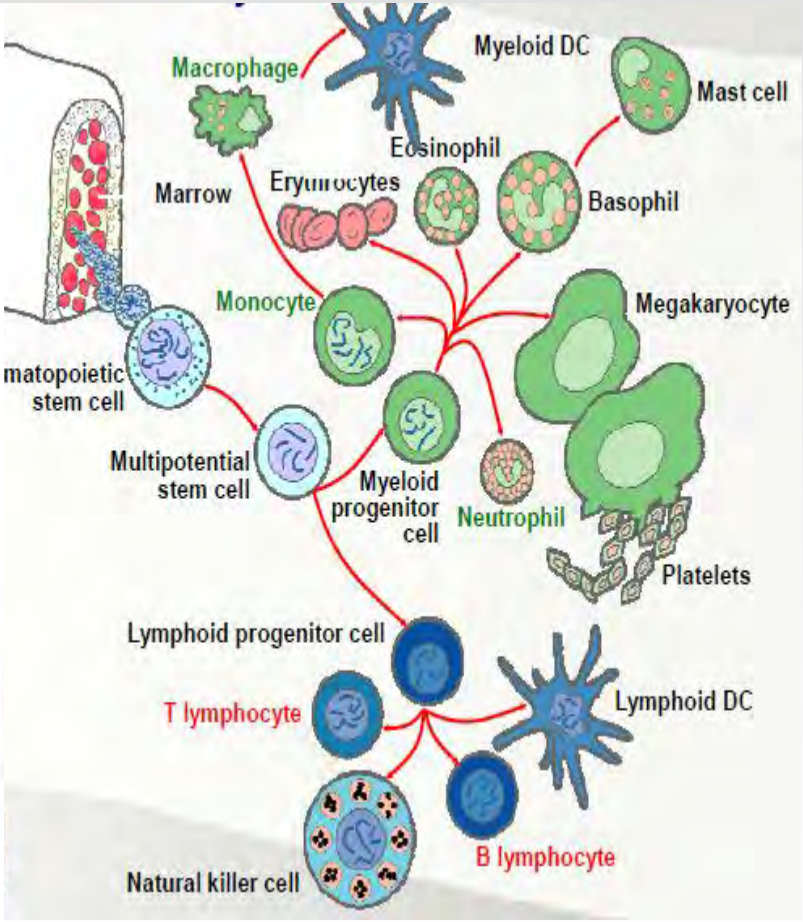


Both systems are interrelated

Santhakumar Manicassamy, Ph.D. & Lisa Butterfield, Ph.D

Cells of Immune System



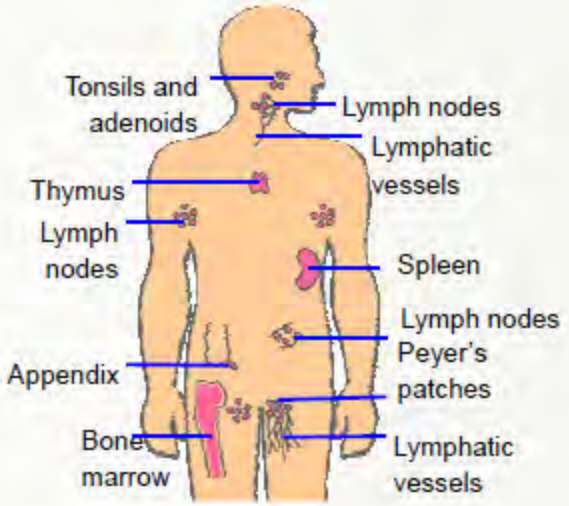


Esteban Celis, M.D., Ph.D; Lisaa Butterfield, Ph.D.

Santhakumar Manicassamy, Ph.D. & Lisa Butterfield, Ph.D

Organs of the Immune System

- Immune system organs are positioned **throughout** the body
- Key organs include the **bone marrow**, the **thymus** and the **spleen**
- Additional lymphoid tissues are found in many parts of the body, especially in the linings of the digestive tract and the airways and lungs--gateways to the body
- These tissues include the tonsils, adenoids, appendix and multiple **lymph nodes**



Esteban Celis, M.D., Ph.D, Lisa Butterfield, Ph.D.

Adaptive Immunity

Adaptive immune responses are acquired and display 4 attributes:

1. Antigen specificity
2. Diversity
3. Immunologic memory
4. Self/non-self recognition

Adaptive Immune System

- Lymphocytes are the **effector** and **regulatory** cells of the adaptive immune system
- These cells display highly diverse receptors for antigen (Ag)
- Each cell expresses receptors for a single Ag (*i.e.*, **respond only to one Ag**)
- Ags are molecules recognized by these receptors, and **elicit a specific immune response only to that Ag**
- Antigen presenting cells (APCs) gather Ags from infected tissues and cancer cells and then go to lymphoid tissues (lymph nodes) to activate naïve T cells
- **Cytokines** and **chemokines** act as soluble messengers between cells of the immune system

Adaptive Immune System

- Adaptive immune responses differ from innate responses in that they exhibit **specificity** and **memory**
  - **Specificity**: ability to recognize and respond to a particular Ag
  - **Memory**: capacity to respond to a second encounter to the same Ag, producing a larger and more rapid response (as compared to the primary Ag exposure)
  - **Memory**: can offer life-time protection and it is the basis for vaccines
- But, adaptive immune responses are much **slower** than innate immune responses

Humoral and Cell-Mediated Immunity

- Adaptive immune responses involve 2 lines of defense: **humoral and cell mediated immunity** (CMI)
  - **Humoral immunity involves B lymphocytes and antibodies (Abs)**
  - Adaptive **CMI involves T lymphocytes**
  - Some **CMI combines Abs and innate immune cells (NK, macrophages)** via Ab-dependent cell cytolysis (ADCC)
- Both B cells and T cells are **derived from precursors in the bone marrow,** that mature in different sites
  - B cells develop in the **bone marrow** and travel to lymphoid tissues, (spleen, lymph nodes) in search of Ag
  - T cells develop and mature in the **thymus** (positive & negative selection) and then migrate to secondary lymphoid organs (lymph nodes & spleen)

Esteban Celis, M.D., Ph.D, Lisa Butterfield, Ph.D.

Components of innate immunity

- Anatomical barriers barriers (skin and mucosal membranes)
- Cellular components (phagocytes, NK cells)
- Humoral components (complement, cytokines)

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Cells of innate immunity

(Internal Defenses)

Cell Type	Principal Function (s)
Neutrophils	Phagocytosis, inflammation
Macrophages	Phagocytosis, inflammation, T-cell activation, tissue repair
NK cells	Killing of infected or tumor cells
Eosinophils	Killing of certain parasites
Mast cells	Inflammation
Dendritic cells	Phagocytosis, activation of naive T-cells

Dendritic Cells (DC)

- DCs are the interface between innate and adaptive immunity
- DCs are immature as they circulate waiting to encounter pathogens. At this point, they are highly phagocytic, but not good stimulators of adaptive T cell responses
- Once they are activated, they secrete cytokines to initiate inflammation and then they migrate to lymph nodes and mature
- As mature DCs they are very efficient APCs for T cell stimulation
- Other APCs: macrophages, neutrophils, B-lymphocytes, monocytes.

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Innate Immunity

Humoral Components

Component	Mechanism
Complement	Lysis of bacteria and some viruses Opsonin Increase in vascular permeability Recruitment and activation of phagocytic cells
Coagulation system	Increase vascular permeability Recruitment of phagocytic cells B-lysin from platelets – a cationic detergent
Lactoferrin and transferrin	Compete with bacteria for iron
Lysozyme	Breaks down bacterial cell walls
Cytokines	Various effects

Innate Immunity vs Adaptive immunity (properties)

Innate	Adaptive
▪ Antigen-independent	▪Antigen-dependent
▪ Non-specific	▪Highly specific
▪ Immediate (hours)	▪Slower (days)
▪ No memory	▪Memory

Innate and adaptive responses work together

- Innate immune responses activate and shape adaptive immunity
- Adaptive immune responses utilize the machinery of innate immunity for effector function

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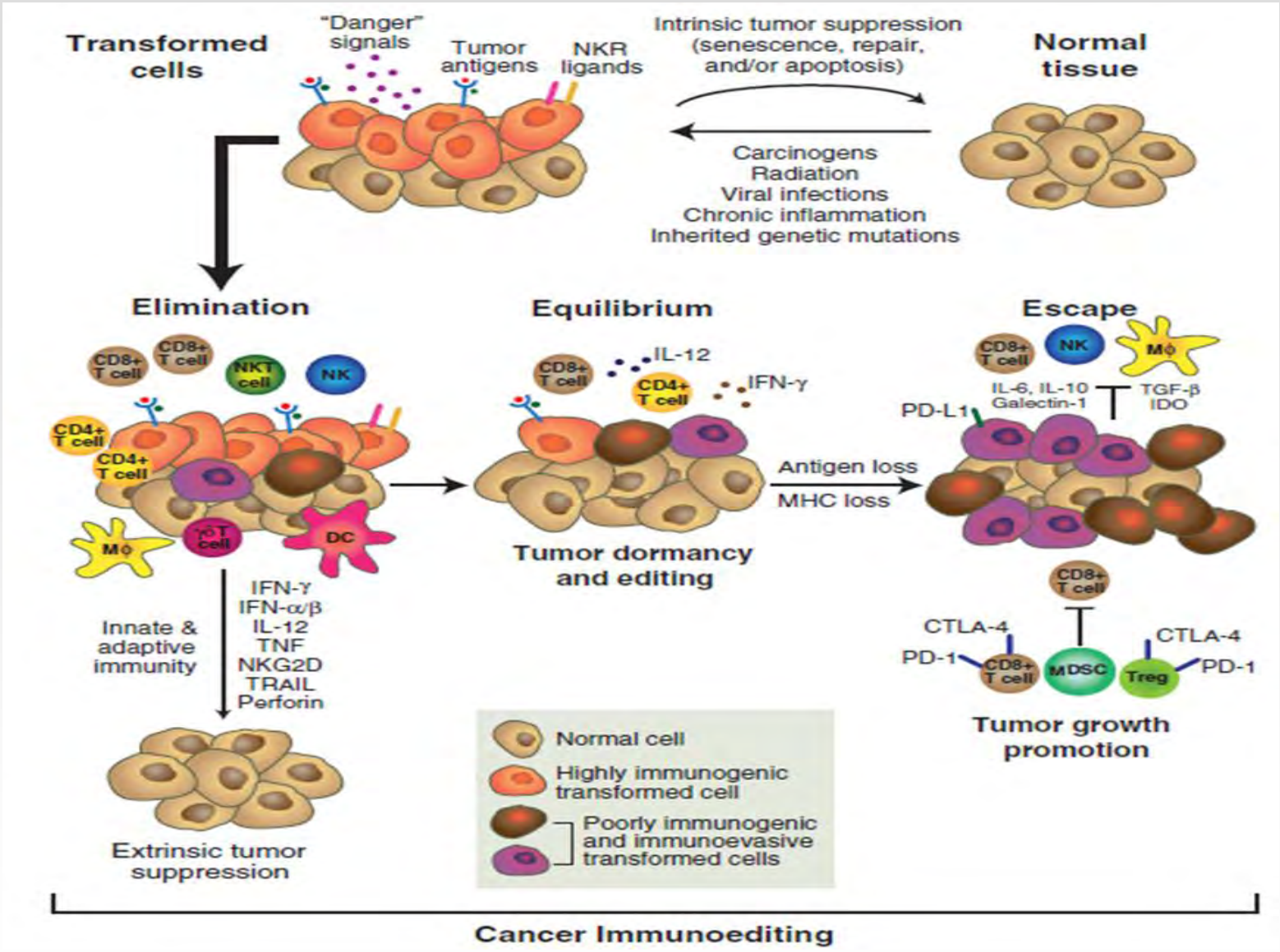
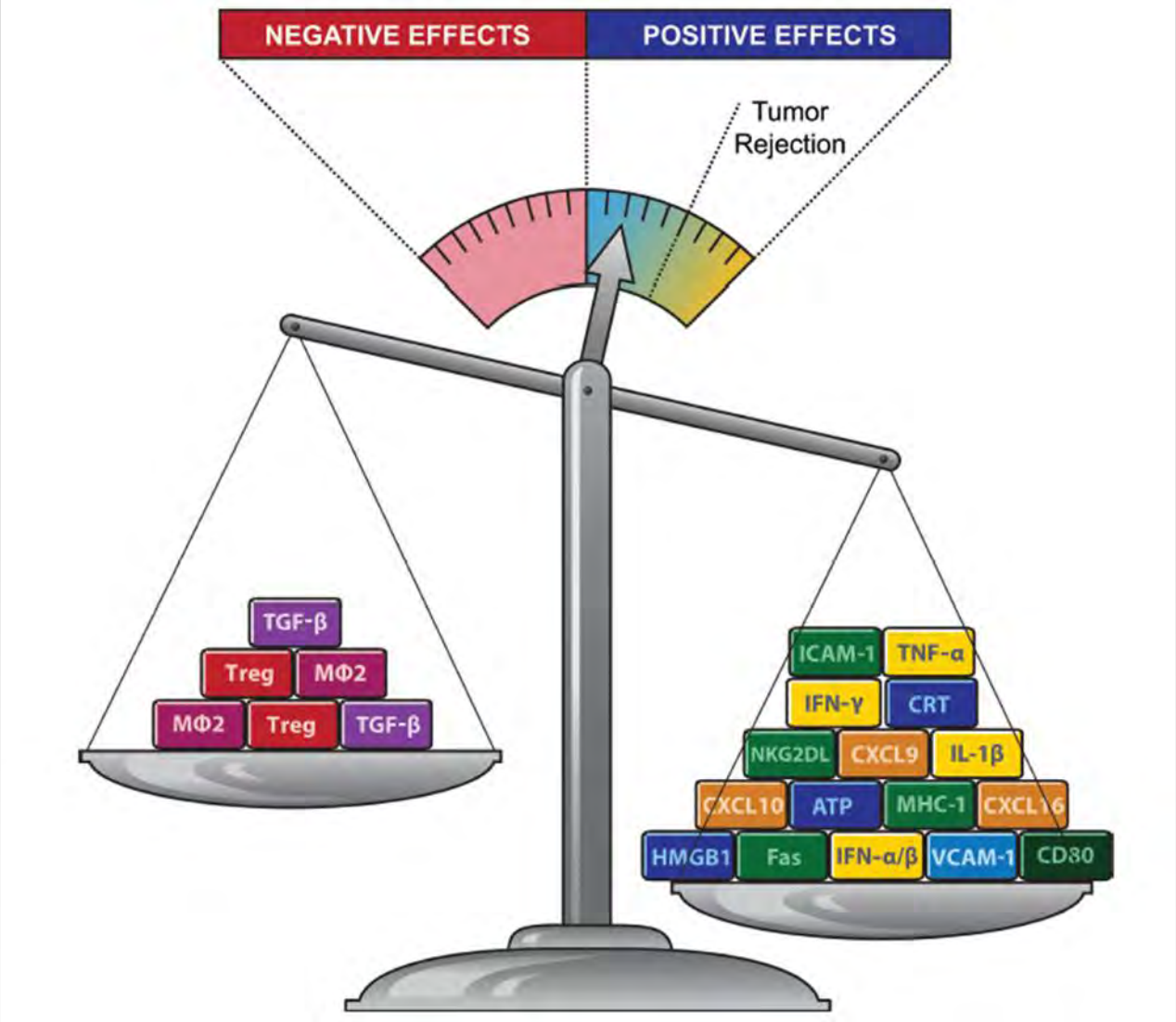
Immune System

Discovery in 2001:

- Immune System not only controls tumor quantity, but also tumor quality (immunogenicity)



Science: 2011:331:25:1565-1570



JNCI: 2013:105:4:256-265

Immunotherapy

- Vaccines
- Immune Modulators
  - Immune Agonists
    - Stimulatory cytokines (IL-2, IL-12, IL-15, TLR etc..)
    - Co-stimulatory molecules (OX-40, GITR, 4-1BB)
  - Immune inhibitors
    - Check point inhibitors (CTLA4, PD1/PDL1, LAG3, TIM3, iDO)
    - Inhibitory cytokines/factors (IL-10, TGFb)

OUTLINE

1. Review of Immune System
2. **Mechanisms of Check Point Inhibitors**
3. Mechanisms of RT cell death
4. Combinations of RT & Immunotherapy

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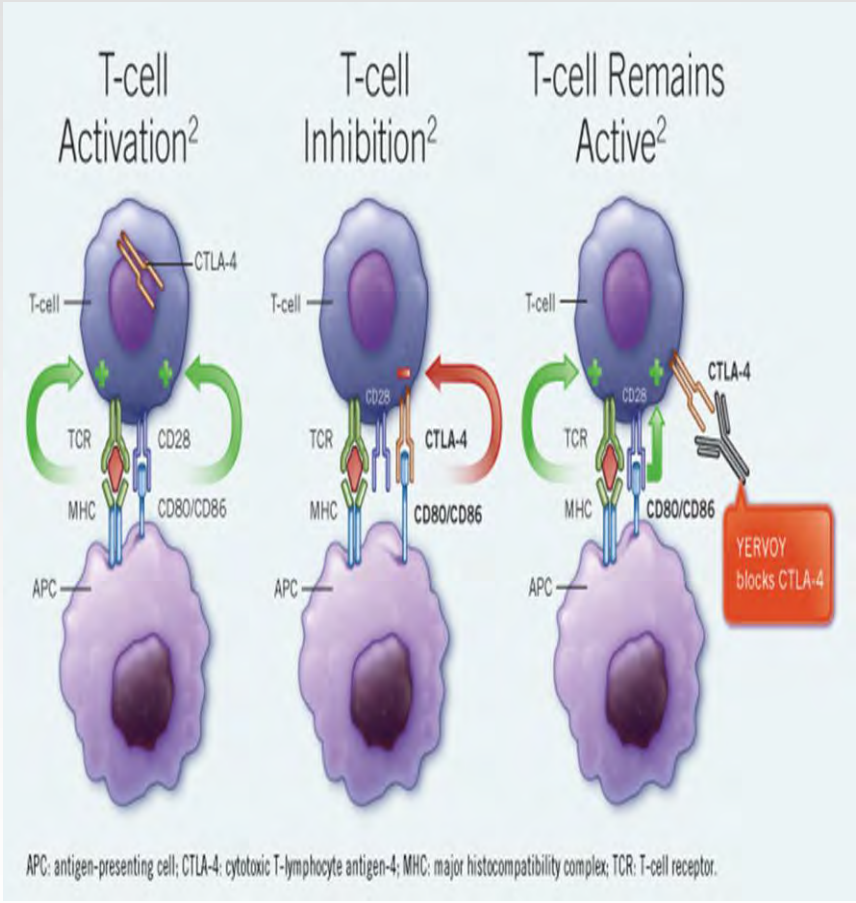
A Comprehensive Cancer Center Designated by the National Cancer Institute

Immune Checkpoint Inhibitor Ipilumimab (Yervoy): Blocks CTLA-4

What other mechanisms are there for the activity of CTLA-4 blockade?

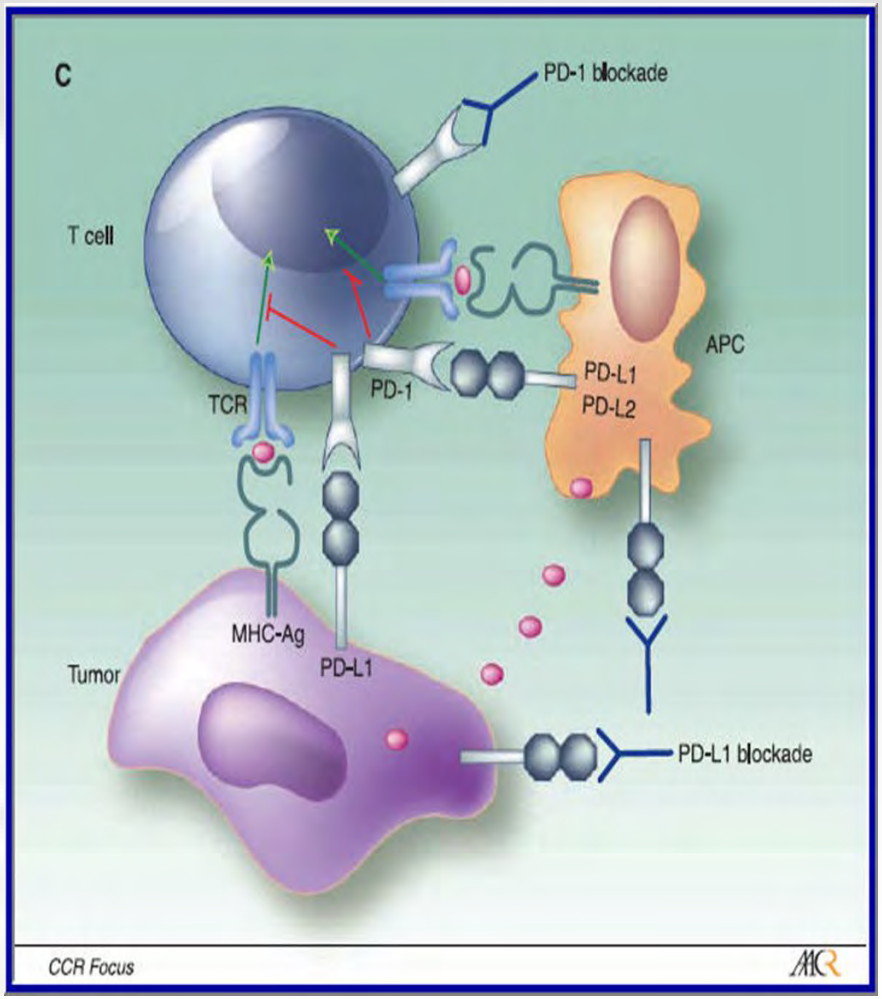
- Ipilimumab is an IgG1 monoclonal antibody
- IgG1 antibodies have ADCC activity
- T regulatory cells express CTLA-4
- Intratumoral depletion of T regulatory cells increases the ratio of Teff to T regulatory cells with enhanced tumor control



Immune Checkpoint Inhibitors
Anti-PD1 & Anti-PDL1

PD-1/PD-L1

- PD-1 inhibits downstream T cell signaling
  - Decreased cytokine production, IL-2 and IFN-γ
  - Decreased Bcl-2
- PD-1 is upregulated on both activated and exhausted T cells
- PD-1 signals through interaction with PD-L1 or PD-L2



Spectrum of PD-1/PD-L1 Antagonist Activity

Active

- Melanoma
- Renal cancer (clear cell and non-clear cell)
- NSCLC – adenocarcinoma and squamous cell
- Small cell lung cancer
- Head and neck cancer
- Gastric and GE junction
- **Mismatch repair deficient tumors**
- Bladder
- Triple negative breast cancer
- Ovarian
- Hepatocellular carcinoma
- Mesothelioma
- Nasopharyngeal Cancer
- Cervical
- **Hodgkin Lymphoma**
- Diffuse large B-cell lymphoma
- Follicular lymphoma
- **Merkel Cell**

Minimal to no activity to single agents:

- Prostate cancer
- Microsatellite Stable Colon cancer
- Multiple Myeloma
- Pancreatic Cancer

Major PD-1/PD-L1 antagonists

- Nivolumab (anti-PD-1)
- Pembrolizumab (anti-PD-1)
- Atezolizumab (MPDL3280A, anti-PD-L1)
- Durvalumab (MEDI-4736, anti-PD-L1)
- Avelumab
- Other PD-1 efforts ongoing from:
  - CureTech/Medivation (CT-011)
  - Sanofi/Regeneron (REGN2810)
  - Novartis (PDR001)
  - Aurigene/Pierre Fabre (AUNP-12)

FDA approval of antibodies targeting immune checkpoints

- 2011 Ipilimumab (BMS) - Melanoma
- 2014 Pembrolizimab (Merck) – Melanoma
- 2014 Nivolumab (BMS) – Melanoma
- 2015 Nivolumab (BMS) – Lung
- 2015 Ipilimumab + Nivolumab (BMS) – Melanoma
- 2015 Pembrolizumab (Merck) – Lung
- 2015 Ipilimumab (BMS) – Adjuvant melanoma
- 2015 Nivolumab (BMS) – Renal cell carcinoma

Number of Open Trials with PD1/PDL1 Agents

- Pembrolizumab: 189
- Nivolumab: 124
- Atezolizumab: 50
- Durvalumab: 15
- Avelumab: 13

Source: ClinicalTrials.gov, accessed on January 19, 2016

OUTLINE

1. Review of Immune System
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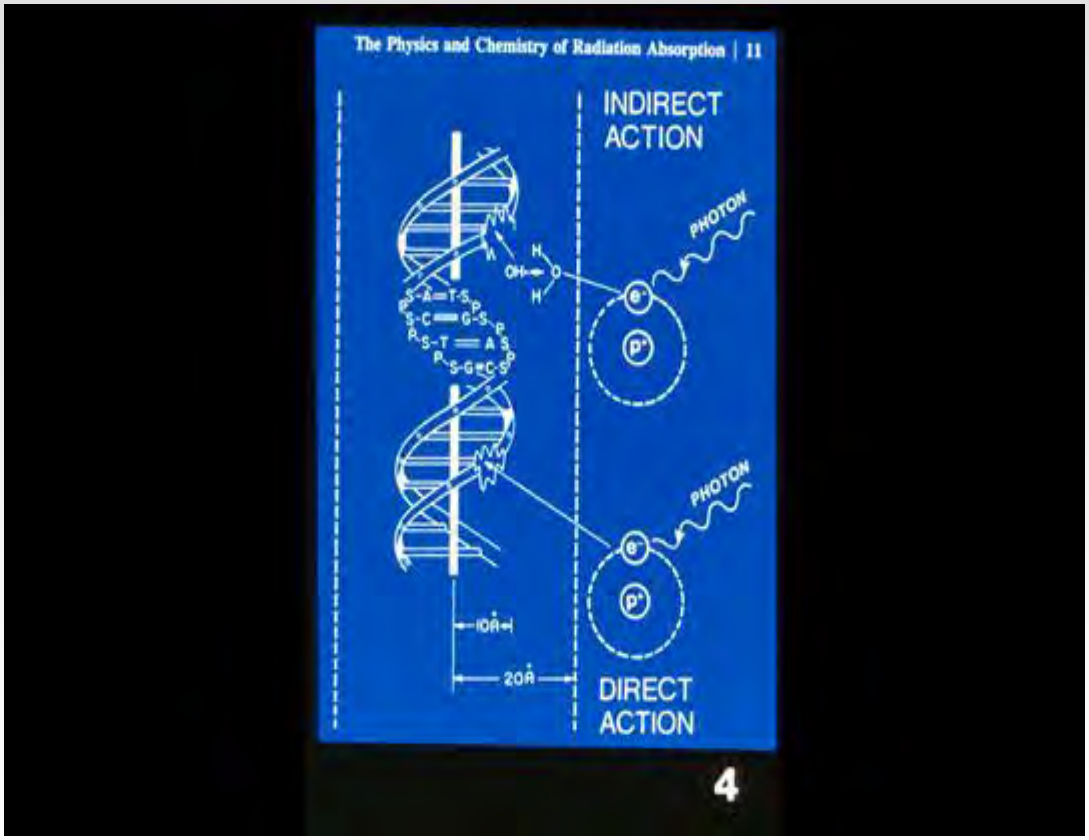
3. **Mechanisms of RT cell death**
4. Combinations of RT & Immunotherapy

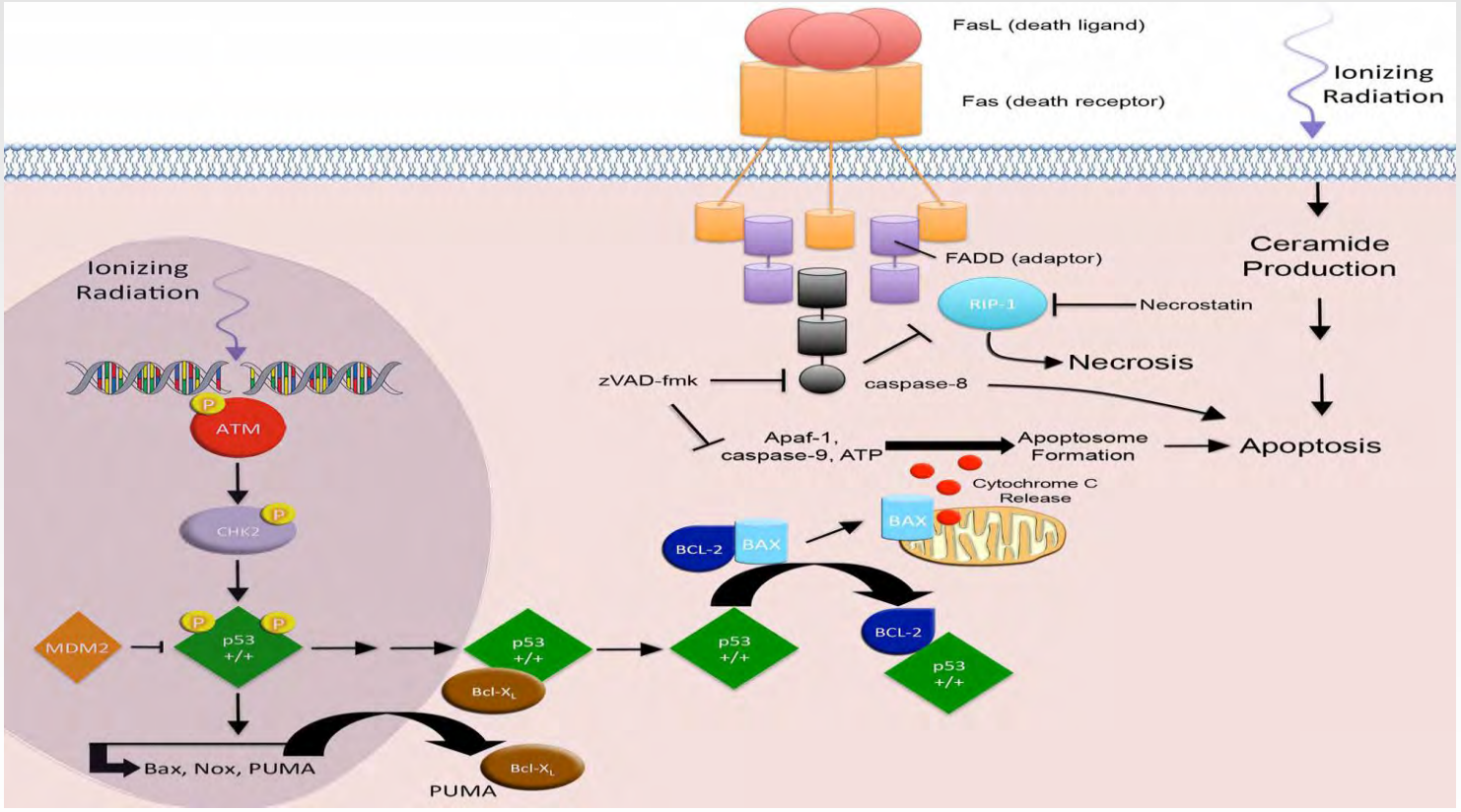
RT Mechanisms of Cell Death 1990



Eric Hall, Ph.D.

RT Mechanisms of Cell Death 2016

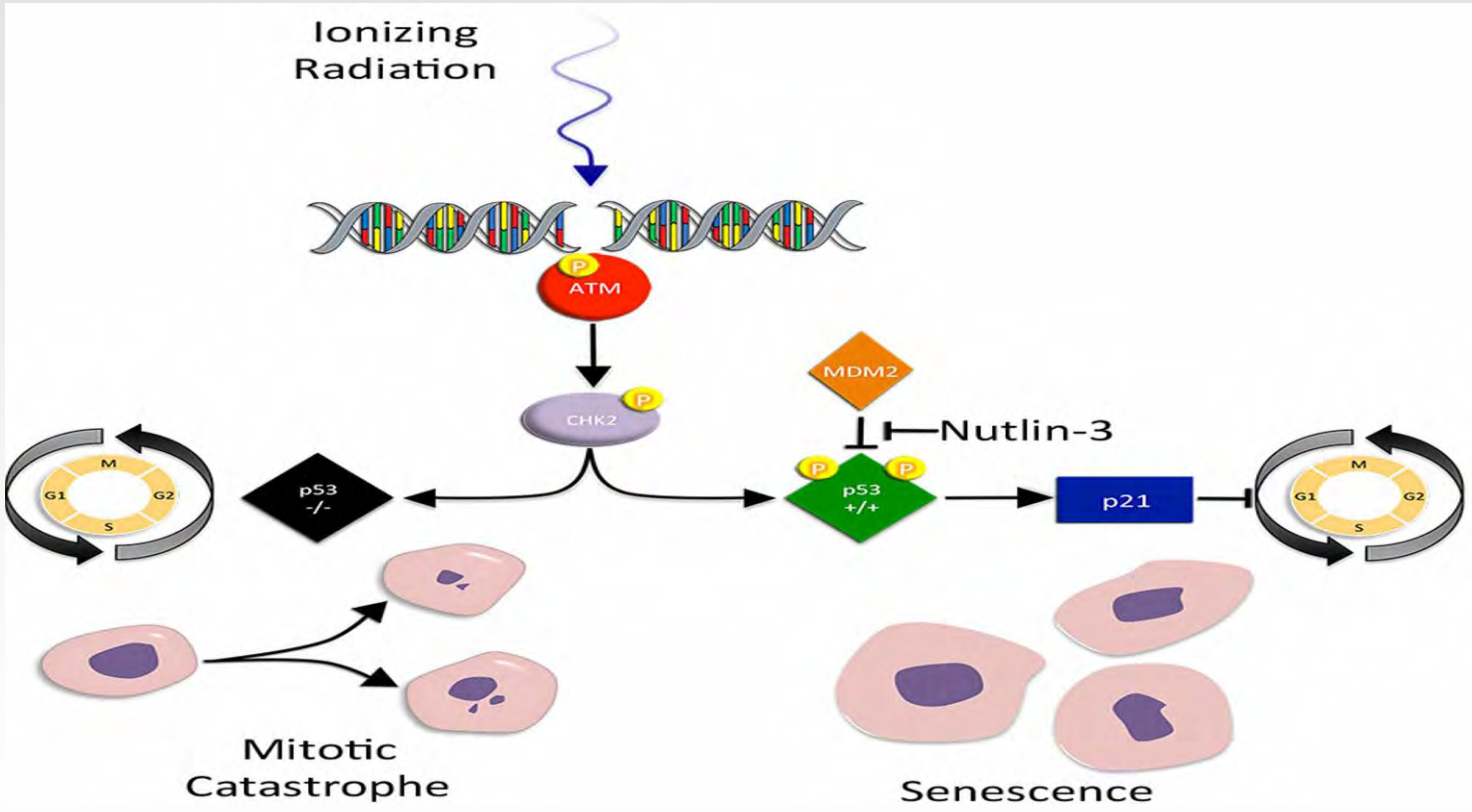
Apoptosis ; Necrosis



Golden E, et al. Frontiers in Oncology, 2012; 2: 88:1-13

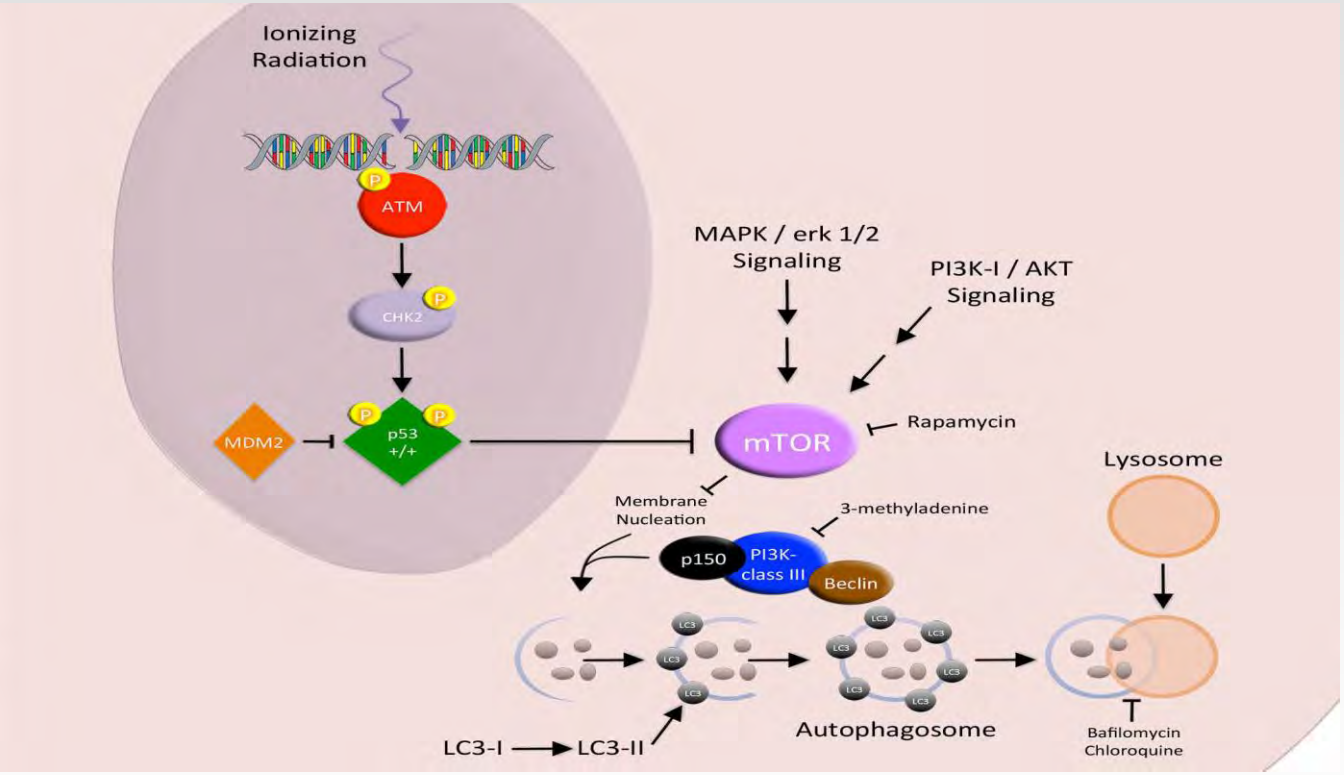
RT Mechanisms of Cell Death 2016

Mitotic Catastrophe; Senescence



Golden E, et al. Frontiers in Oncology, 2012; 2: 88:1-13

RT Mechanisms of Cell Death 2016
Autophagy

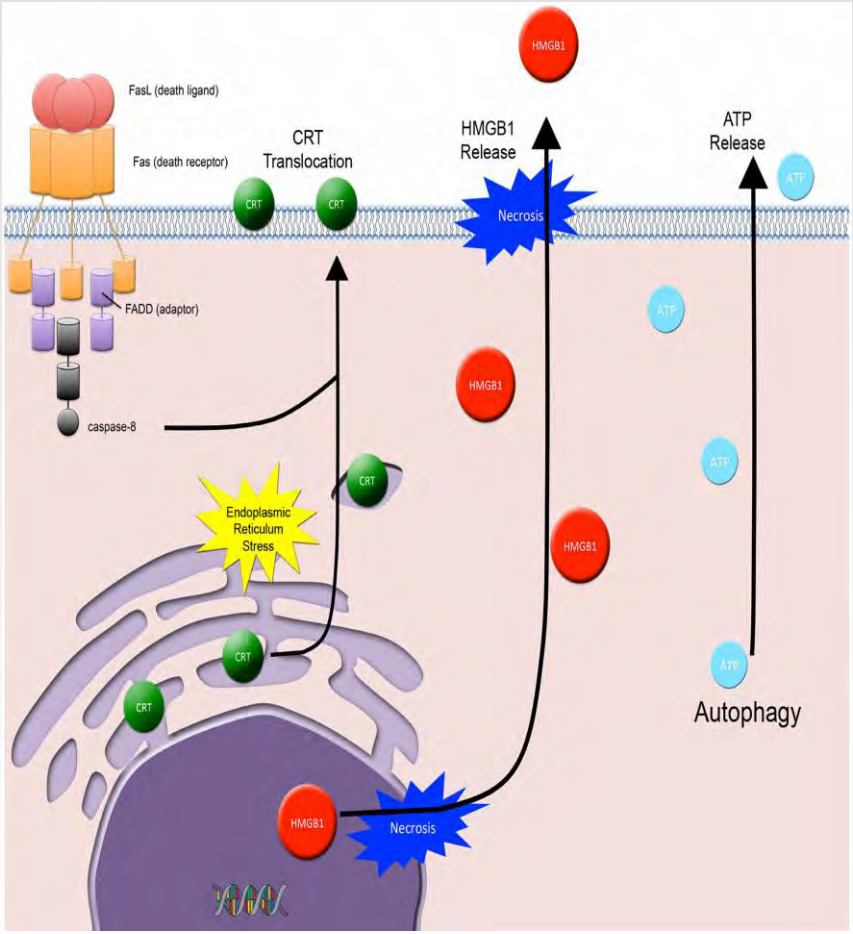


Golden E, et al. Frontiers in Oncology, 2012; 2: 88:1-13

2016 RT Mechanisms of Cell Death
Immunogenic Cell Death

Required Molecular Signals

1. Cell surface translocation of Calreticulin (endoplasmic reticulum resident protein)
2. Extracellular release of High Mobility group protein B1 (HMGB1)
3. Release of ATP



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OUTLINE

1. Review of Immune System
2. Mechanisms of Check Point Inhibitors
3. Mechanisms of RT cell death
4. **Combinations of RT & Immunotherapy**

Immunotherapy and Radiotherapy

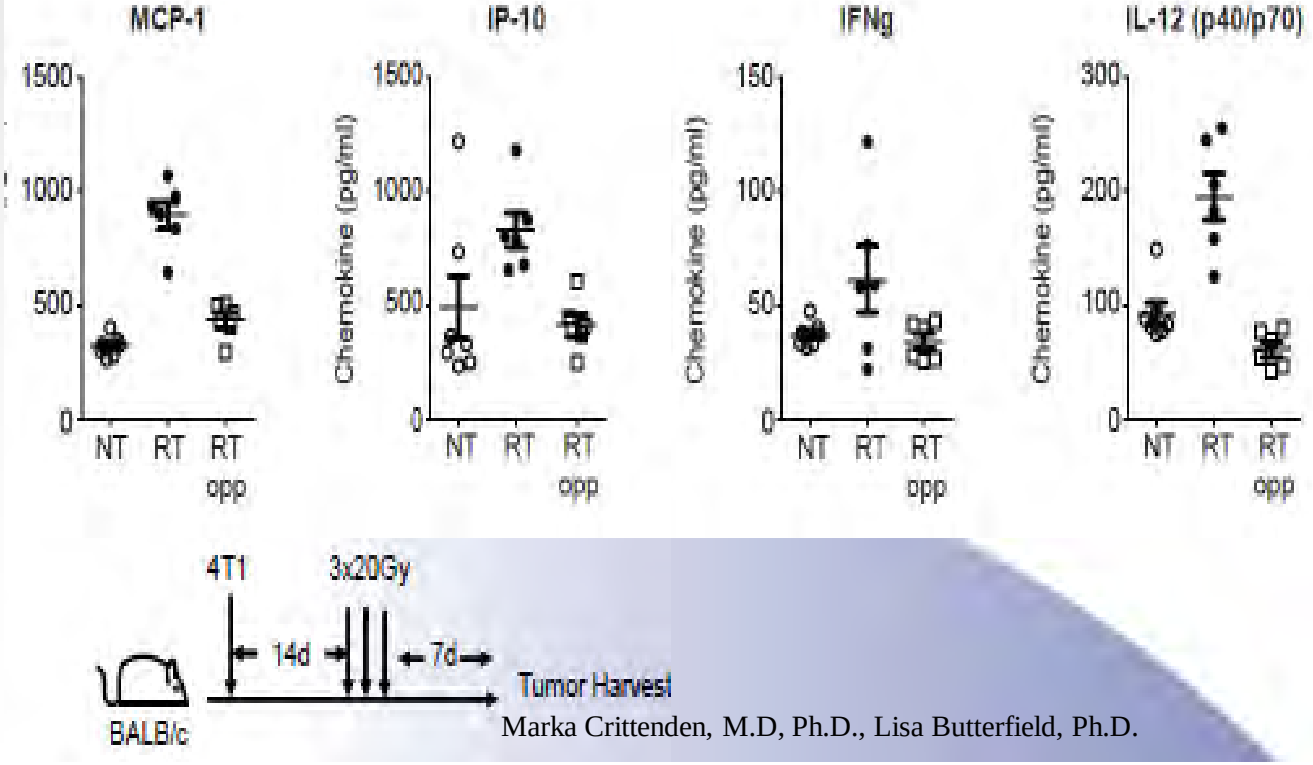
Mechanisms of Synergy

- Synergy 1: The immune system can function to enhance control of irradiated tumors
- Synergy 2: The immune system can function as an *in situ* vaccine or immune modulator and enhance concomitant immunity (abscopal response)

Marka Crittenden, M.D, Ph.D., Lisa Butterfield, Ph.D.

Immunotherapy and Radiotherapy

T cell attracting chemokines in tumors following RT in mouse tumor models



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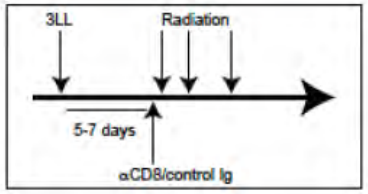
Immunotherapy and Radiation

T cells are important in radiation therapy

i)



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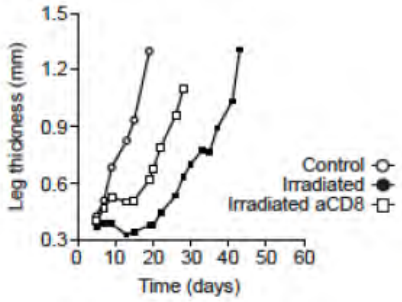
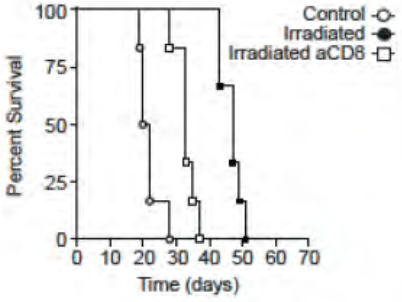


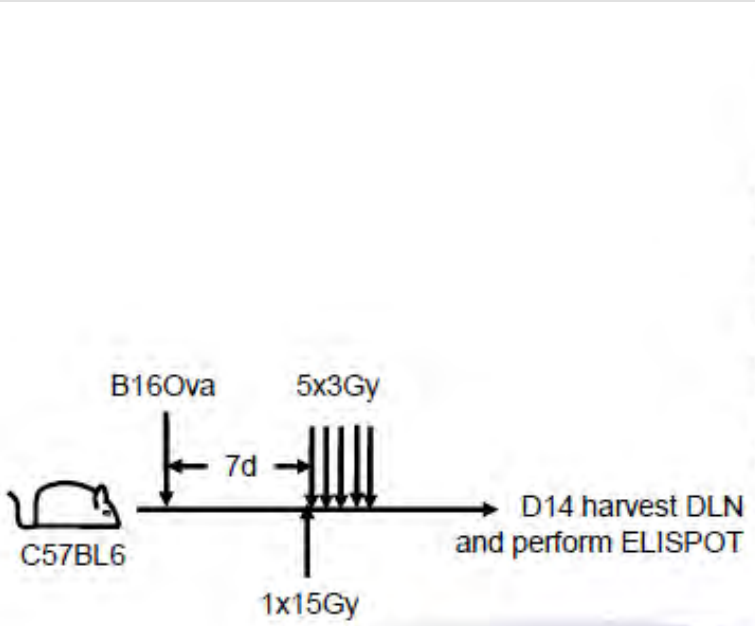
iii)

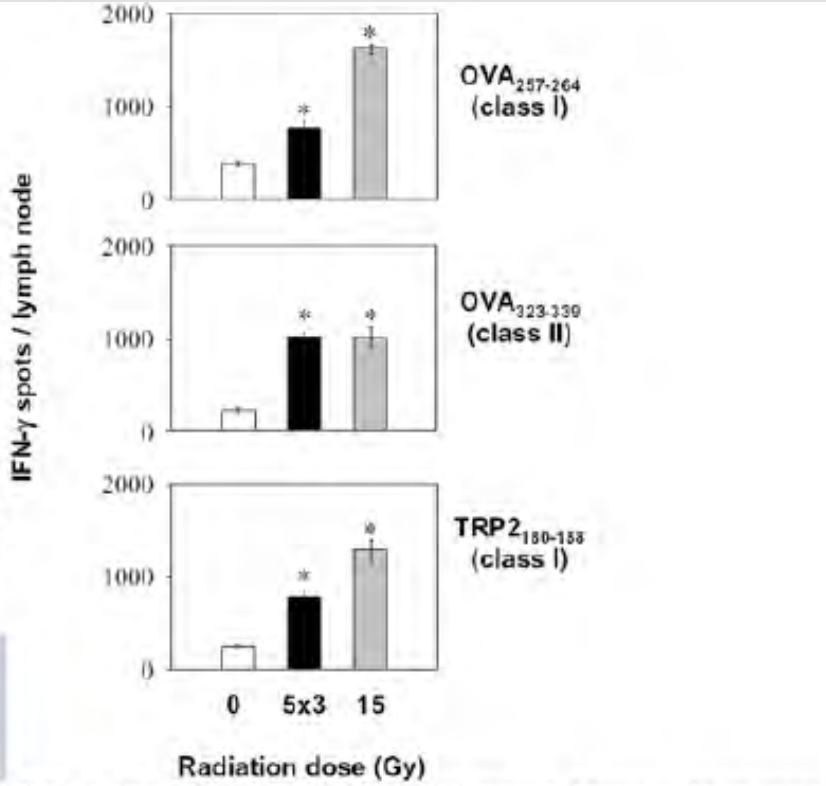


Adjuvant therapy with agonistic antibodies to CD134 (OX40) increases local control following surgical or radiation therapy of cancer in mice

MJ Gough[*,§], MR Crittenden[#,§], M Sarff[†], P Pang[*], SK Seung[*,•], JT Vetto[*,§], HM Hu[*], WL Redmond[*], J Holland[#], and AD Weinberg[*]

Immunotherapy and Radiation Tumor antigen release & enhanced priming in preclinical mouse model

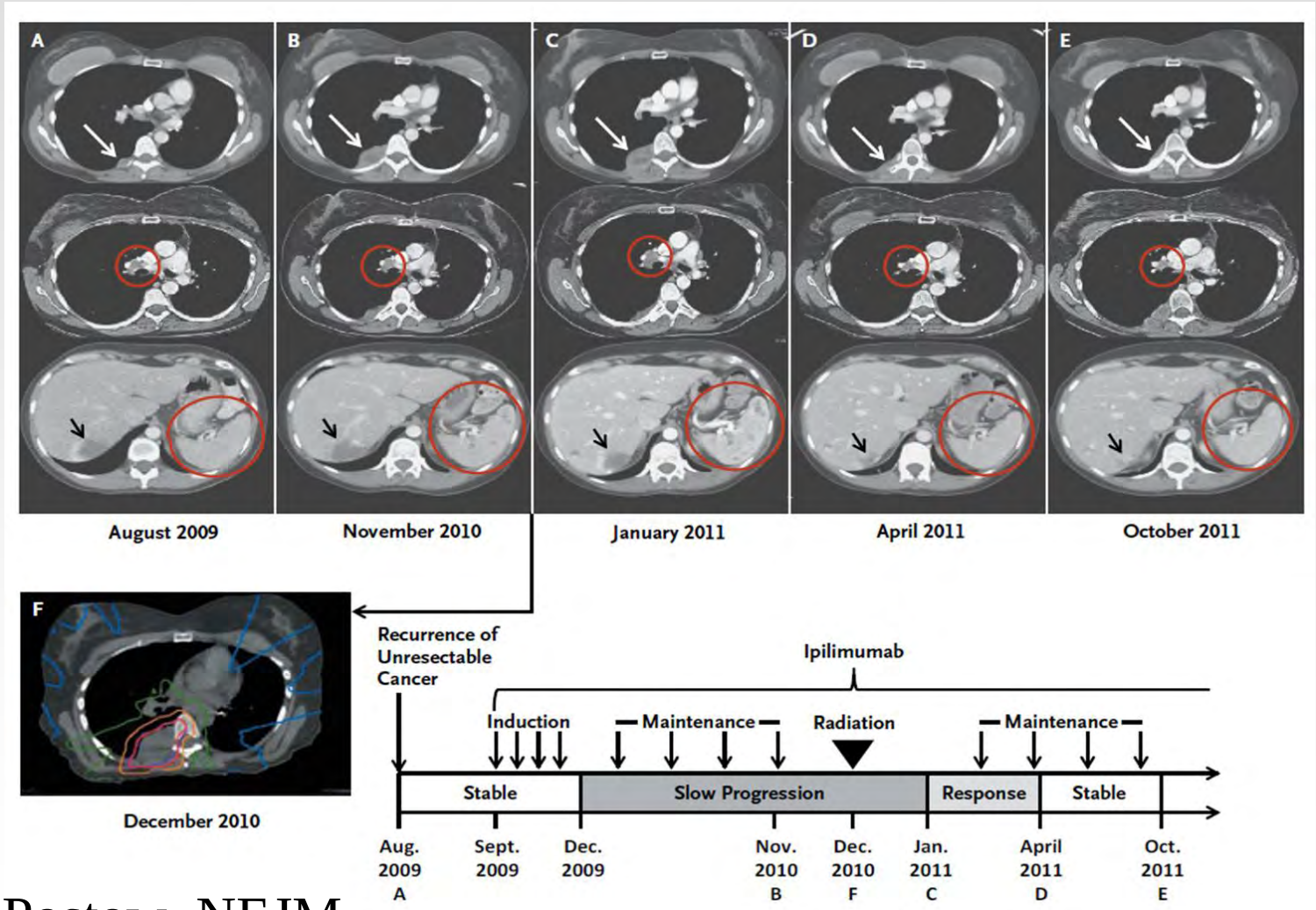




Local Radiation Therapy of B16 Melanoma Tumors Increases the Generation of Tumor Antigen-Specific Effector Cells That Traffic to the Tumor[1]

Amit A. Lugade,[2] James P. Moran,[2] Scott A. Gerber, Robert C. Rose, John G. Frelinger, and Edith M. Lord[3]

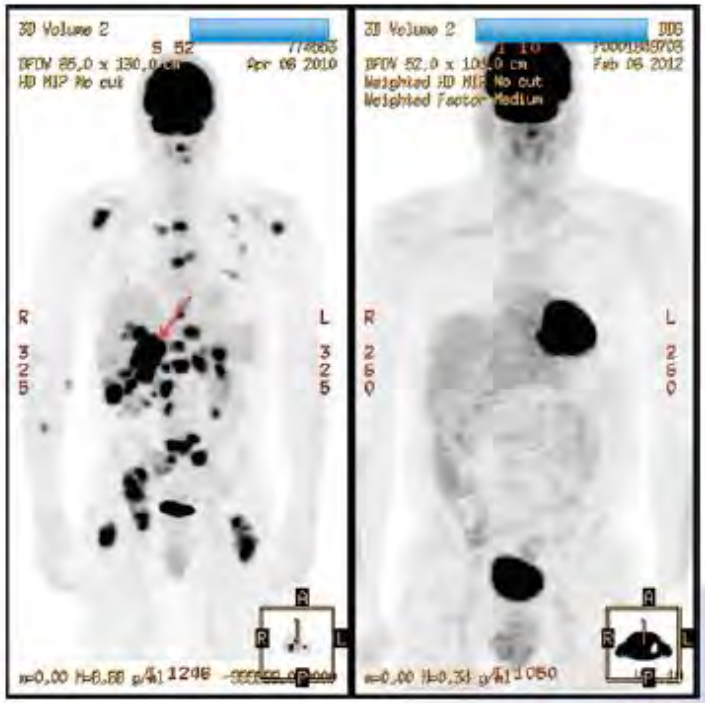
Clinical Case Reports Immunotherapy +RT

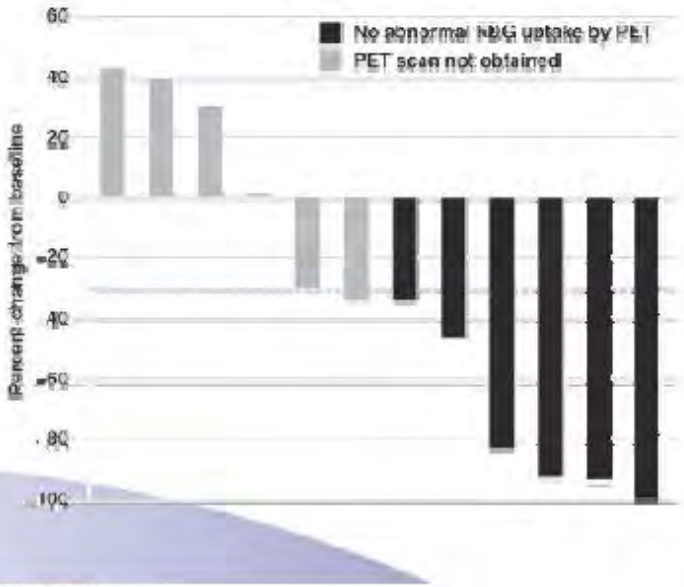


Postow NEJM 2012; 9.5 Gy x 3

Clinical Case 2

Radiation and high dose IL-2





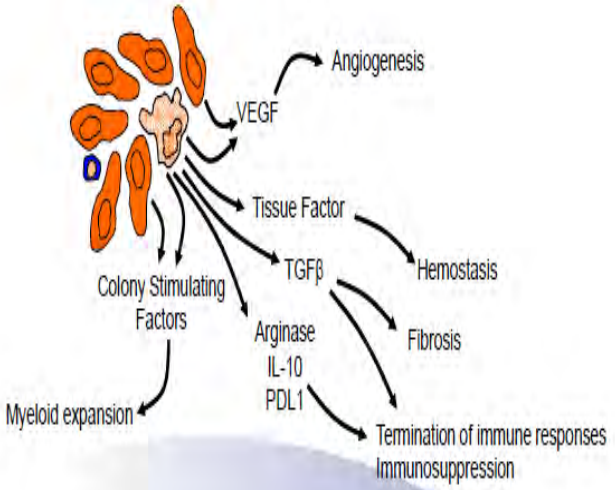
TUMOR RADIOTHERAPY

Phase 1 Study of Stereotactic Body Radiotherapy and Interleukin-2: Tumor and Immunological Responses

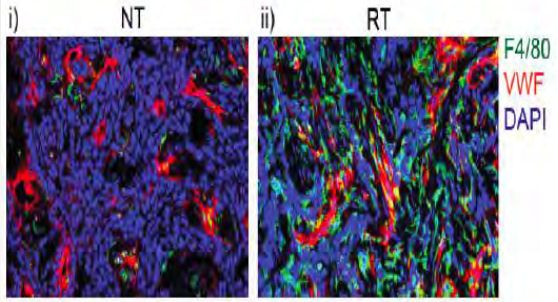
Steven K. Seung,[1,2*] Brendan D. Curti,[1,3*†] Marka Crittenden,[1,2] Edwin Walker,[1] Todd Coffey,[3] Janet C. Siebert,[4] William Miller,[1] Roxanne Payne,[3] Lyn Glenn,[3] Alexandru Bageac,[5] Walter J. Urba[1,3]

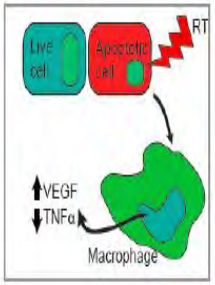
Immunotherapy and Radiation Challenge of Tumor Environment & Myeloid Response to Radiation

M2 macrophages in the tumor



Macrophage influx following radiation

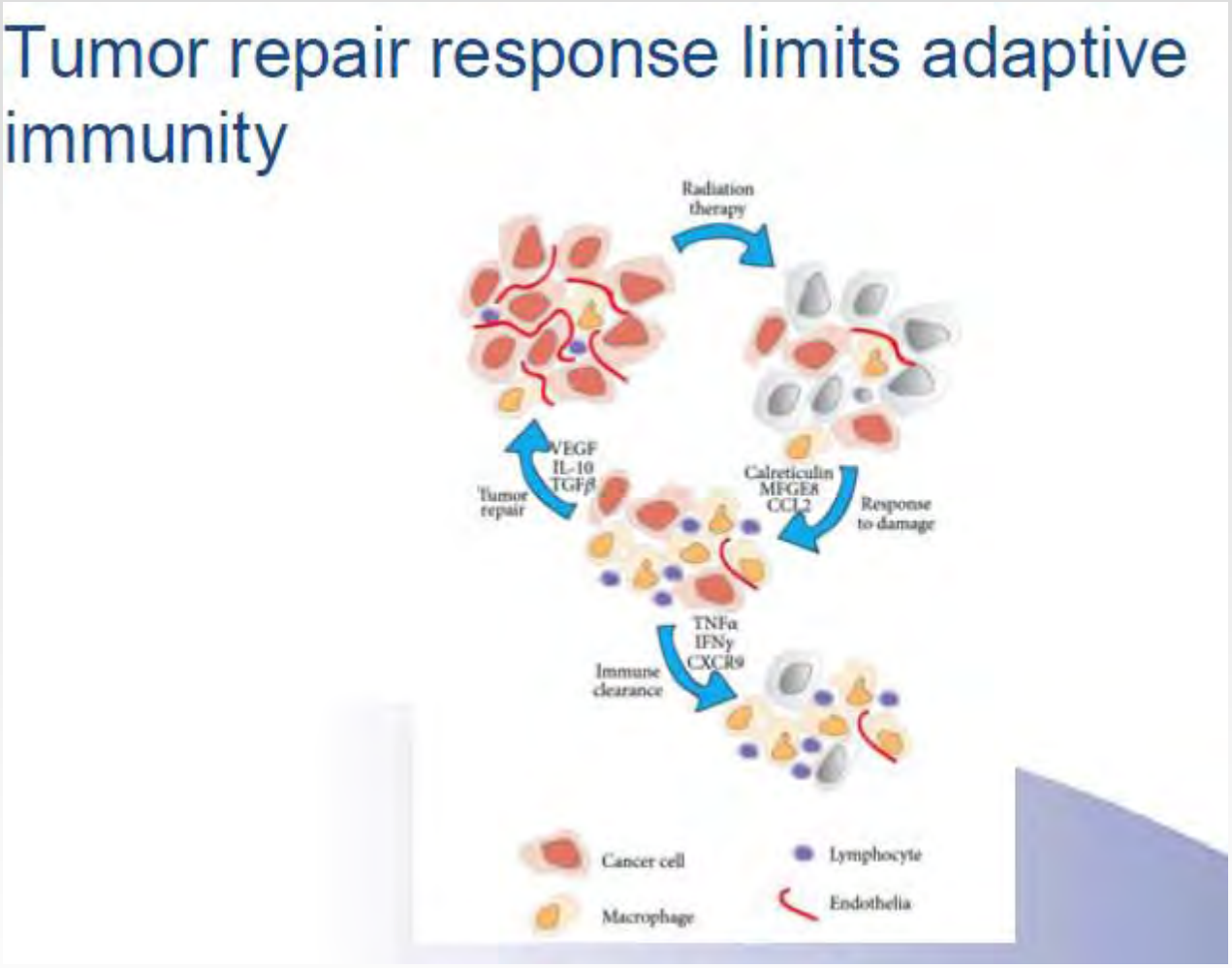




Macrophages Orchestrate the Immune Response to Tumor Cell Death[1]

Michael J. Gough, Alan A. Melcher, Atique Ahmed, Marka R. Crittenden, David S. Riddle, Emmanouela Linardakis, Anja N. Ruchatz, Lisa M. Emilfusen, and Richard G. Vile[2]

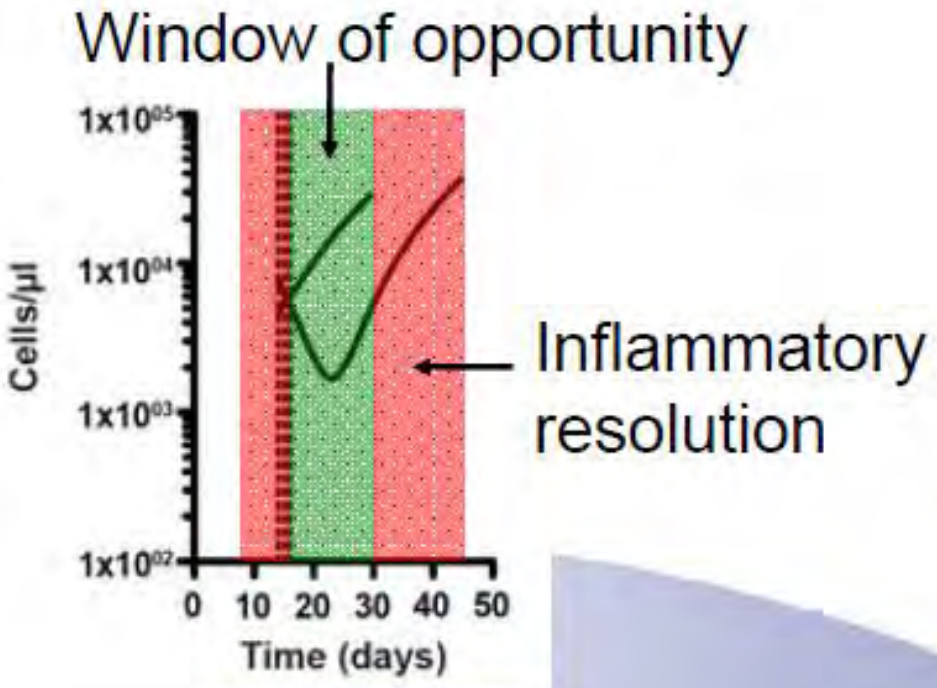
Tumor repair response limits adaptive immunity



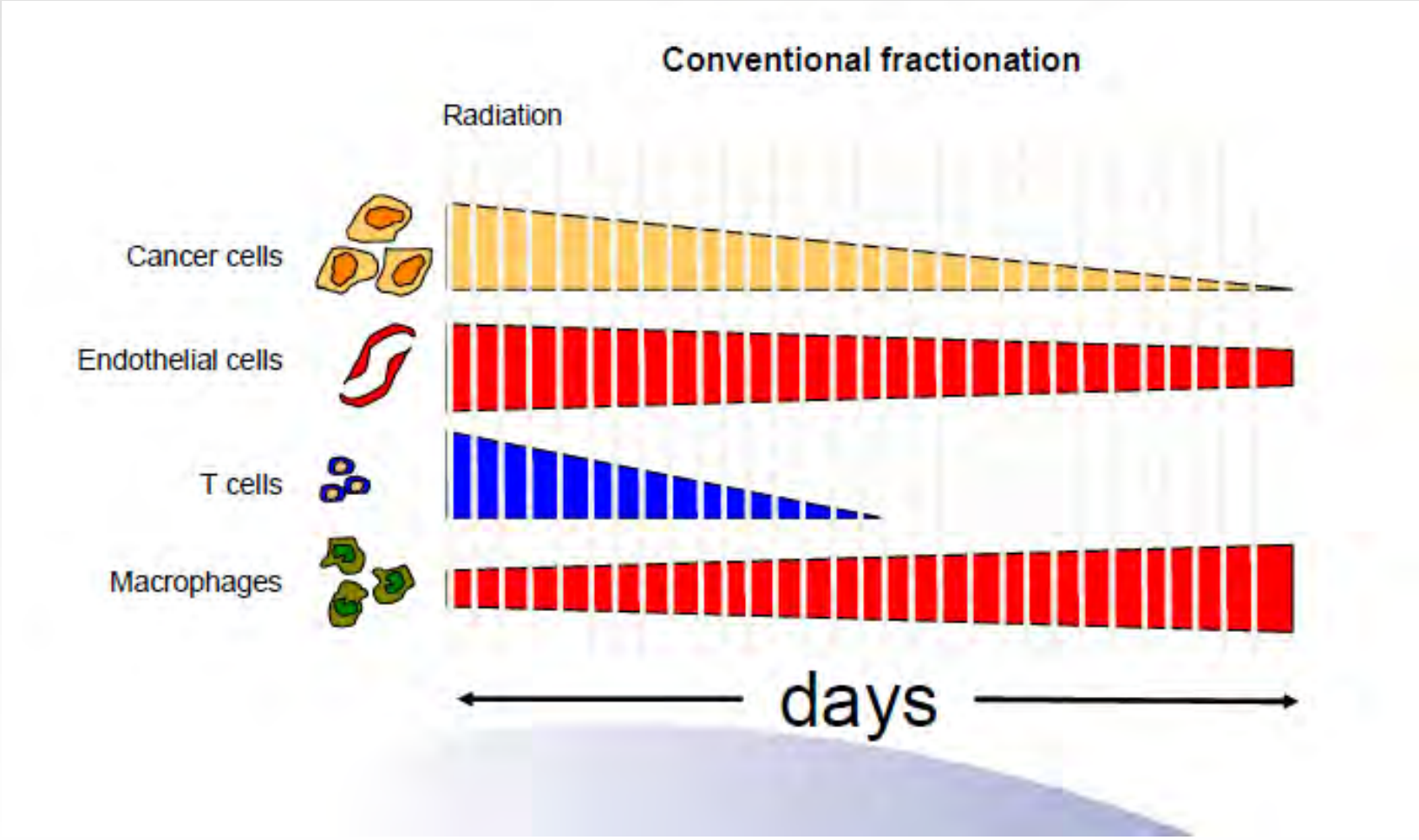
Marka Crittenden, M.D, Ph.D., Lisa Butterfield, Ph.D

Immunotherapy and Radiation

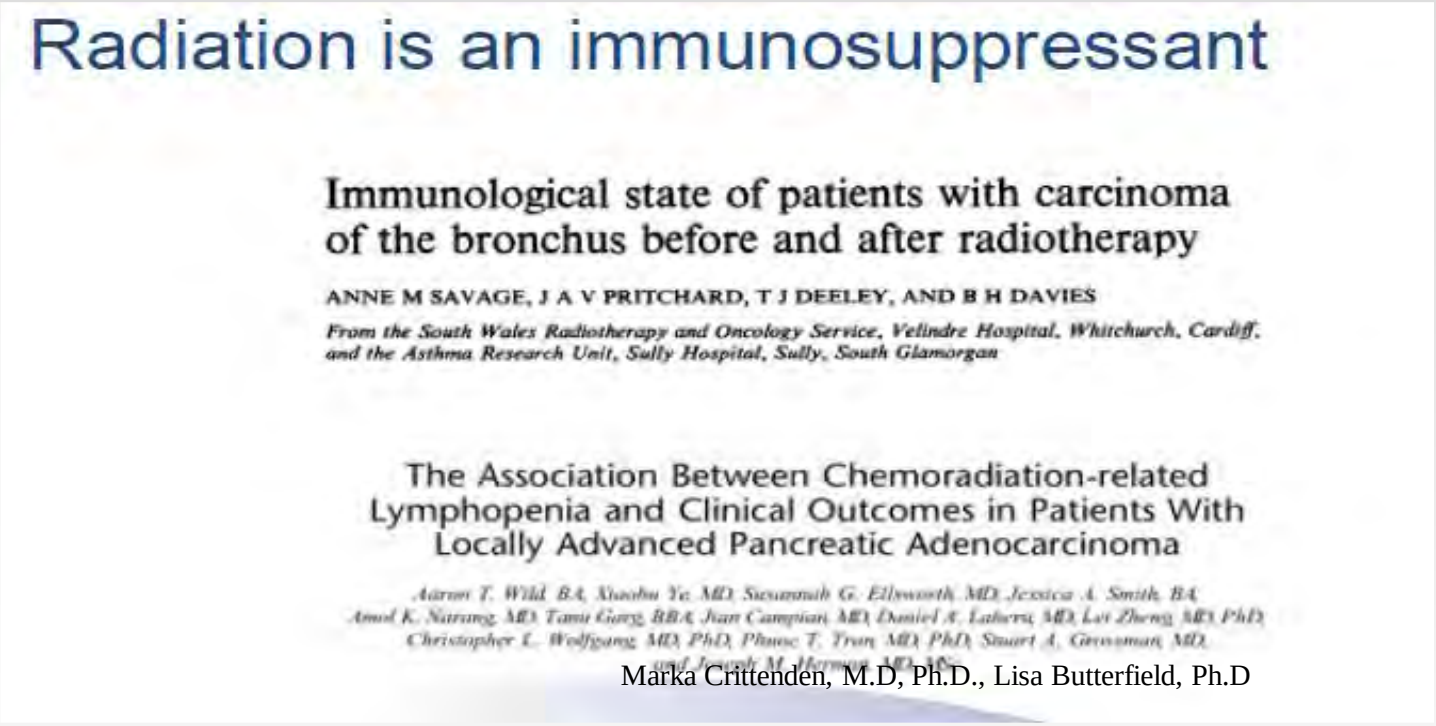
Immunotherapeutic window post-RT



Immunotherapy and Radiation



Radiation is an immunosuppressant



Immunological state of patients with carcinoma of the bronchus before and after radiotherapy

ANNE M SAVAGE, J A V PRITCHARD, T J DEELEY, AND B H DAVIES

From the South Wales Radiotherapy and Oncology Service, Velindre Hospital, Whitchurch, Cardiff, and the Asthma Research Unit, Sully Hospital, Sully, South Glamorgan

The Association Between Chemoradiation-related Lymphopenia and Clinical Outcomes in Patients With Locally Advanced Pancreatic Adenocarcinoma

Aaron T. Wild, BA, Xiaobu Ye, MD, Susannah G. Ellsworth, MD, Jessica A. Smith, BA, Amol K. Narang, MD, Tami Garg, BBA, Juan Campian, MD, Daniel A. Laheru, MD, Lei Zheng, MD, PhD, Christopher L. Wolfgang, MD, PhD, Phuoc T. Tran, MD, PhD, Stuart A. Grossman, MD, and Joseph M. Herman, MD, MSc

Marka Crittenden, M.D, Ph.D., Lisa Butterfield, Ph.D

Increased Post-Treatment Neutrophil-to-Lymphocyte Ratios is an Independent Prognostic Marker for Worse Overall Survival in Patients Receiving Concurrent Chemoradiation for Lung Cancer

Jose G. Bazan, Christian L. Barney, Nicholas Scoville, Karl E. Haglund, John Grecula, Meng X. Welliver, Terence Williams

Accepted for ASTRO 2016

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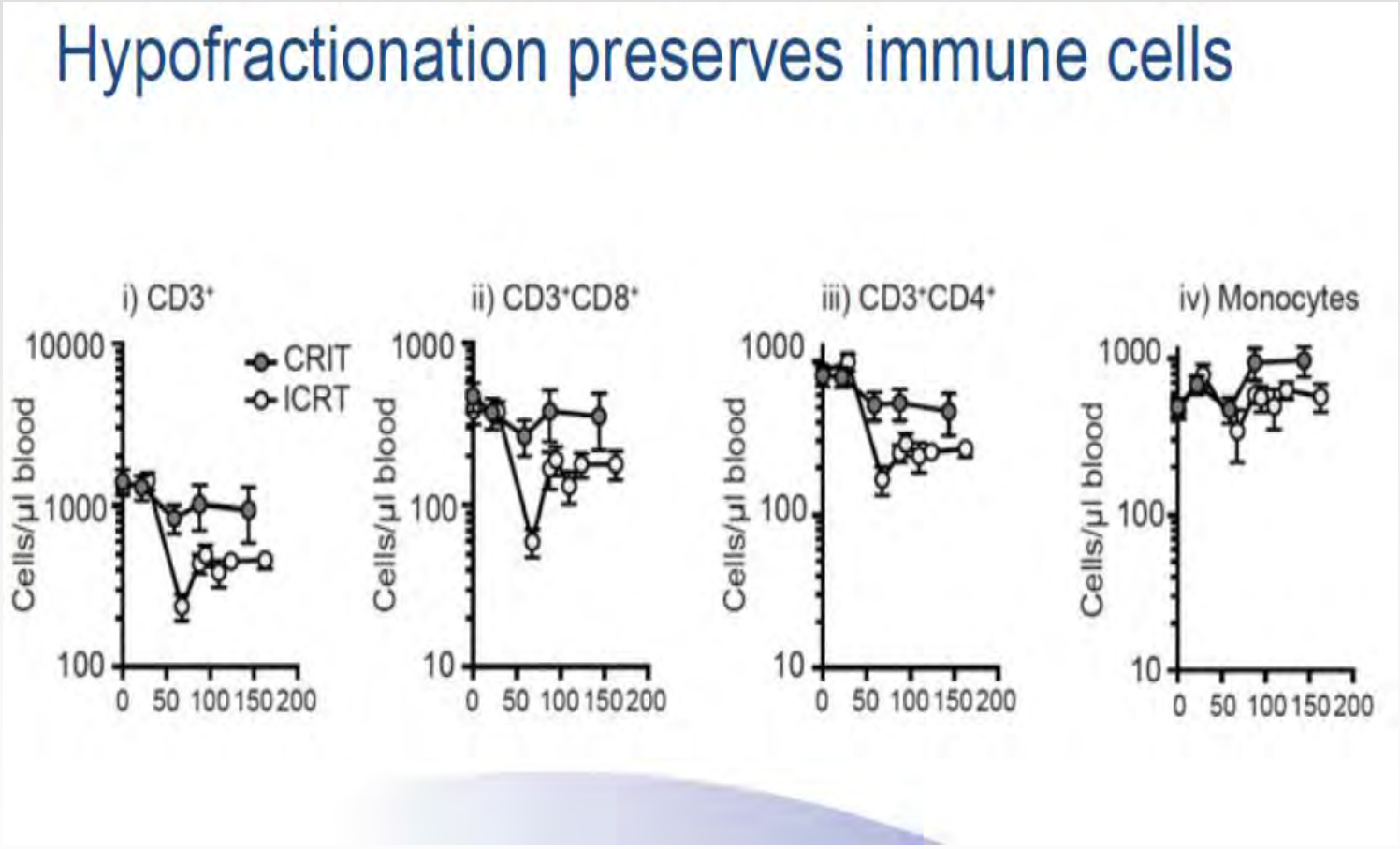
Immunotherapy and Radiotherapy



Marka Crittenden, M.D, Ph.D., Lisa Butterfield, Ph.D.

Immunotherapy and Radiotherapy

Preservation of immune cells with hypofractionation

- Neoadjuvant chemoradiation incorporating conventionally fractionated radiation results in prolonged systemic lymphopenia
- Hypofractionation preserves systemic immune cells so may be a better partner for immunotherapy
- Mice don't model this phenomenon, even when accounting for differences in thymic output

Immunotherapy and Radiation

Outstanding Questions

- What radiation dose and fractionation is best to combined with immunotherapy?
- What is the optimal sequencing and timing of radiation and immunotherapy?
- How do we best address the immune suppression that is associated with radiation?

THANK YOU !

INCLUDING INTRAOPERATIVE RADIOTHERAPY IN THE THERAPEUTIC SCHEME RESULTS IN SIMILAR LOCAL CONTROL IN HIGH AND LOW RISK SARCOMA

E.BOLDO, T.PIQUERES, A.MAYOL, R. LOZOYA, A.BOUCHE, V.MORILLO, J.SANCHEZ, C.FERRER

CONSORCIO HOSPITALARIO PROVINCIAL DE CASTELLON (SPAIN)

INTRODUCTION

Table 1
Prognostic factors in soft tissue sarcoma[a]

Local recurrence	Post metastasis survival	Distant recurrence	Disease-specific survival
Local recurrence at presentation	Size > 10 cm	High grade	High grade
Positive margins		Size > 5 cm	Size > 10 cm
Fibrosarcoma		Size > 10 cm	Deep location
Age > 50		Deep location	Positive margins
		Local recurrence at presentation	Local recurrence at presentation
			Lower extremity site

[a] Adapted from: Pisters P, Leung D, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremity. *J Clin Oncol* 1996;14(5):1679–89.

Brenann MF, International Journal of Surgery, 2013

OBJECTIVE

- TO COMPARE THE LOCAL CONTROL OBTAINED IN HIGH AND LOW RISK SARCOMAS WHEN INTRAOPERATIVE RADIOTHERAPY IS ADDED TO THERAPEUTIC SCHEME (SURGERY WITH OR WHITOUT EXTERNAL RADIOTHERAPY)

PATIENTS AND METHODS

- IOERT DATABASE
- PROTOCOL: DEMOGRAPHICAL AND ONCOLOGICAL DATA.
- ASSOCIATION BETWEEN LOCAL CONTROL AND RISK FACTORS PRESENCE (FISHER´S EXACT TEST AND KAPLAN-MEIER CURVE)
  - HIGH GRADE VS LOW GRADE
  - SIZE >5 CM VS < 5CM
  - DEEP VS SUPERFICIAL LOCATION
  - LOCAL RECURRENCE AT PRESENTATION VS PRIMARY
  - POSITIVE VS NEGATIVE MARGINS
  - AGE >50 VS < 50 YEARS OLD
  - FIBROSARCOMA VS OTHER HISTOLOGY TYPES.

RESULTS

- IORT DATABASE: 114 CASES
- 26 STS
  - EXTREMITY: 17
  - RETROPERITONEAL 4
  - TRUNK: 5
- THERAPEUTIC SCHEME: SURGERY, IORT AND, EXCEPT IN 4 (15%) , EXTERNAL RADIOTHERAPY.

RESULTS

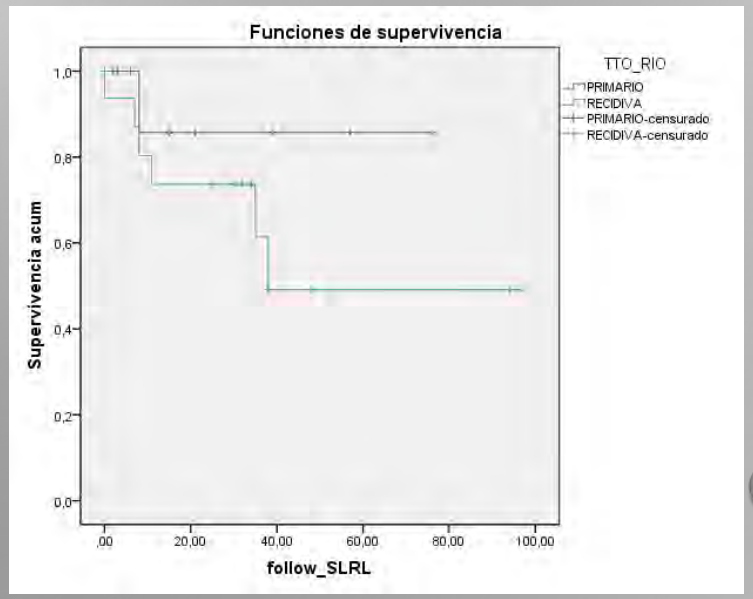
- GRADE
  - HIGH: 8
  - INTERMEDIATE: 5
  - LOW: 13
- SIZE WAS > 5 CM IN 15 CASES (57.6%).
- LOCATION WAS DEEP IN 18 CASES (69.2%).
- LOCAL RECURRENCE AT PRESENTATION WAS PRESENT IN 8 CASES (30%).
- POSITIVE MARGINS WERE FOUND IN 2 CASES (7%).

RESULTS

- PATIENTS WERE >50 YEARS OLD IN 18 CASES (69.2%).
- SARCOMA TYPE:
  - FIBROSARCOMA: 5
  - LIPOSARCOMAS: 8
  - LEIOMIOSARCOMAS: 5
  - SYNOVIAL SARCOMA: 1
  - OTHER : 7
- LOCAL CONTROL: 20 CASES (76.9%) , COULD NOT BE DETERMINED IN 2.

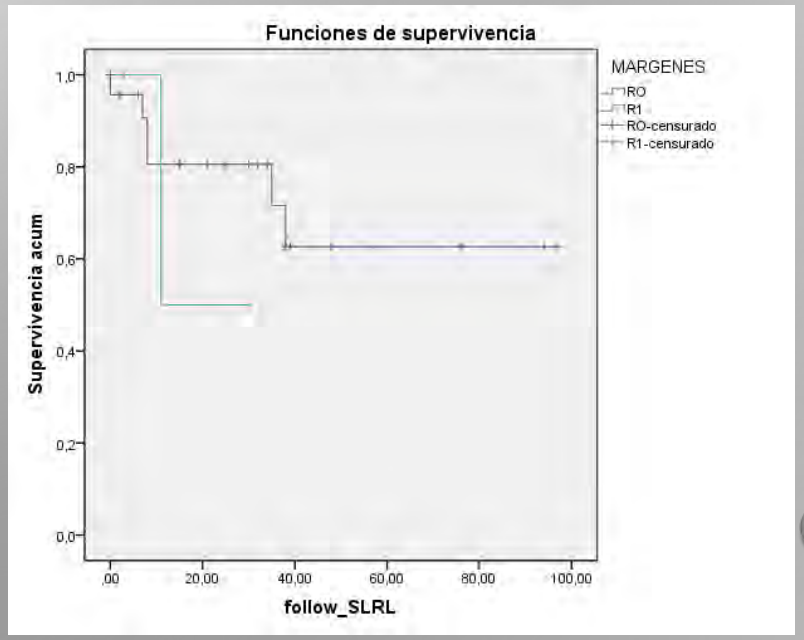
RESULTS-PRIMARY VS RELAPSE

- FET
  - P=0.29
- KMC



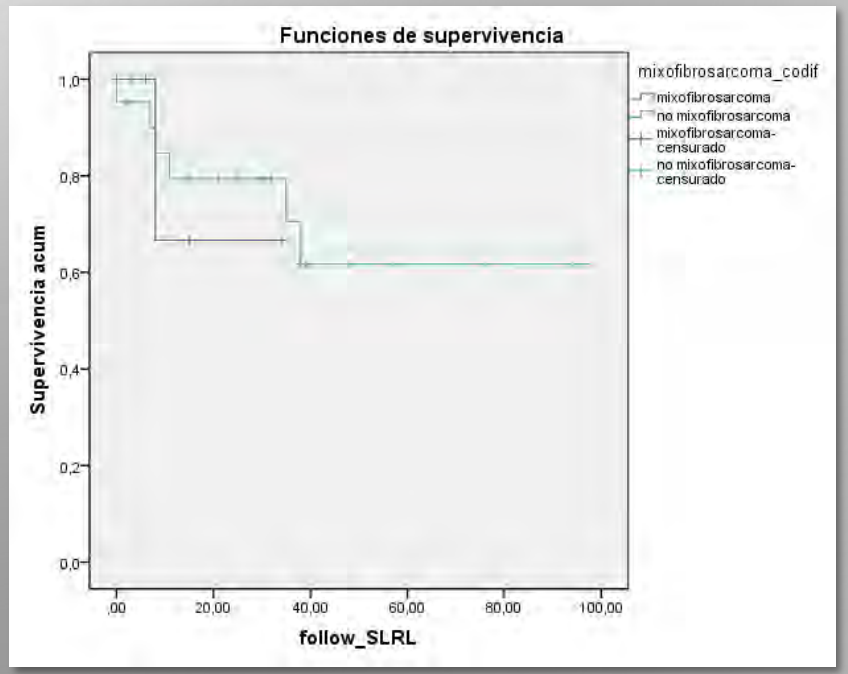
RESULTS- R1 VS R0

- FET
  - P=0.33
- KMC



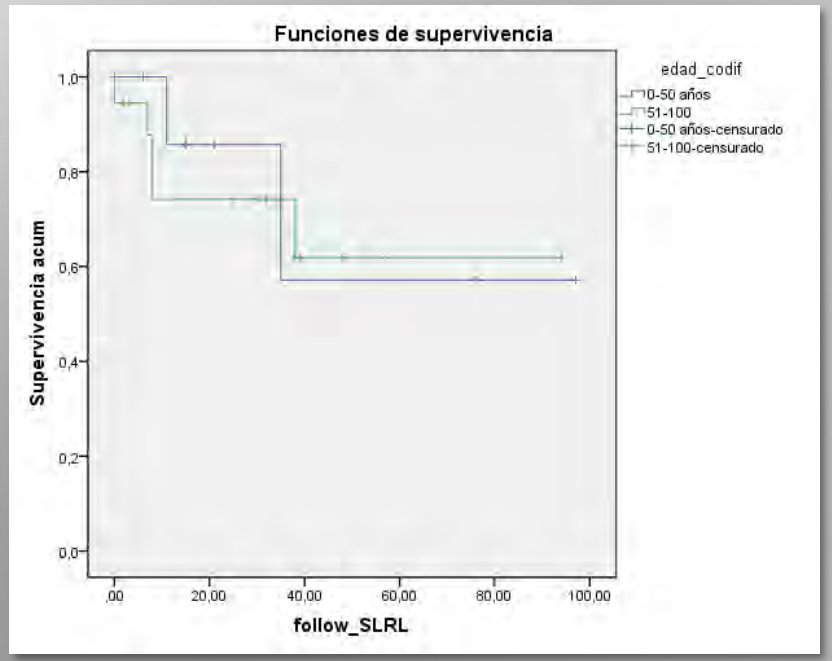
RESULTS FIBROSARCOMA VS OTHER

- FET
  - P=1.0
- KMC



RESULTS AGE > 50 VS < 50

- FET:
  - P=1.0
- KMC

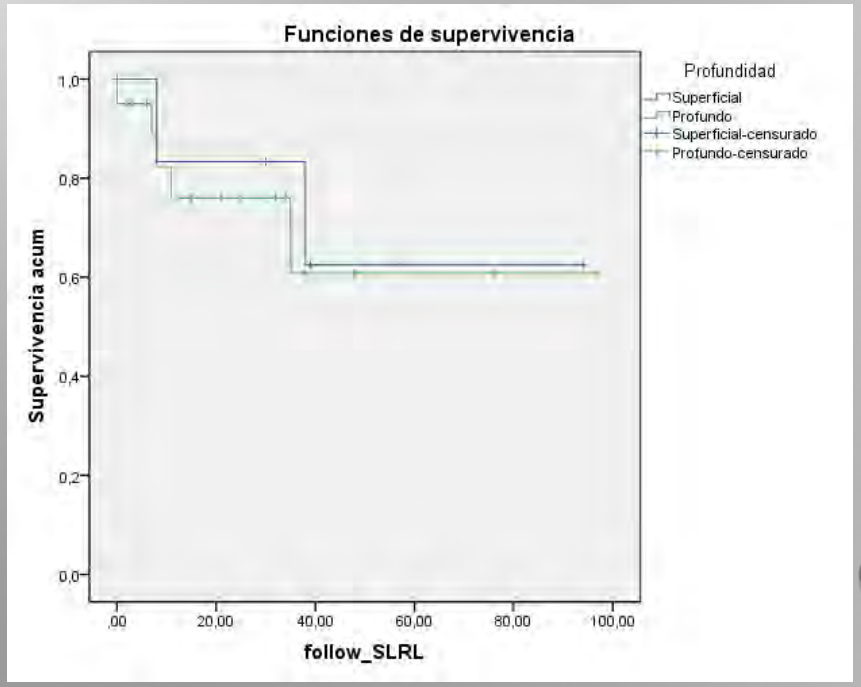


RESULTS-HIGH VS LOW GRADE

- FET:
  - P=0.52
- KMC

RESULTS- DEEP VS SUPERFICIAL

- FET
  - P=0.43
- KMC



RESULTS-SIZE>5 CM VS <5CM

- FET
  - P=0.11
- KMC

CONCLUSION

- IN OUR EARLY EXPERIENCE, WHEN INTEGRATEING IORT IN THE STANDARD THERAPEUTIC SCHEME (SURGERY AND EXTERNAL RADIOTHERAPY), THE PRESENCE OF LOCAL RELAPSE RISK FACTORS SEEMS NOT TO INFLUENCE LOCAL CONTROL ACHIEVEMENT IN STS.

INTRAOPERATIVE RADIOTHERAPY AND VASCULAR RESECTION

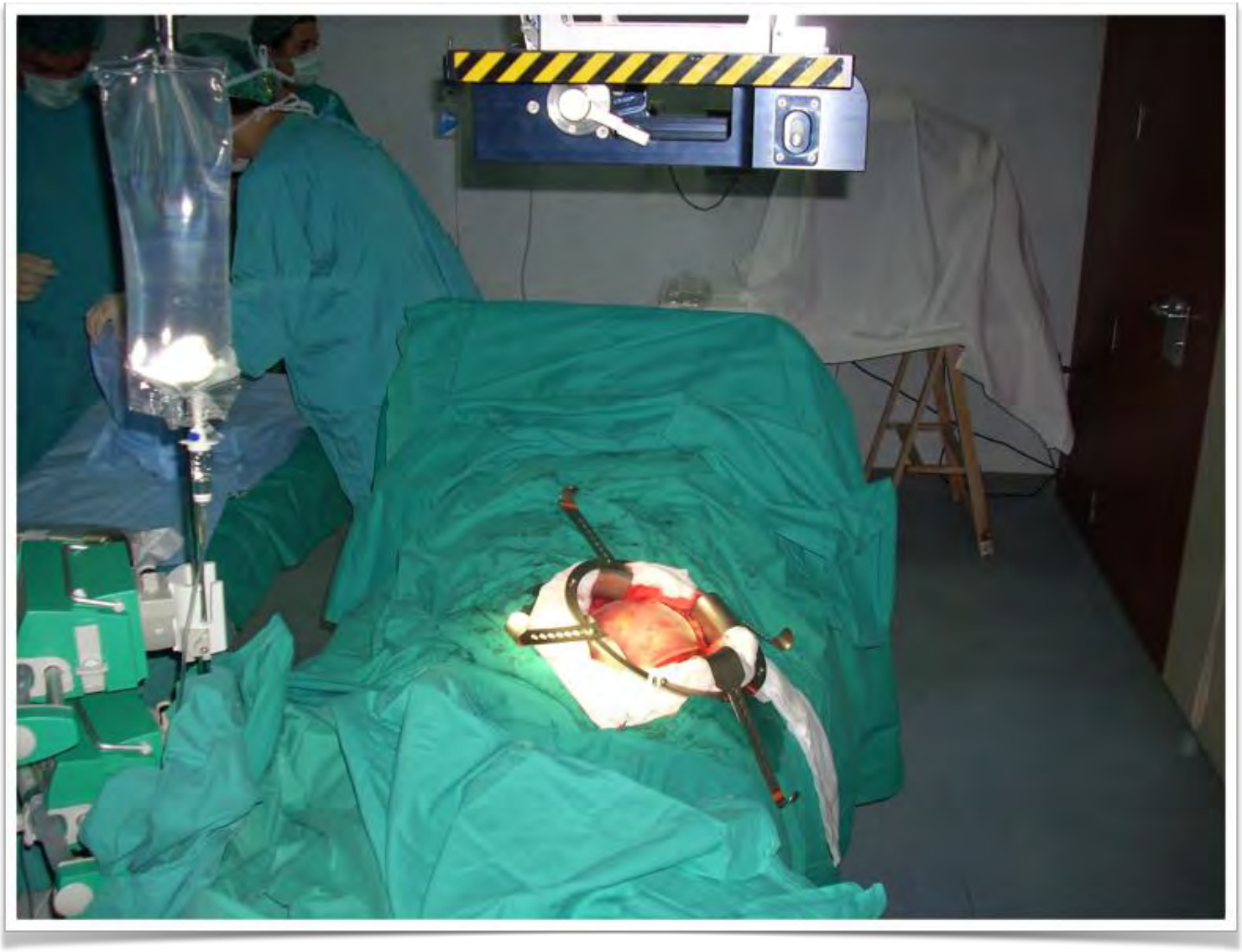
E. Boldo (1) , T. Piquer (2), R. Lozoya (1), A. Mayol (1), J. Molina (3), X. Admeller (3), A. Bouche (2), V. Morillo (2), C. Ferrer (2)
(1) Surgery (2) Radiotherapy (3) Vascular Surgery. Hospital Provincial Castellon. SPAIN

Introduction

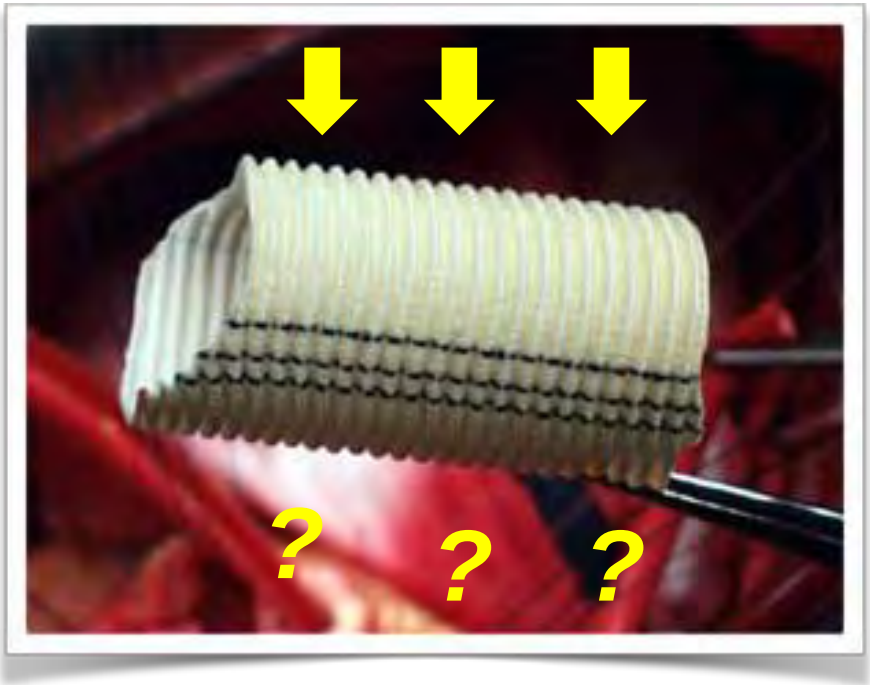
"Intraoperative doses up to 20 Gy appear to contribute minimally to late graft occlusion, while doses > or = 25 Gy contribute to late occlusion with high likelihood. Both intraoperative dose and total radiotherapy dose correlated with late graft occlusion, and with histopathologic changes in the graft and anastomoses"

Johnstone PA, Sprague M, DeLuca AM, Bacher JD, Hampshire VA, Terrill RE, Kinsella TJ, Sindelar WF Effects of intraoperative radiotherapy on vascular grafts in a canine model. Int J Radiat Oncol Biol Phys. 1994 Jul 30;29(5):1015-25

Introduction



Introduction



Introduction

Table III. Vascular interventions

Vascular procedure	Site	Incidence	*n*
Graft		37%	7
	SMA		1
	CIA		2
	SFA		3
	SMV		1
Primary repair		26%	5
	IVC		1
	CIA		1
	CIV		1
	EIA		1
	EIV		1
Ligation/excision		21%	4
	External carotid		1
	Common carotid		2
	Internal iliac		1
Exposure		16%	3
	Aortic bifurcation		3

CIA, common iliac artery; CIV, common iliac vein; EIA, external iliac artery; EIV, external iliac vein; IVC, inferior vena cava; SFA, superficial femoral artery; SMA, superior mesenteric artery; SMV, superior mesenteric vein.

Monnagam et al. Ann Vasc Surg, 2015

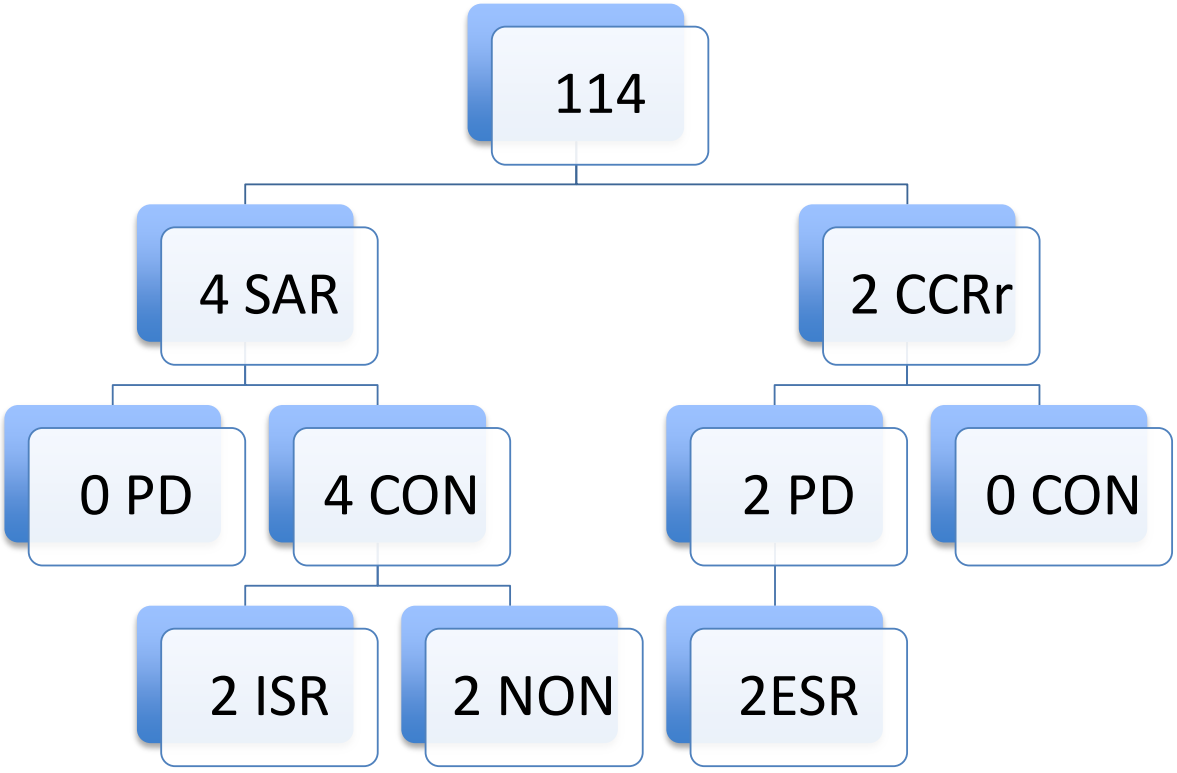
Objective

Report our experience in IORT in tumors requiring vascular resections, specialy in relation with the reconstruction strategies used.

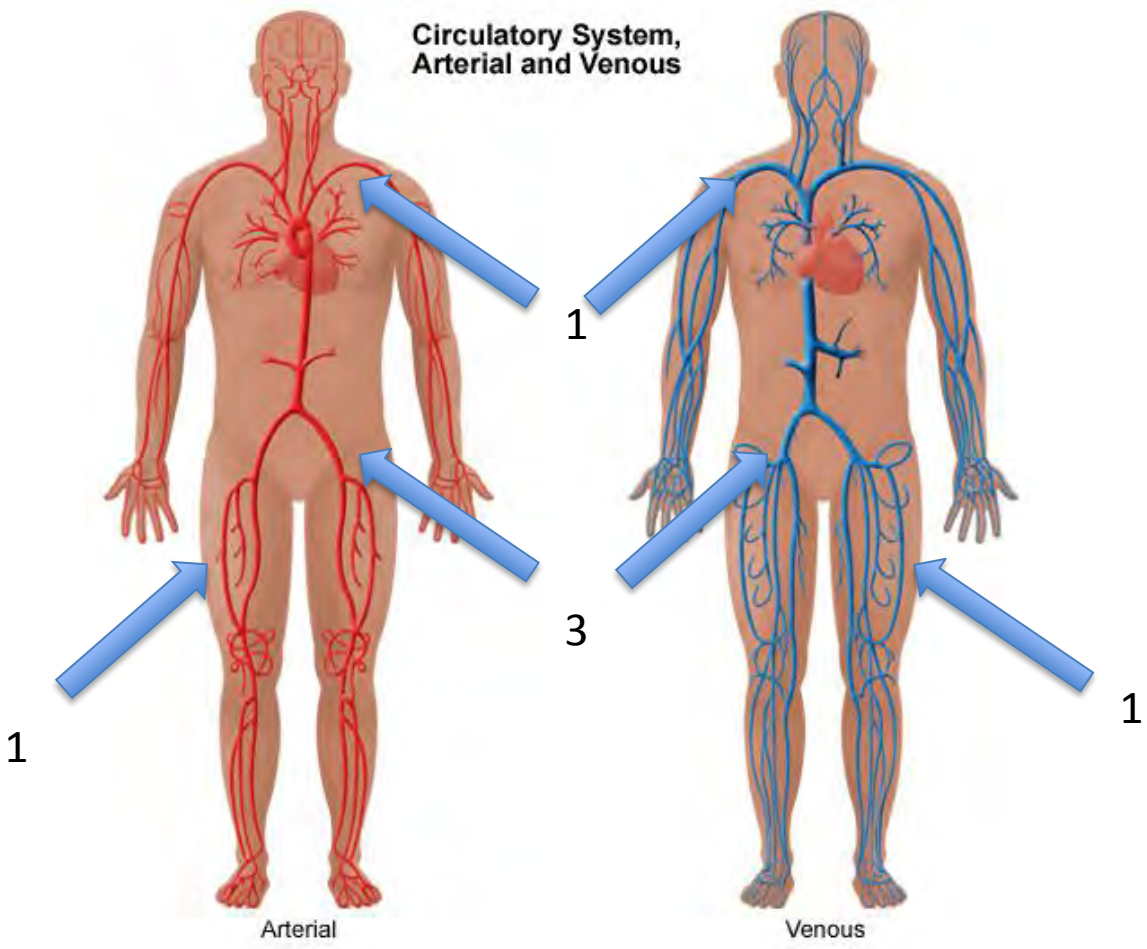
Patients and Methods

- IORT database
- Protocol:
  - Oncological data
  - Vascular data:
    - Type of resection (A/ AV/ V)
    - Location resected vessel/s
    - Timing vascular resection-IORT (PD/CON)
    - Type of vascular reconstruction (in/ex/none)
  - Margins, Dose, Op. time, Infectious complications
- Association Timing/I.Complications: Fisher´s Exact Test

Results

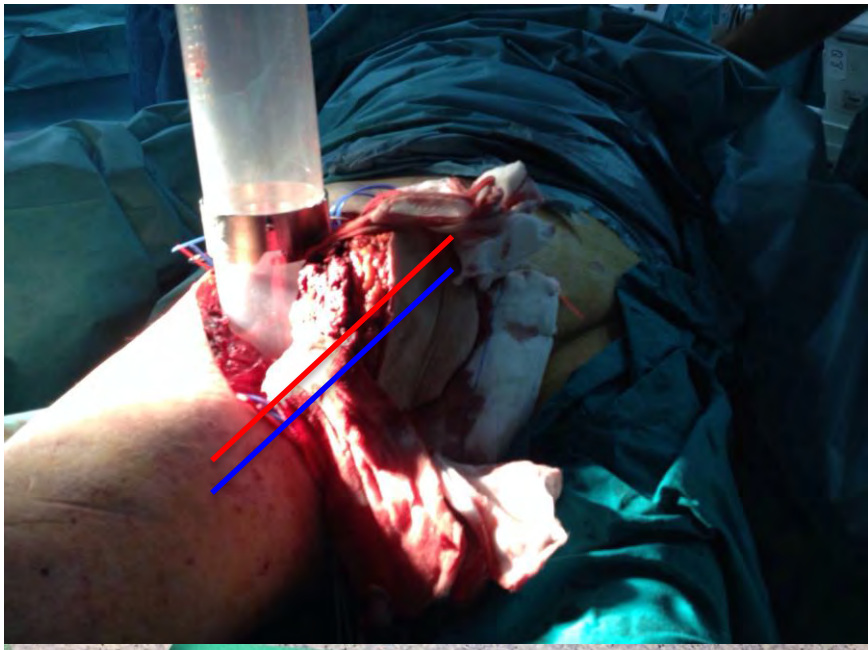


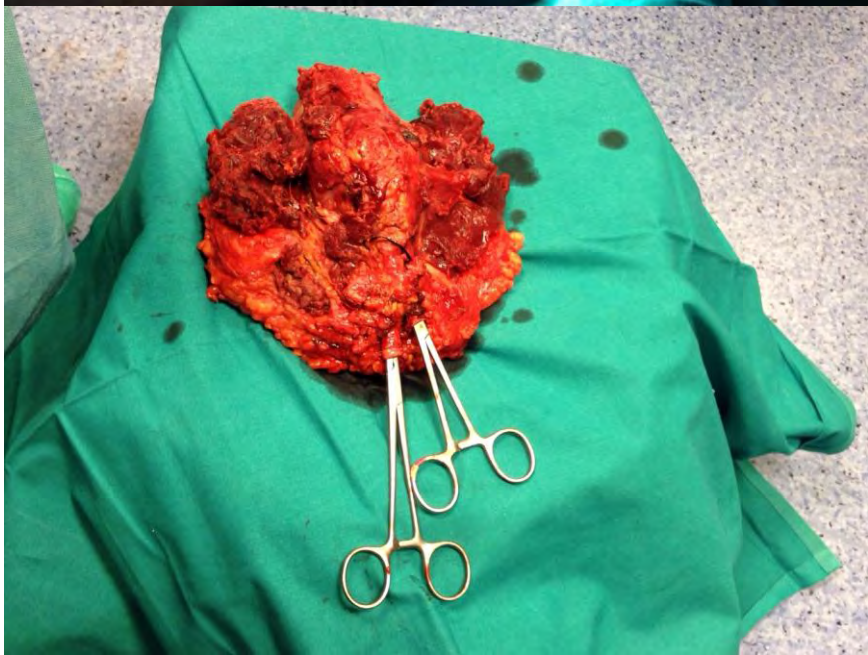
Results


Circulatory System,
Arterial and Venous
1
3
1
1
Arterial
Venous

Results

- IO Dose: 12-17 Gy
- Mean Operative Time: COM 2h> PD
- Resection Margins+: 2/6
- Infectious complications
  - PD (ESR): 0%
  - CON (ISR/NON): 75%
  - FET:
    - P=0.40





Conclusion

- In our initial experience, the strategy of *ex situ* vascular reconstruction performed the days previous to IORT reduce operative time but not infectious complications nor the need to reduce dose in cases requiring vascular resection.

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Radiological pelvic changes after intense adjuvant local therapy including intraoperative presacral electron boost in locally advanced rectal cancer: PREDICTIVE ANALYSIS

Muñoz MM, Serrano JF, Alvarado E, Guerrero LL, Sierra I, Santos M, Lozano M, Calvo F.

Department of Radiation Oncology, Gregorio Marañón General University Hospital

Hospital General Universitario Gregorio Marañón
SaludMadrid
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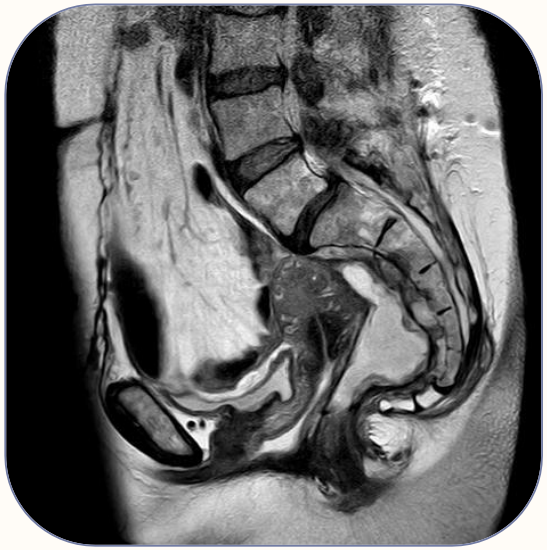
Radiological abnormalities in the presacral area (RAPA) after neoadjuvant treatment **for locally advanced rectal cancer** (LARC) are **complex findings to be interpreted in terms of clinical and pronostic implications**.



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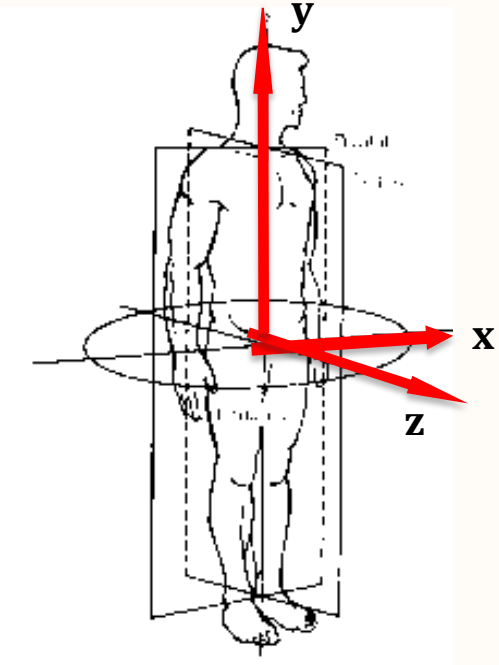
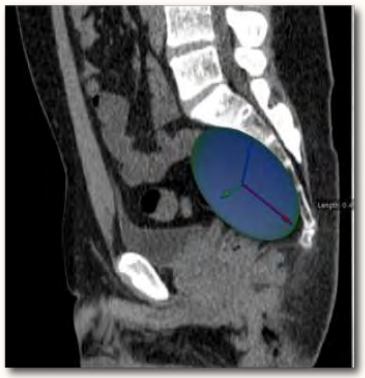
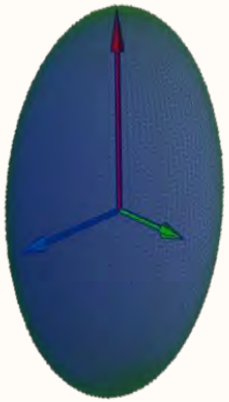
Purpose

To **analyze** the **radiological characteristics** of the **posterior pelvis** and to identify **associated potential risk factors**.







$V(cm^3) = 4/3\pi xyz$

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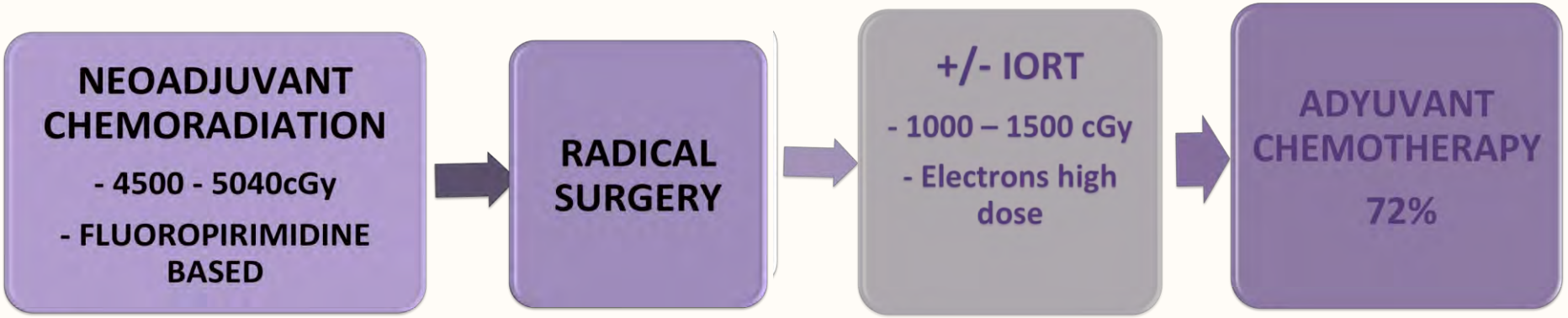
Methods

- From 04/1995 → 12/2010 :

397 p with LARC [≥cT3 (93%) and/or cN + (69%)]



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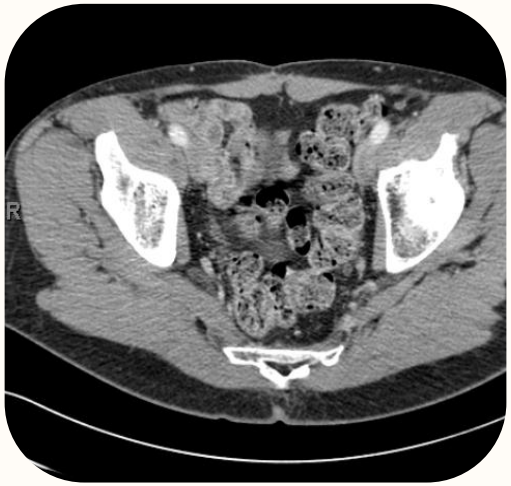
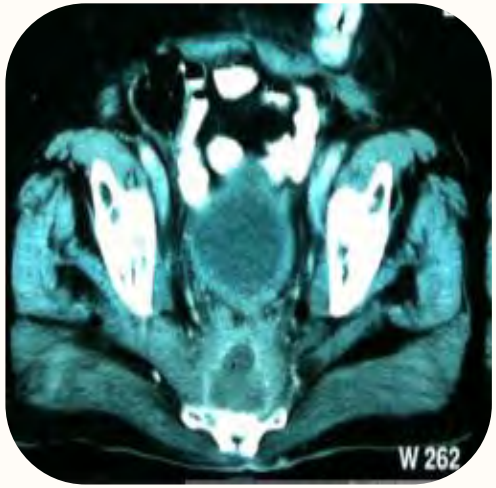
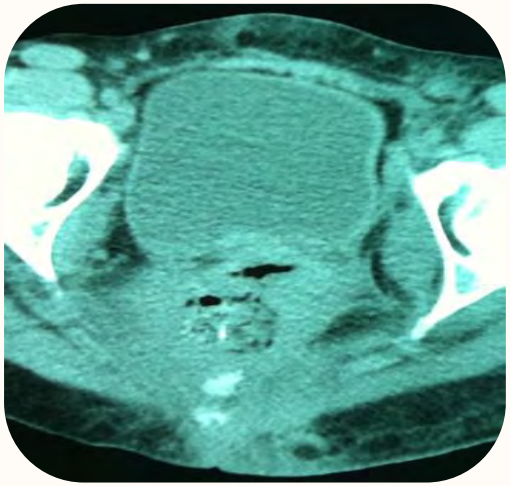
Methods

Differents radiologically changes **(RAPA) were observed, categorized and evaluated during follow-up**.







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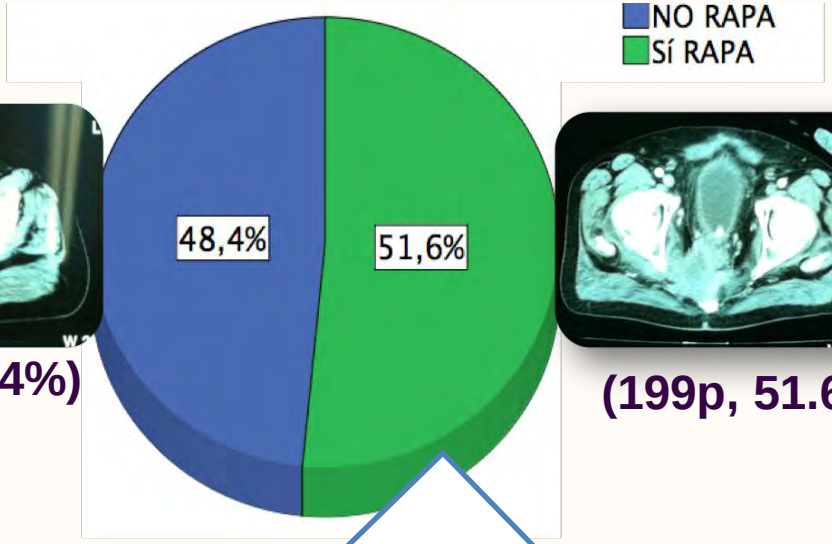
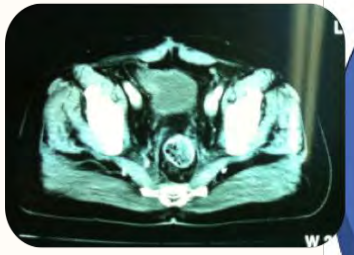
Results



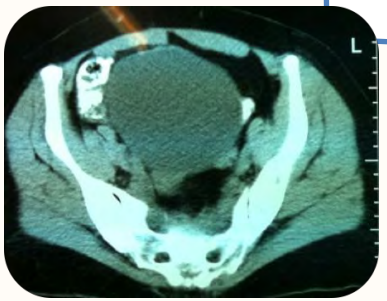
PRESACRAL SPACE NORMAL



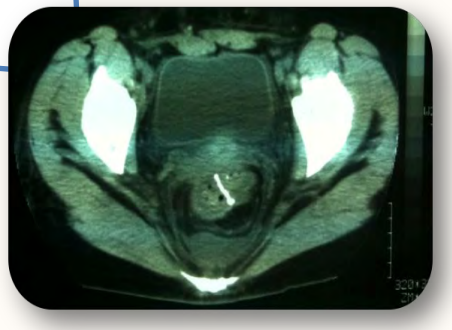
(198p, 48.4%)

RAPA

(199p, 51.6%)



FIBROCICATRICIAL TISSUE (90p, 23%)



PRESACRAL MASS (109p, 28%)

Median follow-up
91 months

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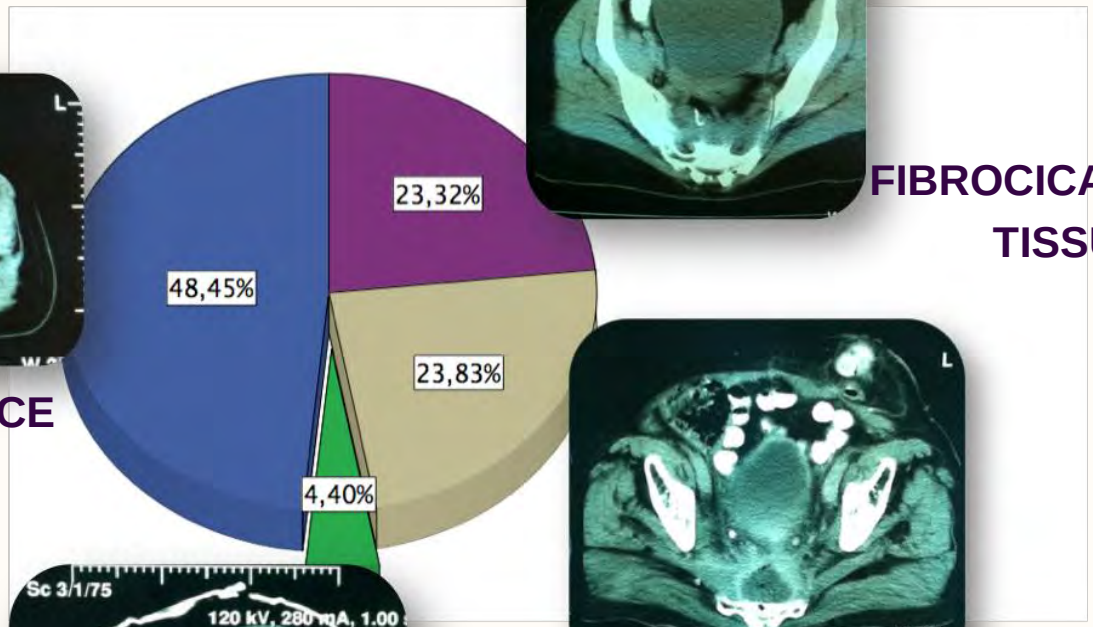
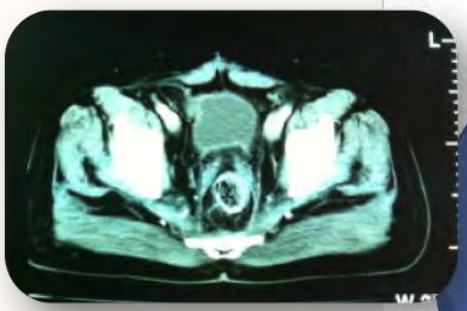
Results

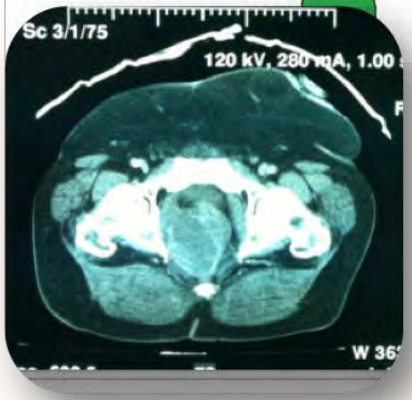




PRESACRAL SPACE NORMAL

FIBROCICATRICIAL TISSUE

NON MALIGNANT MASS



PRESACRAL MALIGNANT RECURRENCE

Median follow-up

91 months

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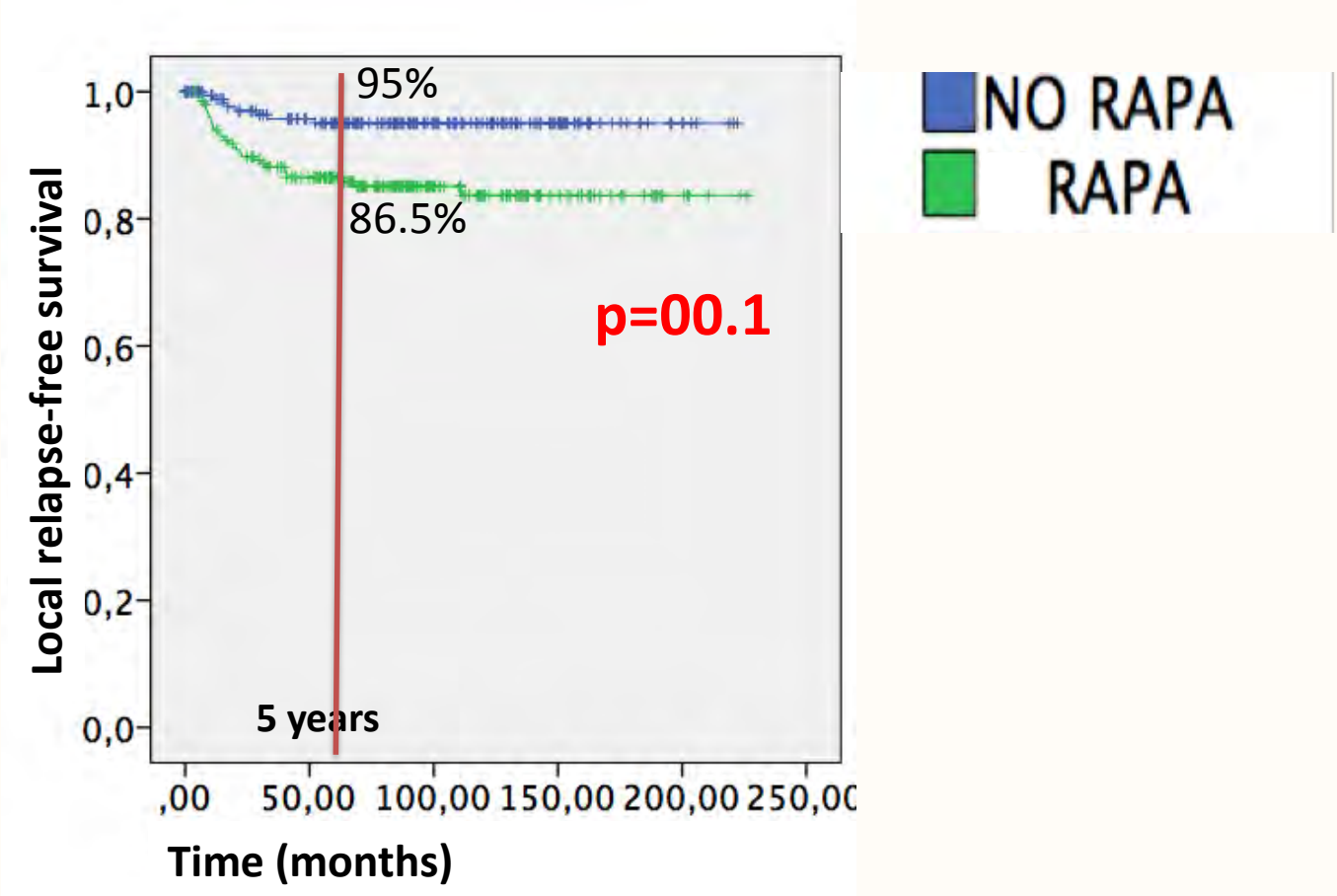
Results



Median follow-up
91 months

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Results

DEVELOPMENT OF RAPA – LOG. REGRESSION MULTIVARIATE MODEL	
POSTOPERATIVE COMPLICATIONS (infection, wound dehiscence and bleeding episodes)	**OR 6.45 [3.68-11.31] p 0.000**
INTRATHEATER SURGICAL TIME (>5 hours)	**OR 1.76 [1.10-2.81] p 0.018**

OR: Odds ratio. IC 95%

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Results

TIME TO DEVELOPMENT OF RAPA – COX REGRESSION MULTIVARIATE MODEL	
POSTOPERATIVE COMPLICATIONS (infection, wound dehiscence and bleeding episodes)	**HR 3.8 [2.89-5.20] p 0.000**
ypN+ SPECIMENS	**HR 1.49 [1.07-2.08] p 0.019**

HR: Hazard ratio. IC 95%.

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Conclusions

The development of post-neoadjuvant RAPA is a **frequent and heterogeneous follow-up event.**

Risk factors predictive of presacral radiological alteration includes: **prolonged surgery (>5 hours), the presence of pro-inflammatory events in the presacral area and radioresistant post-neoadjuvant nodes.**

In clinical practice **post-neoadjuvant RAPA** is **rarely rectal cancer recurrence (4%).**

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THANK YOU.

ISIORT

INTERNATIONAL SOCIETY of INTRAOPERATIVE RADIATION THERAPY

INTRAOPERATIVE RADIOTHERAPY WITH ELECTRONS AND SURGERY IN PRIMARY RECTAL TUMORS:RESULTS OF OUR INSTITUTION

ID-008

Morillo V, Bouché A, Ferrer C, López J, Boldó E, Lozoya R, Mayol A

Consorcio Hospitalario Provincial de Castellón

Fundación Hospital Provincial Castellón

INDEX

INTRODUCTION

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2015
Rectal Cancer

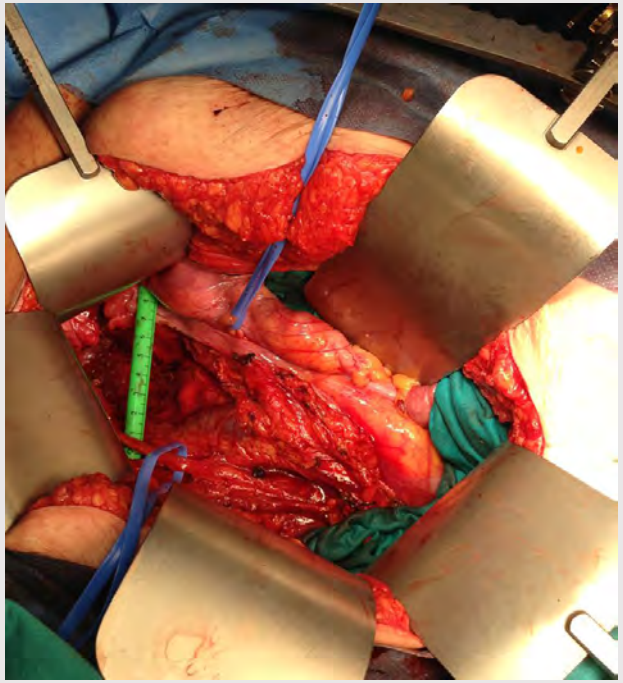
NCCN Guidelines Index
Rectal Cancer Table of Contents
Discussion

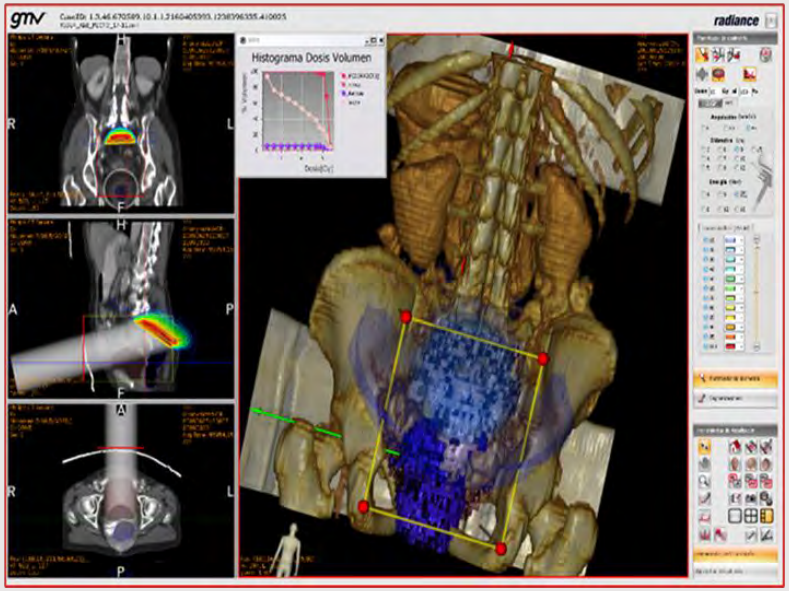
PRINCIPLES OF RADIATION THERAPY

- Radiation therapy fields should include the tumor or tumor bed, with a 2–5 cm margin, the presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures.
- Multiple radiation therapy fields should be used (generally a 3- or 4-field technique). Positioning and other techniques to minimize the volume of small bowel in the fields should be encouraged.
- For postoperative patients treated by abdominoperineal resection, the perineal wound should be included within the fields.
- Intensity-modulated radiation therapy (IMRT) should only be used in the setting of a clinical trial or in unique clinical situations including re-irradiation of recurrent disease after previous radiotherapy.
- Radiation doses:
  - 45–50 Gy in 25–28 fractions to the pelvis.
  - For resectable cancers, after 45 Gy a tumor bed boost with a 2-cm margin of 5.4 Gy in 3 fractions could be considered for preoperative radiation and 5.4–9.0 Gy in 3–5 fractions for postoperative radiation.
  - Small bowel dose should be limited to 45 Gy.
- Intraoperative radiation therapy (IORT), if available, should be considered for very close or positive margins after resection, as an additional boost, especially for patients with T4 or recurrent cancers. If IORT is not available, 10–20 Gy external beam radiation and/or brachytherapy to a limited volume could be considered soon after surgery, prior to adjuvant chemotherapy.
- For unresectable cancers, doses higher than 54 Gy may be required, if technically feasible.

AIMS

- Assessment of toxicity and survival of intra-operative radiotherapy as a boost in presacral area





MATERIALS AND METHODS I

- Retrospective study (December 2008 - March 2016)
  - 19 LARC patients
  - 52.6% were women and 47.4% men
  - Median 56.26 years (range 31-73)
- Classification according to the stage

Stage

	Frequency	Valid Percentage
II	1	5,3
III	17	89,5
IV	1	5,3
Total	19	100,0

- 84.2% received concurrent chemotherapy

MATERIALS AND METHODS II

- Though 94,7% showed free surgical margin (R0)
  - 16.7% showed lymphatic and perineural invasion respectively (5.6 y 11.1%).
- The dose varies according to the intention and the surgical margin

Applicator diameter

	Frequency	Valid Percentage
5 cm	2	10,5
6 cm	7	36,8
7 cm	7	36,8
8 cm	3	15,8
Total	19	100,0

Electron energy

	Frequency	Valid Percentage
6	2	10,5
9	11	57,9
12	4	21,1
15	2	10,5
Total	19	100,0

Dose IOERT

	Frequency	Valid Percentage
10,00	2	10,5
12,00	1	5,3
12,50	13	68,4
15,00	2	10,5
17,50	1	5,3
Total	19	100,0

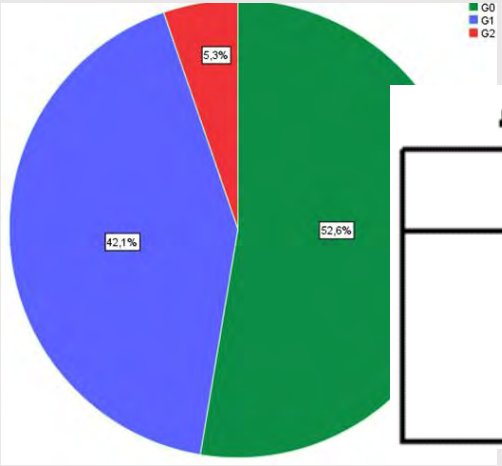
R0:84.2%

R1:10.5%

R2:5.3%

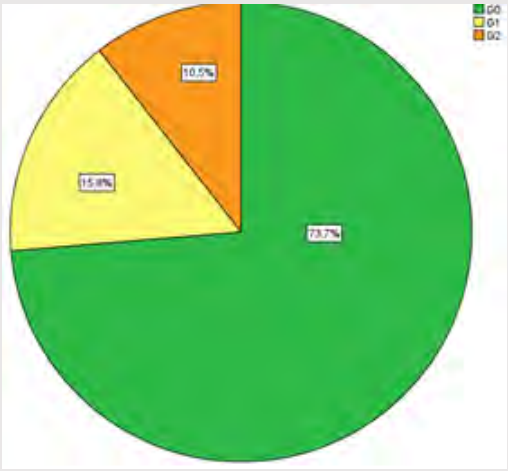
RESULT I

- One of those patients (5.6%) died due to surgical complications.
- Two patients presented neuropathic pain GII with improvement one month after the treatment end.



ACUTE TOXICITY GENITOURINARY

	Frequency	Valid Percentage
G0	10	52,6
G1	8	42,1
G2	1	5,3
Total	19	100,0



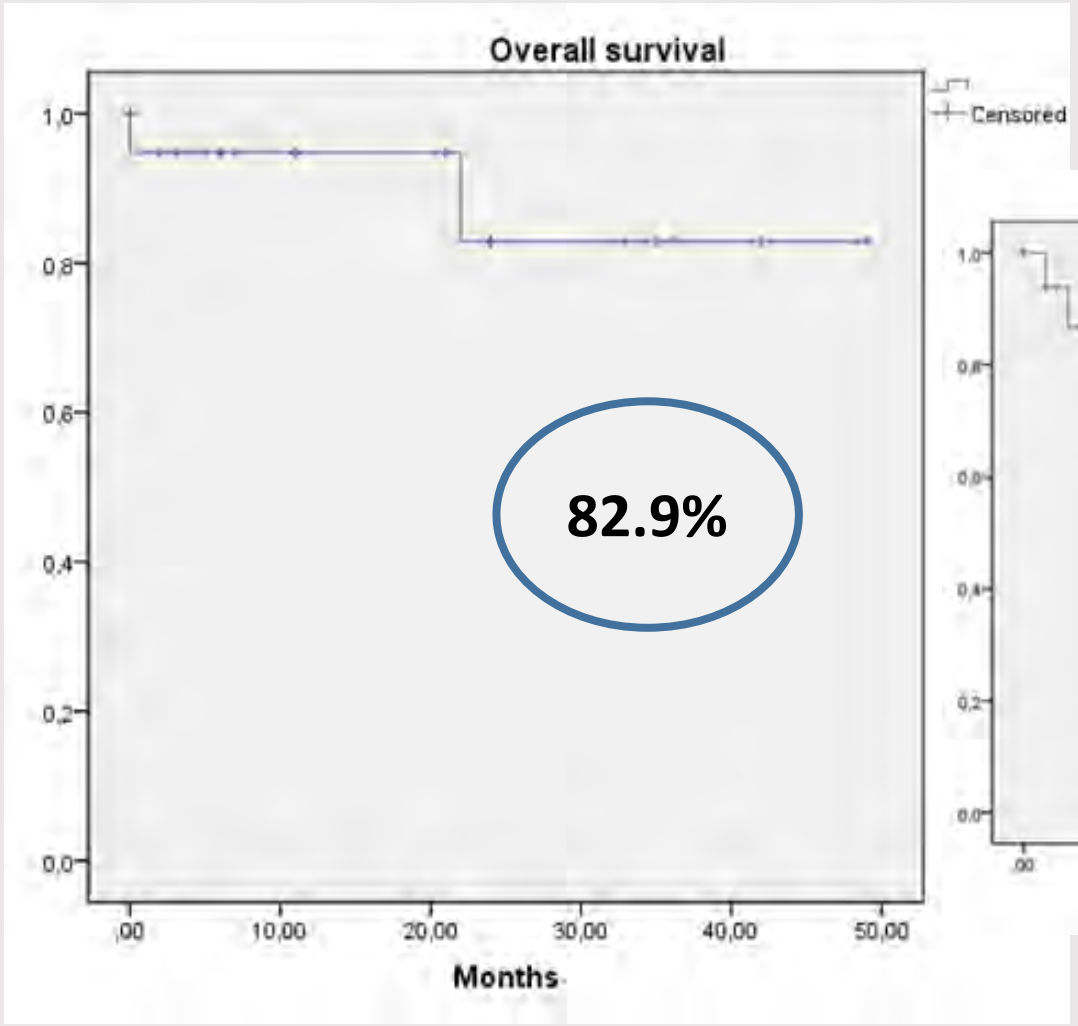
Neuropatin pain

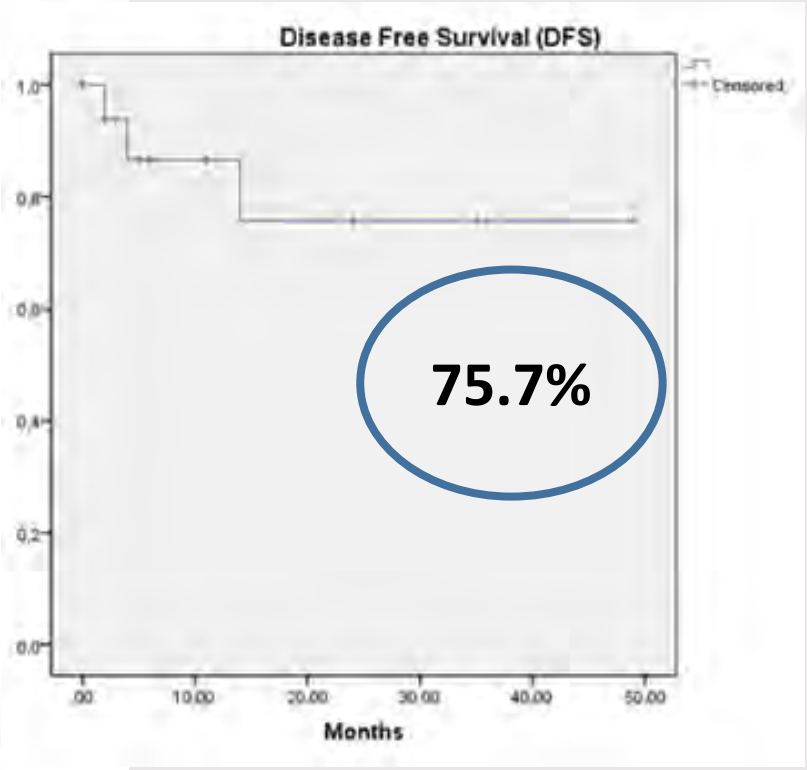
	Frequency	Valid Porcentage
G0	11	57,9
G1	6	31,6
G2 (Moderate)	2	10,5
Total	19	100,0

ACUTE TOXICITY RECTAL

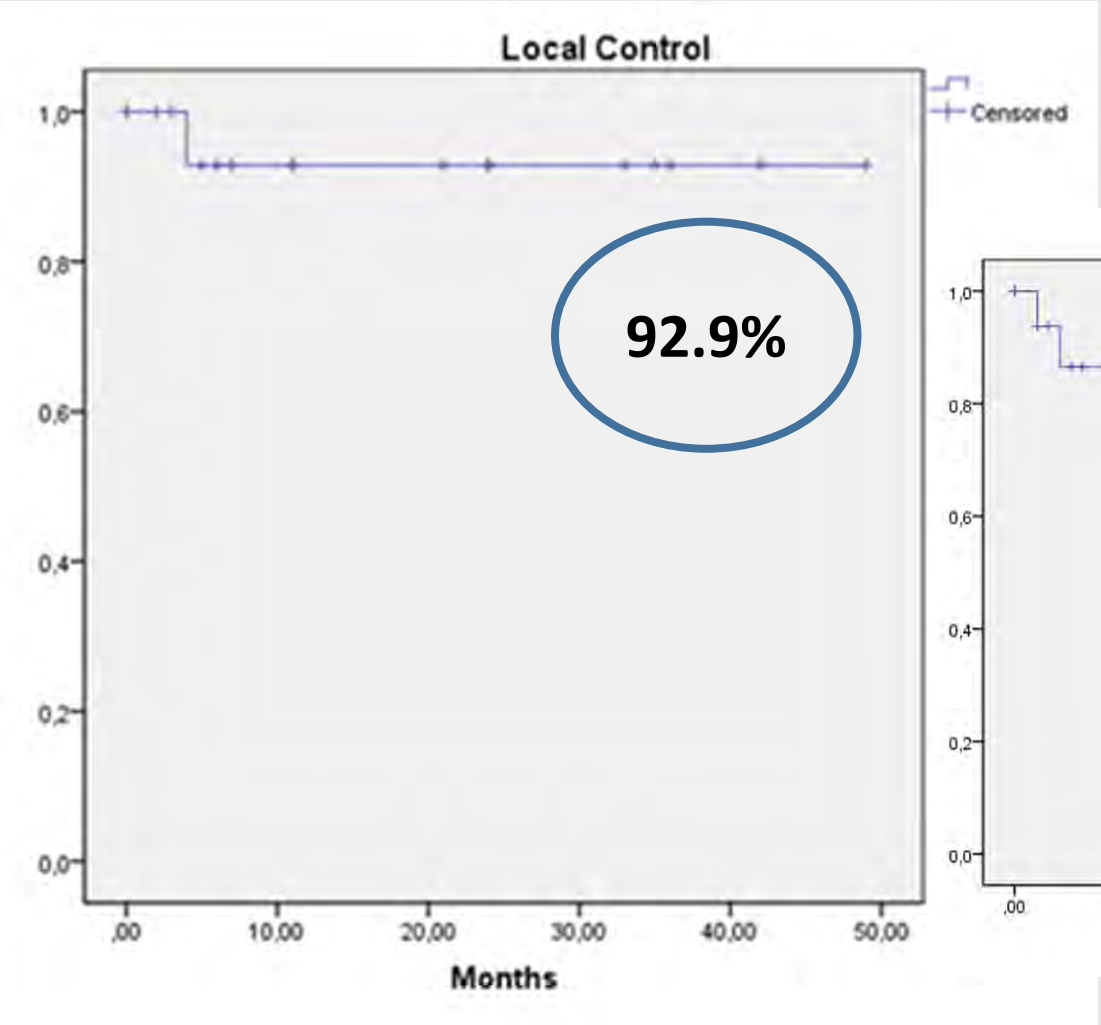
	Frequency	Valid Percentage
G0	14	73,7
G1	3	15,8
G2	2	10,5
Total	19	100,0

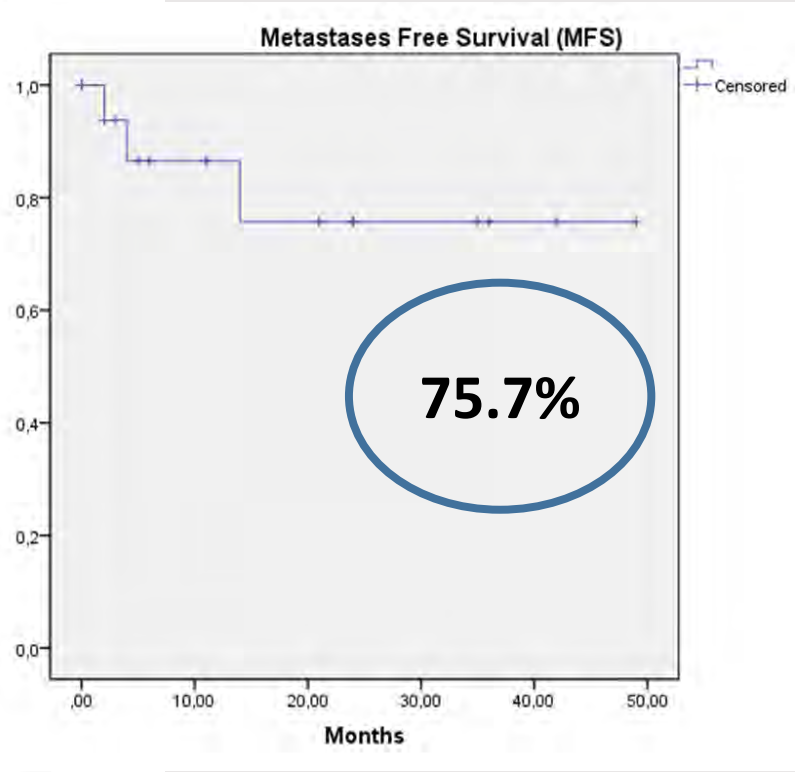
RESULT II


Overall survival
Censored
1,0
0,8
0,6
0,4
0,2
0,0
82.9%
,00
10,00
20,00
30,00
40,00
50,00
Months


Disease Free Survival (DFS)
Censored
75.7%
Months

RESULT III


Local Control
Censored
1,0
0,8
0,6
0,4
0,2
0,0
92.9%
,00
10,00
20,00
30,00
40,00
50,00
Months


Metastases Free Survival (MFS)
Censored
1,0
0,8
0,6
0,4
0,2
0,0
75.7%
,00
10,00
20,00
30,00
40,00
50,00
Months

CONCLUSION

- The use of intraoperative radiotherapy in locally advanced rectal tumour shows acceptable results on locoregional control and minimizes toxicity derived from the selective overimpression on presacral area


THANK YOU
SO MUCH!!!

INTRAOPERATIVE RADIOTHERAPY WITH ELECTRONS AND SURGERY IN PELVIC RECURRENCE: RESULTS OF OUR INSTITUTION

ID-009

Morillo V, López J, Bouché A, Ferrer C, Boldó E, Lozoya R, Mayol A

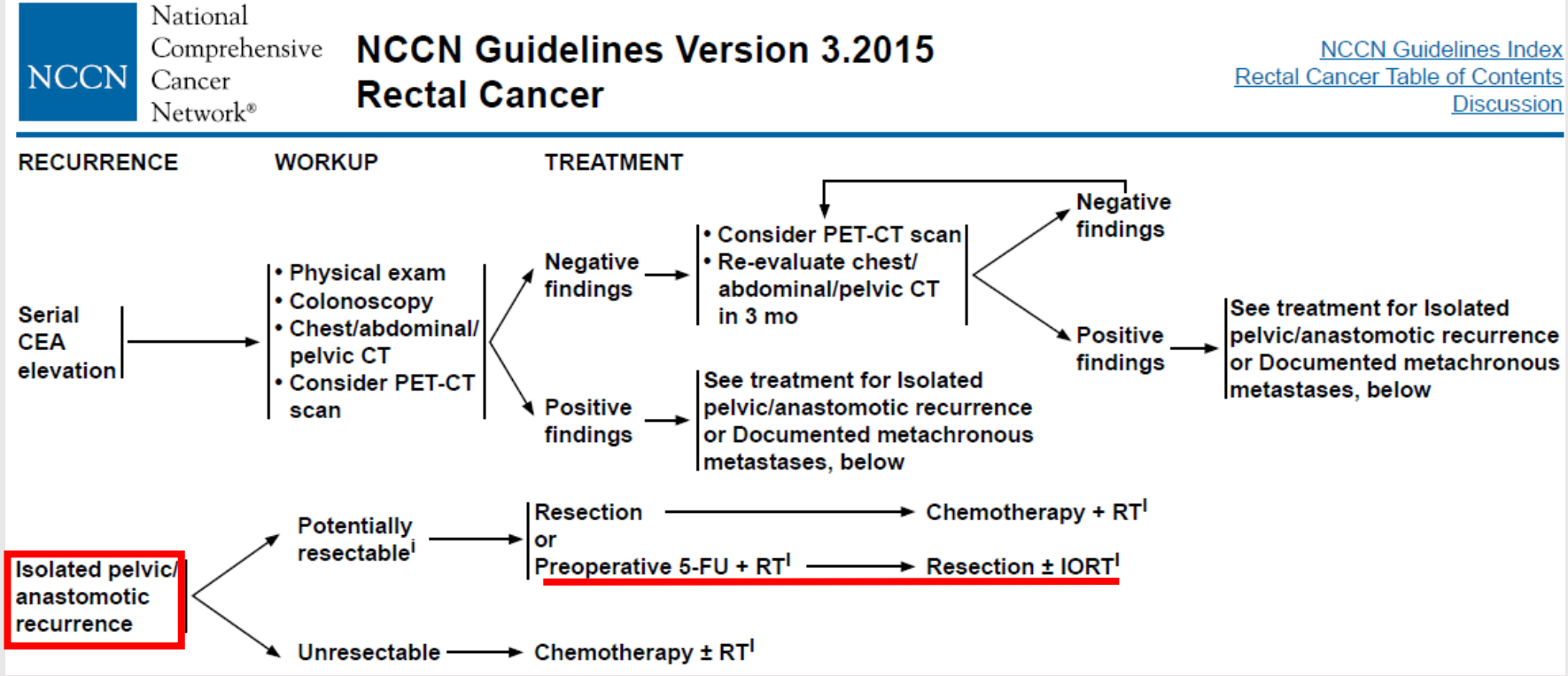
Consorcio Hospitalario Provincial de Castellón

Fundación Hospital Provincial Castellón

INDEX

INTRODUCTION

- The percentage of local relapse after radical treatment in rectal neoplasias is around 25%.
  - 15% die without distant disease and median survival without treatment is around 8 months.



AIMS

- Assessment of rectal recurrence treated with surgery plus IOERT in our institution
  - In terms of:
    - ✓ Locorregional control
    - ✓ Toxicity

MATERIALS AND METHODS I

- Retrospective study (December 2008 - March 2016)
  - 19 rectal recurrence patients
  - 63,2% were men and 36,8% women
  - Median 63,37 years (range 45-82)

PS (PERFORMANCE STATUS)

	Frequency	Valid Percentage
PS 0	5	26,3
PS 1	10	52,6
PS 2	4	21,1
Total	19	100,0

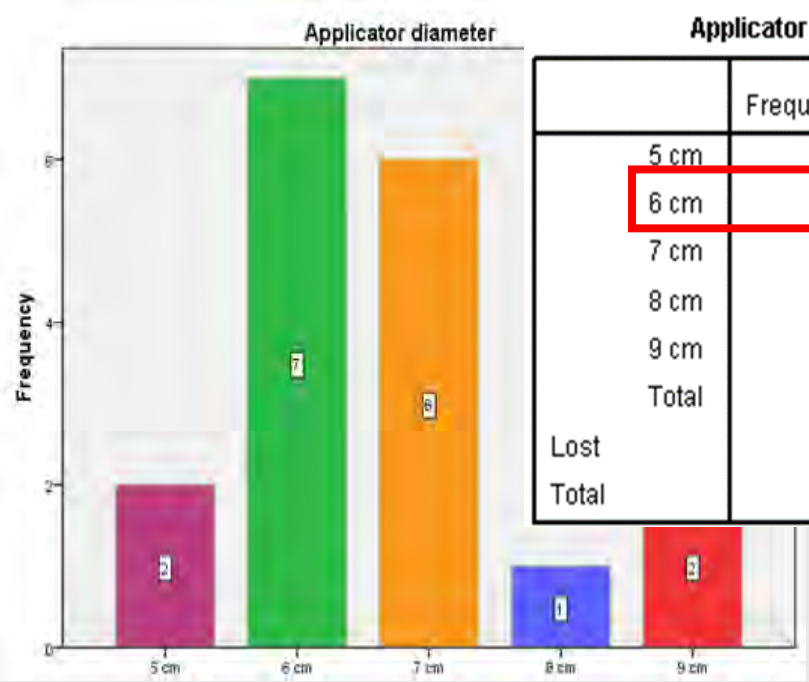
RADIOTHERAPY PREOPERATIVE (RT)

	Frequency	Valid Percentage
Yes	15	78,9
No	4	21,1
Total	19	100,0

	Frequency	Valid Percentage
radical	14	73,7
paliativa	5	26,3
Total	19	100,0

MATERIALS AND METHODS II

- The treatment volume was defined by tumor size plus a margin that contains the area at risk; marked with surgical clips for a correct display.
- The applicator size most frequently used (38,9 %) was 6 cm. The energy of electrons predominance being used 9 Mev (52.6%), range 9-15 MeV.



Applicator diameter

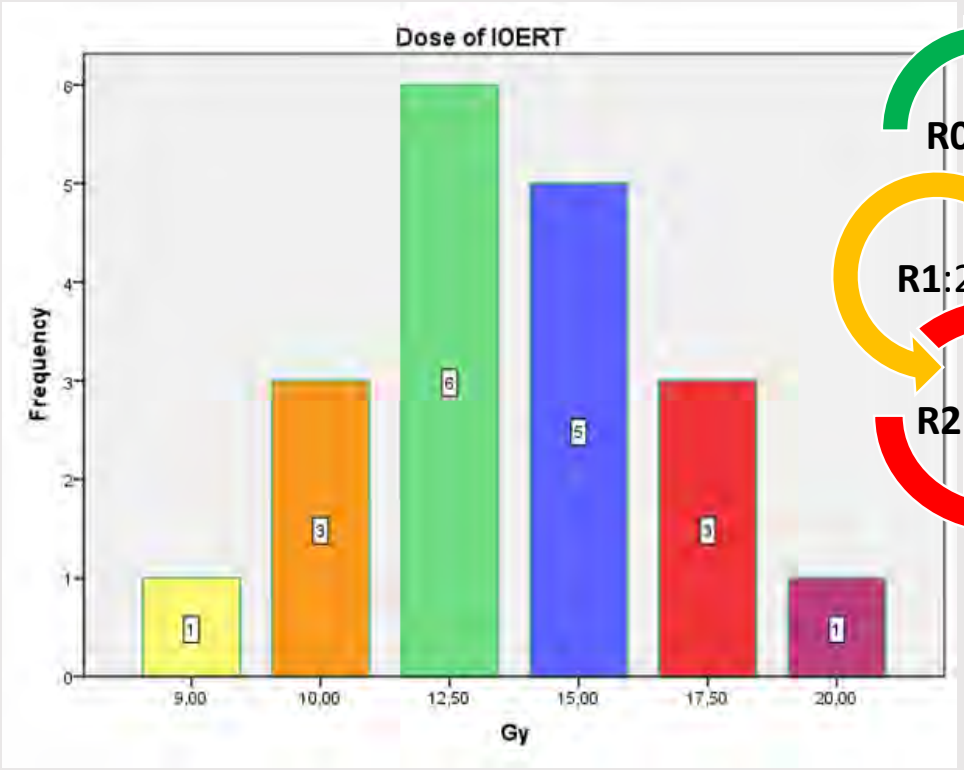
		Frequency	Valid Percentage
	5 cm	2	11,1
	6 cm	7	38,9
	7 cm	6	33,3
	8 cm	1	5,6
	9 cm	2	11,1
	Total	18	100,0
Lost		1	
Total		19	

Energy of electrons

	Frequency	Valid Percentage
6	1	5,3
9	10	52,6
12	5	26,3
15	3	15,8
Total	19	100,0

MATERIALS AND METHODS III

- The IOERT dose varies according to the surgical margin: RO, R1, and R2 with 9-12.5(52.7%),15(26.3%) and 17.5-20 (21.1%) respectively.
- Assessment of toxicity according to RTOG scale.



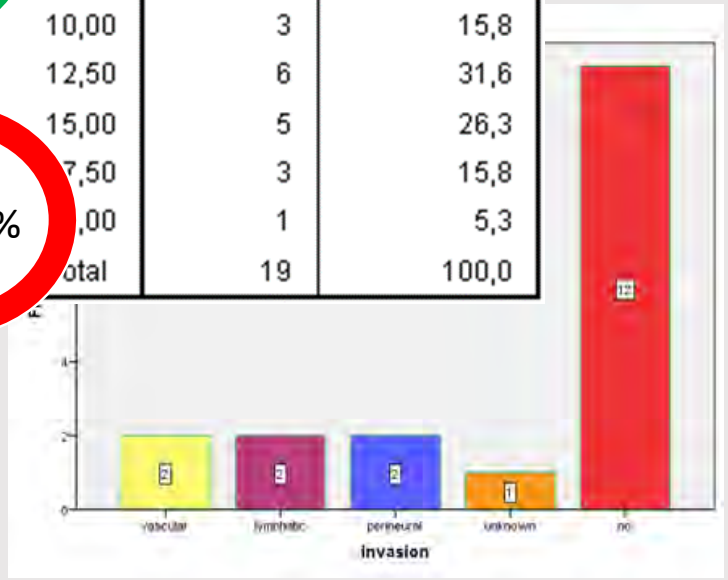
R0:52.7%

R1:26.3%

R2:21.1%

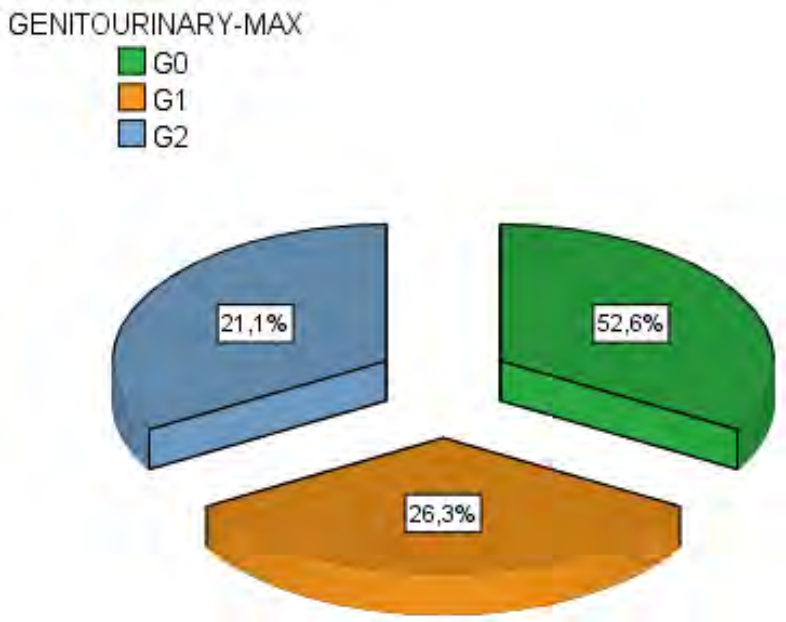
Total dose IOERT

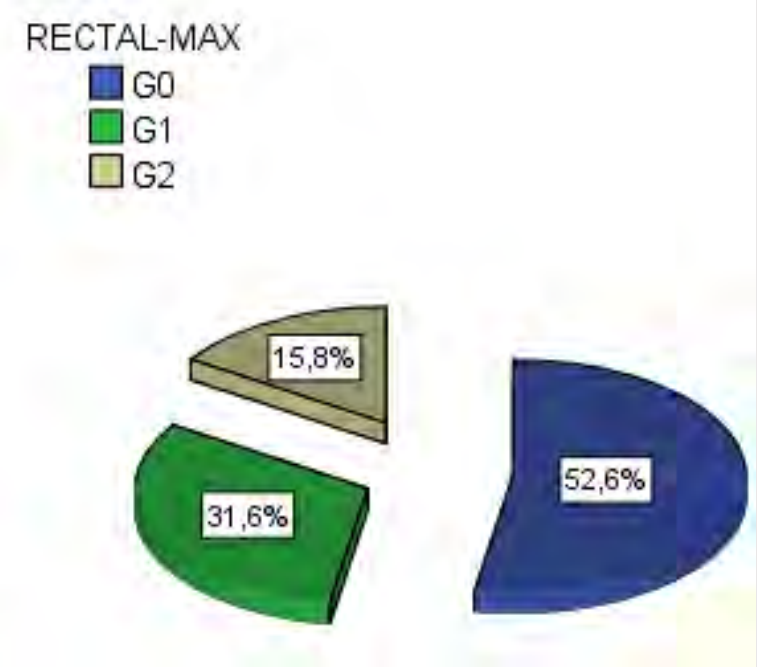
	Frequency	Valid Percentage
9,00	1	5,3
10,00	3	15,8
12,50	6	31,6
15,00	5	26,3
,50	3	15,8
,00	1	5,3
otal	19	100,0



RESULT I

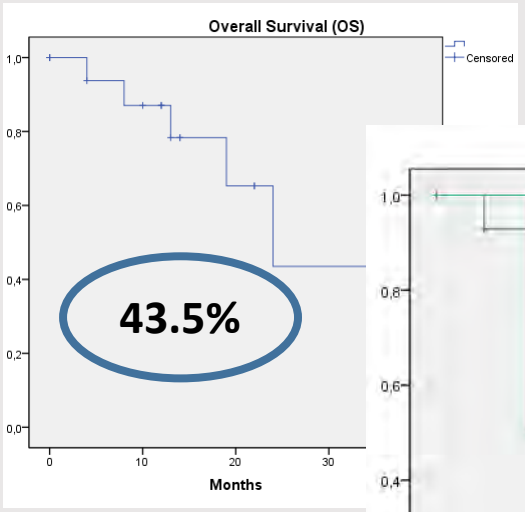
- As for maximum acute toxicity was: grade II rectal 15.8%, moderate neuropathic pain 22.2% and genitourinary in 21.1 %.
- There was no subsequent late toxicity.

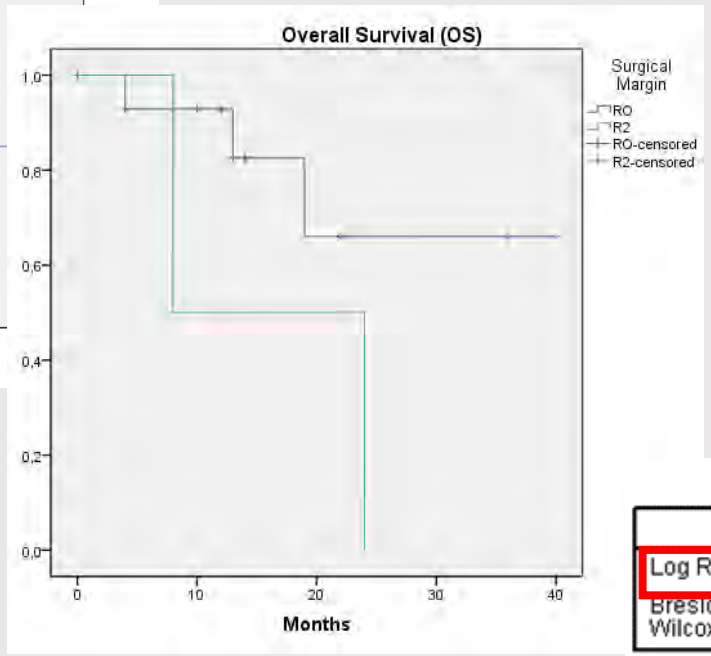




RESULT II

- With a median follow-up of 49 months, the current overall survival of 43.5% is not statistically significant (p = 0.171) vs R0 vs R2.





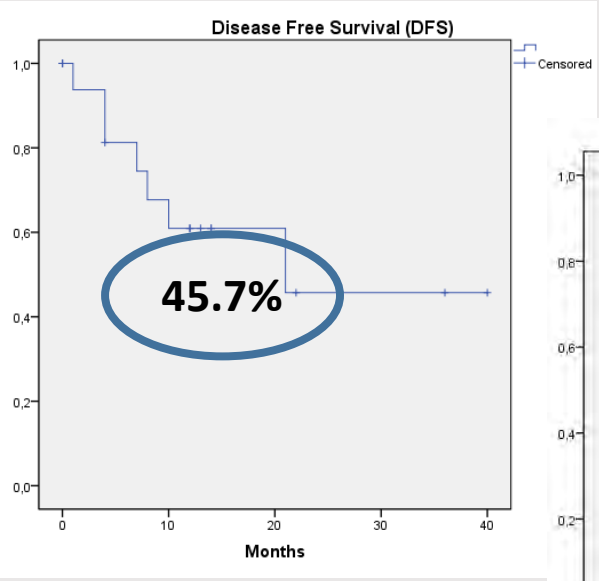
Margin	N° total	N° of events	Censored	
			N°	Percentage
R0	16	3	13	81,3%
R2	3	2	1	33,3%
Global	19	5	14	73,7%

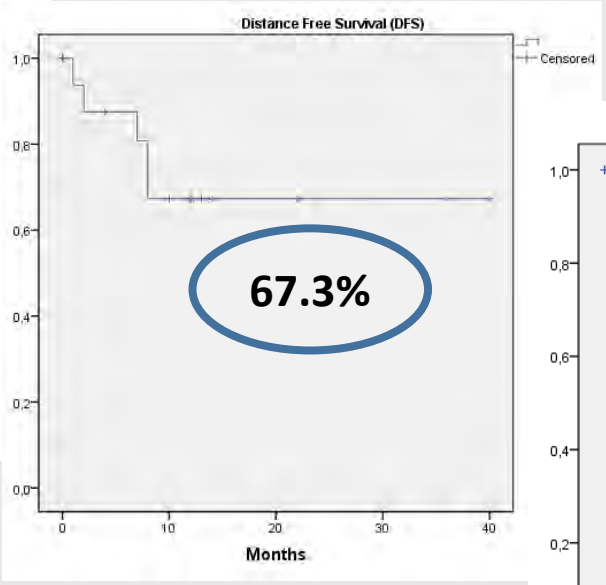
Global comparation

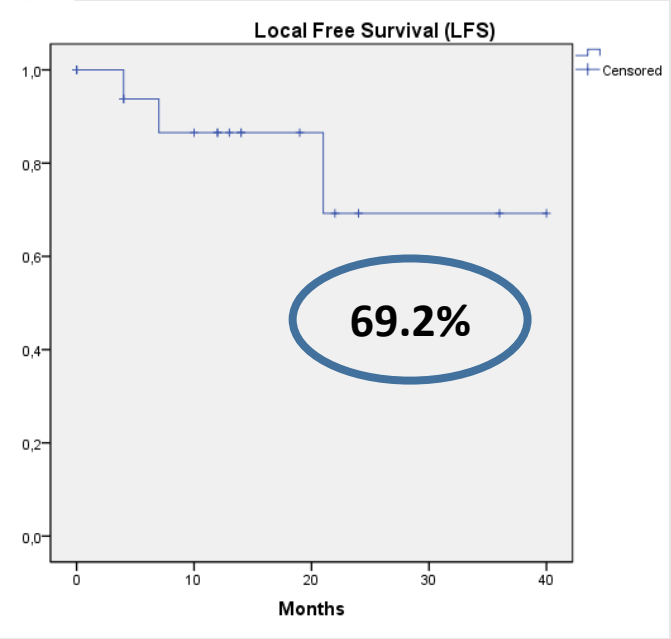
	Chi-cuadrado	gl	Sig.
Log Rank (Mantel-Cox)	1,877	1	,171
Breslow (Generalized Wilcoxon)	1,471	1	,225

RESULT III

- The disease-free survival, distant and local control is about 45.7 %, 67,3% and 69.2% respectively. The dominant pattern of distant relapse: liver and lung.







CONCLUSION

- The use of IOERT in treatment of recurrent rectal can significantly improve local control without increasing the incidence and severity of toxicity.
- Both individualized strategies and longer follow-up are needed


THANK YOU
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PANCREATIC CANCER RESULTS

RESECTION + OPTIMIZED ESCALATED IRRADIATION

Hospital General Universitario Gregorio Marañón

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Comunidad de Madrid

PURPOSE

To evaluate outcomes in patients with resected pancreatic cancer and a dual component of intraoperative electron boost (IOERT) and external beam fractionated irradiation (EBRT).

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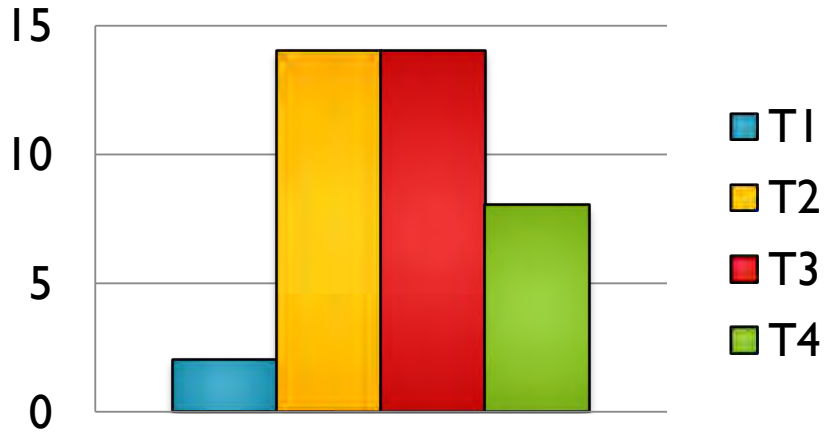
9th International ISIORT Conference

June 24/25th 2016
Novara, Italy

METHODS

From 1995 to 2015: 38 patients were treated with Surgery, EBRT and IORT

Age ranged: 38 to 81 year	**N+: 7 patients**
15 males and 23 females	**Maximal clinical diameter: 6.2cm (median: 2cm)**



Clinical cancer stages:

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METHODS

- Surgical procedures were:
  - 25 duodeno-cephalo-pancreatectomy
  - 6 total pancreatectomy.

- EBRT was combined with concomitant chemotherapy in 73,6%
  - Preoperative 55%
  - Median dose 45Gy (range 45 – 50.4Gy)

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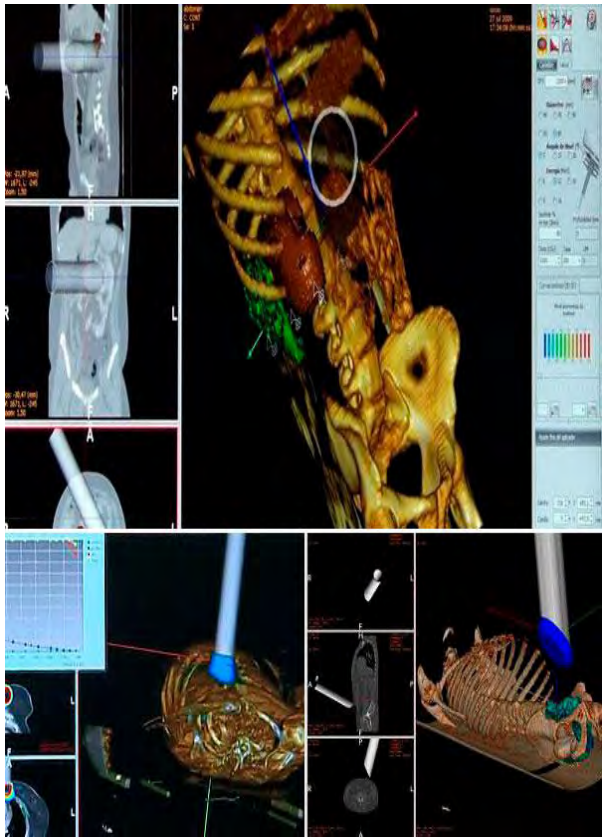
IOERT characteristics were:

Electron Energies	: 6MeV to 18MeV (8MeV 36.8%)
Applicator diameter used	: 8 cm (42.1%)
Doses range	:10Gy to 17.5Gy (Mean dose:12.5Gy)



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RESULTS:

- Postoperative complication rate was 44.7% (17/38).

- With a median follow-up time of 22 months:
  - Loco-regional control (85%)
  - Disease free and overall survival were 36%, 38%, respectively at 3 years.

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RESULTS:

Long term survivors >4 years were 9 patients (32%) included stages:

- T1 1 patient (11%)
- T2 2 patients (22%)
- T3 4 patients (44%)
- T4 2 patients (22%)

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CONCLUSIONS:

Escalated optimized dual component radiotherapy is feasible in resected pancreatic cancer patients with high promotion of local control and proven long-term survivors.

THANK YOU…

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EXTREMITY PRESERVATION
PRIMARY SOFT TISSUE SARCOMAS

RADICAL SURGERY + DOSE-DENSE RADIOTHERAPY

Hospital General Universitario Gregorio Marañón

Comunidad de Madrid

PURPOSE

To analyse extremity control results in patients with soft tissue sarcomas (STS) treated with the combination of surgery, intraoperative electron boost (IOERT) and tridimensional external beam conventional radiotherapy (3DCRT).

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PATIENTS AND METHODS

March 1995→ April 2015.

95 patients were evaluated and treated in the Multidisciplinary Sarcoma Unit with Tri-Modality local therapy.

Median age 50 (age ranged from 1 to 91 year).

Sex
- 50 Males (52,6%)
- 45 Females (47,4%)

Location
- Upper extremity 14 patients (14,7%)
- Lower extremity 81 patients (85,3%)

Histologies:

Lyposarcoma 28 (29,5%)

Malignant Fibrous Hystiocytoma 15 (15,8%)

Synovial sarcoma 13 (13,7%)

Other Data:

Median maximal sarcoma *diameter* 10 cm (ranged from 1 to 25 cm).

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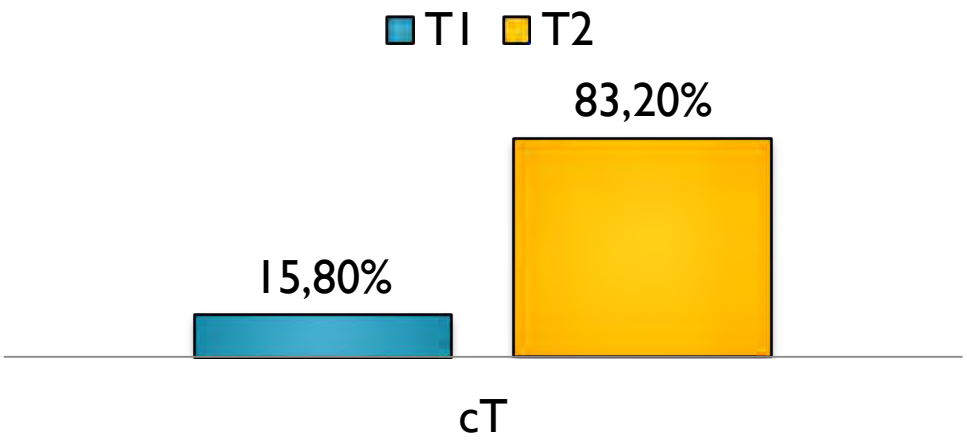
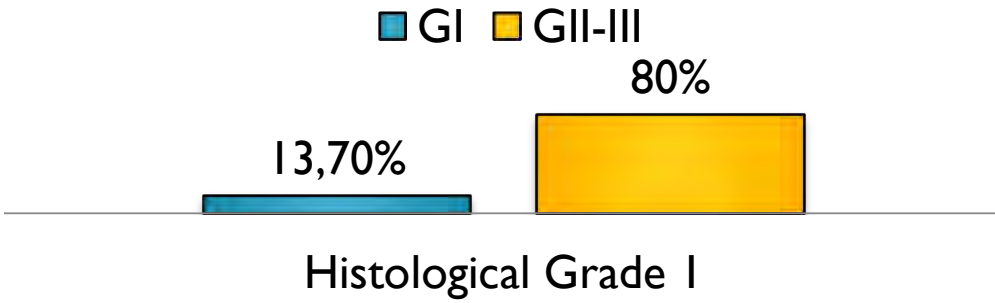
cT



Histological grade



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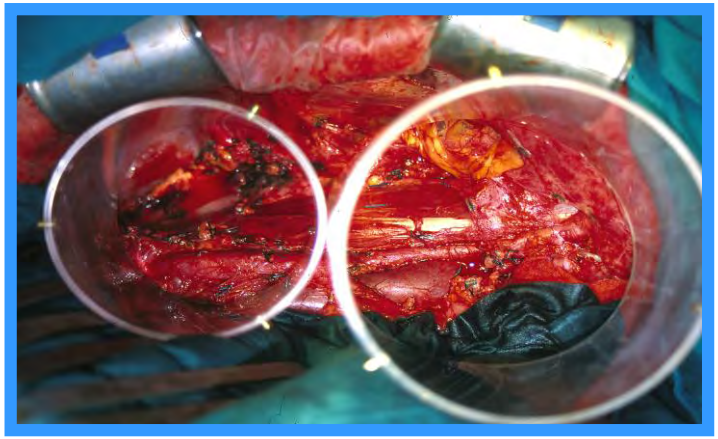
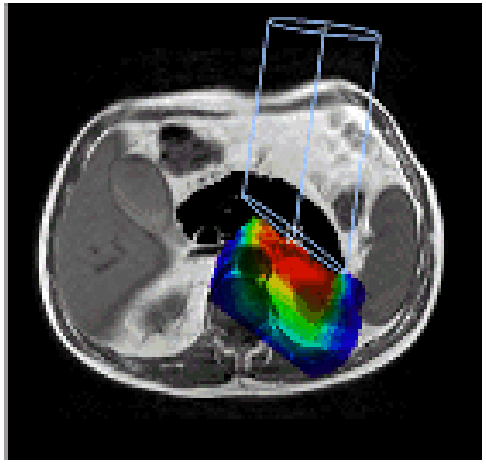
IORT BOOST CHARACTERISTICS:

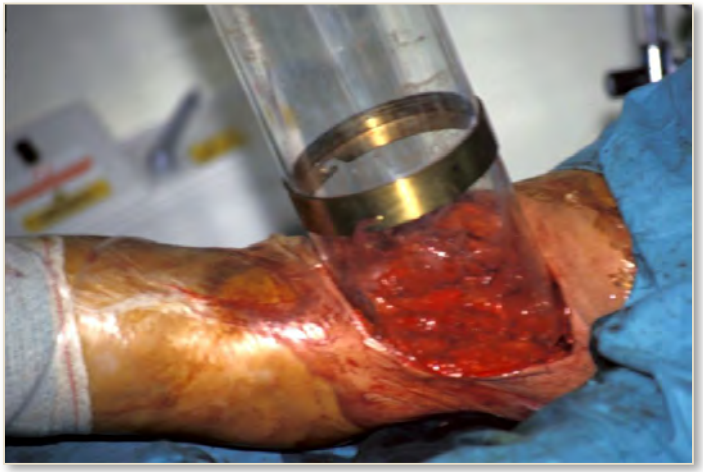
Size ranged 5-15 cm (median size 10 cm).
Energy 4-18 MeV (median Energy 8 MeV).
Dose 750-1500 cGy (12 Gy median dose).

Multiple fields were used in 14% of procedures.





- 84%patients received 3DCRT.
  - 85% postoperatively, median dose 50Gy.
  - Neo or adjuvant chemotherapy was used in 22(23,2%)



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Novara, Italy

RESULTS:

Optimal surgical resection was possible in 84%

Limb spearing surgery was achieved in the majority of patients (98%).

R0 surgical margin was documented in 74 patients (77%).

Postsurgical complication rate was 32,6%.

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RESULTS:

Median follow up of 54 months:

- 9 local recurrence documented (9,5%)
- 31 patients with metastatic outcome (32%) observed.

Survival

- Five year actuarial ***overall*** were 75.9%
- *Five year* ***local recurrence free survival were*** 89,3%.

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CONCLUSIONS:

Dose-dense radiotherapy successfully complements surgical preserving surgery in extremity sarcoma patients in terms of promotion of favourable local outcomes.


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Madrid

INTRA-OPERATIVE RADIOTHERAPY (IORT) FOR LOCALLY ADVANCED ESOPHAGEAL CANCER: PRELIMINARY RESULTS IN A SERIES OF 16 PATIENTS.

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[1] Radiotherapy, [2] Surgery, [3] Medical Physics, University Hospital Maggiore della Carità, Novara

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Purpose

To describe our experience in the use of intraoperative radiotherapy (IORT) as a boost after preoperative chemo-radiotherapy in patients with locally advanced esophageal cancer candidates for surgical resection.

Materials and Methods

From 2007 to 2012, sixteen patients (pts), 11 males and 5 females, aged from 49 to 75 years (mean 61.2, median 59.5) with locally advanced esophageal cancer were enrolled in our institutional protocol after multidisciplinary discussion and were candidate to pre-operative chemo-radiation followed by surgery with IORT boost. Locations were: 2 in upper, 8 in middle, and 6 in lower esophageal third. Pathology was squamous cell carcinoma in 14 cases and adenocarcinoma in 2 cases. Clinical TNM stages were as follow: 5 pts T3N0M0, 6 pts T3N1M0, 2 pts T3N0M1, 1 pts T3N2M0, 1 pts T4N0M0 and 1 pts T4N1M0. The two M1 pts had sub-diaphragmatic lymph nodes enlarged at CT-scan and FDG-PET positive. Pre-operative radiotherapy was prescribed with conformal technique using a treatment plan based on PET/CT fused images to a total dose of 44 Gy in 22 fractions (2 Gy/fraction). Chemotherapy was given concomitantly to radiotherapy with cisplatin and 5-fluorouracil for 2 cycles. IORT was delivered after surgical resection to the tumor bed and/or regional lymph nodal areas by a dedicated linear accelerator (Mobetron, Intraop, Sunnyvale, CA) using electron beams of 6, 9 or 12 MeV to a total dose 10-15 Gy.

Results

Two of 16 pts received preoperative RT alone because of severe renal failure. One pts did not received preoperative external beam radiotherapy because of onset of symptomatic mediastinitis requiring upfront surgery. Three pts developed chemo-related hematologic (G4) and one pt renal/hepatic toxicity (G1). Surgery consisted of total esophagectomy with standard mediastinal lymphadenectomy and neck esogastric anastomosis in 14/16 pts; 1/16 pts received sub-total esophagectomy and neck esogastric anastomosis and 1/16 distal esophagectomy with small curvature gastic resection and splenectomy. Pathological stages were as follow: 2 pT1N0M0, 1 pT2N0M0, 2 pT3N0M0, 7 pT3N1M0, 2 pT3N0M1, 1 pT4N3M0. One pt died just after the surgical procedure. 11/15 pts were R0, 2 R1, and 2 R2. Postoperative complications occurred in 7/15 cases and consisted of pulmonary embolism, gastro-tracheal fistula, gastric perforation with mediastinitis, respiratory distress. At median follow up of 23 months (range 1-77), only one of 16 patients is alive without tumor progression. Causes of death were: 10 tumor progression,1 pulmonary embolism, 1 severe pulmonary distress and 1 of cardiac failure. Tumor progression occurred in two cases for both regional and distant relapse and in 8 cases with distant relapse only.

Conclusion

IORT during surgery for esophageal carcinoma seems to be a feasible procedure and can be combined with preoperative chemo-radiotherapy, although toxicity is not negligable. Larger number of patient and longer follow-up are needed to assess long-term outcome including late side effects, local control and relapse-free and overall survival.

Fundación Hospital Provincial Castellón

In vivo dosimetry in IORT treatments

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Medical Physicist

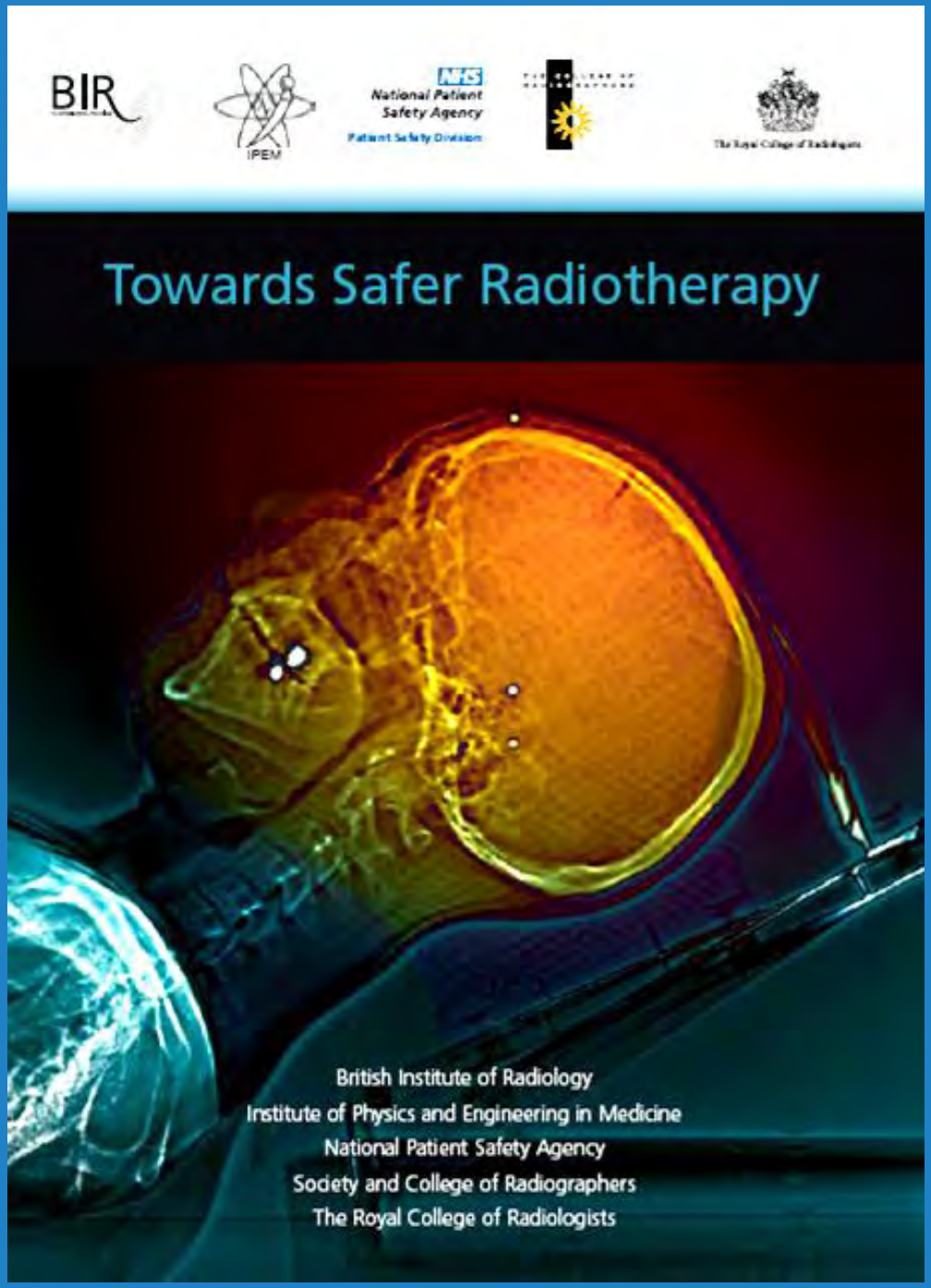
Consorci Hospitalari Provincial de Castelló

DIPUTACIÓ DE CASTELLÓ

GENERALITAT VALENCIANA

In vivo **dosimetry is conceptually easy…**

…but challenging in practice



Recommended by scientific societies

and also regulated

In France

The requirement for in vivo dosimetry (IVD) is one of the French National Cancer Institute (INCa) authorisation criteria for practicing external radiotherapy, an integral part of the system of authorisation for cancer treatment (2007 decree). This requirement was implemented in the framework of the French radiotherapy measures specified in 2007.

Approval criterion no. 15 stipulates: "In vivo dosimetry is to be performed for each technically measurable beam during the first or second irradiation session, as well as at each modification in the treatment". In order to assist radiotherapy centres in observing this requirement as soon as possible and under the best possible conditions, the INCa financed equipment for radiotherapy centres in the private or public sector in the amount of € 3.1M in 2008.

The 2013 French radiotherapy observatory indicates that at the end of December 2012, all the centres that had responded (168/172) were equipped with in vivo dosimetry systems.

68% of the centres use IVD for all their treatments in which beams are technically measurable, with the share of non-technically measurable beams estimated at 21% on average. The most widespread equipment is that of direct readout type, 93% of which uses semiconductor diodes. Most centres have defined an action threshold at 5% discrepancy between the measured dose and the calculated dose.

And in Europe?

A survey was conducted by ASN among 30 European countries (the 27 Member States in June 2013, Norway, Switzerland and Iceland). Twelve countries responded.

IVD is not mandatory for all beams in most European countries (Austria, Finland, Belgium, Germany, Greece, United Kingdom, Estonia, and Lithuania).

IVD has been mandatory in Sweden since 2000, in Denmark since 2001, in Norway since 2004, and is mandatory in the Czech Republic.

In Austria, IVD is mandatory only for total-body irradiation.

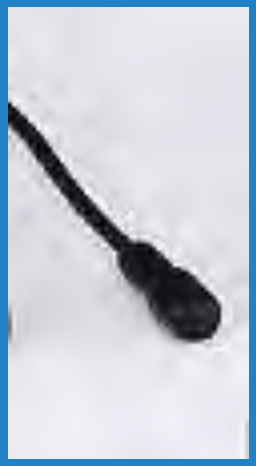
In Finland, quality assurance for treatment planning must include verification of each individual treatment plan using a procedure optimally independent of the treatment planning system. In addition, every total-body irradiation must include an in vivo dose measurement. Use of in vivo dosimetry is also recommended for other types of radiotherapy.

IVD is considered good practice:

- in Belgium: the National Institute for Health and Disability Insurance (INAMI) reimburses four IVD sessions per patient;

- in the United Kingdom: in 2007, the Chief Medical Officer[1] of England wrote in his report that IVD should be progressively introduced.

Specific recommendations for IORT



Detectors – Essential requirements

- Small-sized detectors, handy
- Readout independent of temperature, absorbed dose rate, and beam energy
- Ease of use – Multidisciplinary handling

Major experiences

Different sites, detectors, and irradiation techniques

kV IORT

Courtesy of Elena Aspe
(Carl Zeiss Meditec Iberia)

Australas Phys Eng Sci Med (2010) 33:211–214
DOI 10.1007/s13246-010-0019-3

TECHNICAL PAPER

Thermoluminescence dosimetry for skin dose assessment during intraoperative radiotherapy for early breast cancer

P. Fogg · K. R. Das · T. Kron · C. Fox · B. Chua · J. Hagekyriakou

Received: 7 April 2008 / Accepted: 17 January 2010 / Published online: 9 July 2010

Abstract Dosimetry for intraoperative radiotherapy (IORT) after wide local excision for breast cancer using a 50 kV X-ray needle (Intrabeam) was performed in vivo using thermoluminescence dosimetry. Eight LiF:Mg,Ti chips were placed on the skin around the incision site after wide local excision while the tumour bed was irradiated to

of spherical applicators used in the delivery of IORT targeted at the tumour bed after wide local excision in women with early breast cancer.

The device as described in the literature [1, 2], produces a near isotropic beam at the probe tip of energies 30, 40 and 50 kVp. Treatment applicator sphere sizes range from 1.5

Breast, TLDs, skin dose

International Journal of
Radiation Oncology
biology • physics

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Clinical Investigation: Breast Cancer

In Vivo Dosimetry for Single-Fraction Targeted Intraoperative Radiotherapy (TARGIT) for Breast Cancer

David J. Eaton, M.Sc.,* Bronagh Best,* Chris Brew-Graves, M.Sc.,§ Stephen Duck, M.Sc.,* Tabasom Ghaus, B.Sc.,† Regina Gonzalez, M.Sc.,* Katharine Pigott, M.D.,† Claire Reynolds, B.Sc.,† Norman R. Williams, Ph.D.,§ and Mohammed R.S. Keshtgar, Ph.D., F.R.C.S.‡

*Departments of *Radiotherapy Physics, †Radiotherapy, and ‡Surgery, Royal Free Hospital, University College London, London, England; and §Research Department of Surgery, Division of Surgery and Interventional Science, University College London, London, England*

Received Aug 22, 2011, and in revised form Oct 31, 2011. Accepted for publication Nov 1, 2011

Summary

In vivo dosimetry using thermoluminescent dosimeters may be used to estimate skin doses during single-fraction intraoperative radiotherapy of the breast using

Purpose: *In vivo* dosimetry provides an independent check of delivered dose and gives confidence in the introduction or consistency of radiotherapy techniques. Single-fraction intraoperative radiotherapy of the breast can be performed with the Intrabeam compact, mobile 50 kV x-ray source (Carl Zeiss Surgical, Oberkochen, Germany). Thermoluminescent dosimeters (TLDs) can be used to estimate skin doses during these treatments.

Methods and Materials: Measurements of skin doses were taken using TLDs for 72 patients over 3 years of clinical treatments. Phantom studies were also undertaken to assess the uncertainties resulting from changes in beam quality and backscatter conditions *in vivo*.

Breast, TLDs, skin dose

Medical Physics
The International Journal of Medical Physics Research and Practice

In vivo dosimetry with optically stimulated dosimeters and RTQA2 radiochromic film for intraoperative radiotherapy of the breast

Caleb Price, Aaron Pederson, Chanté Frazier, and John Duttenhaver

Citation: Medical Physics **40**, 091716 (2013); doi: 10.1118/1.4819825
View online: http://dx.doi.org/10.1118/1.4819825

Breast, tumor cavity and skin dose, OSLDs and QA films

Medical Physics
The International Journal of Medical Physics Research and Practice

In vivo dosimetry with radiochromic films in low-voltage intraoperative radiotherapy of the breast

M. Avanzo, A. Rink, A. Dassie, S. Massarut, M. Roncadin, E. Borsatti, and E. Capra

Citation: Medical Physics **39**, 2359 (2012); doi: 10.1118/1.3700175
View online: http://dx.doi.org/10.1118/1.3700175

Breast; tumor cavity, skin, and fascia pectoralis dose; films

IOERT

Ann Surg Oncol (2009) 16:100–105
DOI 10.1245/s10434-008-0172-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Is Electron Beam Intraoperative Radiotherapy (ELIOT) Safe in Pregnant Women with Early Breast Cancer? In Vivo Dosimetry to Assess Fetal Dose

Viviana Galimberti[1], Mario Ciocca[2], Maria Cristina Leonardi[3], Vanna Zanagnolo[4], Baratella Paola[1], Sargenti Manuela[1], Rafaela Cecilio Sahium[1], Roberta Lazzari[3], Oreste Gentilini[1], Fedro Peccatori[5], Umberto Veronesi[1], and Roberto Orecchia[3,6]

[1]Unit of Molecular Senology, Senology Department, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy; [2]Department of Medical Physics, European Institute of Oncology, Milan, Italy; [3]Department of Radiotherapy, European Institute of Oncology, Milan, Italy; [4]Department of Gynecology, European Institute of Oncology, Milan, Italy; [5]Unit of Allogenic Transplantation, European Institute of Oncology, Milan, Italy; [6]University of Milan, Milan, Italy

ABSTRACT Electron beam intraoperative radiotherapy (ELIOT) is a new technique permitting breast radiotherapy to be completed in a single session. Since ELIOT is associated with much reduced irradiation to nontarget tissues,

Although breast cancer is rarely diagnosed in pregnancy (about 1 per 1000), the event has a major, sometimes devastating, emotional impact on the woman. In such cases, mastectomy is the usual treatment, since the cancer

Breast, TLDs, fetal dose

JOURNAL OF APPLIED CLINICAL MEDICAL PHYSICS, VOLUME 16, NUMBER 1, 2015

In vivo dosimetry and shielding disk alignment verification by EBT3 GAFCHROMIC film in breast IOERT treatment

Mara Severgnini,[1a] Mario de Denaro,[1] Marina Bortul,[2] Cristiana Vidali,[3] Aulo Beorchia[3]
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Received 7 May, 2014; accepted 3 September, 2014

Intraoperative electron radiation therapy (IOERT) cannot usually benefit, as conventional external radiotherapy, from software systems of treatment planning based on computed tomography and from common dose verify procedures. For this reason, *in vivo* film dosimetry (IVFD) proves to be an effective methodology to evaluate the actual radiation dose delivered to the target. A practical method for IVFD during breast IOERT was carried out to improve information on the dose actually delivered to the tumor target and on the alignment of the shielding disk with respect to the electron beam. Two EBT3 GAFCHROMIC films have been positioned on the two sides of the shielding disk in order to obtain the dose maps at the target and beyond the disk. Moreover the postprocessing analysis of the dose distribution measured on the films provides a quantitative estimate of the misalignment between the

Breast, films, tumor cavity dose and lung protection transmission and alignment

Medical Physics
The International Journal of Medical Physics Research and Practice

Setup verification and in vivo dosimetry during intraoperative radiation therapy (IORT) for prostate cancer

Antonella Soriani, Valeria Landoni, Simona Marzi, Giuseppe Iaccarino, Biancamaria Saracino, Giorgio Arcangeli, and Marcello Benassi

Citation: Medical Physics **34**, 3205 (2007); doi: 10.1118/1.2750965
View online: http://dx.doi.org/10.1118/1.2750965
View Table of Contents: http://scitation.aip.org/content/aapm/journal/medphys/34/8?ver=pdfcov
Published by the American Association of Physicists in Medicine

Prostate, MOSFETs, bladder-urethral anastomosis dose. 101% [89.3%, 110.5%]

Lemanski *et al. Radiation Oncology* 2013, **8**:191
http://www.ro-journal.com/content/8/1/191

RADIATION ONCOLOGY

STUDY PROTOCOL Open Access

Electrons for intraoperative radiotherapy in selected breast-cancer patients: late results of the Montpellier phase II trial

Claire Lemanski[1], David Azria[1*], Sophie Gourgou-Bourgade[2], Norbert Ailleres[1], Aurelie Pastant[1], Philippe Rouanet[3], Pascal Fenoglietto[1], Jean-Bernard Dubois[1] and Marian Gutowski[3]

Abstract

Background: The Montpellier cancer institute phase II trial started in 2004 and evaluated the feasibility of intraoperative radiotherapy (IORT) technique given as a sole radiation treatment for patients with an excellent prognostic and very low recurrence risk.

Methods: Forty-two patients were included between 2004 and 2007. Inclusion criteria were patients ≥ 65 years old, T0-T1, N0, ductal invasive unifocal carcinoma, free-margin > 2 mm. IORT was delivered using dedicated linear

Breast, diode, median tumor bed dose 100% [84%, 114%]

ELSEVIER

Radiotherapy and Oncology 69 (2003) 285–289

RADIOTHERAPY & ONCOLOGY
JOURNAL OF THE EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

www.elsevier.com/locate/radonline

In vivo dosimetry using radiochromic films during intraoperative electron beam radiation therapy in early-stage breast cancer

Mario Ciocca[a,*], Roberto Orecchia[b], Cristina Garibaldi[a], Elena Rondi[a], Alberto Luini[c], Giovanna Gatti[c], Mattia Intra[c], Paolo Veronesi[c], Roberta Lazzari[b], Giampiero Tosi[a], Umberto Veronesi[c]

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Received 4 December 2002; received in revised form 19 August 2003; accepted 12 September 2003

Abstract

Background and purpose: To check the dose delivered to patients during intraoperative electron beam radiation therapy (IOERT) for early breast cancer and also to define appropriate action levels.

Patients and methods: Between December 2000 and June 2001, 54 patients affected by early-stage breast cancer underwent exclusive IOERT to the tumour bed using a Novac7 mobile linac, after quadrantectomy. Electron beams (5, 7, 9 MeV) at high dose per pulse values (0.02–0.09 Gy/pulse) were used. The prescribed single dose was 21 Gy at the depth of 90% isodose (14–22 mm). In 35 cases, in vivo dosimetry was performed. The entrance dose was derived from the surface dose measured with thin and calibrated MD-55-2 radiochromic films, wrapped in sterile envelopes. Films were analysed 24–72 h after the irradiation using a charge-coupled-device imaging system. Field

Breast, films, tumor bed dose

101.8% [90.1%, 109.9%]

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 3, pp. 952–960, 2005

0360-3016/05/$–see front matter

doi:10.1016/j.ijrobp.2005.02.049

PHYSICS CONTRIBUTION

IN VIVO DOSIMETRY WITH MOSFETS: DOSIMETRIC CHARACTERIZATION AND FIRST CLINICAL RESULTS IN INTRAOPERATIVE RADIOTHERAPY

Rita Consorti, Ph.D.,* Assunta Petrucci, Ph.D.,* Falbo Fortunato,* Antonella Soriani, Ph.D.,† Simona Marzi, Ph.D.,† Giuseppe Iaccarino, Ph.D.,† Valeria Landoni, Ph.D.,† and Marcello Benassi, Ph.D.†

*Unità Operativa di Fisica Sanitaria, H.S. Filippo Neri, Roma, Italy; †Laboratorio di Fisica Medica, Istituto Regina Elena, Roma, Italy

Purpose: To investigate the use of metal oxide silicon field effect transistors (MOSFETs) as *in vivo* dosimetry detectors during electron beams at high dose-per-pulse intraoperative radiotherapy.
Methods and Materials: The MOSFET system response in terms of reproducibility, energy, dose rate and temperature dependence, dose-linearity from 1 to 25 Gy, angular response, and dose perturbation was analyzed in the 6–9-MeV electron beam energy range produced by an intraoperative radiotherapy-dedicated mobile accelerator. We compared these with the 6- and 9-MeV electron beams produced by a conventional accelerator.

Pancreas and breast, MOSFETs, tumor bed dose. 102.1% [93.1%, 111.6%]

Radiotherapy and Oncology 78 (2006) 213-216
www.thegreenjournal.com

IORT dosimetry

Real-time in vivo dosimetry using micro-MOSFET detectors during intraoperative electron beam radiation therapy in early-stage breast cancer

Mario Ciocca[a,*], Valeria Piazzi[a], Roberta Lazzari[b], Andrea Vavassori[b], Alberto Luini[c], Paolo Veronesi[c], Viviana Galimberti[c], Mattia Intra[c], Andrea Guido[b], Giampiero Tosi[a], Umberto Veronesi[c,d], Roberto Orecchia[b]

[a]*Department of Medical Physics,* [b]*Division of Radiation Oncology,* [c]*Division of Senology, and* [d]*Scientific Director, European Institute of Oncology, Milano, Italy.*

Abstract

Purpose: In a previous paper we reported the results of off-line in vivo measurements using radiochromic films in IOERT. In the present study, a further step was made, aiming at the improvement of the effectiveness of in vivo dosimetry, based on a real-time check of the dose.

Materials and methods: Entrance dose was determined using micro-MOSFET detectors placed inside a thin, sterile, transparent catheter. The epoxy side of the detector was faced towards the beam to minimize the anisotropy. Each detector was plugged into a bias supply (standard sensitivity) and calibrated at 5 Gy using 6 MeV electrons produced by a conventional linac. Detectors were characterized in terms of linearity, precision and dose per pulse dependence. No

Breast, MOSFETs, tumor bed dose

100.6% [92%, 110%]

Radiotherapy and Oncology 103 (2012) 188–192

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

IORT in breast cancer

On-line optimization of intraoperative electron beam radiotherapy of the breast

Stefano Agostinelli [a,*], Marco Gusinu [a], Francesca Cavagnetto [a], Stefania Garelli [a], Michele Zeverino [a], Marina Guenzi [b], Renzo Corvò [b,c], Gianni Taccini [a]

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ARTICLE INFO

Article history:
Received 20 May 2011
Received in revised form 12 January 2012
Accepted 19 January 2012
Available online 17 February 2012

Keywords:
IORT

ABSTRACT

Purpose: To optimize the dose delivery to the breast lumpectomy target treated with intraoperative electron beam radiotherapy (IOERT).

Materials and methods: Two tools have been developed in our MU calculation software NEMO X to improve the dose homogeneity and the in-vivo dosimetry effectiveness for IOERT treatments. Given the target (tumor bed) thickness measured by the surgeon, NEMO X can provide auto dose normalization to cover 95% of the target volume with 95% of the prescription dose (PD) and a "best guess" of the expected dosimeter dose (EDD) for a deep seated in-vivo dosimeter. The tools have been validated with

Breast, MOSFETs, tumor bed dose.

Raw data: 109.1% [82%, 125%]

Radiotherapy and Oncology 80 (2006) 288–295
www.thegreenjournal.com

MOSFET detectors

Clinical implementation of MOSFET detectors for dosimetry in electron beams

Esther J. Bloemen-van Gurp*, Andre W.H. Minken, Ben J. Mijnheer, Cary J.G. Dehing-Oberye, Philippe Lambin

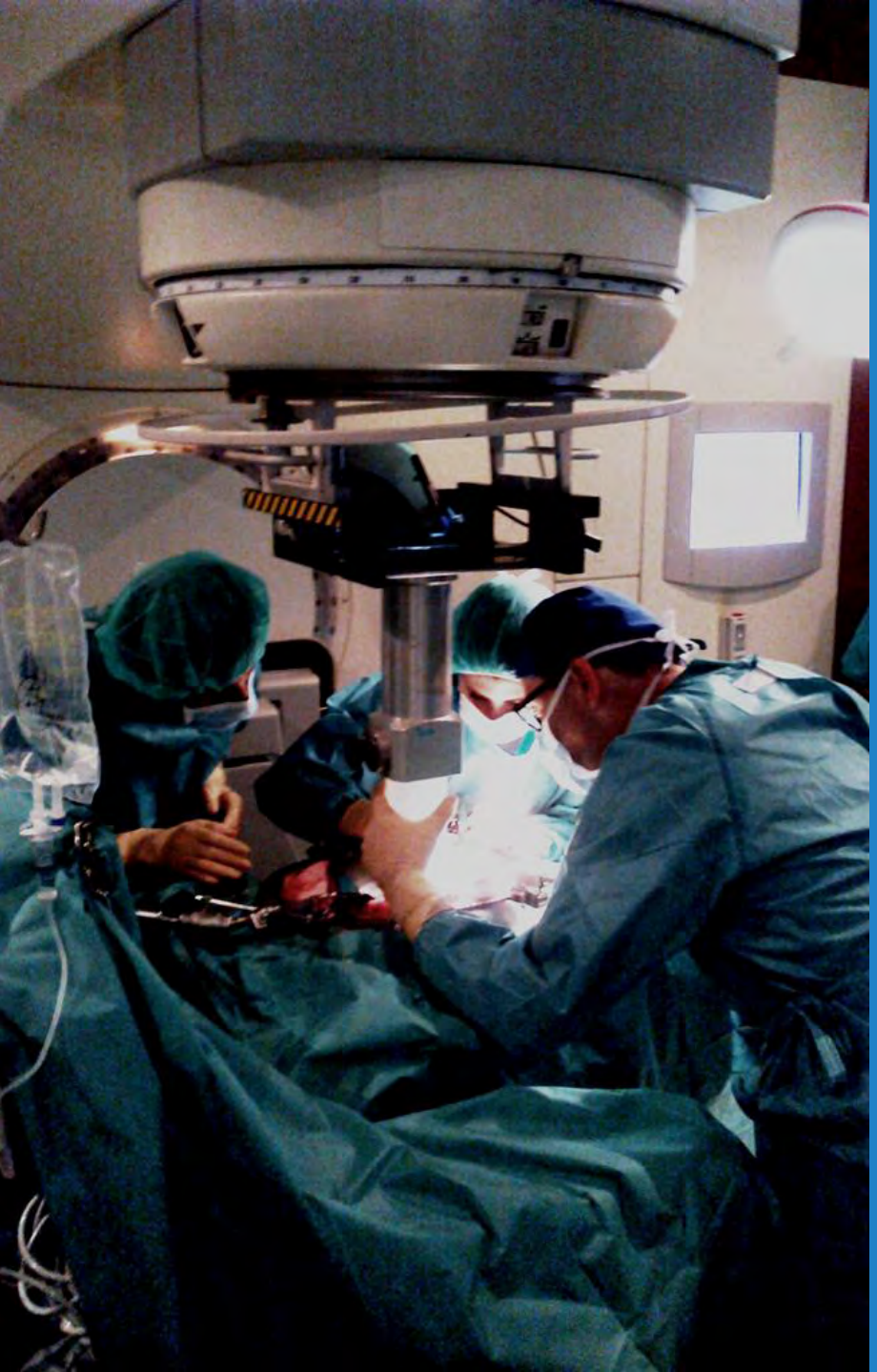
Department of Radiation Oncology (MAASTRO), University Hospital Maastricht, Maastricht, The Netherlands

Abstract

Background and purpose: To determine the factors converting the reading of a MOSFET detector placed on the patient's skin without additional build-up to the dose at the depth of dose maximum (D_{max}) and investigate their feasibility for in vivo dose measurements in electron beams.

Materials and methods: Factors were determined to relate the reading of a MOSFET detector to D_{max} for 4–15 MeV electron beams in reference conditions. The influence of variation in field size, SSD, angle and field shape on the MOSFET reading, obtained without additional build-up, was evaluated using 4, 8 and 15 MeV beams and compared to ionisation chamber data at the depth of dose maximum (z_{max}). Patient entrance in vivo measurements included 40 patients, mostly

Various sites, MOSFETs, tumor bed dose 99.3% [91.9%, 104.7%]



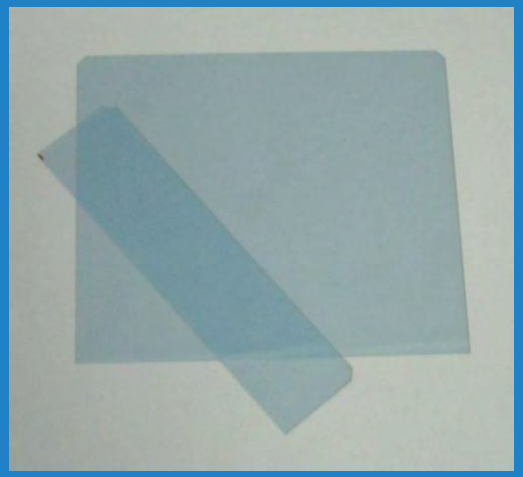
In vivo dosimetry in the Consorcio Hospitalario Provincial de Castellón

First questions

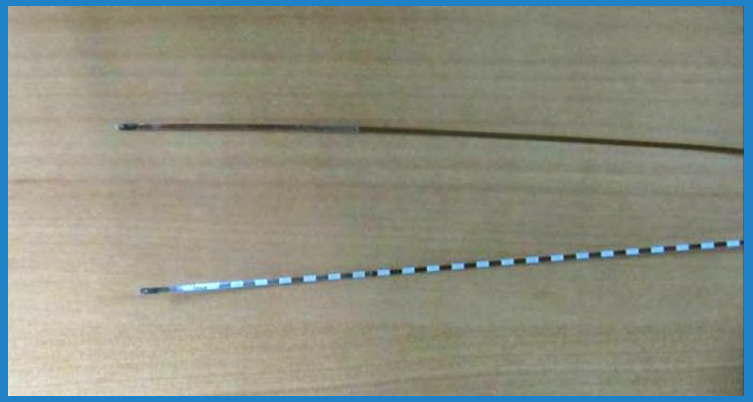
- various localizations with a fixed linac?
- films or MOSFETs?

Our detectors

Radiochromic film
Gafchromic MD-55-2



MOSFETs
mobile TN-502RDM-H



Our aim: to evaluate detectors performance and to measure absorbed dose delivered to tumor bed

Dosimeters handling – film

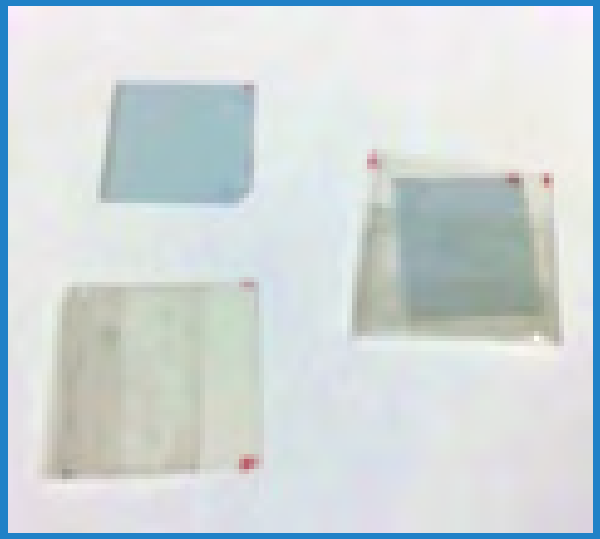
The film is cut into pieces of 1,5 cm × 1,5 cm

Every piece is packed between two plastic pieces of 2 cm × 2 cm

Sterilization by means of gas plasma

Placement onto the tumor bed

After the treatment, enveloping materials removed and film sterilized again to ensure safe processing



Courtesy of Ana Bouché

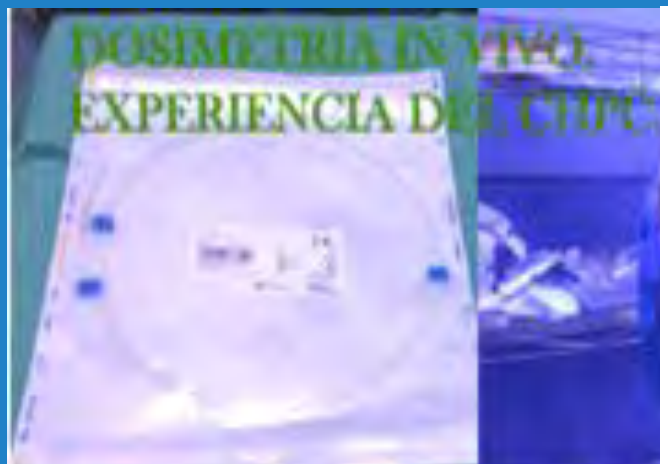
Dosimeters handling – MOSFET

Insertion into a bronchus sterile catheter

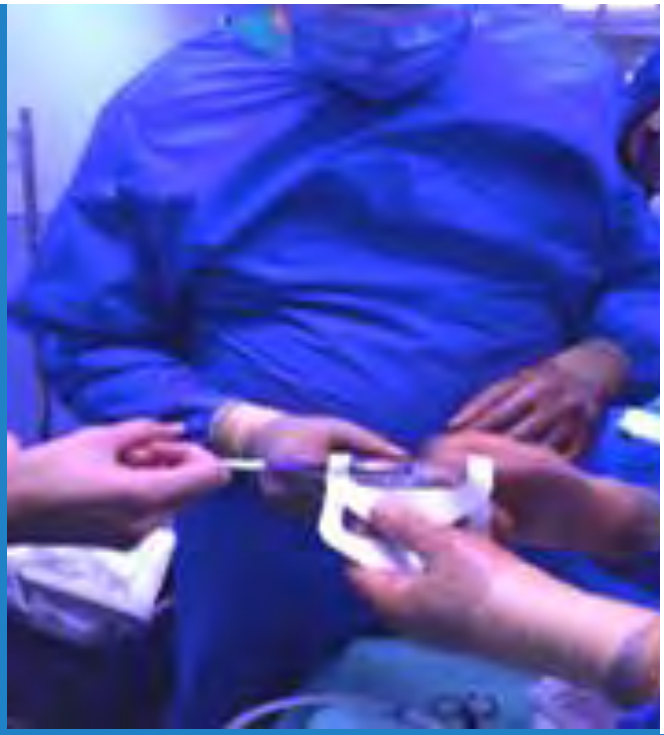
Attachment onto the tumor bed

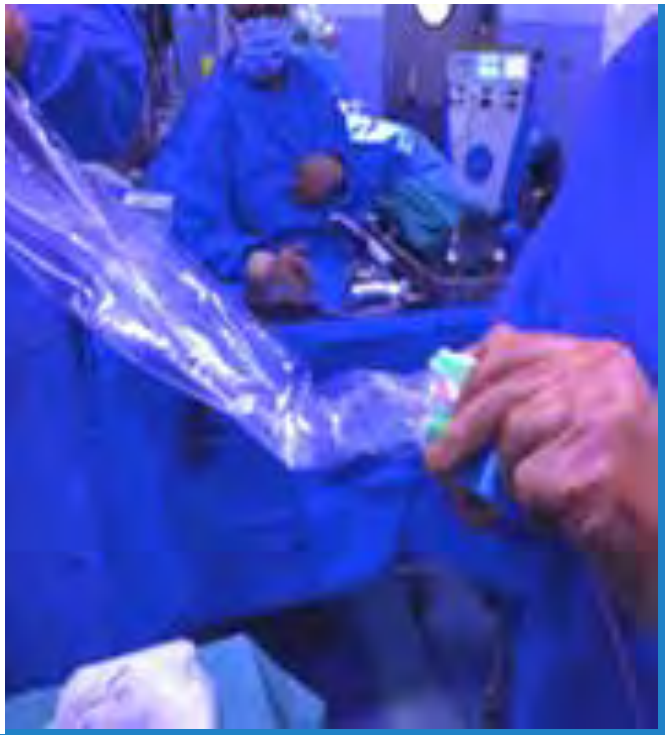
After the treatment the absorbed dose is recorded

Removal, wash, and storage for future uses

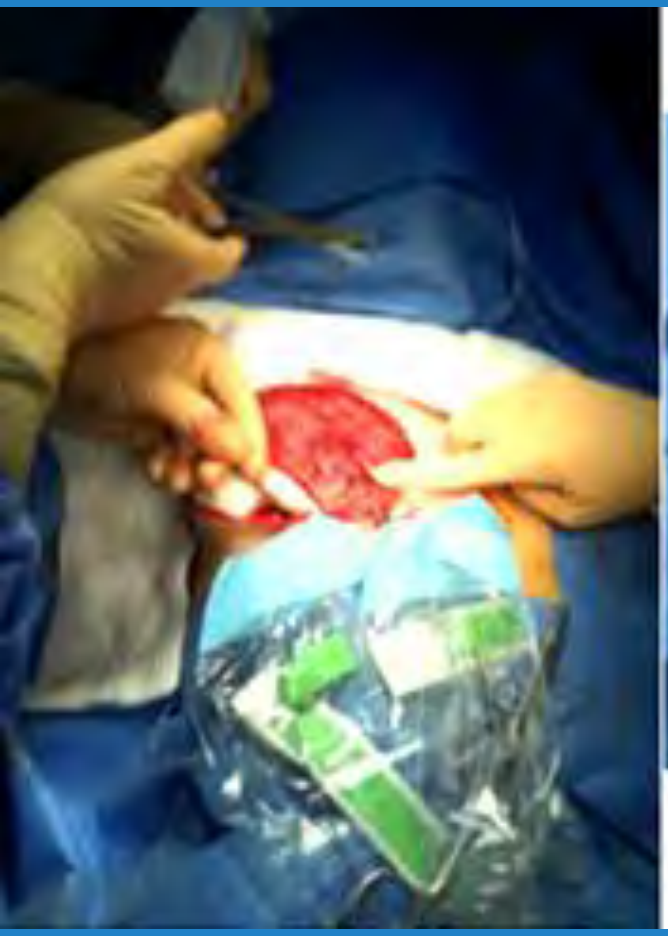








Courtesy of Ana Bouché



Courtesy of Ana Bouché

Calibration

Reinforced mobile MOSFET mobile TN-502RDM-H: linear relationship between absorbed dose and voltage difference

$$D = c\Delta V$$

Gafchromic MD-55-2 film: polynomial fit between absorbed doses and pixel values (red channel)

$$D = a_3 p^3 + a_2 p^2 + a_1 p + a_0$$

- Daily linac output
- Plastic slabs
- $z = z_{ref}$
- SSD = 100 cm

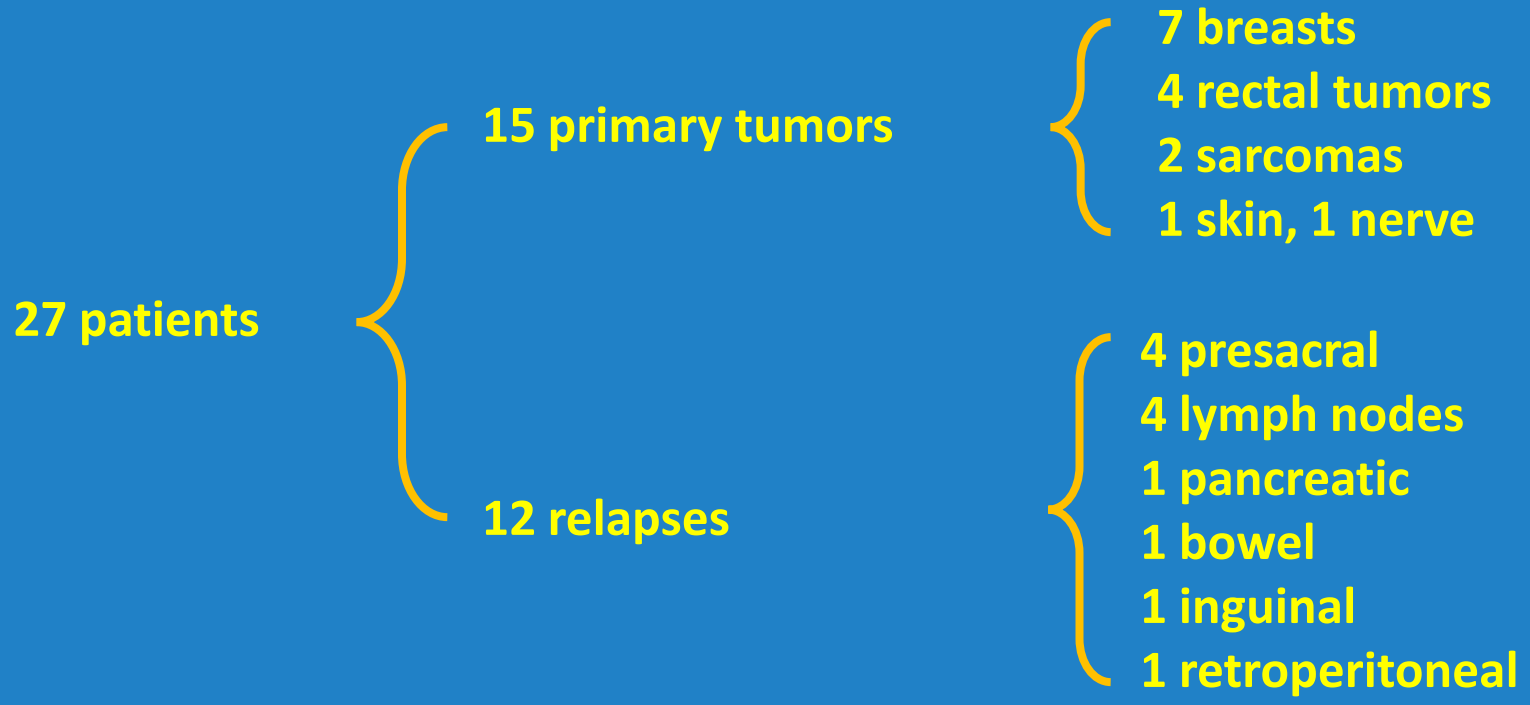
Estimation of uncertainties

Sources

- Absorbed dose delivered by the linac (< 1%)
- Detector readout (the main component)
- Lack of linearity of absorbed dose (rises with MUs and when the ratio Dose/MU diminishes, < 1%)

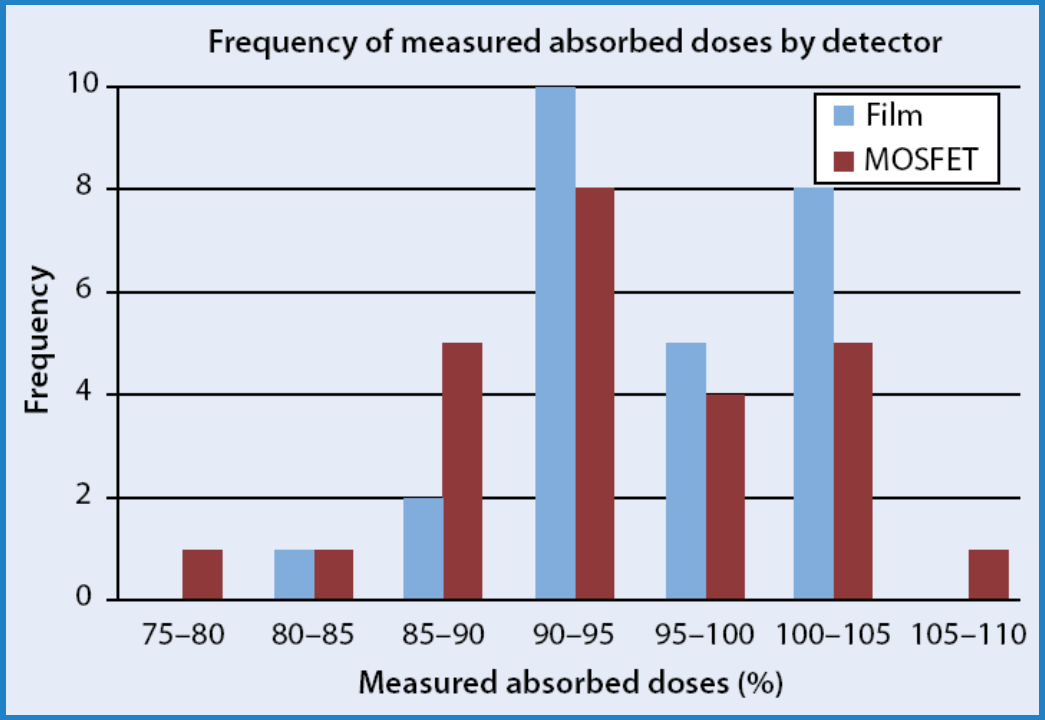
Results

First clinical experience with 27 patients



59 measurements at treatment zones

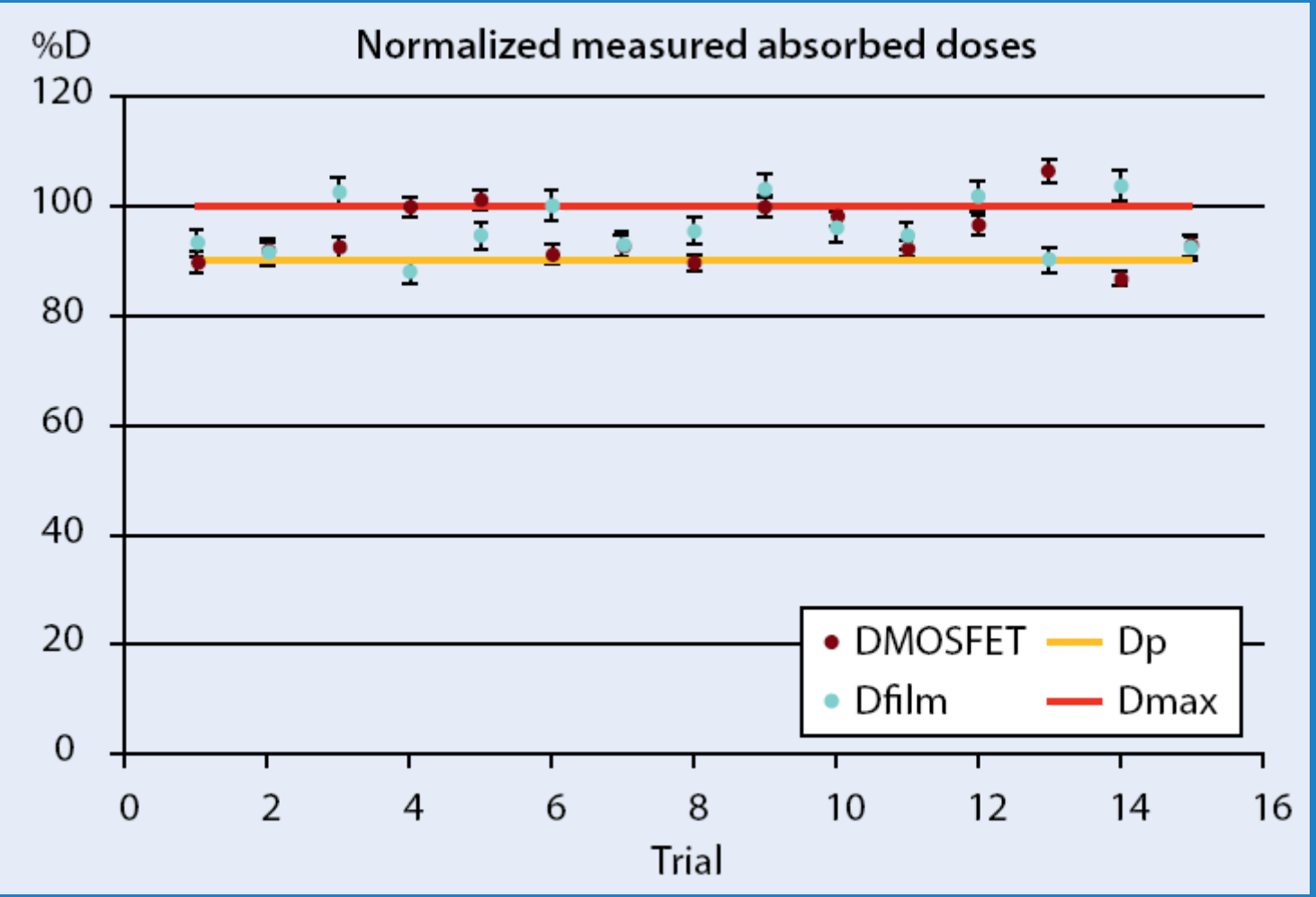
Measurements after dismissing outliers (deviation > 3s)



Detector	MOSFET	Film
Number of samples	25	26
Normalized absorbed doses (%)		
Minimum	78.0	82.8
Median	92.9	95.3
Mean	93.5	96.0
Standard deviation	6.5	5.5
Interquartile range	8.4	7.4
Maximum	106.6	103.9

The samples are homogeneous: Wilcoxon rank-sum test with p=0.109

Paired measurements, both detectors in bed



Relative uncertainties: 2.2% and 2.8% (k=1)

Samples no significantly shifted, p=0.363

Paired measurements, both detectors in bed

Tabl-e 4 Descriptive statistics of the selected measurements performed at the same plane of the tumor bed classified by type of detector

Detector	MOSFET	Film
Number of samples	15	15
Normalized absorbed doses (%)		
Minimum	86.9	88.4
Median	92.9	95.0
Mean	95.0	96.4
Standard deviation	5.4	5.0
Interquartile range	8.6	9.2
Maximum	106.6	103.9

Contingency tables – associations

Between kind of detector and incompatibility?

		incompatible		Total
		no	yes	
detector	MOSFET	21	4	25
	film	21	5	26
Total		42	9	51
Fisher's exact test		*p*		0.526

NO association

Between treating a breast or another localization and incompatibility?

		incompatible		Total
		no	yes	
Breast	no	34	6	40
	yes	8	3	11
Total		42	9	51
Fisher's exact test		*p*		0.295

NO association

Between radiation oncologist impression on difficulty and incompatibility?

		incompatible		Total
		no	yes	
Difficult	yes	16	4	20
	no	26	5	31
Total		42	9	51
Fisher's exact test		*p*		0.501

NO association

Conclusions

In vivo **dosimetry is basically successful, even with the studied factors**

Detector choice should depend on user factors (budget, training, reporting needs, etc.) and not on detector factors

Concerned and committed surgeons are crucial to succeed

Original article

Strahlenther Onkol 2014
DOI 10.1007/s00066-014-0689-y
Received: 21 October 2013
Accepted: 13 May 2014

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In vivo dosimetry in intraoperative electron radiotherapy

microMOSFETs, radiochromic films and a general-purpose linac

Intraoperative electron radiotherapy (IOERT) is a highly selective radiotherapy technique aimed at restricted anatomic volumes during surgical oncology treatment. It consists of single-fraction irradiation with a high delivered absorbed dose after direct visual examination of the tumor bed by means of an electron beam [1]. Currently, it is being revisited and reported on intensively [2–4].

creas. The differences between intended and measured absorbed doses ranged from −6.9 to 11.6%.

Ciocca et al. [7] performed entrance absorbed dose measurements on 45 breast cancer patients irradiated with NOVAC7 and LIAC mobile linacs. The differences between intended and measured absorbed doses ranged from −7.6 to 10%.

Soriani et al. [8] also used a NOVAC7

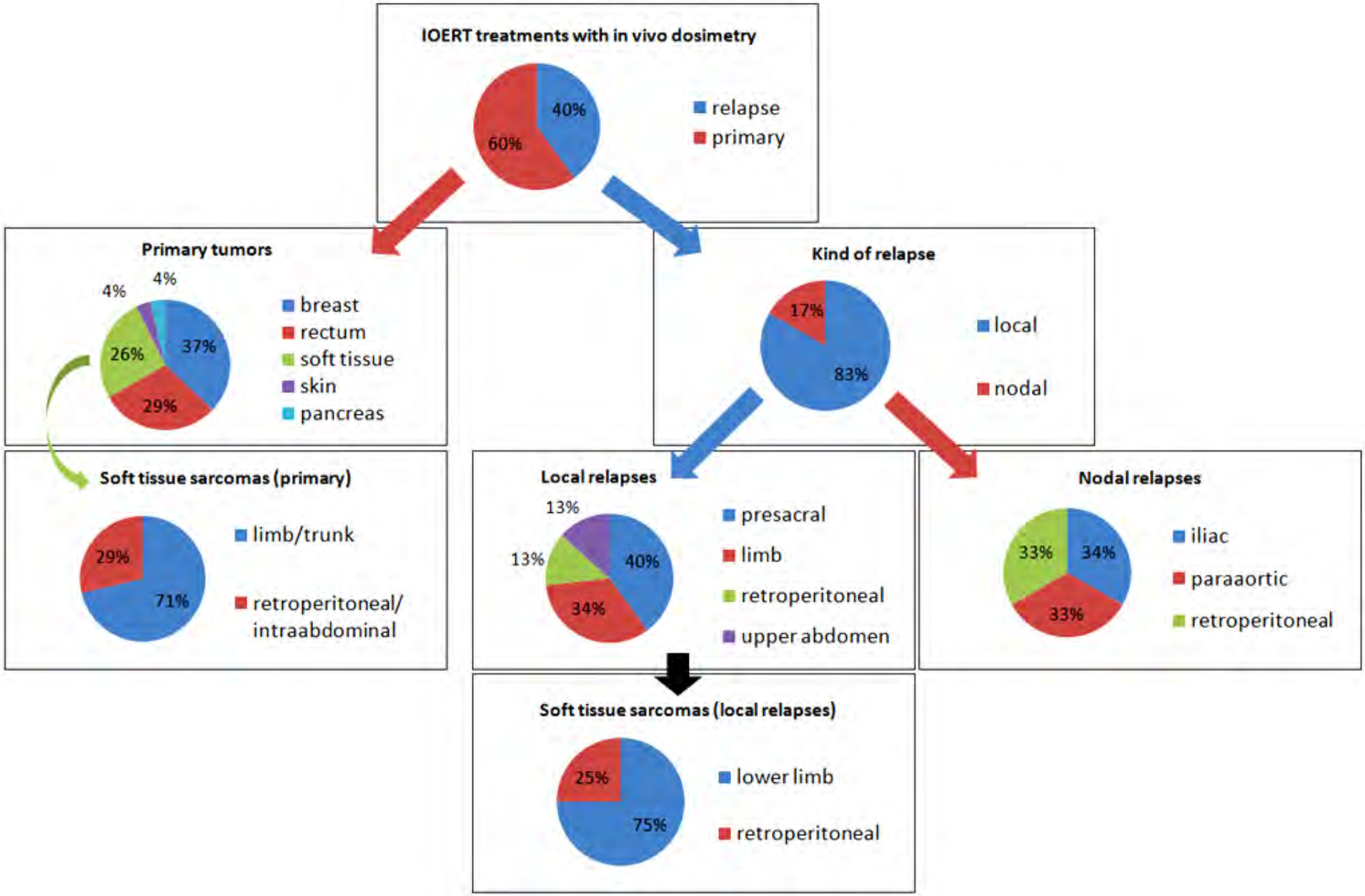
Krengli et al. [11] presented a study of 38 patients with locally advanced prostate cancer irradiated with a Mobetron mobile linac. Film dosimetry focused on measuring absorbed dose to the rectum.

Here, our aim was to share our experience in in vivo dosimetry with both MOSFETs and radiochromic films with patients undergoing IOERT using a general-purpose linac. We report the intrin-

Second question

In vivo dosimetry as a feasible program?

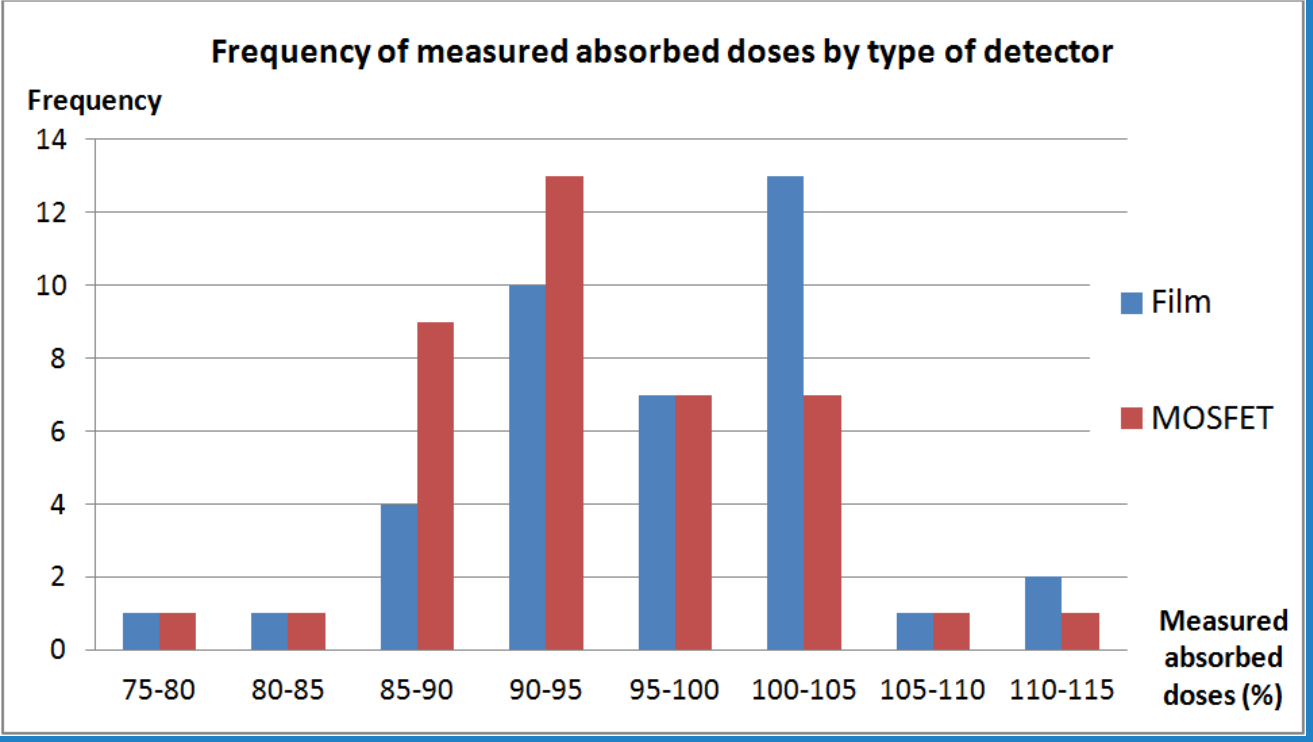
45 patients, 27 primary tumors, 18 relapses



Dosimetric parameters

Table 1 Distribution of dosimetric parameters, f stands for their relative frequency

Applicator diameter (cm)	f	Energy (MeV)	f	Bevel angle (°)	f	Prescribed dose (Gy)	f
4	4 %	4	6 %	0	56 %	5	6 %
5	2 %	6	17 %	30	33 %	9	8 %
6	35 %	9	52 %	45	10 %	10	8 %
7	23 %	12	19 %			12	4 %
8	13 %	15	6 %			12.5	33 %
9	13 %					15	17 %
10	6 %					17	4 %
12	4 %					17.5	6 %
						21	13 %



Feasible

Successful

Table 3 Descriptive statistics of the paired measurements

% Absorbed dose	MOSFET	Film
Minimum	78.0	72.0
1st quartile	90.2	92.4
Median	92.5	97.3
2nd quartile	97.6	103.0
Maximum	111.6	123.4
Mean	93.9	97.9
Standard deviation	6.8	9.7

Thirty pairs of values for which the prescribed dose was 90 % and the maximum absorbed dose delivered was 100 %

López-Tarjuelo et al. Radiation Oncology (2016) 11:41
DOI 10.1186/s13014-016-0621-y

Radiation Oncology

RESEARCH Open Access

Implementation of an intraoperative electron radiotherapy in vivo dosimetry program

Juan López-Tarjuelo[1*], Virginia Morillo-Macías[2,3], Ana Bouché-Babiloni[2], Enrique Boldó-Roda[4], Rafael Lozoya-Albacar[4] and Carlos Ferrer-Albiach[2,5]

Abstract

Background: Intraoperative electron radiotherapy (IOERT) is a highly selective radiotherapy technique which aims to treat restricted anatomic volumes during oncological surgery and is now the subject of intense re-evaluation. In vivo dosimetry has been recommended for IOERT and has been identified as a risk-reduction intervention in the context of an IOERT risk analysis. Despite reports of fruitful experiences, information about in vivo dosimetry in intraoperative radiotherapy is somewhat scarce. Therefore, the aim of this paper is to report our experience in developing a program of in vivo dosimetry for IOERT, from both multidisciplinary and practical approaches, in a consistent patient series. We also report several current weaknesses.

Methods: Reinforced TN-502RDM-H mobile metal oxide semiconductor field effect transistors (MOSFETs) and Gafchromic MD-55-2 films were used as a redundant in vivo treatment verification system with an Elekta Precise fixed linear accelerator for calibrations and treatments. In vivo dosimetry was performed in 45 patients in cases involving primary tumors or relapses. The most frequent primary tumors were breast (37 %) and colorectal (29 %), and local recurrences among relapses was 83 %. We made 50 attempts to measure with

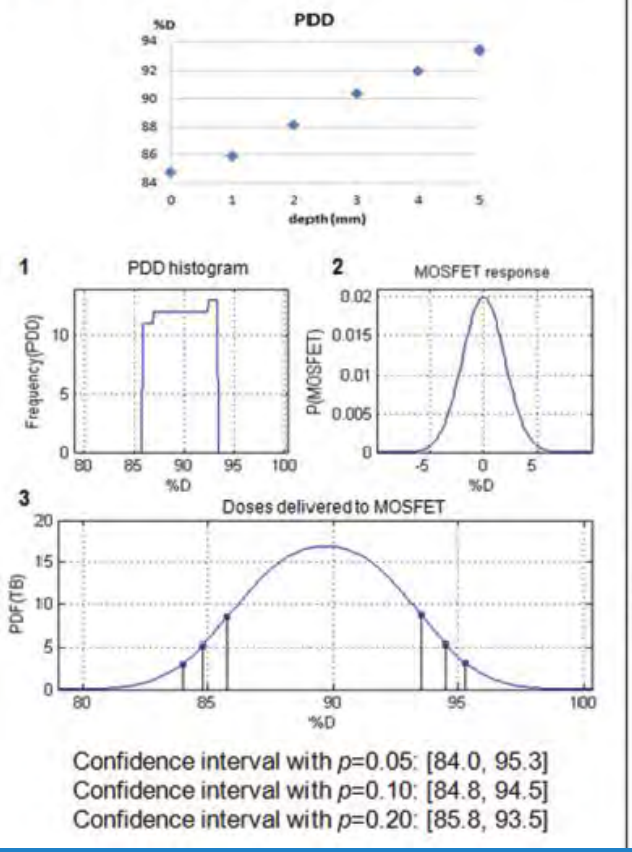
Third question

How to derive predictive action levels?

Physical model with 30 MOSFET measurements

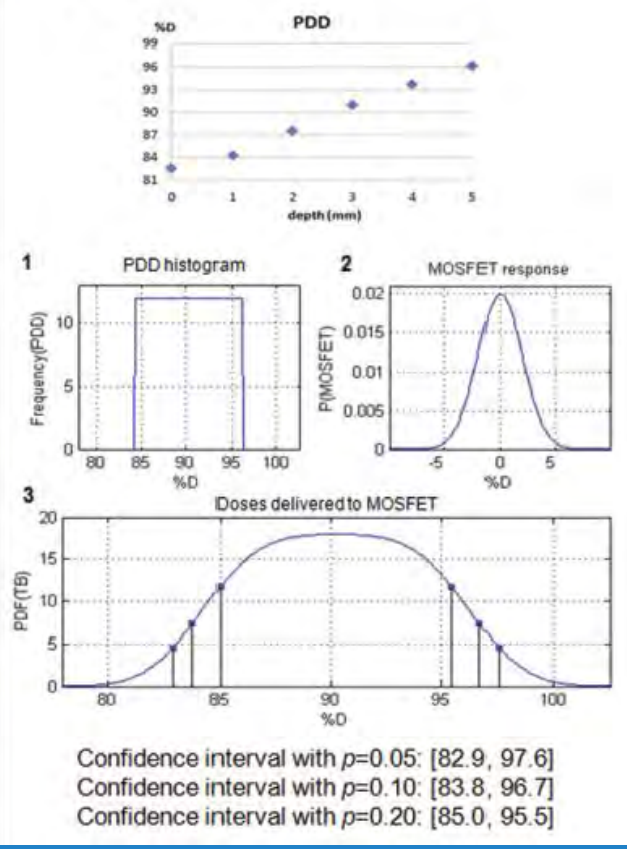
Convolution of the involved 5 mm of PDD with detector response (2%)

a) 5 cm, 9 MeV, 30°



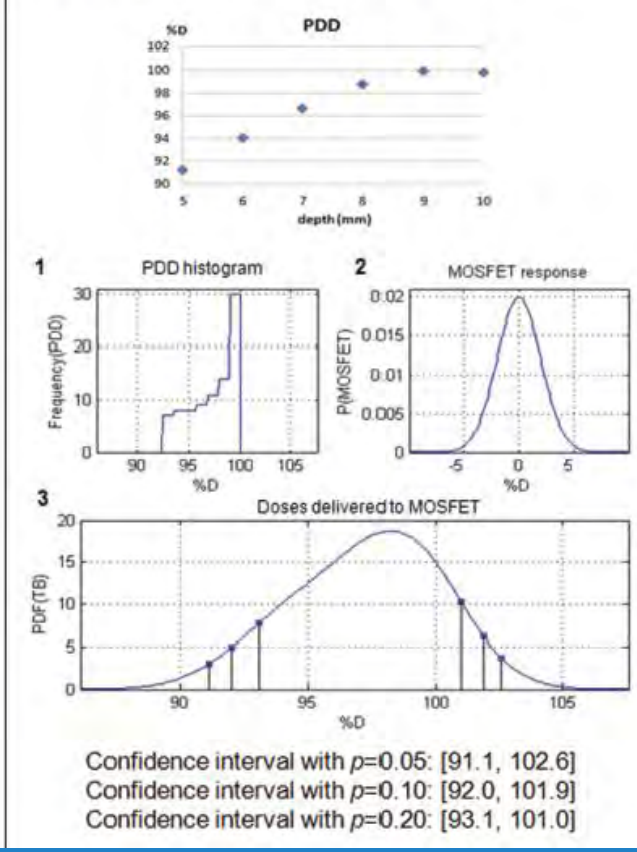
Confidence interval with p=0.05: [84.0, 95.3]
Confidence interval with p=0.10: [84.8, 94.5]
Confidence interval with p=0.20: [85.8, 93.5]

b) 6 cm, 9 MeV, 45°



Confidence interval with p=0.05: [82.9, 97.6]
Confidence interval with p=0.10: [83.8, 96.7]
Confidence interval with p=0.20: [85.0, 95.5]

c) 7 cm, 4 MeV, 0°, 5 mm bolus

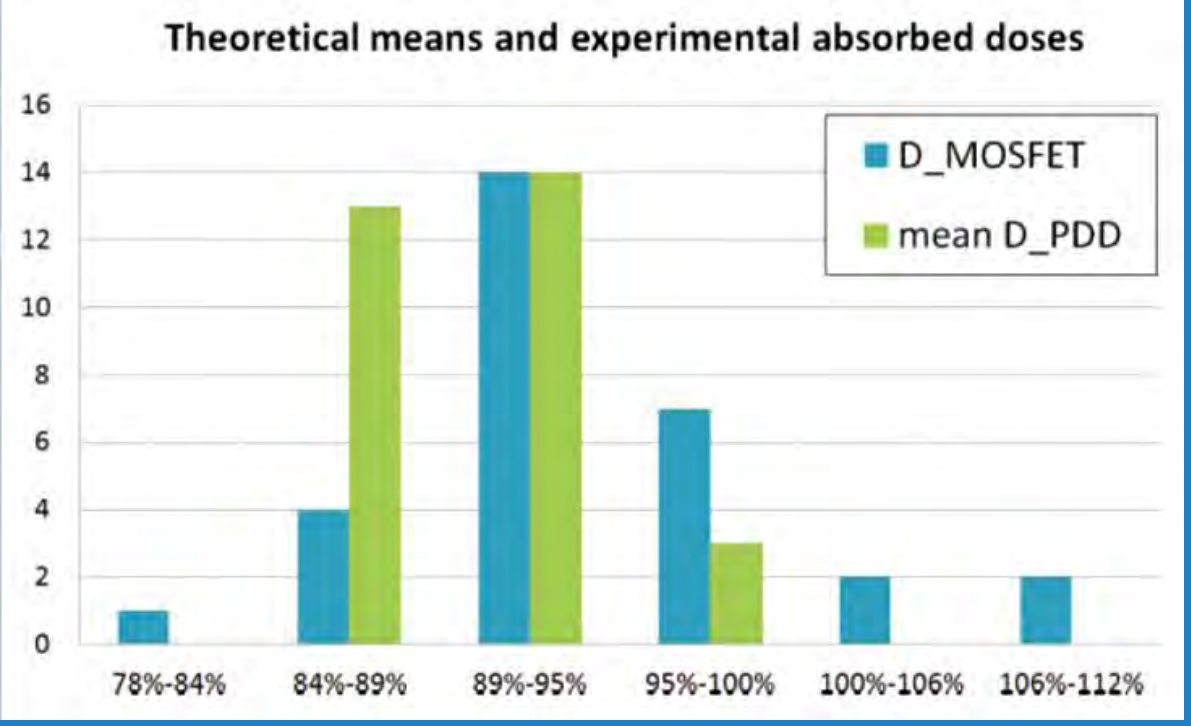


Confidence interval with p=0.05: [91.1, 102.6]
Confidence interval with p=0.10: [92.0, 101.9]
Confidence interval with p=0.20: [93.1, 101.0]

We also made comparisons with the mean of the PDD portion considered

For example, if $u_c(y)$ is dominated by a component of uncertainty evaluated from a rectangular distribution whose bounds are assumed to be exactly known, it is possible [if $t_p(\nu_{\text{eff}}) > \sqrt{3}$] that $y + U_p$ and $y - U_p$, the upper and lower limits of the interval defined by U_p, could lie outside the bounds of the probability distribution of the output quantity Y. Such cases must be dealt with on an individual basis but are often amenable to an approximate analytic treatment (involving, for example, the convolution of a normal distribution with a rectangular distribution [10]).

Applicator diameter, (cm)	Energy, (MeV)	Bevel angle, (°)	5-mm Bolus Present	Mean PDD, %	Lower AL, %, $P = .05$	Upper AL, %, $P = .05$	Confidence Interval Width, %	D_{MOSFET}, %	Result of Comparison
4	12	30		93.9	89.3	99.3	10.0	96.8	Inside
5	9	30		89.1	84.0	95.3	11.3	91.4	Inside
6	6	0	Yes	93.0	88.5	98.8	10.3	93.0	Inside
6	9	0		86.8	82.2	92.0	9.8	98.4	Greater
6	9	30		87.9	83.0	94.2	11.2	86.4	Inside
6	9	45		89.2	82.9	97.6	14.7	100.1	Greater
6	9	45		89.2	82.9	97.6	14.7	101.5	Greater
6	9	45		89.2	82.9	97.6	14.7	100.2	Greater
6	12	0		89.2	84.5	94.4	9.9	90.0	Inside
6	12	30		89.6	84.7	95.2	10.5	86.3	Inside
6	12	45		89.6	84.9	96.4	11.5	104.9	Greater
6	15	0		91.4	87.0	96.5	9.5	111.6	Greater
6	15	30		90.5	86.2	95.9	9.7	86.9	Inside
7	4	0	Yes	96.9	91.1	102.6	11.5	90.7	Lower
7	9	0		85.9	81.1	91.3	10.2	97.2	Greater
7	9	0	Yes	91.4	87.2	96.3	9.1	90.7	Inside
7	9	30		86.8	81.6	93.0	11.4	106.6	Greater
7	9	30		86.8	81.6	93.0	11.4	90.0	Inside
7	12	30		88.5	84.3	94.3	10.0	92.4	Inside
8	4	0	Yes	97.0	91.3	102.6	11.3	92.6	Inside
8	6	30		87.4	81.3	95.5	14.2	92.9	Inside
8	12	30		87.6	83.4	93.2	9.8	92.9	Inside
9	6	0	Yes	92.4	87.7	98.3	10.6	90.0	Inside
9	9	30		87.2	81.9	93.5	11.6	78.0	Lower
9	9	30		87.2	81.9	93.5	11.6	92.2	Inside
9	12	0		88.8	84.5	93.9	9.4	91.8	Inside
10	9	0	Yes	91.6	87.6	96.6	9.0	91.4	Inside
10	12	0	Yes	93.8	89.7	98.3	8.6	97.7	Inside
12	4	0	Yes	96.7	91.0	102.5	11.5	87.0	Lower
12	6	0	Yes	93.8	88.8	99.4	10.6	95.8	Inside



Procedure theoretical mean: 90.3%

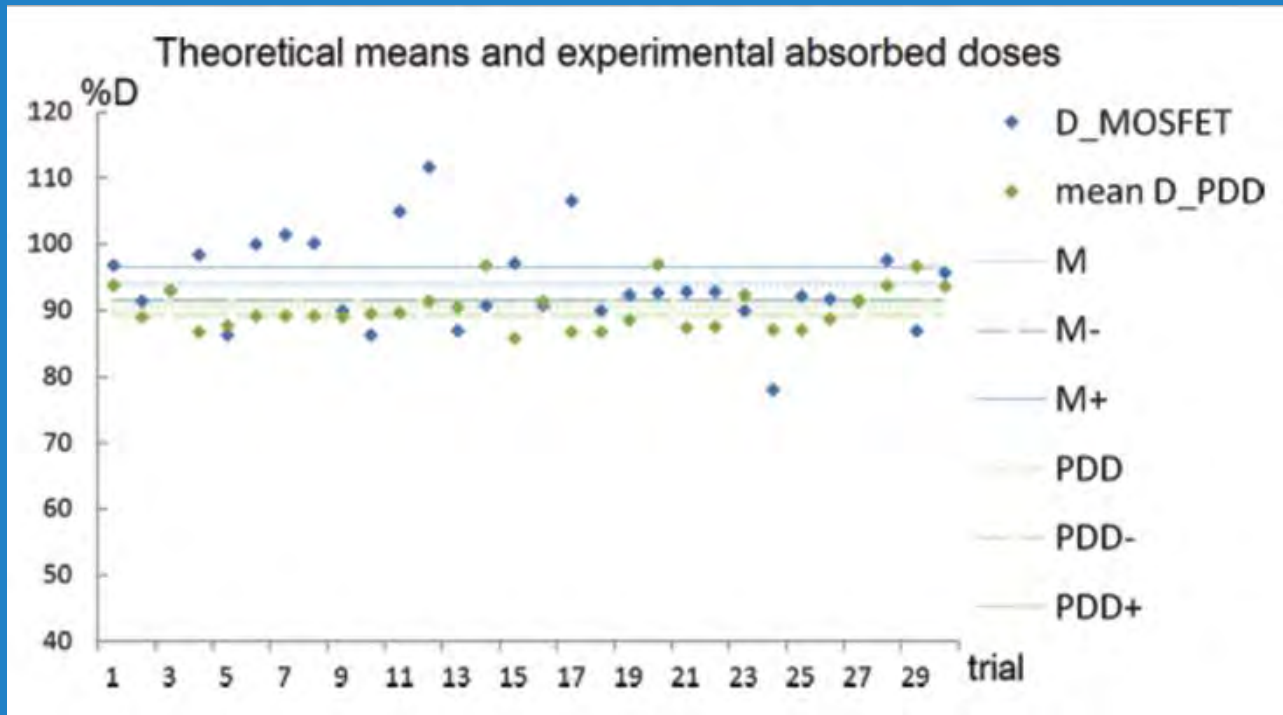
***In vivo* data mean: 93.9%**

Significantly shifted (p=0.023)

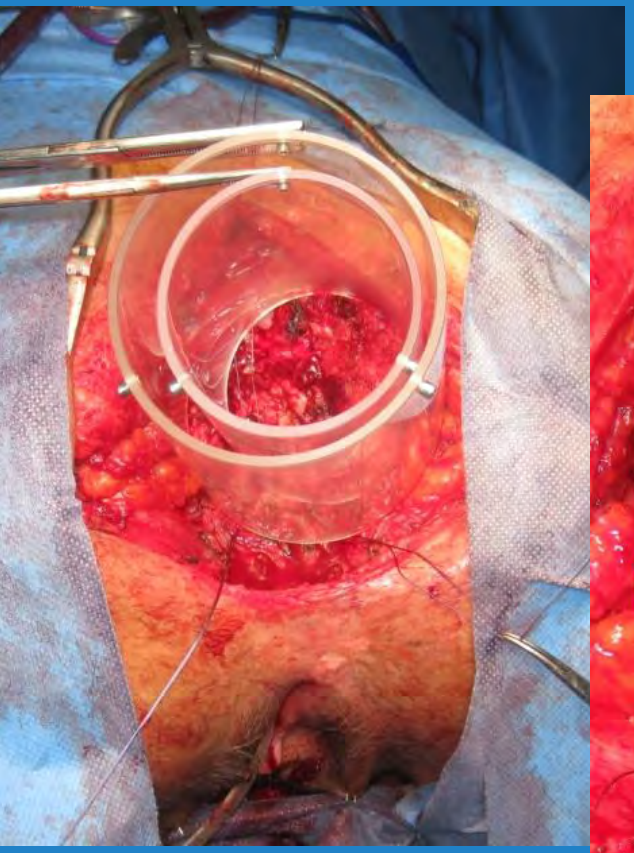
95% confidence intervals

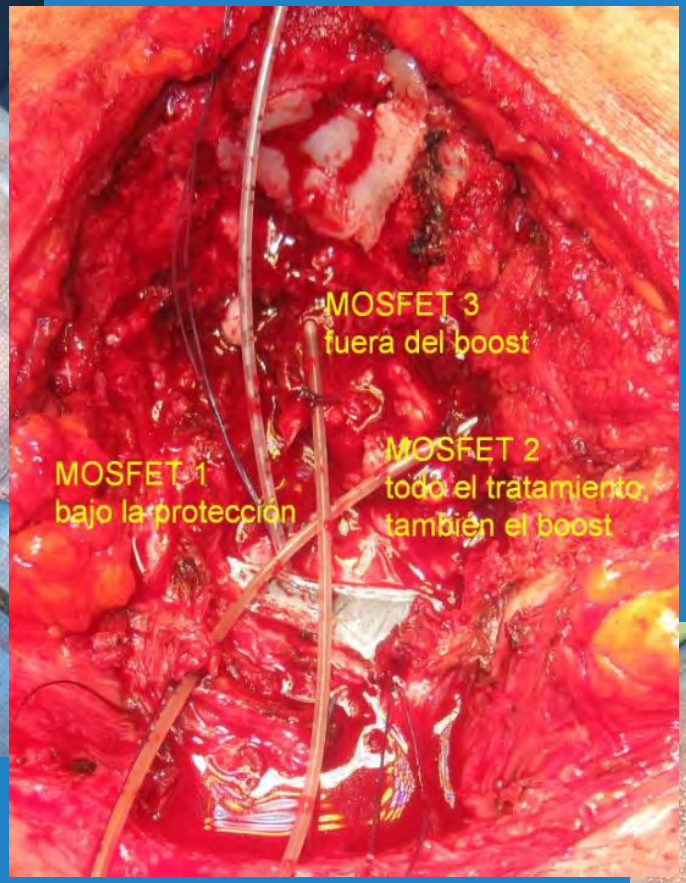
89.2% and 91.4%;

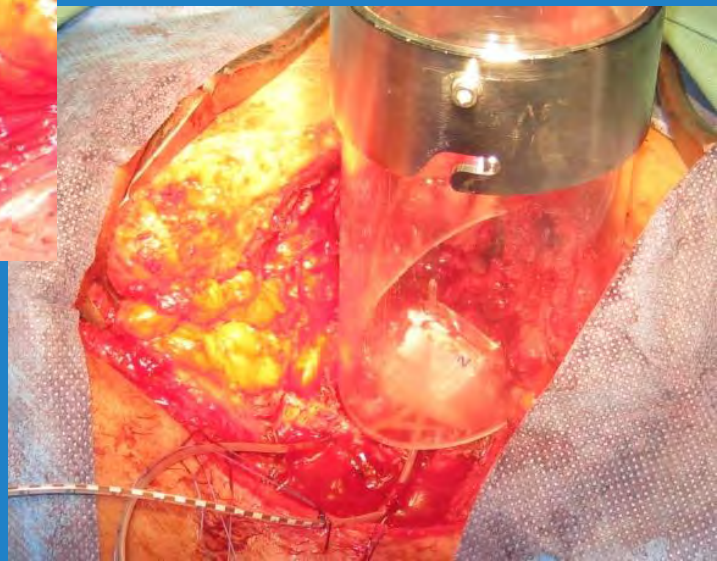
and 91.6% and 96.4%.



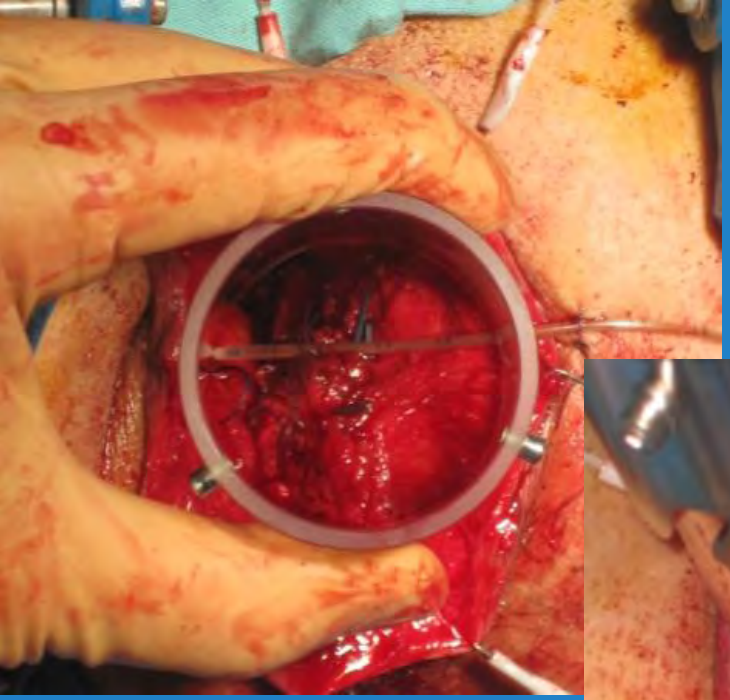
Bed relief can be very pronounced

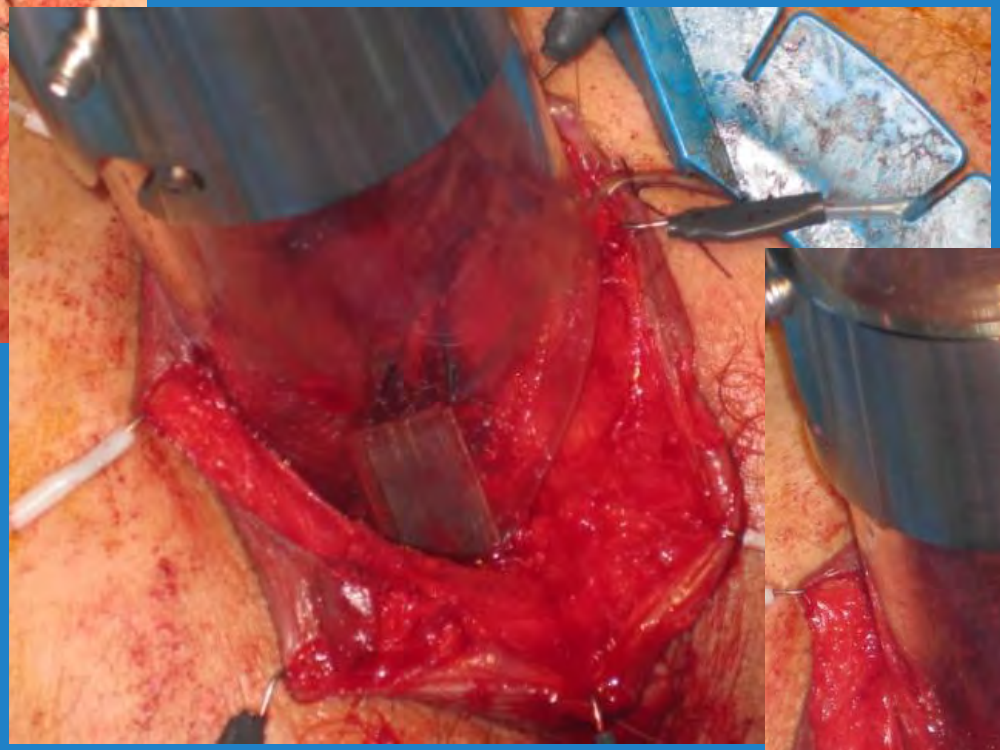


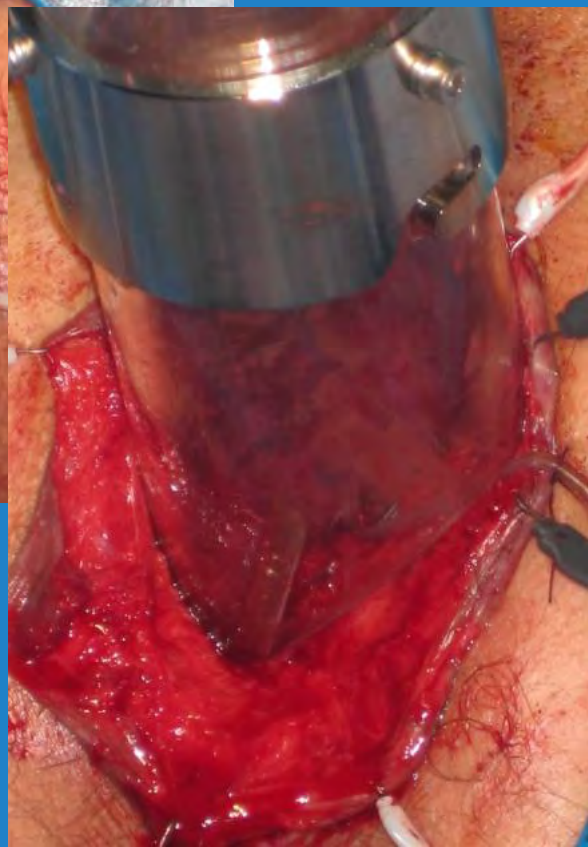




and detector placement, tricky







Conclusions

It is difficult to obtain very precise measurements

Wide set of localizations. Good global results, central values inside the treatment band (93%-94%).

Range of deviations higher than in studies on a unique localization

Films as a redundant system, compatible with MOSFETs (97.9% ± 3.6%, p=0.112)

Difference with respect the model (+3.6%). 27% of data above the upper limit → blood? obliquity? → we would need a detector localization system and more precise dosimeters

Original Article

Defining Action Levels for In Vivo Dosimetry in Intraoperative Electron Radiotherapy

Technology in Cancer Research & Treatment
1–7

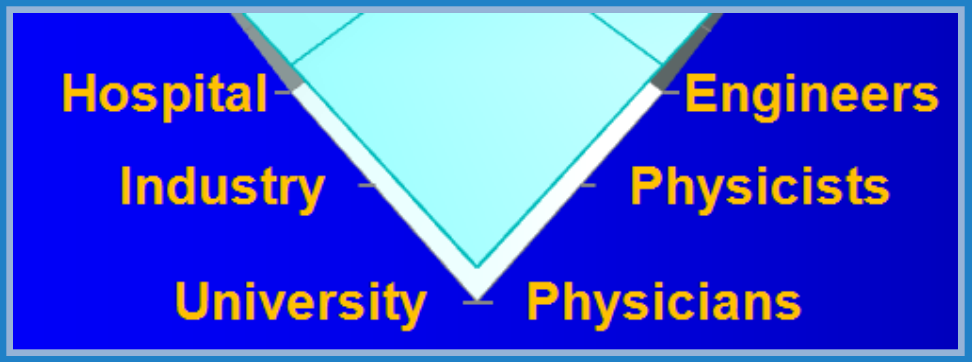
DOI: 10.1177/1533034615588196
tct.sagepub.com
SAGE

Juan López-Tarjuelo, MSc[1], Virginia Morillo-Macías, MD, PhD[2], Ana Bouché-Babiloni, MD[2], Carlos Ferrer-Albiach, MD, PhD[2,3], and Agustín Santos-Serra, MSc[1]

Abstract

In vivo dosimetry is recommended in intraoperative electron radiotherapy (IOERT). To perform real-time treatment monitoring, action levels (ALs) have to be calculated. Empirical approaches based on observation of samples have been reported previously, however, our aim is to present a predictive model for calculating ALs and to verify their validity with our experimental data. We considered the range of absorbed doses delivered to our detector by means of the percentage depth dose for the electron beams used. Then, we calculated the absorbed dose histograms and convoluted them with detector responses to obtain probability density functions in order to find ALs as certain probability levels. Our in vivo dosimeters were reinforced TN-502RDM-H mobile

Acknowledgements



- PI08/90473
- PSE-300000-2009-5
- PI09/90628
- IPT-300000-2010-3
- PI11/01659

Ana Bouché, Carlos Ferrer, Virginia Morillo, Naika Luquero, Juan Carlos Ruiz, Irene Torres, Agustín Santos, Juan David Quirós, Jorge Bonaque, Laura Vidueira, Miguel Guasp, Noelia de Marco, Rafael García, Ernest Sanfeliu, Verónica González, José Ramón Rodríguez

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Thank you for your attention!

@JotaEle1978

9th International ISIORT Conference
June 24/25th 2016
Novara, Italy

Challenges in IORT dosimetry: the mission of the AIFM working group, its experience and working hypotheses

Dr. Loris Menegotti Trento - Italy
Dr. Stefano Andreoli Bergamo - Italy
Dr. Raffaella Romagnoli Bologna - Italy

AIFM: IORT workgroup

It was started in 2014 and
23 Italian IORT centres actively participate today

10 subgroups of work:

- **Dosimetry** loris.menegotti@apss.tn.it
- **Commissioning & QA for dedicated LINACs** sandreoli@hpg23.it
- **Monte Carlo calculation** giorgio.russo@ibfm.cnr.it
- **Management & Safety** paolo.scalchi@ulssvicenza.it
- **Report of the treatment** stefania.guariglia@ospedaleuniverona.it
- **In vivo Dosimetry** francesca.cavagnetto@hsanmartino.it
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- **50 kV (intrabeam)** gsartor@cro.it
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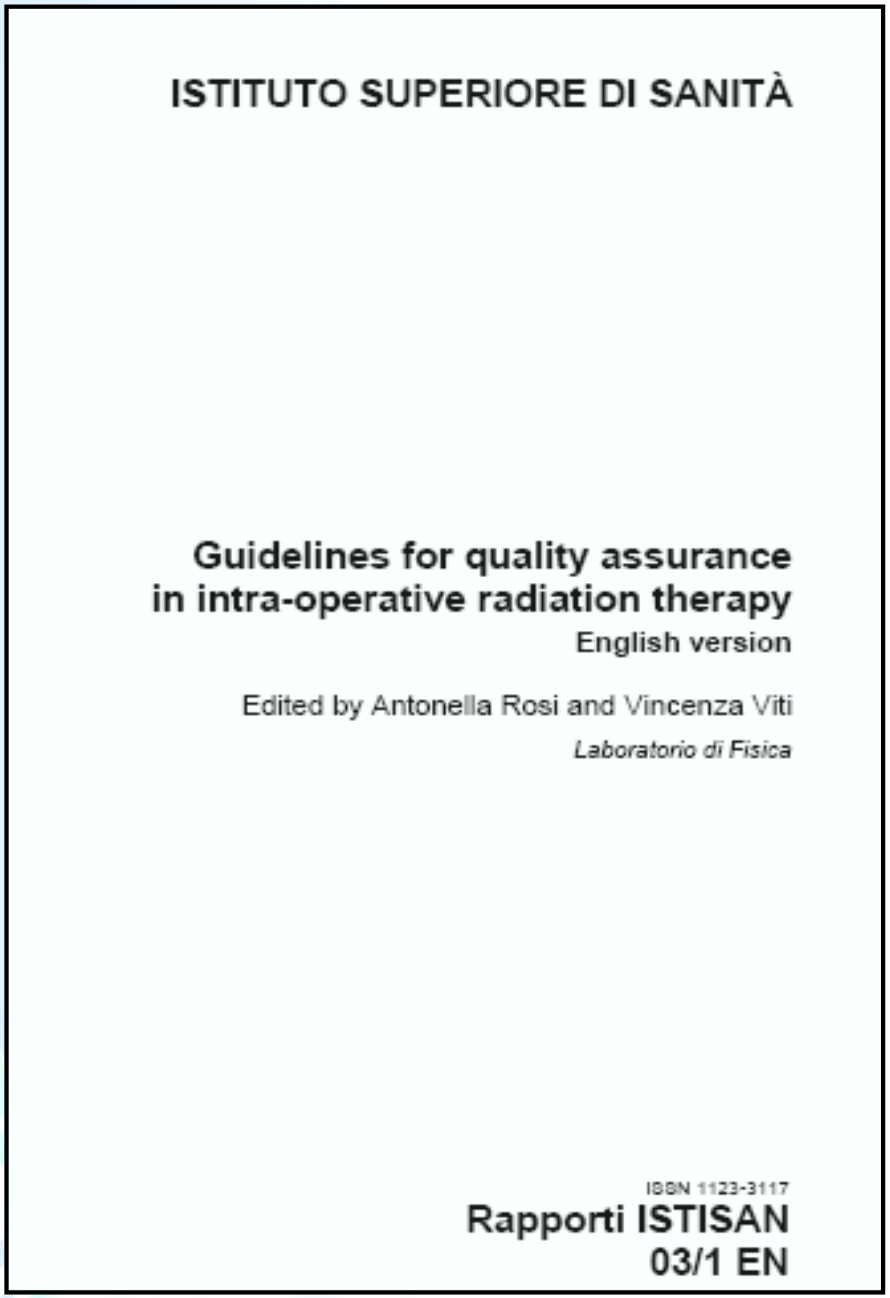
- **HTA** roberta.visentin@apss.tn.it

In 2003…



ISTITUTO SUPERIORE DI SANITÀ

Guidelines for quality assurance in intra-operative radiation therapy

English version

Edited by Antonella Rosi and Vincenza Viti

Laboratorio di Fisica

ISSN 1123-3117

Rapporti ISTISAN 03/1 EN

“Mission”

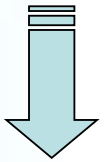
- Updating the current ISS guidelines
- define a shared procedure for the IORT method.
- Write a new AIFM report of integration of ISS guidelines

Summary

- Reference dosimetry
- Relative dosimetry
- In vivo dosimetry
- MC calculation
- Special cases

Dosimetry in reference conditions

For dedicated accelerators, characterised by a high dose/pulse, **it is impossible** to follow all the recommendations of the protocols (IAEA, AAPM)



Ionization chambers cannot be employed and no published dosimetry protocol can be used."

IAEA TRS-398

$D_{w,Q} = k_{t,p} * k_{pol} * k_s * M_Q * N_{D,w,Q0} * K_{Q,Q0}$

Conventional Dose-per-pulse:
the TVA method

$$k_s = a_o + a_1\left(\frac{M_1}{M_2}\right) + a_2\left(\frac{M_1}{M_2}\right)^2$$

BUT

This works for only 0.1-0.6 cGy/pulse

"In these guidelines (AAPM TG 72, ISS),

for the mesurement of the absorbed dose to water in reference conditions the use of the absolute dosimetric system of **Fricke** *is recommended. "*

A good solution is represented also by **Alanine dosimetry"**

Physicists like ionization chambers!

Fricke: chemical dosimeter based on a solution of iron sulphate

New methods for k_{sat} evaluation

"**Di Martino**" Method

"Ion recombiantion correction for very high dose-per-pulse high-energy electron Beams";

Med. Phys. 32 (7), 2204-2210 (2005)

"**Guerra**" Method

"Charge collection efficiency in ionization chambers exposed to electron beams with high dose per pulse";

Phys. Med. Biol. 51 (24), 6419-6436 (2006)

During these years several Italian centers have tested these methods, by comparing ionometric results with Fricke or Alanine.

They have shown to work well.

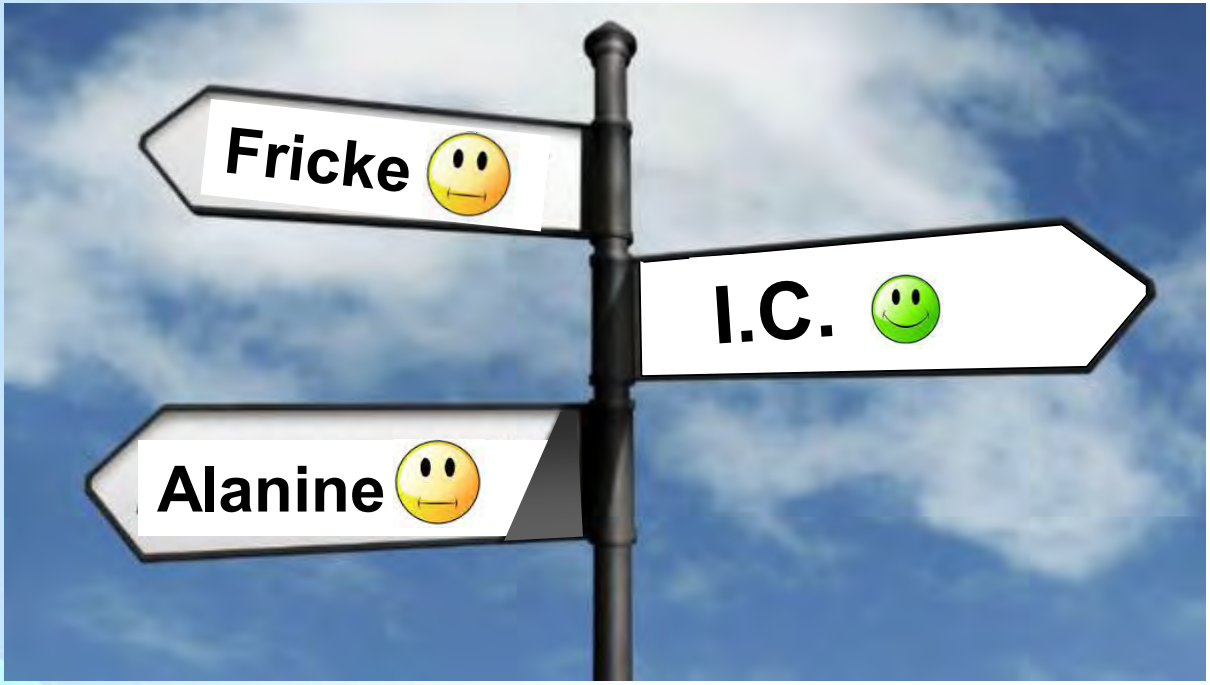
a paper was submitted for publication at "Medical Physics" : "Use of parallel-plate ionization chambers in reference dosimetry of NOVAC and LIAC mobile electron linear accelerators for intraoperative radiotherapy: a multi-center survey. " P. Scalchi et al.

→ 64 energies were checked

The main information in this paper is the potential to use the ionization chamber instead of the chemical dosimetry to calibrate the LINAC

It is under evaluation awaiting publication……..

So Today…



We'd like to suggest to the ISS (and we hope also to IAEA) the new guidelines,

in which these ionometric methods are accepted as new standards.

Subgroup: In vivo dosimetry

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  - IRCCS-A.O.U.San Martino-IST
  - Genoa, ITALY
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Moretti Eugenia	Ospedale di Udine - Udine
Piazzi Valeria	Multimedica spa - Castellanza (VA)
Princivalli Mara	AULSS n°9 - Treviso
Romagnoli Raffaella, Magi Silvia	Ospedale Bellaria - Bologna
Russo Giorgio	Ospedale G.Giglio – Cefalù (PA)
Scalchi Paolo	ULSS 6 - Vicenza
Servegnini Mara	A.O.U.T.S.Ospedali Riuniti - Trieste
Simonato Franca	Istituto Oncologico Veneto - Padova
Soriani Antonella	Istituto regina Elena - Roma
Tabarelli Paola, Marco Liotta	Fondazione Mauregi - Pavia
Terenzi Manuel	A.USL Romagna – (RN)

State of the art

23 centers (1 center uses conventional Linac)

- In vivo dosimetry is perfomed in 16 centers
  → of this: 14 centers it is a routine practice (about 70%)

- MOSFET or Gafchromic™

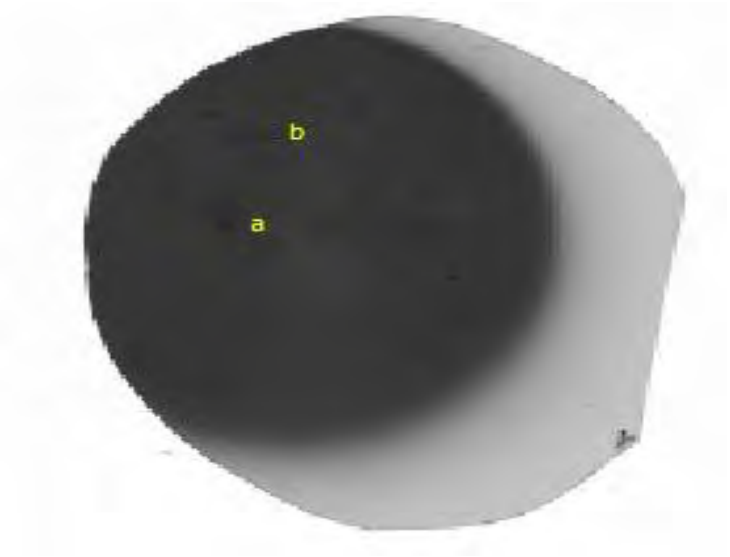
What to check?

- **Beam output** using a dosimeter arranged on the target surface: 5 centers
- **Target dose delivered** with the dosimeter in the deeper part, embedded together with the shield (for breast treat.): 7 centers
- **Double checks** (input and output dose to the target) in 4 centers

Recommended:

Setup checks using GAFchromic above the shielding disc

- **Essential:** at the beginning with all the surgeons
- **Recommended:** always



Work in progress

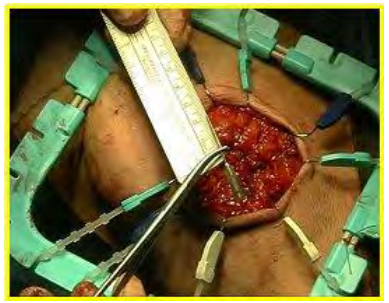
A chapter in the Report of the AIFM group, containing the main guidelines to:

- perform in vivo dosimetry,
- calibrate dosimeter,

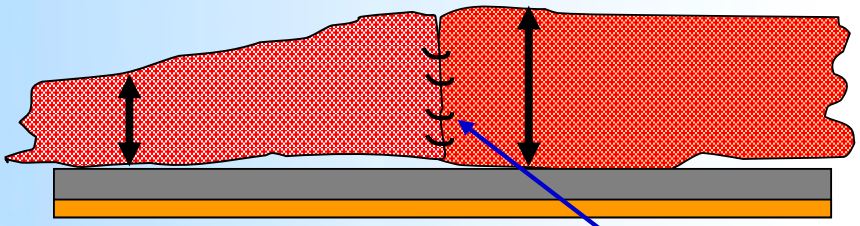
and containing the main Bibliography

- review article

Ideal dosimetry/"real patient"!

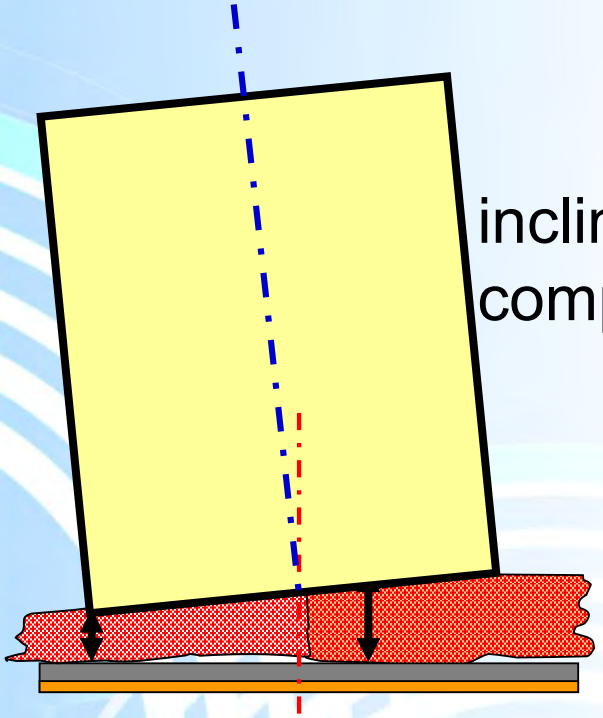


- **we haven't a specific TPS**

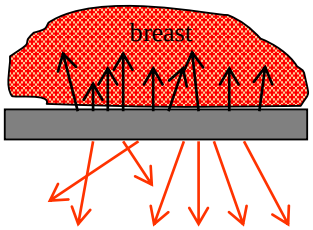


different thickneses
(breast density isn't equal to water)

discontinuity of the target
(due to sutures)



inclination of the applicator
compare to the disc



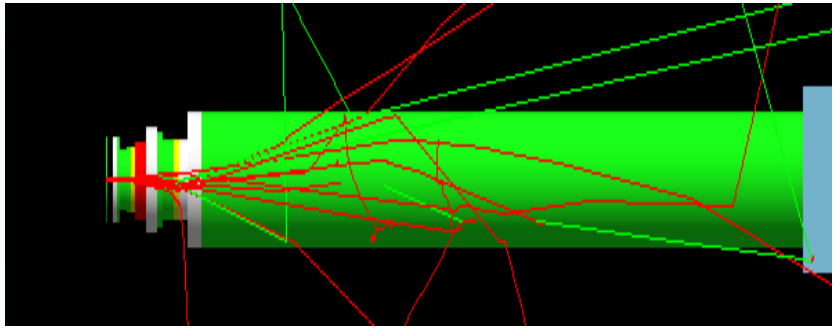
Backscatter from
the att. disc

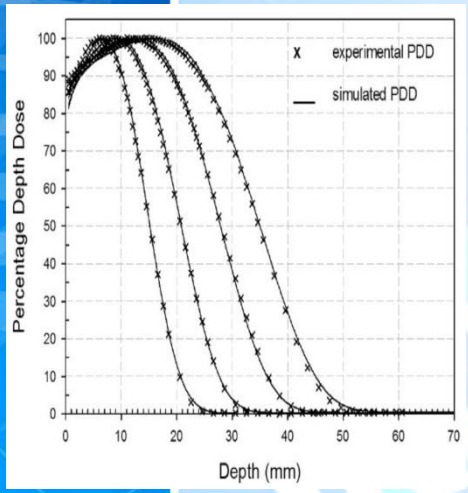
Monte Carlo Geant 4 simulation

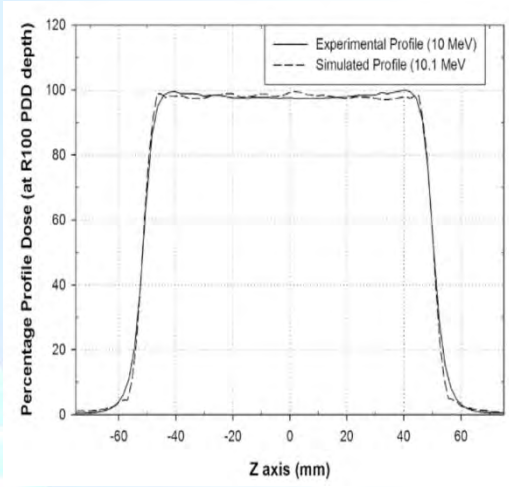
Representative: Dr. Giorgio Russo
Collaborators: Dr. Carlo Casarino
Dr. Debora Lamia

The advanced Geant4 example *iort_therapy* simulates the electron beam generated by the Novac7 acceleration system.

It is possible to obtain PDD curves, dose distributions and information about energy, simmetry and homogeneity of the electron beams.







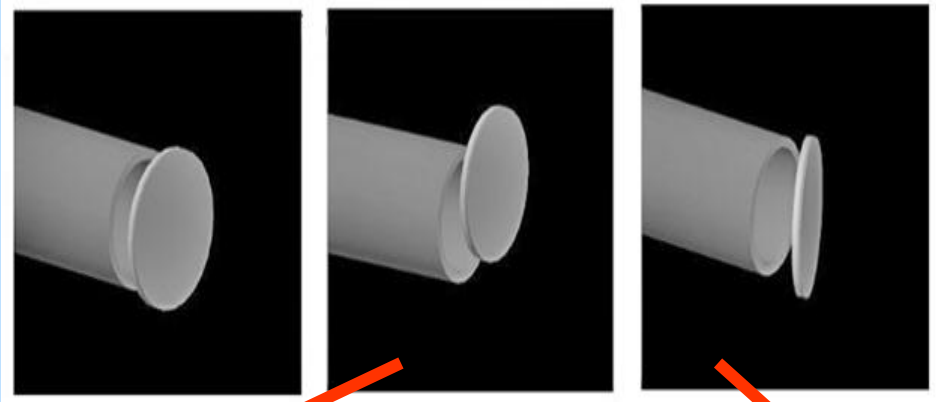
	Nominal Energy	Field Size (cm)	Symmetry (%)	Homogeneity (%)
Exper.		10.26	100.58	101.81
Simul.	10	10.25	102.60	103.79
% Difference		0.1	2.0	1.9
Exper.		10.26	100.40	101.01
Simul.	8	10.23	102.04	102.40
% Difference		0.3	1.6	1.4
Exper.		10.23	100.39	102.00
Simul.	6	10.19	102.12	103.69
% Difference		0.4	1.0	1.7
Exper.		10.10	100.79	101.15
Simul.	4	10.18	102.12	104.52
% Difference		0.8	1.0	3.3

	Nominal Energy	R100 (mm)	R90 (mm)	R50 (mm)	R30 (mm)	R_p (mm)	$\bar{E}_0$ (MeV)	E_{0p} (MeV)
Exper.		15.08	24.32	34.80	39.07	45.24	8.11	9.23
Simul.	10	15.01	24.18	34.64	38.94	45.01	8.07	9.18
% Difference		0.5	0.6	0.5	0.3	0.5	0.5	0.5
Exper.		12.18	19.32	28.06	31.75	37.00	6.54	7.58
Simul.	8	12.43	19.69	27.89	31.50	36.62	6.50	7.50
% Difference		2.0	1.9	0.6	0.8	1.0	0.6	1.0
Exper.		8.60	14.09	20.78	23.72	27.92	4.84	5.77
Simul.	6	9.48	14.35	20.83	23.71	27.68	4.85	5.72
% Difference		1.4	1.8	0.2	0.04	0.9	0.2	0.9
Exper.		6.56	10.14	15.18	17.44	20.68	3.54	4.33
Simul.	4	6.51	10.26	15.18	17.45	20.60	3.54	4.31
Difference		0.8	1.2	0.0	0.06	0.4	0.0	0.5

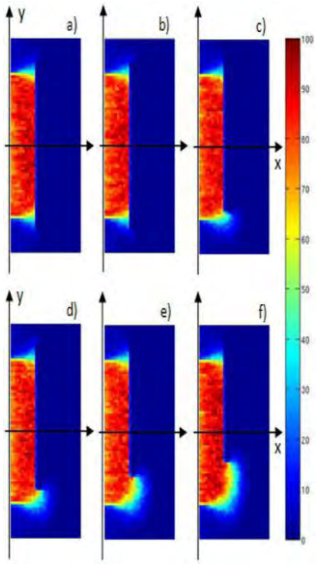
[G. Russo et al. JOURNAL OF APPLIED CLINICAL MEDICAL PHYSICS, Vol. 13, issue 5, 2012]

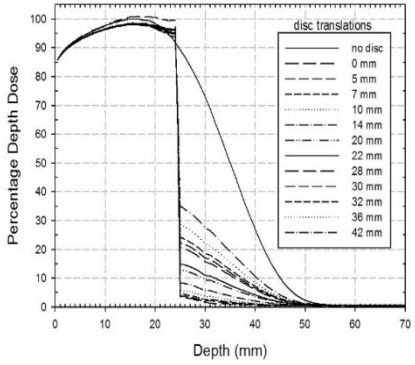
MC simulation

Studies about the possible misalignment and/or the rotation of the protection disc used for breast IORT treatments

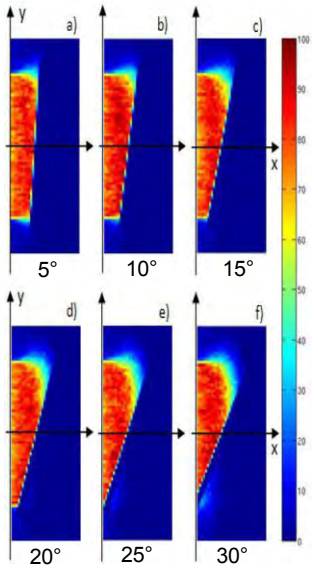


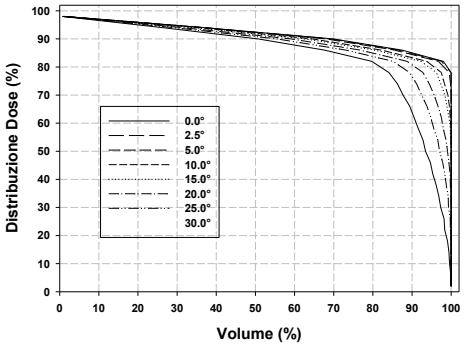
Geant4 image of the protection disc simulation





Dose distributions at different possible translations of the disc



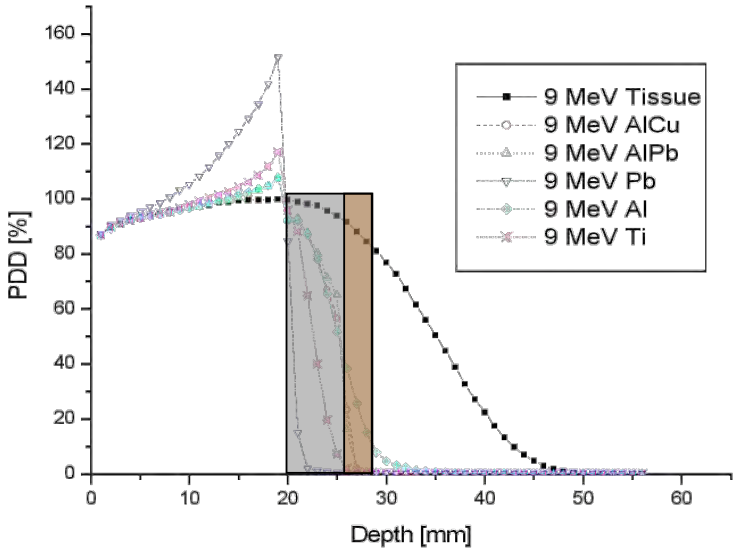


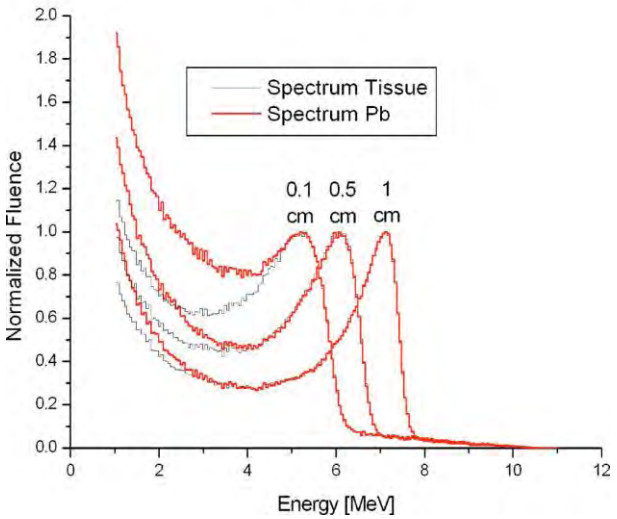
Dose distributions at different possible rotations of the disc

[G. Russo et al. JOURNAL OF APPLIED CLINICAL MEDICAL PHYSICS, Vol. 13, issue 5, 2012]

MC simulation

Montecarlo simulation (BEAMnrcMP, DOSXYZnrcMP - release 2007) of the PDD with different attenuators





- disc Al+Cu: optimal
- disc only Al: insufficient attenuation

Med. Phys. 34 (12), December 2007

Monte Carlo investigation of breast intraoperative radiation therapy with metal attenuator plates

A. Martignano
Department of Medical Physics, S. Chiara Hospital, APSS Trento, Italy and School of Medical Physics, Padova, Italy

L. Menegotti and A. Valentini
Department of Medical Physics, S. Chiara Hospital, APSS Trento, Italy

An experimental attenuation plate to improve the dose distribution in intraoperative electron Beam radiotherapy for breast cancer

T Oshima et al.

PMB 54 (2009) 3491-3500

Special IORT applications in breast patients

Representative: Federica Cattani
Collaborators: Rosa Luraschi, Sabrina Vigorito, Elena Rondi, Stefania Comi

European Institute of Oncology

1. Pregnant women

2. Cardiac implantable electronic devices carriers

A chapter about it will be insert in the AIFM report

Pregnant women

Is electron beam intraoperative radiotherapy safe in pregnant women with early breast cancer?

In vivo dosimetry to assess fetal dose

A couple of TLDs were positioned on **non** pregnant patients skin in 4 different positions and in uterus

Prescribed dose	Right ovary	Left ovary	Suprapubic	Sub-diaphragmatic	Uterus
Gy	mGy	mGy	mGy	mGy	mGy
21	0.925	1.001	0.776		0.57
21	0.453	0.443	0.384	1.639	0.3
12	0.677	0.557	0.435	2.902	0.366
21	0.881	0.814	0.682	1.98	0.485
12	0.314	0.293	0.576	7.758	0.261

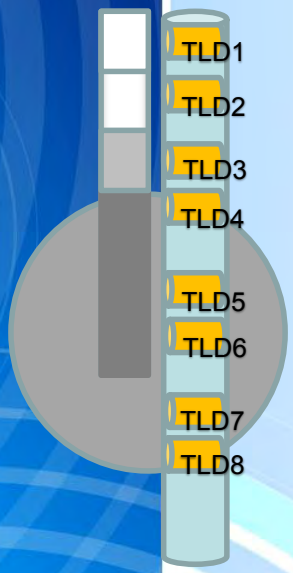
In December 2011 a pregnant woman, affected by early stage breast cancer, underwent conservative surgery and ELIOT full dose (21 Gy at 90% isodose) during the 15th gestation week

Comparing the data on the skin between non pregnant women and the pregnant one, we evaluated that the expected dose to the foetus should have been 0.84 mGy

ELIOT offers the pregnant woman the choice of receiving breast-conserving surgery, without exposing her baby to a significant radiation risk, and preserves her breast

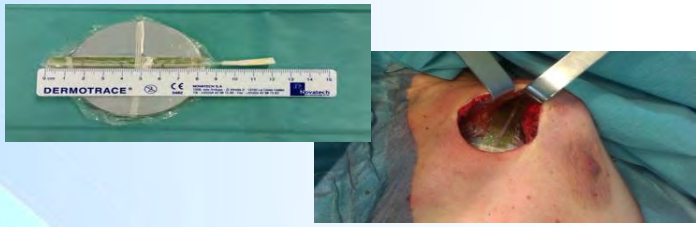
Cardiac implantable electronic devices carriers

Two catheters with 8 TLDs

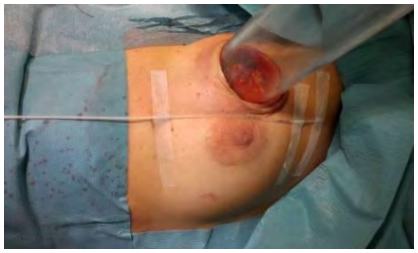


The first catheter was attached to the thoracic shielding

The catheter tip was positioned in the subclavicular region, where a cardiac device would be placed



The second catheter was placed on the patient skin, parallel to the first one, next to the applicator



ELIOT seems to be safe for patients using cardiac devices as long as the minimum distance of 2.5 cm is kept between the cardiac device edge and the applicator wall

OSPEDALE BELLARIA

LIAC 10 MeV

Raffaella Romagnoli
Bologna, Italy

Percentage Depth Dose
&
Transverse Dose Profiles

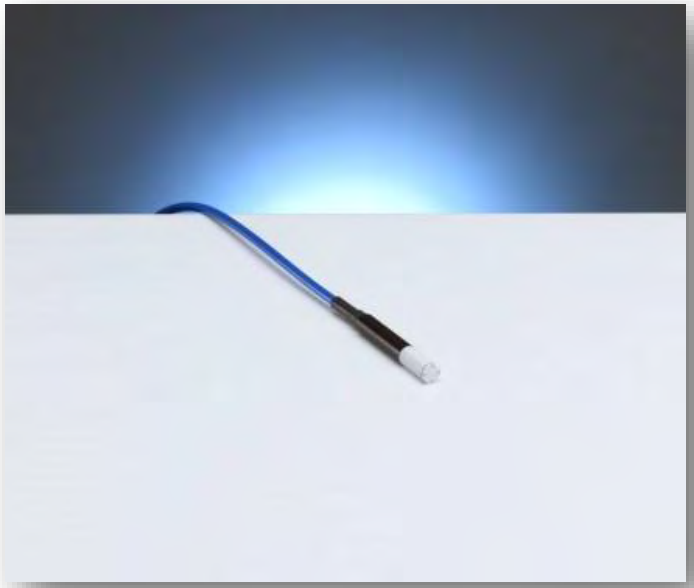
- MP3-XS PTW water phantom
- Electrometer: PTW Tandem
- Energies: 4, 6, 8, 10 MeV
- Diameters: 6 and 10 cm
- Depth: effective point of measurement at dmax

IBA EFD diode

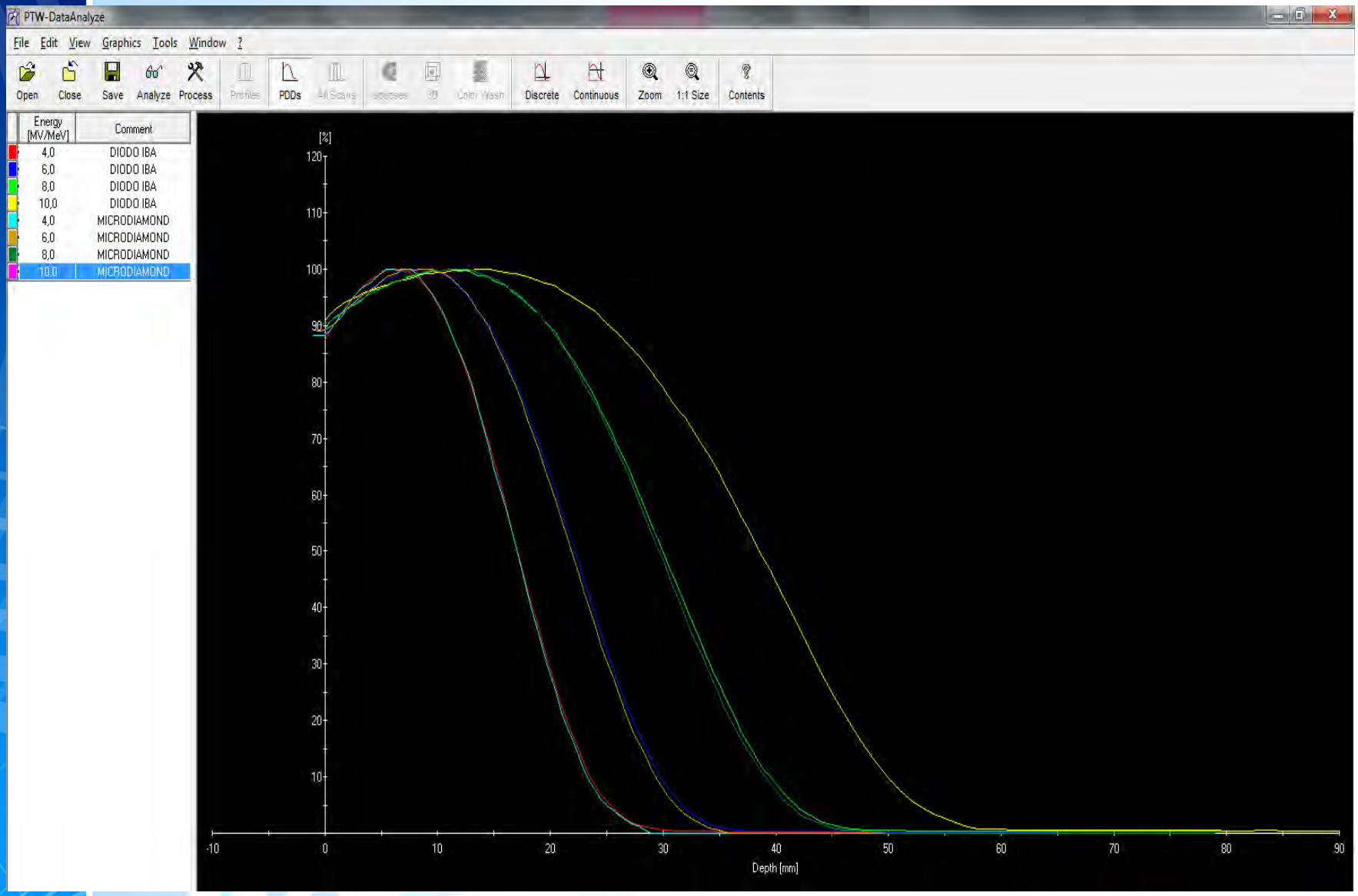
- Nominal sensitive volume: 0.019 mm³,
- Radius 1 mm,
- Thickness 0.06mm

PTW µDiamond TM 60019

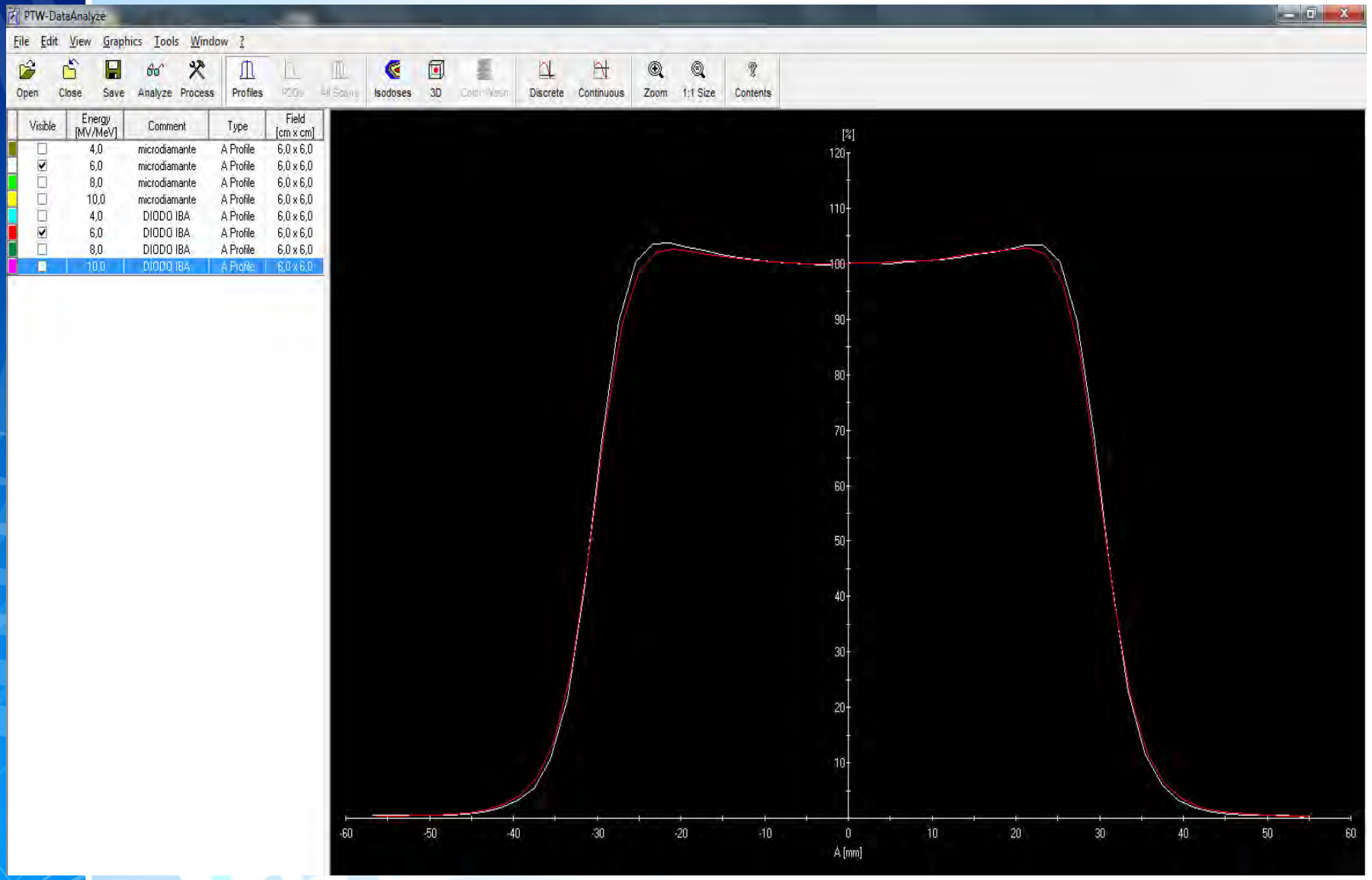
- Nominal sensitive volume: 0.004 mm³,
- Radius 1.1 mm,
- Thickness 1 µm



PDD


PTW-DataAnalyze
File Edit View Graphics Tools Window ?
Open Close Save Analyze Process Profiles PDDs All Scans Isodoses 3D Color Wash Discrete Continuous Zoom 1:1 Size Contents
Energy [MV/MeV] Comment
4,0 DIODO IBA
6,0 DIODO IBA
8,0 DIODO IBA
10,0 DIODO IBA
4,0 MICRODIAMOND
6,0 MICRODIAMOND
8,0 MICRODIAMOND
10,0 MICRODIAMOND
[%]
120
110
100
90
80
70
60
50
40
30
20
10
-10
0
10
20
30
40
50
60
70
80
90
Depth [mm]

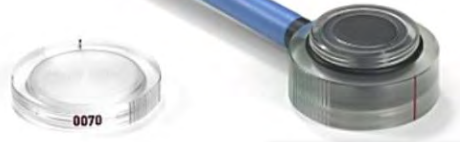
Transverse Dose Profile



Output Factor

- MP3-XS PTW water phantom
- Electrometer: PTW Unidos
- Energies: 6 & 8 MeV
- Diameters: 3, 4, 5, 6, 8 and 10 cm (reference)
- Depth: effective point of measurement at dmax

PTW 34045
Advanced Markus



PTW 34001
Roos Chamber

PTW 60019
µicroDiamond

PTW 60017
Diode E

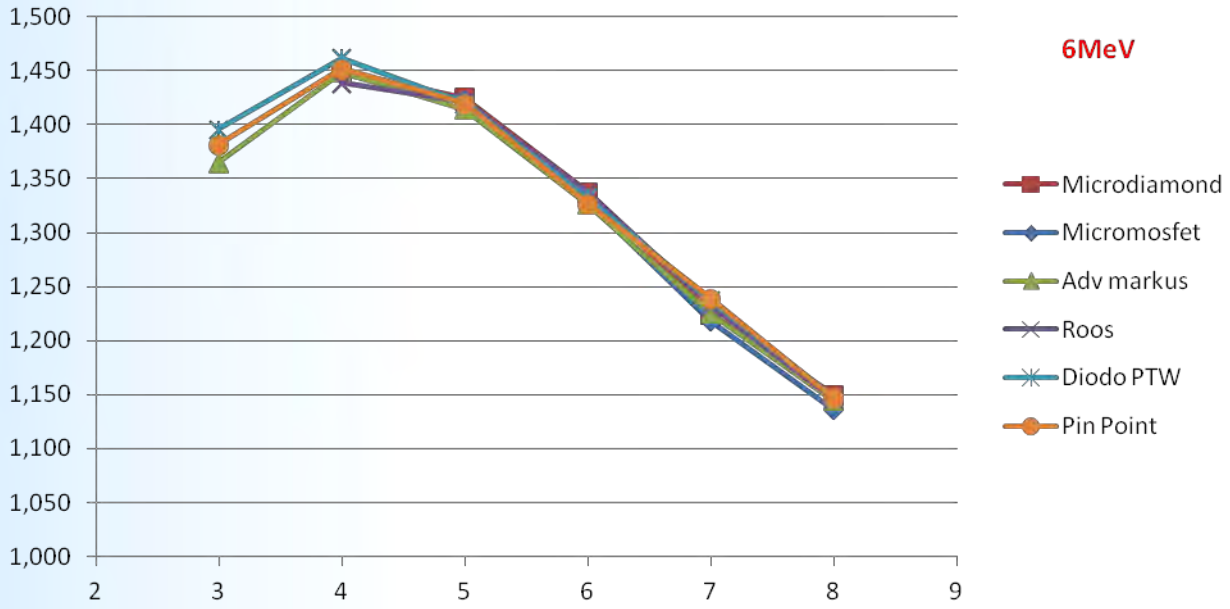
PTW 31016
Pin Point 3D

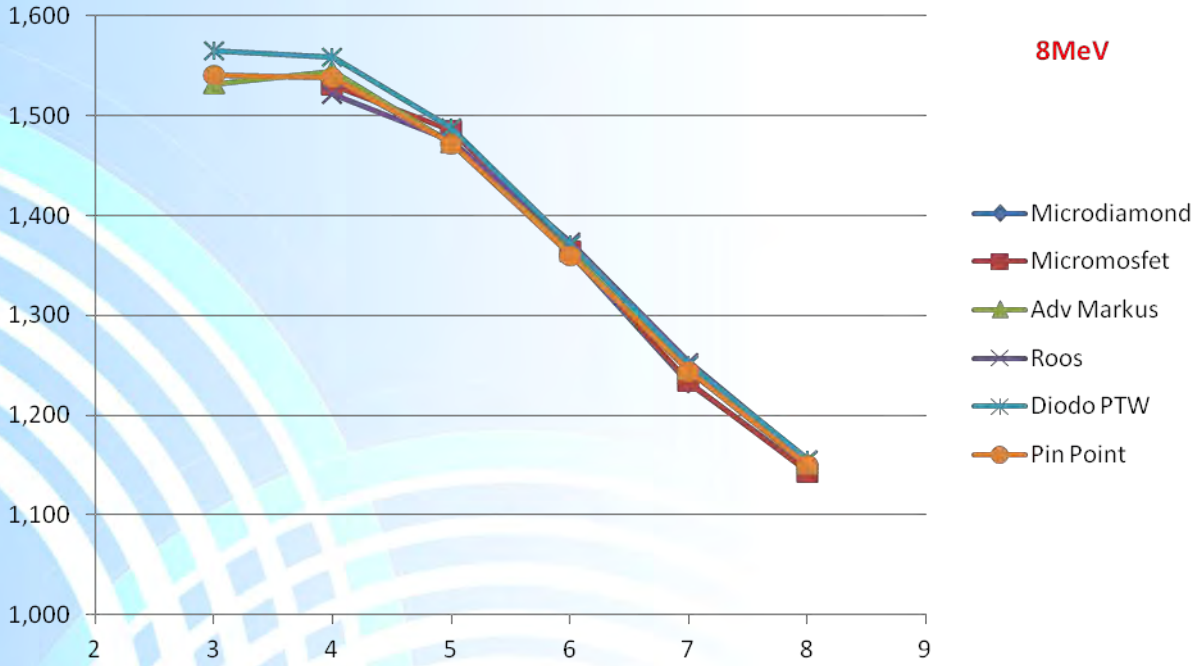
CAUTION!

Always correct for k_{sat} and k_{pol}

(here k’’’ Laitano – Guerra model)

Output Factor





OF: %differences

Energy	Diff % µicrodiamond/Pin Point				
	8	7	6	5	4
6 MeV	0,3	-1,1	0,8	0,4	-0,1
8 MeV	-0,3	-0,9	0,1	0,1	0,0

Energy	Diff % µicromosfet/Pin Point				
	8	7	6	5	4
6 MeV	-0,9	-1,7	0,1	0,2	-0,3
8 MeV	-0,6	-0,9	0,4	0,9	-0,5

Energy	Diff % AM/Pin Point					
	8	7	6	5	4	3
6 MeV	-0,2	-1,1	0,0	-0,4	-0,2	-1,2
8 MeV	0,2	0,1	0,2	0,0	0,4	-0,6

Energy	Diff % ROOS/Pin Point				
	8	7	6	5	4
6 MeV	-0,1	-0,6	0,8	0,1	-0,9
8 MeV	0,5	0,7	1,0	0,2	-1,1

Energy	Diff % DIODO/Pin Point					
	8	7	6	5	4	3
6 MeV	0,1	-0,2	0,4	0,0	0,7	1,0
8 MeV	0,5	0,5	0,8	1,1	1,4	1,6

Multi-Institutional Intercomparison

Different LINAC

- Novac 7
- Novac 11
- LIAC 10
- LIAC 12

Different detectors

- Fricke chemical dosimeter
- Diodes (IBA and PTW)
- µicroDiamond
- µicroMosfet
- gaf-chromic
- Roos chamber
- Adv.Markus chamber
- Markus chamber
- ppc-05 chamber
- Pinpoint chamber….

And Montecarlo!

Conclusions: PDD and TDP

- PTW µicroDiamond detector is a suitable dosimeter for dedicated IOERT LINAC
- Many detectors available in any center can be used with good accuracy for PDD and TDP measurements

Conclusions: Output Factor

- For applicators down to 4 cm, different detectors are in good agreement.

  Discrepancies for 3 cm applicators have to be clinically considered

- Many detectors available in any center can be used with good accuracy for OF measurements

Future developments

Characterization at 4 & 5 MeV?

PTW µicroDiamond

Useful Ranges

Radiation quality	100 keV ... 25 MV photons (6 ... 25) MeV electrons
Field size [2)]	(1 x 1) cm² ... (40 x 40) cm²
Temperature	(10 ... 35) °C, (50 ... 95) °F
Humidity range	(10 ... 80) %, max 20 g/m³

PTW 60017 Diode

Radiation quality:
(6 ... 25) MeV electrons
^{60}Co ... 25 MV photons

Future developments

- Validation of other detectors
- To define which measurements for the validation of a detector
- EQUAL ESTRO TLD for OF
- To define which parameters to measure for relative dosimetry
- Role of Montecarlo

Thank you for your attention

IORT anti-tumoral activity in Breast Cancer includes the molecular alteration of the post-surgical microenvironment

9TH INTERNATIONAL ISIORT CONFERENCE

NOVARA 24/25TH JUNE 2016

Gustavo Baldassarre, MD
Molecular Oncology Unit
CRO-National Cancer Institute
Aviano - Italy

Question

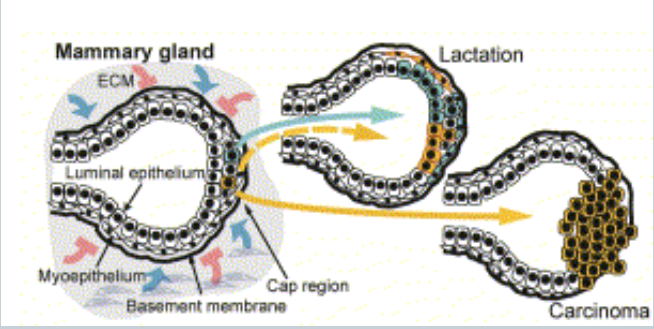
If 60% of primary breast tumors are multifocal as evidenced by RNM studies

why

approximately 90% of the recurrences occurs at the site of wound?

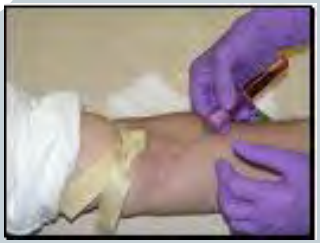
Background

- Since more than 30 years now it has been hypothesized that tumors act as wounds that do not heal (Dvorak NEJM, 1986)
- We have then learned that tumor development and progression is the result of a complex interaction between cancer cells and local microenvironment
- A normal microenvironment can preserve the tissue architecture even in the presence of predisposed cells thereby preventing tumor progression
- Vice versa an aberrant microenvironment can promote the mutated cells to form tumors



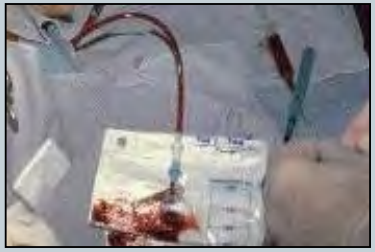
WF & Serum Collection

- The day prior to surgery the patient receive a blood drawing;



Drawing of Pre-surgery Serum

- **At the end of the surgery (with or without IORT) drainage fluid from breast surgical wound (WF) is collected for 24 hours;**



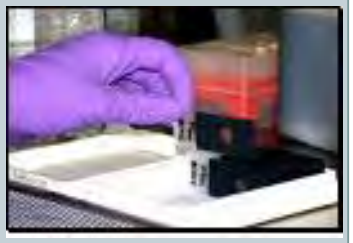
Drainage of Post-surgery Serum (**WF**)

- Both the Pre-surgery serum and the WF are promptly sent to the Experimental Oncology Lab where they are processed, aliquoted and stored at -80° C until needed.

Exp.Onc. Lab

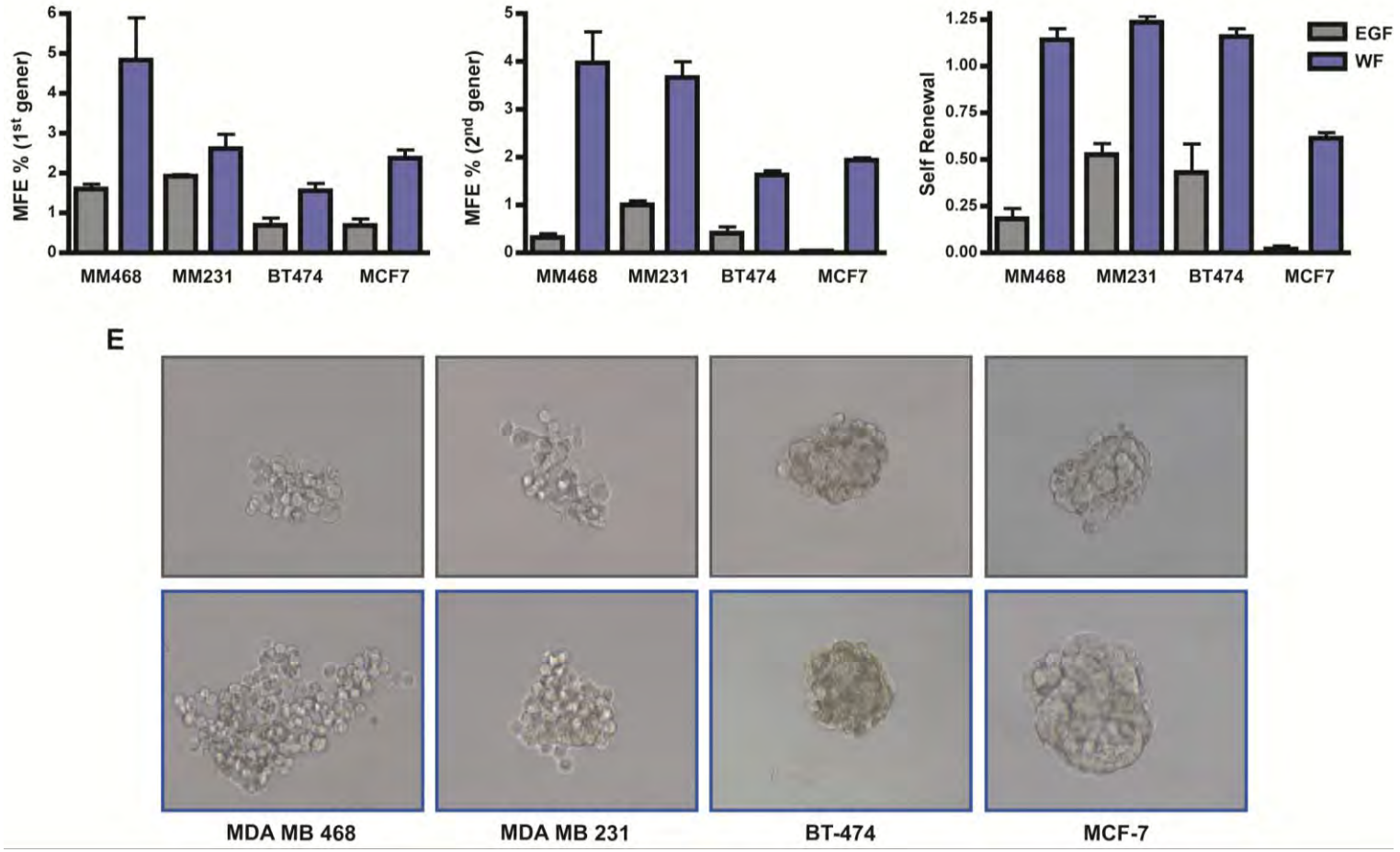
processing...

centrifuging...



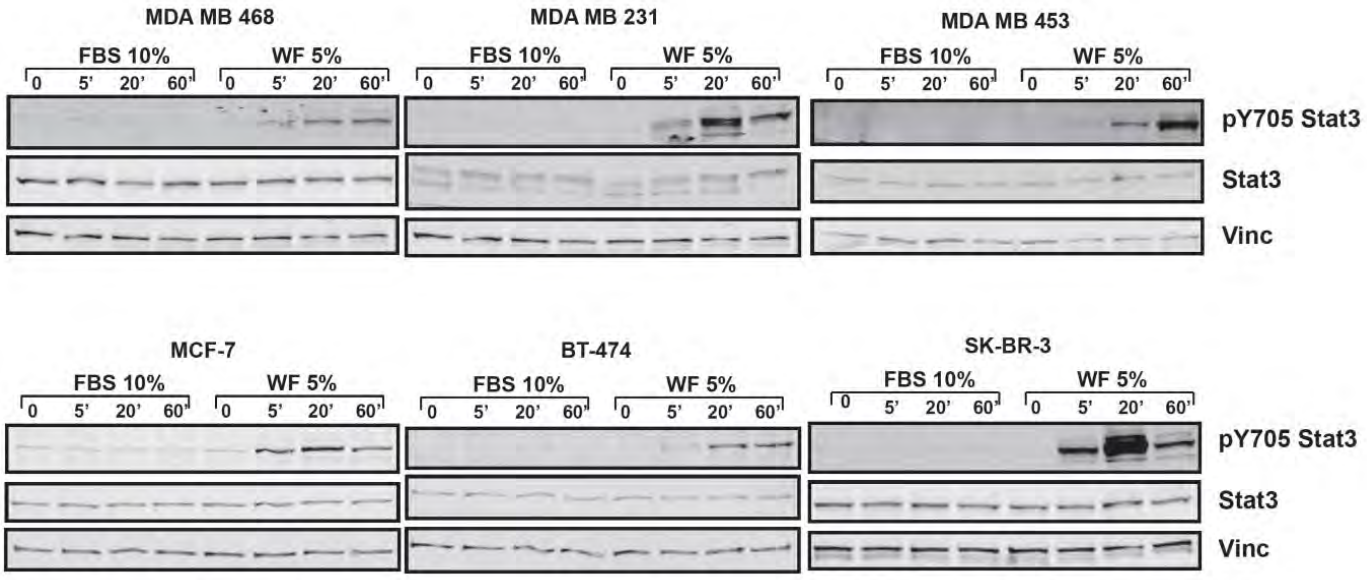
and storage.

WF stimulate self-renewal of breast cancer cell lines



Segatto I, et al. 2014

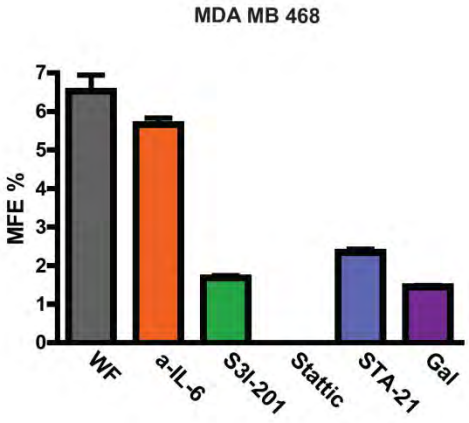
WF very efficiently activate STAT3 in Breast Cancer Cell Lines

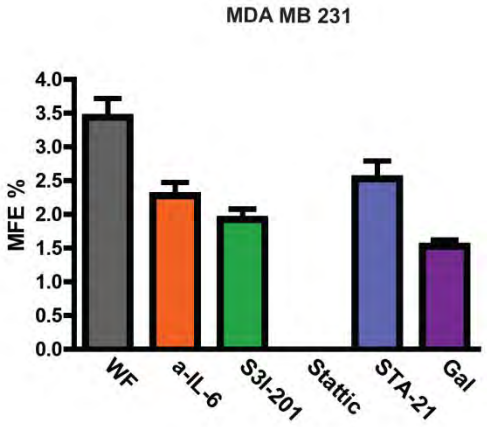


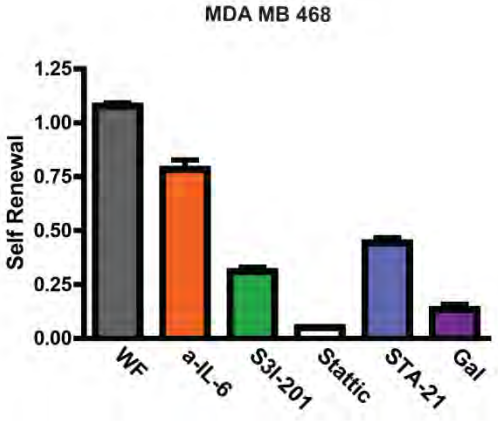
	pY701 STAT1	pY690 STAT2	pY705 STAT3	pY694/Y699 STAT5A/B	pY641 STAT6
UNSTIMULATED	9	8	51	27	7
STIMULATED	25,5	12	186,5	27	7
FOLD INDUCTION	2,83	1,5	3,66	1	1

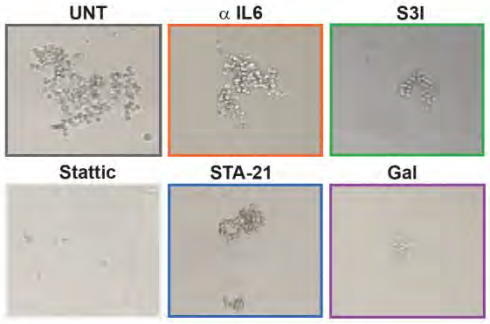
Segatto I, et al., 2014

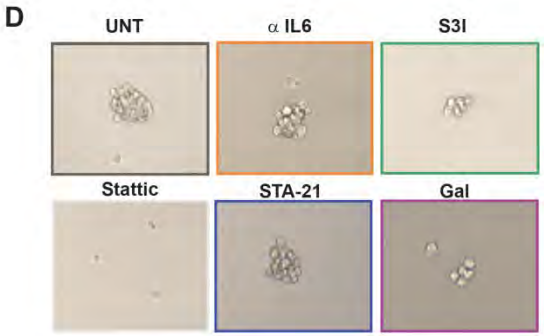
WF stimulate self-renewal of breast cancer cell lines *via* STAT3





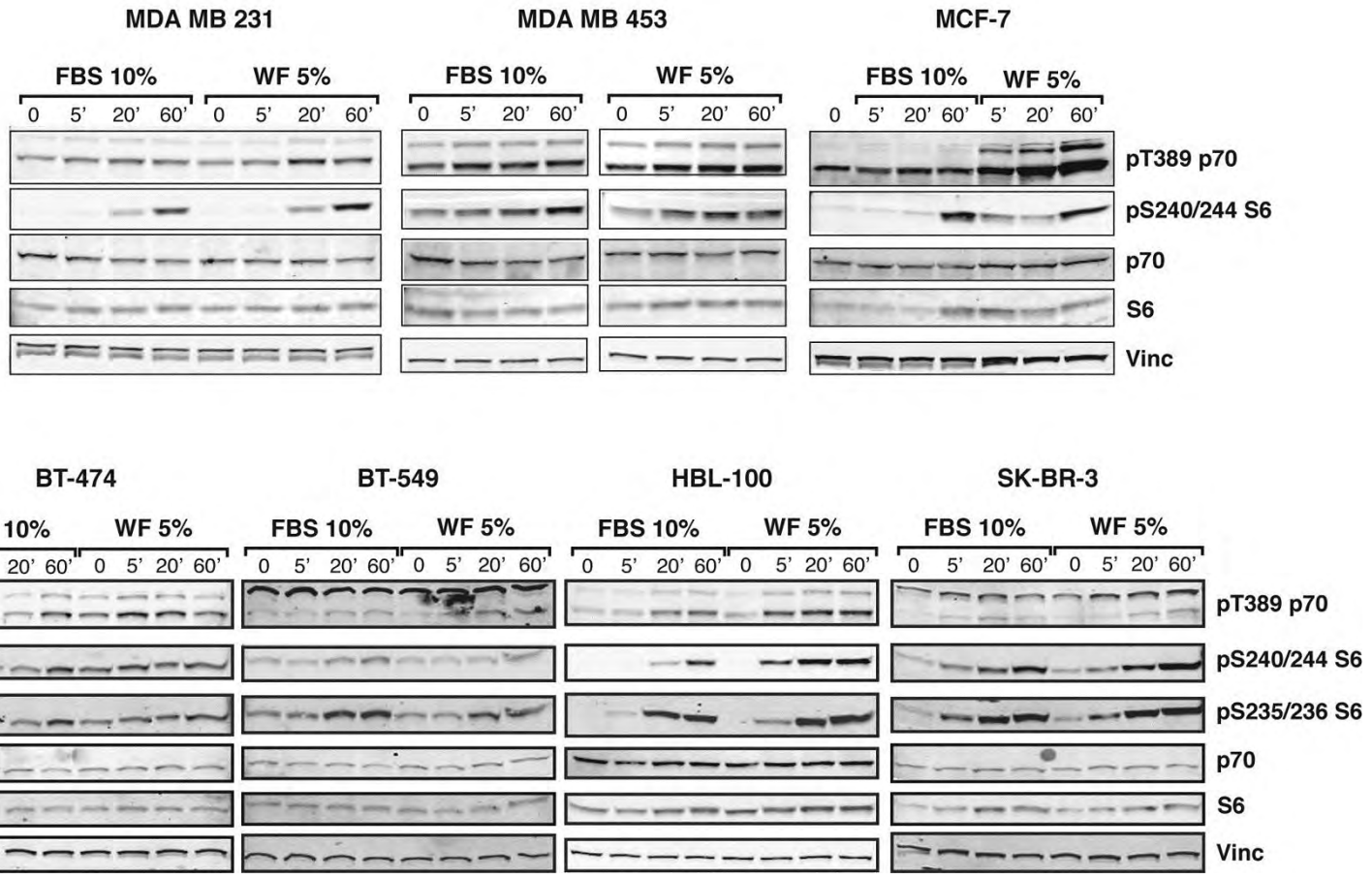






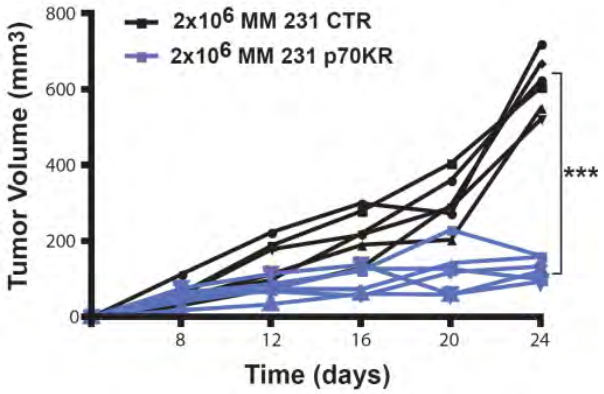
Segatto I, et al. 2014

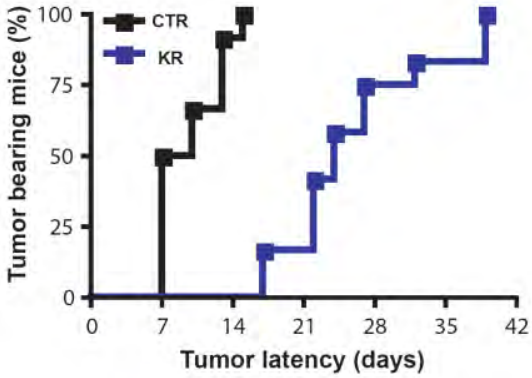
WF very efficiently activate p70S6K in Breast Cancer Cell Lines

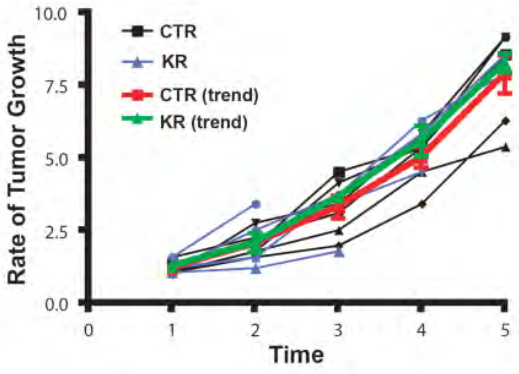


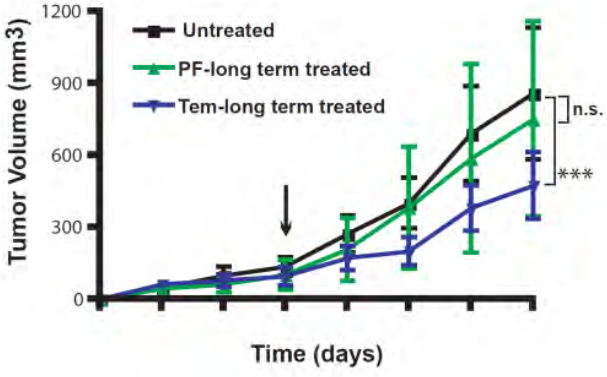
Segatto I, et al., Mol. Onc. 2014

Primary tumor growth is altered by impairing p70S6K activity



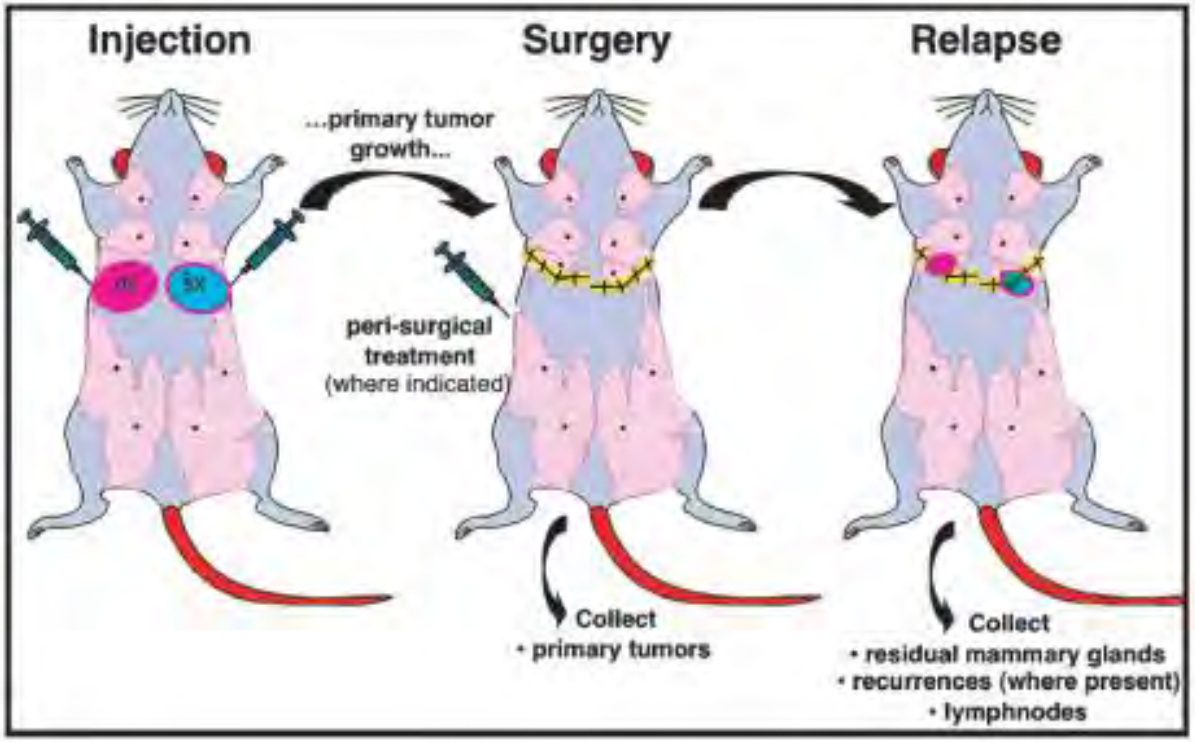






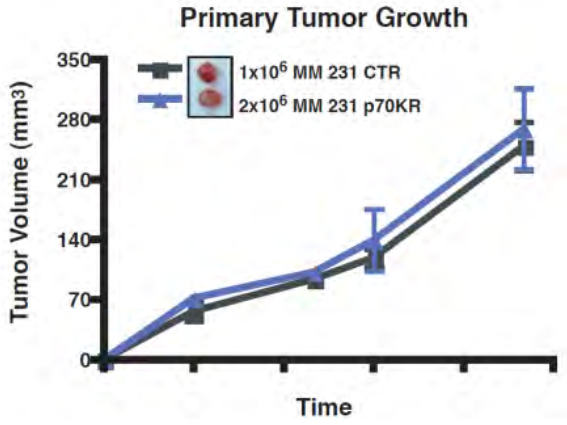
Segatto I, Berton S, et al., JMCB 2013

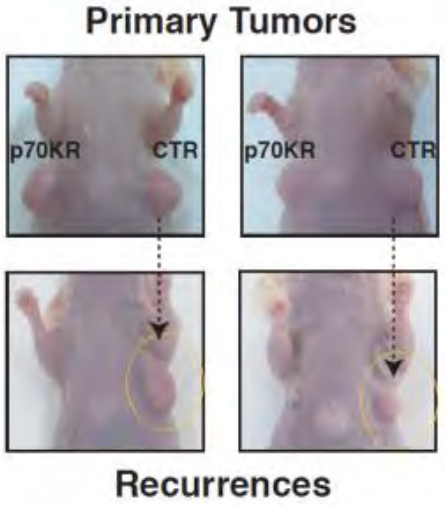
A Mouse model of BC Recurrence formation

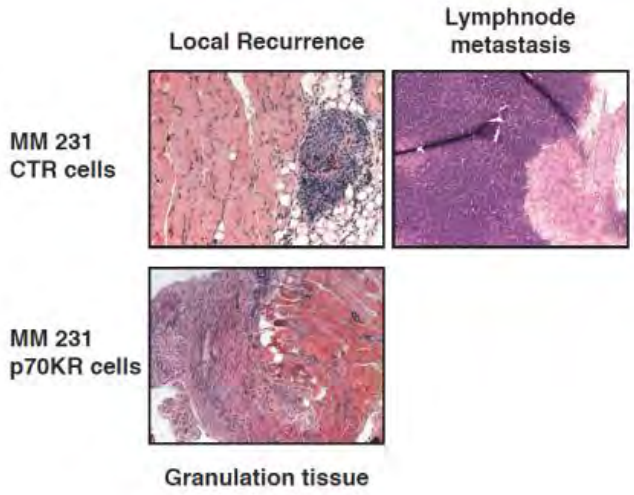


Segatto I, Berton S, et al., JMCB 2013

Local recurrence of breast cancer is significantly prevented by impairing p70S6K activity

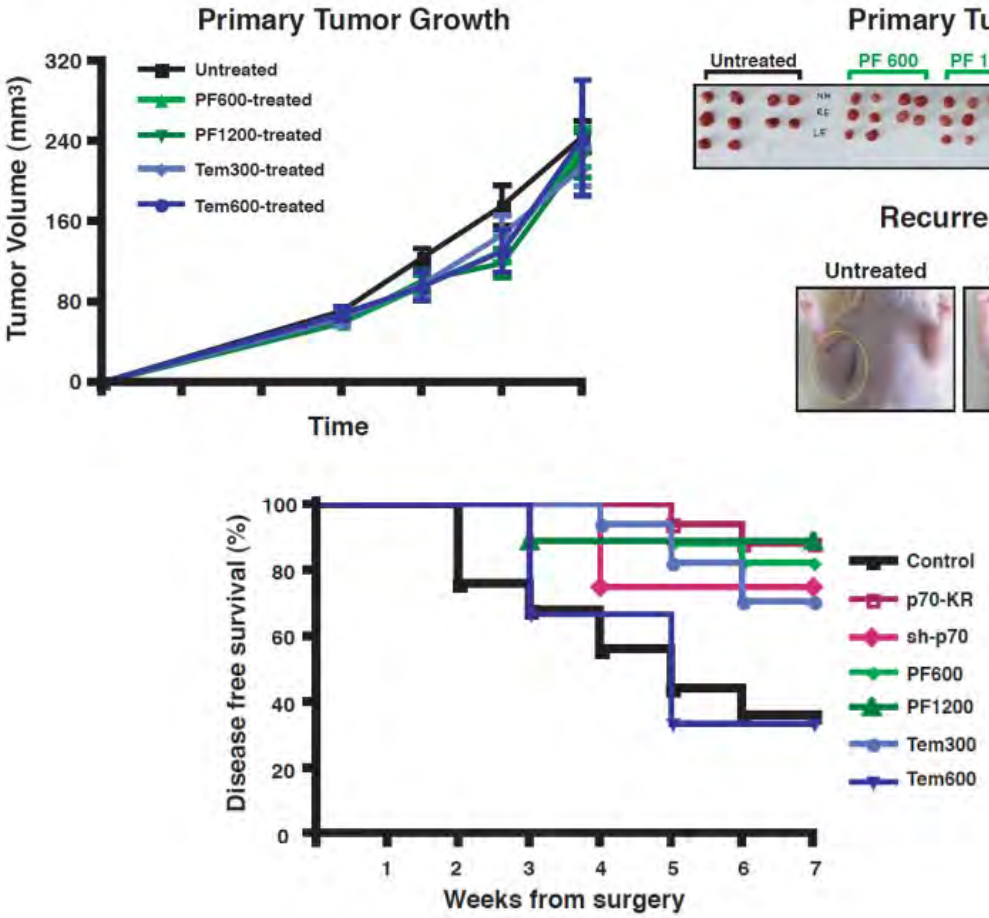






Segatto I, Berton S, et al., JMCB 2013

Local recurrence of breast cancer is significantly prevented by impairing p70S6K activity (II)



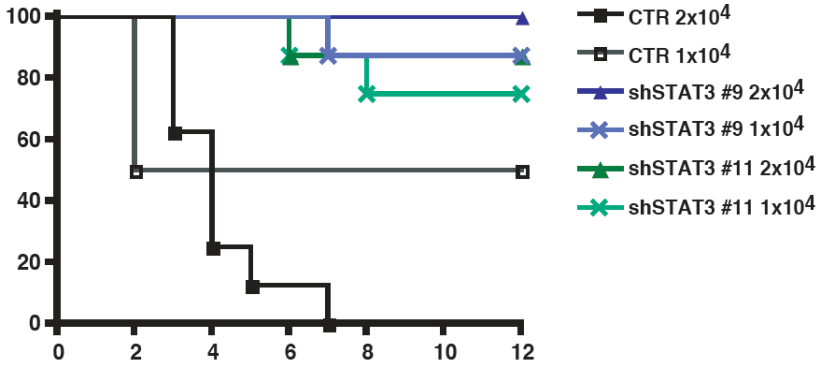
Segatto I, Berton S, et al., JMCB 2013

STAT3 inhibition significantly decreases tumor take rate and recurrences formation

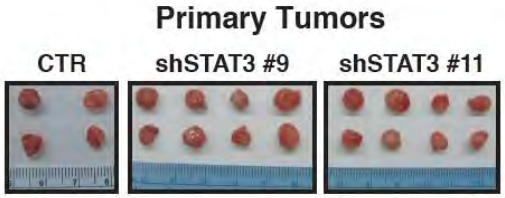
CRO AVIANO

Tumor Take Rate

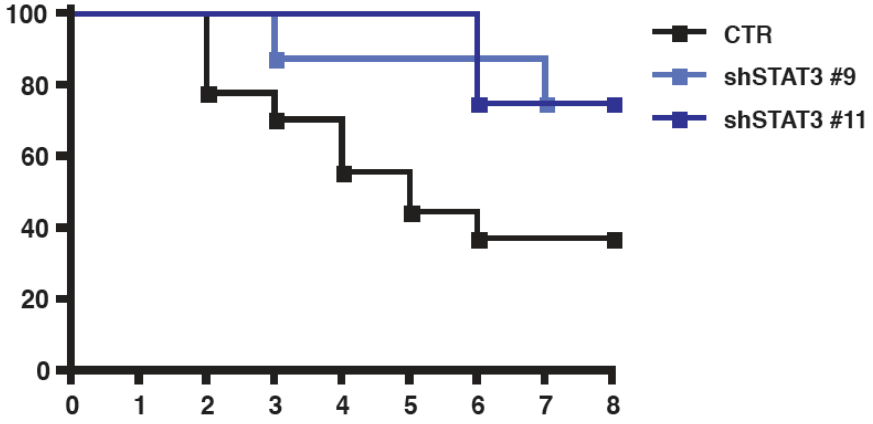
# of cells	MM231 CTR	MM231 sh-STAT3
2×10^6	14/14 100%	11/14 78%
2×10^5	10/10 100%	8/10 80%
1×10^5	4/4 100%	6/8 75%
5×10^4	4/4 100%	5/8 62%
2×10^4	8/8 100%	3/16 19%
1×10^4	4/8 50%	1/16 6%



Recurrences



Cells	Recurrence formation	
MM231 CTR	17/27	63%
MM231 shSTAT3 #9	2/8	25%
MM231 shSTAT3 #11	2/8	25%



Segatto I, et al., Submitted 2014

Conclusions (I)

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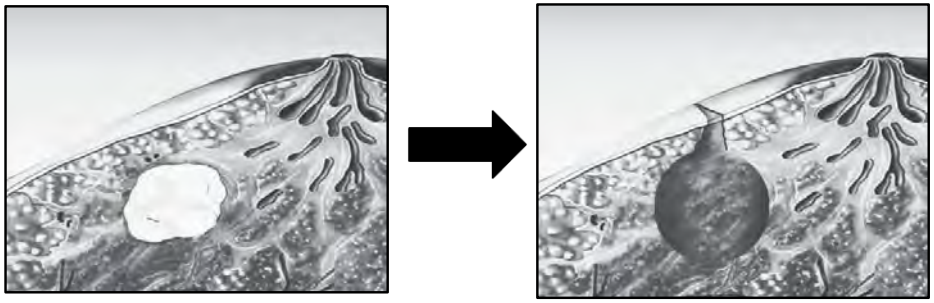


Breast Cancer

Lumpectomy

Tumor Removal

Wound Response

Cure ?

p70S6K Activation

Stat3 Activation

Timely administration of Specific Inhibitors

Survival in "hostile" microenvironment

Tumor Initiating Properties

Cure ?

Stimulation of residual Cancer cells proliferation

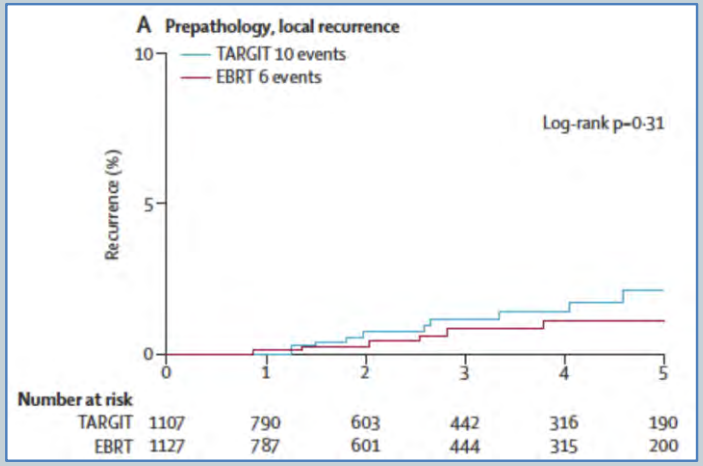
Recurrence

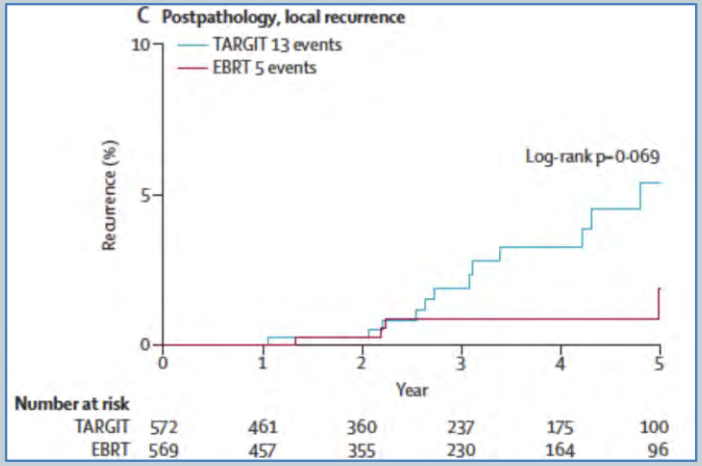
Background

- In this context clinical and experimental evidences collected in breast cancer suggest that **surgery** itself, **by activating the wound healing response**, may provide residual **cancer cells** of the growth factors necessary to **re-grow locally** and/or at distant sites

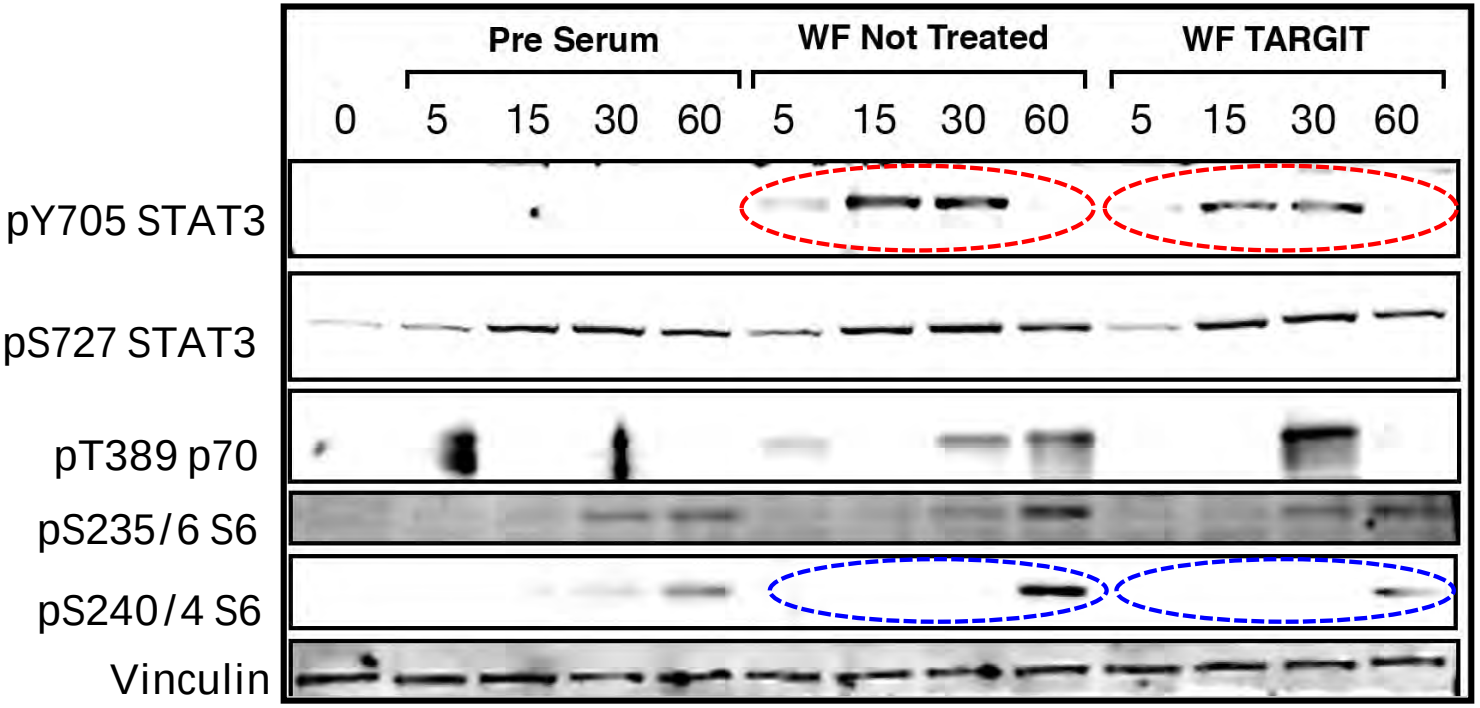
- Accordingly, after breast conserving surgery, External Beam Radiotherapy reduces by 1/3 the risk of loco-regional recurrences

- Recent evidences suggest that **IORT with Intrabeam** is **not inferior** to EBRT in controlling recurrences formation **when timely applied**.





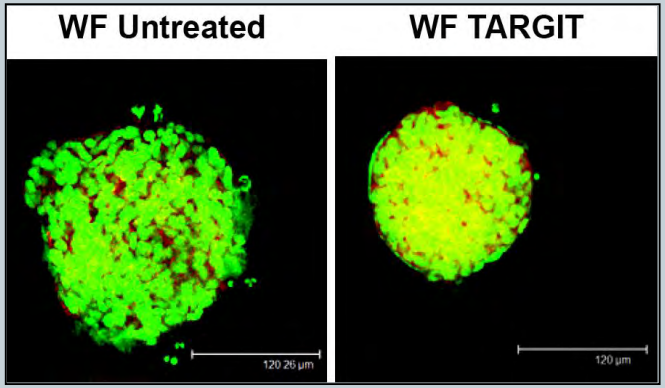
IORT alters the ability of breast-derived WF to stimulate p70S6K and STAT3 activation

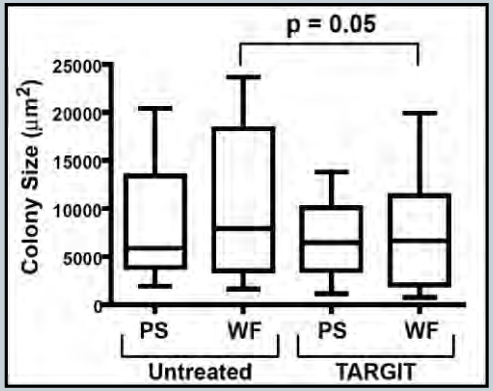


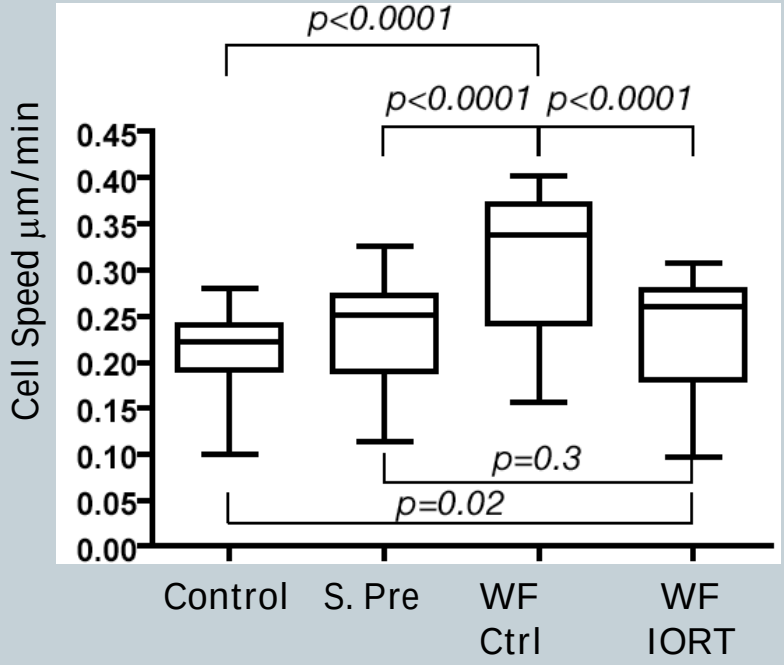
Do p70S6K and STAT3 signaling pathways play a role in BC recurrence formation?

Belletti, et al. Cin. Cancer Res. 2008 14: 1325

IORT treatment impairs the WF-induced BC cell growth and motility in 3D-matrices

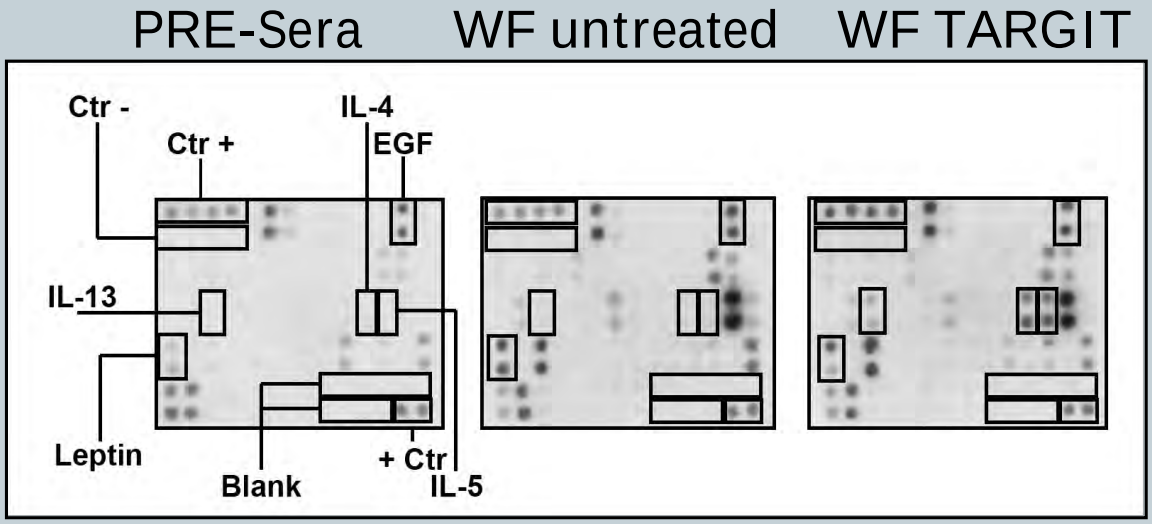






MCF-7 in MATRIGEL

IORT with Intrabeam alters the proteomic profile of wound fluid

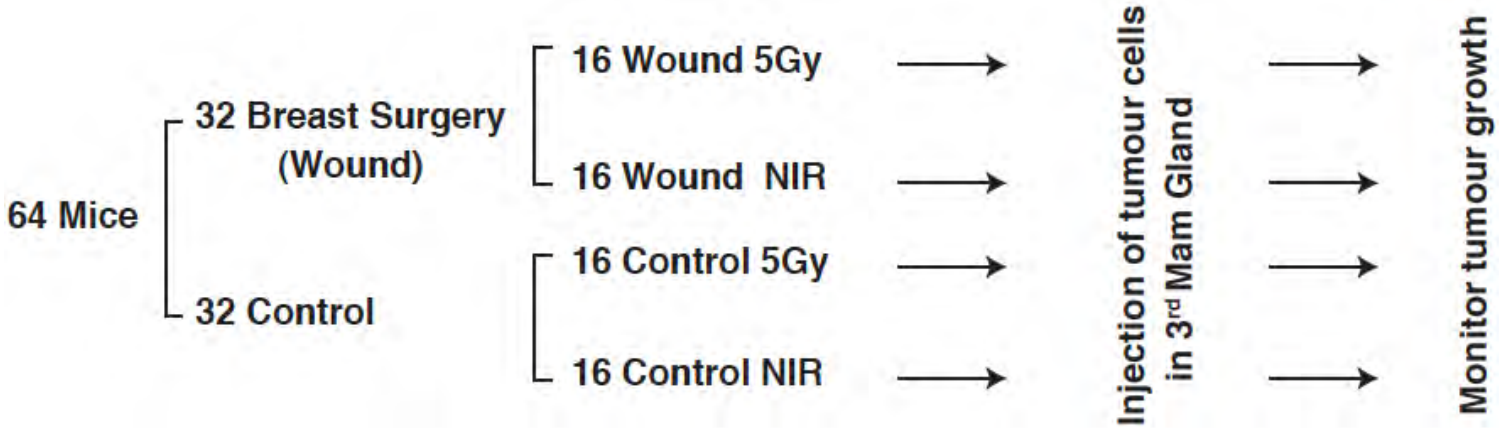


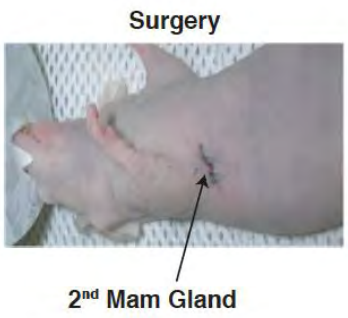
✓ **Does IORT Radiotherapy affect tumor growth independently from cell killing?**

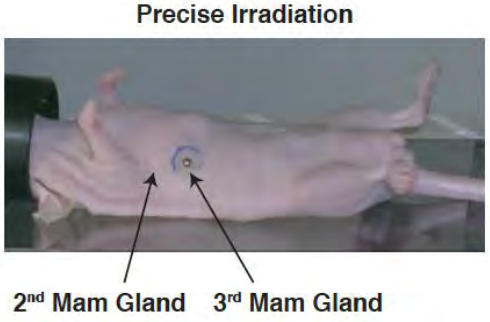
✓ Which are the molecular mechanisms involved in the response to IORT?

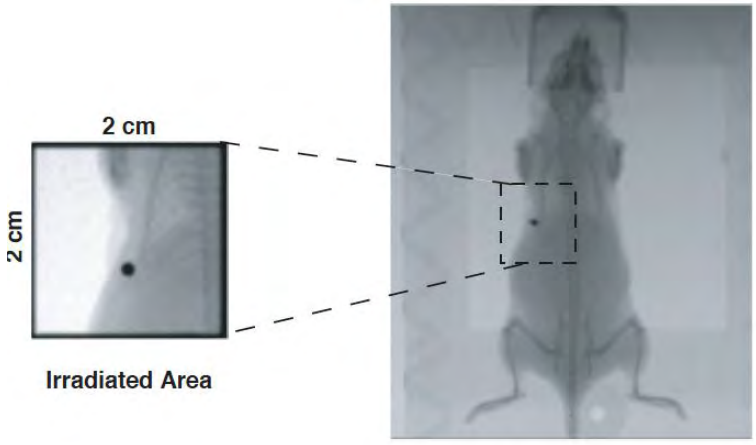
Belletti, et al. Cin. Cancer Res. 2008 14: 1325

Could Radiotherapy affect tumor growth independently from cell killing?



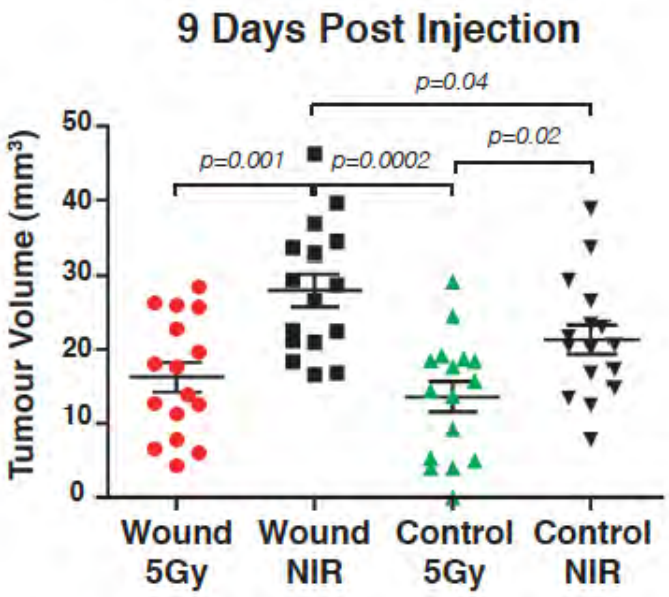


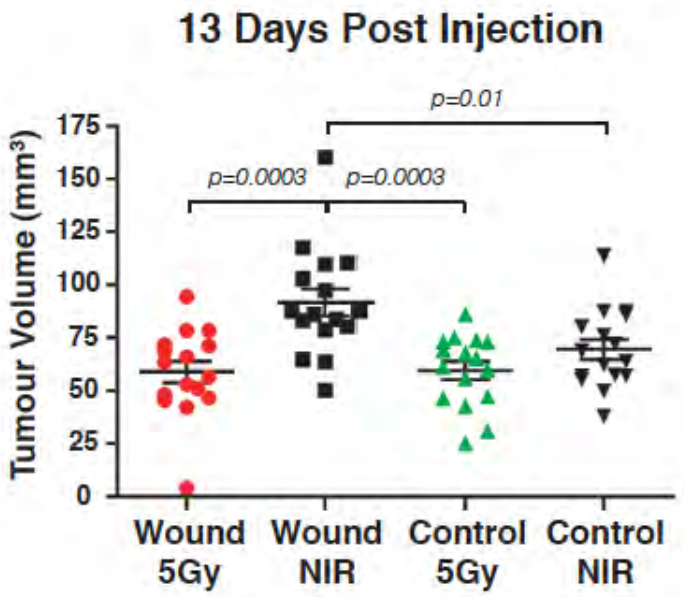




Fabris, Berton et al. Oncogene 2016

Radiotherapy affects tumor growth by impairing wound-induced proliferation





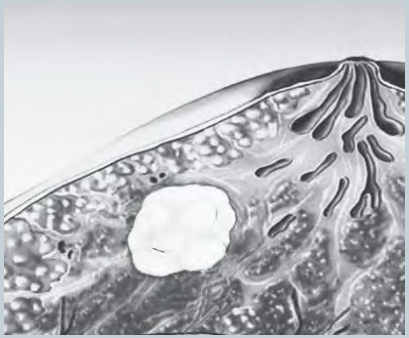
Fabris, Berton et al. Oncogene 2016

Open Questions

- ✓ Does Radiotherapy affect tumor growth independently from cell killing?
- ✓ Which are the molecular mechanisms involved in the response to IORT?

Targeted intraoperative (IORT) radiation therapy with INTRABEAM® : the TARGIT protocol

CRO AVIANO

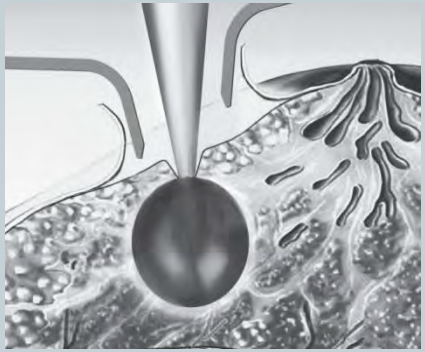


Step 1

The position of the tumor is determined

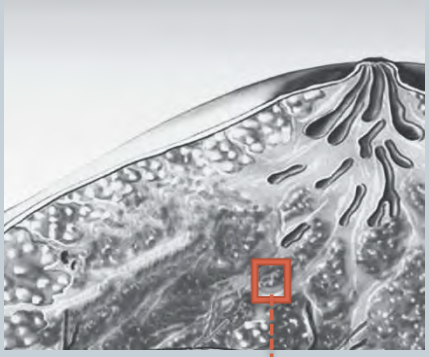
Step 2

The tumor is surgically removed



Step 3

The INTRABEAM applicator tip is positioned in the tumor cavity in the breast



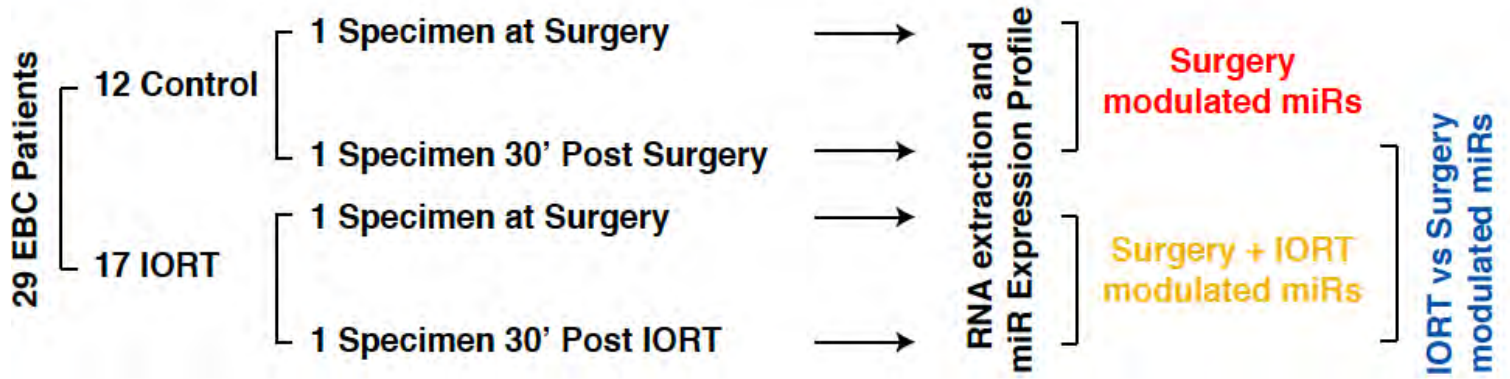
Step 4

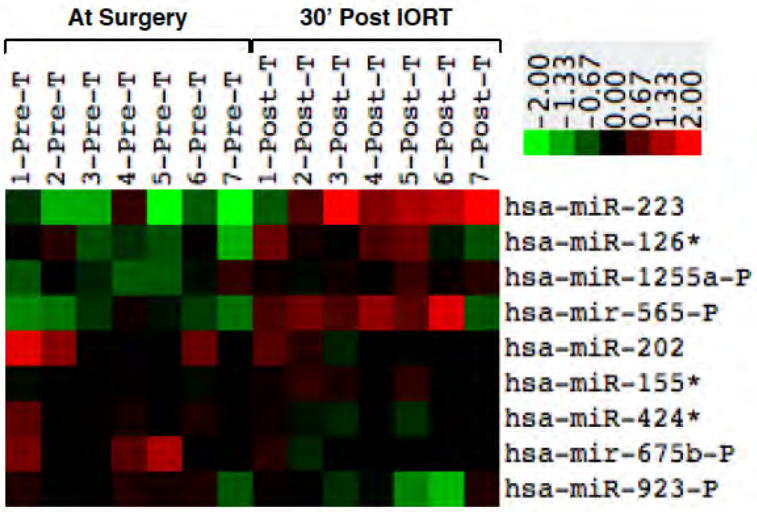
The radiation is applied for about 30 minutes. The applicator is removed and the incision closed

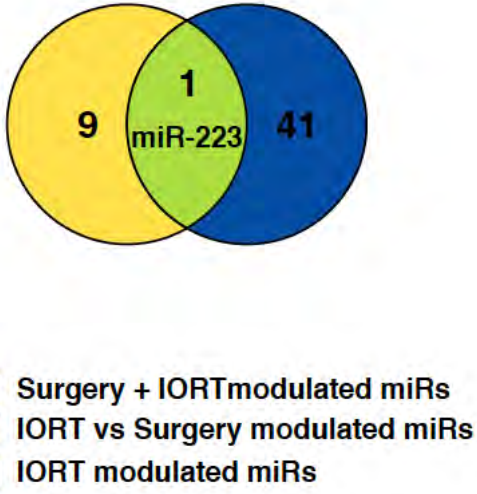
Collection of one normal breast peritumoral specimen

Collection of a second IORT-treated normal breast peritumoral specimen 30' after the end of treatment

IORT affects miRs expression profile in post-operative breast tissues







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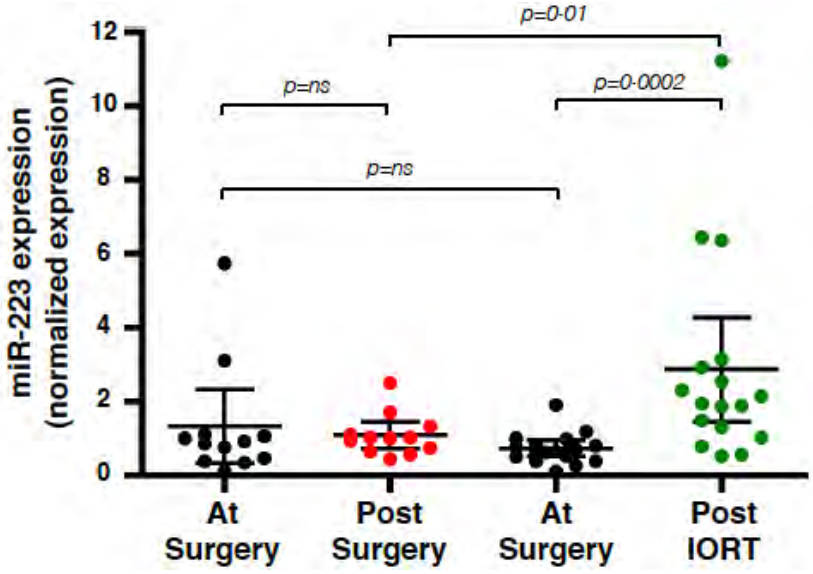
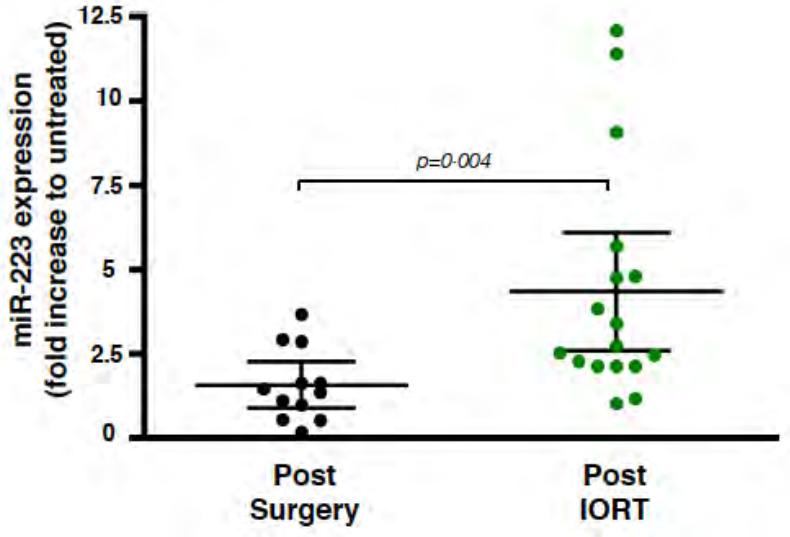
IORT specifically induces miR-223 expression





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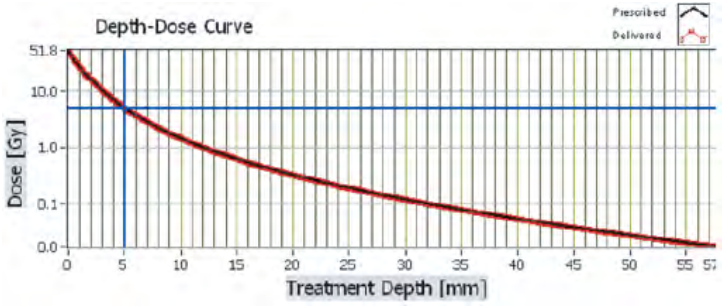
Generation of a mouse model of IORT

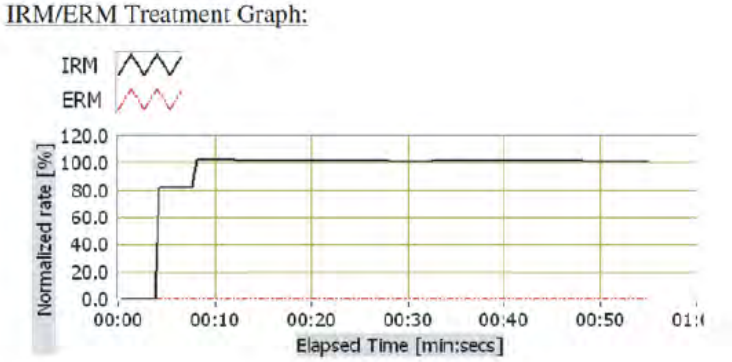
IntraBeam

Breast Surgery

Tobacco Pouch

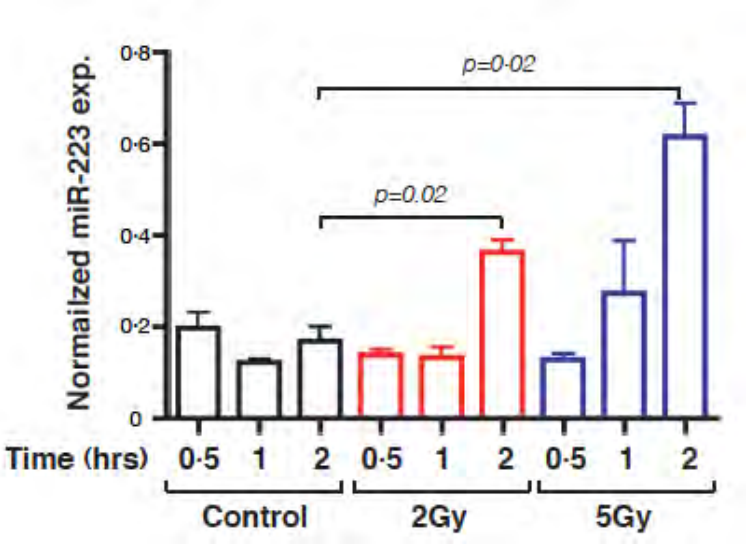
Irradiation

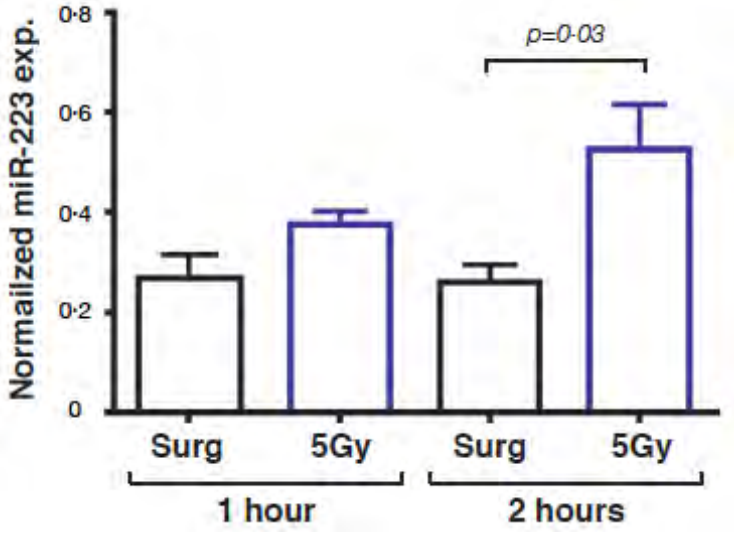




Fabris, Berton et al. Oncogene 2016

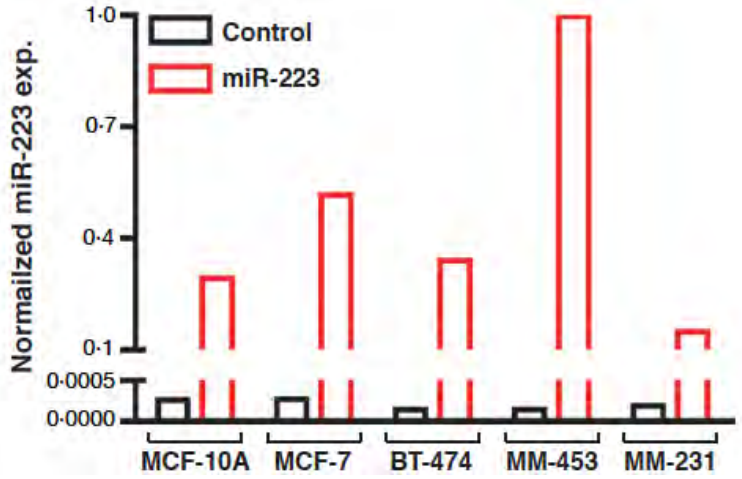
miR-223 is induced in mouse by IORT in dose and time-dependent manner

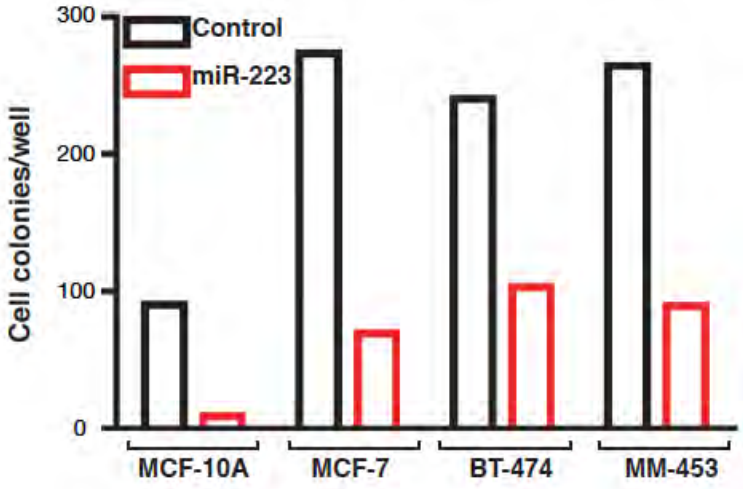




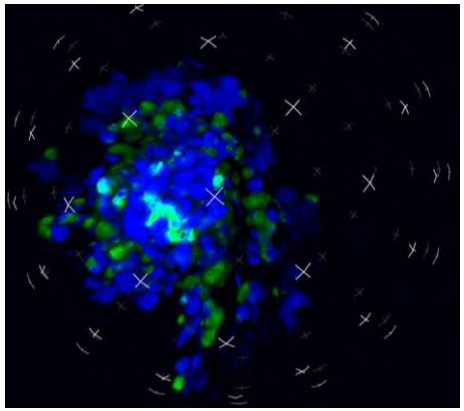
Fabris, Berton et al. Oncogene 2016

miR-223 overexpression controls normal- and breast cancer-cells growth induced by WF

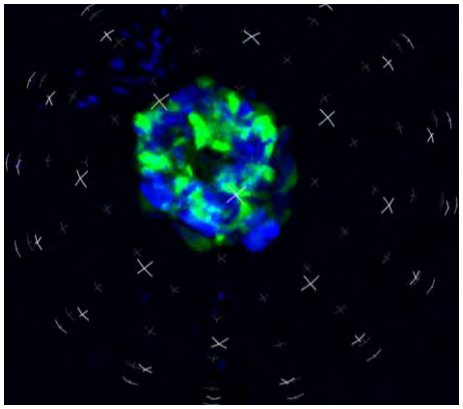




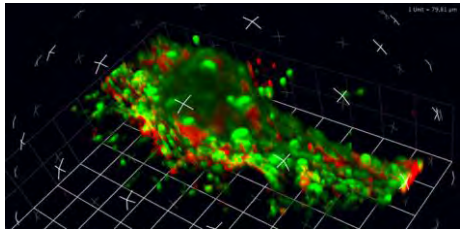
MCF-10A
control miR



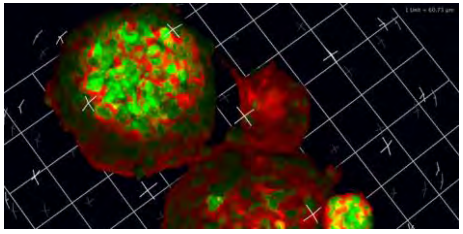
MCF-10A
miR-223



BT-474
control miR

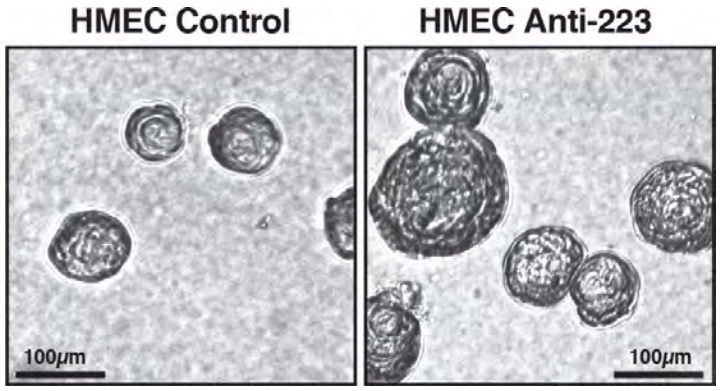


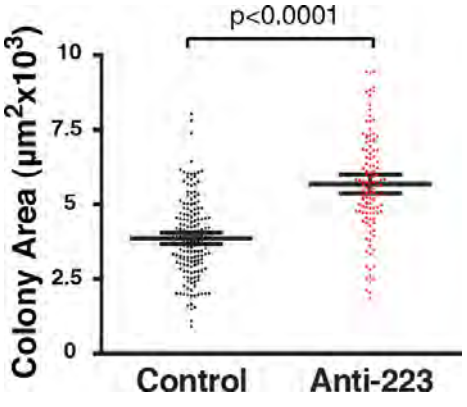
BT-474
miR-223

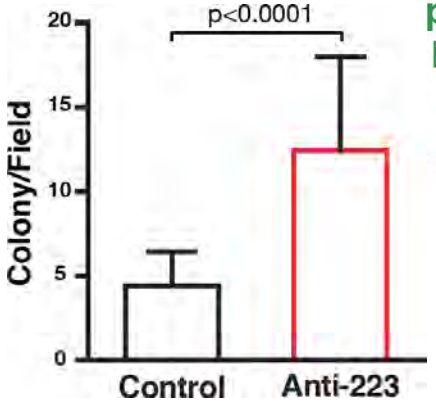


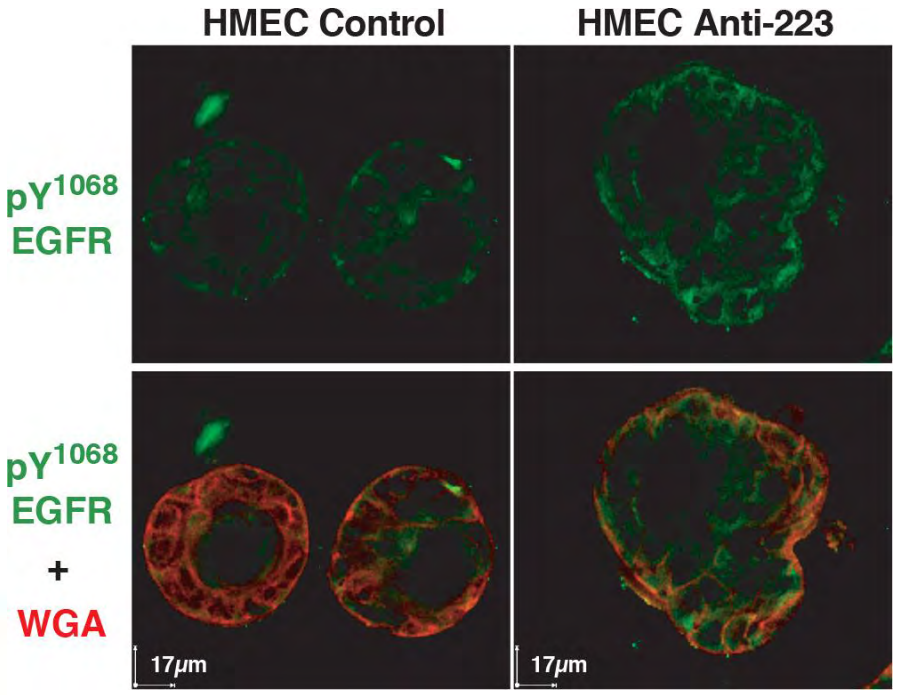
Fabris, Berton et al. Oncogene 2016

miR-223 knock-down alters normal breast cancer-cells growth induced by WF



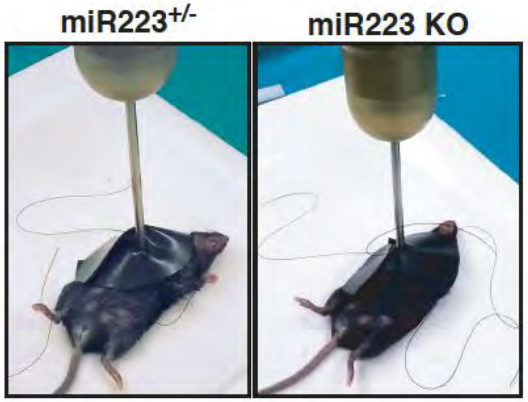


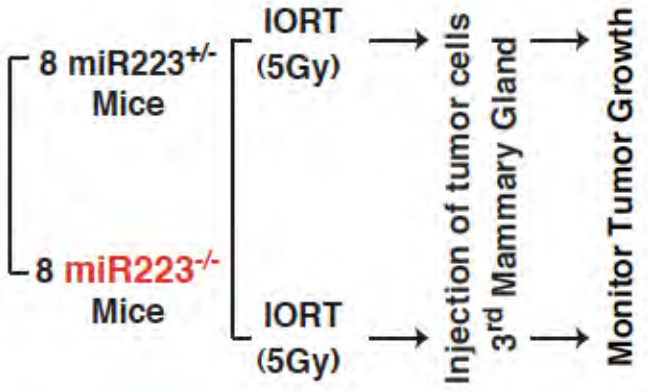


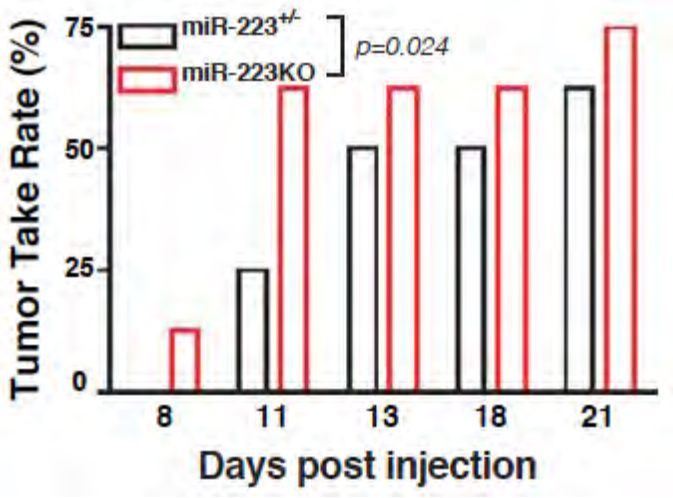


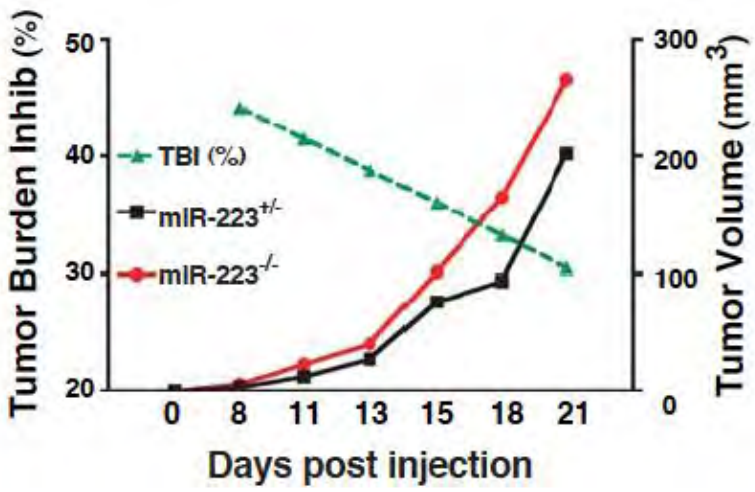
Fabris, Berton et al. Oncogene 2016

miR-223 absence partially impairs the tumor inhibition induced by IORT in mouse



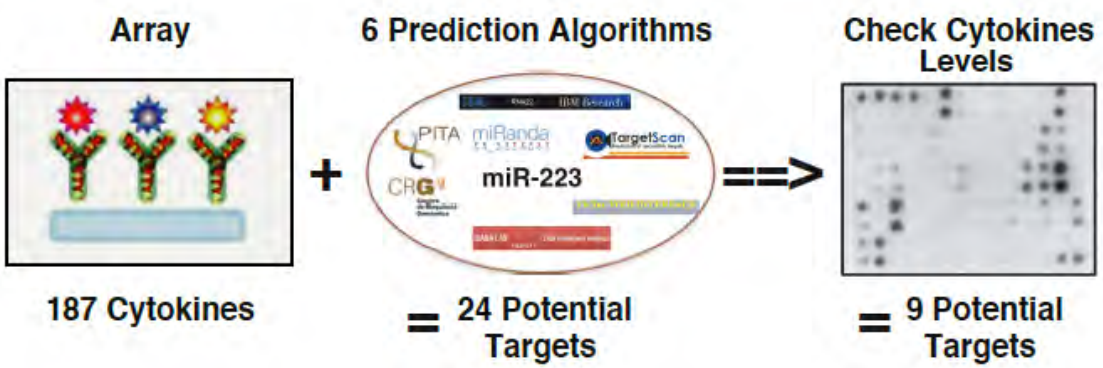




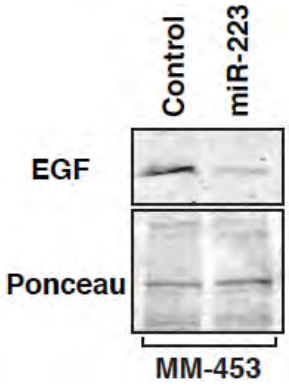


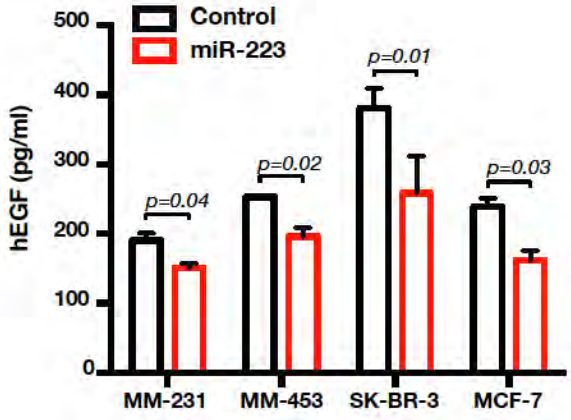
Fabris, Berton et al. Oncogene 2016

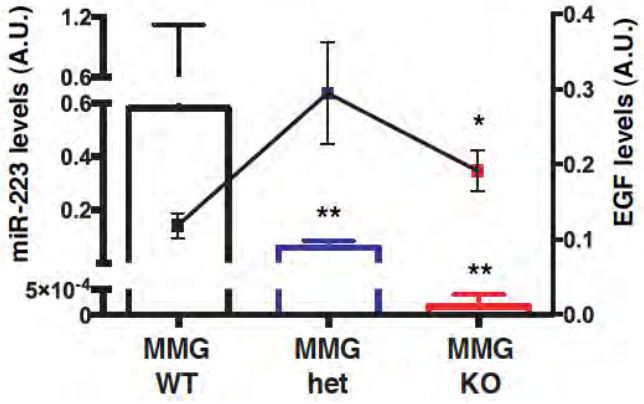
EGF is a miR-223 targets in breast tissues



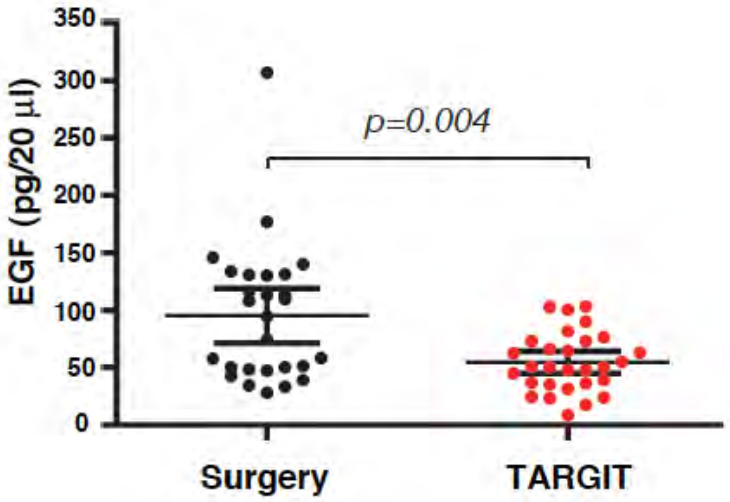
ADIPOQ
FGF7
ICAM1
LIF
CCL3
CSF1
PRL
TIMP2
EGF

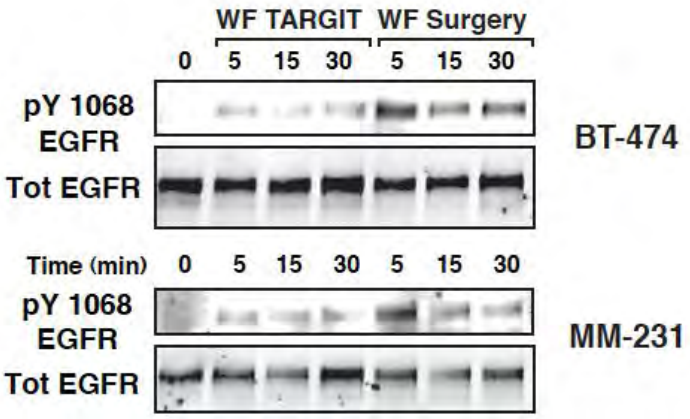






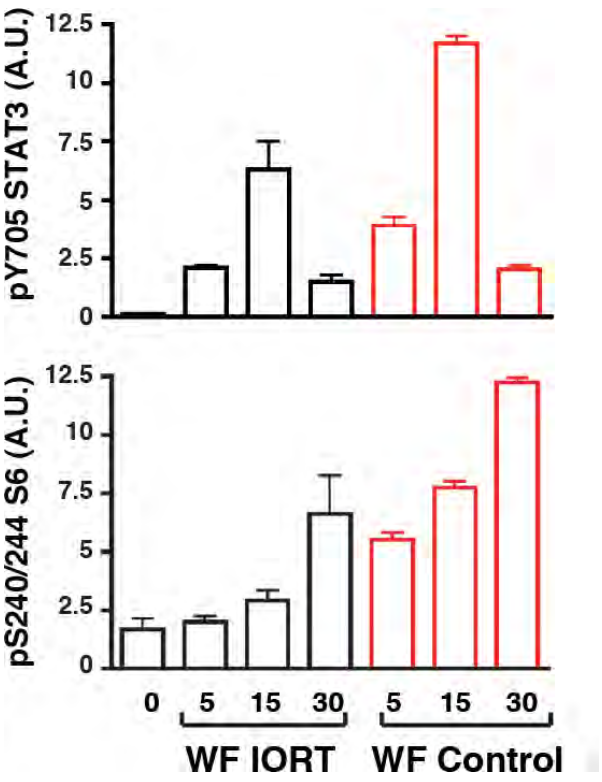
Wound fluids from TARGIT treated patients have low EGF levels and fail to properly activate EGFR

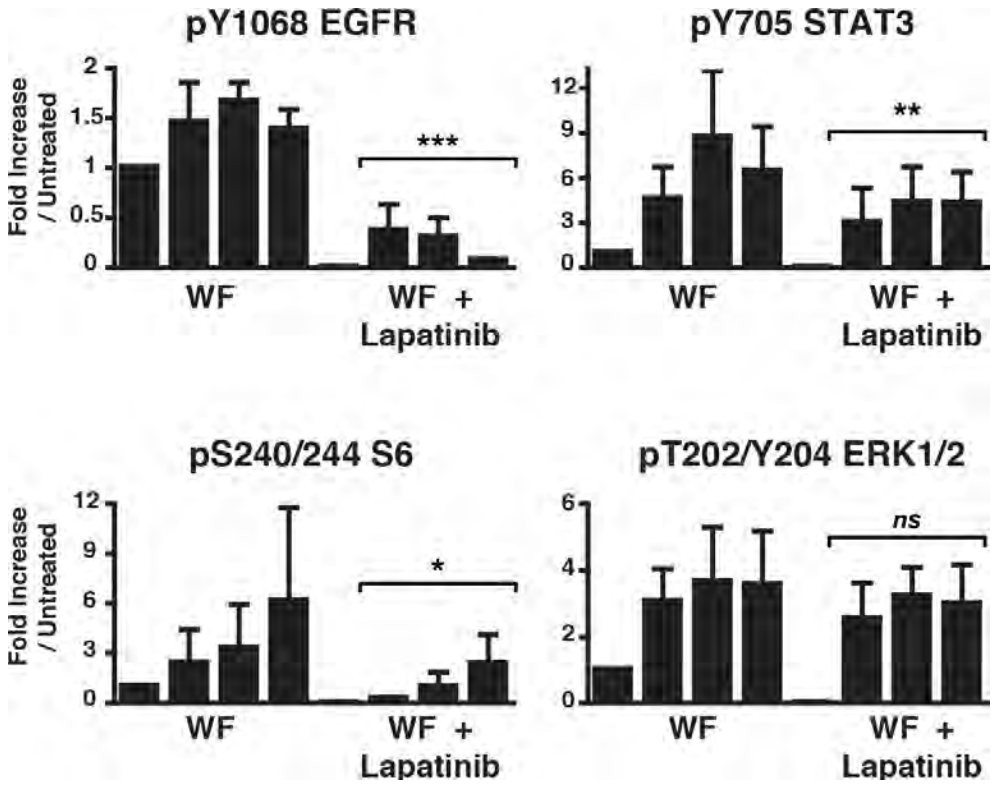




Fabris, Berton et al. Oncogene 2016

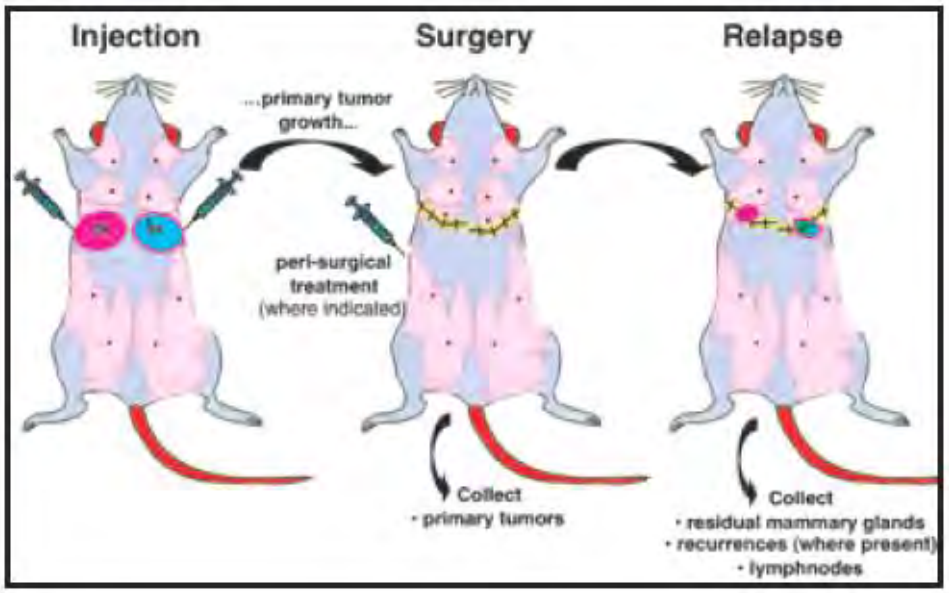
P70 and STAT3 activation by WF is inhibited by IORT and EGFR inhibitors

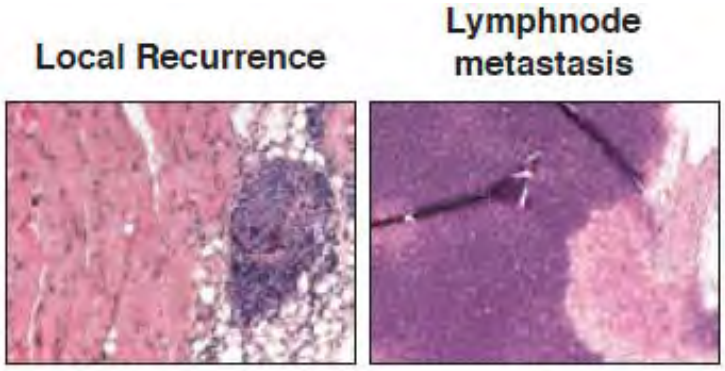




Fabris, Berton et al. Oncogene 2016

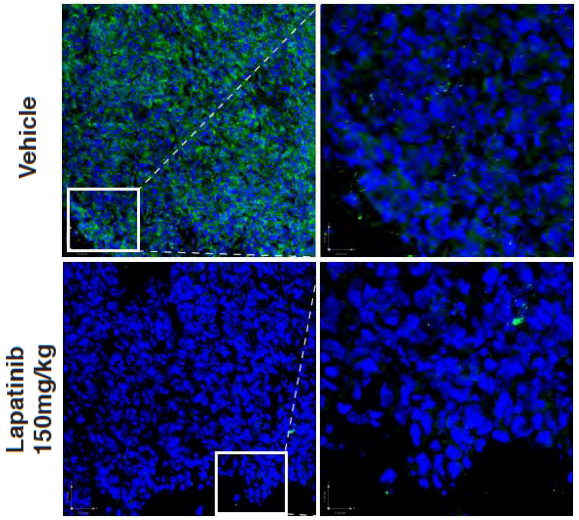
A Mouse model of Recurrences formation

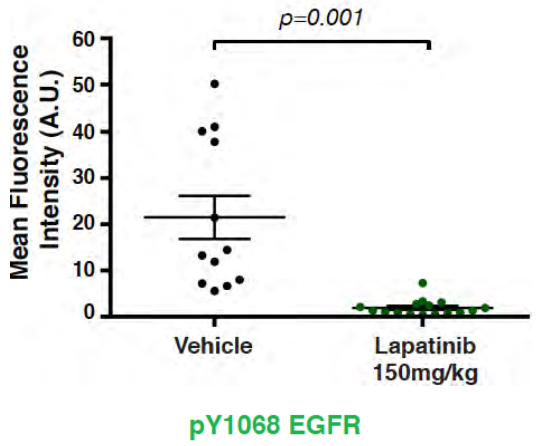


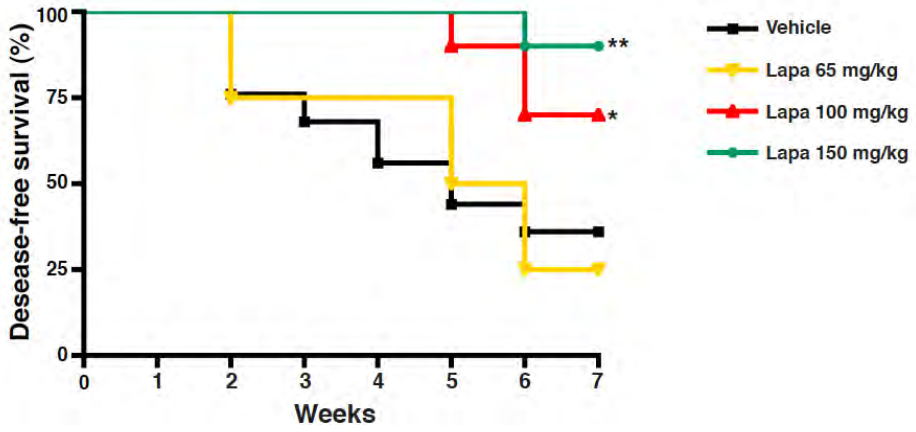


Segatto, Berton et al. JMCB 2013

Blockage of EGFR/HER2 signaling is sufficient to prevent BC recurrences formation

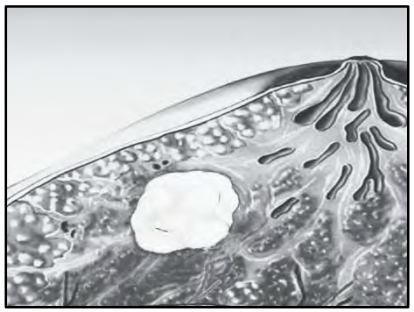




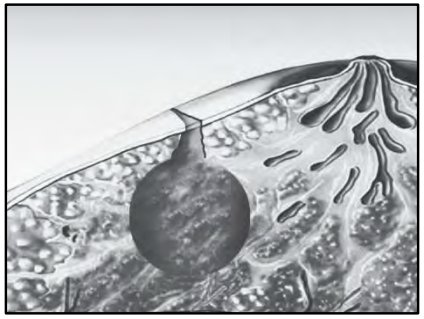


Fabris, Berton et al. Oncogene 2016

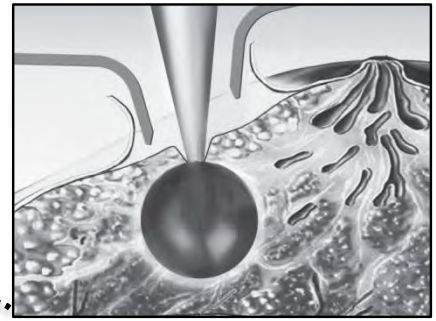
Possible roles of IORT



Breast Cancer



Lumpectomy



IORT

?

Tumor Removal

Wound Response

miRs Modification
(e.g. miR-223)

Cure ?

Growth Factor Production
(E.g. EGF)

Cancer Cells Killing

Stimulation of residual
Cancer cells proliferation

Recurrence

Cure ?

Clinical implications

- ✓ Surgery and the consequent inflammatory response caused by wounding represent factors favoring the BC proliferation and may attract "residual" BC cells to the site of surgery;
- ✓ Our data may explain the high rate of recurrences observed at the site of surgical wound;
- ✓ We also proved that Radiotherapy prevents wound induced cancer cell growth likely through the regulation of miR-233/EGF expression
- ✓ The fact that miR-223 impairs EGF/EGFR signaling opens the way to the design of new peri-operative treatments based on the use of clinically available EGFR inhibitors, to restrain loco-regional and distant recurrences;
- ✓ Altogether, our data also suggest that for anticancer therapies to be really effective it will be necessary not only to find the **right treatment** for the **right patient** (carrying the most relevant target) but also to choose the **right timing** of administration.

ACKNOWLEDGEMENTS

CRO National Cancer Institute -Aviano- Italy

Experimental Oncology 2

Barbara Belletti, PhD and PI
Linda Fabris, PhD
Ilenia Segatto, PhD
Francesca Citron, PhD Student
Maura Sonego, PhD
Stefania Berton, PhD

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Pathology Unit

Tiziana Perin, MD

Dr. George Calin, MD, PhD, **MDA Cancer Center, Houston, Texas**
Dr. Robert Bristow, MD, PhD, **Ontario Cancer Center, Toronto, Ontario**

La Direzione Scientifica

CRO INTRAMURAL RESEARCH GRANTS – 2011/2012 Cal

ASSOCIAZIONE ITALIANA PER LA RICERCA SUL CANCRO

Ministero della Salute

REGIONE AUTONOMA FRIULI VENEZIA GIULIA

This work is dedicated to the memory of Prof. Mauro G. Trovò

9th International ISIORT Conference
June 24/25th 2016
Novara, Italy

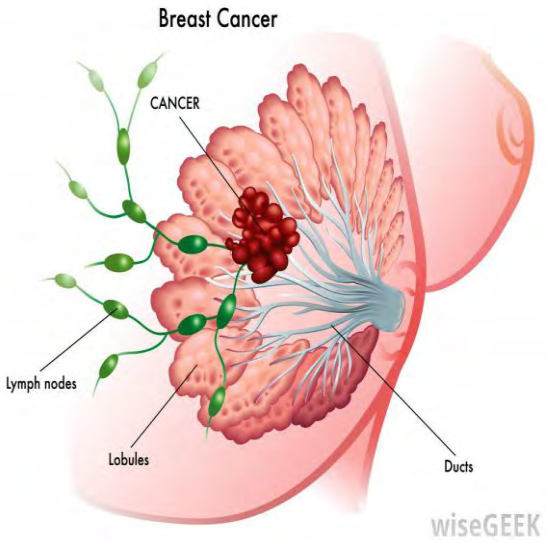
Intraoperative radiotherapy impairs breast cancer stem cell phenotype increased by surgical wounding

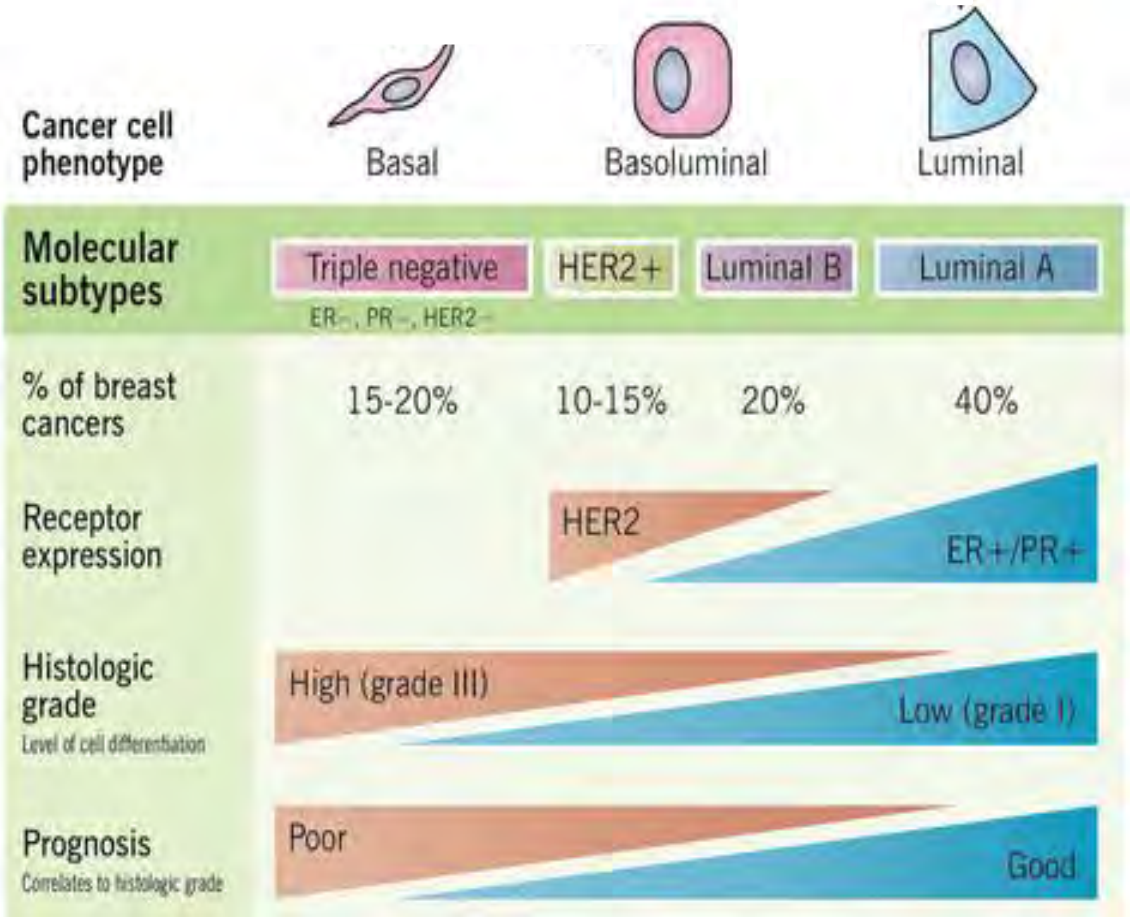
Kulcenty K, Zaleska K, Suchorska W, Kruszyna M, **Murawa D**

Greater Poland Cancer Centre, Poznań, Poland

wielkopolskie centrum onkologii

Breast cancer biology and treatment



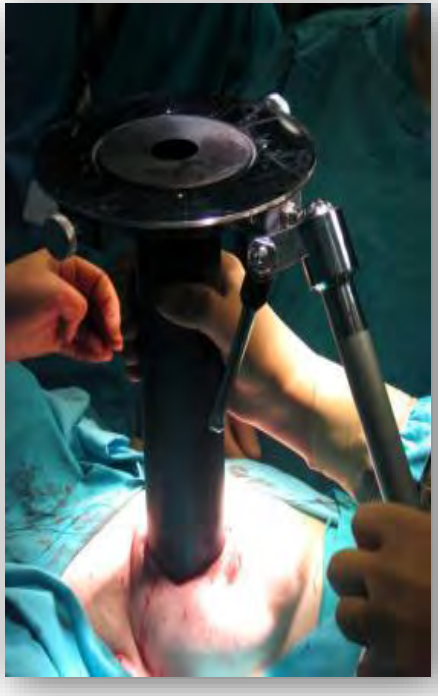


Treatment:

- whole breast irradiation
- chemotherapy
- hormone therapy

Tumor recurrence after conservative treatment -

- 80-90% of tumor recurrence after surgery occur in the same quadrant as the primary cancer
- 90% of cancer cells are located in 4 cm around tumor
- **Tumor bed requires higher radiation dose than whole body radiotherapy (BOOST)**



Mobetron IntraOPMedical Inc.
(Santa Clara, USA)

IORT

Resection of the early breast tumor (up to 30 mm) is followed by BOOST radiation of 10 Gy per tumor bed and surrounding tissues.

What are the advantages of intraoperative RT?

- Saving the surrounding tissue by a gradual decrease in radiation dose and moving away the healthy tissue (skin)
- A more balanced distribution of the dose
- Extremely precise irradiation of the target area - particularly important in the era of oncoplastic surgery
- The surgeon and radiation oncologist precisely identify the volume of tissue which must be irradiated after the act of tumor removal

Wound fluids promotes tumor metastasis

British Journal of Cancer (2001) 85(4), 490–492
© 2001 Cancer Research Campaign
doi: 10.1054/ bjoc.2001.1989, available online at http://www.idealibrary.com on IDEAL®

Hypothesis

http://www.bjcancer.com

Does surgery modify growth kinetics of breast cancer micrometastases?

R Demicheli, P Valagussa and G Bonadonna

Istituto Nazionale Tumori, via Venezian 1, 20133, Milano, Italy

Summary Surgery should be considered as a major perturbing factor for metastasis development in laboratory animals. The differer time distribution of mortality for 1173 patients undergoing mastectomy in comparison with 250 untreated patients suggests that primar tumour removal could result in changes of the metastatic process even for breast cancer. © 2001 Cancer Research Campaig http://www.bjcancer.com

Keywords: breast cancer; growth kinetics; micrometastases; surgery signals; tumour dormancy

Surgery

Volume 133, Issue 5, May 2003, Pages 547–555

ELSEVIER

SURGERY

Original Communications

Increased surgical stress promotes tumor metastasis * ** ★

Yasunori Tsuchiya, Shigeaki Sawada, Isaku Yoshioka, Yasukata Ohashi, Mitsuhiro Matsuo, Yuko Harimaya, Kazuhiro Tsukada, Ikuo Saiki

Nat Clin Pract Oncol. 2007 Dec;4(12):699-710.

Tumor dormancy and surgery-driven interruption of dormancy in breast cancer: learning from failures.

Demicheli R[1], Retsky MW, Hrushesky WJ, Baum M.

⊕ Author information

Abstract

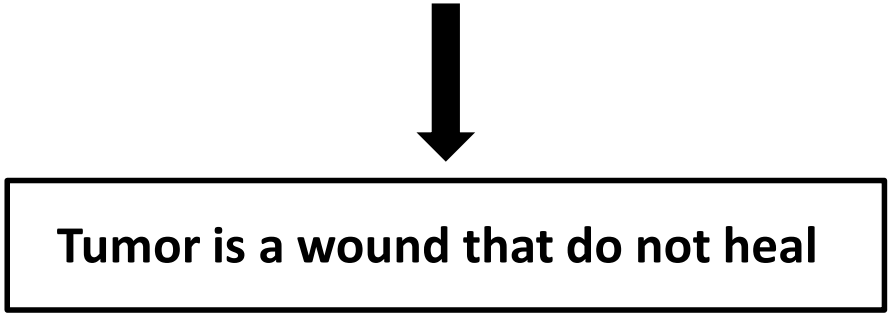
Primary tumor removal, usually considered intrinsically beneficial, can perturb metastatic homeostasis, and for some patients results in the acceleration of metastatic cancer. The continuous-growth model is required to yield to an interrupted-growth model, the implications of which are episodes of tumor dormancy. This Review analyzes the recent evolution of two paradigms related to the development of breast cancer metastases. The evolution of the paradigms described herein is supported by a growing body of findings from experimental models, and is required to explain breast cancer recurrence dynamics for patients undergoing surgery with or without adjuvant chemotherapy.

Published data suggest that the wound healing process after surgery alters the area surrounding the original tumor and the modified microenvironment is more favorable for the tumor recurrence, probably due to stimulatory effects of post-surgical fluids.

Wound fluids promotes tumor metastasis

Wound healing and cancer progression have striking similarities including:

- inflammation
- angiogenesis
- rearrangement of the molecular matrix around the cells



Activation of the „wound response signature" is highly prognostic of poor survival in BC patients which strongly suggests the potential relevance of the wound response induced by surgery.

Wound fluids promotes tumor metastasis

- Apart the mere dose augmentation effect and the high topographic precision in delivery, it was hypothesized that immediate irradiation during surgery has implications on the tumor microenvironment abrogating the proliferative cascade induced by surgical wound healing (Demicheli R Br J Cancer 2001, Tsuchida Y. Surgery. 2003).

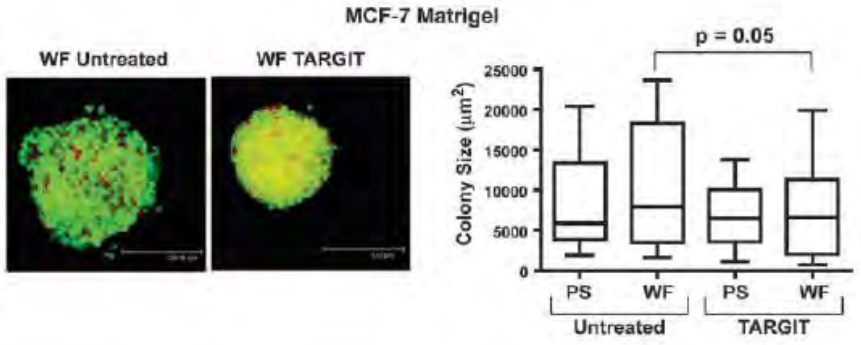
- The published data suggest that the wound healing process after surgery alters the area surrounding the original tumor also around the scar, and the modified microenvironment is more favourable for the tumor to recur. Local recurrence after surgery is particularly common in tumors characterized by HER2 overexpression (Menard S, Clin Canc Res. 2002).

- It was shown that wound fluids contain growth factors inducing proliferation of HER2-positive breast cancers (Tagliabue E Lancet. 2003).

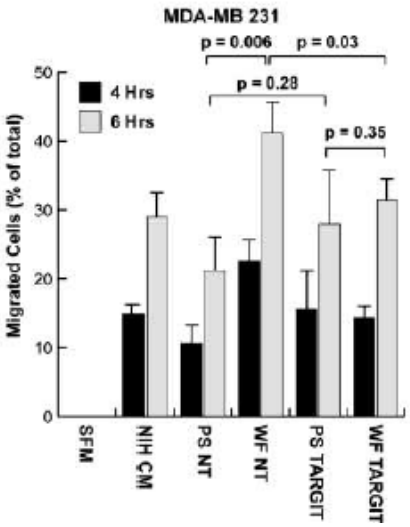
Wound fluids promotes tumor-initiating features of breast cancer cells

Not only radiotherapy affects cell survival; also surgery has an impact on tumor microenvironment. Belletti et al. demonstrated the stimulatory effect of post-surgical drainage fluids harvested from a group of patients after IORT treatment and patients after breast conserving surgery on breast cancer cells. It was shown that wound fluids from conservative surgery (without IORT) can stimulate proliferation, migration and invasion of breast cancer cell lines while fluids collected after IORT demonstrated different properties (Belletti B, Clin Cancer Res. 2008).

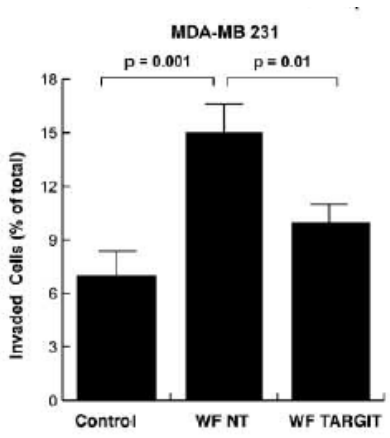
PROLIFERATION



MIGRATION



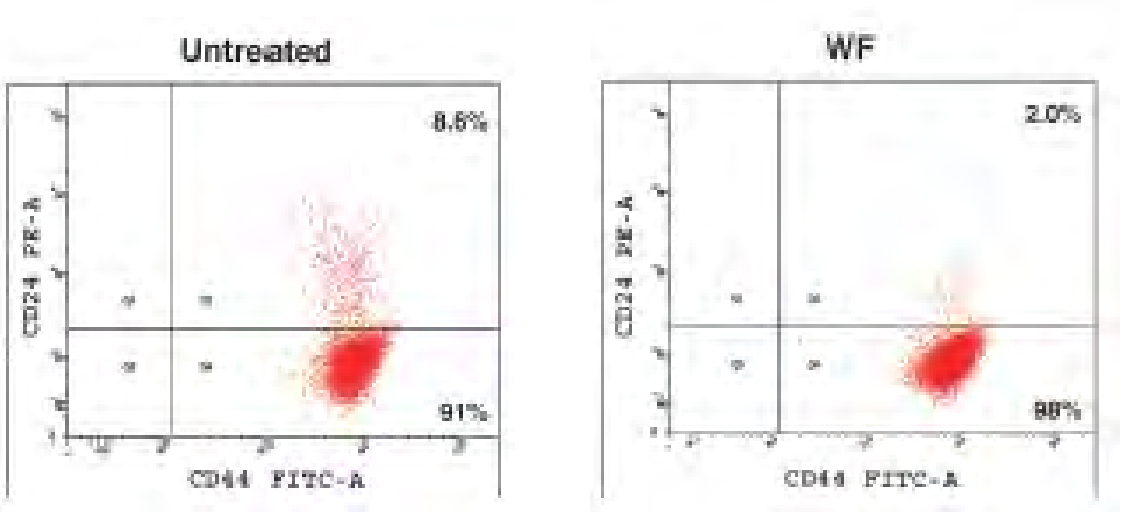
INVASION



Belletti B, Clin Cancer Res. 2008

Wound fluids promotes stem-like features of breast cancer cells

The presence of wound fluids induced the increase in the $CD44^{high}/CD24^{-/low}$ markers in MDA-MB-231 cells, associated with breast cancer stem cells subpopulation.



Belletti B, Oncotarget, 2014

IORT of early breast cancer

The aim of this study was to evaluate the influence of surgical wound fluids from IORT treatment compared to fluids from conservative breast surgery on $CD44^{+}/CD24^{low}$ phenotype, cancer stem cell markers and epithelial to mesenchymal transition in luminal and basal subtype of breast cancer cells.

Study Group

Group 1: breast cancer patients after conservative breast cancer surgery (quadrantectomy) which underwent the procedure of Intraoperative Radiotherapy (IORT) up to a single dose of 10 Gy per tumor bed and surrounding tissue **(RT-WF)**

Group 2: breast cancer patients after breast cancer surgery (quadrantectomy) **(WF)**

Parameters	WF	RT-WF
Group size	20	24

Maximal tumour size – 30 mm

Study Group

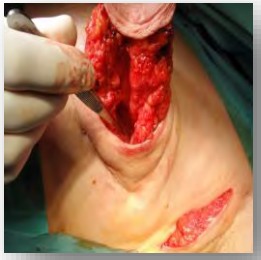
Classification	Immunoprofile	Other characteristics	Example cell lines
Luminal A	ER$^+$, PR$^{+/-}$, HER2$^-$	Ki67 low, endocrine responsive, often chemotherapy responsive	MCF-7 T47D
Luminal B	ER$^+$, PR$^{+/-}$, HER2$^+$	Ki67 high, usually endocrine responsive, variable to chemotherapy. HER2$^+$ are trastusumab responsive	BT474
Basal	ER$^-$, PR$^-$, HER2$^-$	EGFR$^+$ and/or cytokeratin 5/6$^+$, Ki67 high, endocrine nonresponsive, often chemotherapy responsive	MDA-MB-468
Claudin-low	ER$^-$, PR$^-$, HER2$^-$	Ki67, E-cadherin, claudin-3, claudinin-4 and claudinin-7 low. Intermediate response to chemotherapy	BT549, MDA-MB-231
HER2	ER$^-$, PR$^-$, HER2$^+$	Ki67 high, trastusumab responsive, chemotherapy responsive	SKBR3,

EGFR, epidermal growth factor receptor; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

Holliday and Speirs *Breast Cancer Research* 2011 **13**:215

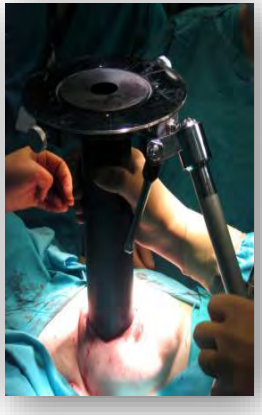
Plan of the experiment

Surgery



+

+/- IORT

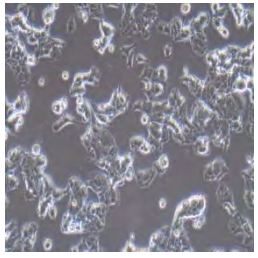


7 days →

Wound fluid

→ Collection of wound fluids **+/-** IORT

Cell



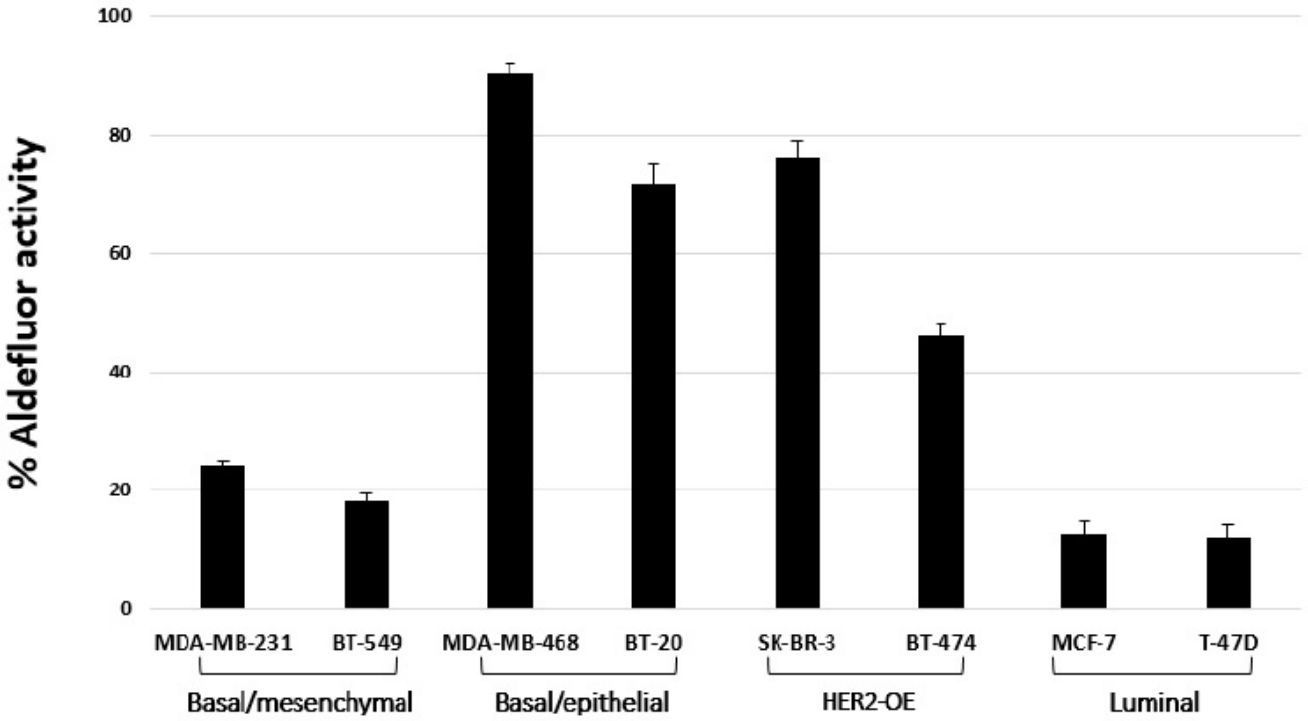
+ 10% **RT-WF/WF** in complete medium

4 days →

ANALYSIS:

- FACS – **CD44+/CD24-** phenotype
- **RT-qPCR** cancer stem cells phenotype

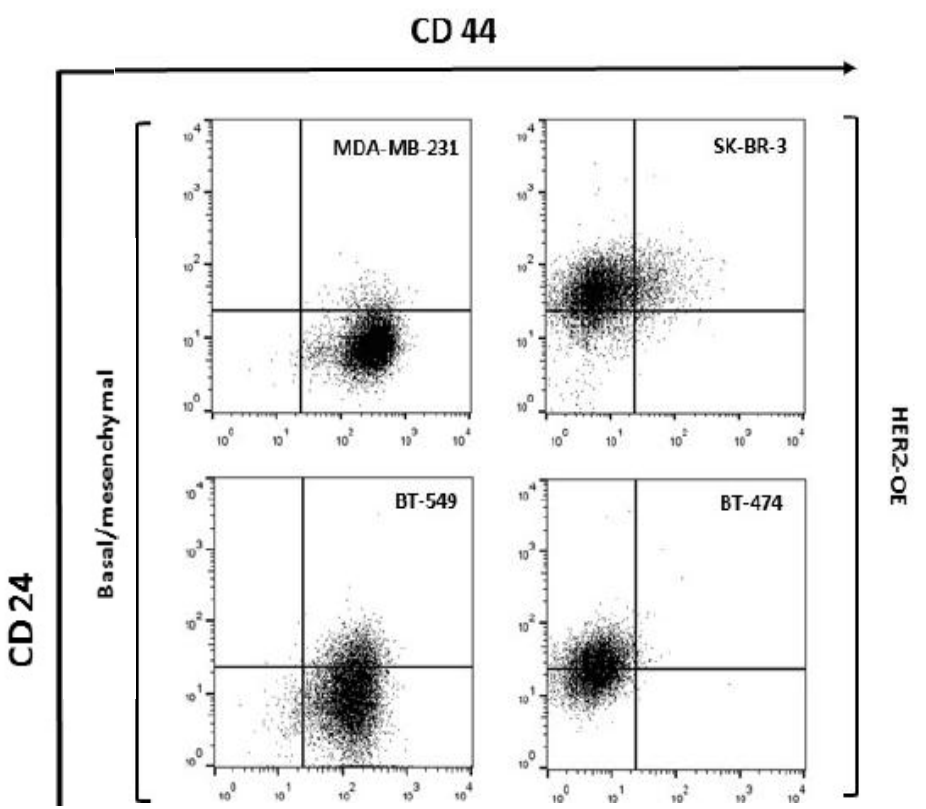
Phenotypic characterisation of a panel of a breast cancer cell lines – CD44/CD24 stem cell like phenotype

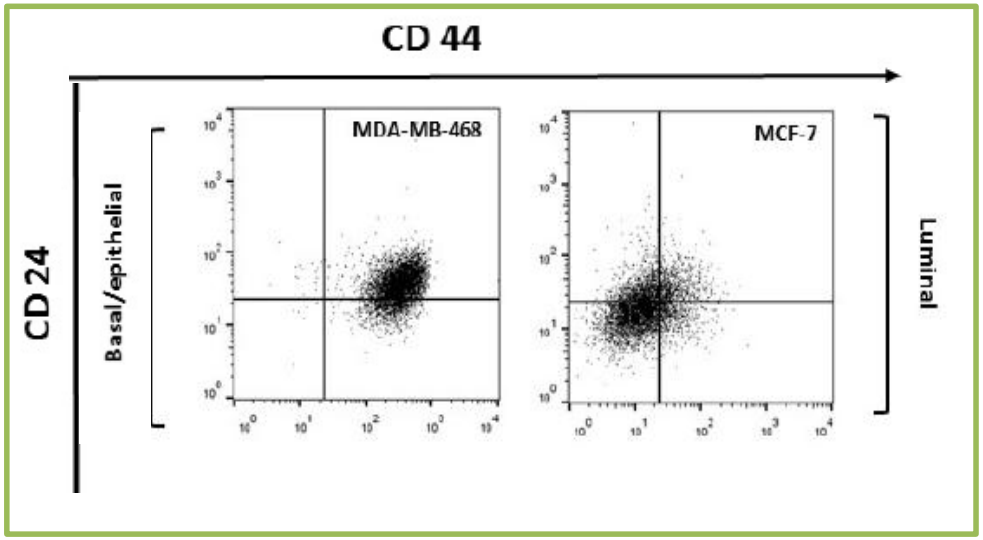


The ALDH 1 positive subpopulation varied between human breast cancer cell lines according to distinct molecular subtypes. Basal/epithelial and HER2 overexpressing protein cell lines represent strong activity of ALDH1. Plotted is the mean of two independent experiments.

Zaleska, Murawa 2016

Phenotypic characterisation of a panel of a breast cancer cell lines – CD44/CD24 stem cell like phenotype





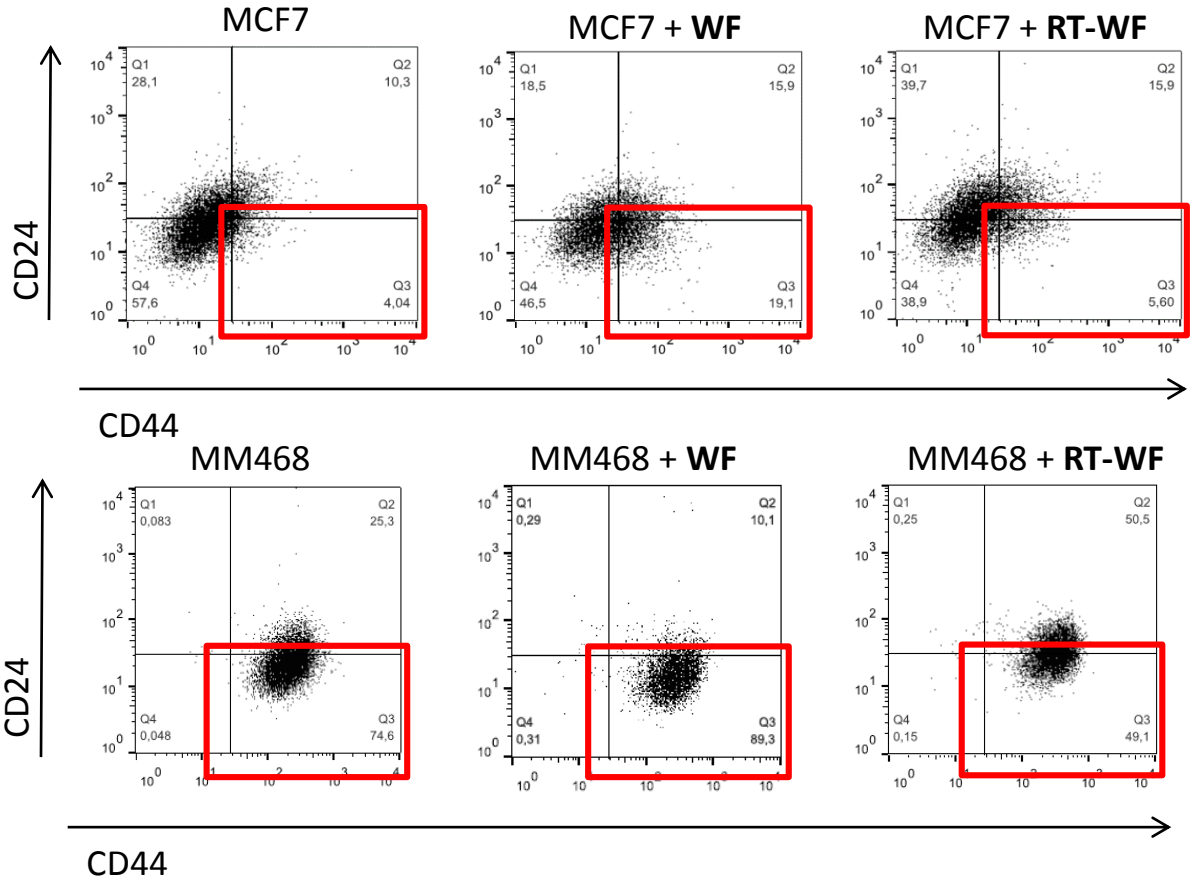
$CD44^{+}/CD24^{low}$

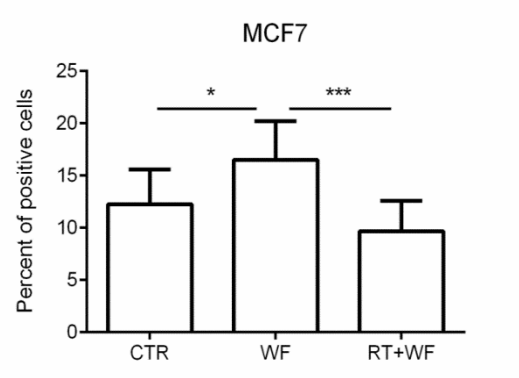
cancer stem cell phenotype

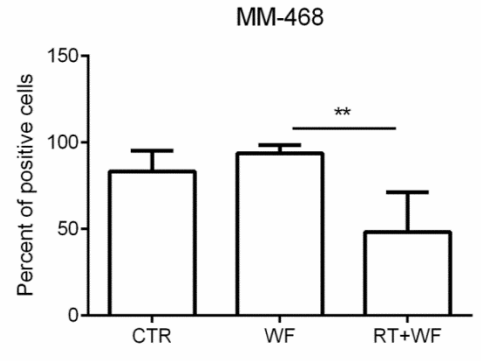
Subpopulations of $CD44^{+}/CD24^{-/low}$ positive cells in human breast cancer cell lines according to distinct molecular subtypes. Basal-like cell lines are mainly constituted by cells with high level of CD44 and low CD24 populations. Plotted is the mean of three independent experiments.

Zaleska, Murawa 2016

IORT treatment impairs the ability of WF to induce cancer-stem cells phenotype in the luminal and basal subtype of breast cancer cells



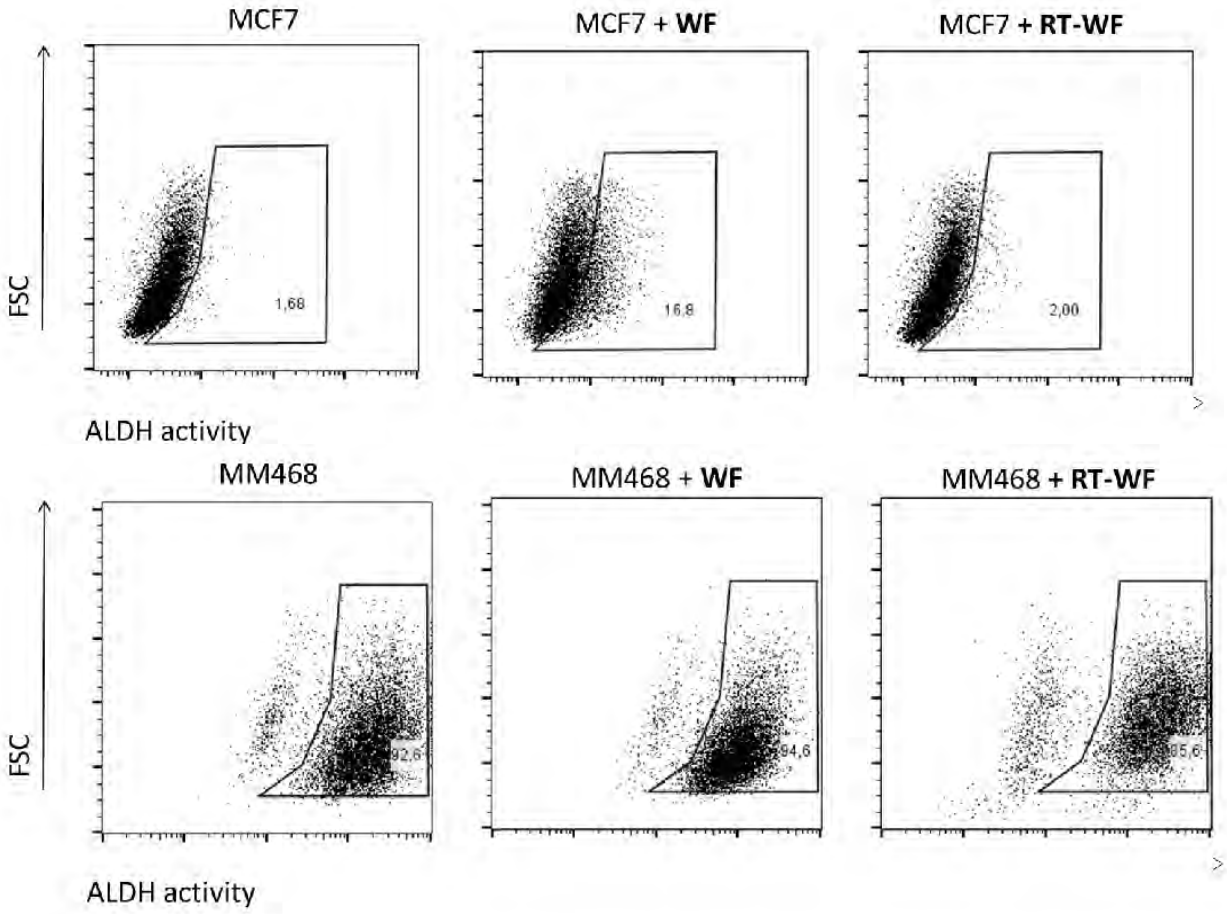


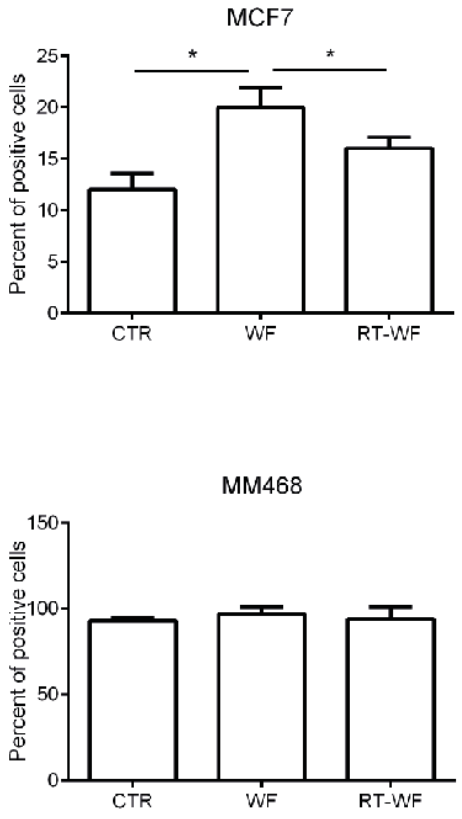


The luminal MCF-7 cell line was mainly constituted by CD24 positive cell, nevertheles a small population of $CD44^{+}/CD24^{-/low}$ decresed significantly due to incubation with RT-WF. Triple negative cell line (MM468) demonstrated stimulating effect of WF and inhibiting of RT-WF compared to control group.

Zaleska, Murawa 2016

Surgical wound fluids affect the aldehyde dehydrogenase activity



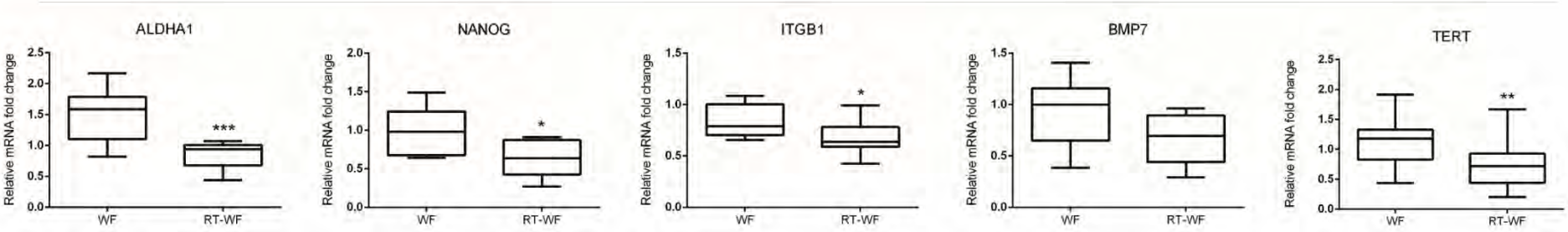


Surgical fluids both from conservative surgery and the IORT procedure induced ALDH activity compared to control group. In luminal MCF7 cell line, surgical wound fluids collected from patients who underwent surgery alone demonstrated stronger stimulating effect compared to the group with the IORT procedure. Triple negative MM-468 cell line did not demonstrate almost any difference in ALDH1 activity between the control group and the treated cells.

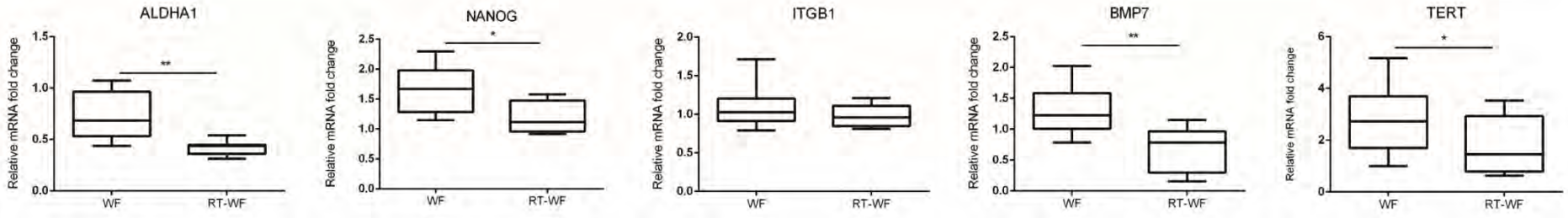
Zaleska, Murawa 2016

IORT treatment affects pluripotency and stemness profile in a luminal and basal subtype of breast cancer cells

Luminal MCF7 cell line



Basal MM-468 cell line

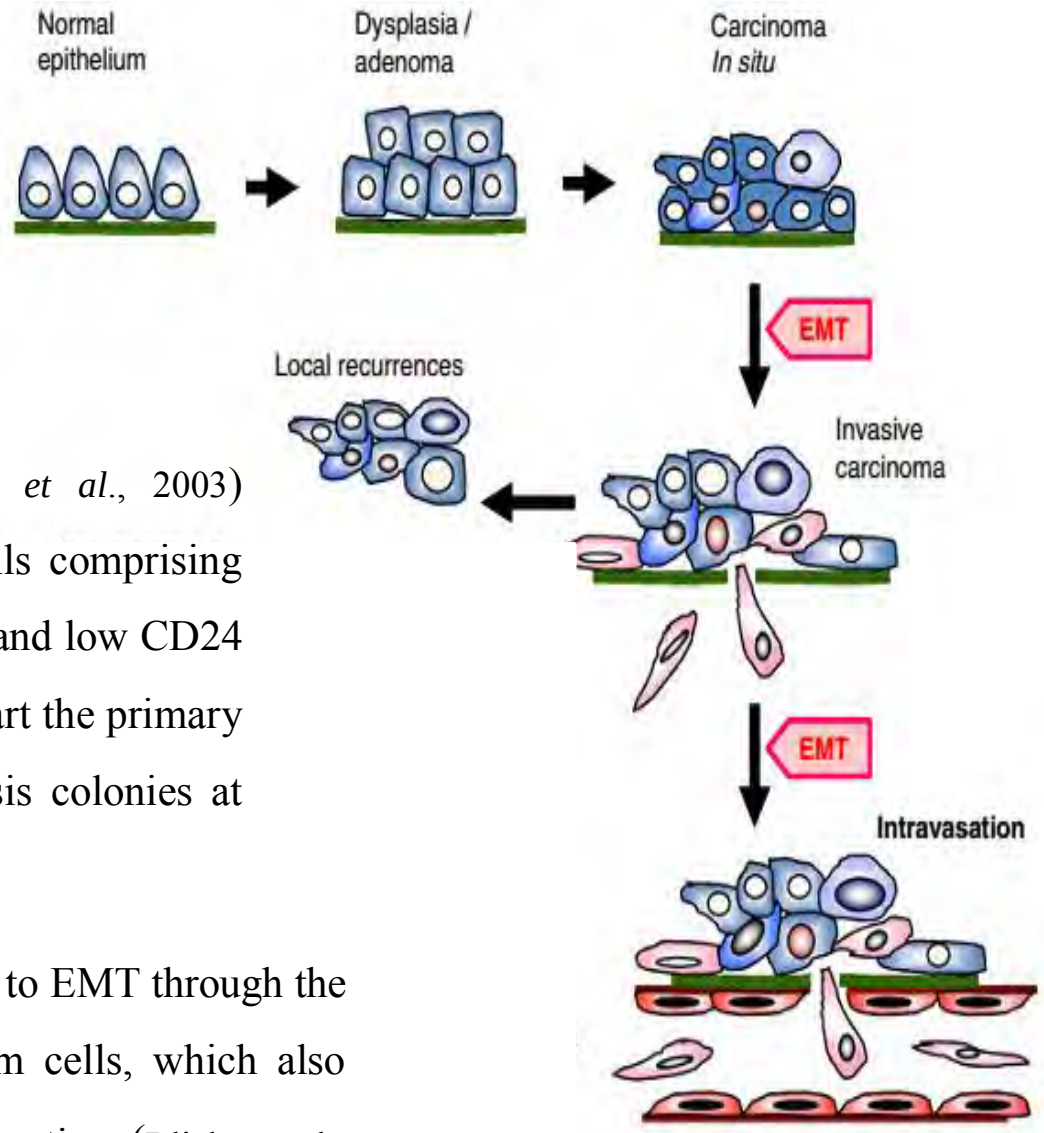


The expression of all analysed markers respresenting stemness profile of luminal and basal subtype of breast cancer cells was significantly increased in group of wound fluids from conservative surgery. IORT treatment decresed those markers in both analysed cell lines.

Kulcenty, Suchorska, Murawa

Tumor progression via epithelial to mesenchymal transition

Epithelial to mesenchymal transition (EMT) process, first described in embryonic development, is one of the main mechanism involved in breast cancer metastasis.



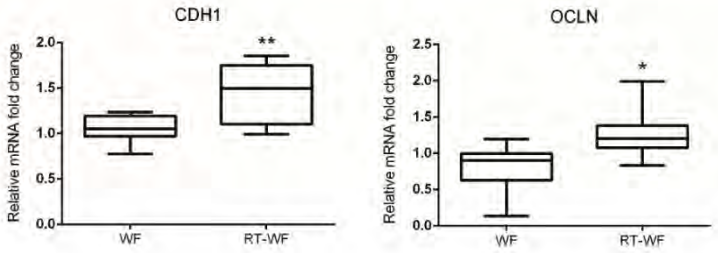
The paradigm of early metastasis (Al-Hajj *et al.*, 2003) suggests that a fraction of primary tumor cells comprising stem cell-like characteristics with high CD44 and low CD24 ($CD44^{high}/CD24^{-/low}$) have the potential to depart the primary tumor site relatively early and form metastasis colonies at distant sites.

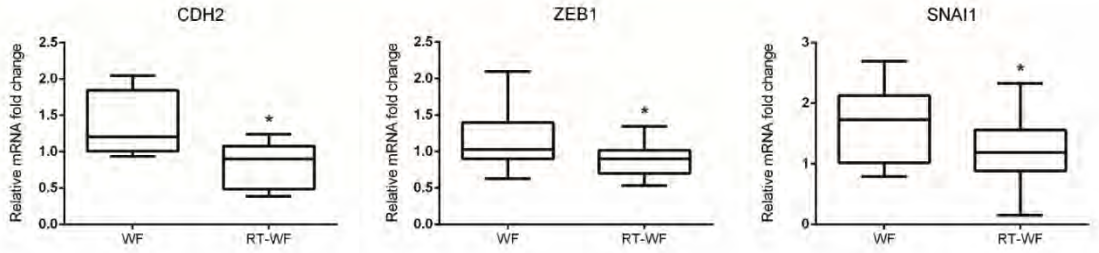
$CD44^{high}/CD24^{-/low}$ phenotype has been linked to EMT through the mesenchymal attributes of breast cancer stem cells, which also have dramatically enhanced malignant properties (Blick et al., Journal of Mammary Gland Biology and Neoplasia, 2010).

Devika Gunasinghe, Cancer Metastasis Rev, 2012

IORT treatment affects epithelial to mesenchymal transition in a luminal and basal subtype of breast cancer cells

Luminal MCF7 cell line

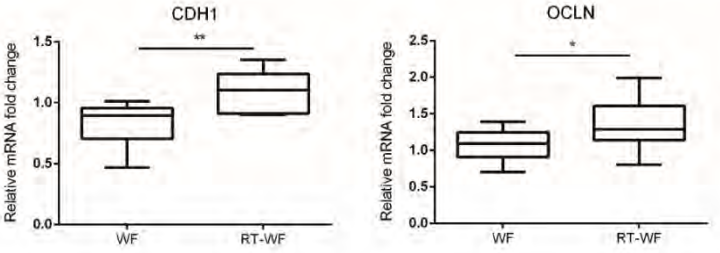


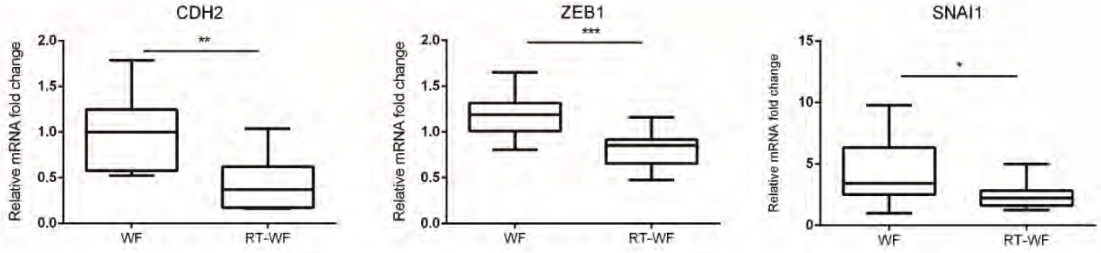


Epithelial markers ↑

Mesenchymal markers ↓

Basal MM-468 cell line





Kulcenty, Suchorska, Murawa

Acknowledgments

Radiobiology Lab:

- Katarzyna Kulcenty, PhD
- Karolina Zaleska, MsC
- Igor Piotrowski (student)
- Wiktoria Suchorska, PhD

Surgeon:

- Dawid Murawa, MD, PhD

Physicist:

- Marta Kruszyna, MsC

TARGiT®

Academy

Radiobiological Aspects

Elena Sperk, MD

Slides: Courtesy of C. Herskind

ROYALFREE world class care and expertise

UCL

UMM UNIVERSITÄTSMEDIZIN MANNHEIM

Medizinische Fakultät Mannheim der Universität Heidelberg

Universitätsklinikum Mannheim

Cleveland Clinic

The Intraoperative Device

low-energy X-rays: 30-50 kV

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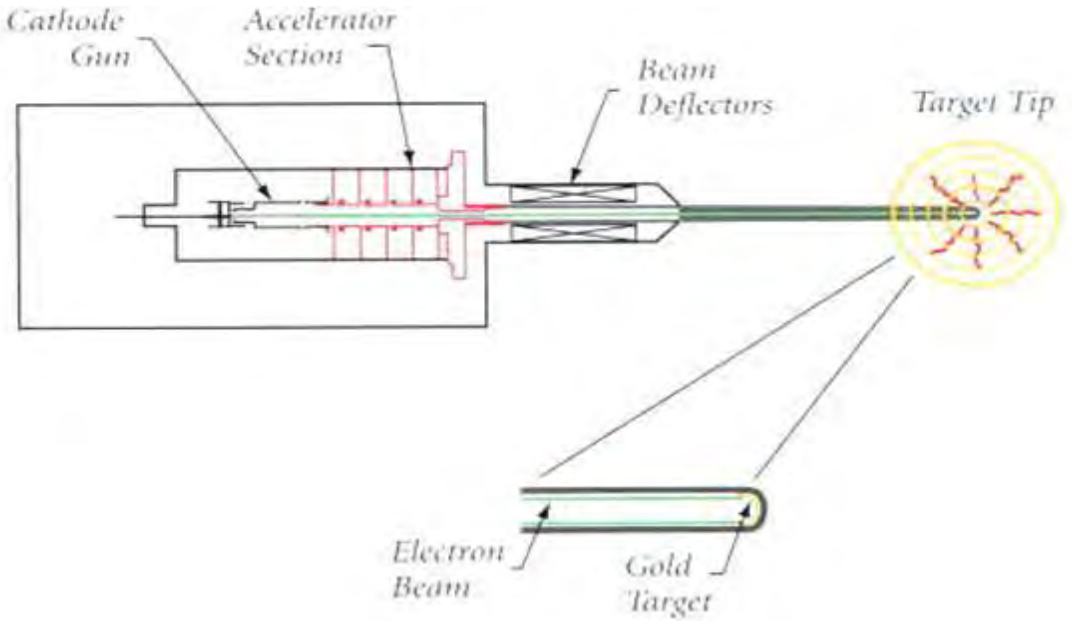

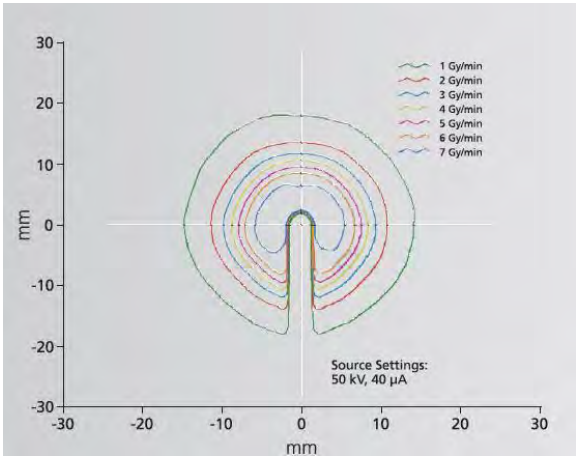

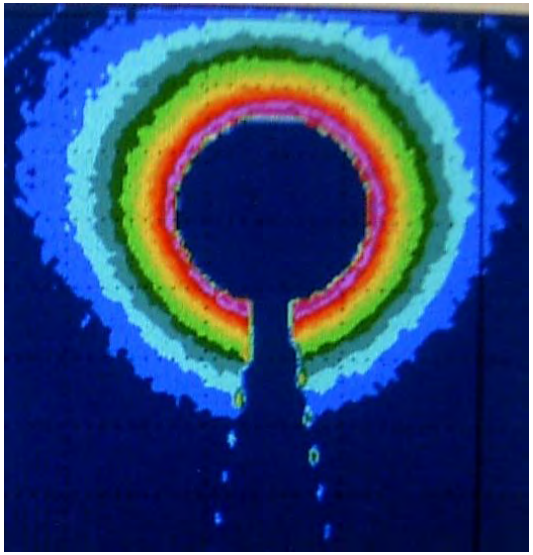

A Novel Mobile Device for Intraoperative Radiotherapy (IORT)

U. Kraus-Tiefenbacher Onkologie 2003; 26:596-5998

Characteristics of Intrabeam X-rays

Differences from External Beam RadioTherapy

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Low-energy X-rays (50 kV vs 6 MV)

point source: intensity decreases with distance ($\propto 1/dist^2$)

stronger energy absorption (attenuation), less penetration

➔ most of the dose is deposited in a ***small volume***

radiation quality: enhanced relative biologic effectiveness (***RBE***)

Lower dose rate

Repair of damage during protracted irradiation (20-50 min)

Single dose, no fractionation

Sparing of late-reacting normal tissue (NT) ?

Dose must be reduced: by how much ?

Effect on residual tumour cells ?

No delay between surgery and RT

No repopulation of tumour cells during wound healing (~ 5 weeks)

Radiation Quality
And
DNA damage

Courtesy of C. Herskind

Different types of ionizing radiation

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1) <u>Sparsely</u> ionising radiation: photons (γ- & X-rays), electrons

high energy low absorption ⇔ high penetrance

low energy high absorption ⇔ low penetrance

2) <u>Densely</u> ionising radiation: heavy particles

protons, neutrons

α-rays (atomic nucleus of Helium: He^{2+})
very high energy absorption
very low penetrance

Heavy ions, e.g. C-ions
moderate to very high energy absorption
moderate to very low penetrance

Radiation quality: ionisation density

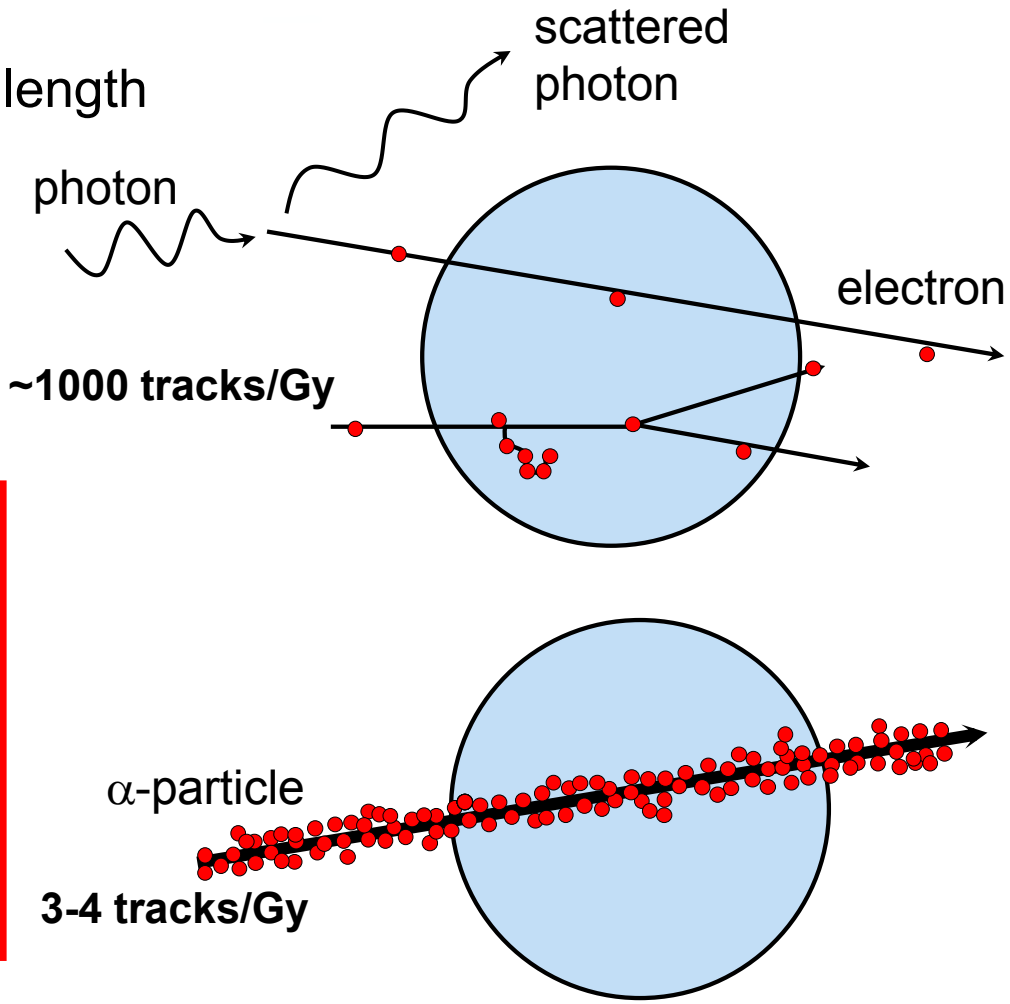
Linear Energy Transfer (LET):
Mean energy deposited per track length
- measured in keV/µm

Photons, electrons: **low-LET**
typically **0.2-2 keV/µm**

10-40 keV photons: **4-6 keV/µm**

i.e. an order of magnitude lower than

Heavy particles: **high-LET**
typically **50-200 keV/µm**



Adapted from Goodhead, Health Phys (1988)

Target molecule: DNA

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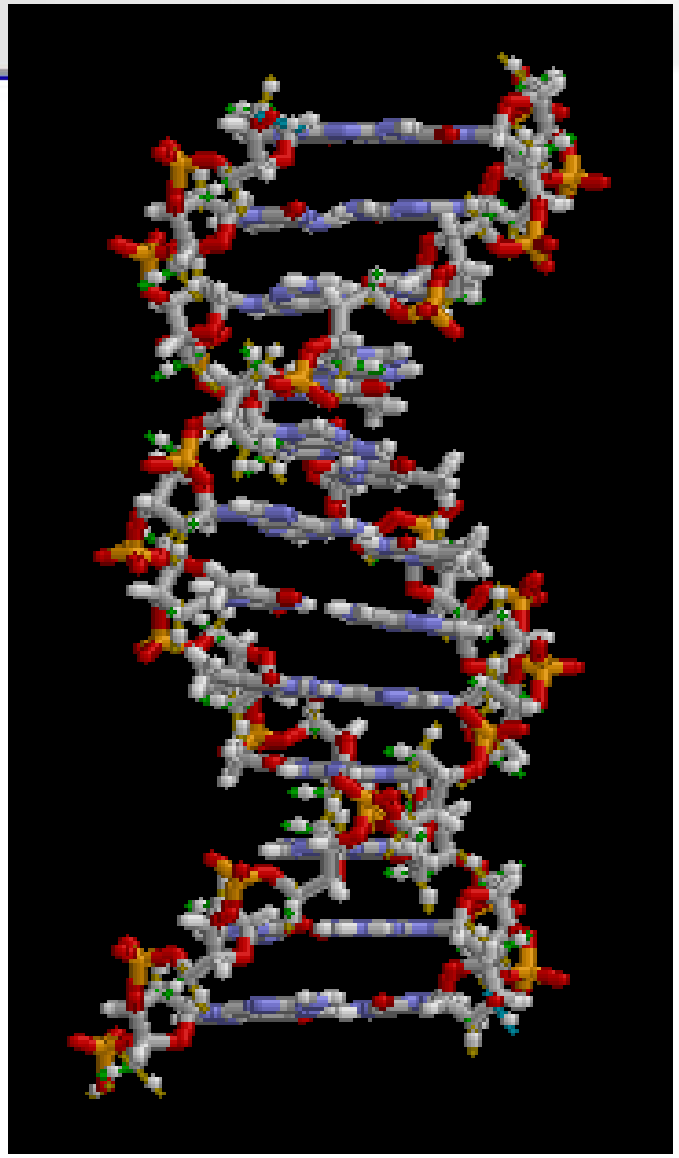
Double helix (∅ 2.3 nm)

Sugar-phosphate backbone:
deoxyribose-phosphate

Base pairing: **A=T, T=A**
C≡G, G≡C

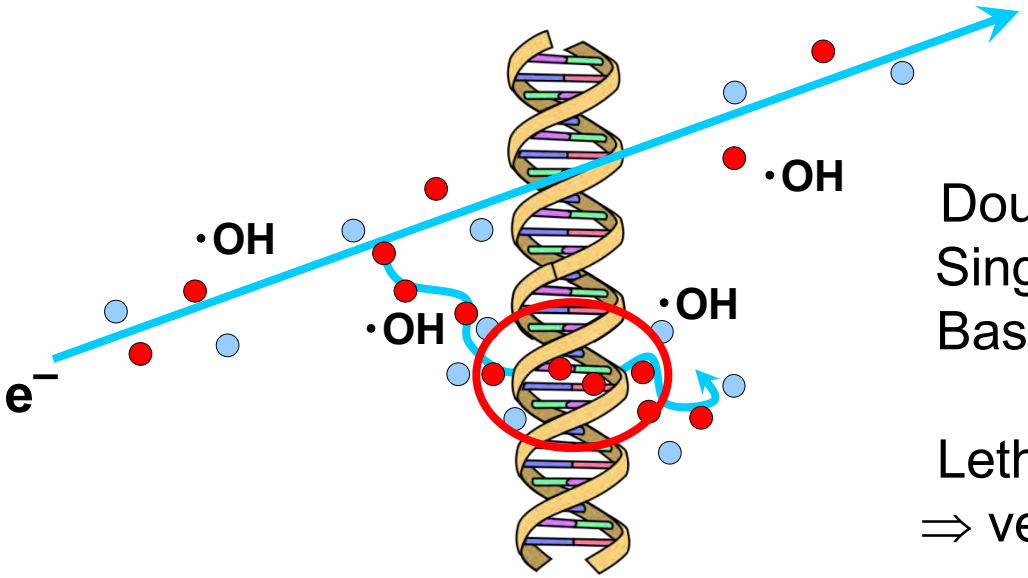


http://en.wikipedia.org/wiki/File:ADN_animation.gif

Induction and repair of DNA damage

Approx. 50% of the energy loss of a fast electron is deposited in ionisation events

● Ionisation ○ Excitation



http://commons.wikimedia.org/wiki/File:DNA_simple.svg

For low LET:
~25% direct action
ionisation directly in DNA
~75% indirect action
via aqueous radicals (OH)

Double-strand breaks	~ 40 per Gy
Single-strand breaks	~ 1000 per Gy
Base damage	~ 3000 per Gy
Lethal lesions	~ 0.5 per Gy

⇒ very efficient repair of most lesions

Residual, complex damage is important

Electron track ends produce DNA DSB and complex damage

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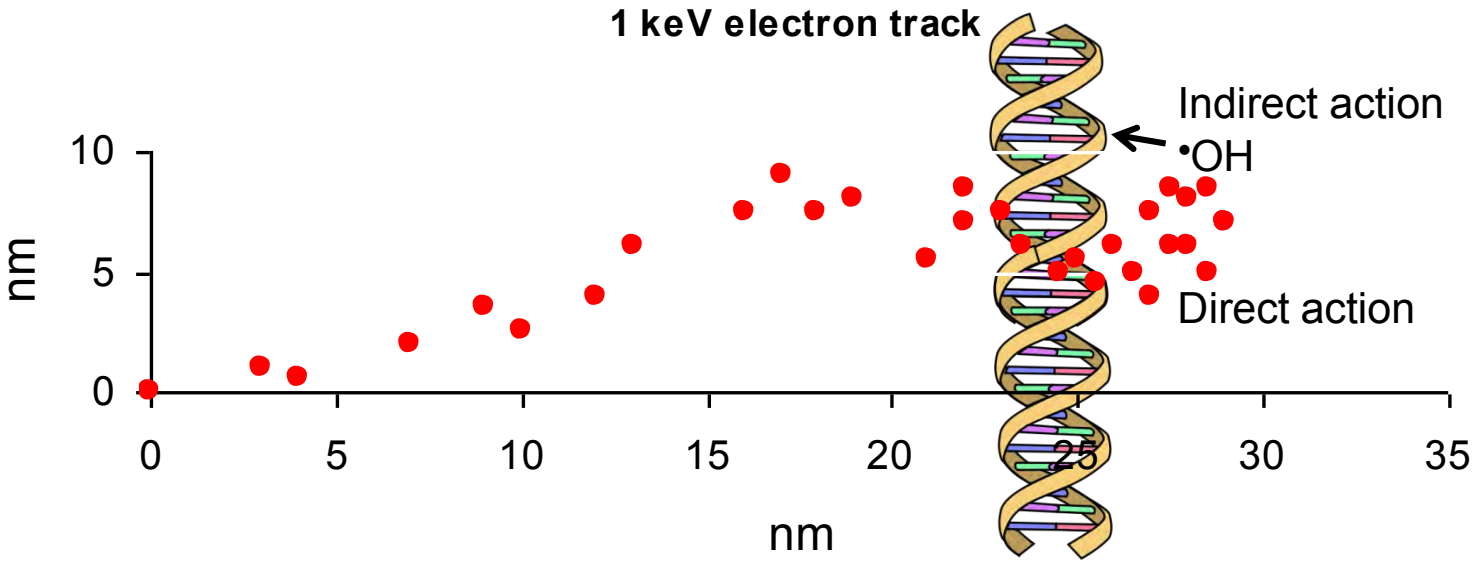
Schematic track of 1 keV electron and DNA helix



http://commons.wikimedia.org/wiki/File:DNA_simple.svg

Idea adapted from Chapman & Gillespie (1981) & Wouters, Begg in „Basic Clin. Radiobiol.“ (2009)

Low-energy X-rays deposit a larger proportion of their dose in track ends

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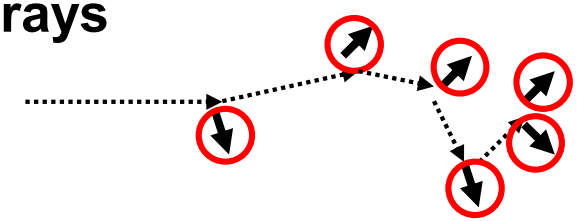
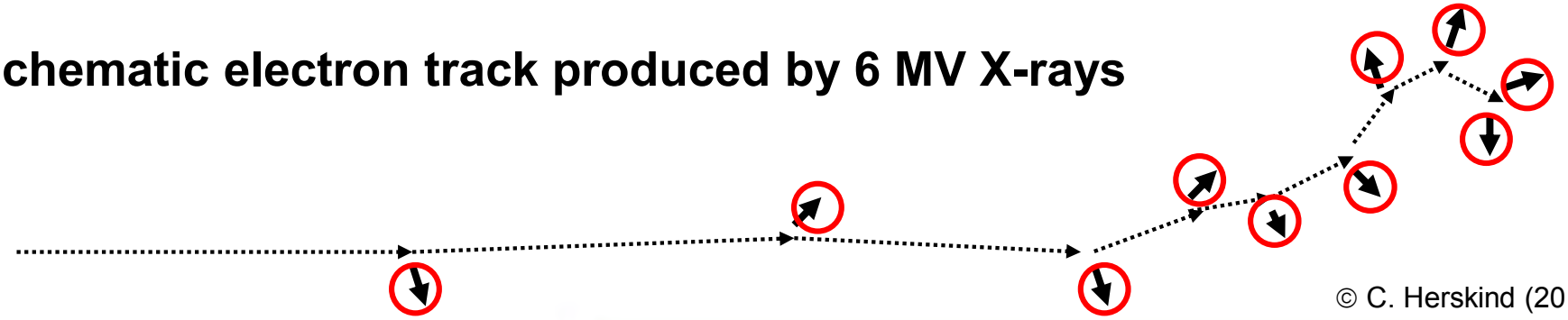
Electron track ends:

Schematic electron track produced by 50 kV X-rays



Schematic electron track produced by 6 MV X-rays



Courtesy of C. Herskind

Take home message (I)

- The radiation quality is characterized by the ionisation density: Linear Energy Transfer (LET)
- Track ends of fast electrons produce double strand breaks and complex lesions in DNA, most is repaired
- A small fraction of residual damage which cannot be repaired or is misrepaired are lethal
- Low-energy X-rays deposit a larger fraction of dose in track ends compared with high-energy X-rays

Courtesy of C. Herskind

Relative Biologic Effectiveness

Relative Biologic Effectiveness (RBE)

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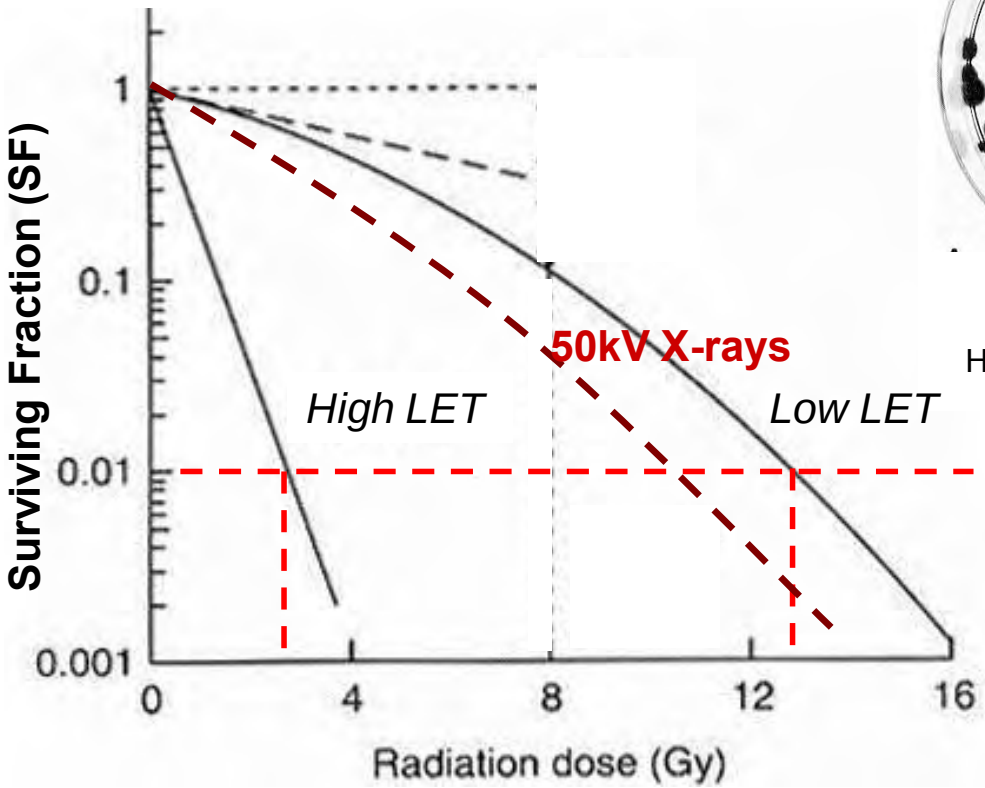
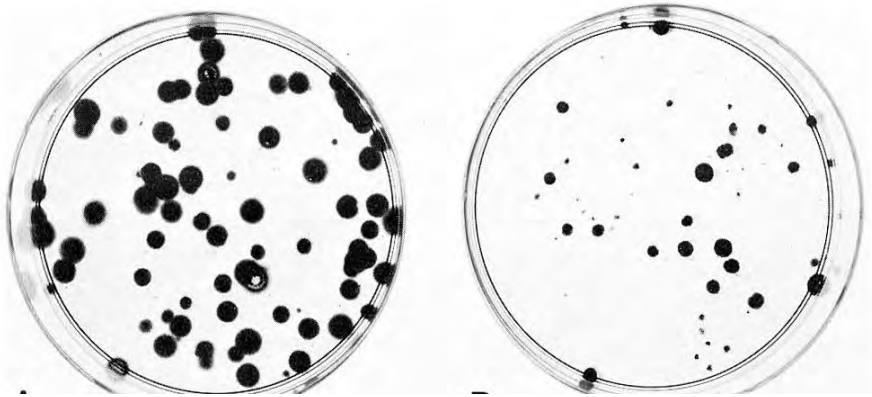
Cell survival curves



M.C. Joiner in: Joiner & van der Kogel (Eds)„ Basic Clinical Radiobiology, 4th ed., 2009



Unirradiated **Irradiated**

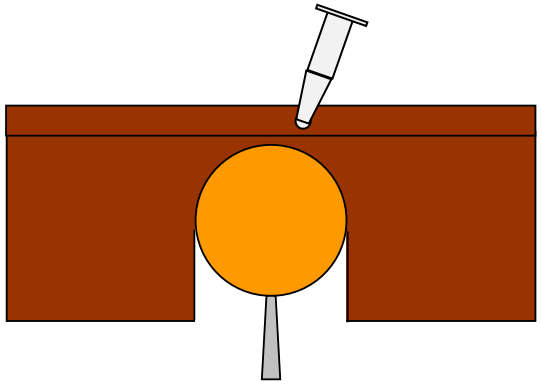
Hall & Giaccia„ Radiobiology for the Radiologist, 6th ed., 2006

RBE = ratio of physical doses producing same effect

$$RBE: D_{ref(MeV\ photons)}/D_{test}$$

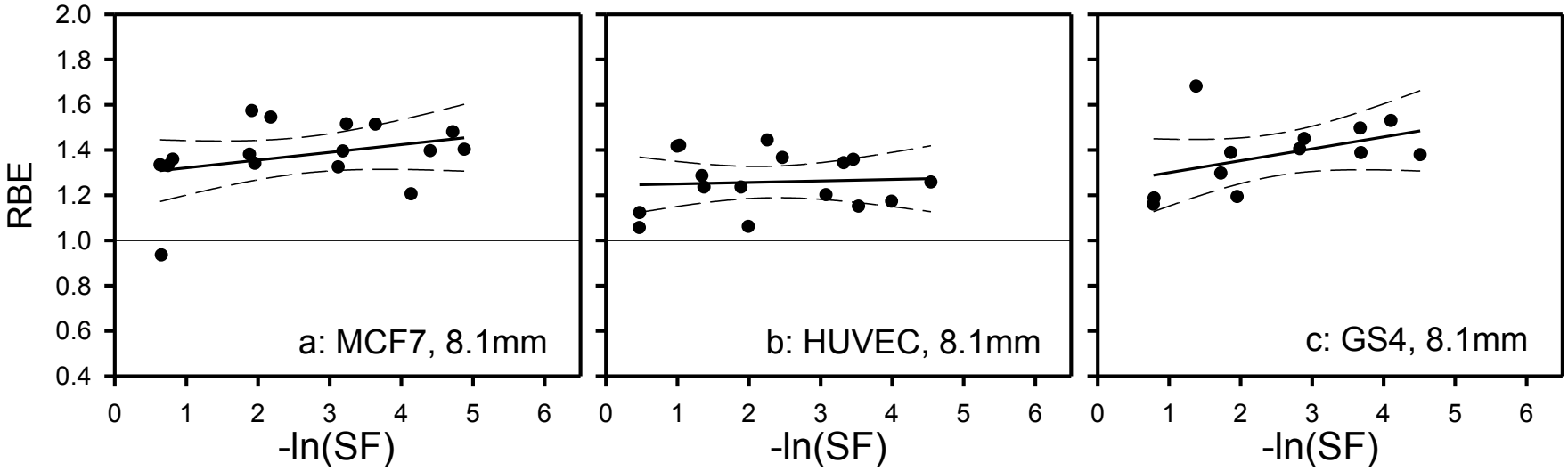
$$D_{ref} = RBE \times D_{test}$$

Experimental determination of RBE in tumour-bed phantom *in vitro*



Spherical breast applicator (4.0 cm diam.): RBE=1.35 [c.i. 1.2;1.5] in 8 mm distance from applicator surface (2.0 cm from source)

Liu et al.(2013), Int J Radiat Oncol Biol Phys 85:1127-33



Take home message (II)

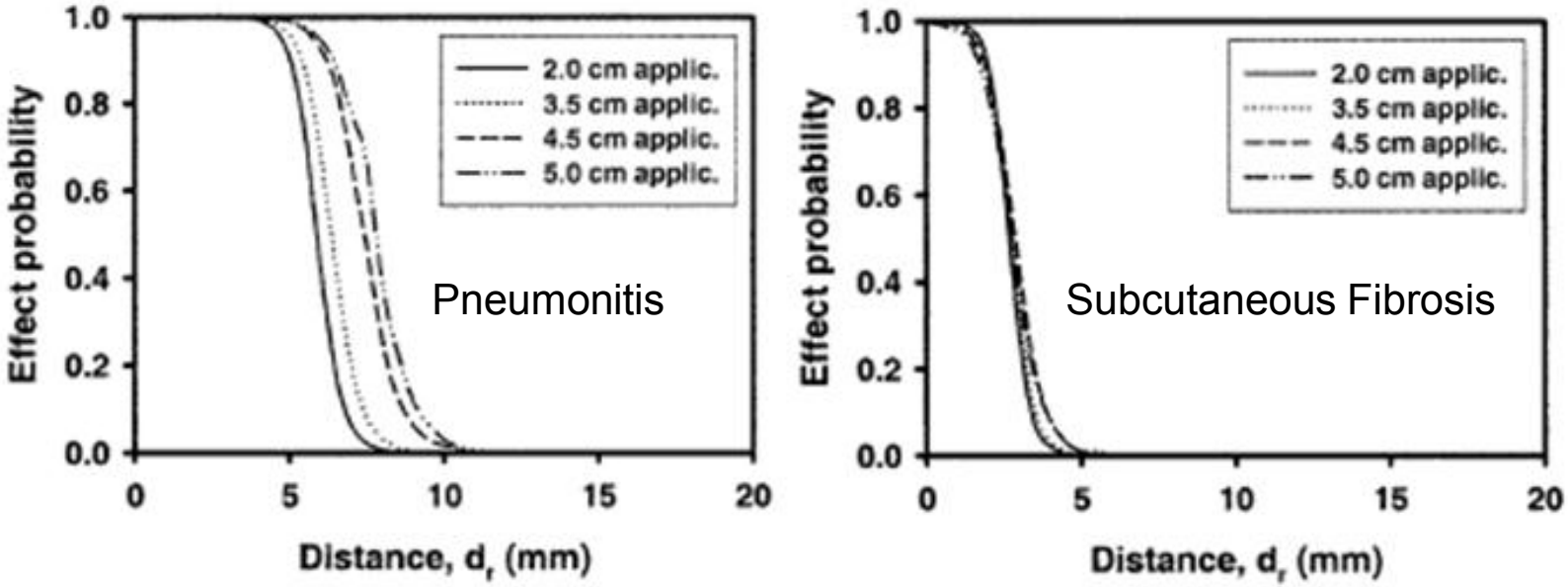
- The radiation quality affects the Relative Biologic Effectiveness (RBE)
- Theoretical and experimental evidence suggests enhanced RBE values in the range of 1.0 to 1.5

Estimates of Normal Tissue Effects and Risk of Recurrence

Modelling late effect probability as function of distance from the applicator

Herskind et al., Radiat. Res. 163 (2005)

Including the effect of recovery



The curves are displaced away from the applicator surface and the displacement is greater for the larger diameters. ED_{50} is reached at 5.9-7.8 mm. The risk becomes negligible at larger distances (lung)

For different applicator diameters the probability of developing subcutaneous fibrosis is the same. This end point requires higher doses than pneumonitis, the volume at risk for developing fibrosis is smaller than that for pneumonitis

Estimated extent of late reaction under different assumptions for RBE

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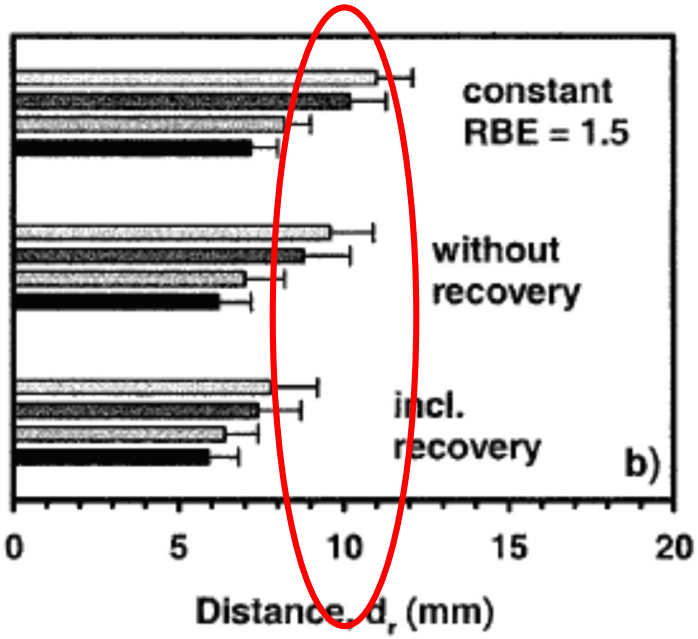
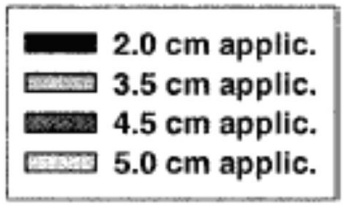
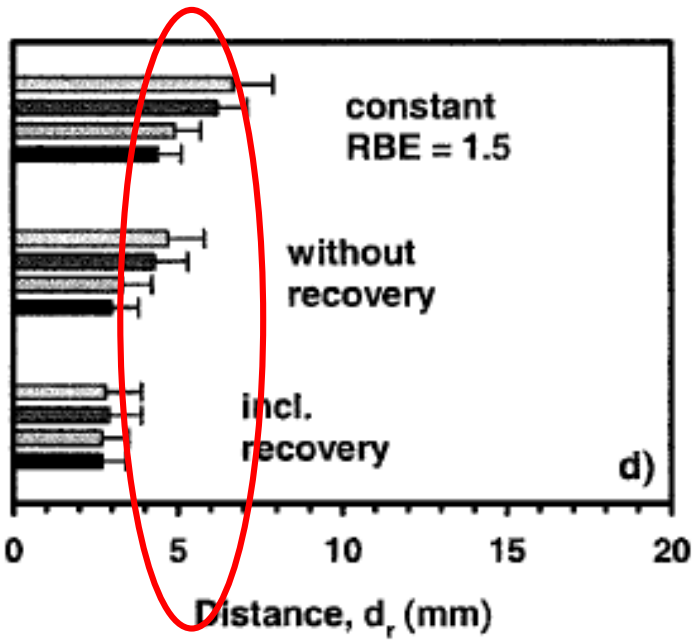
Pneumonitis





Subcutaneous Fibrosis



Pneumonitis is limited to ~ 10-12 mm distance even if RBE = 1.5

Thus the thorax wall offers sufficient protection of the lung

Epigenetic regulation of diacylglycerol kinase alpha promotes radiation-induced fibrosis

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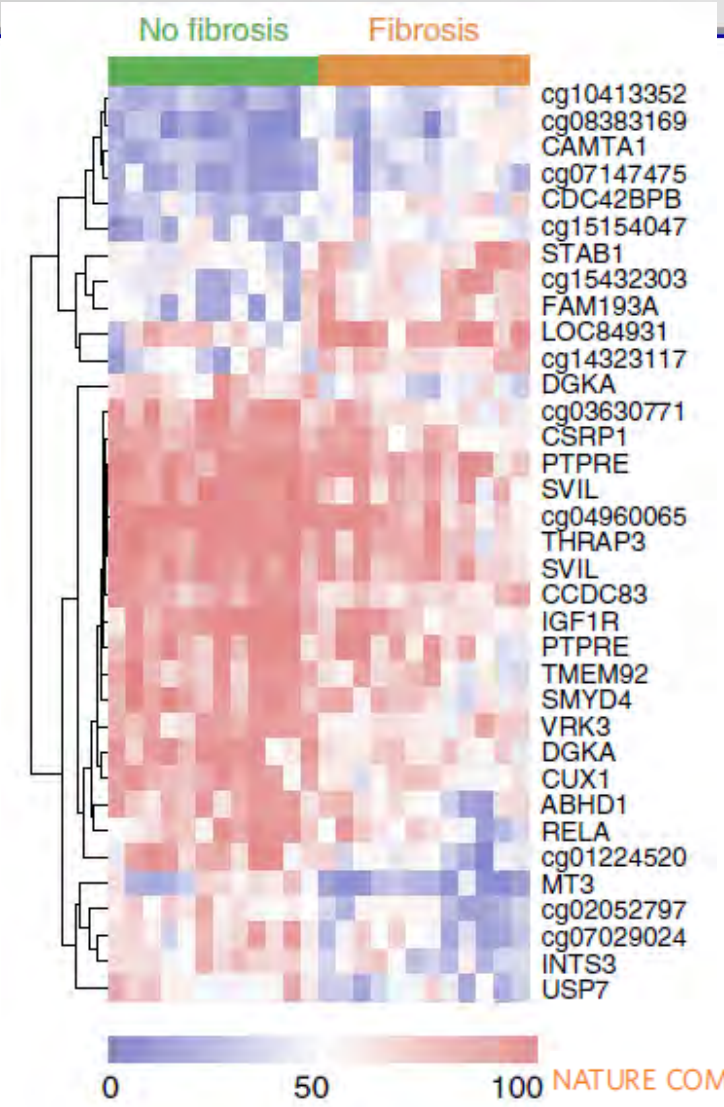
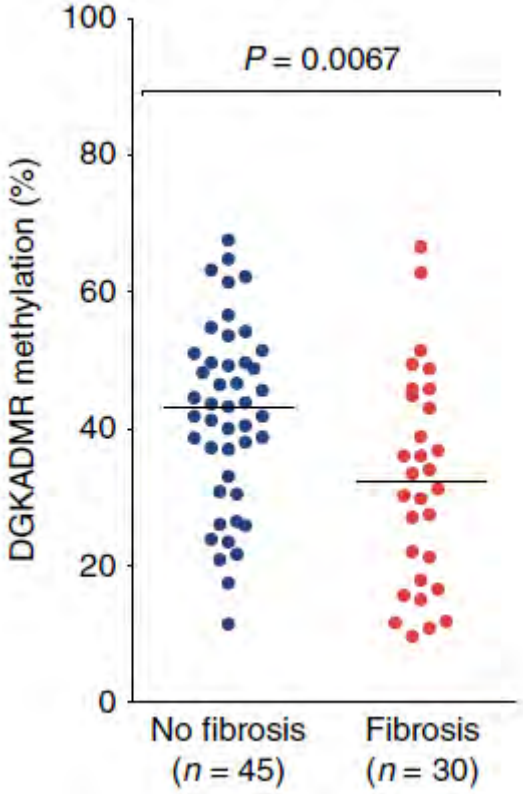


Christoph Weigel[1], Marlon R. Veldwijk[2], Christopher C. Oakes[1,†], Petra Seibold[3], Alla Slynko[4], David B. Liesenfeld[5], Mariona Rabionet[6], Sabrina A. Hanke[7,8], Frederik Wenz[2], Elena Sperk[2], Axel Benner[4], Christoph Rösli[7,8], Roger Sandhoff[6,9], Yassen Assenov[1,10], Christoph Plass[1], Carsten Herskind[2], Jenny Chang-Claude[3], Peter Schmezer[1] & Odilia Popanda[1]



NATURE COMMUNICATIONS | 7:10893 | DOI: 10.1038/ncomms10893 | www.nature.com/naturecommunications

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Courtesy of C. Herskind

Risk of Local Recurrence: - "Sphere of Equivalence"

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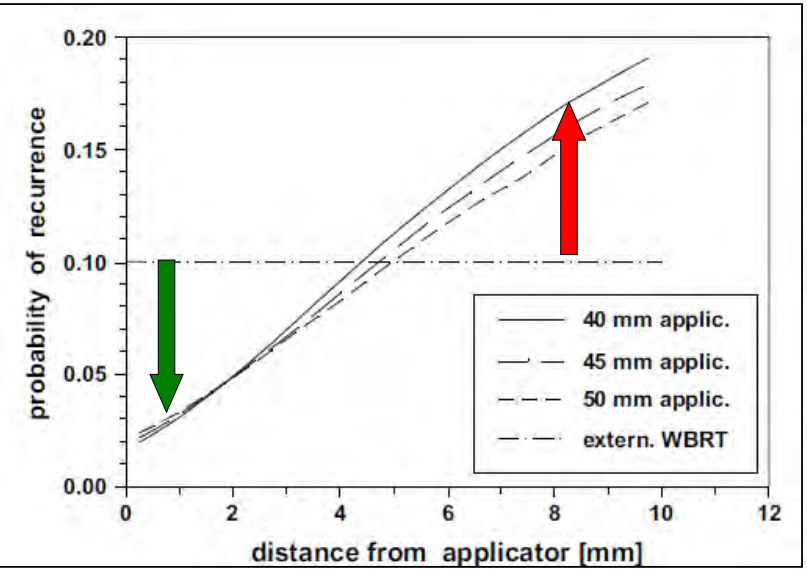

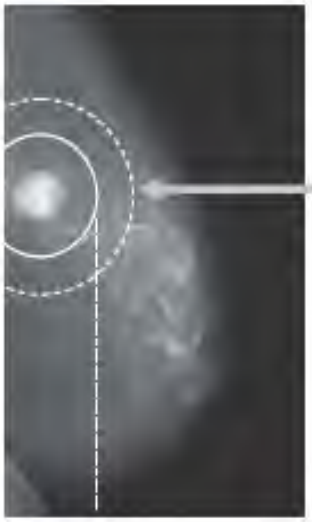

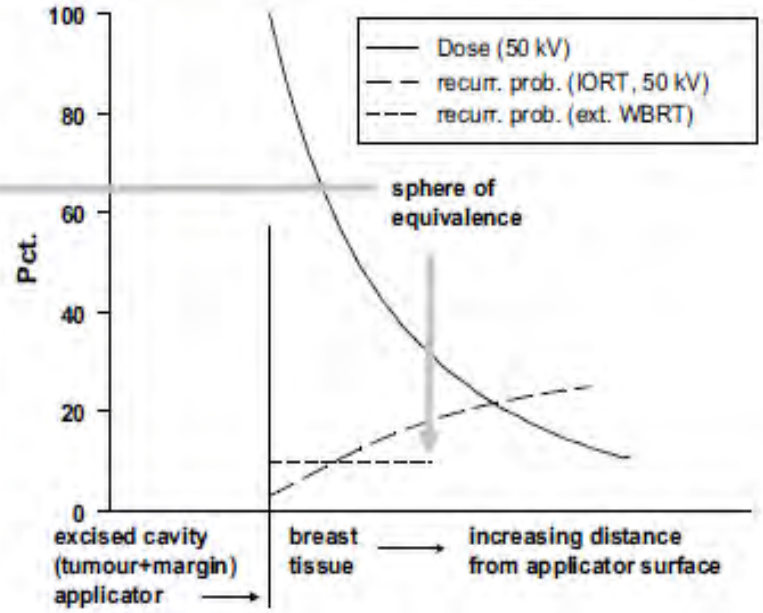

For IORT, the probability of recurrence increases as the absorbed dose decreases with depth in the tumour bed. For external beam RT, the probability is constant.

Sphere of equivalence in relation to excised tumour plus 10 mm margin. The relative dose and probability of recurrence are given on the y-axis as function of distance.

20 Gy single dose at the applicator surface ⟹ Equivalent Dose EQD2= 67.8-73.0 Gy Exceeds 50 Gy given in a standard course of external beam radiotherapy

High doses are better tolerated if the volume is small ("volume effect")

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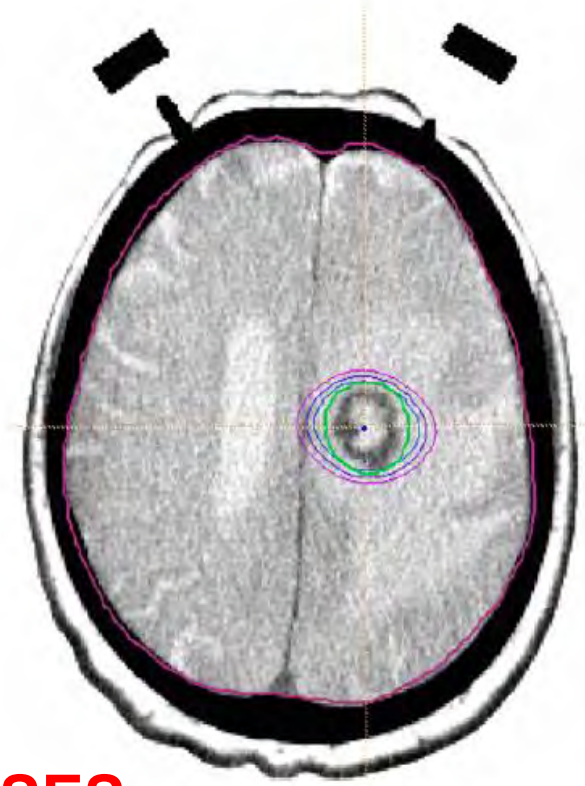
High dose to small volume:
radiosurgery (e.g. brain, liver, lung)

$$1-P=\prod_{i}\left\{\left[NTD_2(i)/NTD_2(D_{50})\right]^{k}+1\right\}^{-v(i)/V}$$

1-p	probability without necrosis
V	volume of brain
NTD	normalised total dose à 2 Gy
v(i)	volume receiving NTD
NTD2(D50)	NTD inducing 50% risk of necrosis

Flickinger 1989



BE CAREFUL WITH HIGH SINGLE DOSES:
VOLUME MATTERS!

Very large dose fractions have proved efficient in stereotactic body radiotherapy

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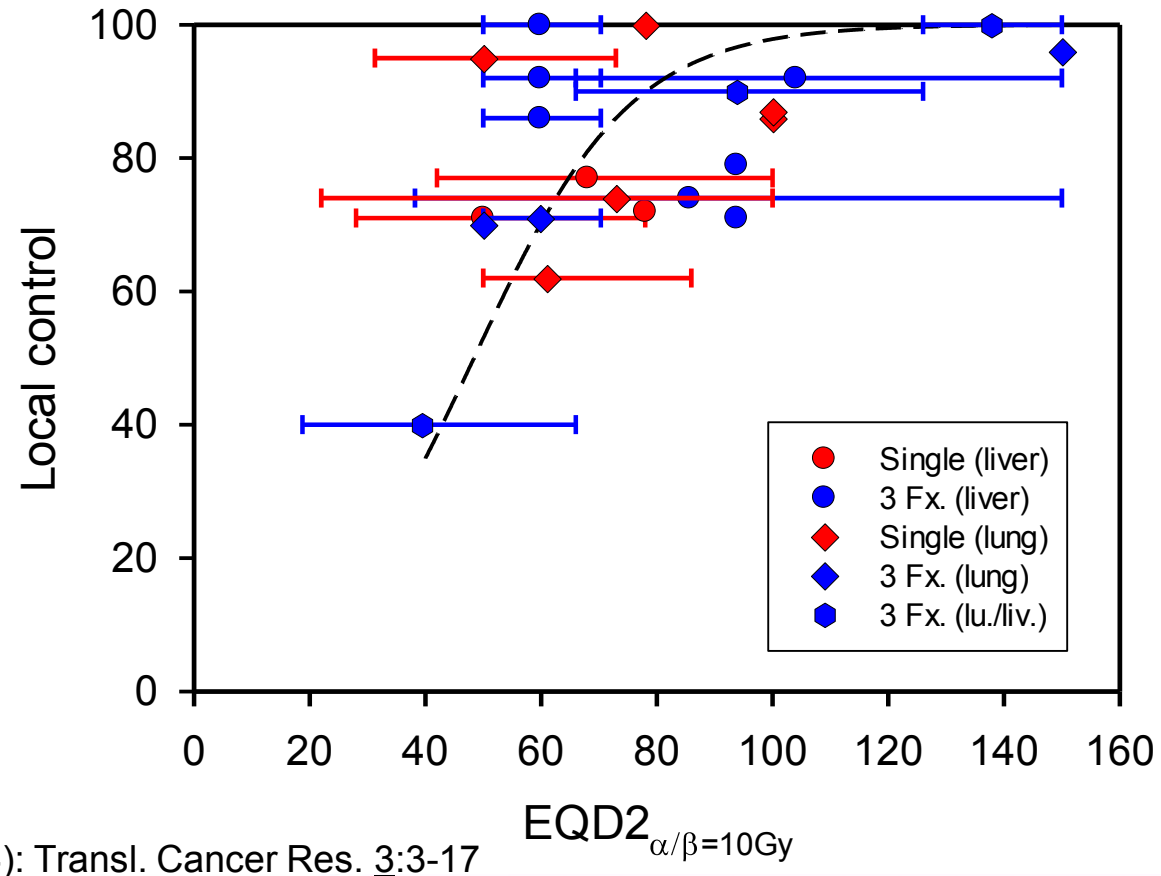
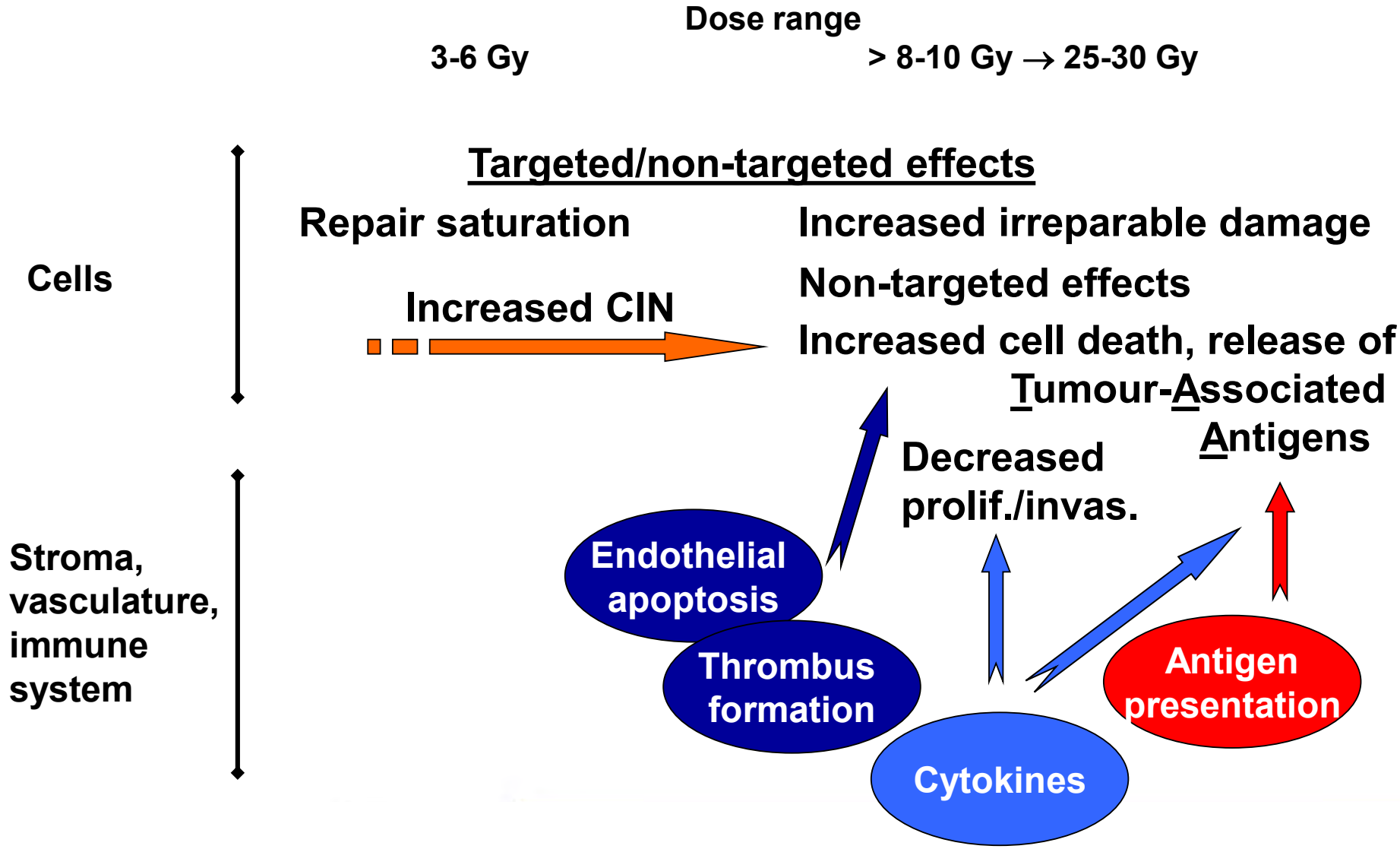
Data from studies reviewed in Siva et al. (2010), J Thorac Oncol 5:1091-9
and Hoyer et al. (2012), Radiother Oncol 82:1047-57



Herskind, Wenz (2014): Transl. Cancer Res. 3:3-17

Courtesy of C. Herskind

Model of potential biological effects of very large dose fractions



Herskind, Wenz (2014): Transl. Cancer Res. 3:3-17

Take home message (III)

- Modelling normal tissue reaction estimates
  - Pneumonitis limited to < 10-12mm dist. from applicator surface
  - Subcut. fibrosis limited to < 3-6mm dist. from applic. surface
- Modelling risk of recurrence predicts a „Sphere of equivalence“ for local control relative to EBRT
- Small volumes of normal tissue are able to tolerate higher radiation doses (volume effect)
- High single doses of RT may induce additional biological effects compared with daily dose fractions of 2 Gy

Courtesy of C. Herskind

Conclusions

- Increased RBE of low-energy photons (may be influenced by repair of sublethal damage during protracted irradiation: 30-50 min)
- Lack of fractionation
  - Irradiation at the time of surgery eliminates proliferation of residual tumour cells during the delay between surgery and radiotherapy, and between fractions during conventional radiotherapy
- Highly localized dose distribution: high dose to small volume
  - Radiobiological model suggests that the surviving fraction of the tumour cells at the applicator surface will be smaller than for whole-breast radiotherapy. This partly compensates the increase in cell survival at larger distances, predicting a **"Sphere of Equivalence"**
  - Late NT reaction is limited to a small volume (dose distribution). The high single dose is better tolerated in small volumes
- Biol. effects of high single doses (nontargeted/vascular/ immune)

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Herskind C, Wenz F. (2014). Radiobiological aspects of intraoperative tumour-bed irradiation with low-energy X-rays (LEX-IORT). Transl Cancer Res 3:3-17

IORT with low energy kV x-rays worldwide

TARGiT® Academy

Thank you for your attention!

elena.sperk@umm.de

IntraOp®

Worldwide Technical and Clinical Review of Mobetron Usage

Presented at 9th International ISIORT Conference

June 2016

IntraOp Mobetron: Integrating Radiation and Surgical Oncology

Optimized for the OR

- Portable and Self-Shielded
- Soft Docking Laser Alignment System
- Treatment Time: 2 Minutes

Established Radiation Technology

- Over 70,000 Patients Treated Clinically
- Traditional Electron Energies (6, 9, 12 MeV)
- Accurate & Uniform Dosimetry

Improved Patient Results

- Right Dose, Right Depth, Right Volume
- Shorter Treatment Cycle
- Lower Overall Dose
- Minimal Impact to Healthy Tissue

Leading Institutions in 16 Countries Utilize Mobetron to Improve Patient Care

STANFORD HOSPITAL & CLINICS
Stanford University Medical Center

MASSACHUSETTS GENERAL HOSPITAL

UCSF Medical Center

NAGOYA UNIVERSITY HOSPITAL
名古屋大学医学部附属病院

MAYO CLINIC

catharina ziekenhuis

University Hospital Heidelberg

Avera

Philipps Universität Marburg

UNC
LINEBERGER COMPREHENSIVE CANCER CENTER
N.C. CANCER HOSPITAL

St. Joseph Health
St. Joseph Hospital

University Hospitals
Case Medical Center

Institut Jules Bordet

Scripps

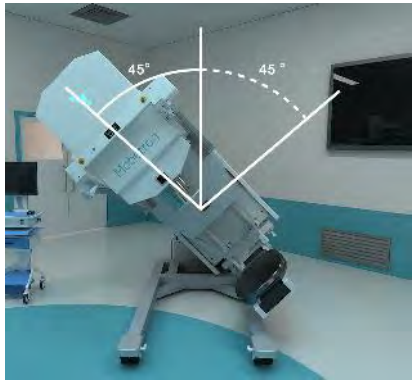
MCH
Medisch Centrum Haaglanden

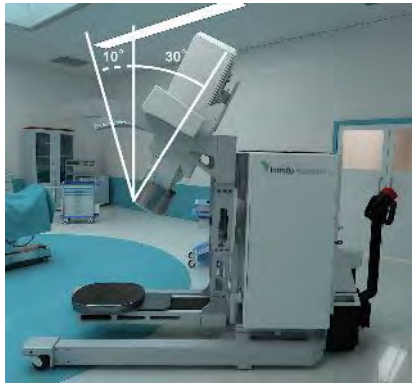
THE OHIO STATE UNIVERSITY
COLLEGE OF MEDICINE

NHS

IntraOp Mobetron

World's Only Self-Shielded Mobile Electron IORT Device





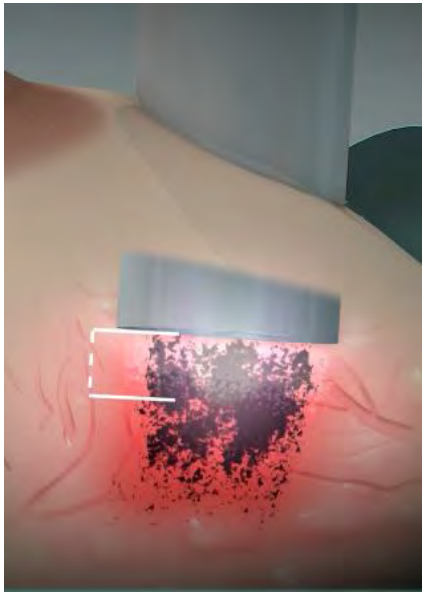
Key Features

- **Energies: 6, 9, 12 MeV**
- **Depth: 1-4 cm D_{80}**
- **Shielding: less than 6µSv @ 3 meters**
- **Motion Control:**
  - **Rotation: +/- 45º, Tilt +10º / - 30º**
  - **Lateral/Longitudinal: +/- 5cm:**
- **Soft docking laser alignment system**
  - **Ensures accuracy and safety**
- **Touch Screen Console**
  - **Intuitive, Real-Time Control and Diagnostics**
- **Simple Daily QA System**
  - **AAPM TG72 Compliant**

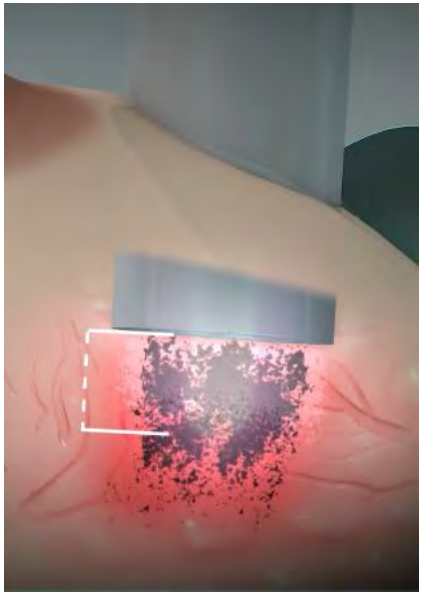
The Mobetron

Delivers the Right Dose at Right Depth for the Right Volume

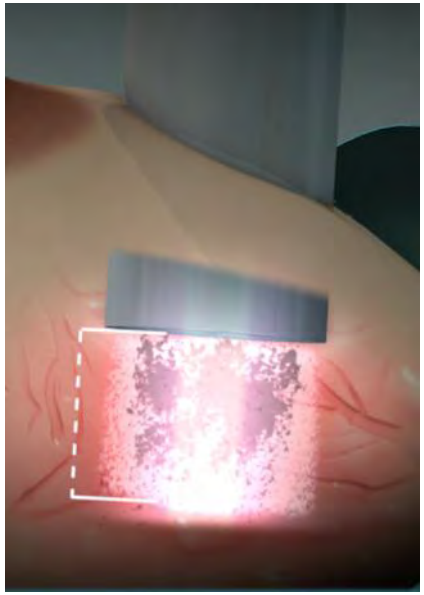
Depth of Penetration in tissue or muscle



6 MeV
Depth: 2cm (D80)



9 MeV
Depth: 3cm (D80)



12 MeV
Depth: 4cm (D80)

2 year output variation < 1.5%

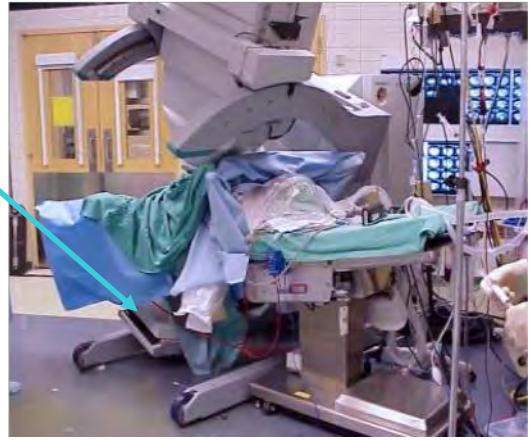
2-year energy variation, < 1 mm

Source: Beddar, 2005

Mobetron

Proprietary Technology Minimizes Size and Stray Radiation

- X-Band Technology Shrinks the Size by 66%
- Low Beam Current Reduces Leakage
- “Sculpted” Shield around Accelerator Eliminates Bend Magnet
- Fixed Collimator Reduces Stray X-rays
- Integrated Beam Stopper

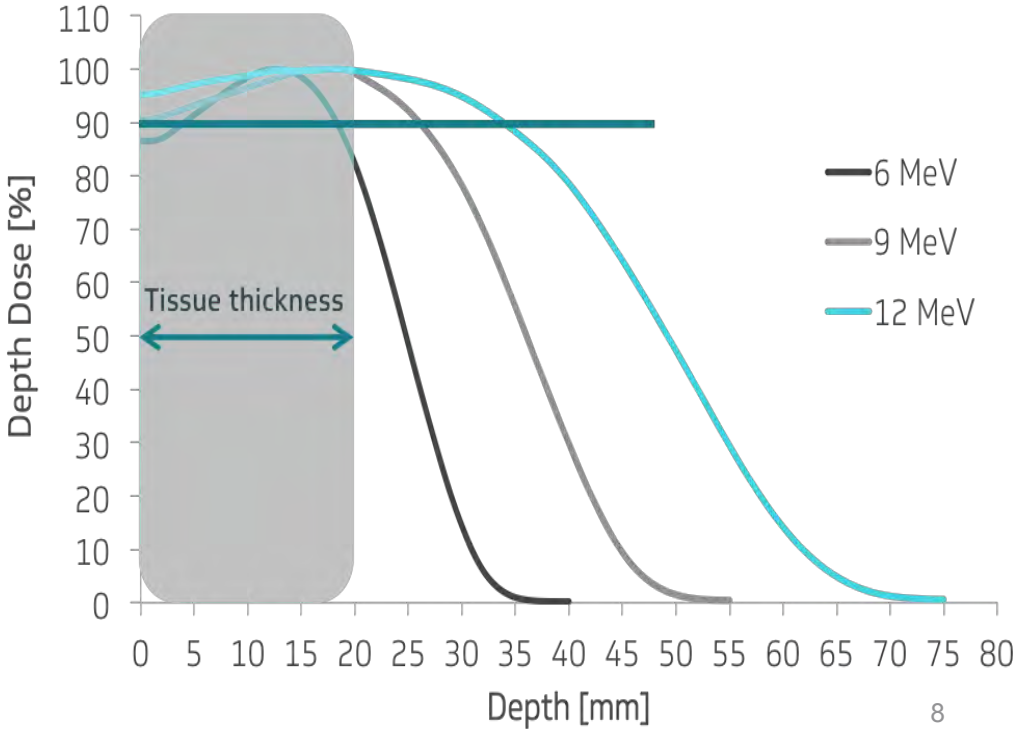


Applicator and Clamping Solutions Ensure Precise Treatment

- **Metal Applicators:**
  - Diameter: 3 – 10 cm (5mm Increments)
  - Length: 30 cm
  - Angles: 0º, 15º, 30º, 45º
  - Thickness: 2mm
  - Standard Steam Sterilization
  - Low Leakage
  - Custom Applicators Available (ie. Sarcoma)
- **Clamps:**
  - Standard All Metal Clamp
    - Easily Sterilized
    - Ratchets for Quick and Firm Positioning
  - Pneumatic Arm Clamp
    - Easy one hand positioning

Clear Boluses for Treatment Flexibility

- **Boluses:**
  - 5mm & 10mm Thickness
  - Increases Surface Dose for Lower Energies
  - Flexible Penetration Depth (5 mm Increments)
  - Ensures Uniform Tissue Surface



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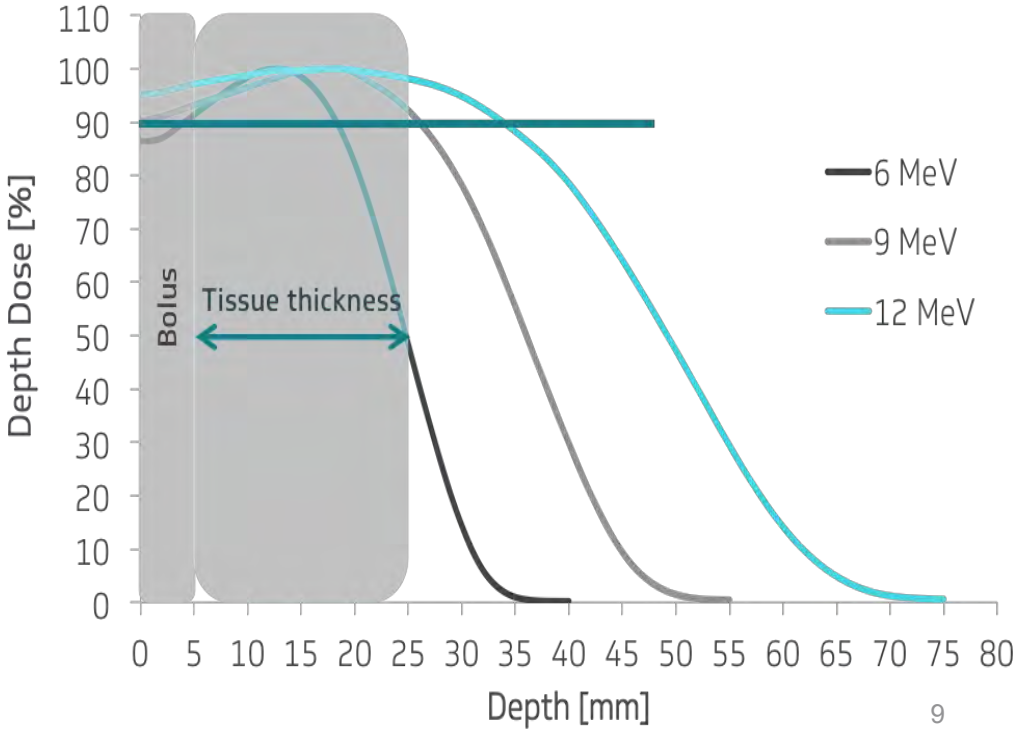


Electron IORT Improves Local Control in Virtually Every Tumor Site

Breast Cancer

- WBI with Boost
- APBI Single Fraction

Over 30,000 Patients Treated with Electron IORT

Locally Advanced or Recurrent Cancers

- Pancreatic
- Colorectal
- GYN
- Head & Neck
- Extremity Sarcoma
- Retroperitoneal Sarcoma

Over 35,000 Patients Treated with Electron IORT

Emerging Indications

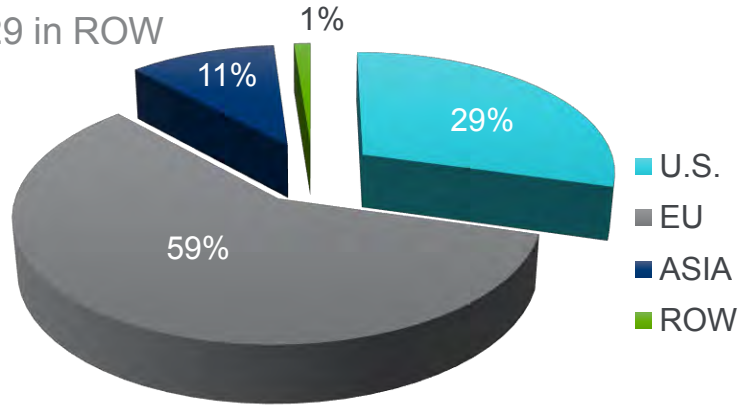
- Lung
- Pediatric
- Prostate
- Bladder
- Gastric
- Esophageal
- CNS
- Others

- Mature and Robust Data
- Robust Data

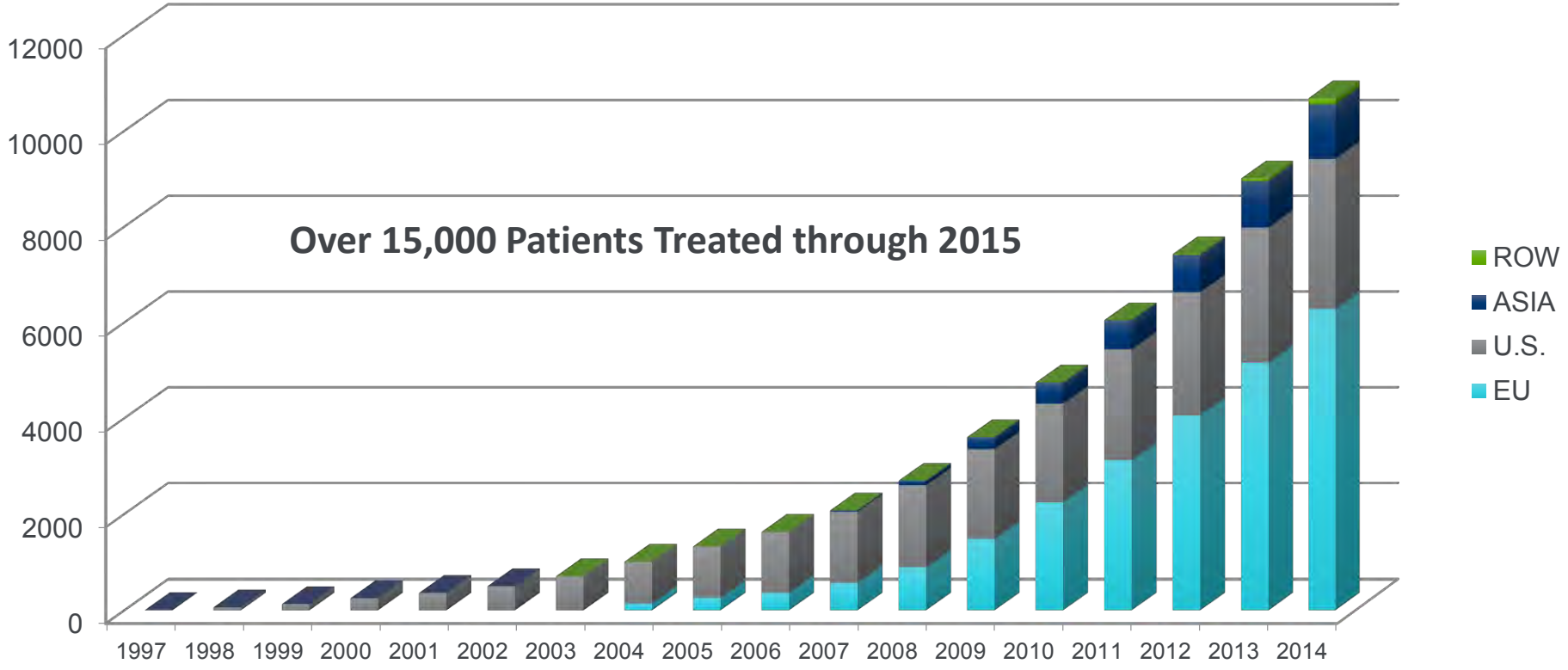
Introduction

- Contacted 54 Mobetron users in 14 countries, who were in clinical operation prior to December 31, 2014.
- 50 Centers provided complete or partial responses or expressed their interest to do so.
- We can estimate that at these 50 centers around 10,683 patients have been treated (by the end of 2014)
  - 6,276 in Europe, 3,136 in the U.S., 1,142 in Asia and 129 in ROW

When includes 2015 and missing centers, we can conservatively estimate that over 15,000 patients have already been treated with the Mobetron.



Cumulative Growth of Total Mobetron Cases, Worldwide

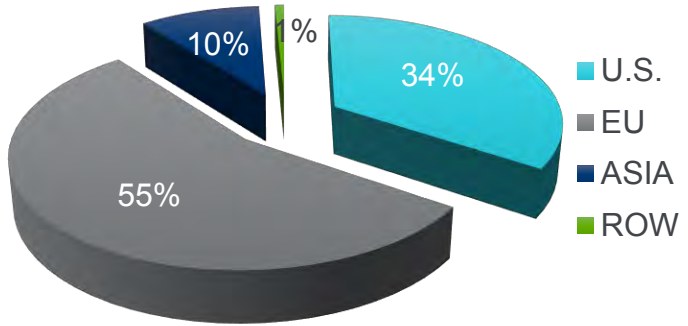


Source: IntraOp Mobetron User Database (~80% of Active Users)

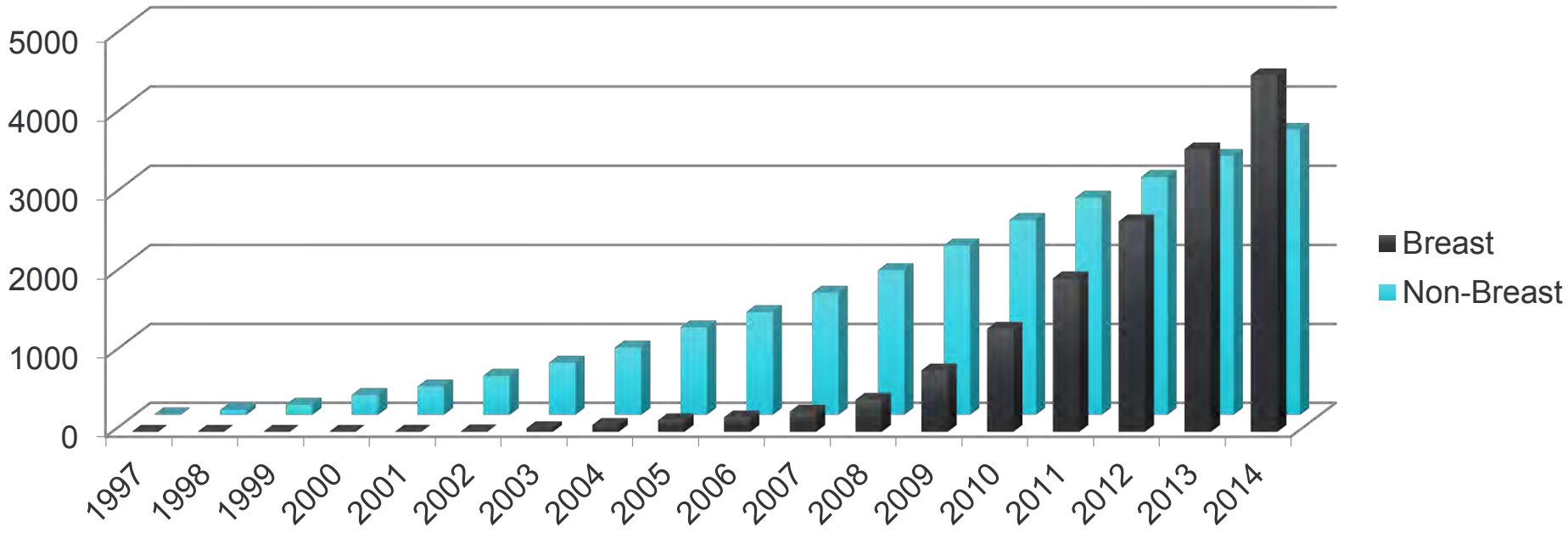
Treatment Data Characteristics

- For data received:
  - Out of 10,683 patients treated, a total of 8,111 patients were analyzed of which 4,508 (56%) were treated for breast.
  - In Europe: 4,456 patients were analyzed of which 3,680 (83%) were breast.
  - In the U.S.: 2,790 patients were analyzed of which 557 (20%) were breast.
  - In Asia: 805 patients were analyzed of which 267 (33%) were breast.
  - In ROW: 60 patients analyzed of which 4 (7%) were breast.

Distribution of analyzed data



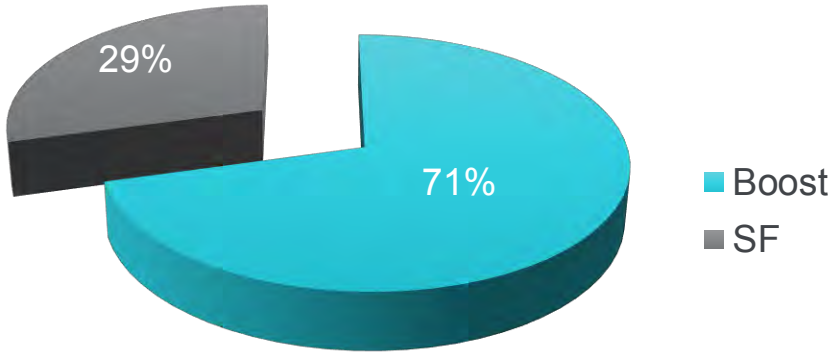
Cumulative Growth of Analyzed Mobetron Cases, Worldwide



Breast

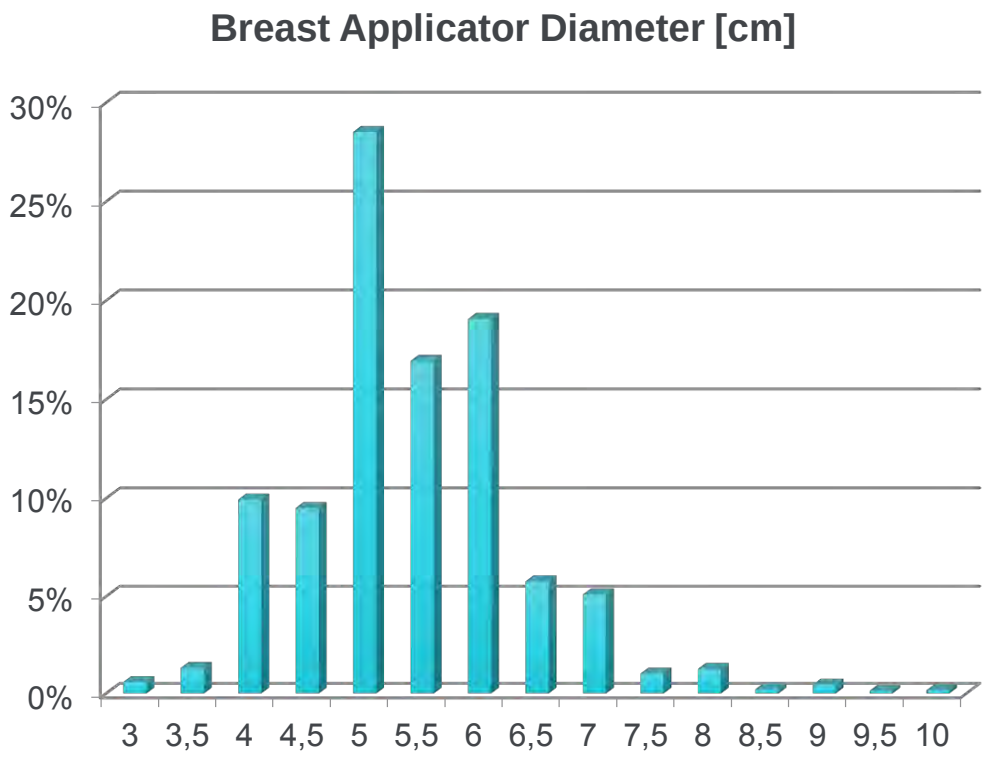
Breast data characteristics

- For the breast data received:
  - 71% of breast patients were treated as a boost (75% EU, 72% U.S., 16% Asia).
  - 29% of boost treatments followed by 3 weeks EBRT.
  - 48% were treated at 9 MeV; 26% at 6 MeV; and 24% at 12 MeV (2% @ 4 MeV).



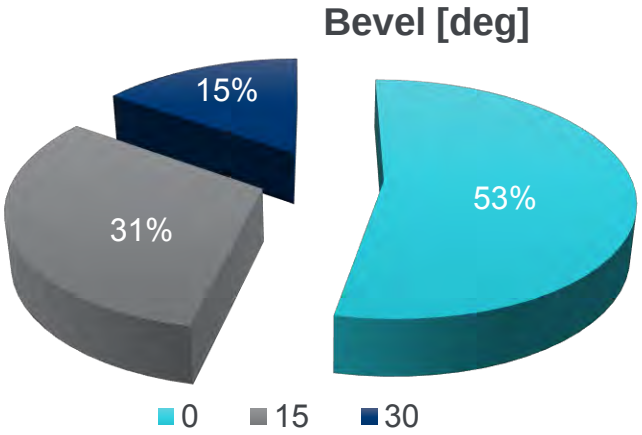
Breast data characteristics (continued)

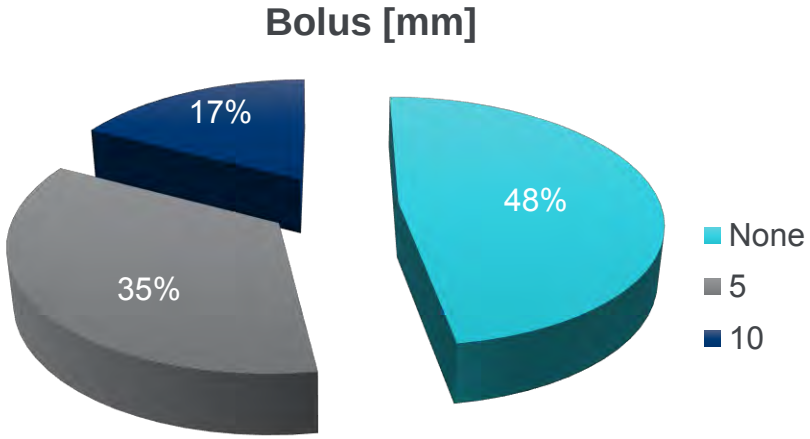
- For the breast data received:
  - 84% of patients were treated with FS between 4-6 cm.
  - 35% of patients were treated with a ½ cm sized applicator.
  - 3% of patients were treated with a FS > 7 cm.



Breast data characteristics (continued)

- For the breast data received:
  - 53% treated with 0° bevel, 31% with 15° bevel; and 15% with 30° bevel.
  - 52% used bolus; 5 mm bolus was used 2x as often as the 10 mm bolus
  - 54% used Chest-Wall Protectors (in 81% SF & in 37% Boost treatments)

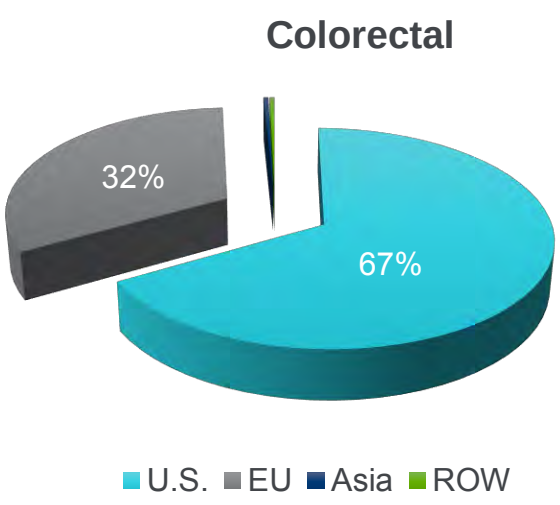


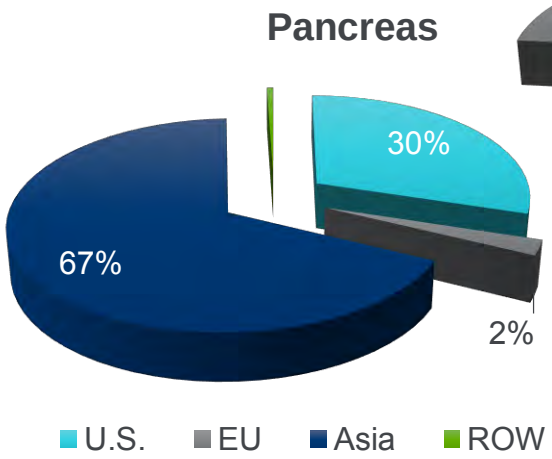


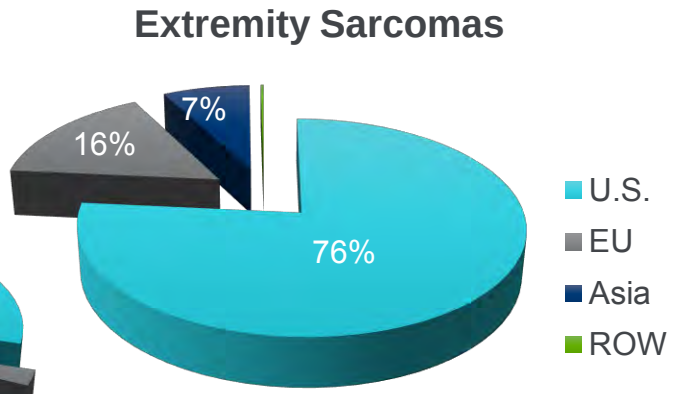
Non-Breast

Non-Breast Data characteristics

- For Non-breast data main sites were: Colorectal (21%), Pancreas (15%), Extremity Sarcomas (22%) and RPS (8%).

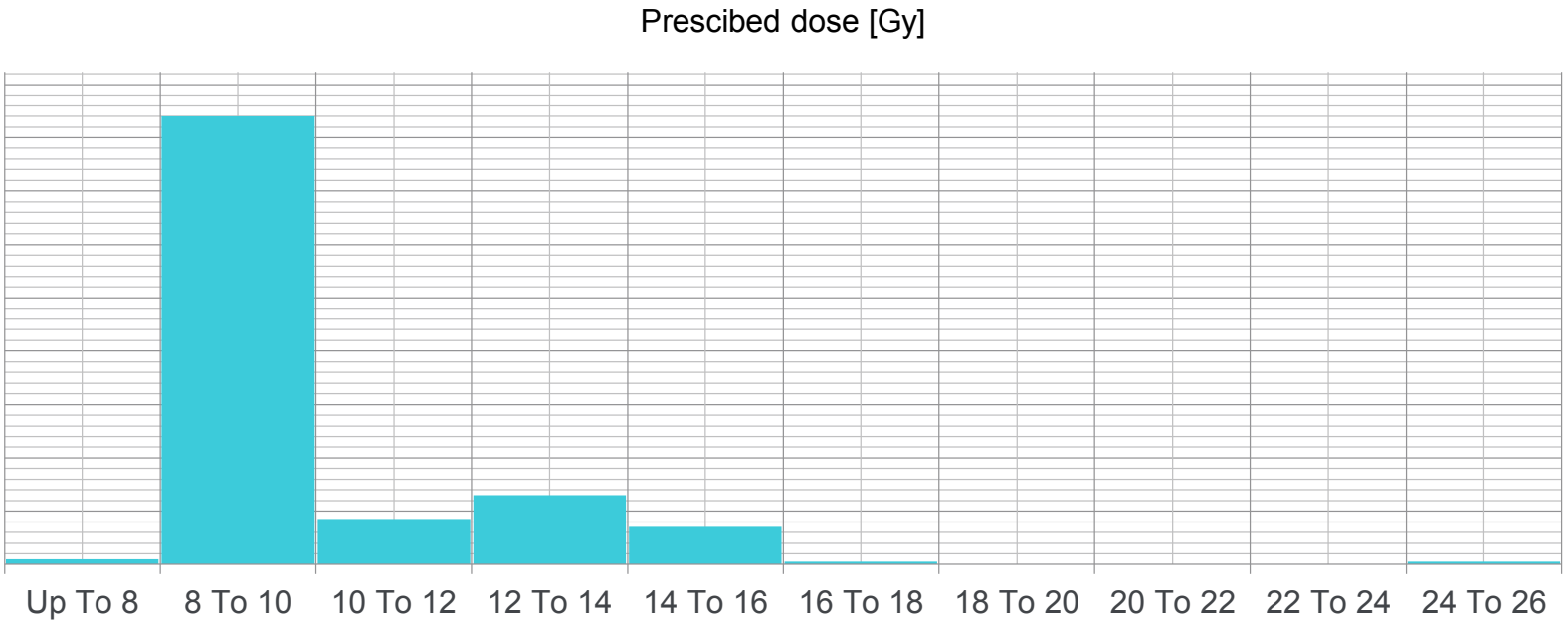






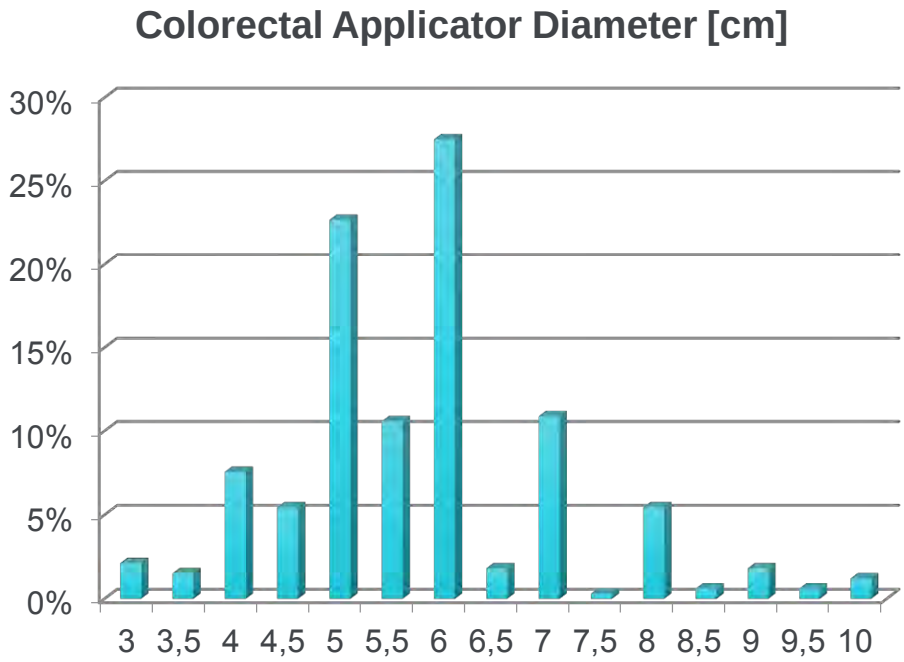
Colorectal data characteristics

- For the colorectal data received:
  - 50% were treated at 9 MeV; 35% at 6 MeV; and 10% at 12 MeV (5% @ 4 MeV).



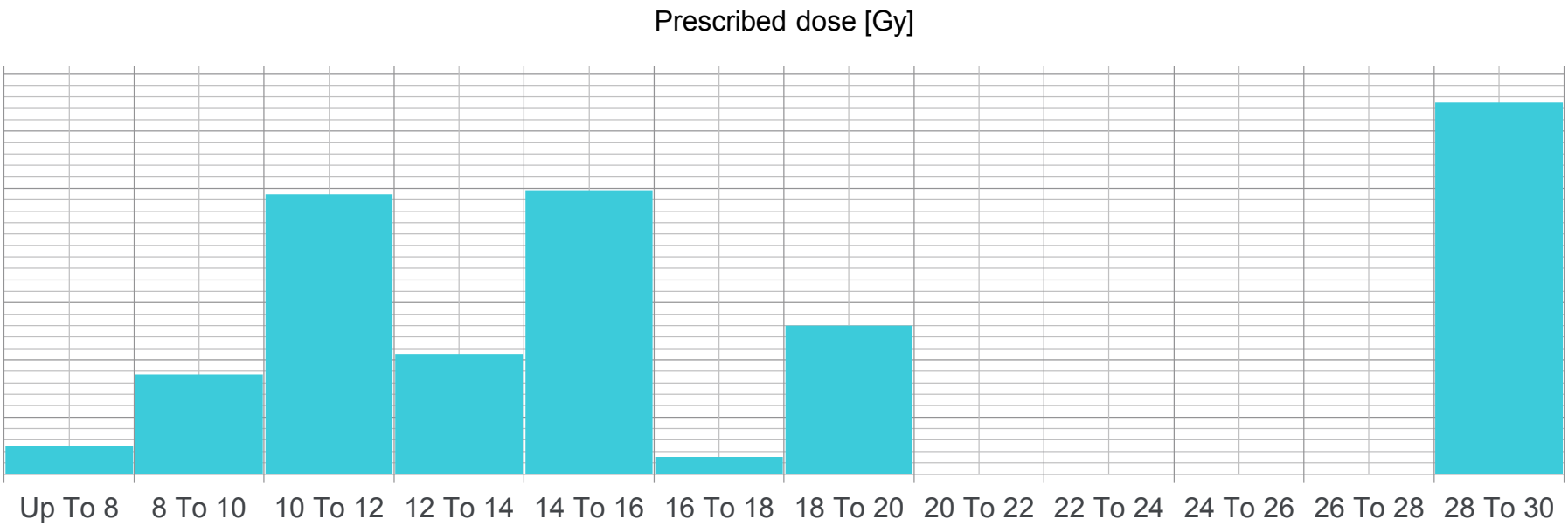
Colorectal data characteristics (continued)

- For the colorectal data received:
  - 86% of patients were treated with FS between 4-7 cm.
  - 21% of patients were treated with a ½ cm sized applicator.
  - 88% treated with 30º bevel and 4% with 15º bevel.
  - 41% used bolus; 5 mm bolus was used 2x as often as the 10 mm bolus.



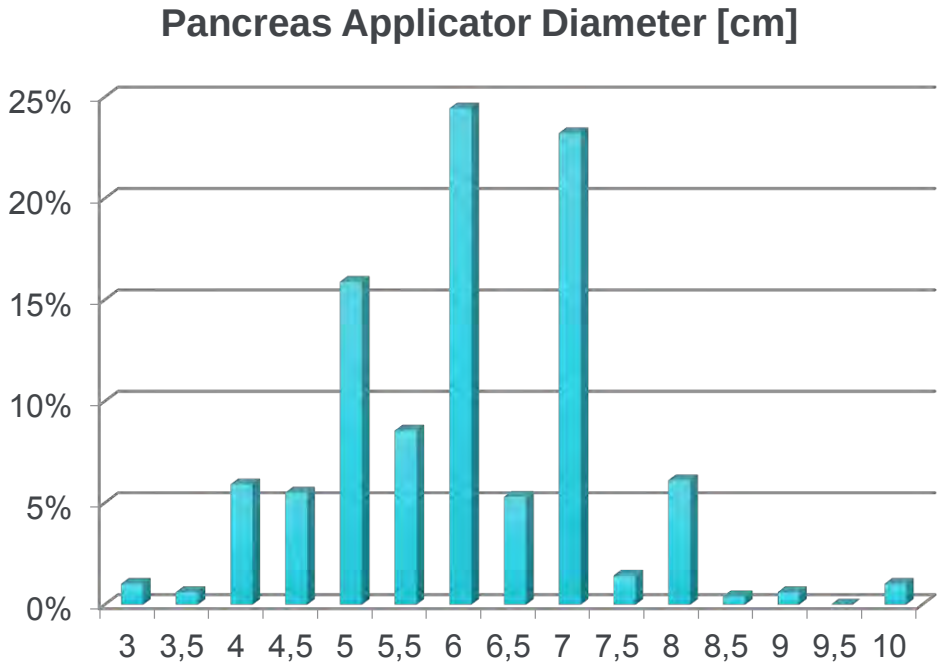
Pancreas data characteristics

- For the pancreas data received:
  - 49% were treated at 12 MeV; 26% at 9 MeV; and 24% at 6 MeV (1% @ 4 MeV).



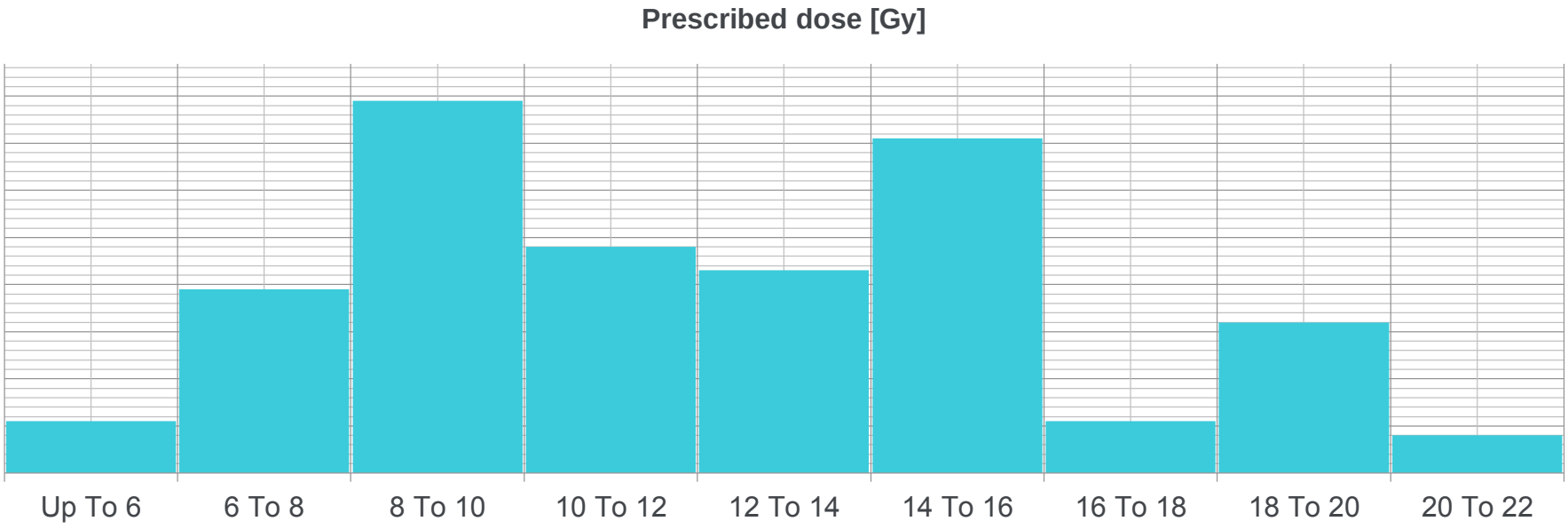
Pancreas data characteristics (continued)

- For the pancreas data received:
  - 77% of patients were treated with FS between 5-7 cm (53% FS 6 - 7cm).
  - 22% of patients were treated with a ½ cm sized applicator.
  - 73% treated with flat applicator. 15º and 30º bevel used in 12% and 16% cases respectively.
  - In 92% cases no bolus used.



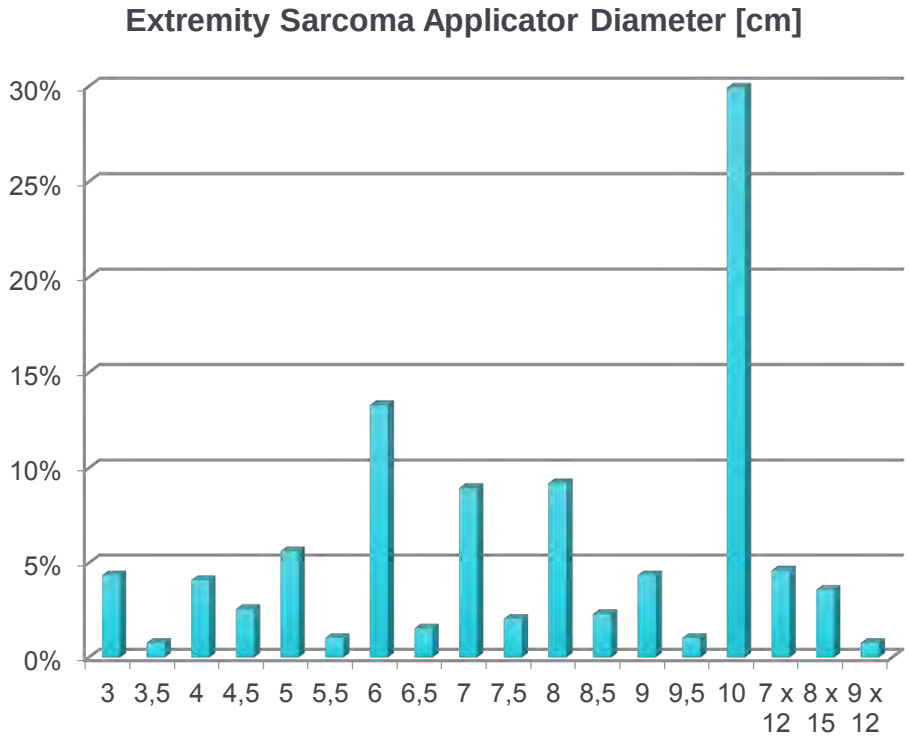
Extremity Sarcoma data characteristics

- For the extremity sarcoma data received:
  - 46% were treated at 9 MeV; 45% at 6 MeV; and 8% at 12 MeV (1% @ 4 MeV).



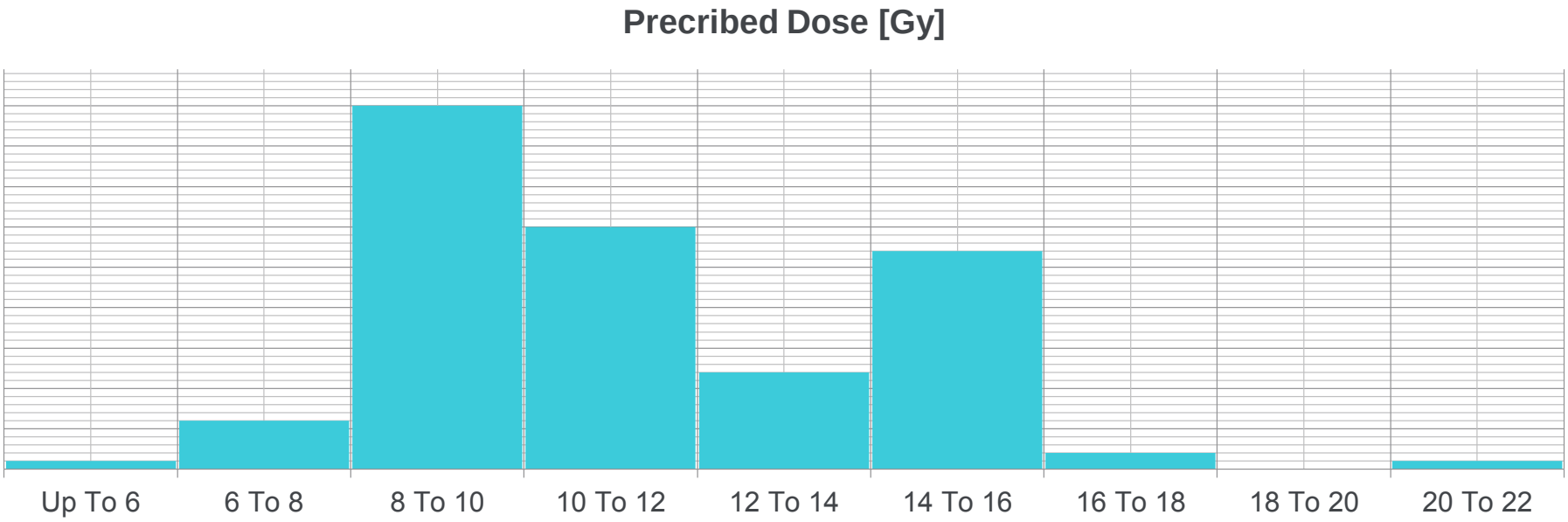
Extremity Sarcoma data characteristics (continued)

- For the extremity sarcoma data received:
  - 30% of patients were treated with 10 cm applicator.
  - In 13% cases more than one field required to cover the target.
  - Dedicated ‘sarcoma’ applicators used in 10% treatments.
  - 12% of patients were treated with a ½ cm sized applicator.
  - 39% treated with flat applicator. 15^{o} and 30^{o} bevel used in 13% and 48% cases respectively.



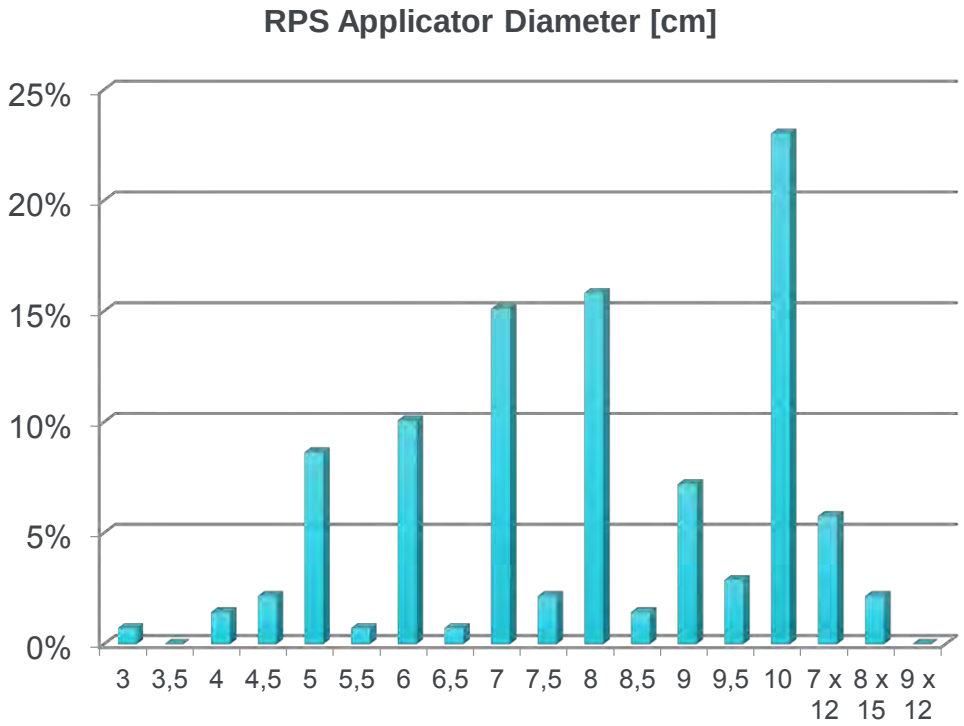
RPS data characteristics

- For the RPS data received:
  - 58% were treated at 9 MeV; 22% at 6 MeV; and 19% at 12 MeV (1% @ 4 MeV).



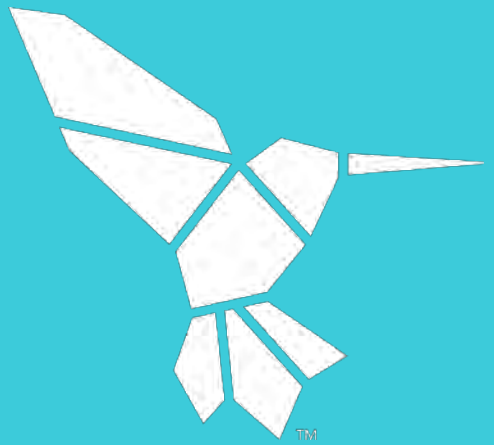
RPS data characteristics (continued)

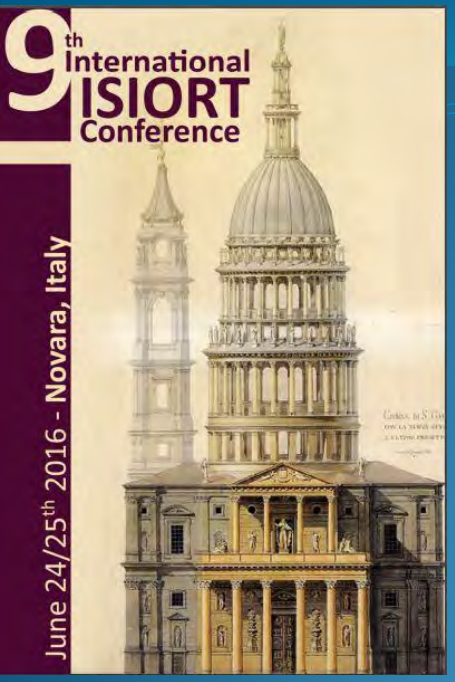
- For the RPS data received:
  - 23% of patients were treated with 10 cm applicator.
  - In 14% cases more than one field required to cover the target.
  - Dedicated ‘sarcoma’ applicators used in 8% treatments.
  - 11% of patients were treated with a ½ cm sized applicator.
  - 34% treated with flat applicator. 15^{o} and 30^{o} bevel used in 8% and 58% cases respectively.



Treatment Application Characteristics

Tumor	Energy [MeV]			Applicator diameter [cm]	Bevel [deg]			½ cm sized applicators
	6	9	12		0	15	30	
Breast	26%	48%	24%	4 – 6 (84%)	53%	31%	15%	35%
Colorectal	35%	50%	10%	4 – 7 (86%)	8%	4%	88%	21%
Pancreas	24%	26%	49%	5 – 7 (77%)	73%	12%	16%	22%
Sarcoma-Extremity	45%	46%	8%	10 (30%)	39%	13%	48%	12%
Sarcoma-RPS	22%	58%	19%	10 (23%)	34%	8%	58%	11%





A real time in vivo dosimeter integrated in the radiation protection disk for IORT breast treatment

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[2]E. Cagni, [2]A. Botti, [1]A. Ciccotelli, [4]L. Strigari

1)Sordina IORT Technologies Spa, Aprilia, Italy
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3) National Institute of Nuclear Physics - Section of Bologna, Italy
4) National Cancer Institute Regina Elena, Roma, Italy

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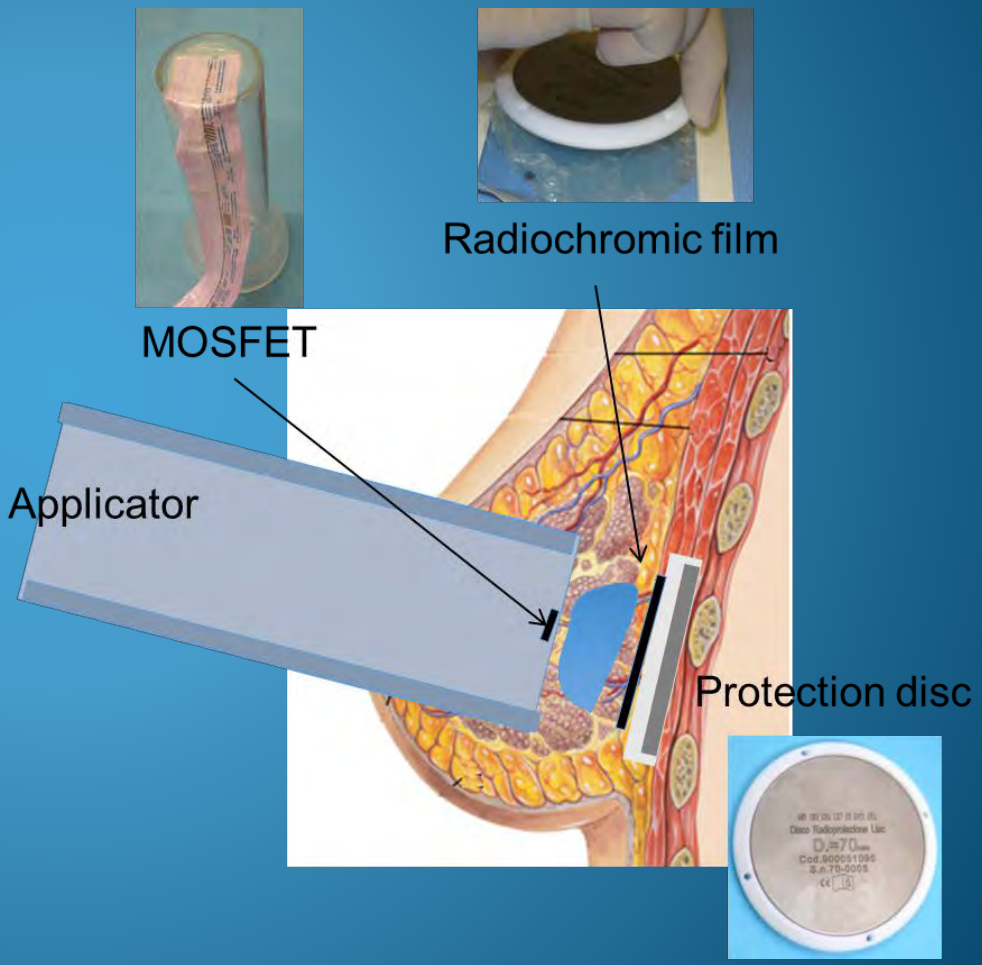
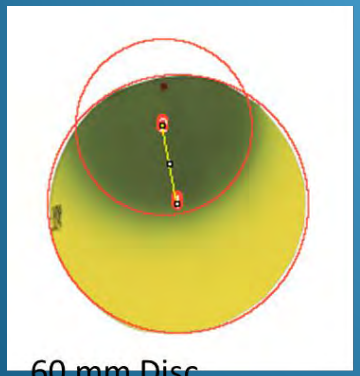
IORT: current practice with linacs

- An electron beam (4-12 MeV) is delivered in one session by a mobile LINAC.
- A protection disc is inserted under tissue to be treated.
- The correct alignment of the protection disc is verified by surgeon by touch when the disc is no more visible.
- The entrance dose is measured in *one point* (MOSFET) at applicator output.
- The dose delivered to the target is measured *offline* (radiochromic film) above the protection disc.

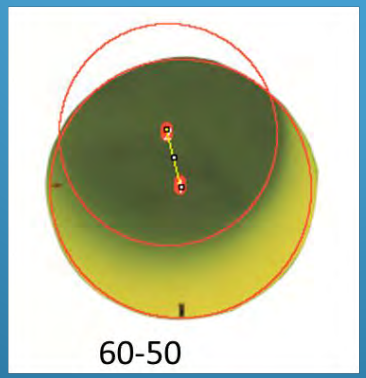


Critical points

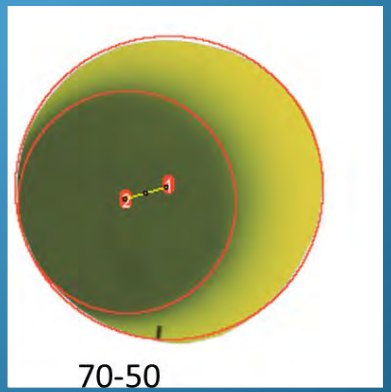
- The blackened area of the gafcromic film also allows to check the centering of the protections disc during the IORT treatment delivery.
- The monitoring of the dose on the target is done in one or two points just at the end of the treatments (MOSFET) or hours, on the entire beam region, by the end of treatment session. This could causes uncertainties on the dose delivered to tissue during the treatment.
- Healthy tissues that are posed under the target (ribs, lung, etc..) need to be protected, but correct positioning of the protection disc is verified .. when it is too late & the fraction of acceptable alignments is far from 100%. Some examples of wrong alignment:



60 mm Disc
40 mm Applicator

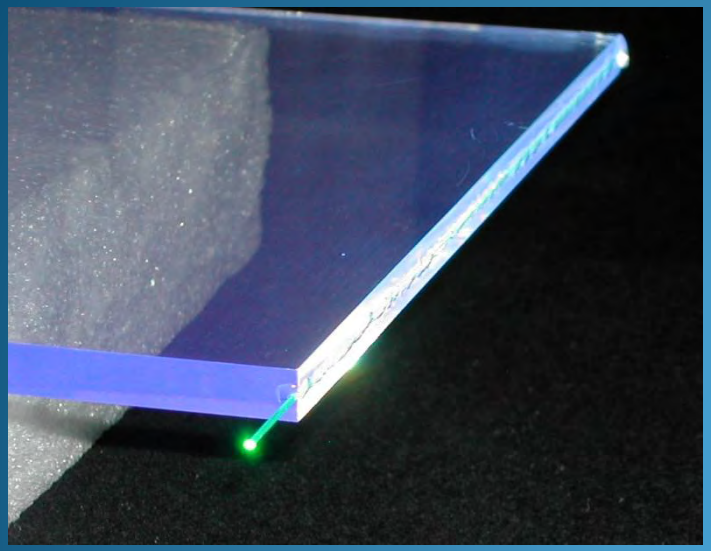


60-50



70-50

Plastic scintillator



- Cast sheet of polyvinyl toluene or polystyrene doped with organic scintillating molecules;
- emits violet light proportionally to the dose deposited in the detector volume;
- light collection with Wave Length Shifting (WLS) fiber (green light);
- WLS fiber coupled to photodetector.

–**Main properties**:

- water equivalent, no perturbation of beam;
- no energy dependence, linear to dose;
- high rates capability;
- negligible temperature dependence;
- high radiation tolerance;
- low cost.

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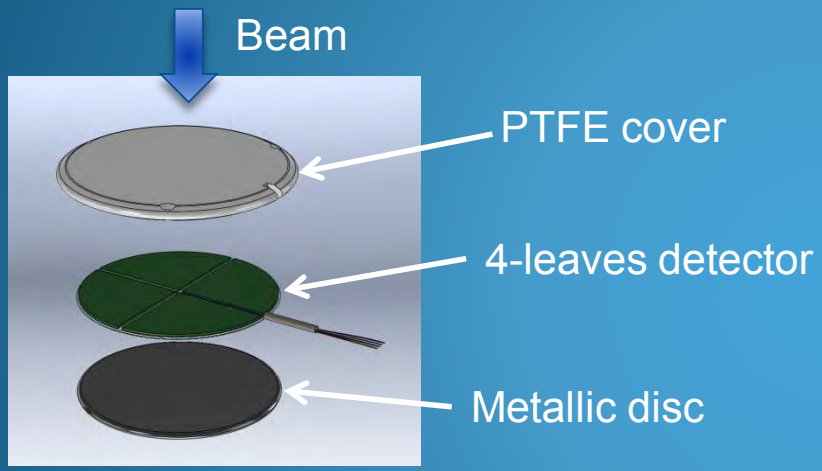
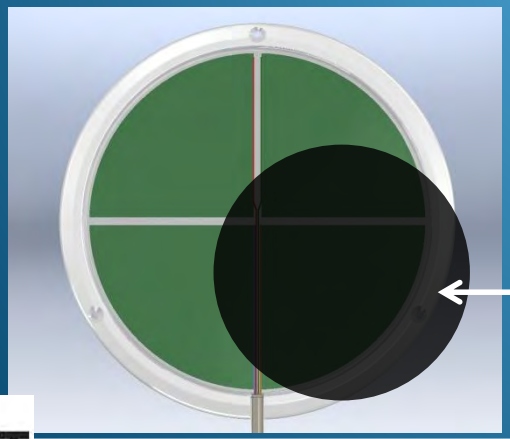
Proposed solution

- Insert a scintillator detector between the metallic disc and its PTFE cover that compose the protection disk.
- Detector formed by 4 leaves, with independent WLS fibers.
- If the beam is centered on the disc, each leaf produces the same light output.





A new dosimeter is proposed that provides in real time (IT Patent TO2014A000943):

- the correct centering of the protective metallic disc.
- the on-line measurement of the integral dose.

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First prototype & preliminary tests

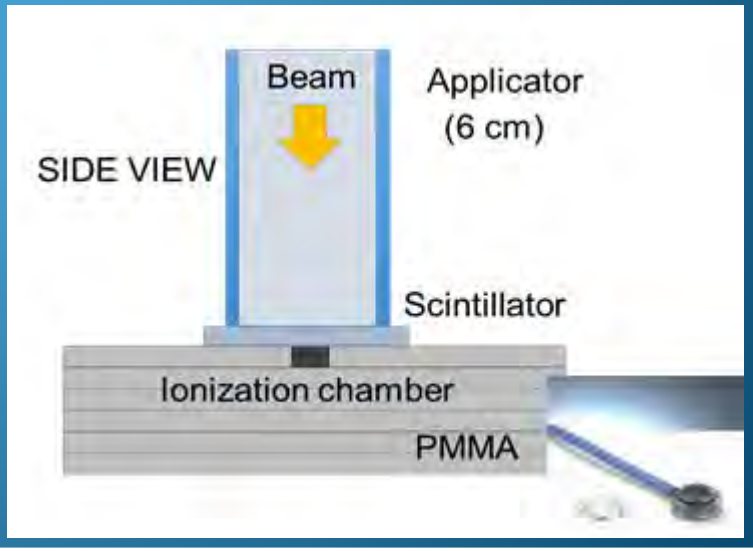
UNDER BEAM:
plastic scintillator tile & optical fiber

REMOTE READOUT:
photodiode & fast ADC

- Light → *Photodiode* → analog signal → *Fast ADC* → digital pulse shape (20 ns sampling time).
- Each pulse shape is visible online and recorded for offline analysis.

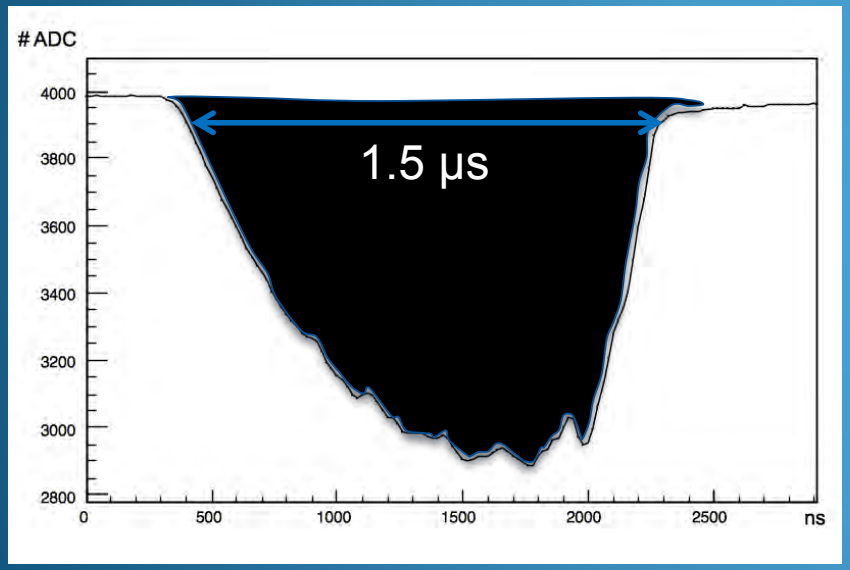
The prototype was irradiated with a LIAC 10 MeV model (SIT) at ASMN-IRCCS in order to:

- measure the linearity of scintillator response under the electron beam;
- compare its dose measurements with a calibrated ionization chamber (Advanced Markus, PTW).



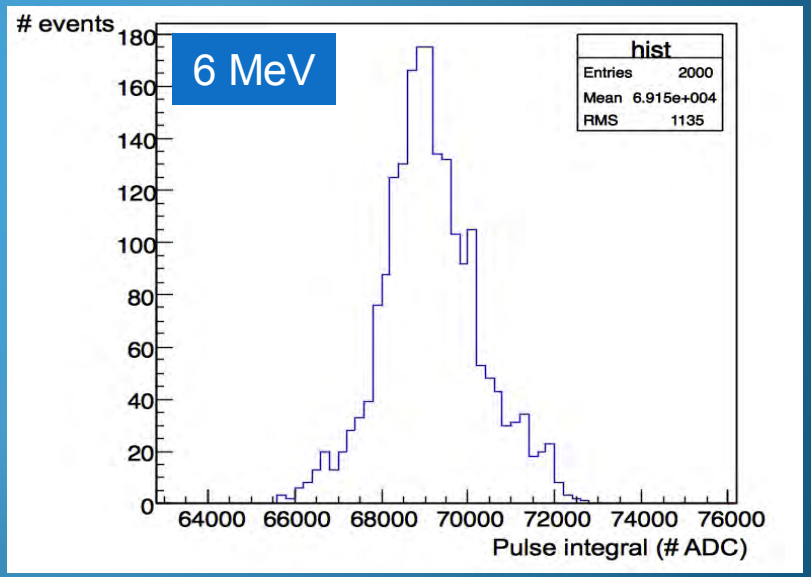
Pulse shape & integrated charge

- The ADC samples (every 20 ns) the pulse shape corresponding to the light output of the scintillator (proportional to dose) for each bunch of Linac electrons



- The area of the pulse shape (integrated charge) correspond to the dose delivered to scintillator by a single burst of the Linac (~ 1 cGy)

- The histogram of the integrated charge of 2000 pulses gives an indication on the uniformity of dose delivered by each pulse
- Less single pulse dose uniformity at higher beam energies



- The integral of the histogram is proportional to the total dose

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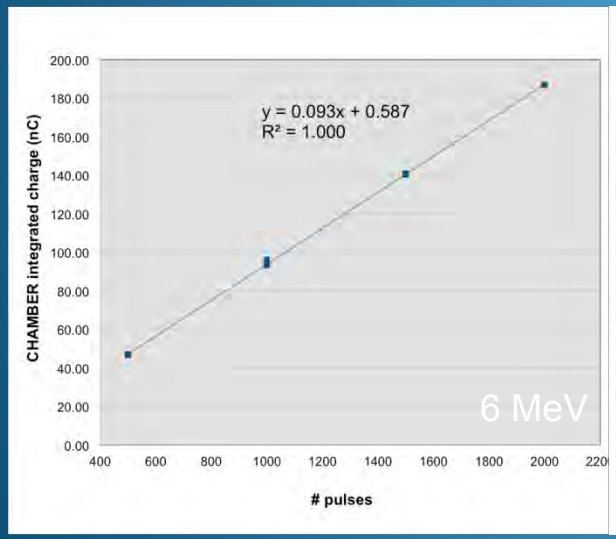
Results: linearity & correlation

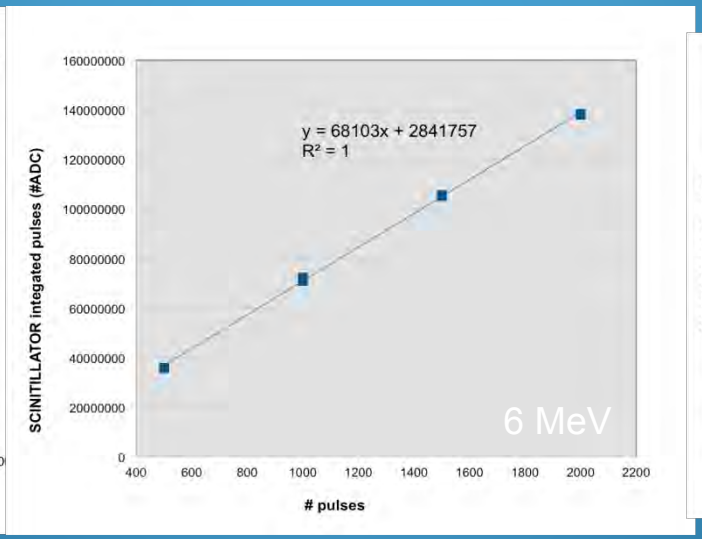
Measure the dose delivered in various runs with different numbers of pulses:

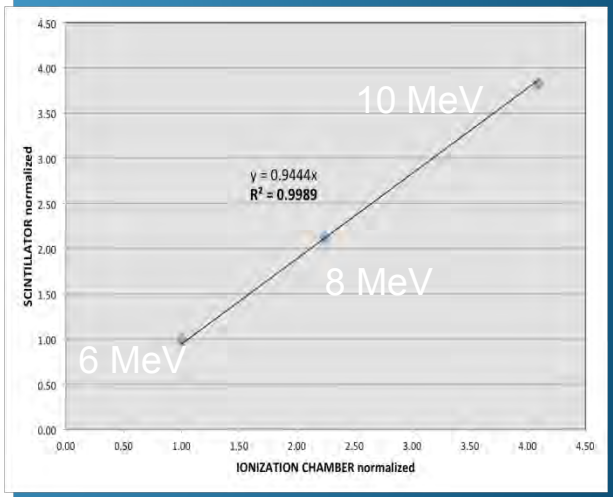
IONIZATION CHAMBER (total charge read out by electrometer)

SCINTILLATOR (sum of the integrated charges of all pulses)

Dose measured by the scintillator & chamber at different energies and d/p (2000 pulses):







The response of scintillator is linear, as in the case of ionization chamber, and both detectors show a very good correlation.

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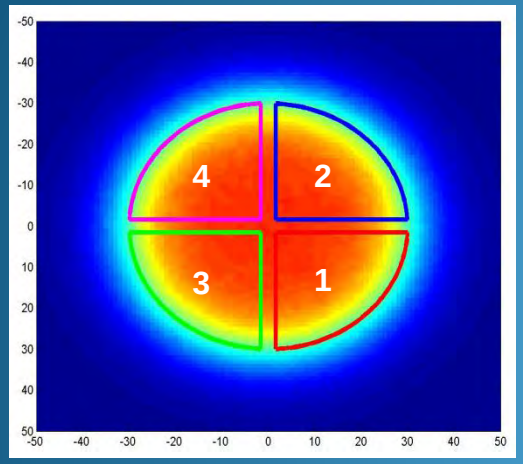
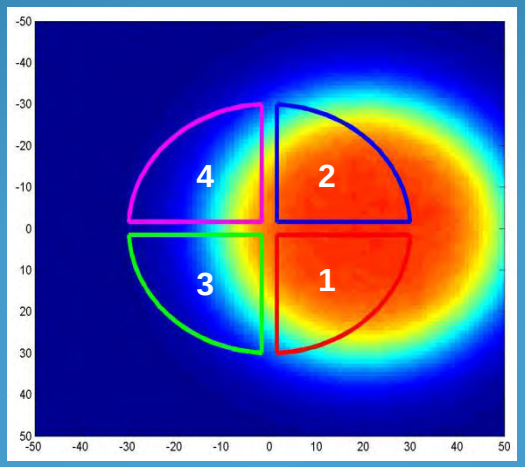
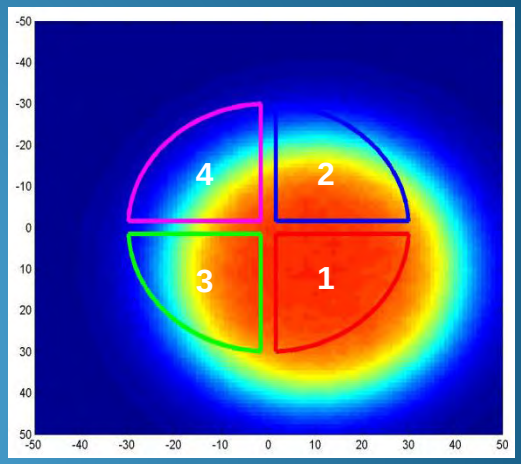
Monte Carlo simulations

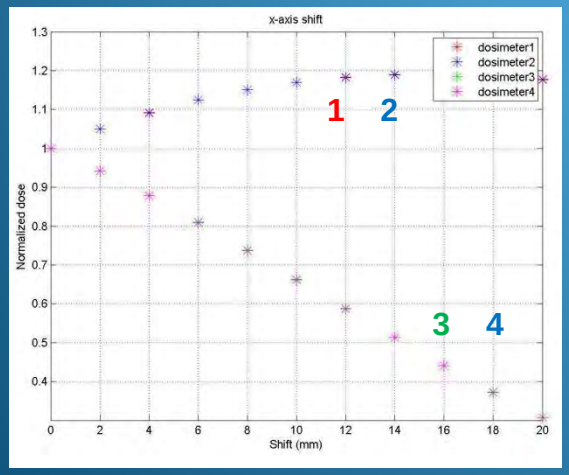
Translation effects of the IORT applicator on the four-leaf detector: MC code EGSnrc / BEAMnrc [Iaccarino G, PMB 2011], beam energy of 10MeV, cone of 60 mm, detector diameter of 70 mm (1 mm thick), depth in tissue of 27mm, light blue isodose of 90%.



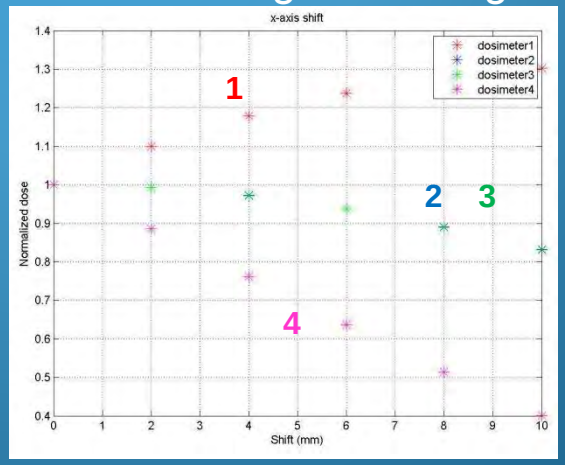




Lateral translation



Translation along a leaf-diagonal



Each leaf has its own pattern of response

Conclusions

The proposed plastic scintillator for in vivo dosimeter improves the IORT clinical practice since it makes:

- a check of the right position of the protection disc with very small dose (~ 1 cGy); the surgeon could correct the positioning of the disc before delivering the treatment.
- a real time check of the protection disk position;
- a real time check of the dose delivery over the whole treatment.

First one-leaf prototype tested with positive results (sensitivity, linearity, absolute dose measurement,..).

Next steps:

- engineering and validation;
- Certification – fourth quarter 2016/first quarter 2017

SIT

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Distributore su territorio italiano:

TECNOLOGIE AVANZATE

Roberta Lazzari
European Istitute of Oncology, Milano

IEO Arc

New Applications and Treatment Simulation Software

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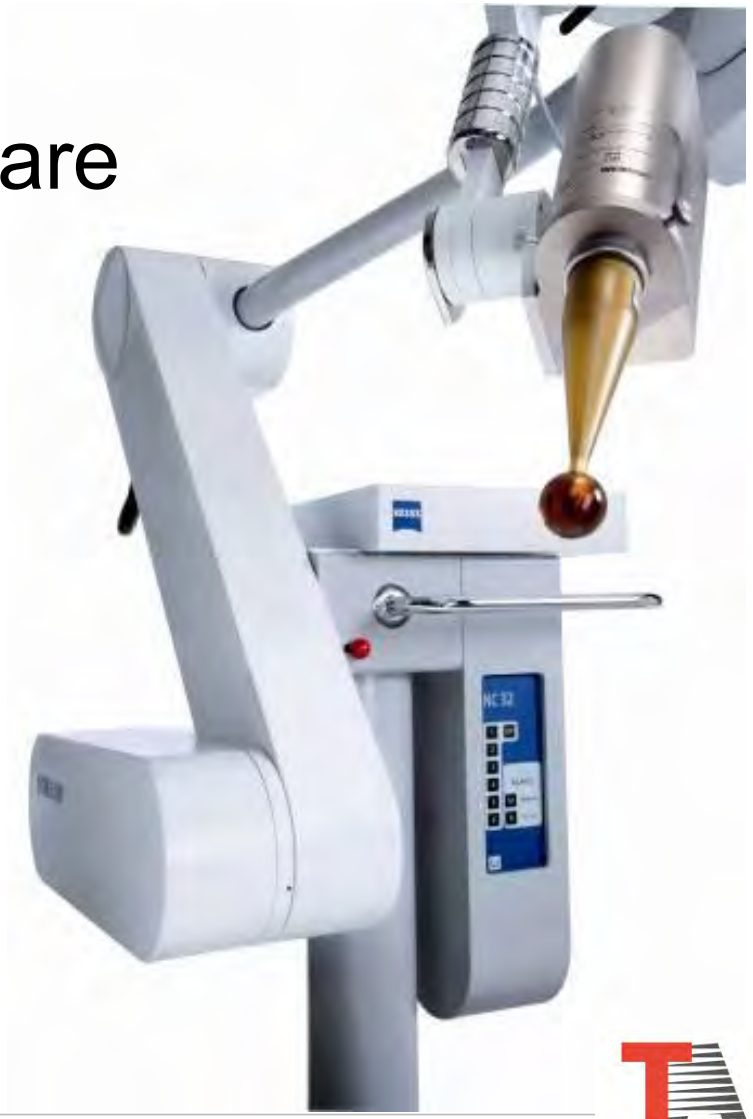
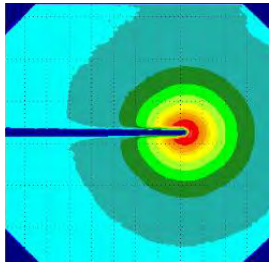
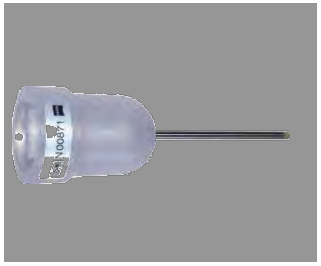
TARGIT Therapy System

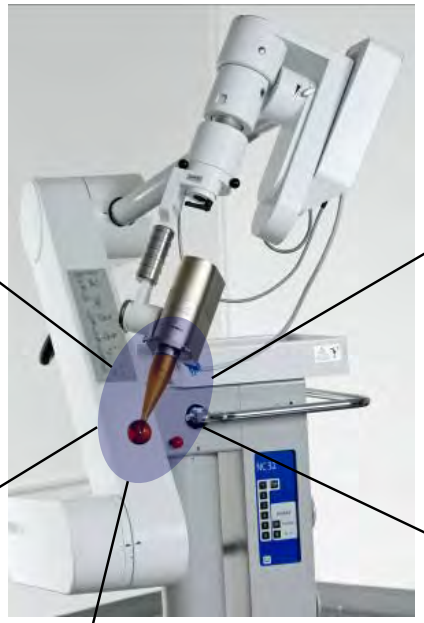


INTRABEAM® becomes a flexible Platform for the Radiation Oncologist

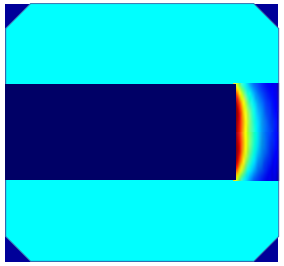
Spine Metastases

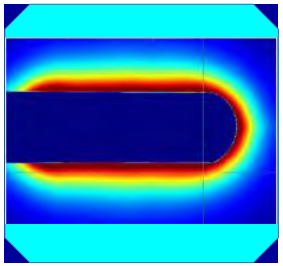




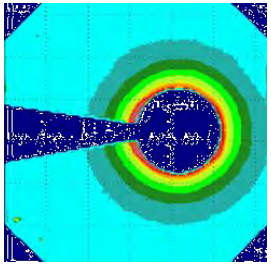


GI Tumors

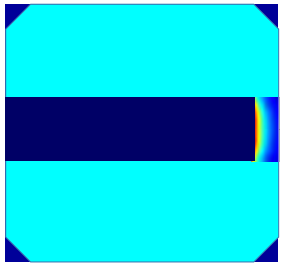




Gyn Tumors



Breast Cancer



Skin Cancer

TECNOLOGIE AVANZATE

IEO Arc

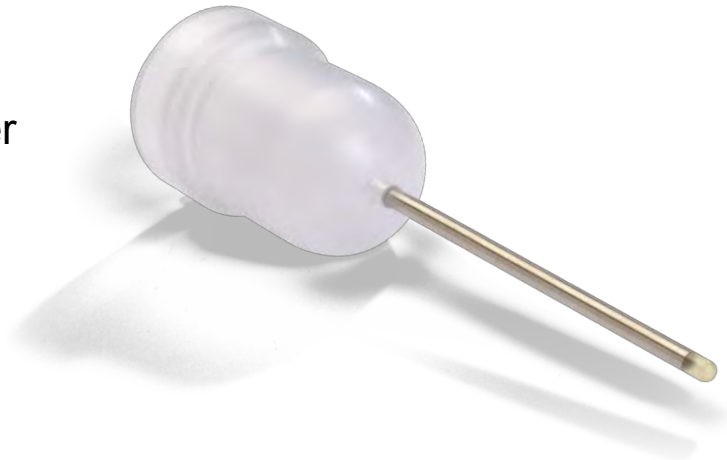
KYPHO-IORT

INTRABEAM
Targeted Radiotherapy in Oncology

INTRABEAM Needle Applicator

Applicator Specifications

- Exterior Probe diameter: 0.4 cm diameter
- Allows minimally invasive access
- Spherical-shaped dose distribution
- Single usage



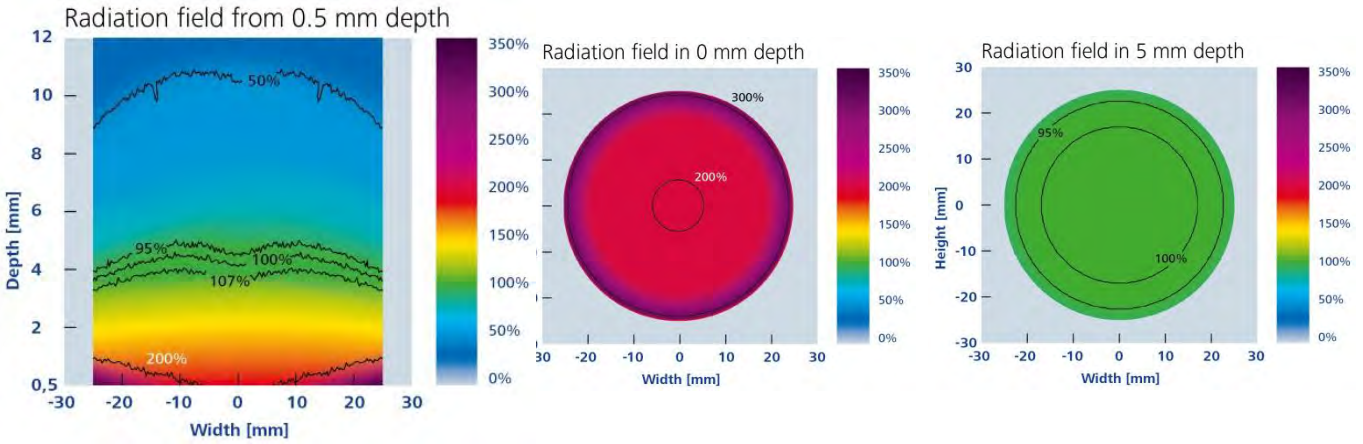
Presentation in standard session in the afternoon…

INTRABEAM® Surface Applicator

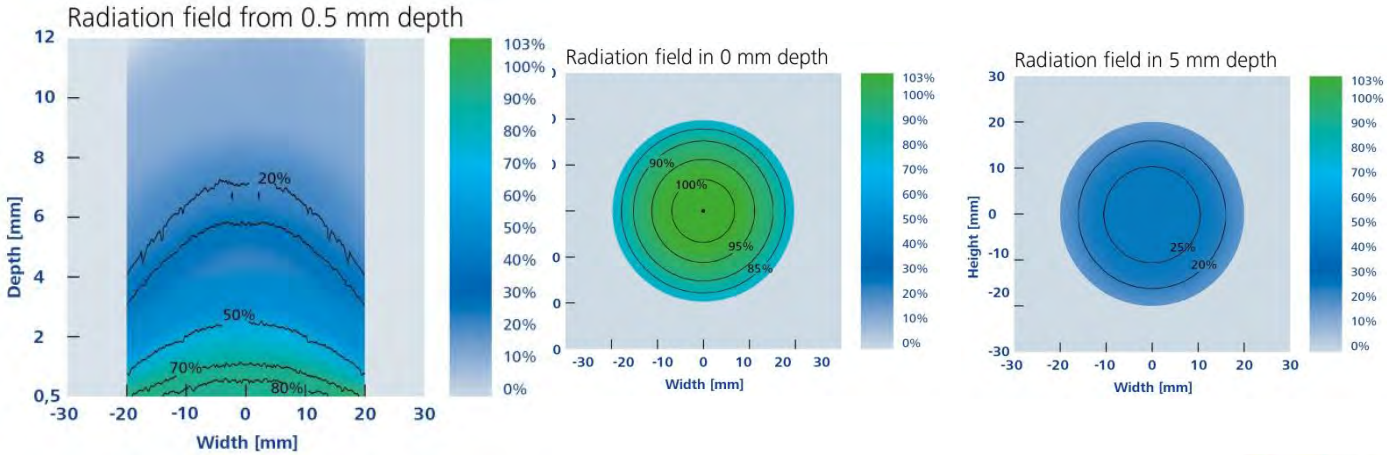
Treatments of surface areas
Generates an optimized flat radiation field
A position marker allows fixation of the treatment area
Applicators are sterilizable
Diameter 1,2,3 and 4 cm

Flat and Surface Applicators: Radiation Properties

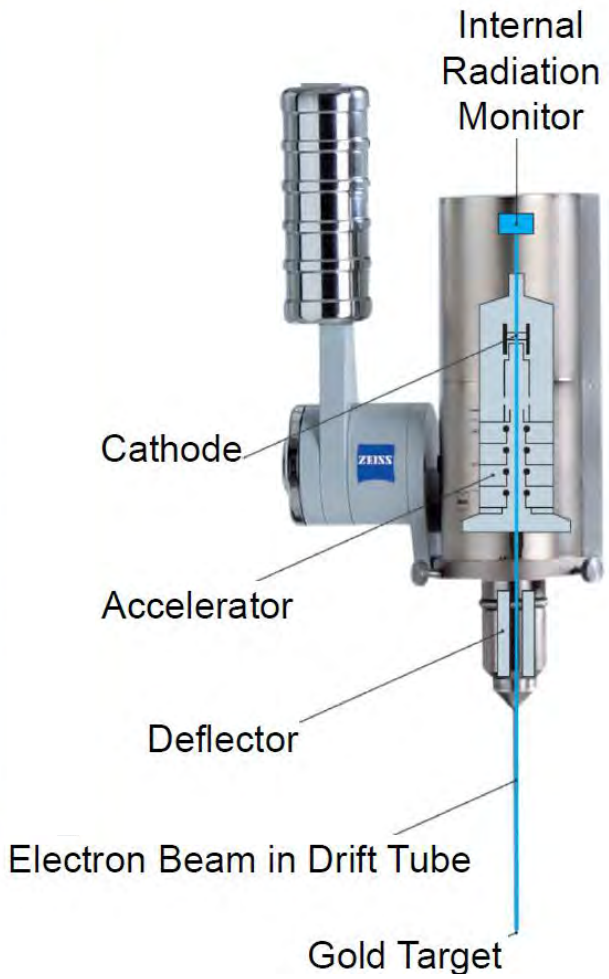
Flat Applicators
1 – 6 cm

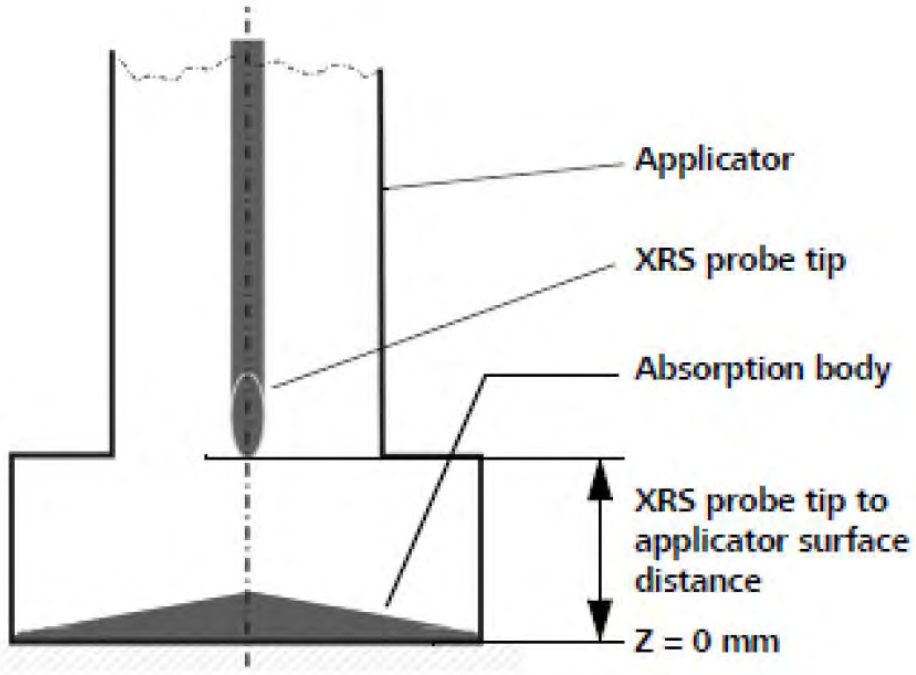


Surface Applicators
1 – 4 cm



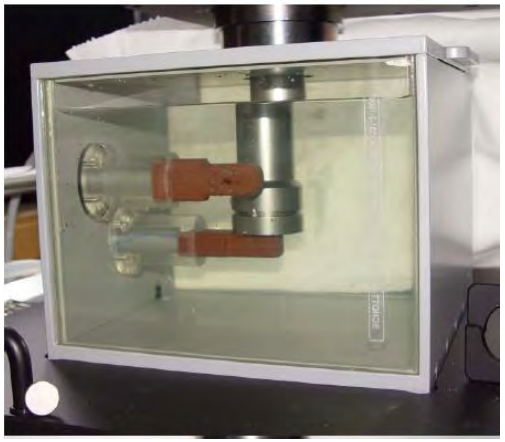
INTRABEAM® Surface Applicator



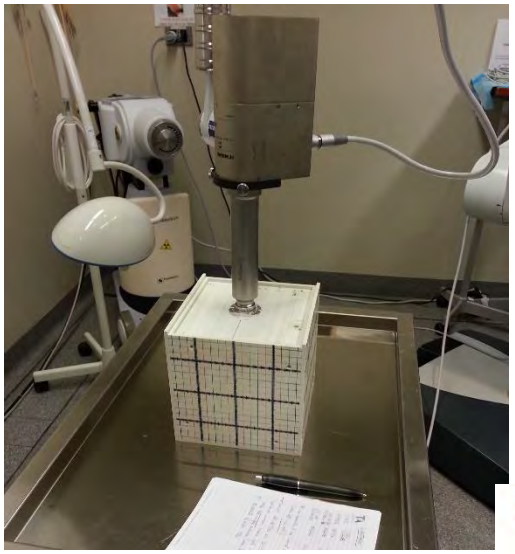


FLAT AND SURFACE DOSIMETRY AT EIO, Milan

- **DOSIMETRY WITH WATER PHANTOM TO OBTAIN THE TRANSFER FUNCTION IN ORDER TO INSERT THE CORRECT DOSE PRESCRIPTION ON THE SOFTWARE**



- **DOSIMETRY WITH SOLID WATER (15x15x15 cm) and gafchromic film**

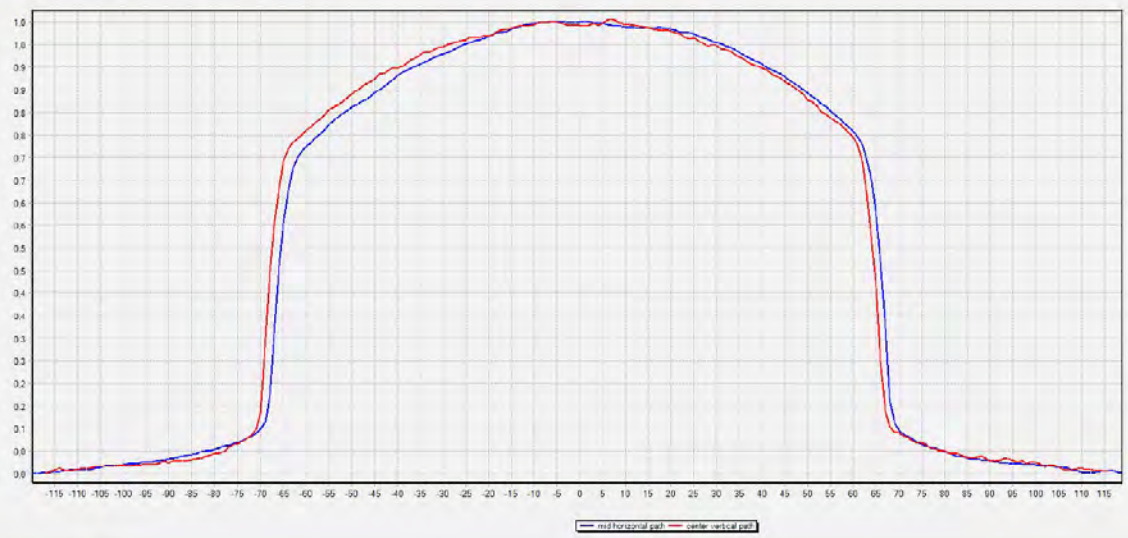


DOSE PROFILE RESULTS FOR SURFACE AT EIO

Depth 4mm

Surface dose distribution is optimized at 0mm depth

Charts 'Dose film' flatness symmetry analysis



all profiles red

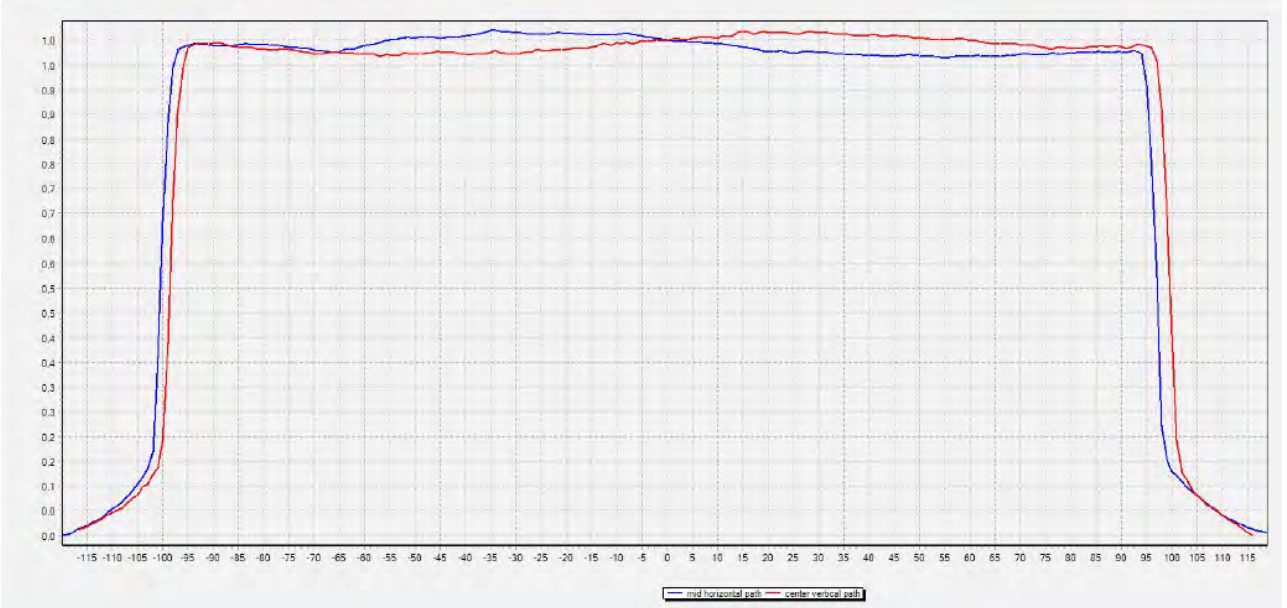
Property	Mid horizontal	Center vertical	Average
Field width	45.8 mm	46.4 mm	46.1 mm
Offset to isocenter	0.3 mm	0.7 mm	0.5 mm
Flatness	125.4 %	123.8 %	124.6 %
Flattenet area	36.6 mm	37.1 mm	36.9 mm
Flatness max CAX ratio	100.2 %	100.6 %	100.4 %
Symmetry	2.2 %	0.9 %	1.5 %
Symmetry area	36.6 mm	37.1 mm	36.9 mm
Penumbra left	5.7 mm	5.0 mm	5.3 mm
Penumbra right	4.4 mm	4.6 mm	4.5 mm
Penumbra distance ratio	79.0 %	80.0 %	79.5 %

DOSE PROFILE RESULTS FOR FLAT AT EIO Milan

Depth 4mm

Flat dose distribution is optimized at 5mm depth

Charts 'Dose film' flatness symmetry analysis

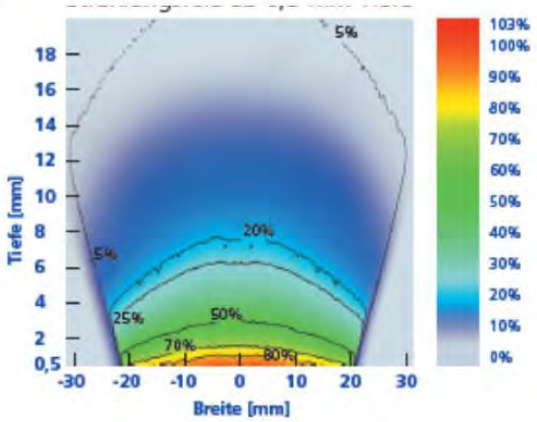


all profiles red

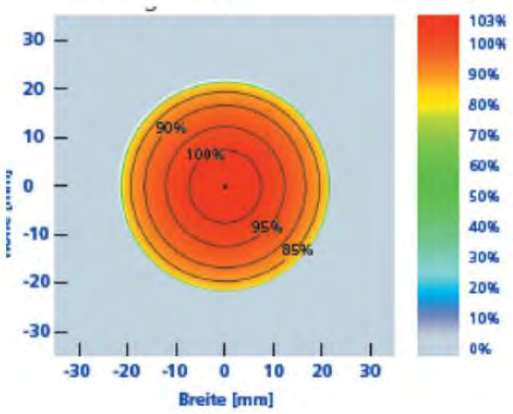
Property	Mid horizontal	Center vertical	Average
Field width	69.6 mm	69.4 mm	69.5 mm
Offset to isocenter	0.6 mm	0.1 mm	0.3 mm
Flatness	105.7 %	105.4 %	105.5 %
Flattenet area	55.7 mm	55.5 mm	55.6 mm
Flatness max CAX ratio	102.0 %	101.9 %	101.9 %
Symmetry	-0.9 %	0.2 %	-0.3 %
Symmetry area	55.7 mm	55.5 mm	55.6 mm
Penumbra left	0.9 mm	0.9 mm	0.9 mm
Penumbra right	0.5 mm	0.7 mm	0.6 mm
Penumbra distance ratio	98.0 %	97.6 %	97.8 %

TREATMENT TIME: surface applicators

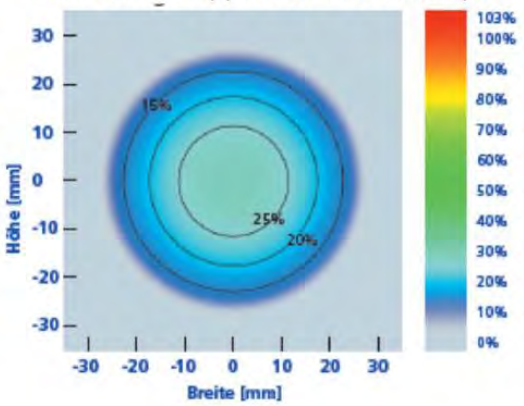
4 cm surface Applicator



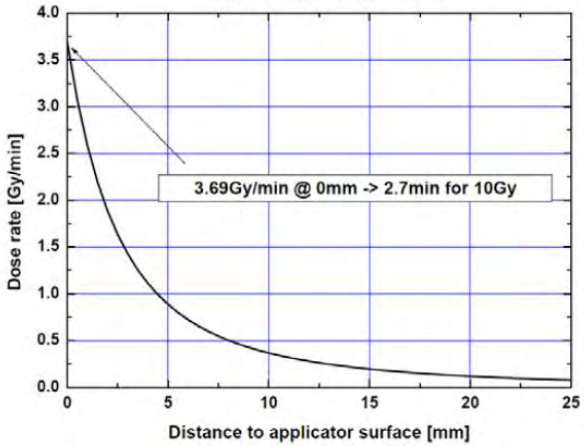
4 cm surface Applicator in 0 mm depth



4 cm surface Applicator in 5 mm depth



3cm Surface Applicator

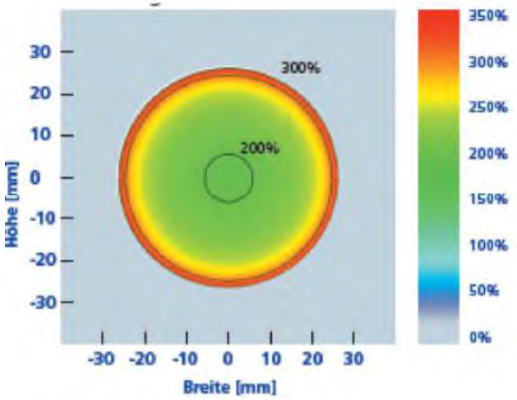


1 cm surface => 0.62 min for 10 Gy @ 0 mm
2 cm surface => 1.80 min for 10 Gy @ 0 mm
3 cm surface => 2.70 min for 10 Gy @ 0 mm
4 cm surface => 4.50 min for 10 Gy @ 0 mm

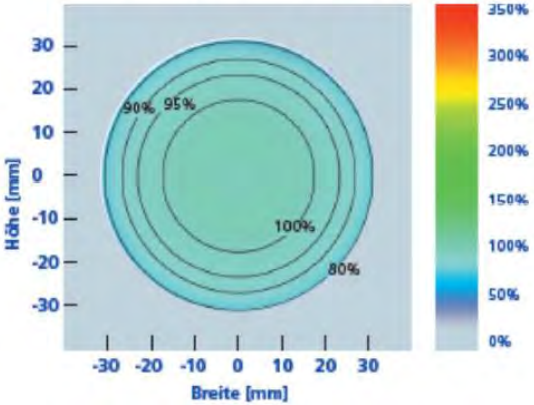
TREATMENT TIME: flat applicators

1 cm flat =>	6.8 min	for 10 Gy @ 5 mm
2 cm flat =>	14.7 min	for 10 Gy @ 5 mm
3 cm flat =>	23.0 min	for 10 Gy @ 5 mm
4 cm flat =>	34.1 min	for 10 Gy @ 5 mm
5 cm flat =>	43.3 min	for 10 Gy @ 5 mm
6 cm flat =>	52.6 min	for 10 Gy @ 5 mm

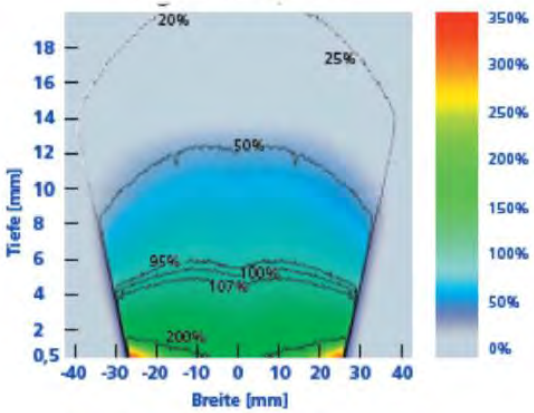
5 cm flat Applicator in 0 mm depth



5 cm flat Applicator in 5 mm depth



5 cm flat Applicator



Superficial x-ray in the treatment of basal and squamous cell carcinomas

Superficial x-ray therapy

Viable nonsurgical option for the treatment of primary BCC and SCC:

- when surgical intervention is declined
- unadvisable
- associated with significant cosmetic or functional limitations.

Cognetta AB, Howard BM, Heaton HP, Stoddard ER, Hong HG, Green WH. Superficial x-ray in the treatment of basal and squamous cell carcinomas: a viable option in select patients. J Am Acad Dermatol. 2012 Dec;67(6):1235-41. doi: 10.1016/j.jaad.2012.06.001.

Radiotherapy in the management of
basal cell carcinomas

3-9 fractions / week, 3,0 – 5,0 Gy

Total dose: 45 Gy

• Schmid-Wendtner M, Volkenandt M: Röntgenweichstrahltherapie melanozytärer Tumoren der Haut. Manual Maligne Melanome, Tumorzentrum München 2003, Zuckschwerdt Verlag München

• Peter RU, Plewig G: Strahlentherapie dermatologischer Erkrankungen, Berlin, Wien: Blackwell Wiss.-Verlg., 1996

Radiotherapy in the management of squamous cell carcinomas*

3-9 fractions / week, 3,5 – 5,0 Gy

Total dose: 45 Gy - 60 Gy

•Schmid-Wendtner M, Volkenandt M: Röntgenweichstrahltherapie melanozytärer Tumoren der Haut. Manual Maligne Melanome, Tumorzentrum München 2003, Zuckschwerdt Verlag München
•Peter RU, Plewig G: Strahlentherapie dermatologischer Erkrankungen, Berlin, Wien: Blackwell Wiss.-Verlg., 1996
*Spinozelluläres Karzinom, Plattenepithelkarzinom. Epithelioma spinocellulare

Radiotherapy in the management of malignant melanoma

Miescher Protokoll:

Doses range from 5 x 10 Gy for two weeks

X-rays: 5-6 x 20 Gy
total dose of 100-120 Gy

- Schmid-Wendtner M, Volkenandt M: Röntgenweichstrahltherapie melanozytärer Tumoren der Haut. Manual Maligne Melanome, Tumorzentrum München 2003, Zuckschwerdt Verlag München
- Peter RU, Plewig G: Strahlentherapie dermatologischer Erkrankungen, Berlin, Wien: Blackwell Wiss.-Verlg., 1996

Radiotherapy in the management of epidemic Kaposi's sarcoma

Doses range from 10 to 30 Gy, according to tumor response and toxicity

Total dose: 45-70 kV X-rays, depending on tumor size and location

Doses of 15 Gy for oral lesions, 20 Gy for lesions involving eyelids, conjunctiva, and genitals, have been shown to be sufficient to produce shrinkage of the tumor and good palliation of the symptoms

For the cutaneous EKS, we propose 30 Gy given in a local field, using a fractionated scheme with small size applicators.

Kirova YM, Belembaogo E, Frikha H, Haddad E, Calitchi E, Levy E, Piedbois P, Le Bourgeois JP. Radiotherapy in the management of epidemic Kaposi's sarcoma: a retrospective study of 643 cases. Radiother Oncol. 1998 Jan;46(1):19-22.

RADIANCE

Treatment Simulation Software

RADIANCE: Treatment simulation software

• **What is *RADIANCE* ?**

Software developed by a spanish company, partner of Zeiss: GMV

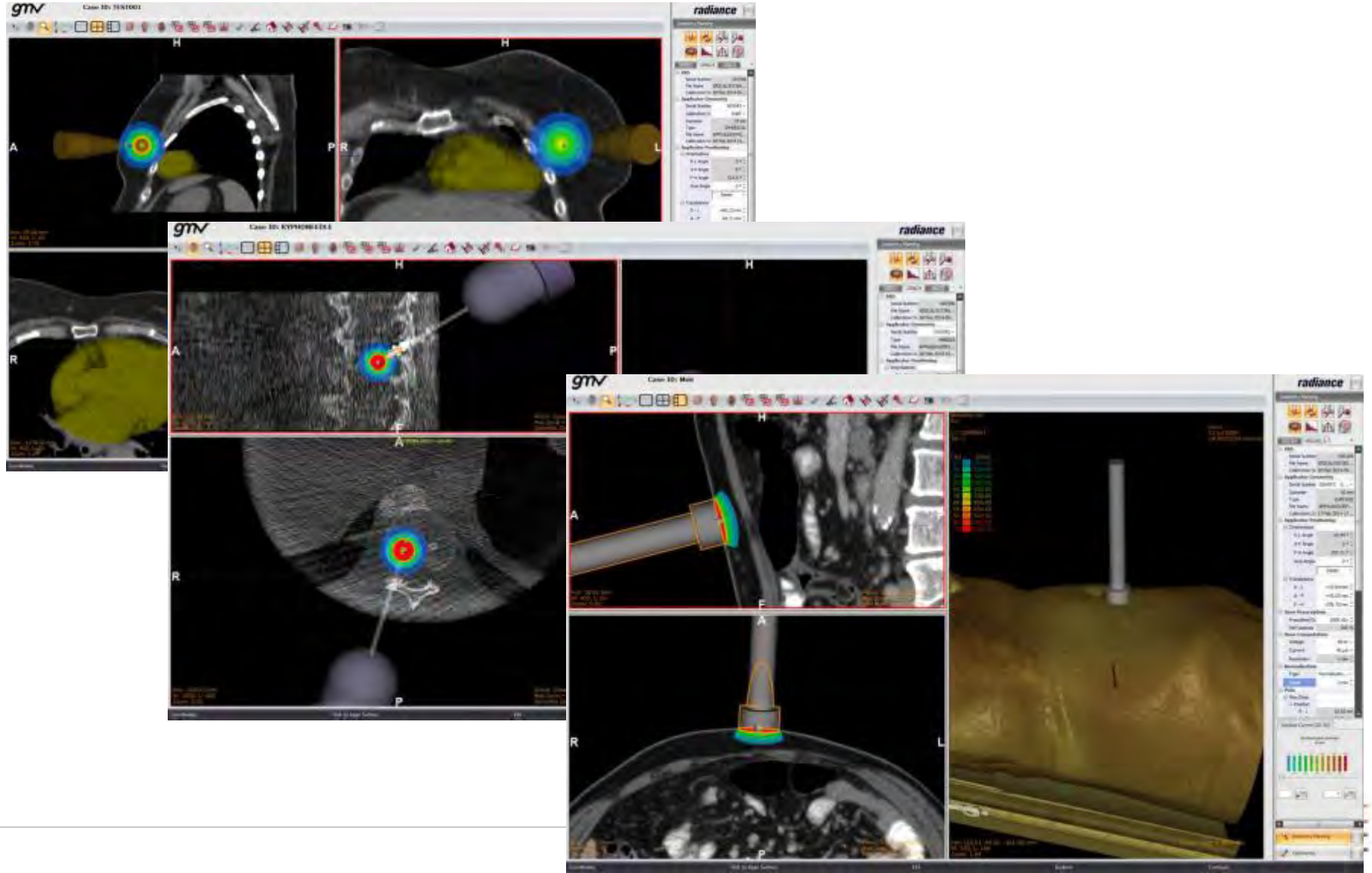
• ***RADIANCE:* What is it used for?**

To plan and simulate the treatment with Intrabeam before delivering to the patients.

• ***RADIANCE: what does it do?***

From a preoperative image of the patient (CT scan) it simulates the Intrabeam applicators so calculating the dose distribution.

RADIANCE: Treatment simulation software



radiance: applicators

- Spherical Applicators

- Needle Applicators

- Flat Applicators

- Surface Applicators

radiance: when is it used? Planning phases

PRE-PLANNING 1
Different alternative approaches
No time constrains

INTRA-PLANNING 2
Re-plan in the OR as necessary
Display the dose distribution after updating the planning

POST-PLANNING 3
Review for quality control and follow-up of the patient
Compare with control images

PREOP IMAG

POST IMAG OR
INTRA IMAG

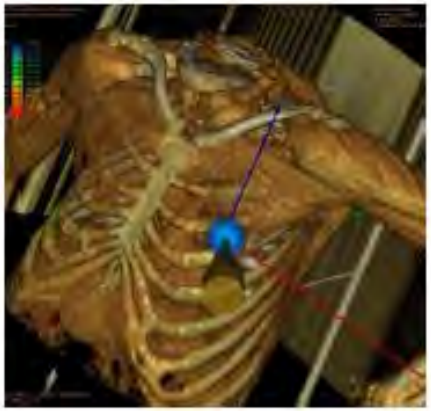
INTRA IMAG OR
PREOP IMAG

radiance: workflow

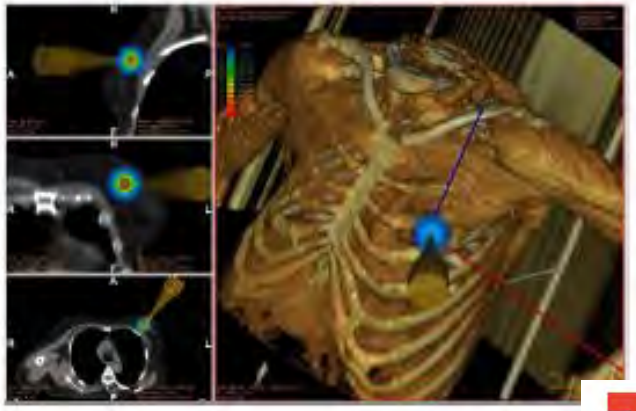
SEGMENTATION → **SIMULATION** → **DOSE COMPUTATION**

- Gross Tumor Volume (GTV)
- Resected Volume (STV)
- Organs at risk

- Patient orientation
- Applicator parameters
- Applicator position and orientation



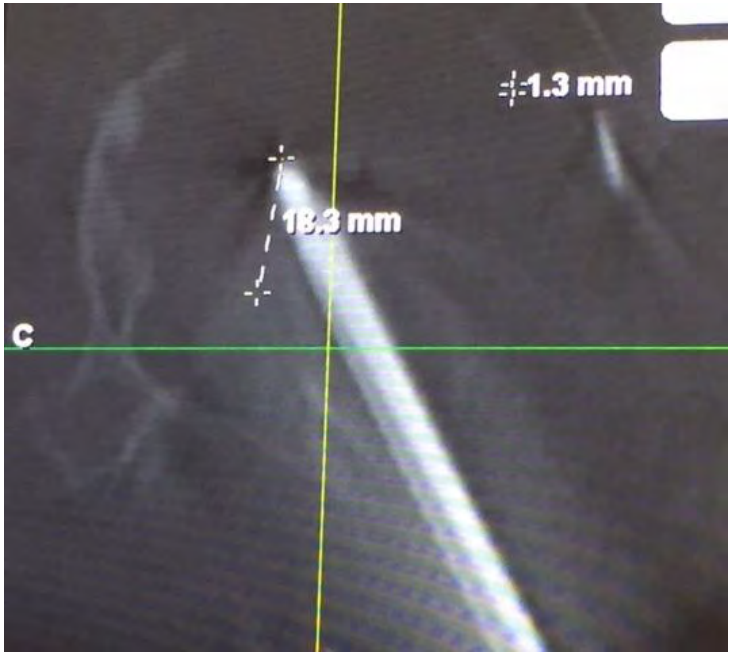
- Use the DVH and 2D/3D images to confirm that the dose at the selected percentage covers the target area protecting the risky healthy areas



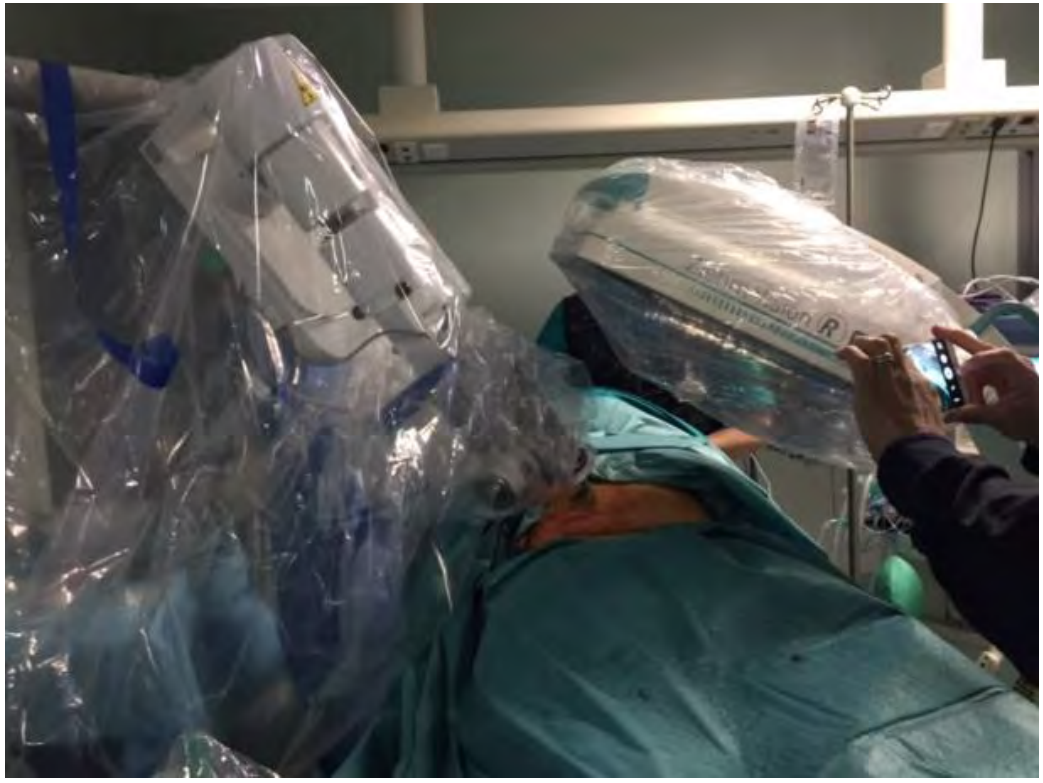
V-IORT

INTRABEAM
Targeted Radiotherapy in Oncology

PRESCRIPTION

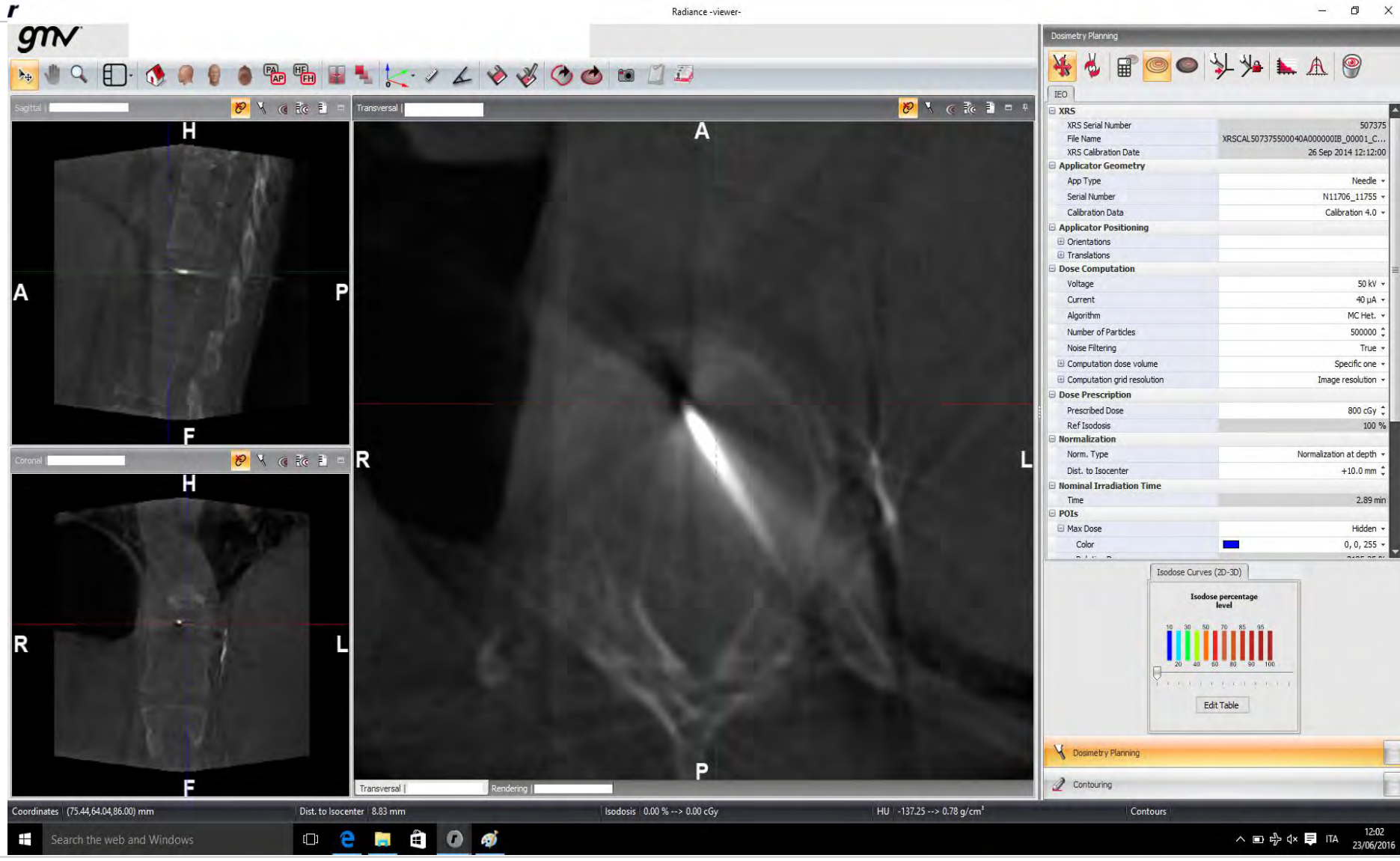


FLUOROSCOPY

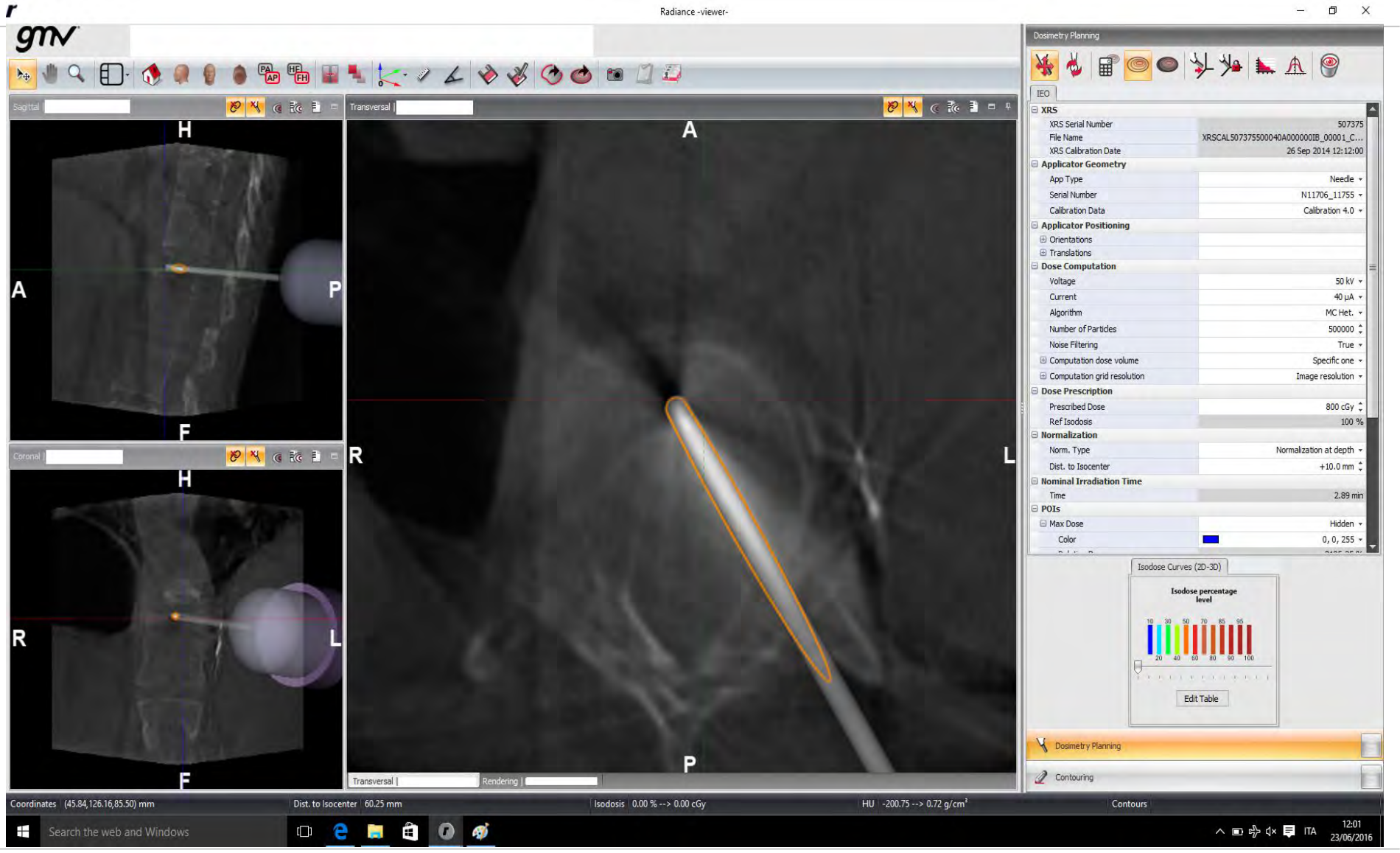


C - ARM DIGITAL FLUOROSCOPY

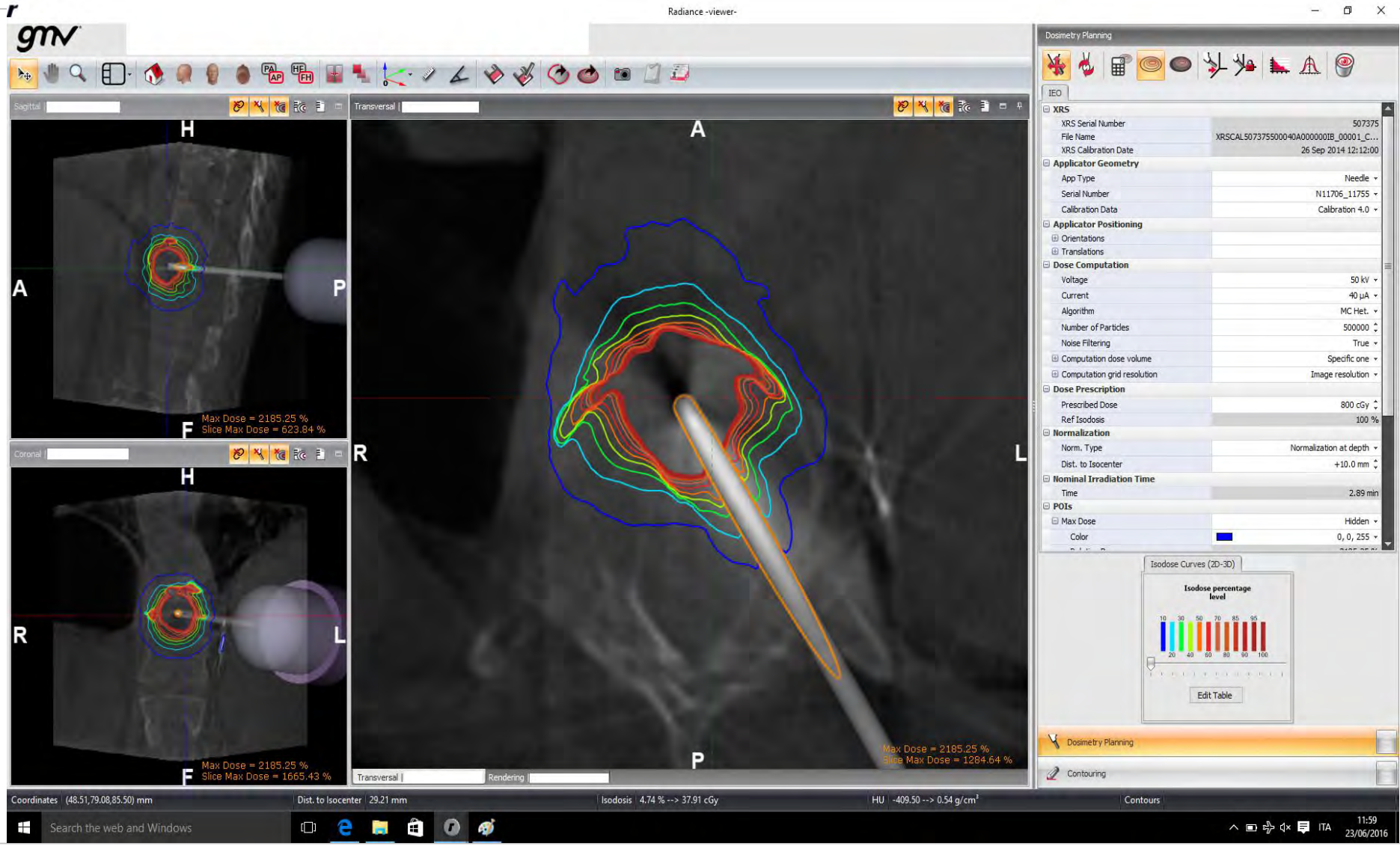
Radiance: EIO V - IORT post-planning



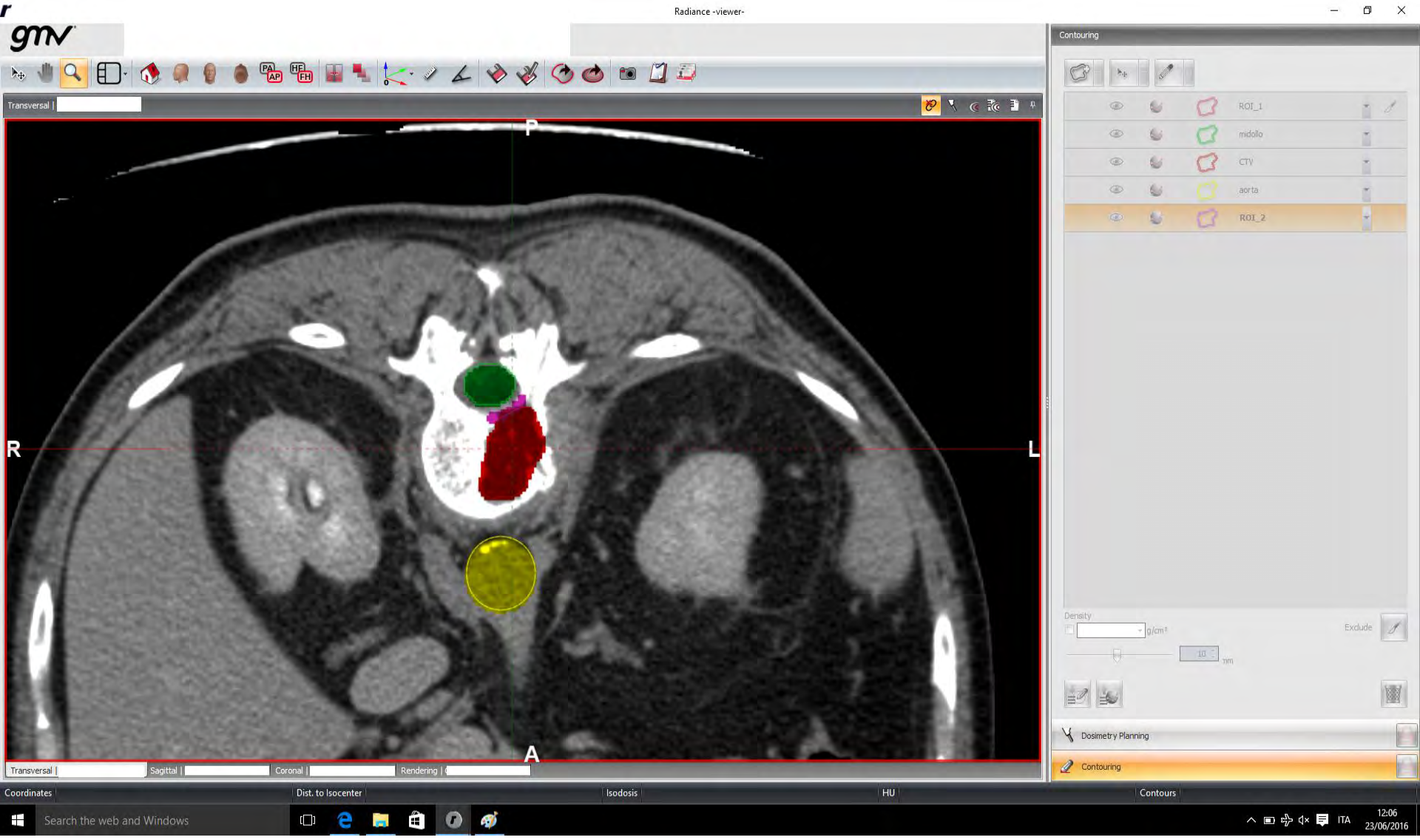
Radiance: EIO V - IORT post-planning



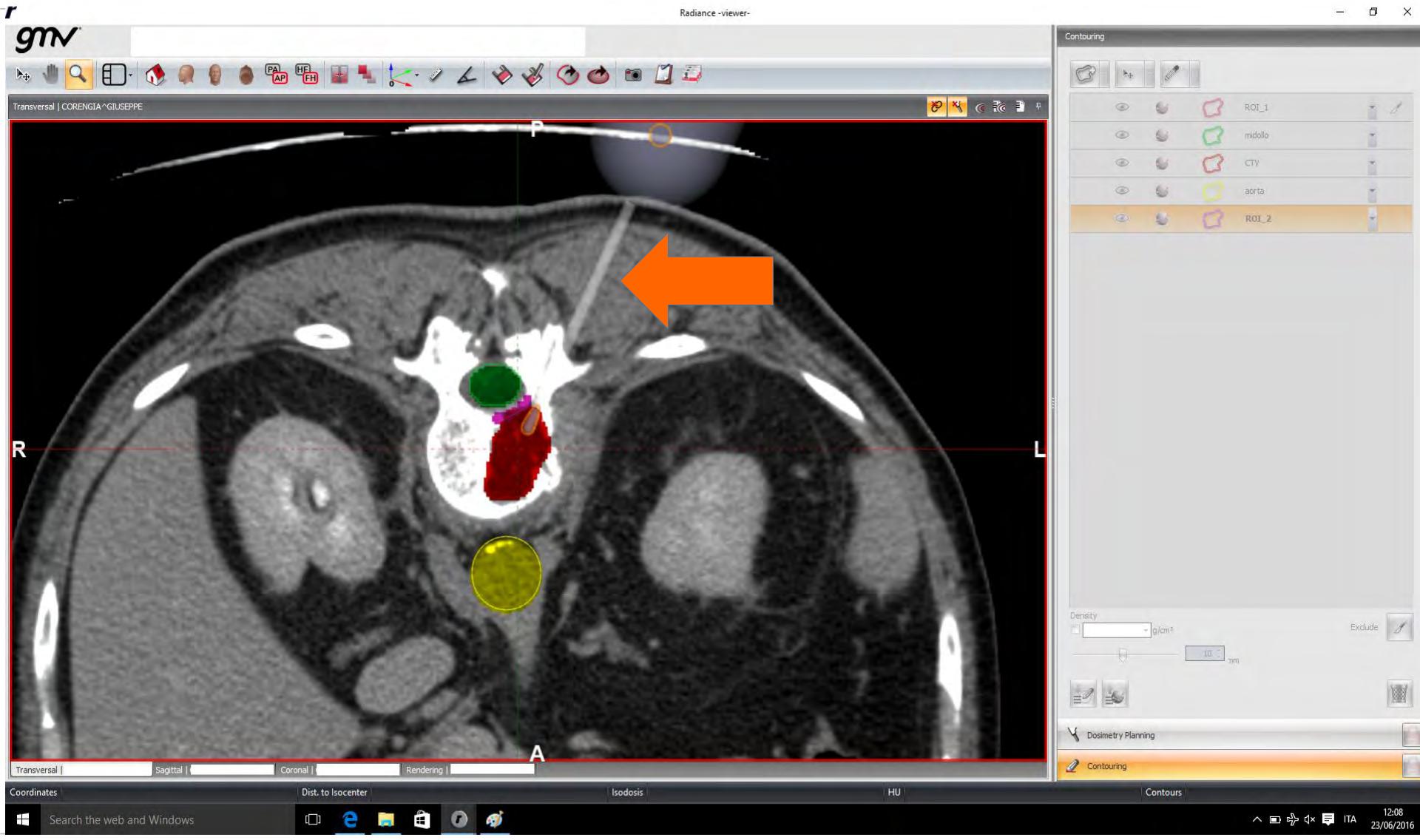
Radiance: EIO V - IORT post-planning



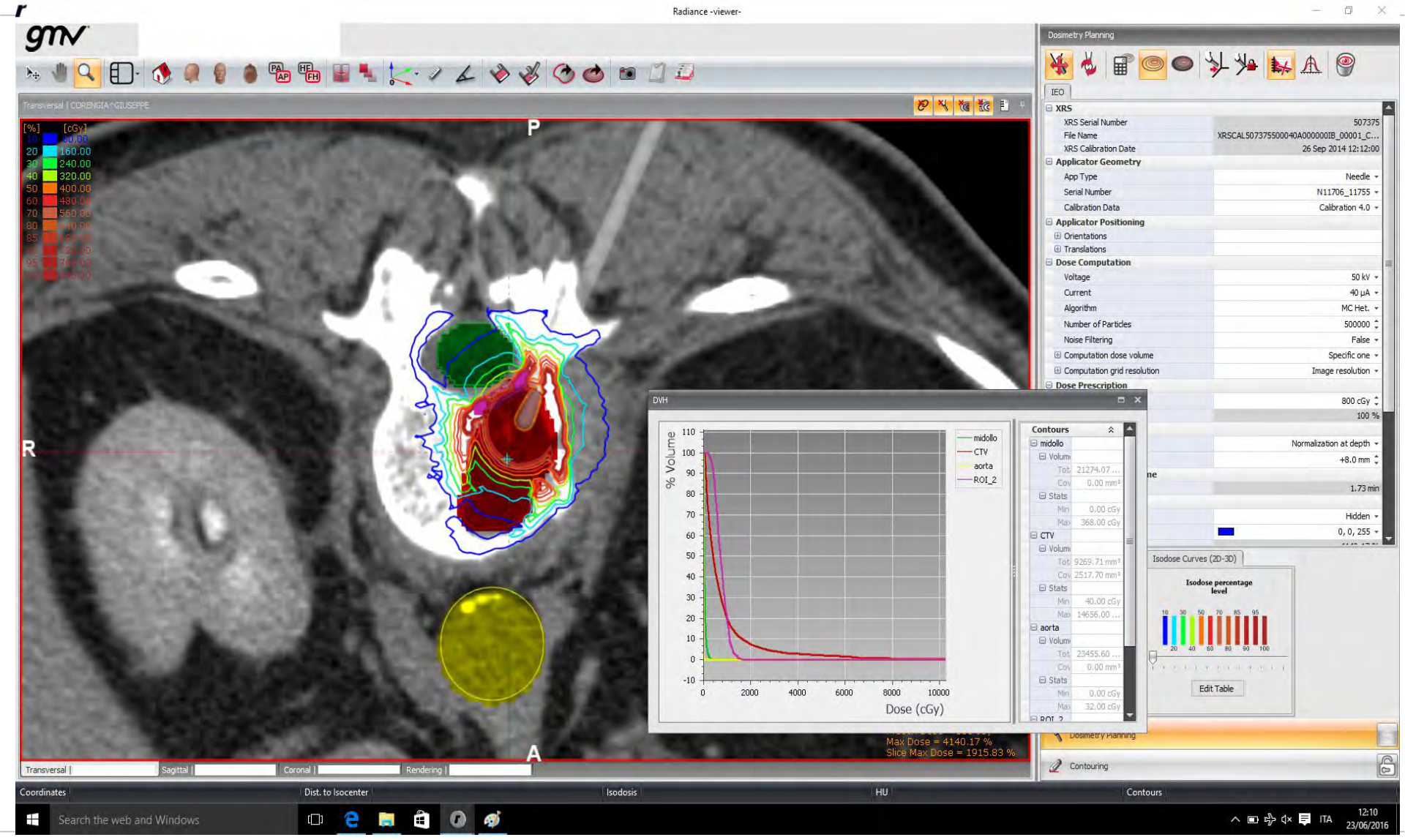
Radiance: EIO V - IORT pre-planning



Radiance: EIO V - IORT pre-planning



Radiance: EIO V - IORT pre-planning



radiance: treatment simulation software

Conclusions:

• PRE or POST planning application

• immediate dose distribution by DVH ready to be evaluated by clinicians (INTRA planning)

• performs several «real time» simulations in order to find the best one for the patient

radiance: treatment simulation software

CERTIFICADO CE DE SISTEMA DE GARANTÍA DE CALIDAD TOTAL
de acuerdo con el Anexo II (excepto punto 4) de la Directiva 93/42/CEE

EC FULL QUALITY ASSURANCE SYSTEM CERTIFICATE
In accordance with Annex II (except Section 4) of Directive 93/42/EEC

Certificado nº/Certificate no	Fecha de validez/Date of validity		ON nº/NB no
2011 01 0751 CT	Desde/From 13-01-2011	Hasta/To 11-01-2016	0318

A favor de/In favour of:

Fabricante/Manufacturer:
Nombre/Name: GMV AEROSPACE AND DEFENSE, S.A.U.
Dirección/Address: c/ Isaac Newton nº 11; 1-28760 TRES CANTOS (Madrid)

Para el producto/For the product:

Categoría/Category: Productos electromédicos/Electromedical products
Grupo genérico/Generic group: Sistemas para la [illegible] Planning System
Tipo/Type: Especificados en el Anexo de este Certificado/As specified in the Annex to this Certificate

Emitido de acuerdo con el [illegible]

GMV AEROSPACE AND DEFENSE, S.A.U.
c/ Isaac Newton nº 11; 1-28760 TRES CANTOS (Madrid)

[illegible] que cumple los requisitos del anexo II [illegible]
This certificate is granted in accordance with Annex II [illegible]

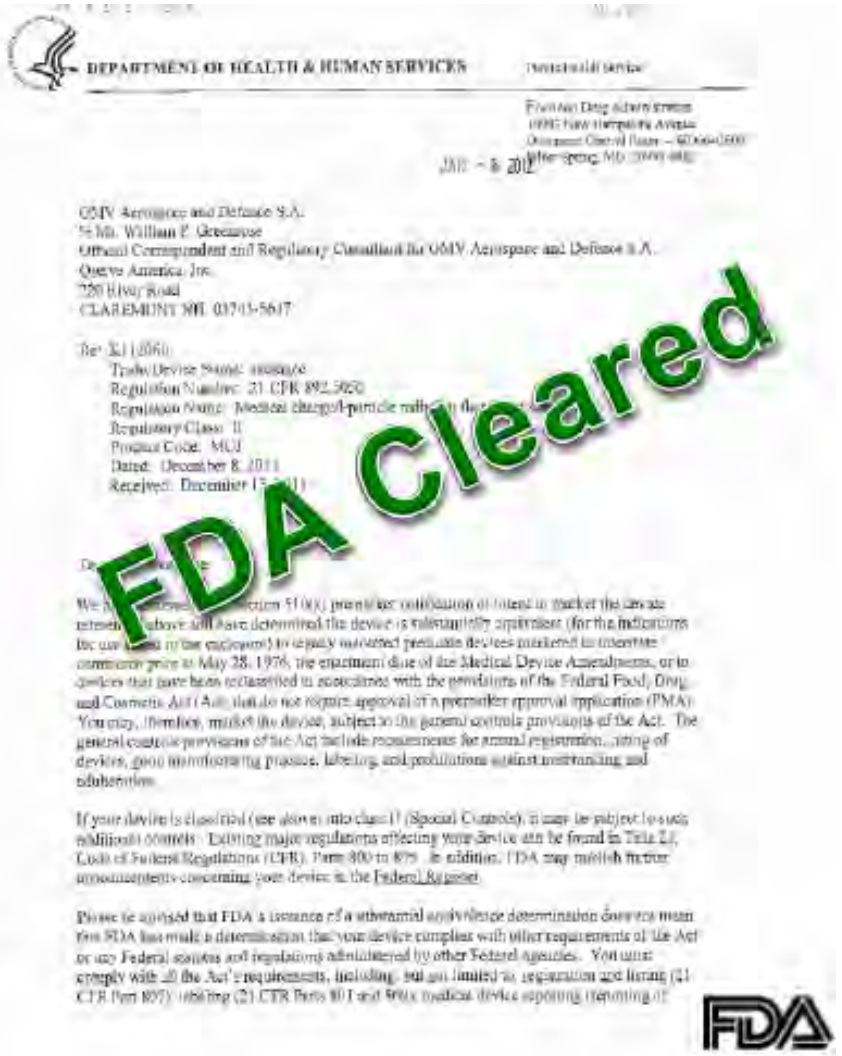
Este certificado de conformidad de la auditoría del sistema completo de garantía de calidad y del examen de la documentación técnica [illegible] nº 2010/0751/CT y otorga el derecho a colocar el marcado CE de conformidad [illegible] de la Directiva.
This certificate is issued on the full quality assurance system audit, and the examination of the technical documentation submitted in annex to [illegible] and guarantees that the device/s [illegible] fulfils the requirements of the Directive.

Madrid, a 12 de enero de 2011

La Directora,
Belén Crespo Sánchez-Cascarejo

CE
0318

CE certified



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
[illegible]
Silver Spring, MD [illegible]

JAN - 6 2012

GMV Aerospace and Defense S.A.
% Mr. William F. Greenlaw
Official Correspondent and Regulatory Consultant for GMV Aerospace and Defense S.A.
Qserve America, Inc.
720 Hwy 8 East
CLAREMONT NH 03743-5617

Re: K113060
Trade/Device Name: [illegible]
Regulation Number: 21 CFR 892.5050
Regulation Name: Medical charged-particle radiation therapy system
Regulatory Class: II
Product Code: MUJ
Dated: December 8, 2011
Received: December [illegible], 2011

Dear [illegible]

We [illegible] section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into class II (Special Controls), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); medical device reporting (reporting of

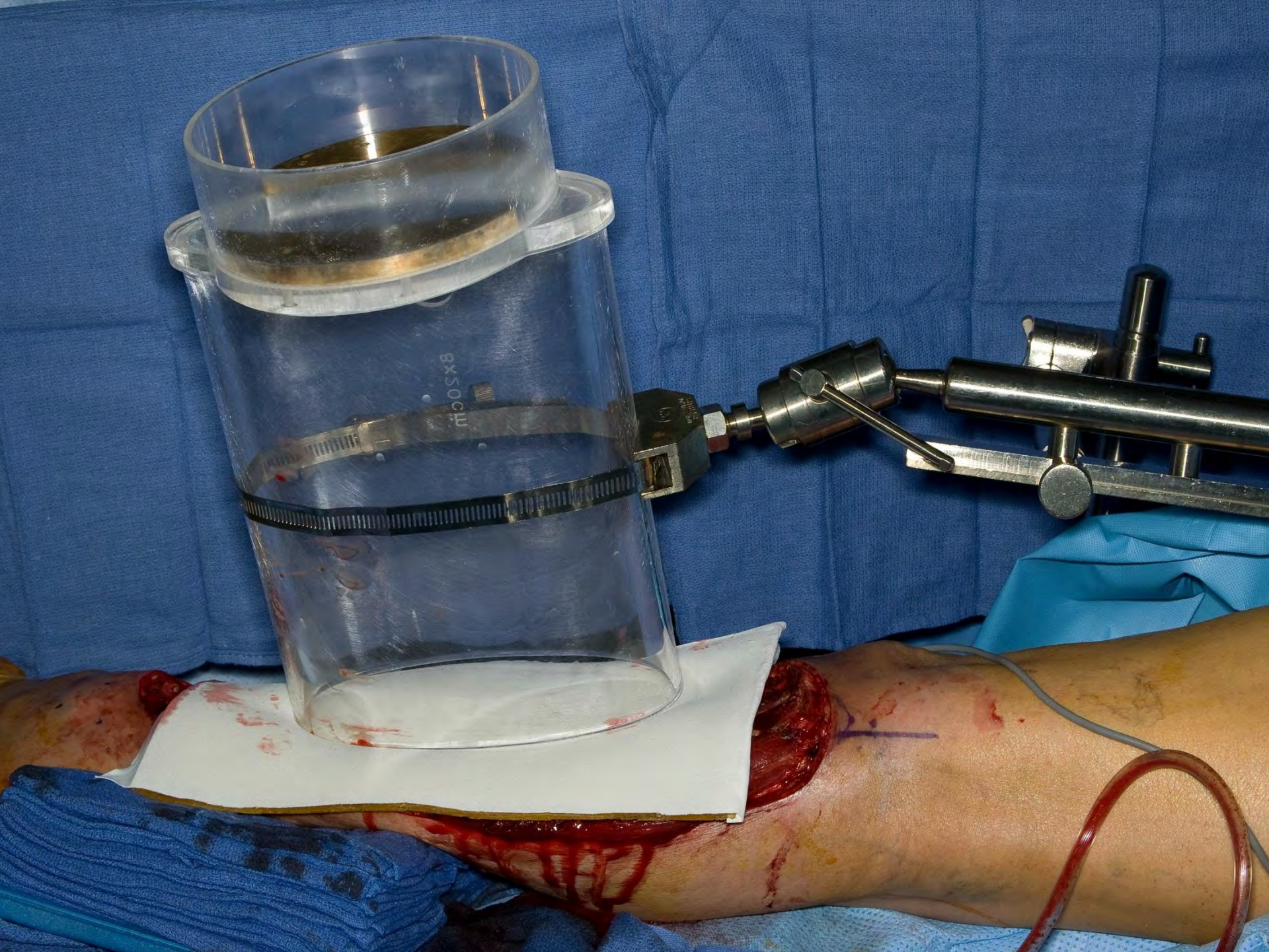
FDA

FDA Cleared

Long-term survivors after IORT: a lesson to be learned

Michael G. Haddock, MD

Mayo Clinic, Rochester, MN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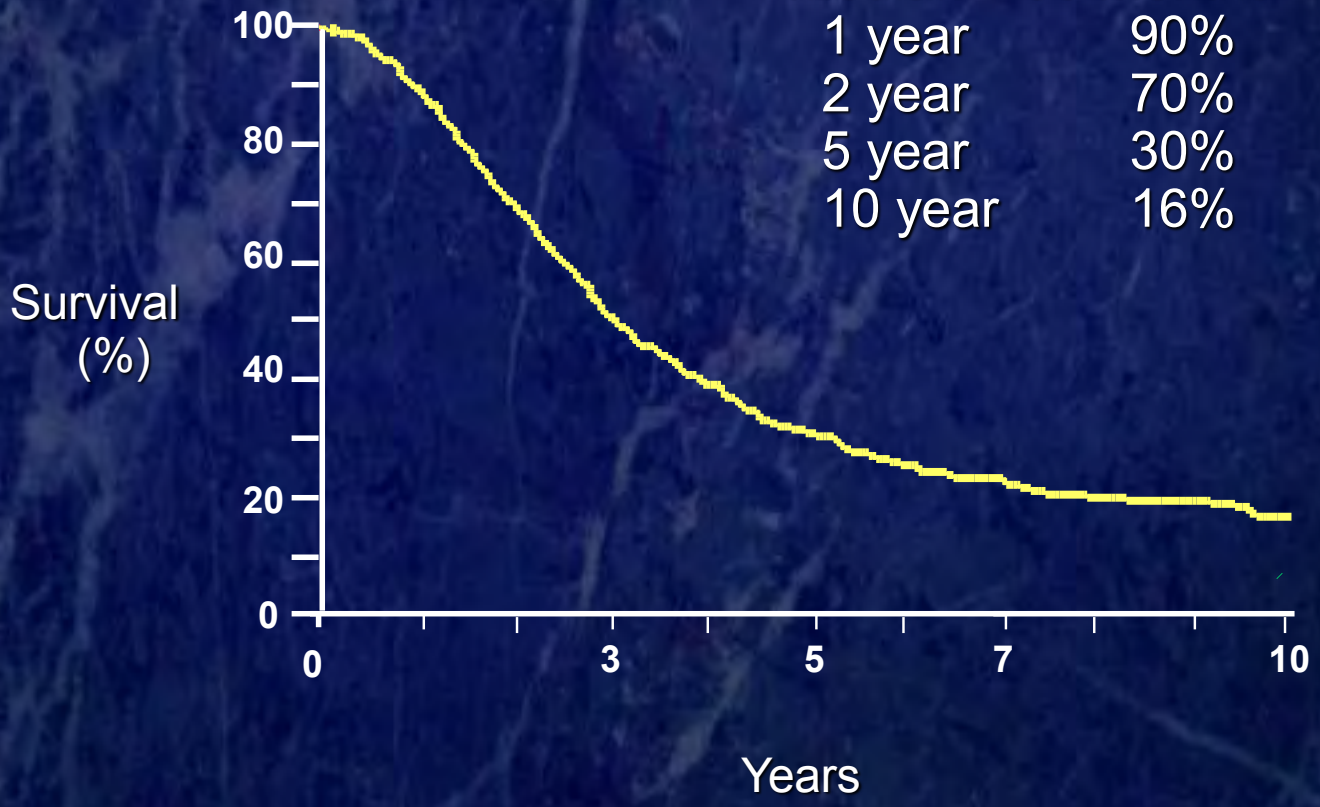
Overall Survival

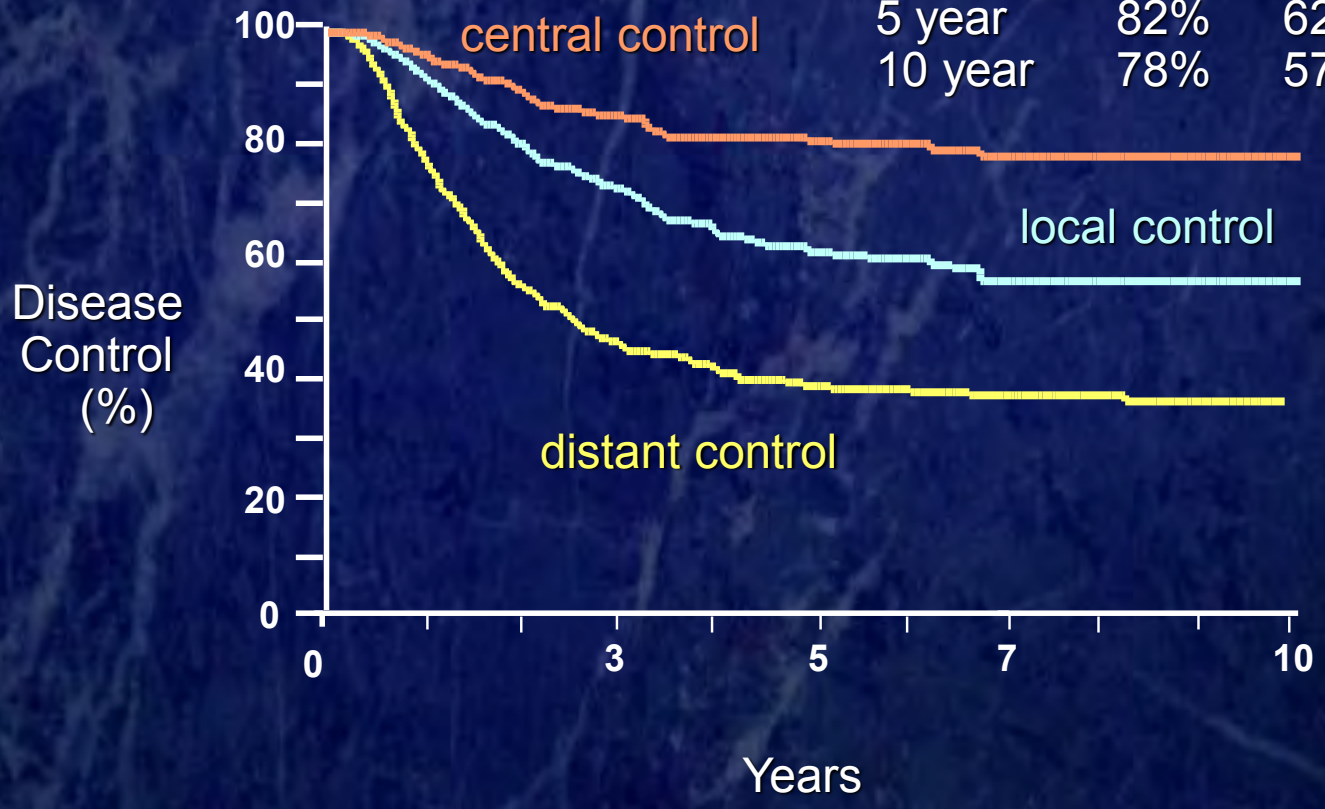
Recurrent Colorectal IOERT

Survival	
median	36 months
1 year	90%
2 year	70%
5 year	30%
10 year	16%



Disease Control - Recurrent Colorectal Ca

Endpoint	CC	LC	DC
crude	87%	74%	51%
1 year	96%	92%	78%
2 year	90%	80%	56%
5 year	82%	62%	38%
10 year	78%	57%	36%



Primary Colorectal IOERT - Mayo

Treatment or Tumor Related Toxicities

	Grade of toxicity				
	1	2	3	4	Total n = 56
Gastrointestinal					
Fistula	0	0	0	0	0
Obstruction	4%	2%	16%	2%	23%
Soft tissue					
Abscess	0	2%	9%	2%	13%
Wound	0	7%	5%	4%	16%
Neuropathy	18%	9%	5%	0	32%
Genitourinary					
Ureter	0	5%	11%	0	16%
Bladder	2%	4%	5%	0	11%

Gunderson, IJROBP 37(3):601-14, 1997.

Primary Colorectal IOERT - Mayo

Treatment or Tumor Related Toxicities

	Total n = 77	Grade 3 or 4
Gastrointestinal		
Fistula	8%	0
Obstruction	14%	10%
Soft tissue		
Abscess	3%	1%
Wound	9%	3%
Neuropathy	19%	2%
Genitourinary		
Ureter	12%	6%
Bladder	7%	1%
Sexual Dysfunction	6%	1%

Mathis Ann Surgery 248:592-598, 2008

Primary Colorectal IOERT - Mayo

IOERT Dose vs. Grade 2-3 Neuropathy

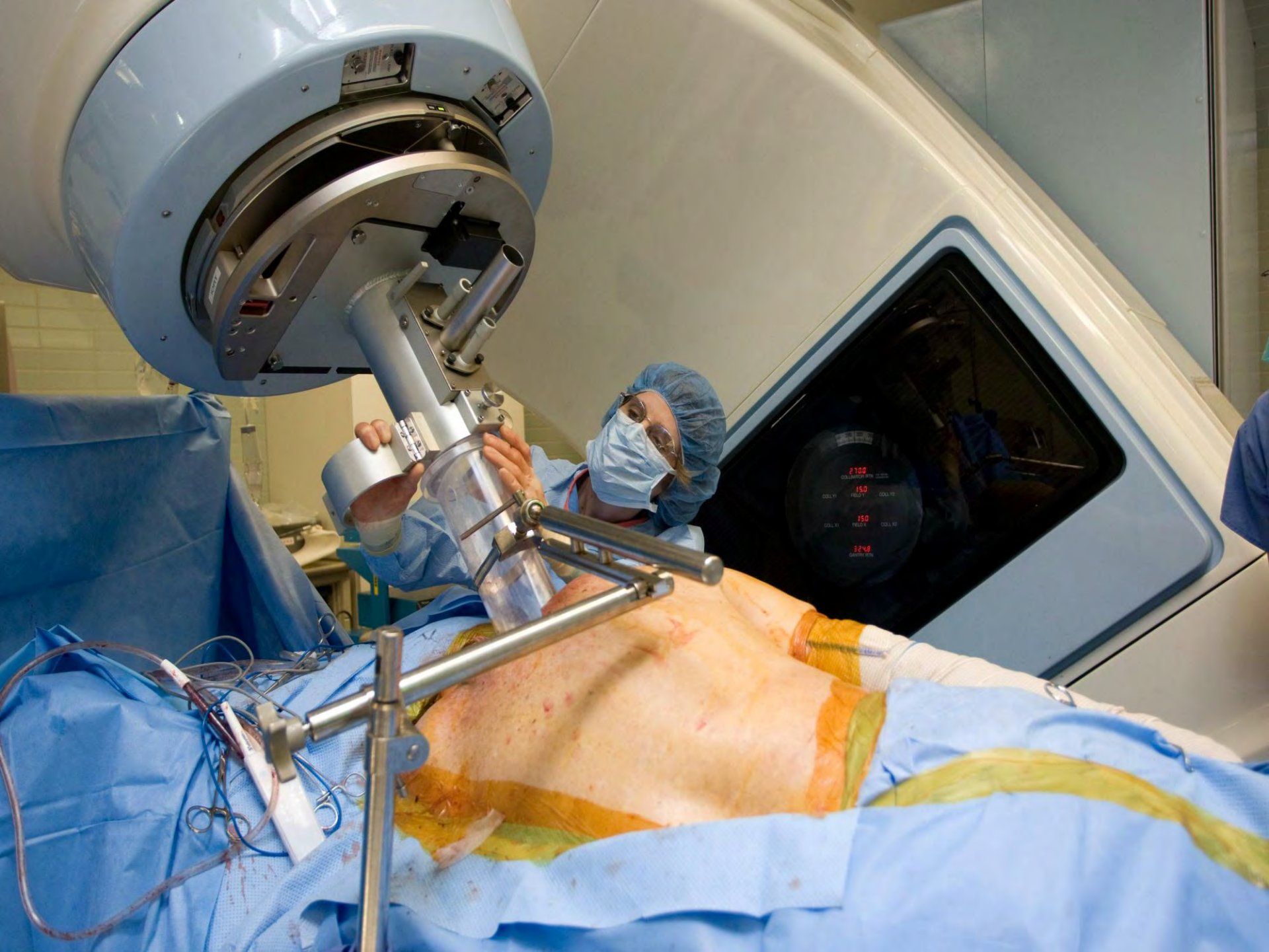
Disease presentation	IOERT dose ≤ 12.5 Gy No. (%)	IOERT dose ≥ 15 Gy No. (%)	p
Primary*	1/29 (3)	6/28 (21)	0.03
Primary + recurrent**	3/58 (5)	25/129 (19)	0.01
Recurrent, no prior EBRT	4/56 (7)	18/103 (17)	0.12

*57 IOERT fields in 55 patients, Gunderson, IJROBP 37(3):601-14, 1997.
**130 IOERT fields in 123 patients, Gunderson, Dis Colon Rectum 39:1379, 1996

IOERT Related Severe Toxicity

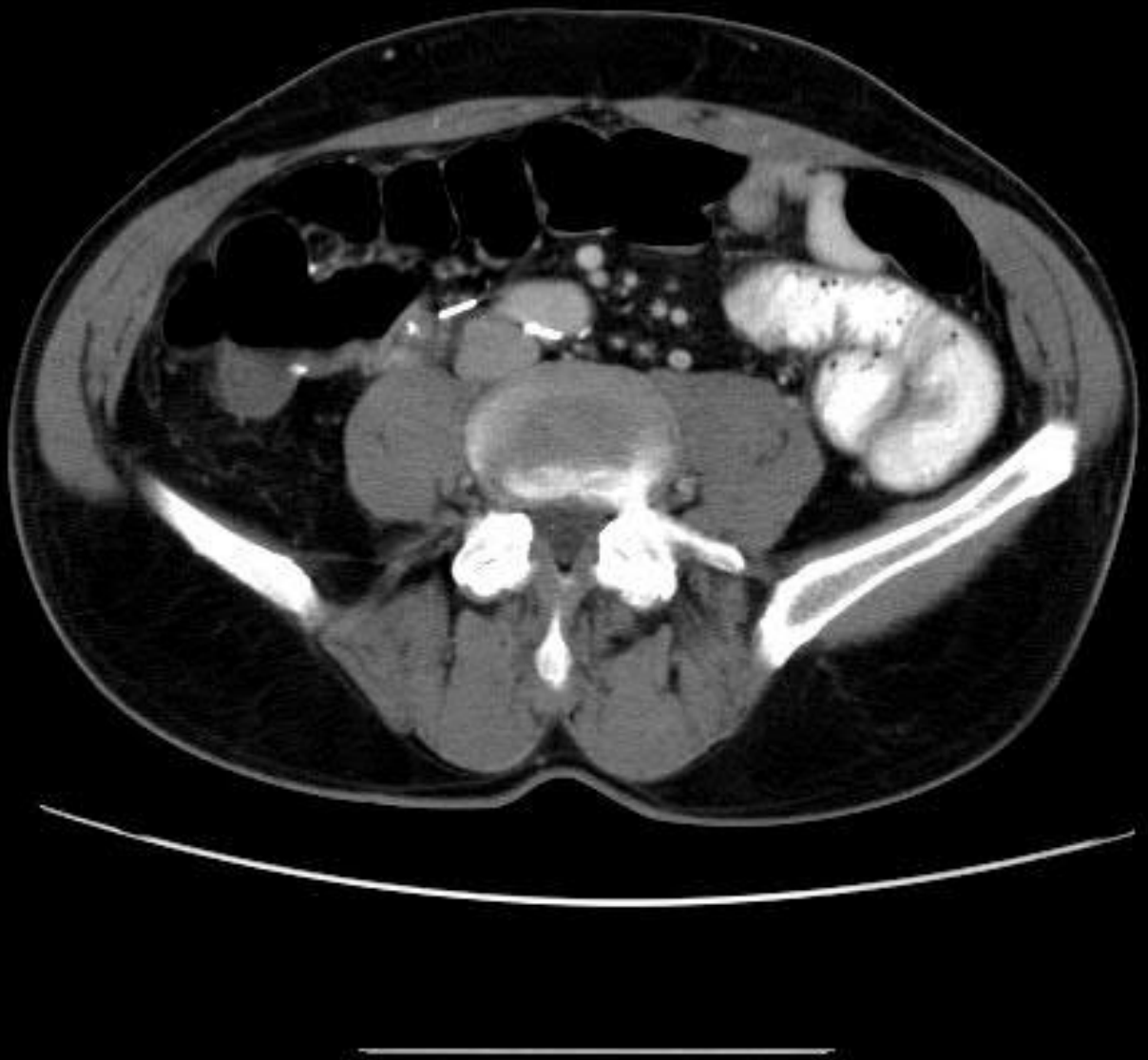
Recurrent Colorectal Cancer

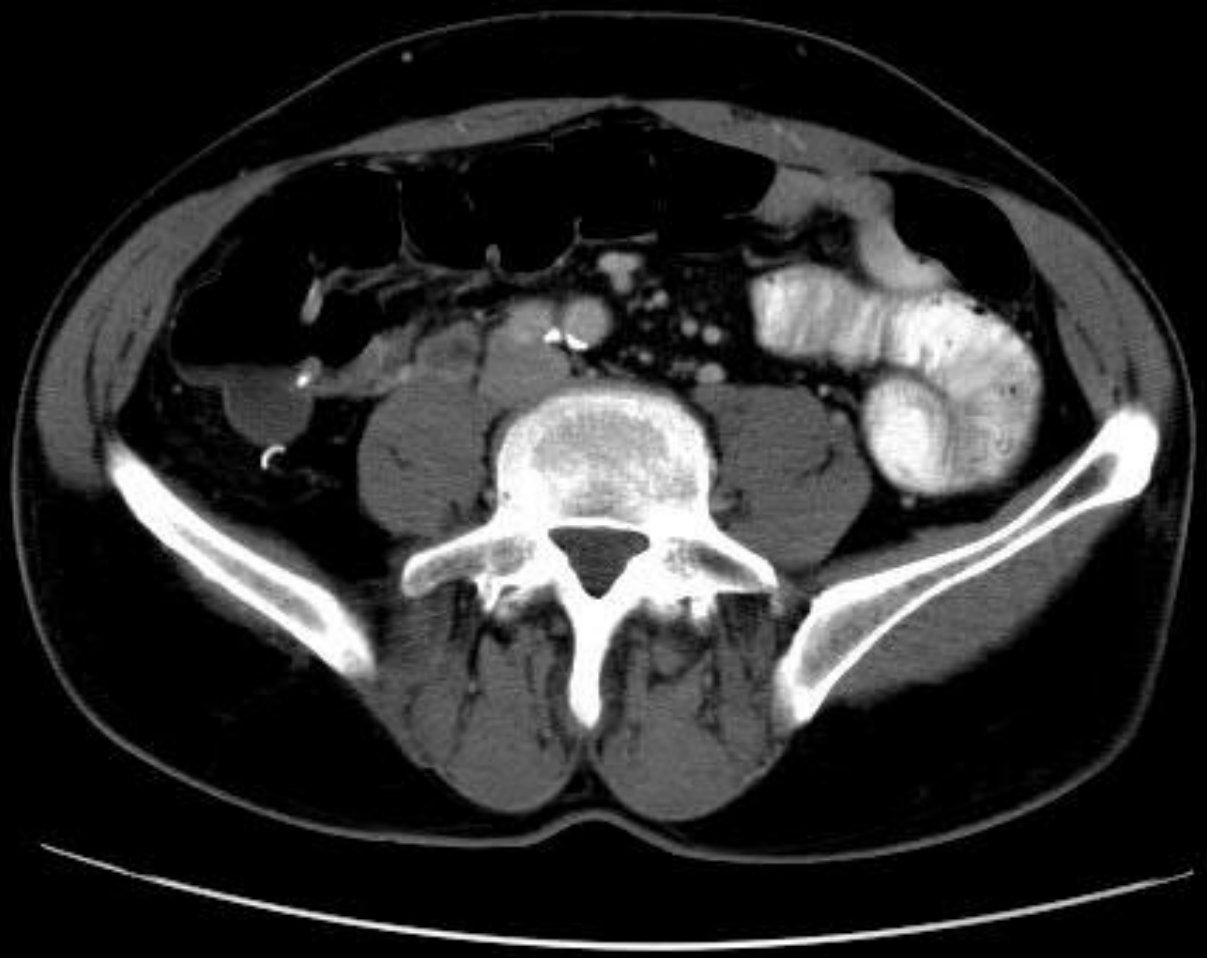
- 66 (11%) pts experienced 98 ≥ grade 3 IOERT related toxicities
  - GI fistula/obstruction 7 (1%)
  - soft tissue (abscess/fistula/fibrosis) 42 (7%)
  - neuropathy 18 (3%)
  - ureteral obstruction 18 (3%)
  - other 11 (2%)



Case #1

- 70 yom with T4N0 cecal cancer
- Resection with positive radial margin
- No adjuvant therapy
- Tumor bed relapse one year later


MAYO CLINI


MAYO CLINI

Case #1
Recurrent Colon Cancer

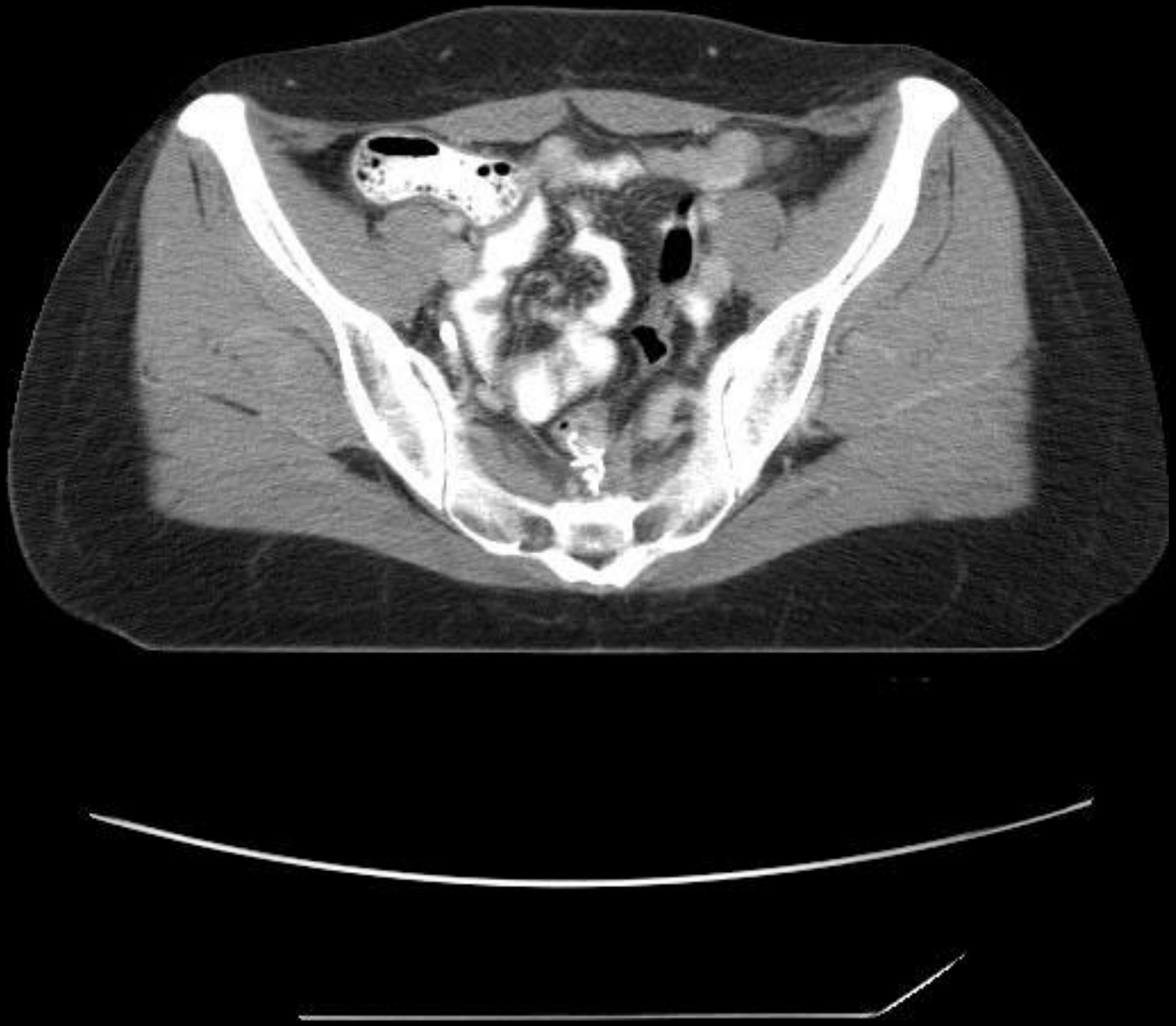
- EBRT: 5040 cGy in 28 fractions
- Concomitant 5-FU
- Resection: 3 nodular masses
  - All gross disease resected
  - IOERT 1250 cGy, 6 x 11 cm ellipse
  - Ureter in the field
- 6 month 5-FU + leucovorin

Case #1
Recurrent Colon Cancer

- NED at 8 years
- R ureteral obstruction requiring chronic stent

Case # 2
Recurrent Rectal Cancer

- 29 yof with T3N2 rectal cancer at 12 cm
- LAR, 9 of 26 nodes +, margins –
- 6 months of 5-FU + leucovorin
- 1 year later: anastomotic and presacral relapse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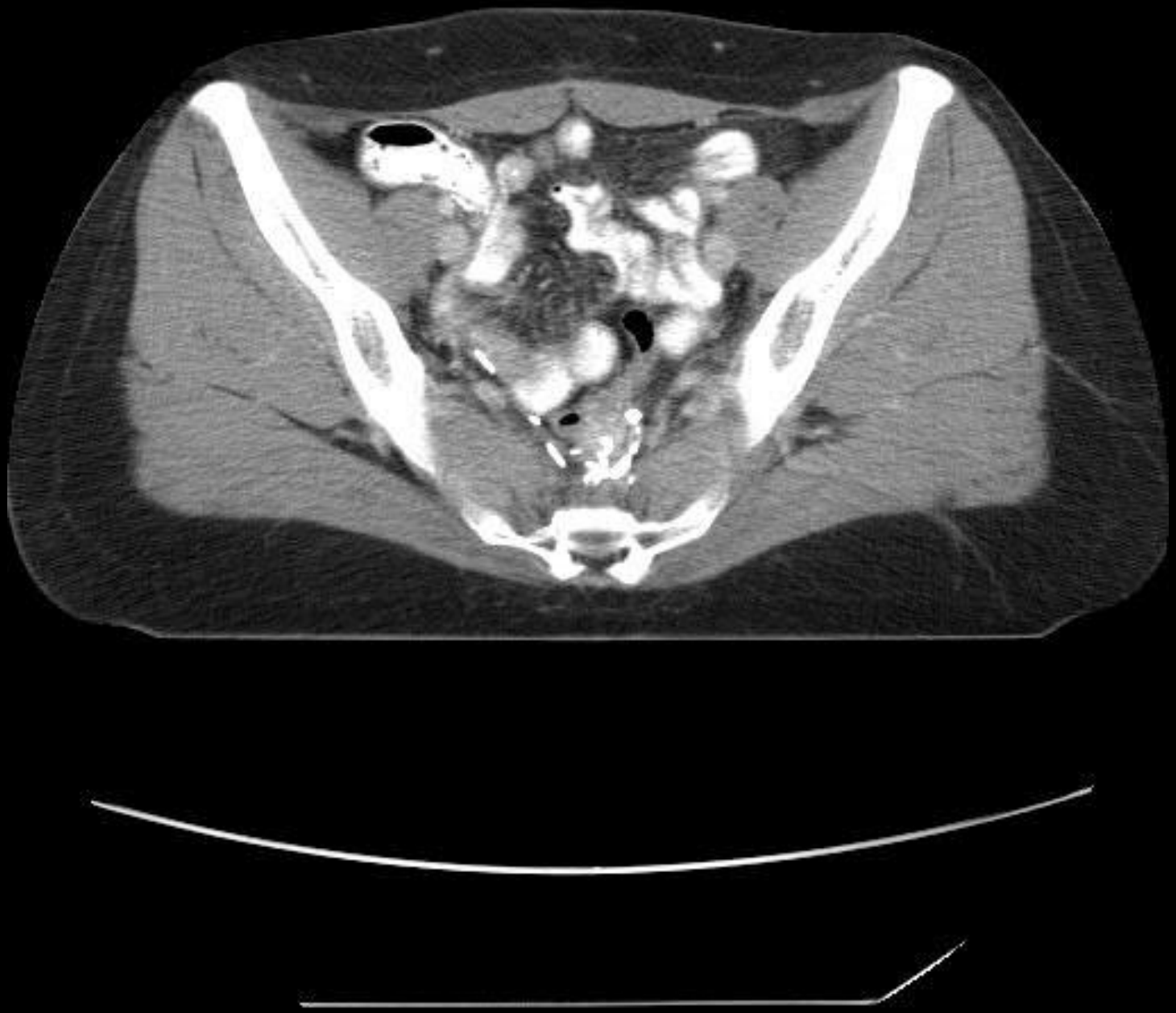

MAYO CLINI

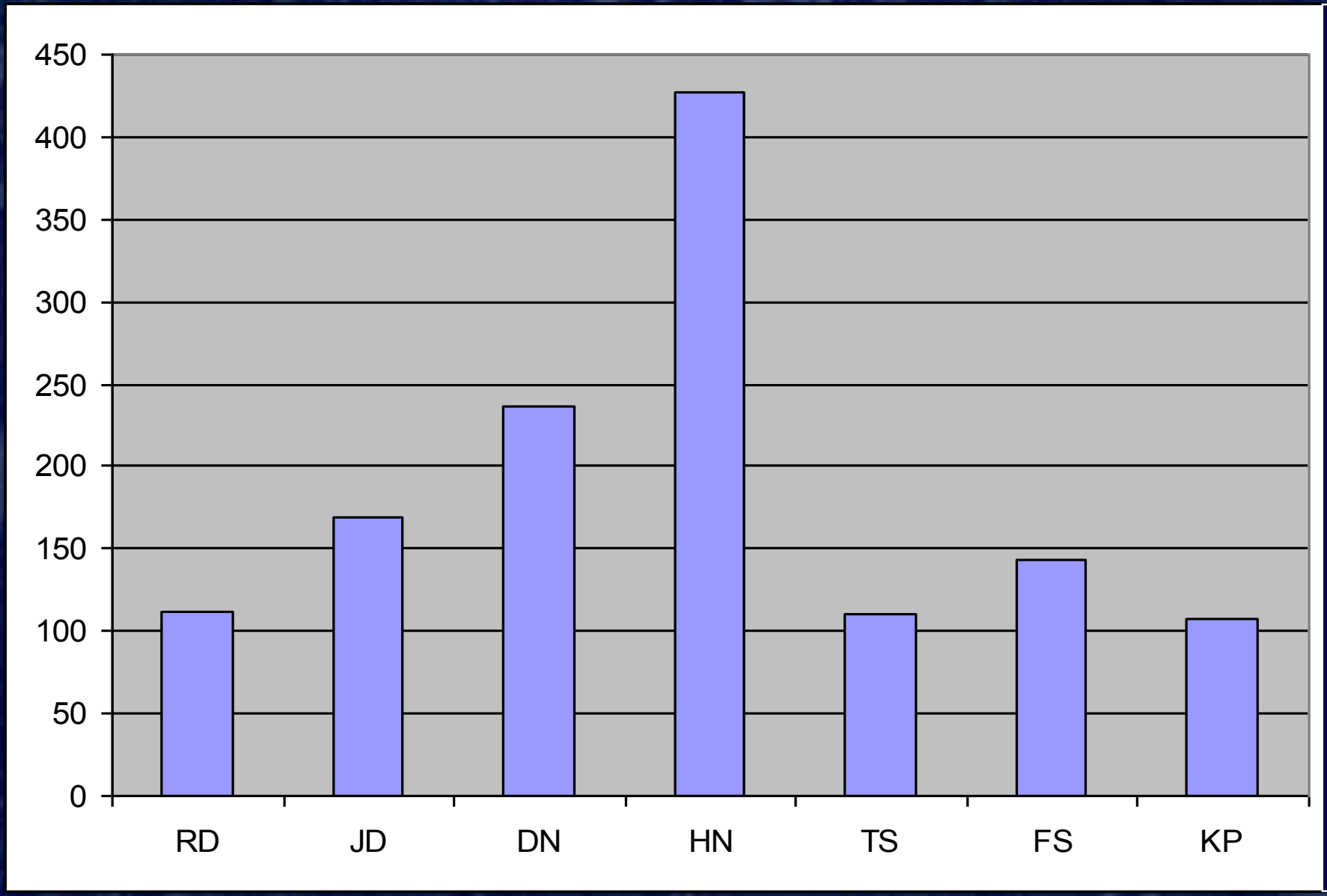
Case # 2
Recurrent Rectal Cancer

- EBRT 5040 cGy in 28 fxs with 5-FU
- Proctectomy with coloanal anastomosis
- R1 resection
- IOERT 1500 cGy, 6.5 cm cone, 9 MeV

Case # 2
Recurrent Rectal Cancer

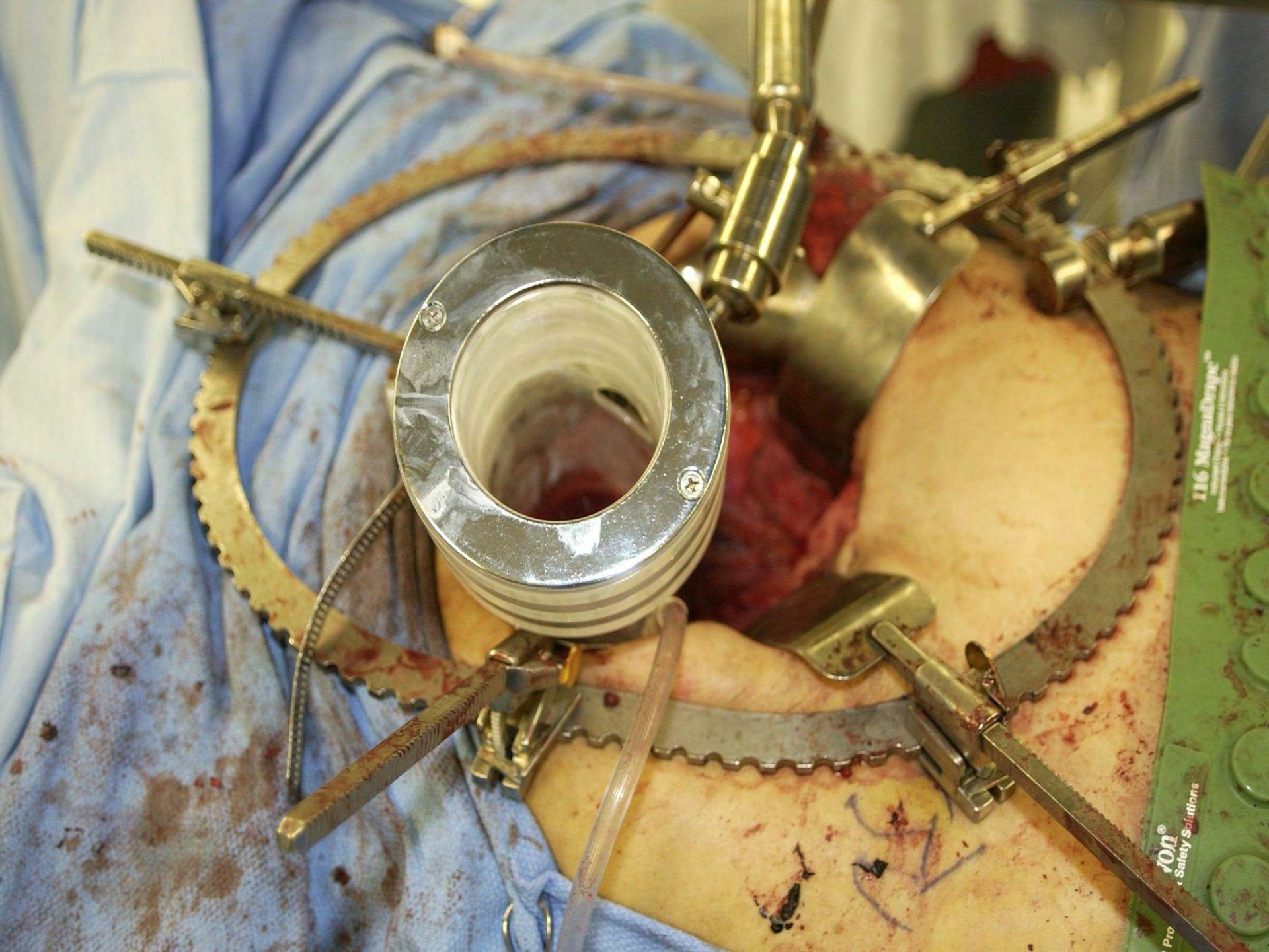
- J-pouch fistula requiring resection and permanent colostomy at year 5
- Stress urinary incontinence
- NED at 10 years

Total IOERT Cases per Surgeon



IORT for Ovarian Cancer
Case Presentation

- 1991: 35 yof TAH-BSO for endometriosis
- 1994: L oophorectomy: adenosarcoma
- 1996: recurrence R ureter, R nephrectomy
- 1997: recurrence bilateral pelvis:
  resection + IOERT 10 Gy to both sidewalls, 50.4 Gy EBRT
- 2006: NED, autotransplant kidney for 5 cm distal stricture



MAYO IOERT
Survival and Disease Control

Group	# pts	Median S	5 Year Actuarial S	CC	LC	DC
GYN	121	20 mo.	25%	73%	66%	52%
GU	49	20 mo.	29%	87%	80%	19%
RECTAL	304	34 mo.	24%	72%	50%	28%

IORT

- IORT is an effective means of dose escalation
- IORT requires an intense multi-disciplinary effort
- Long-term survival is possible with recurrent advanced cancer
- Chronic toxicities common but manageable

UNIVERSITY HOSPITAL
UNIKLINIKUM
SALZBURG
LANDESKRANKENHAUS

Long term effects of Breast Boost IOERT: the Salzburg Experience

F. Sedlmayer, C. Fussl, G. Fastner

Salzburg, Austria

UNIVERSITY HOSPITAL
UNIKLINIKUM
SALZBURG
LANDESKRANKENHAUS

Long term effects of Breast Boost IOERT: the Salzburg Experience

Cosmesis

Secondary Tumors

F. Sedlmayer, C. Fussl, G. Fastner

Salzburg, Austria

Cosmetic Evaluation:
265 Pat. Med 5a post IOERT (36-96 Mo)

5-Points-Scoring System Van Limbergen E 1989 & Harris JR 1979

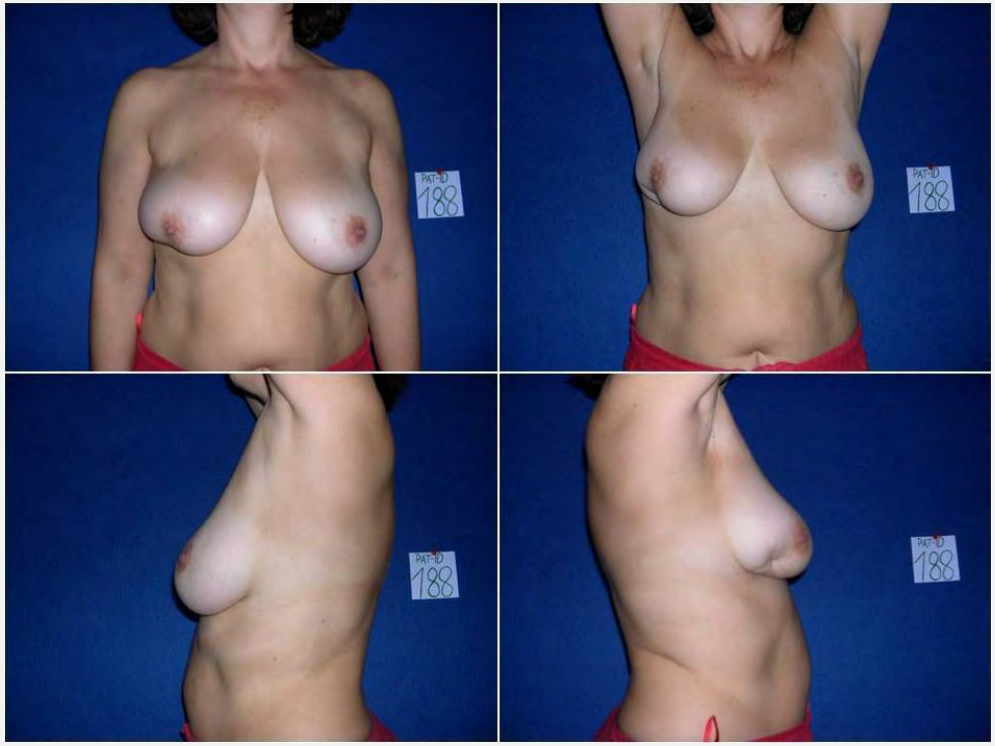
E_0: Excellent

E_1: Good

E_2: Moderate

E_3: bad

E_4: complication



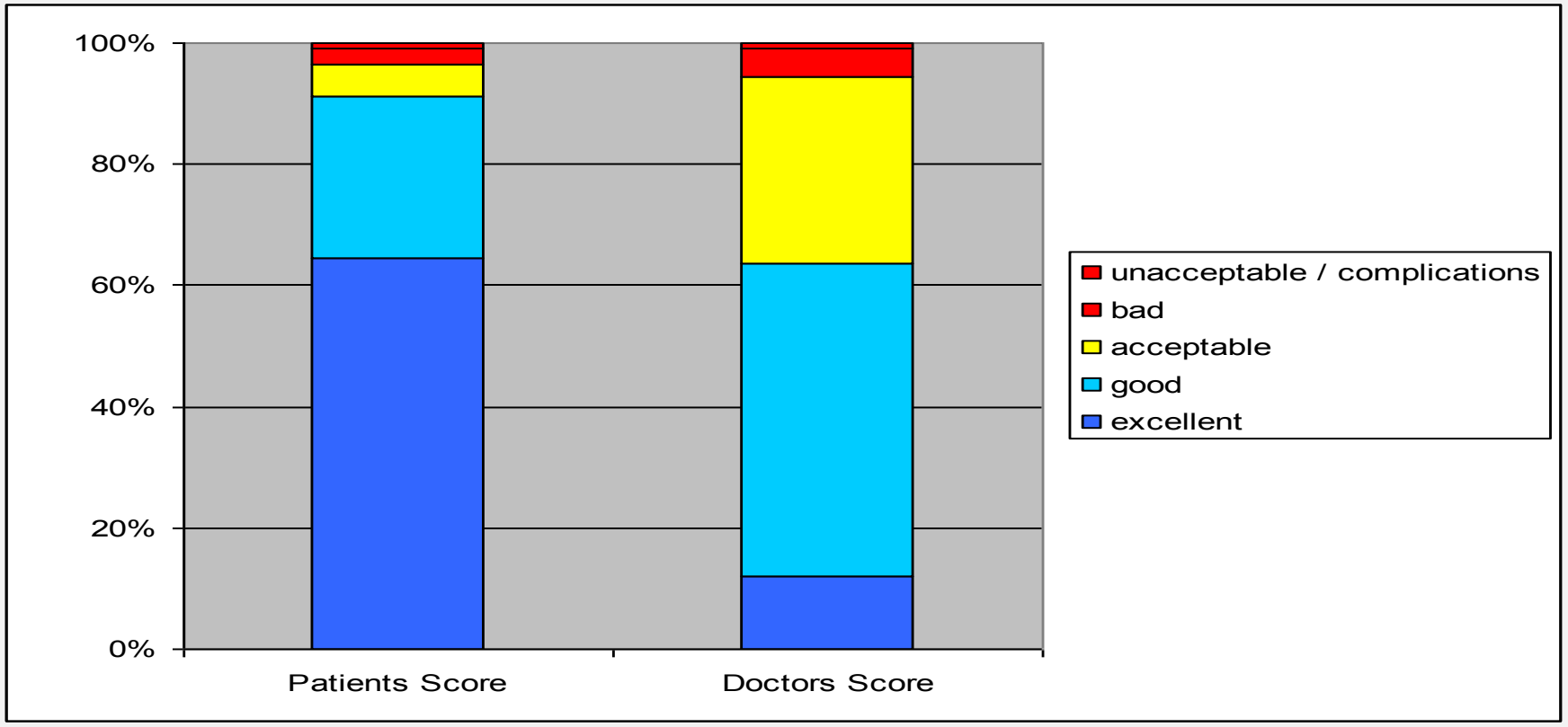
E_0-E_1: satisfactory

E_0-E_2: acceptable

E_3-E_4: Unacceptable

Double evaluation : Patient (subjective) , Doctors (Objective)

Results (Sbg): 265 pts. med. 5 years post IOERT (36-96mths)



Patients: 93% excellent/good

Physicians: 96 % acceptable

No Teleangiectasia !!!

Does Boost IOERT affect long-term cosmetic outcome?

- **Age** and **applicator diameter** (rather as surrogate for length of surgical scar) showed **significant negative impact**
- **No** impact of
  - **tumor-stage,**
  - **grading,**
  - **electron-energy**
  - **boost-volume**

No negative impact of any factors attributable to IOERT

Secondary cancers (SC)

- **Long term analysis of 770 Pats.**
- **Median FUP : 121 months**
- **Med. Age at diagnosis: 58 y (22 – 89)**

Secondary cancers (SC)

Tumor site	patients
breast	**41**
gastrointestinal	13
gynecological	11
hematological	6
brain	3
lung	5
skin	9
urological	7
head and neck	2
combinations	5
ns	8

Total:

110 SC = 14,2%

- **Contralat. Breast: 5,3%**
  (annual rate 0.5%)
- **Other sites: 8,9%**
  (annual rate 0.87 %)
- **Lung: 0,65%**

Mid - long term sequelae following Boost IOERT

- **Excellent cosmesis after 5 y, no negative impact of IOERT related factors**
  - ***? superior to external boost in comparison to reports after high-dose EBRT boosts*** *[Poortmans Radiother Oncol 2009]* ***or BT***
- **No excess of secondary cancers after 10 years in comparable age groups treated without IOERT**
- **No information on cardiovascular sequelae**


بسم الله الرحمن الرحیم

INTRA OPERATIVE RADIATION THERAPY
RADIO BIOLOGICAL ASPECT

9th International ISIORT Conference

2016

Novara, Italy

24 & 25 JUNE

Professor Mohammad E Akbari

Surgical Oncologist

Cancer Research Center

SBUMS, Tehran Iran, crc@sbmu.ac.ir

❖PRINCIPLES OF RADIATION THERAPY

MAX DOSE IRRADIATED
SUITABLE SITE IRRADIATED
LOWER FRACTIONATION
NEIGHBOR SAFETY
LESS COMPLICATION

CONVENTIONAL/IORT COMPARISON

Conventional(EBRT)

_ Low Dose

_ Fractionated

_ Tissue Tolerance

_ Delay to Treat

_ Time and frequencies

_ Site questionable irradiation

_ …

IORT

Most tolerable Dose

Exactly on Time

Exactly on Site

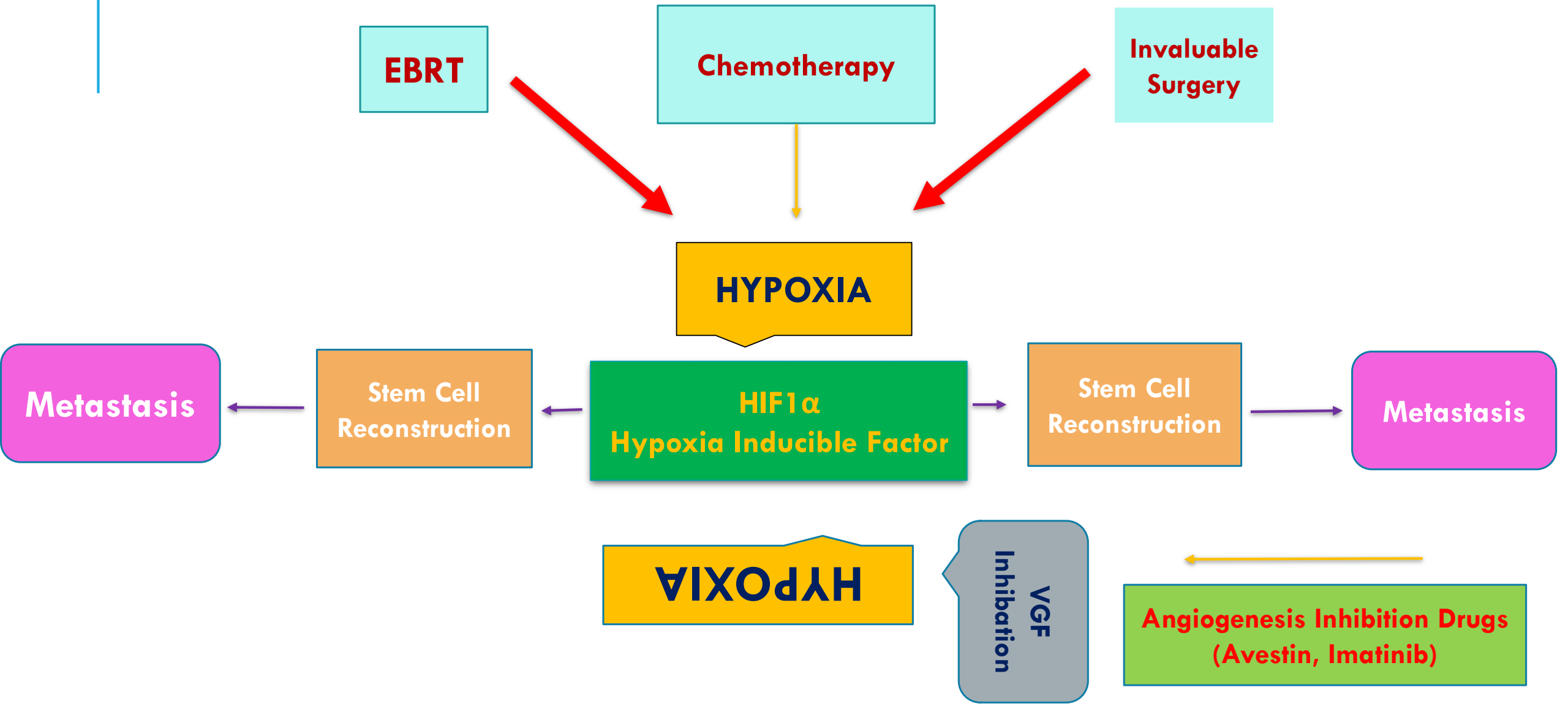
Neighbor Safety

Economically profitable

Very low complication(s)

…

ARE WE DO THE BEST FOR OUR PATIENTS?



More

Power

Less

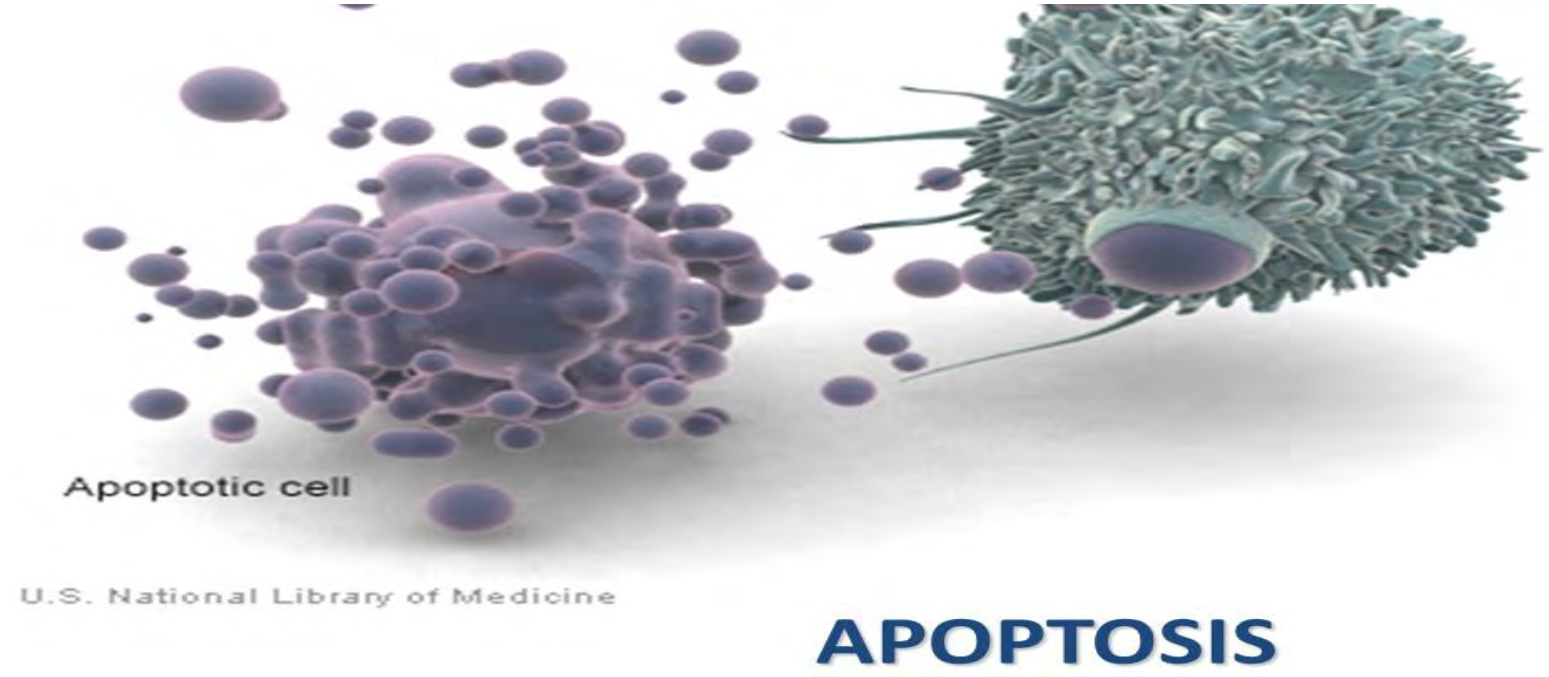
Time

More Effectiveness?

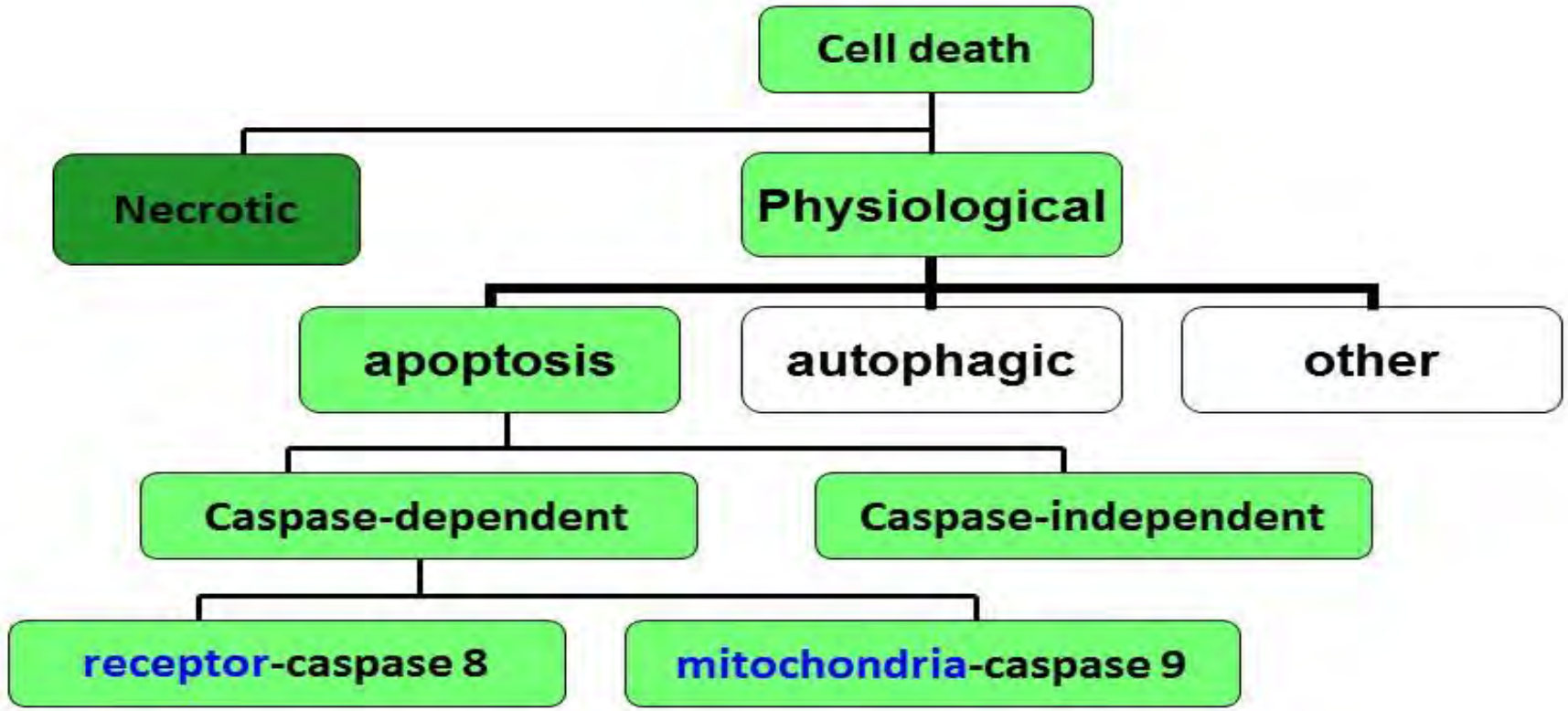
CONTEXT OF HYPOTHESIS OF IORT EFFECT

- Since more than 1000 years now it has been hypothesized that tumors act as wounds that don't heal (Avecina, 1000 & nowadays Dvorak NEJM, 1986)
- Lesson learned that tumor development and progression is the result of a complex interaction between cancer cells (cancer stem cell) and local microenvironment
- A normal microenvironment preserve the tissue architecture even in the presence of predisposed cells thereby preventing tumor progression
- Vice versa an aberrant microenvironment can promote the mutated cells to form tumors
- Epigenetic role in producing and transferring microenvironment?

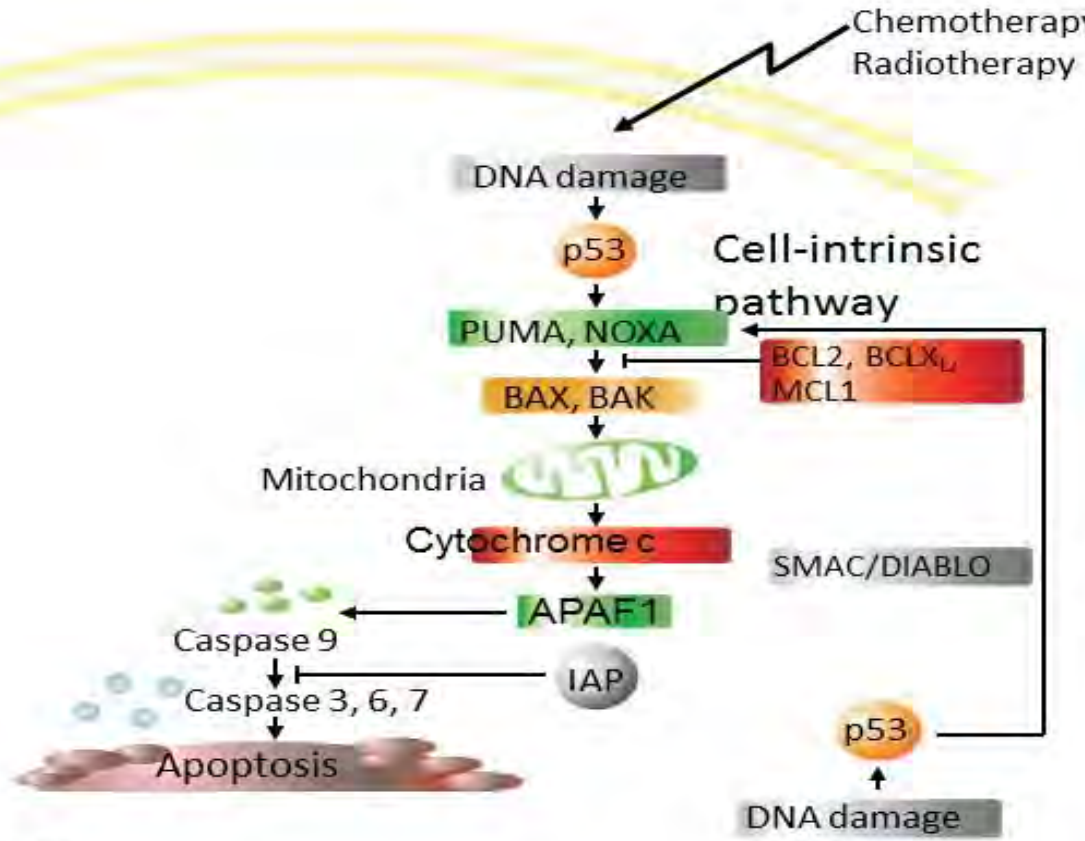
RADIOBIOLOGICAL EFFECT OF IORT



Classification of cell death



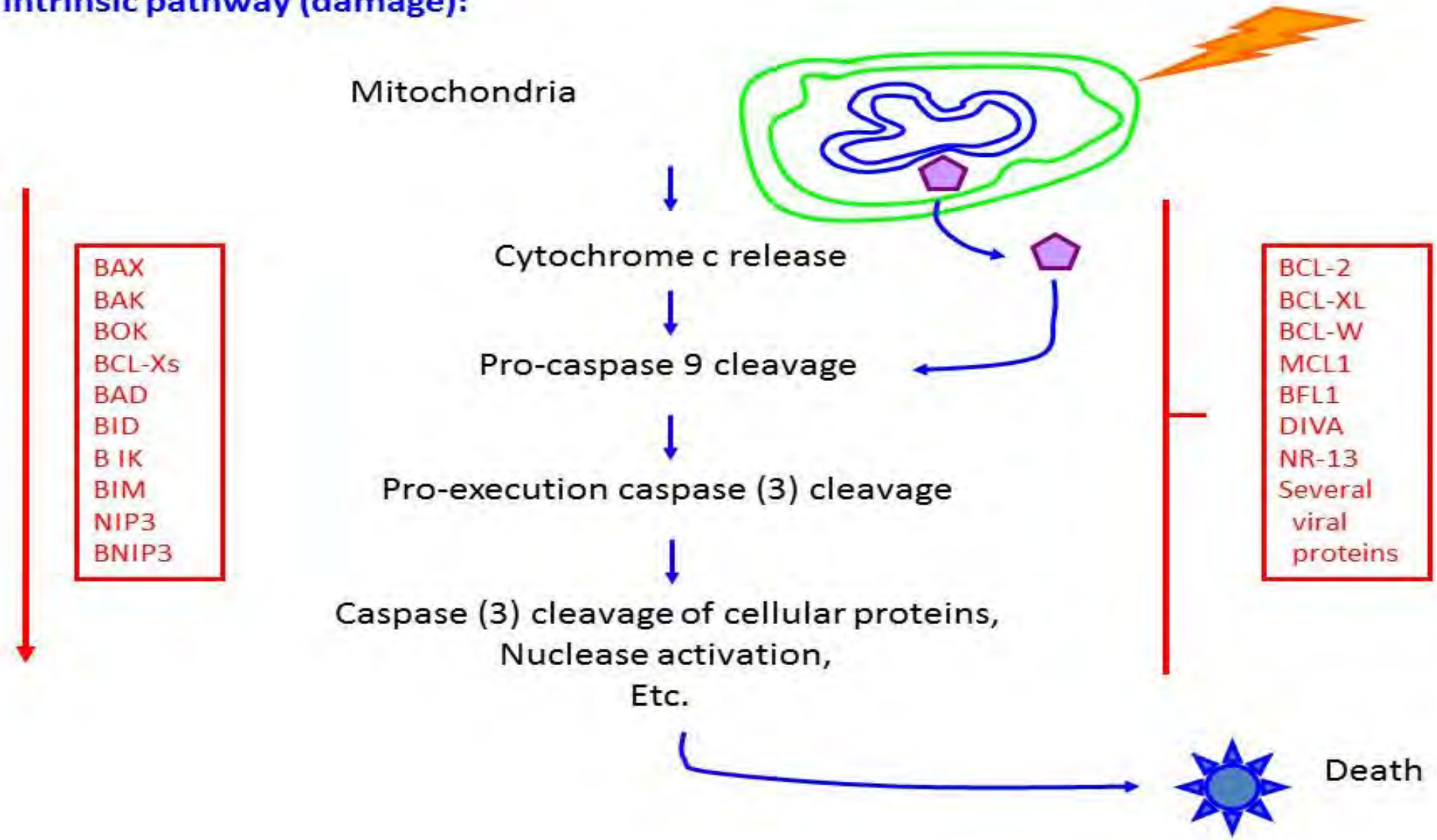
The Intrinsic Apoptosis Pathway



Adapted from Ashkenazi A. Nat Rev Cancer 2002;2:420–430.
APAF1, apoptotic protease activating factor-1; BAK, BCL2 homologous antagonist/killer; BAX, BCL2-associated protein; BCL2, B-cell chronic lymphocytic leukemia/lymphoma 2; BCLX$_L$, BCL2-like 1; IAP, inhibitor of apoptosis protein; MCL1, myeloid cell leukemia sequence 1 (BCL2-related); PUMA, p53-upregulated modulator of apoptosis; SMAC/DIABLO: second mitochondria-derived activator of caspase/direct IAP binding protein with low pI.

APOPTOSIS: control

Intrinsic pathway (damage):



The Intrinsic Apoptosis Pathway

- The intrinsic pathway is triggered by the p53 tumor-suppressor in response to DNA damage and other types of severe cell stress
- Conventional anticancer therapies, such as chemotherapy and radiotherapy, activate this pathway via p53
- p53 activates the intrinsic pathway through transcriptional upregulation of pro-apoptotic members of the BCL2 family of proteins such as PUMA and BAX
- BAX causes the release of cytochrome *c* from the mitochondria, which together with the adaptor APAF1, activate the initiator caspase 9
- Caspase 9 activates the effector caspases 3, 6, and 7, which are responsible for destroying critical components of the cell, and inducing apoptosis
- p53 is inactivated by mutations in more than half of human cancers

Methods of Apoptosis Analysis

- Molecular expression and caspase mediated cleavage
- Membrane associated changes (Annexin V and Ceramide-sphingomyelin pathways)
- Nuclear morphology (condensation, apoptotic bodies, endonuclease activity)
- Analysis: IHC, flow cytometry, DNA electrophoresis, cell staining, TUNEL assay

- **Proteomics**

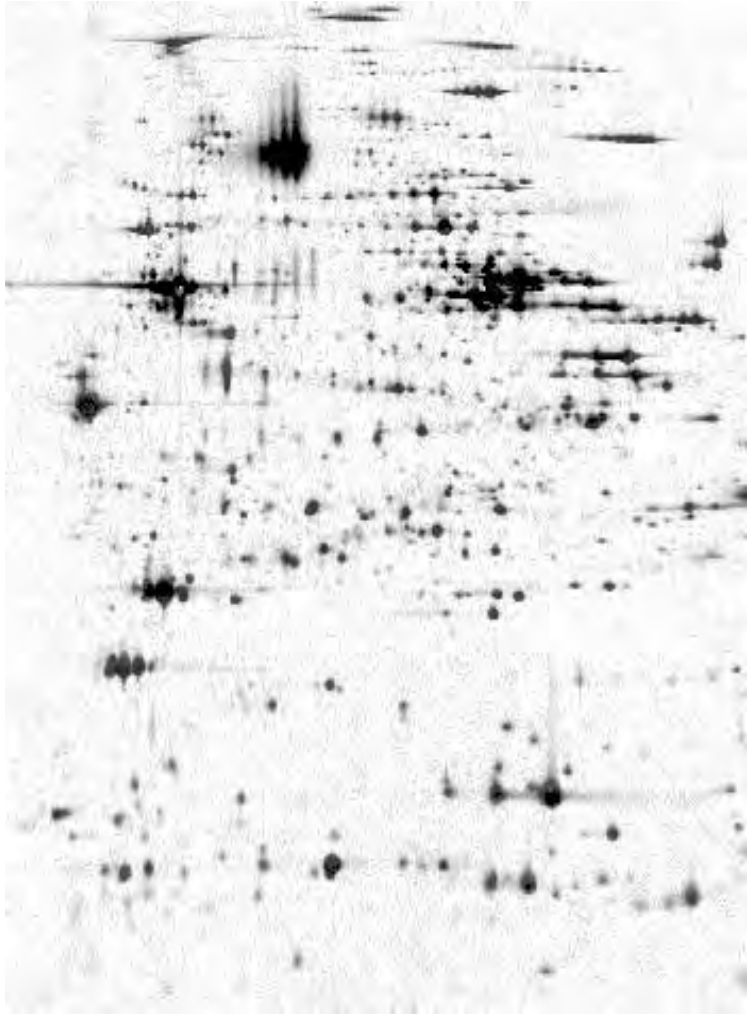
SO HOW DOES IT WORK?

Proteins are resolved, sometimes on a massive scale. Protein separation can be performed using 2-D gel electrophoresis,

- `usually separates proteins first by ***isoelectric point*** and then by ***molecular weight***.

Once proteins are separated and quantified, they are identified

Individual spots are cut out of the gel and cleaved into peptides with proteolytic enzymes



OUR RESEARCH DESIGNEE

- Wound Fluid Proteomics Investigation
- Tissue Proteomics Investigation

❑ Sampling (Tissue Proteomics Investigation):

- collected following breast-conserving surgery in 1 patients whom had received radical IORT with LINAC (21 Gray dose):

✓ Normal tissue Before IORT

✓ Normal tissue After IORT

✓ Margin tissue Before IORT

✓ Margin tissue After IORT

✓ Tumor tissue

WOUND FLUID

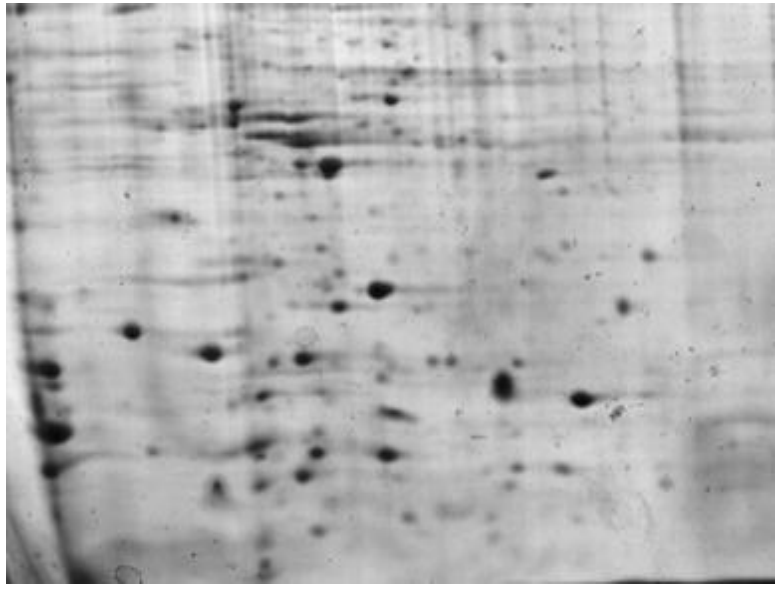
24 hours after surgery from:

Irradiated and non Irradiated cases

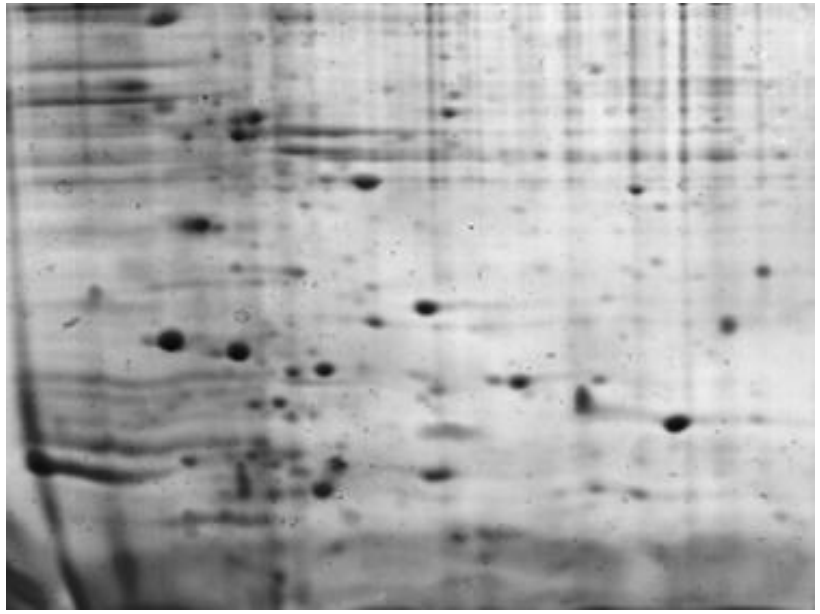
RESULT

- 562 Proteins spot was detected in all gels electrophorese
- 560 proteins spot was the same in two gel electrophorese (normal tissue before and normal tissue after IORT)
- 558 proteins spot was the same in two gel electrophorese (margin tissue before IORT and Tumor)
- 543 proteins spot was the same in two gel electrophorese (margin tissue before and after IORT)
- ✓12 proteins spot were increased after IORT in Margin tumor bed compared to the same tissue before IORT
- ✓7 proteins spot were decreased after IORT in Margin tumor bed compared to the same tissue before IORT

MARGIN TISSUE BEFORE IORT AND TUMOR (NO SIGNIFICANCE)

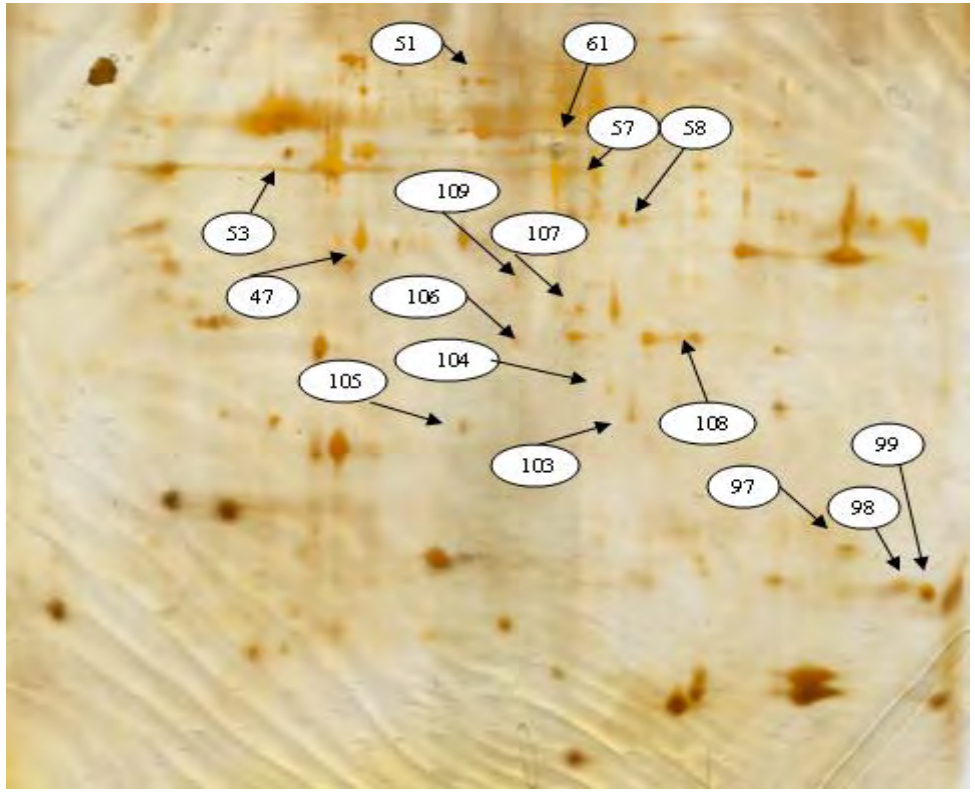


Before IORT

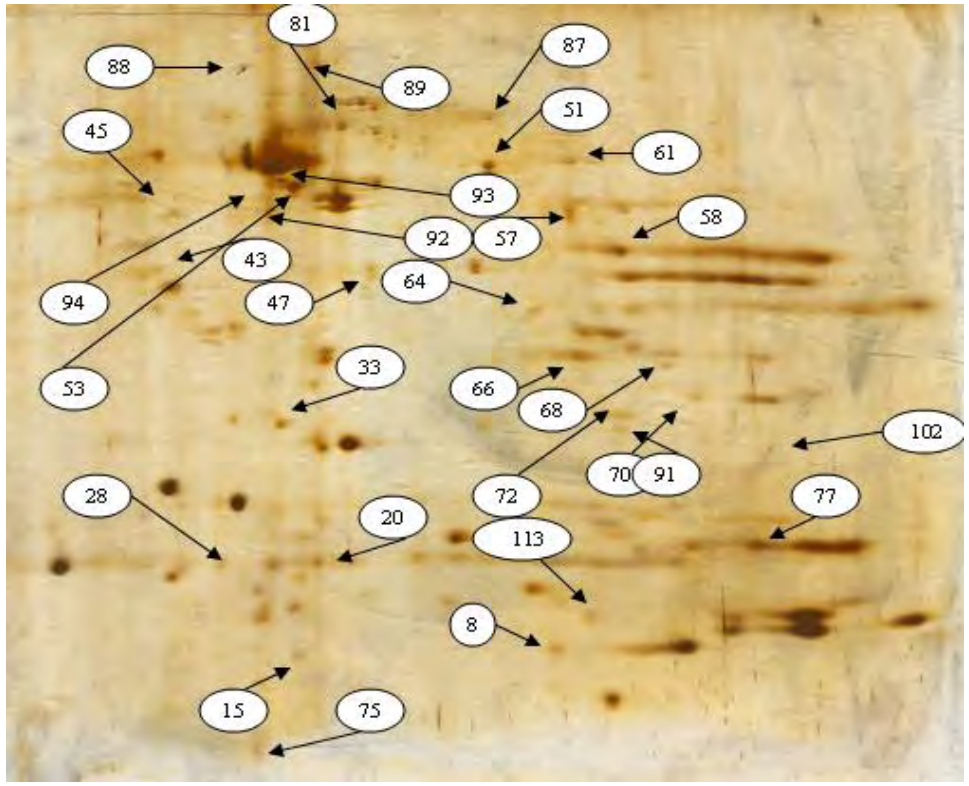


tumor

MARGIN TISSUE BEFORE AND AFTER IORT



After IORT



Before IORT

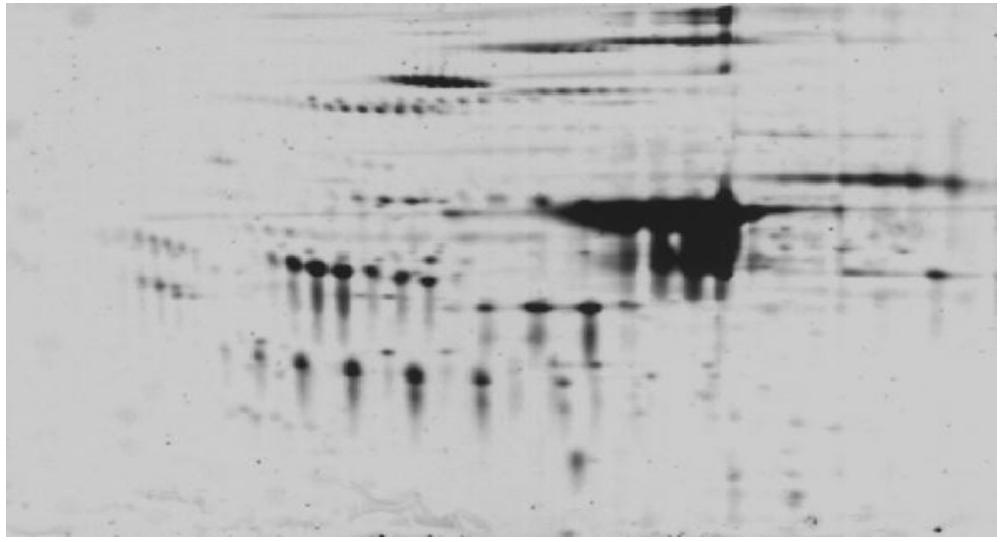
REPORT

ID Number	gray scale C	gray scale E	ID Number	gray scale C	gray scale E	
8	28005	----------	92	36305	----------	
15	26534	----------	93	47771	----------	
20	31421	----------	96	31141	----------	
28	26276	----------	102	29852	----------	
33	25222	----------	113	32521	----------	
43	29381	----------	97	----------	32755	
45	27816	----------	98	----------	31234	
64	27456	----------	99	----------	37992	
66	34270	----------	103	----------	28019	
68	26627	----------	104	----------	24217	
70	25015	----------	105	----------	26874	
72	26994	----------	106	----------	26232	
75	26110	----------	107	----------	29017	
77	41962	----------	108	----------	28088	
81	38258	----------	109	----------	29230	
87	29987	----------	47	21635	31529	
88	27642	----------	51	32362	41307	
89	36336	----------	57	32681	41038	
90	22323	----------	61	31780	42861	
91	27180	----------	53	49637	34314	
94	47056	----------	58	33636	24897	

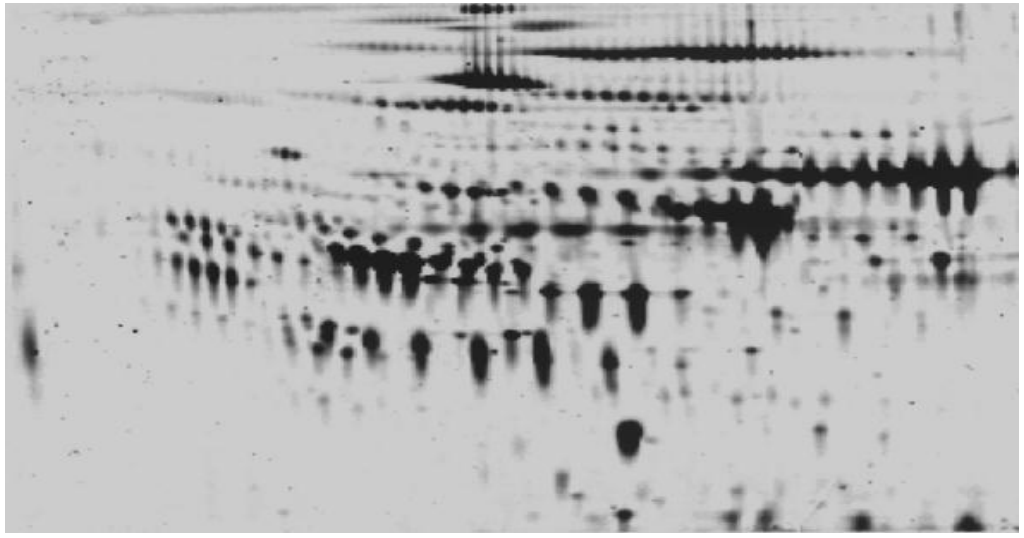
PROTEOMIC PROFILE

WOUND FLUIDS (WF), COLLECTED OVER 24 H FOLLOWING BREAST-CONSERVING SURGERY IN PATIENTS SURGICAL, THE LEFT GEL HAD RECEIVED ADDITIONAL *IORT* , IMMEDIATELY AFTER THE SURGICAL EXCISION AND THE RIGHT GEL IS CONTROL GROPE.

- 178 Proteins spot was detected in two gel electrophorese
- ✓144 proteins spot was the same in two gel electrophorese
- ✓28proteins spot were increased in sample vs. control
- ✓6 proteins spot were decreased in sample vs. control

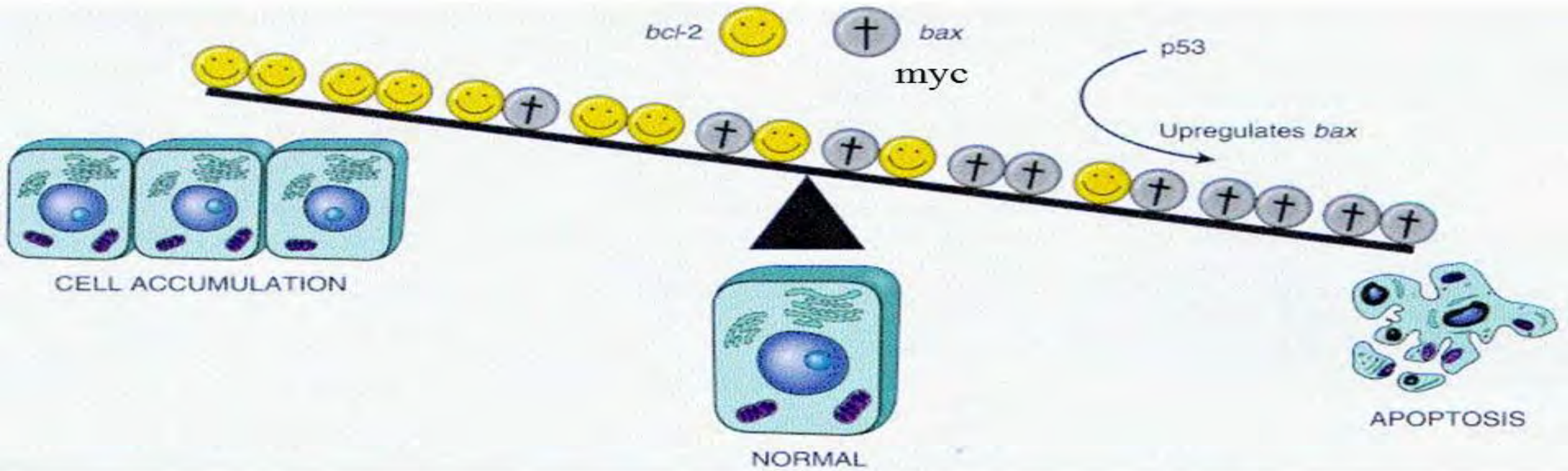


Sample



Control

The Apoptotic Balance in Normal Cell Hierarchies

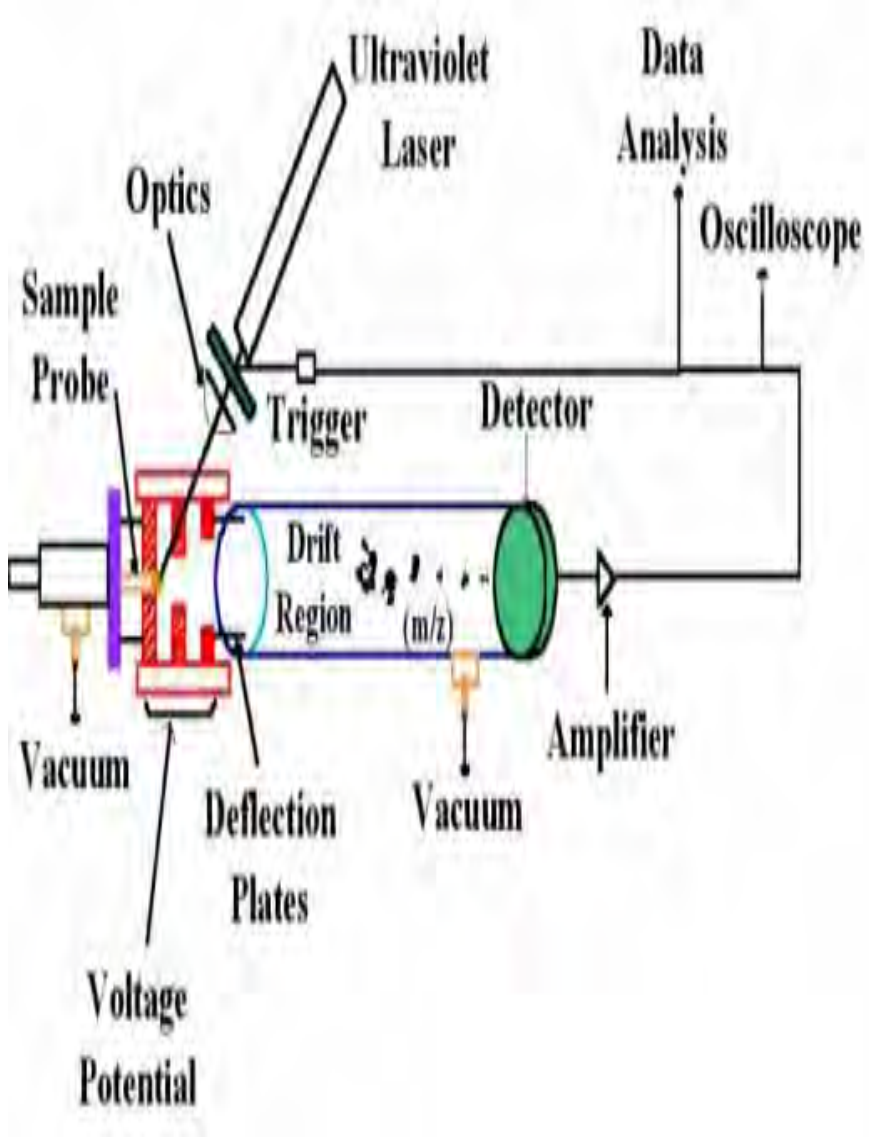


If Abnormal Accumulation of Mutant Cells due to loss Of Apoptotic Control (ie, increased bcl-2 or mutant p53 or loss of myc control) = Tumour Formation

SO HOW DOES IT WORK?

In a MALDI-TOF mass spectrometer, the ions can also be deflected with an electrostatic reflector that also focuses the ion beam.

Thus, the masses of the ions reaching the second detector can be determined with high precision and these masses can reveal the exact chemical compositions of the peptides, ***and therefore their identities!***



TARGETED INTRAOPERATIVE RADIOTHERAPY (TARGIT), TRAIL

Targeted Intraoperative Radiotherapy Impairs the Stimulation of Breast Cancer Cell Proliferation and Invasion Caused by Surgical Wounding

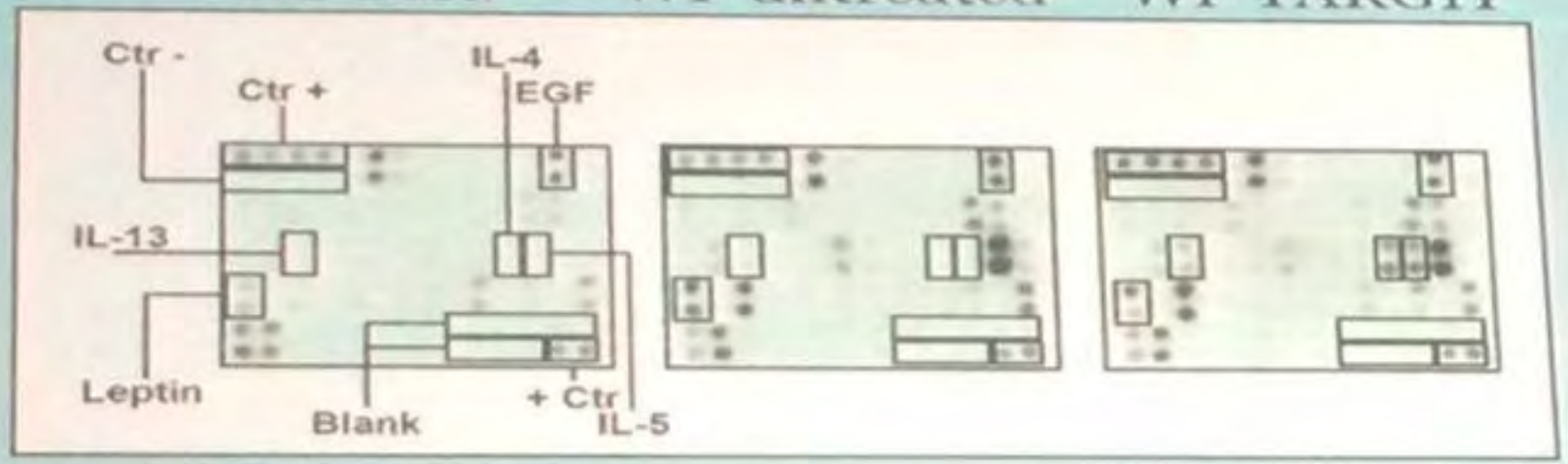
Experimental Design:

- studied normal and mammary carcinoma cell growth and motility are affected by surgical wound fluids (WF), collected over 24 h following breast-conserving surgery in patients whom had received additional *TAR*Geted *I*ntraoperative radio*T*herapy (TARGIT) immediately after the surgical excision.
- The ***proteomic profile*** of the WF and their effects on the activation of intracellular signal transduction pathways of breast cancer cells were also analyzed.

Results:

- WF stimulated proliferation, migration, and invasion of breast cancer cell lines.
- **The stimulatory effect was almost completely abrogated when fluids from TARGIT-treated patients were used. These fluids displayed altered expression of several cytokines and failed to properly stimulate the activation of some intracellular signal transduction pathways, when compared with fluids harvested from untreated patients.**

IORT WITH INTRABEAM ALTERS THE PROTEOMIC PROFILE OF WOUND FLUID



✓ **Does IORT Radiotherapy affect tumor growth independently from cell killing?**

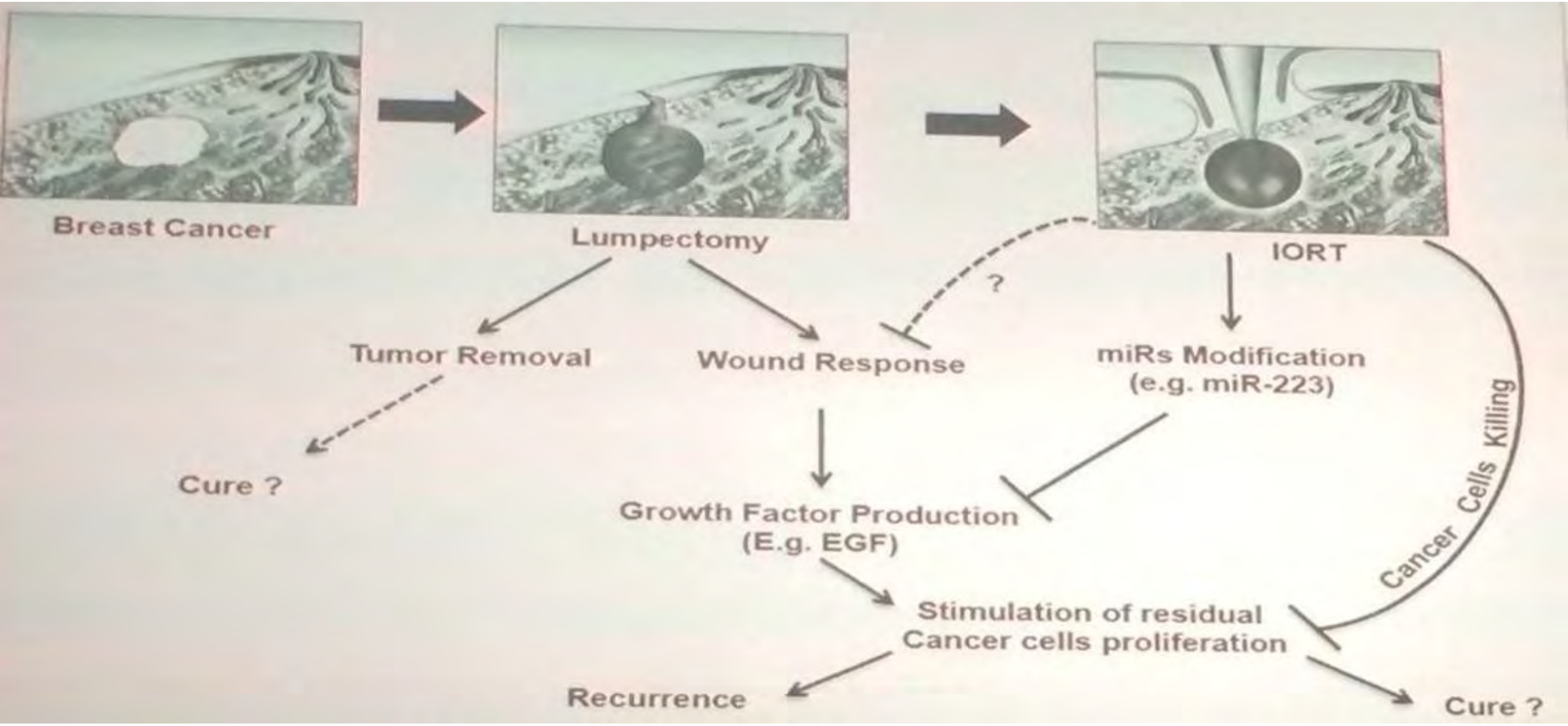
✓ Which are the molecular mechanisms involved in the response to IORT?

Belletti, et al. Cin. Cancer Res. 2008 14: 1325

OTHERS METHODS IN FUTURE…

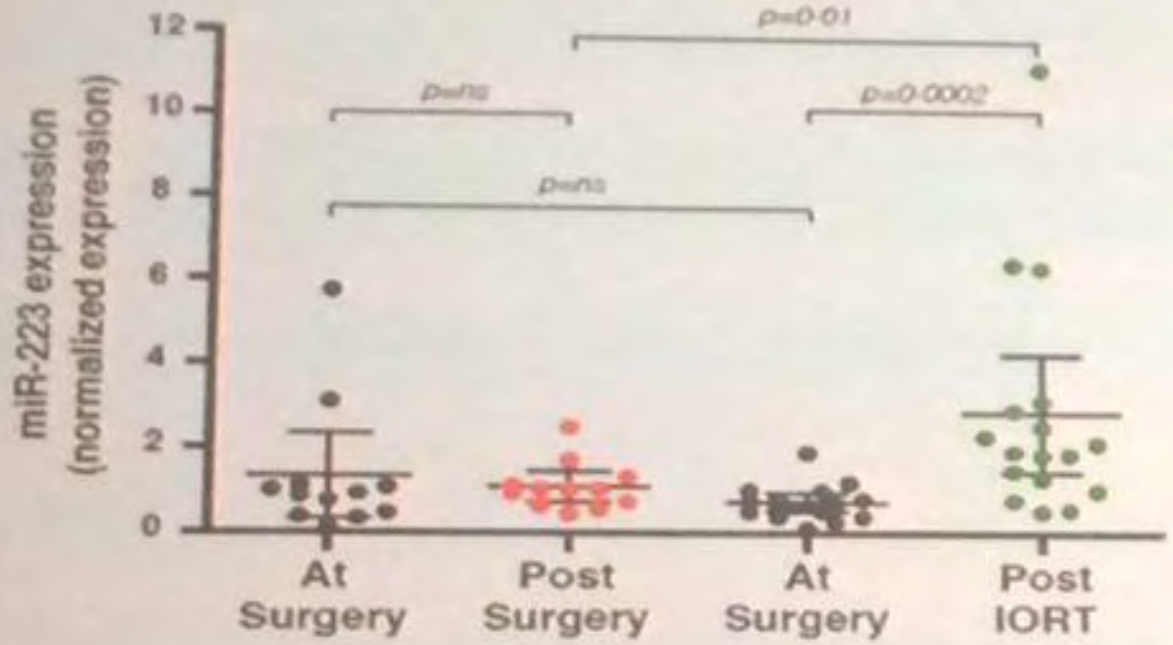
- ELISA
- Western blot
- Primary cell culture
- Flow cytometry
- TUNEL assay

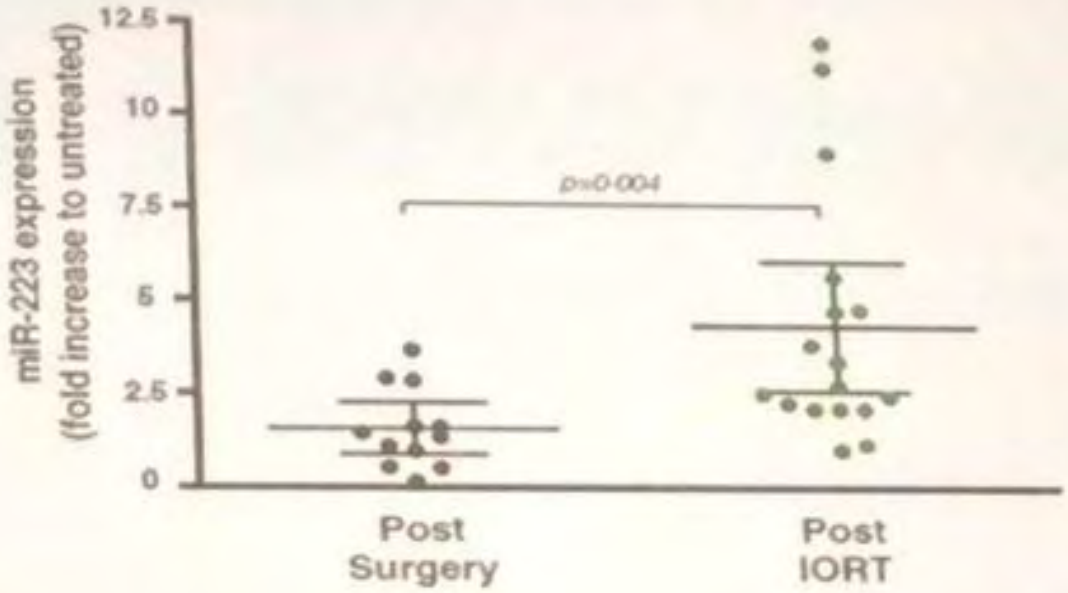
POSSIBLE ROLES OF IORT



Fabris, Berton et al. Oncogene 2016

IORT SPECIFICALLY INDUCES MIR 223 EXPRESSION





Fabris, Berton et al. Oncogene 2016

KRANKENHAUS
BARMHERZIGE
SCHWESTERN
Linz

BREAST IOERT AND SHIELDING DISCS
-
MORE THAN A SIDEKICK?

Novara, 25.06.2016

Daniel Hamedinger

KRANKENHAUS
BARMHERZIGE
SCHWESTERN
Linz

What kind of shielding discs are in use?

Attenuation plate – low dose IOERT

KRANKENHAUS BARMHERZIGE SCHWESTERN Linz

Institute	Dose	Thoracic wall protection
Linz	10Gy to the 90% isodose	PMMA disc (if needed)
Veronesi et al. (Milano)	12Gy to the 90% isodose	Al+Pb disc
Düsseldorf und Citta di Castello (Italy)	10Gy to the 90% isodose	no disc
Reitsamer et al. (Salzburg)	9Gy to the 90% isodose	no disc
HIOB Studie (Salzburg)	10Gy to the 90% isodose	no disc
Zhang et al. (Beijing, China)	8Gy @dmax	n/a
Reggio Calabria (Italy)	8-15Gy	n/a
Lemanski et al. (Montpellier)	9-20Gy to the 90% isodose	n/a

Attenuation plate – high dose IOERT

KRANKENHAUS BARMHERZIGE SCHWESTERN Linz

Institute	Dose	Thoracic wall protection
Linz	21Gy @dmax	PMMA disc
Citta di Castello (Italy)	21Gy to the 90% isodose	n/a
Mussari et al. (Trient)	22Gy or 24Gy @dmax	Al+Pb disc
Lemanski et al. (Montpellier)	21Gy to the 90% isodose	n/a
Veronesi et al. (Milano)	21Gy to the 90% isodose	Al+Pb disc
Maluta et al. (Verona)	21Gy @dmax	PMMA disc
Osti et al. (Roma)	21Gy to the 90% isodose or @dmax	Al+Pb disc
Sawaki et al. (Nagoya, Japan)	21Gy to the 90% isodose	Cu+PMMA disc
Cuneo (Italy)	21Gy to the 90% isodose	Stainless steel + PMMA disc

Physical Properties

Monte Carlo investigation of breast intraoperative radiation therapy with metal attenuator plates.

Martignano et al., Med.Phys 2007

KRANKENHAUS BARMHERZIGE SCHWESTERN Linz

- 3 mm Pb
  - 40+% backscatter dose
- 6 mm Al + 3 mm Pb
  - around 10% backscatter dose

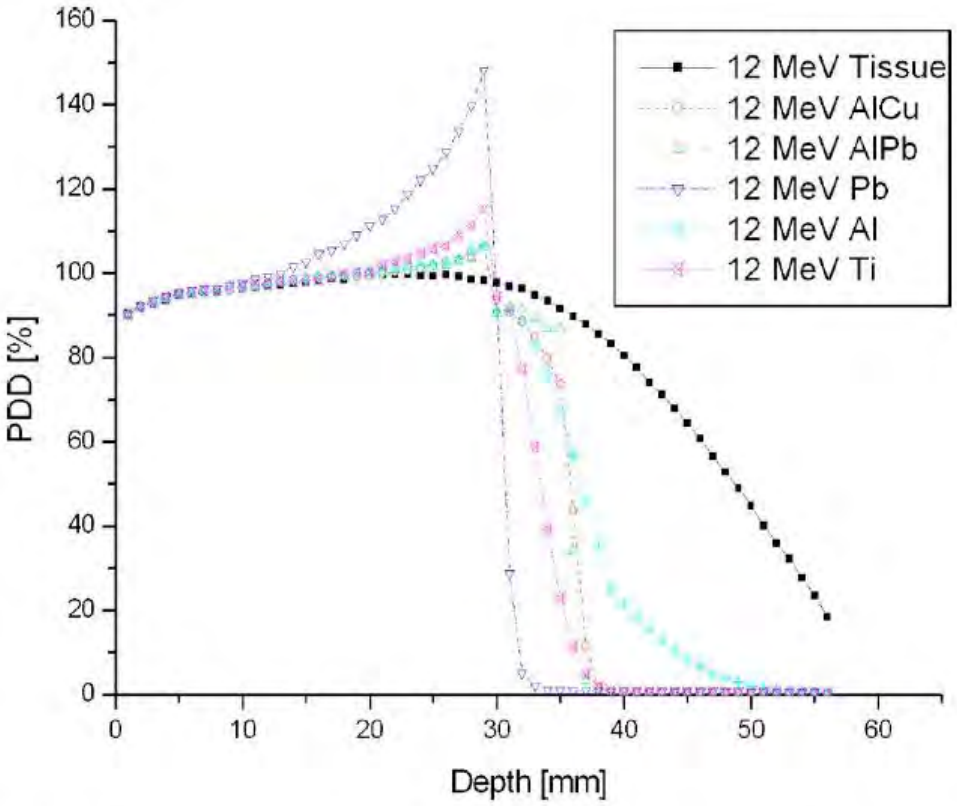


FIG. 5. Percent depth dose on beam axis for five different attenuator plates: (a) 6 mm Al+3 mm Cu; (b) 6 mm Al+3 mm Pb; (c) 3 mm Pb; (d) 9 mm Al; (e) 9 mm Ti. Plates are located after 3 cm of tissue. DOSXYZnrc MC code simulation; 12 MeV nominal energy.

An experimental attenuation plate to improve the dose distribution in intraoperative electron beam radiotherapy for breast cancer.

Oshima et al., Phys. Med. Biol., 2009

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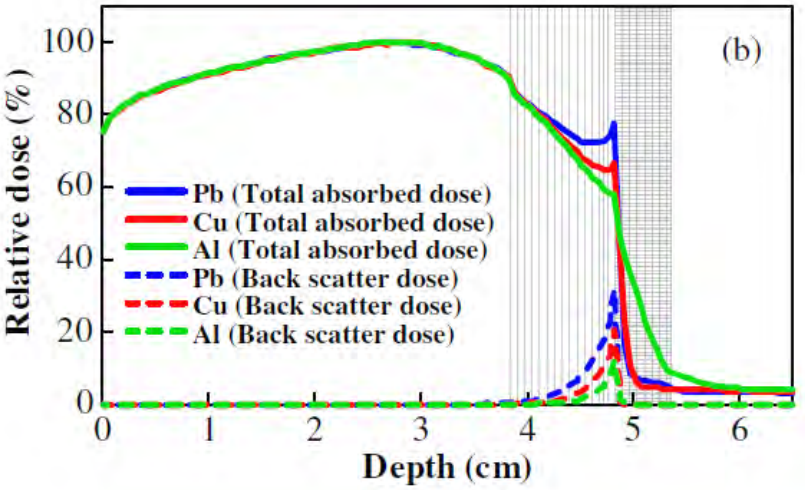
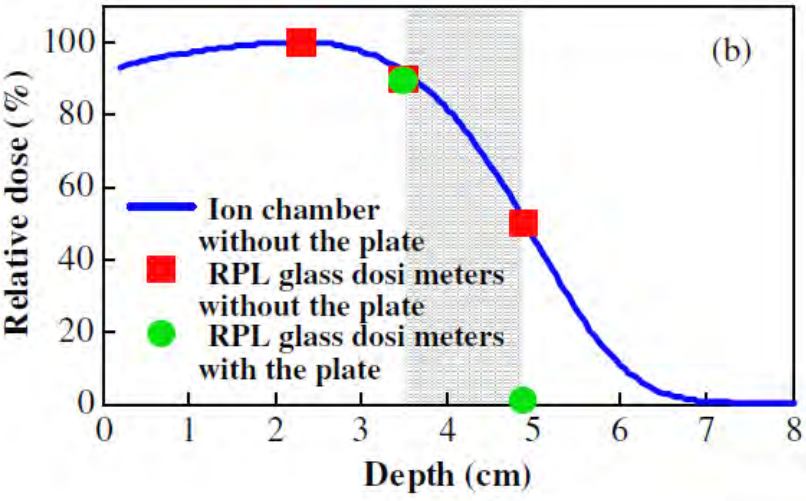
- PMMA to reduce backscatter
- Manufactured a prototype
  - 7mm PMMA
  - 3mm Cu
  - 2mm PMMA





12mm thickness; 10,4mm diameter

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Implications for the clinical outcome

e.g. ELIOT

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- 11% backscatter dose according to ELIOT talk from dott. Stefania Comi 4mm Al + 5 mm Pb.

- Question to the audience:
  - Influence on necrosis rate?
  - „We identified a higher occurence of fat necrosis in the intraoperative radiotherapy group than in the external radiotherapy group.“ ELIOT, Veronesi et al., Lancet 2013

Final remark

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- Would it be good to replace the metal only attenuation plates with their PMMA coated metal attenuation plates if no surgical aspects speak against the slightly bigger thickness?
  - Shielding capability is comparable
  - Backscatter is reduced

FONDAZIONE SALVATORE MAUGERI
CLINICA DEL LAVORO E DELLA RIABILITAZIONE
I.R.C.C.S.

VARIABLES AFFECTING DISC ATTENUATOR ALIGNMENT IN BREAST IORT

G. B. Ivaldi, P. Tabarelli De Fatis, M. Liotta, A. Malovini

Radioterapia Fondazione Maugeri - Pavia

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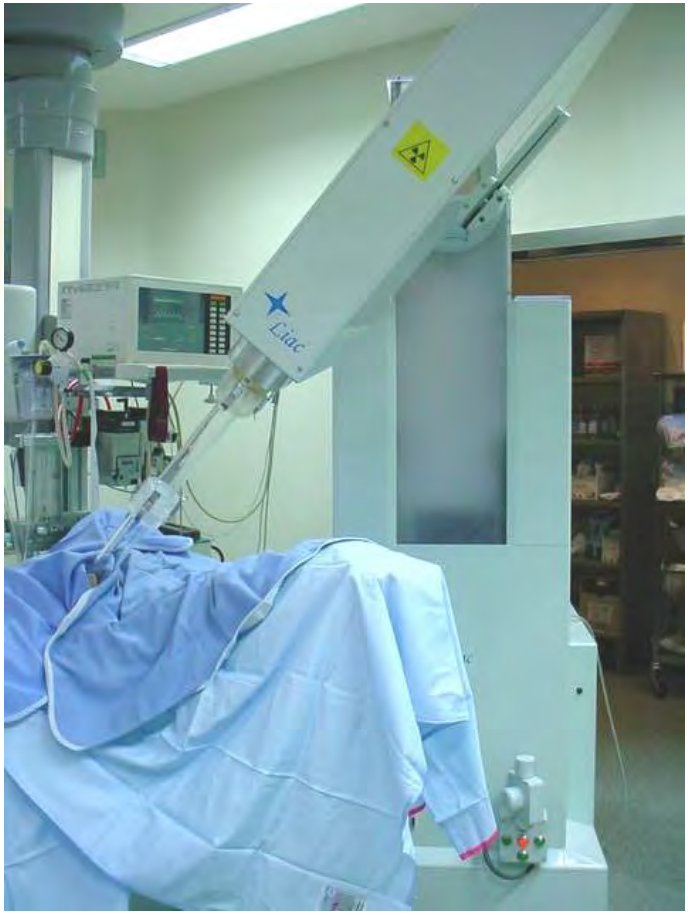
Methods

January 2013 –April 2016

- **116 women**
- **IORT with LIAC SIT™**
- **Collimator 4-9 cm**
- **Energies: 6 -12 Mev**



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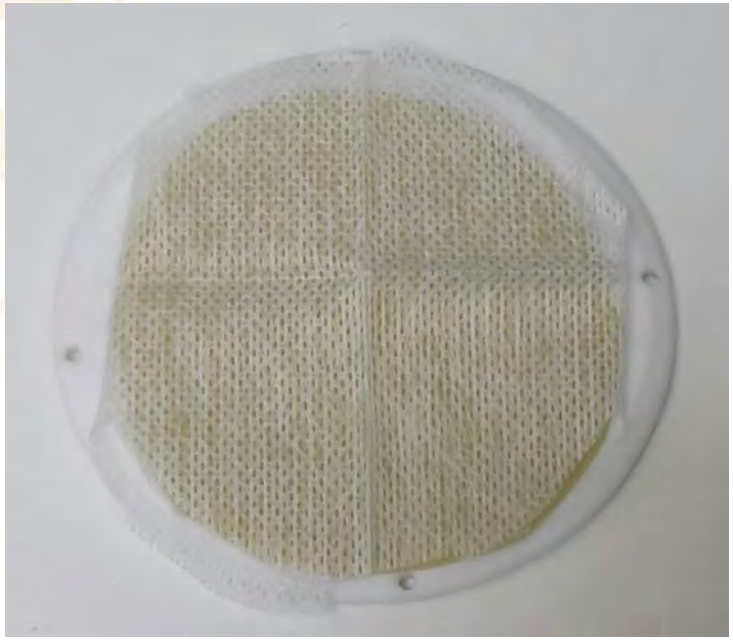
I.R.C.C.S.

Methods

January 2013 –April 2016

To check disk – collimator aligment ⟶ Radiochromic film on disk



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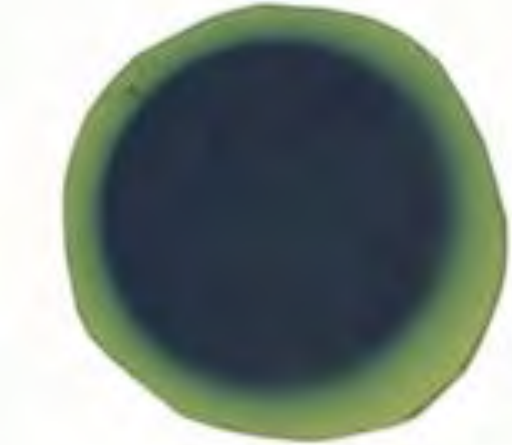
I.R.C.C.S.

Collimator to disc aligment



Good

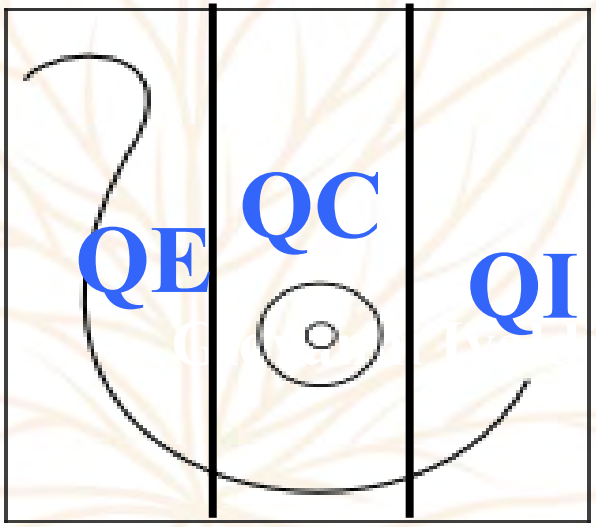
Intermediate

Bad

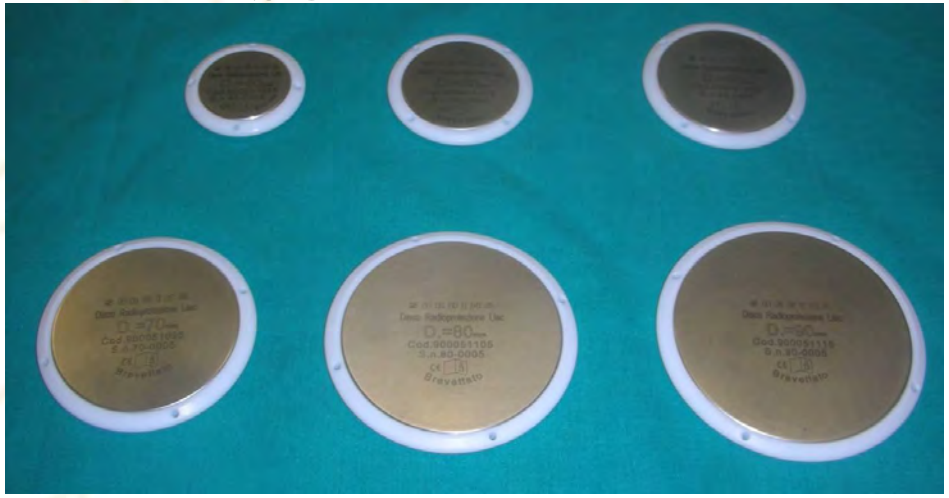
Aim (I)

Evaluate Variables affecting disc – coll aligment

TUMOUR SITE



DISC DIAMETER



APPLICAT TO DISC DIFF (DCD)

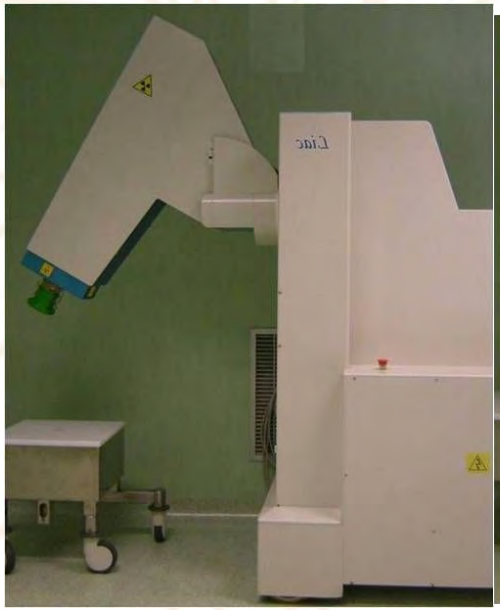
(DCD < 3 or ≥3 cm)

Aim (II)

Evaluate Variables affecting disc – coll aligment

SURGEON

PITCH



ROLL

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I.R.C.C.S.

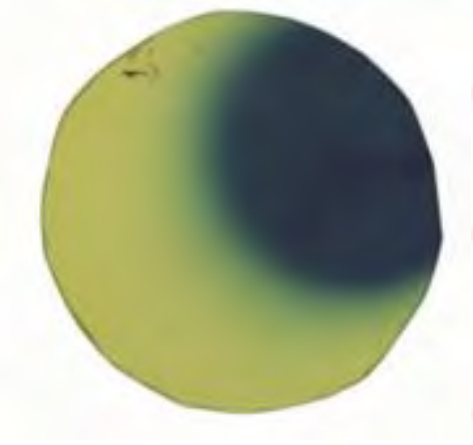
Uni and multivariate analysis to correlate

- Tumour site
- Disk diameter
- DCD
- Pitch
- Roll
- Surgeon

Diff%

Diff%

(<7) (7-14) (> 14)



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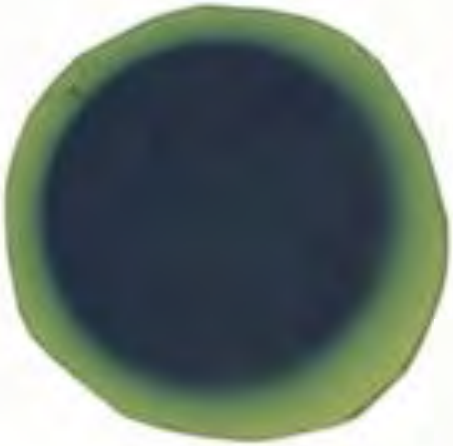
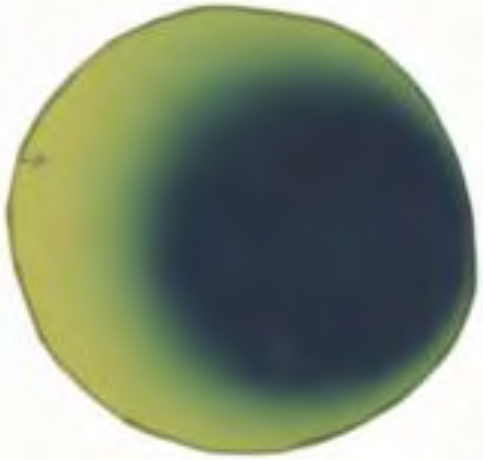
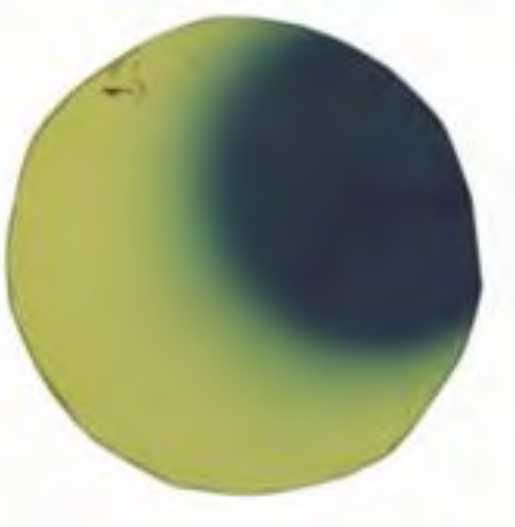
Pre-set score range



Good Diff% <7%,





Bad Diff > 14%

Intermediate Diff% 7-14%,

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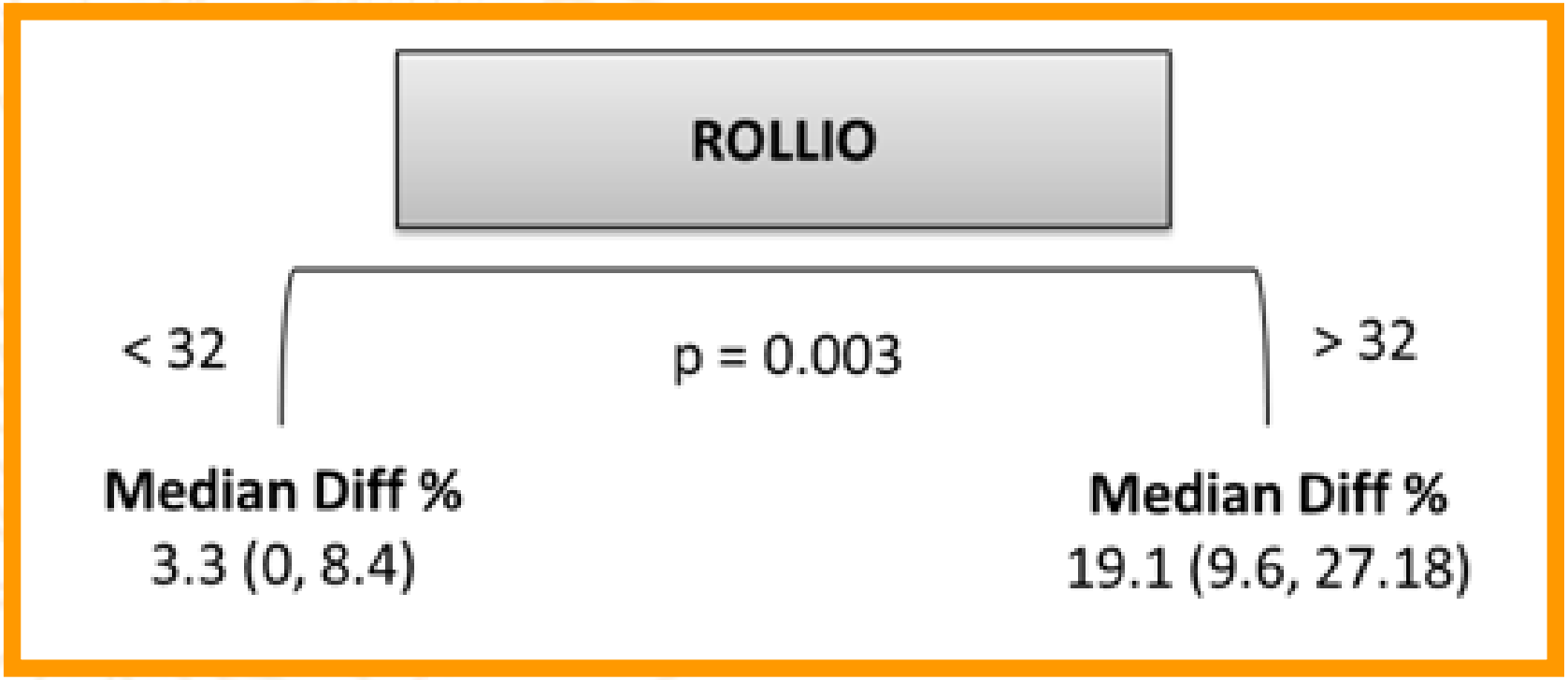
I.R.C.C.S.

Results: Univariate analysis (Diff%)

Variable	Value	Median (IQR) or Sperman coefficient	p-value
SEDE			0.261
	OC	8.4 (3.4, 10.6)	
DIA_DISCO			0.022*
	6	47 (24.9, 53.9)	
	7	17.3 (2.6, 26.55)	
	8	10.2 (1.9, 21.75)	
	9	3.05 (2.45, 4.65)	
DIFF_APP_DISCO			0.008*
	< 3	19 (9.5, 34.8)	
	≥ 3	9.5 (1.6, 21.2)	
PROFONDITA		+ 0.01	0.886
ROLLIO		+ 0.25	0.039*
BECCHEGGIO		+ 0.33	0.007*

Multivariate analysis



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I.R.C.C.S.

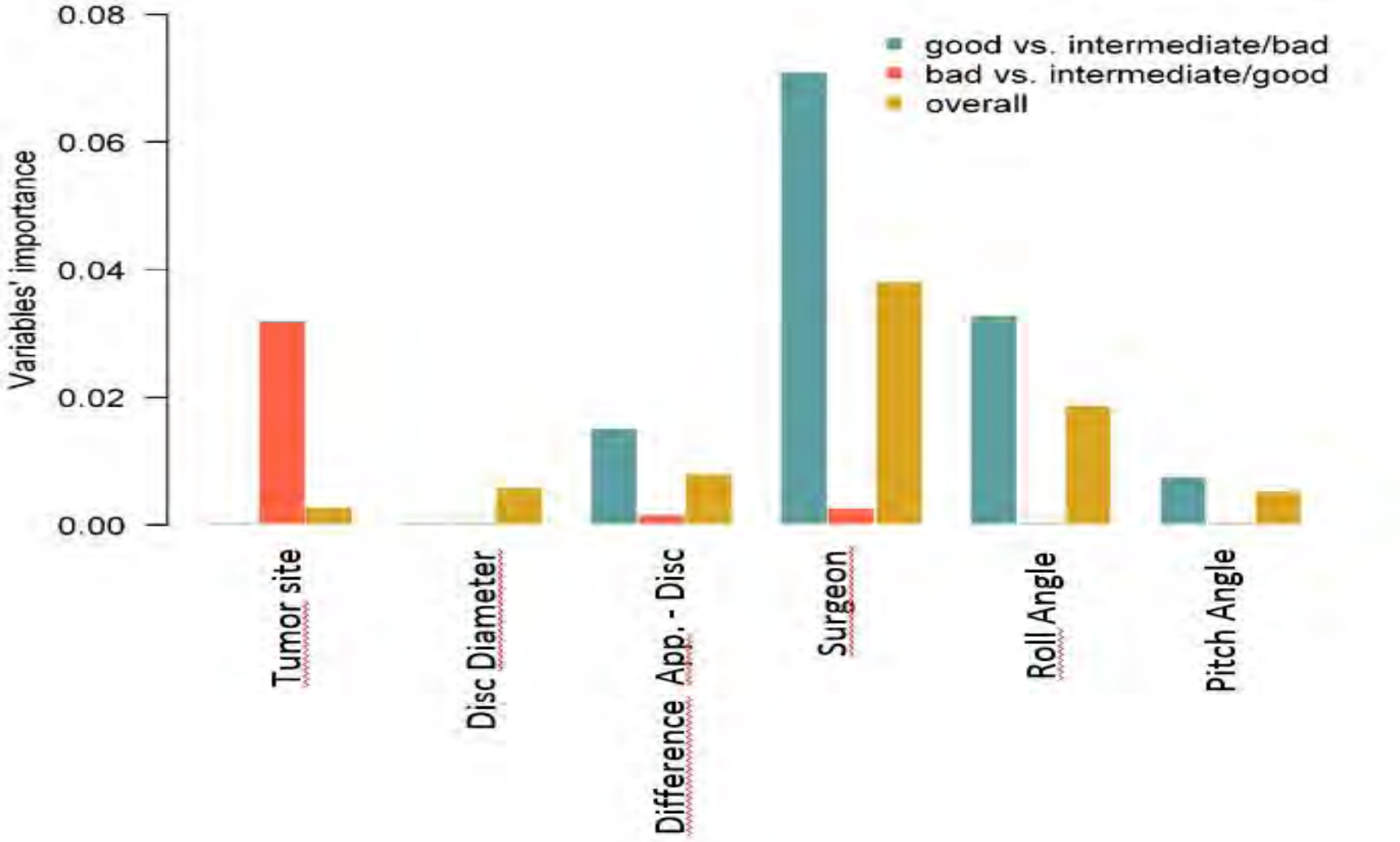
Univariate tests

considering Diff% discretized into 3 intervals

		Quality of the alignment			
		Good	Intermediate	Bad	
		Good	Intermediate	Bad	
Variable	Value	Diff ≤ 7%	7% < Diff ≤ 14%	Diff > 14%	p-value
SEDE	QC	8 (47.06%)	6 (35.29%)	3 (17.65%)	0.049*
	QE	22 (35.48%)	10 (16.13%)	30 (48.39%)	
	QI	12 (41.38%)	2 (6.9%)	15 (51.72%)	
	≥ 3	35 (43.21%)	14 (17.28%)	32 (39.51%)	
CHIRURGO	1	23 (56.1%)	6 (14.63%)	12 (29.27%)	0.108
	2	10 (30.3%)	5 (15.15%)	18 (54.55%)	
	3	7 (26.92%)	6 (23.08%)	13 (50%)	
	4	2 (22.22%)	1 (11.11%)	6 (66.67%)	
DIA_LESIONE		1.2 (1.2, 1.2)	1.4 (1.4, 1.4)	1.25 (1, 1.65)	0.071
PROFONDITA		1.5 (1.5, 1.5)	1.2 (1.2, 1.2)	1.1 (1.02, 1.55)	0.765
ROLLIO		15 (15, 15)	20 (20, 20)	20 (20, 30)	0.041*
BECCHEGGIO		5 (5, 5)	9 (9, 9)	8 (5, 10)	0.132

Variables importance in discriminating among the 3 aligment classes

Multivariate tests



Conclusions – Risk of Misaligment

- Non central quadrant
- DCD < 3cm
- High roll angles (DCD > 3 cm)


Thank you

In vivo dosimetry by EBT3 GAFCHROMIC films during IOERT breast treatment

Manco Luigi

Post-graduate School in Medical Physics, University of Bologna,Italy

Medical Physics Unit, Sant'Anna University Hospital, Ferrara,Italy

Introduction

In vivo dosimetry in IOERT:

- high single dose delivered during treatment
- lack of an individualized treatment plan
- limited choise of detectors

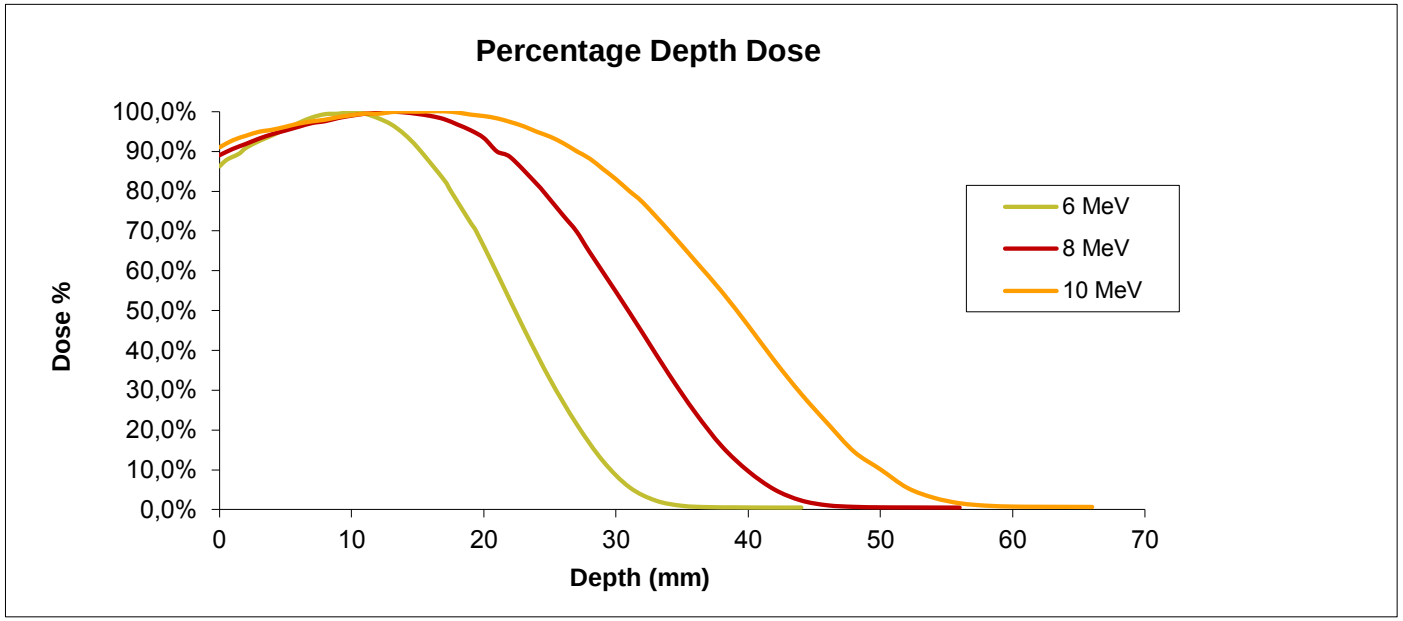
Patients & Materials

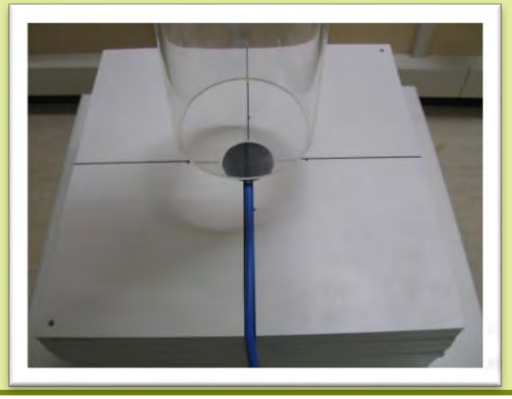
From 09/04/2014 to 06/05/2015	9 Gy	21 Gy
6 MeV	13	12
8 Mev	12	18
10 MeV	2	9
Age (median)	32-50(43)	61-75(70)
Total	66 patients	

Key points

1. LIAC Commissioning & Quality Controls
2. Film Calibration
3. Film positioning during surgery
4. Film reading

1. Liac Commissioning



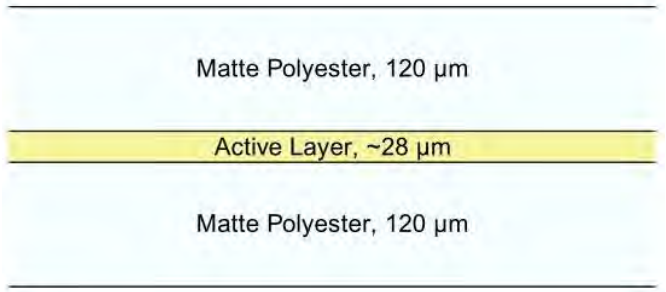


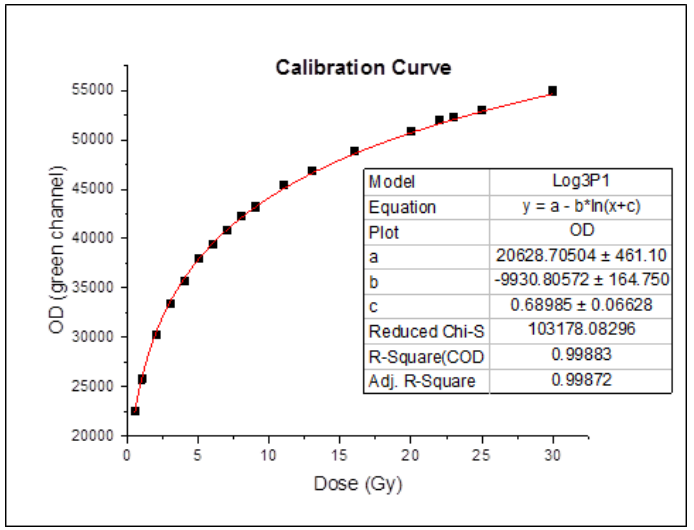
Dose monitoring system:

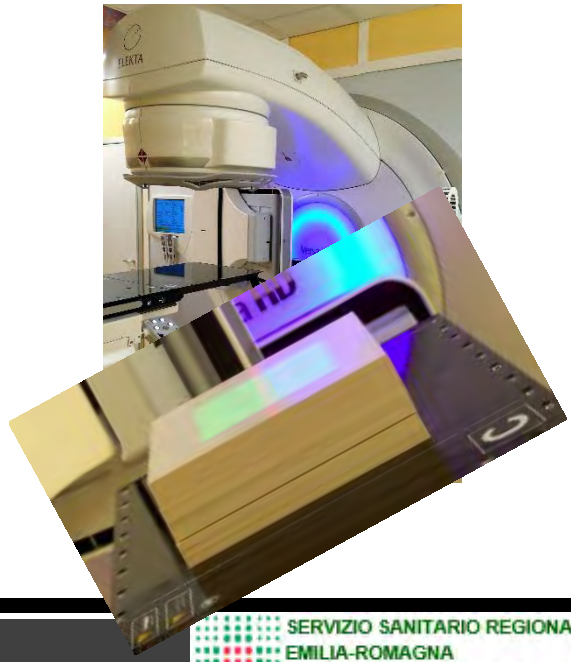
- long time stability ±3%
- short time stability ±1%

2. GAFCHROMIC calibration

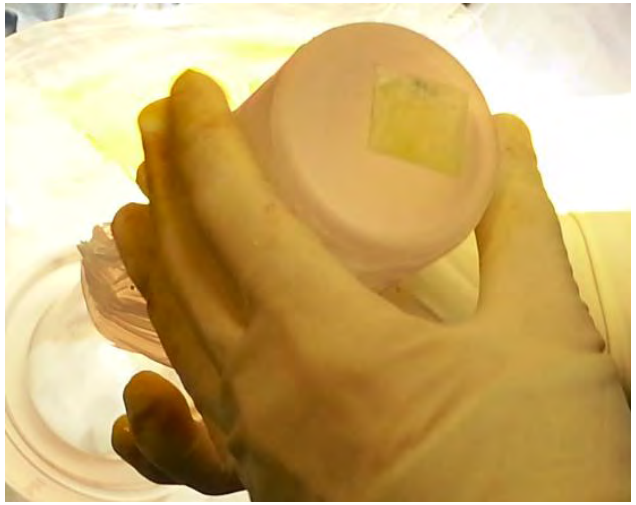
- Solid water-equivalent phantom RW3-PTW
- Large well-charactirezed uniform radiation field
- Measure of absolute dose at the calibration reference depth
- 5 x 5 cm^2 films



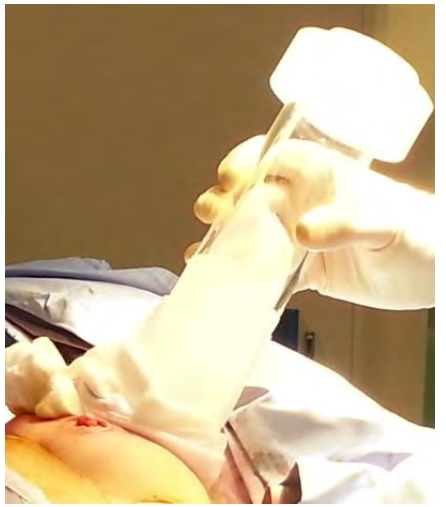


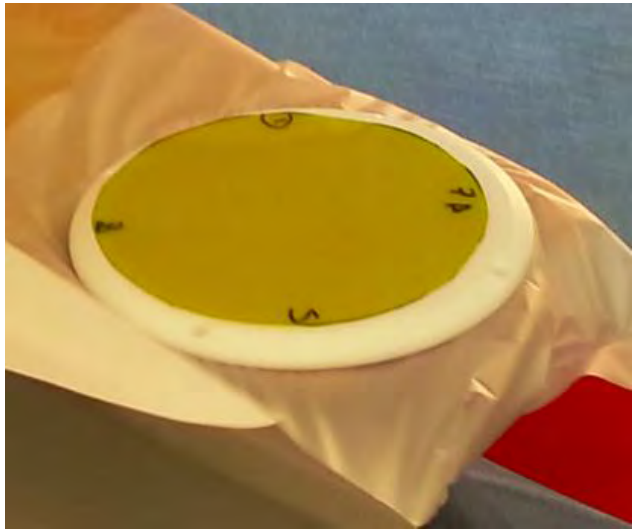


3. Film positioning during surgery

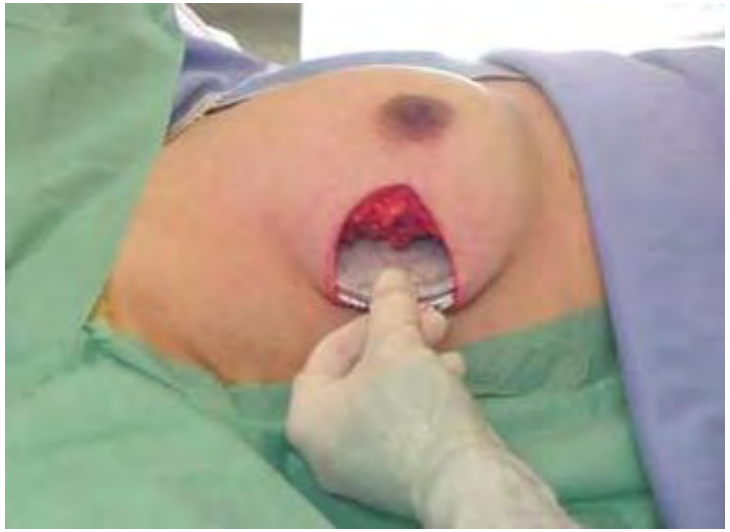


Entrance Dose



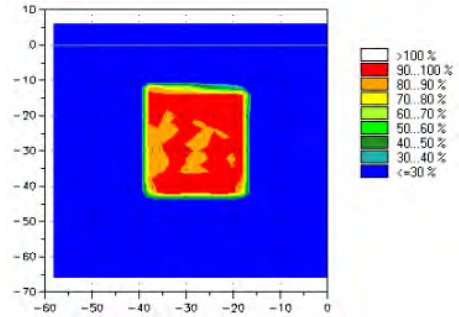


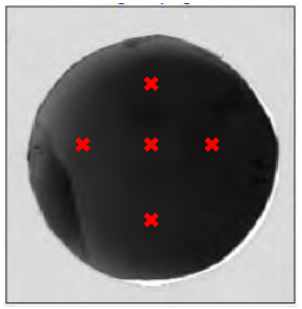
Delivered Dose

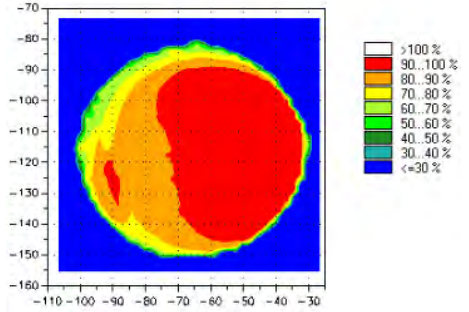


4. Film reading

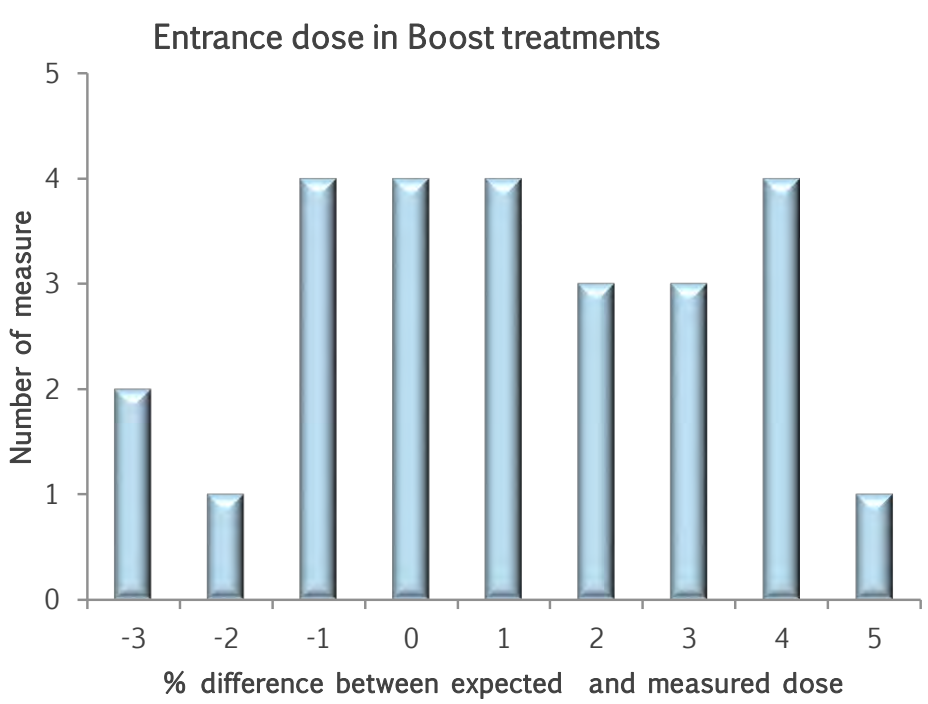
- 48hrs after exposure
- Positional accuracy
- Landscape scanning orientation
- RGB mode – green channel
- Converting optical density into absolute dose
- 5 measure points

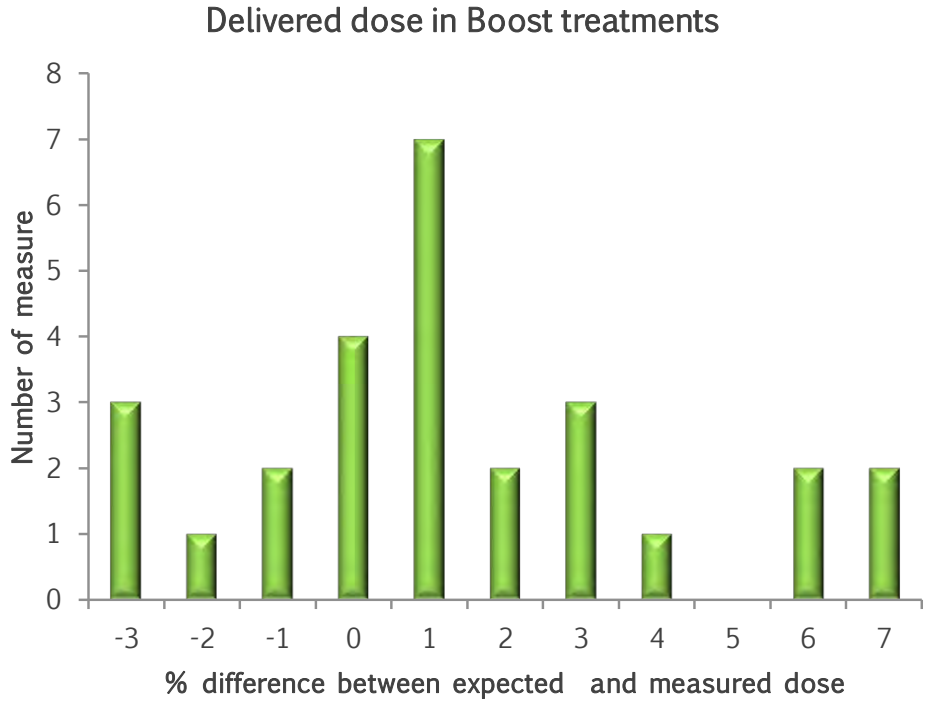




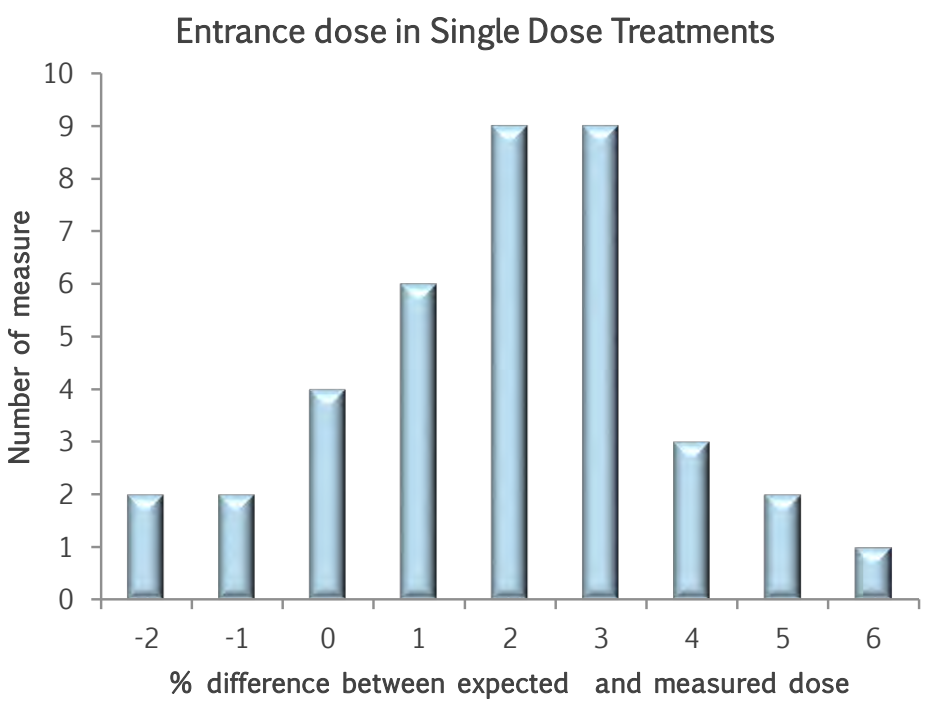


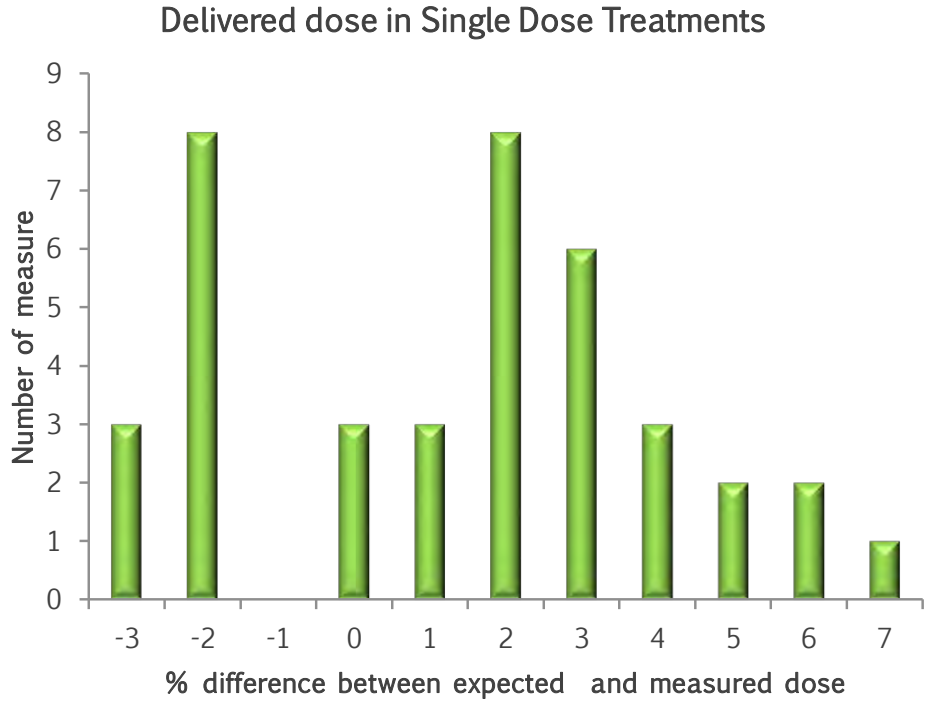
Results: 9 Gy


Entrance dose in Boost treatments
Number of measure
0
1
2
3
4
5
-3
-2
-1
0
1
2
3
4
5
% difference between expected and measured dose


Delivered dose in Boost treatments
Number of measure
0
1
2
3
4
5
6
7
8
-3
-2
-1
0
1
2
3
4
5
6
7
% difference between expected and measured dose

Results: 21 Gy





Conclusions

- GAFCHROMIC EBT3 film positioned on the shielding disc are effective dosimeters for IOERT without any drawbacks in the clinical practice
- Post-processing of irradiated EBT3 films allows to obtain a detailed dose map of the target, the absolute dose delivered and an estimate of the area of the film outside the shielding
- Agreement between measured and expected dose found, is quite good with percentage difference less than 8%

Acknowledgements

Radiation Oncologists

Dr. Stefanelli A.

Dr. Zini G.

Surgeons

Dr. De Troia A.

Dr. Carcoforo P.

Medical Physicists

Dr. Fabbri S.

Dr. Hernandez Flores F.

Dr. De Guglielmo E.

Dr. Turra A.

THANKS FOR YOUR ATTENTION !

COMPARISON OF MOBETRON 1000 AND MOBETRON 2000 FOR IOERT

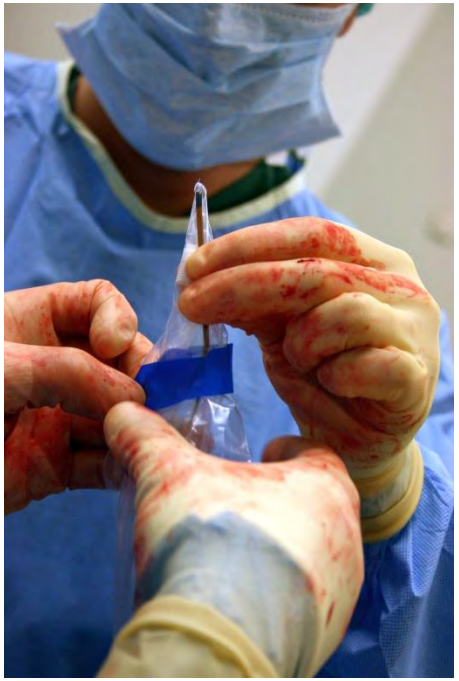
Anna L. Petoukhova, Ko van Wingerden, Jaap van Egmond, Peter Koper, Heleen Ceha, Tanja Stam, Mariet Peeters, Mohamed El Kadaoui, Jeffrey Tan, Henk Struikmans

Radiotherapy Centre West, Medical Center Haaglanden - Bronovo, The Hague, The Netherlands

25 June 2016, ISIORT, Novara

IOERT for Rectal Cancer

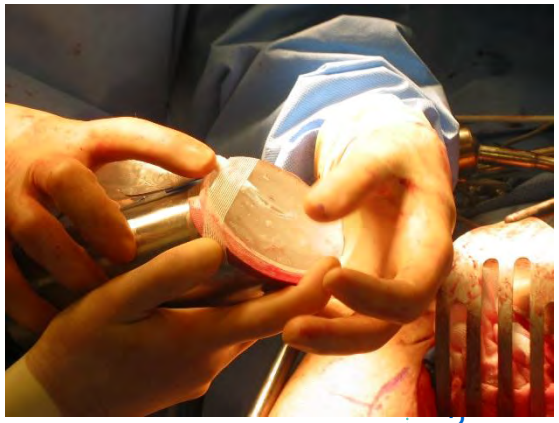
Mobetron 1000



June 2007 till January 2016

39 patients with either locally advanced or recurrent rectal cancer (11.1 Gy prescribed at 100% isodose):

- *In vivo* dosimetry with MOSFETs (metal-oxide semiconductor field-effect transistors) (ESTRO 2008)
- Analysis of the clinical results



IOERT for Partial Breast

Mobetron 1000

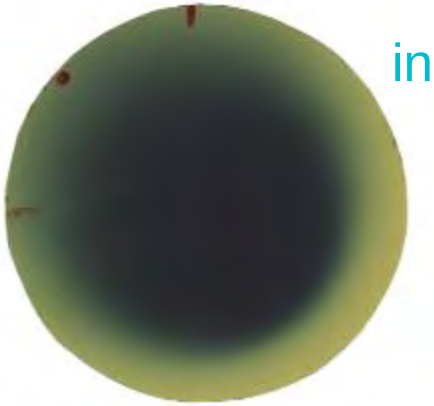
RCWEST
RADIOTHERAPIECENTRUM WEST

May 2010 till January 2016

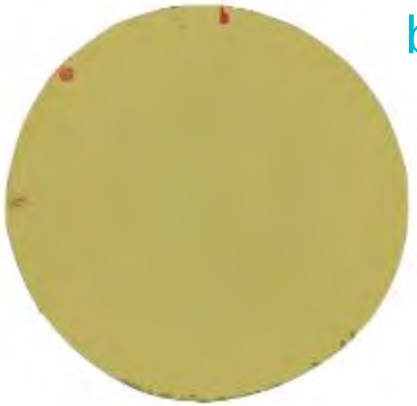
384 elderly ("low risk") breast cancer patients were treated with IOERT (23.3 Gy prescribed at 100% isodose):

- Pilot study May 2010 till January 2011
- Phase II study since January 2011
- *In vivo* dosimetry with MOSFETs or/and Gafchromic films for 47 patients (ESTRO 2015)

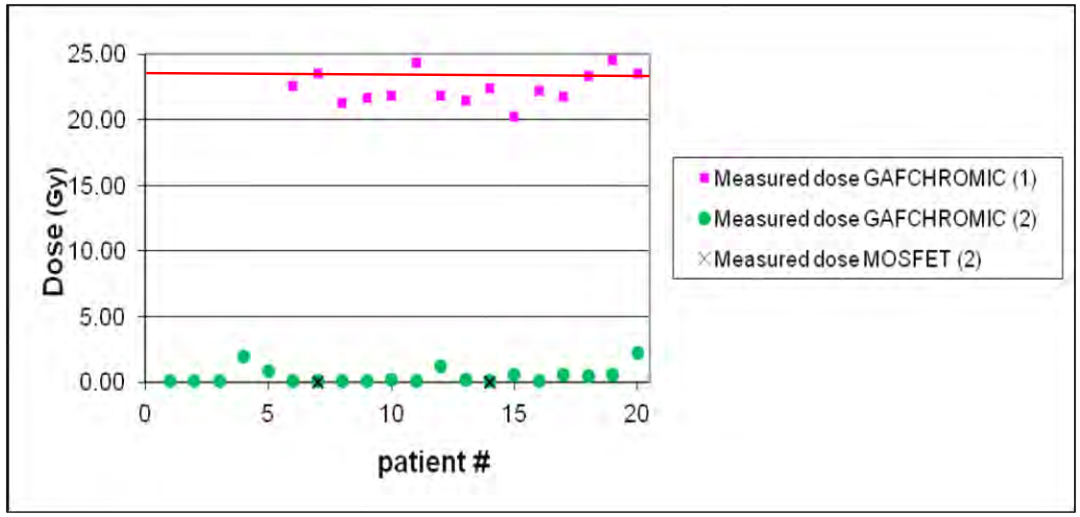
9 MeV, applicator diameter 4.5 cm, bevel 0 degree, protection plate 7 cm



in front of



behind



Mobetron 2000

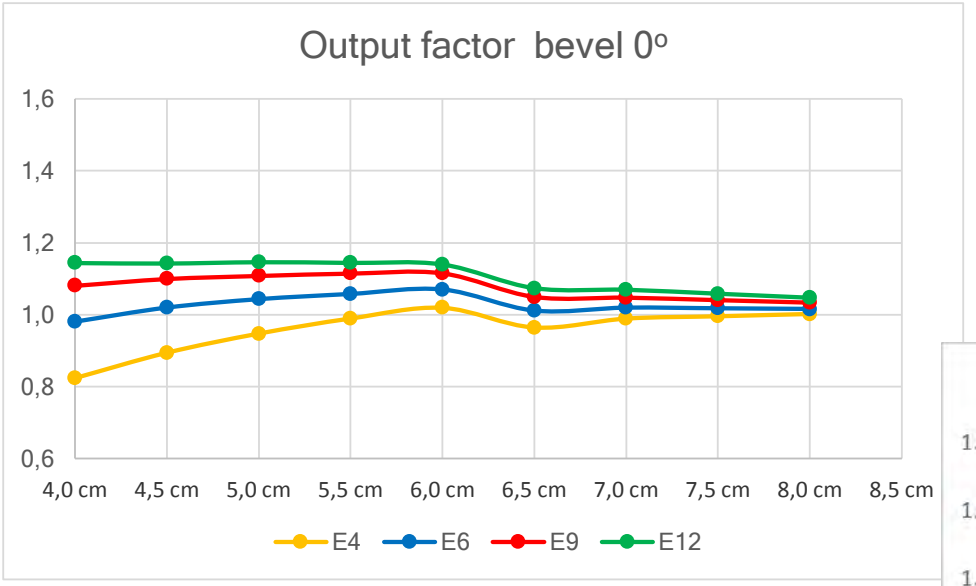
- Applicators: from 4 till 8 cm in steps of 0.5 cm
- Bevel: 0°, 15°, 30° and 45°

- Three electron energies: 6, 9 and 12 MeV
- Head Tilt: +10°/- 30° instead of +30°/- 30°

Output factors

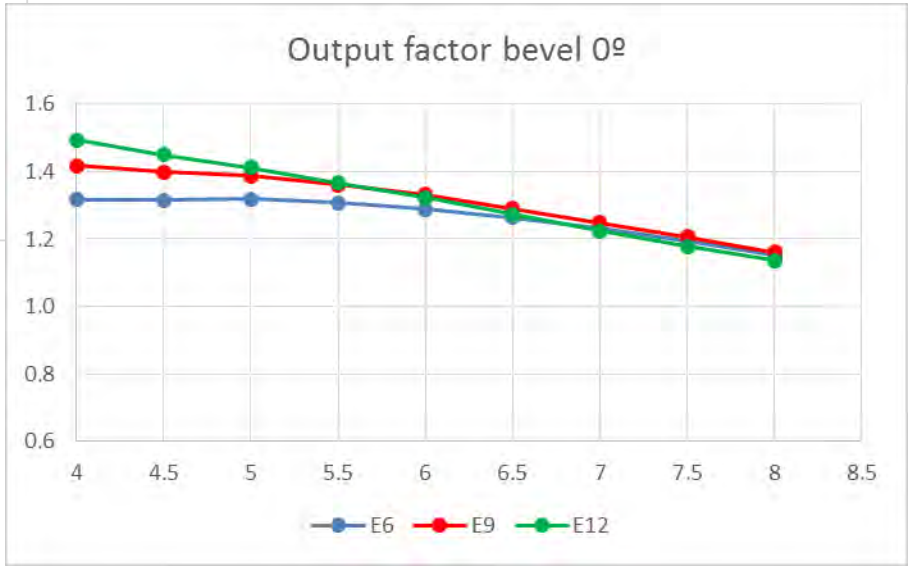
Mobetron 1000

Two piece narrow bore applicators.



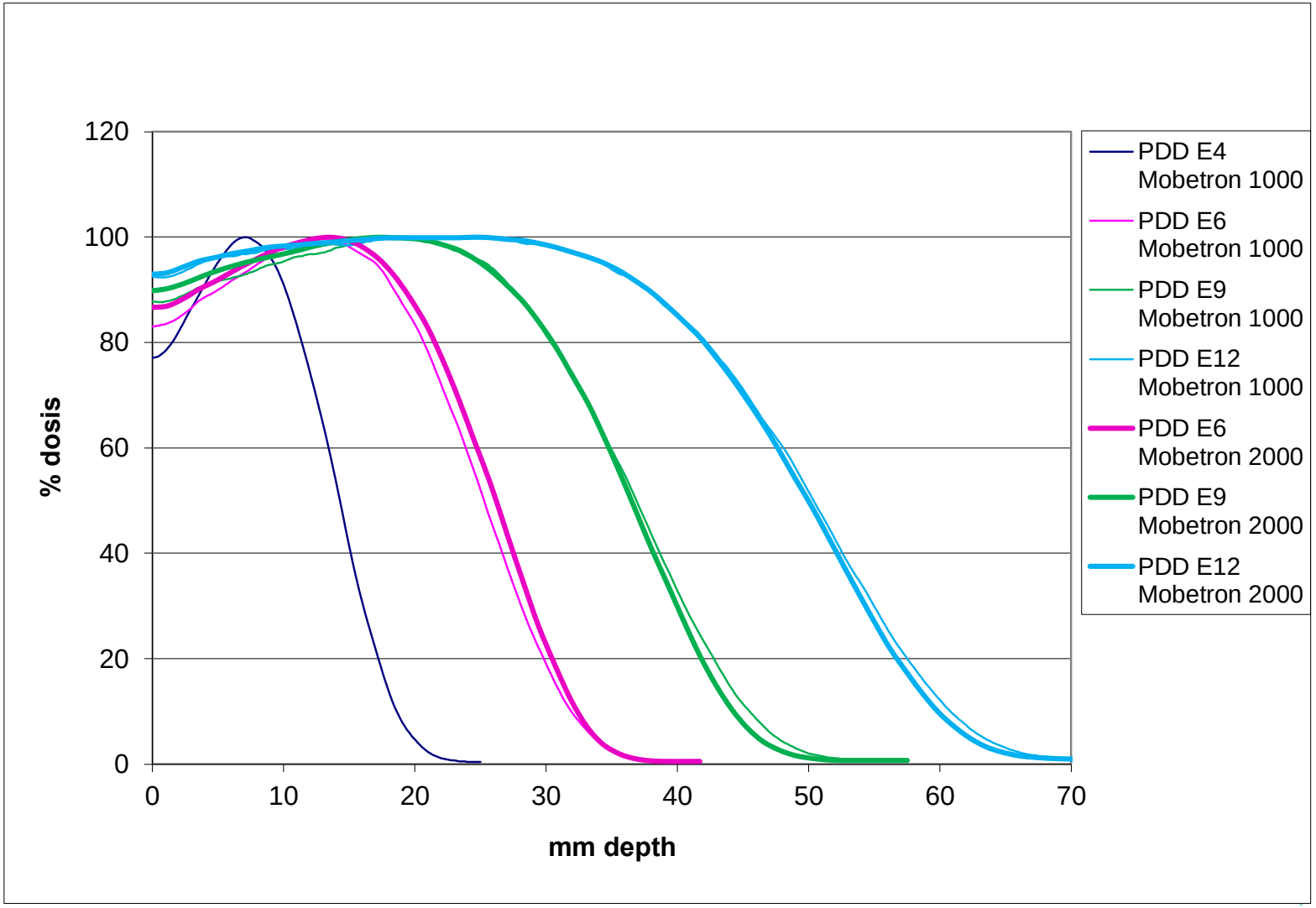
Mobetron 2000

One piece wide bore applicators



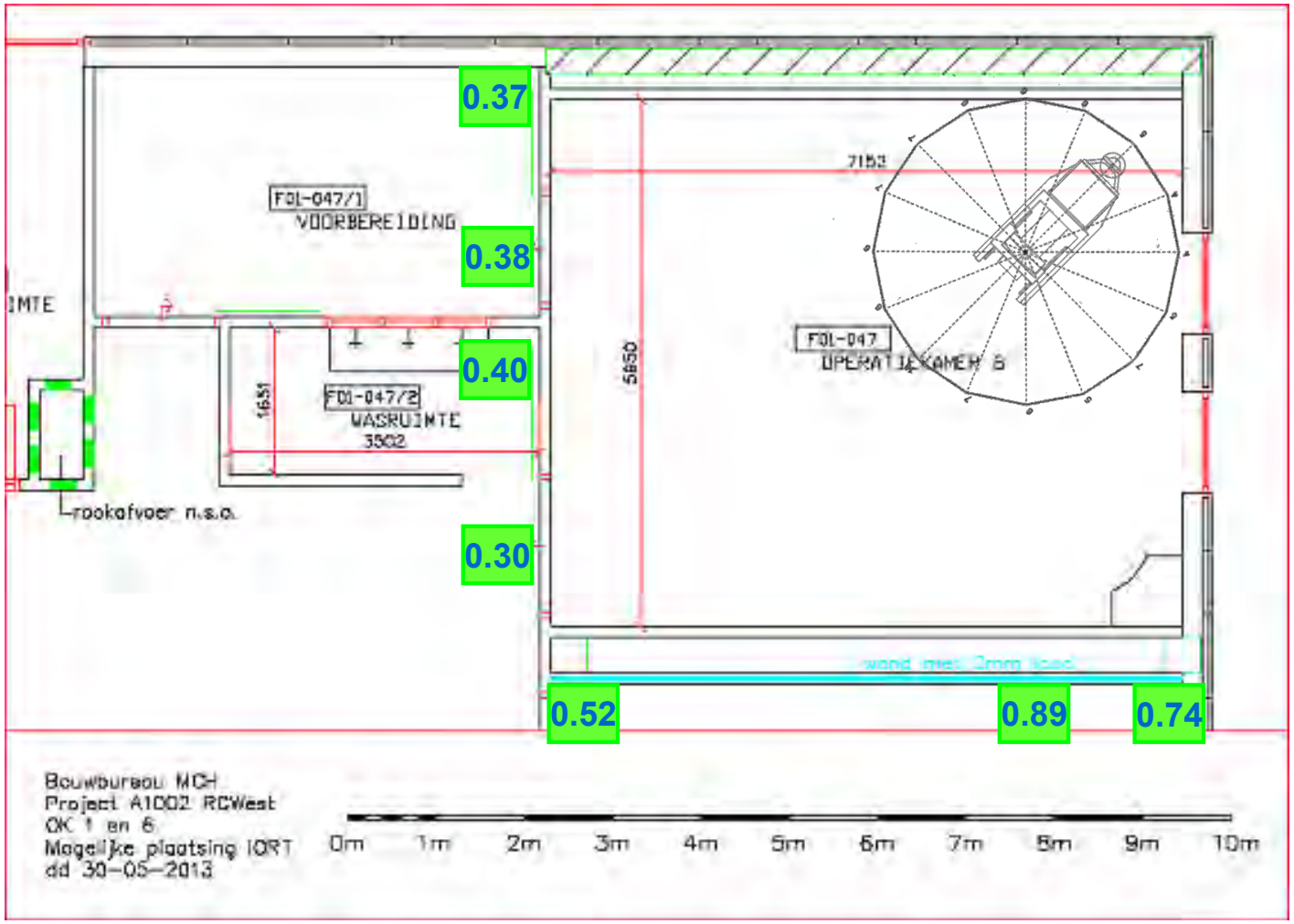
Central axis depth dose profiles

10 cm applicator



Calculated doses around OR

250 APBI and 20 rectal patients per year

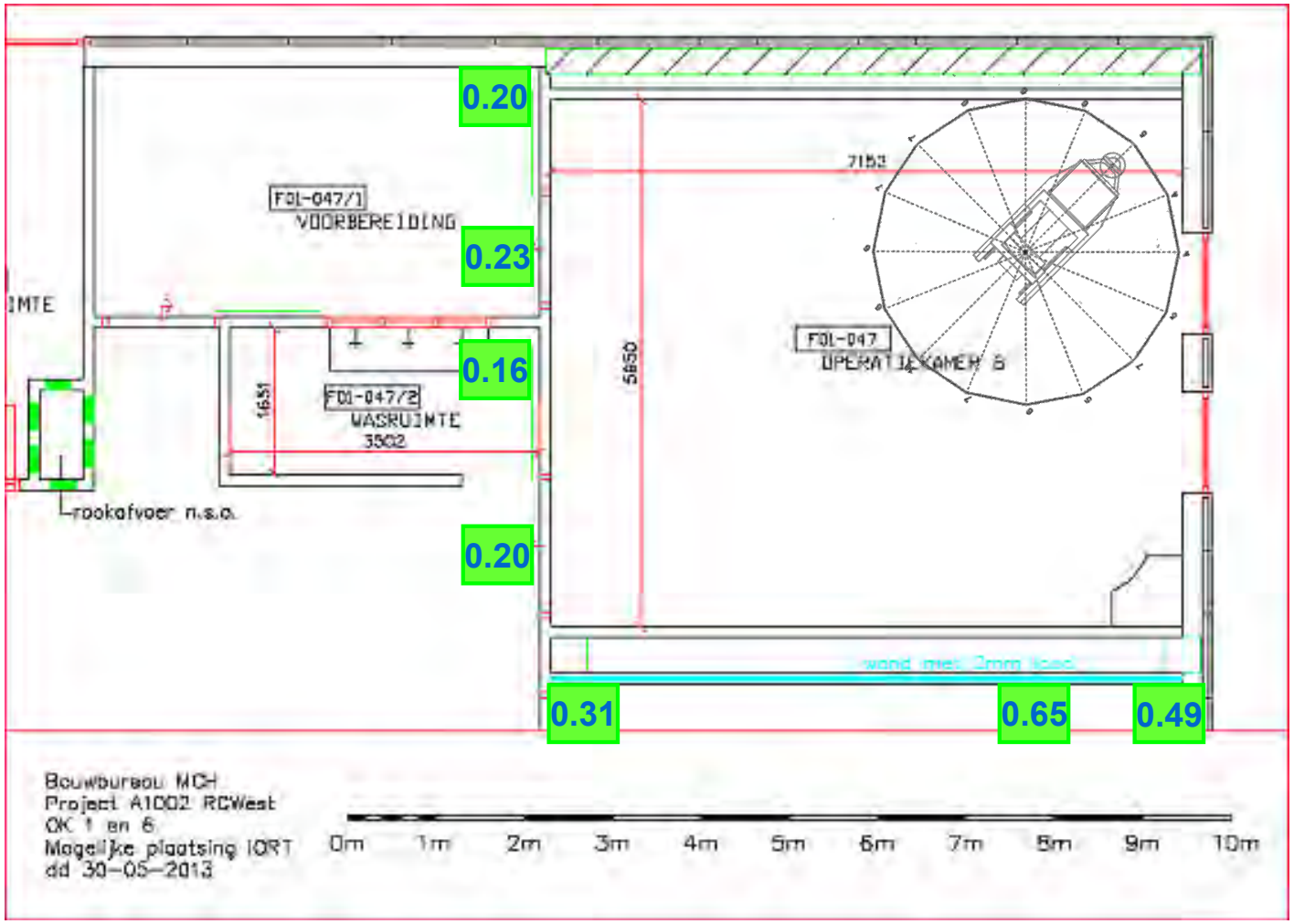


in mSv/year

Dose Limit in The Netherlands: 1 mSv per year

Measured doses around OR

250 APBI and 20 rectal patients per year



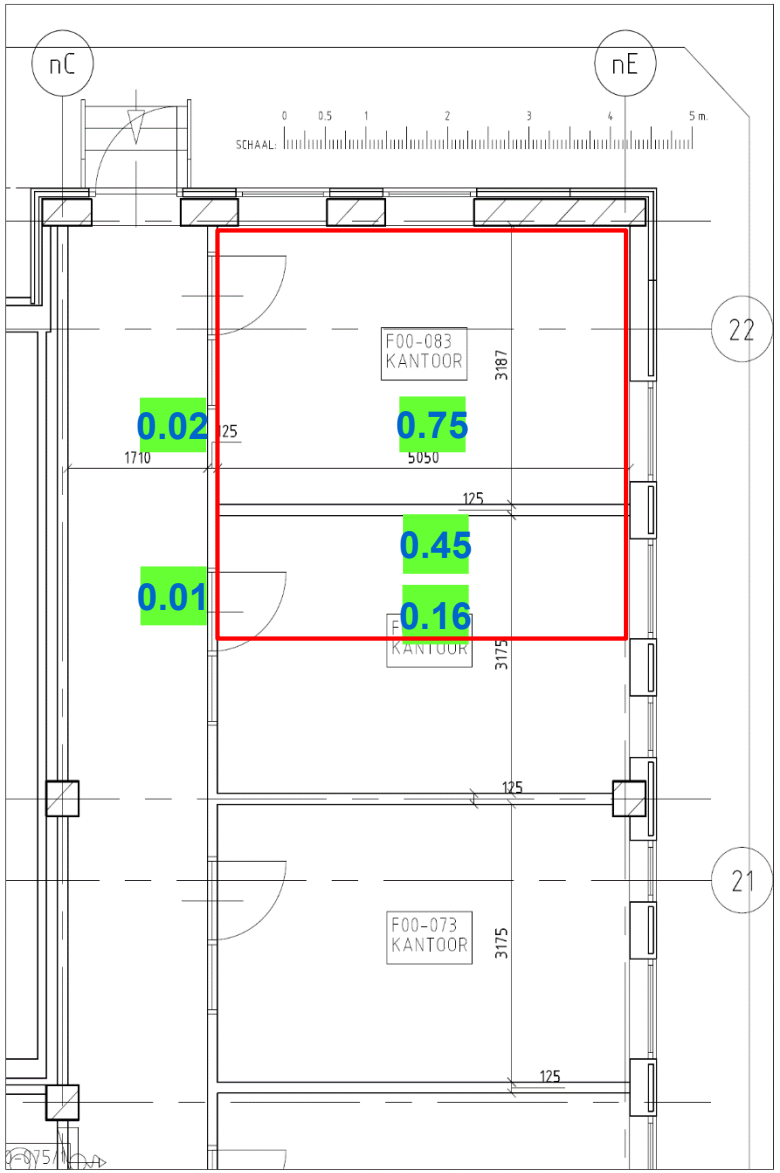
Victoreen 451p survey meter

Dose Limit in The Netherlands: 1 mSv per year

Floor below OR

250 APBI and 20 rectal patients per year

25 cm concrete +
iron plate:
size 5 * 5 m^2
thickness 10 cm



At 3.3 meter:
in mSv/year

50 APBI and 20 rectal patients per year :
25 cm concrete =>
within 1 mSv/year

Conclusions

- We are satisfied with the radiation performance, stability and technical characteristics of Mobetron 2000

- For our workload of 250 APBI and 20 rectal patients per year, we need an iron plate (additional to 25 cm concrete) in the ceiling of the floor below OR to stay within 1 mSv/year.

Future plans

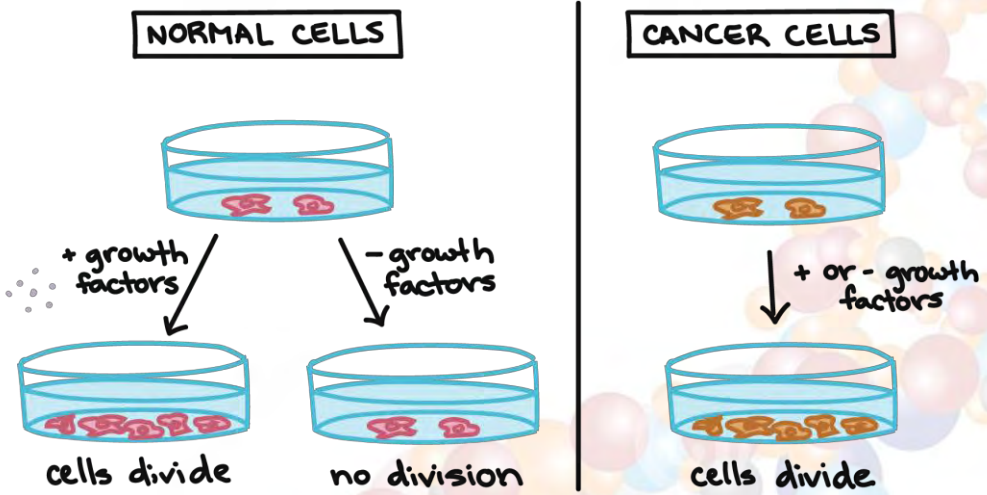
- We will continue using IOERT in breast cancer (APBI and will start using IOERT as a boost) and in rectal cancer.
- Furthermore, we intend to start using IOERT for new tumour sites.

9th International ISIORT Conference
June 24/25th 2016
Novara, Italy

APOPTOTIC PATHWAY ACTIVATION IN PROSTATE NEOPLASTIC CELLS AFTER 12 GY-IORT: AN IN VIVO RADIOBIOLOGICAL MODEL.

UPO
UNIVERSITÀ DEL PIEMONTE ORIENTALE

Carla Pisani, MD, PhD student



Radiation-induced death cell: well known in fractionated RT

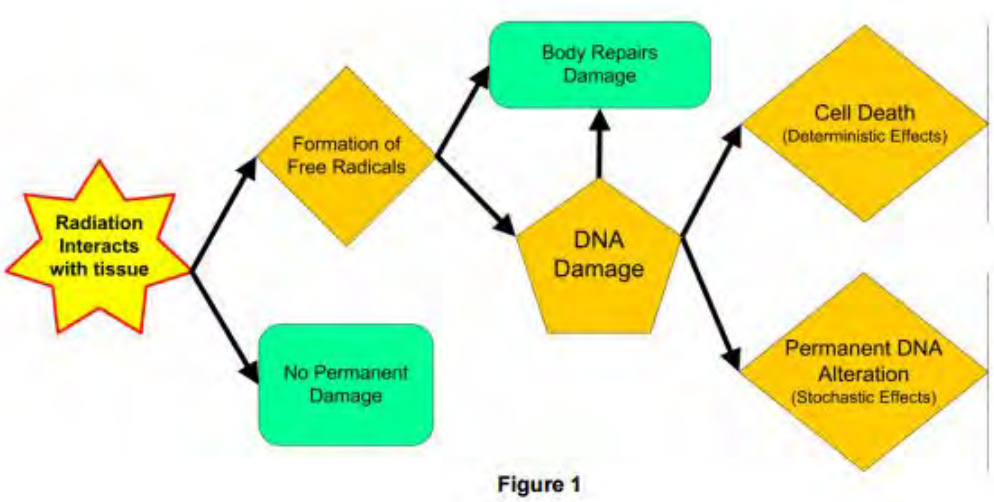
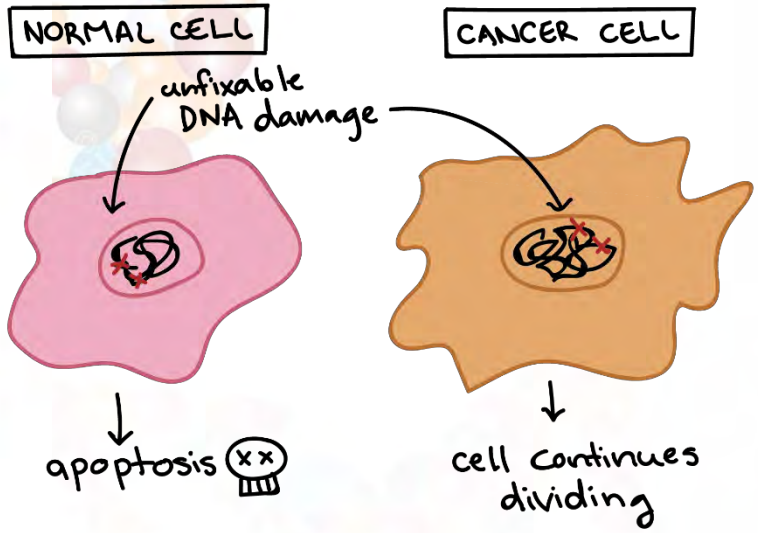


Figure 1



Kerr JF. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer 1972
Dewey WC. Radiation-induced apoptosis: relevance to radiotherapy. Int J Radiat Oncol Biol Phys 1995
Strasser A. Apoptosis signaling. Annu Rev Biochem 2000
Shinomiya N. New concepts in radiation-induced apoptosis. J Cell Mol Med 2001

Radiation-induced death cell: so little known in single shot RT..

Single high-dose

Activation in vivo of pre-exhising pro-apoptotic proteins

Inhibition in vivo of pre-exhising anti-apoptotic proteins

ki-67

p53

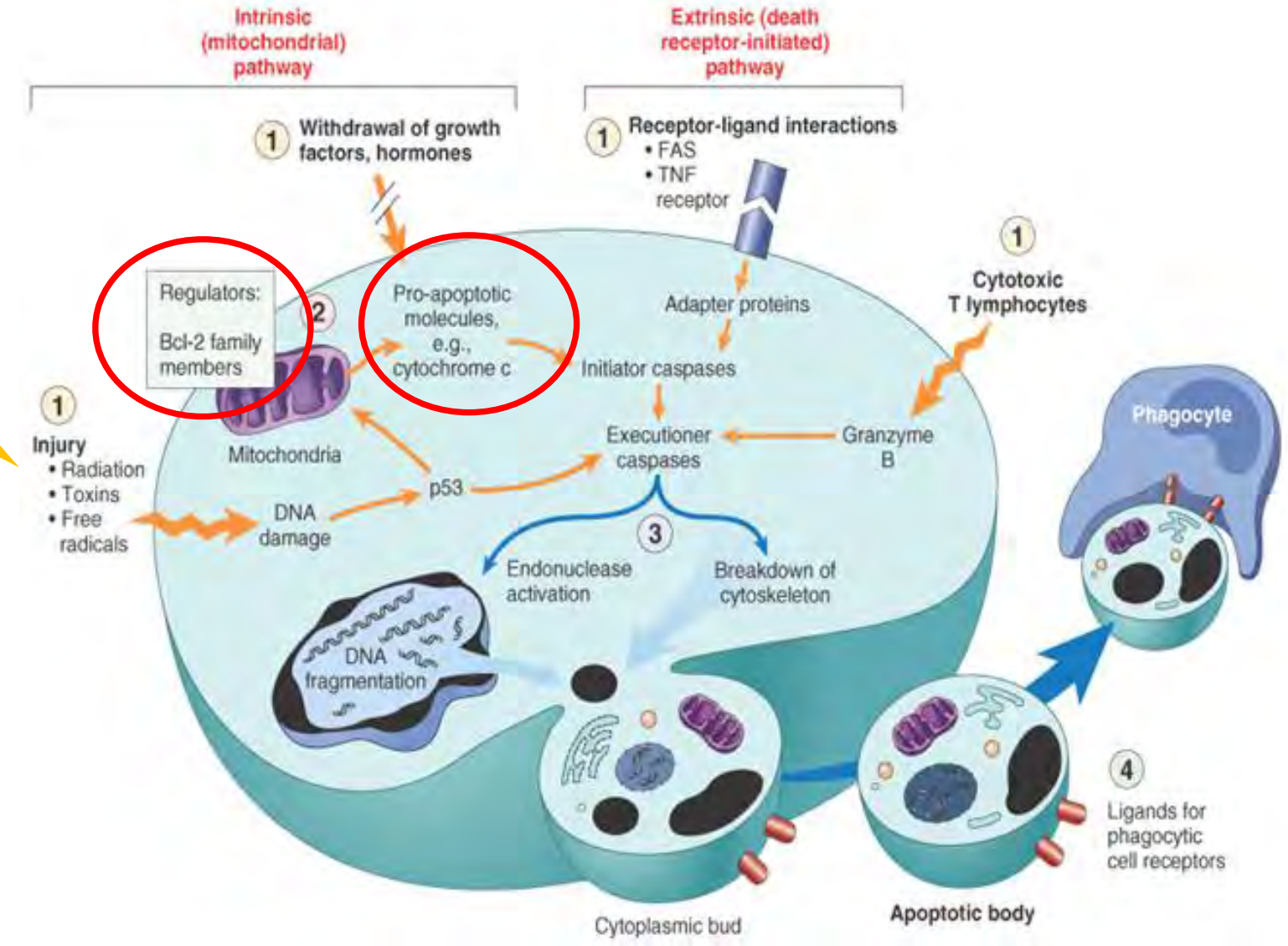
Bax

Bcl-2

- Tumor cells on biopsy specimens
- Tumor cells, PIN cells and healthy tissue cells after 12 Gy IORT

Radiation-induced death cell: so little known in single shot RT..

12 Gy



122 IORT + radical prostatectomy (2005, september – 2016, may)

12 Gy IORT

Patients selection:
- Preliminary study / Feasibility study
- Biopsy specimens
- No adjuvant hormono-therapy

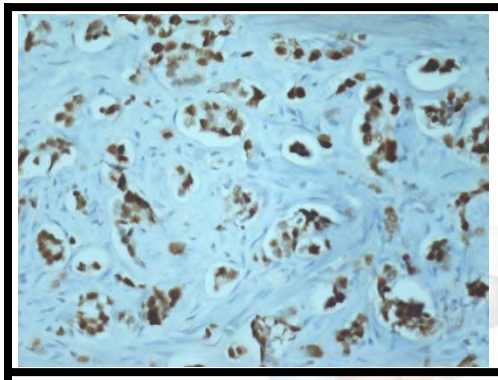
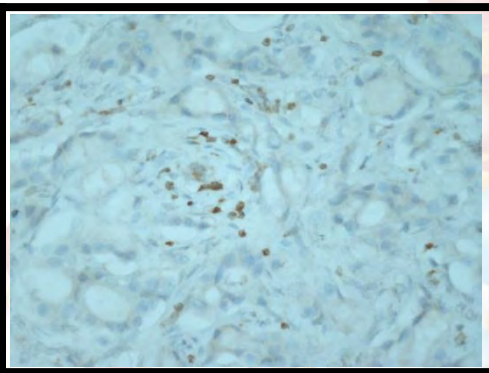
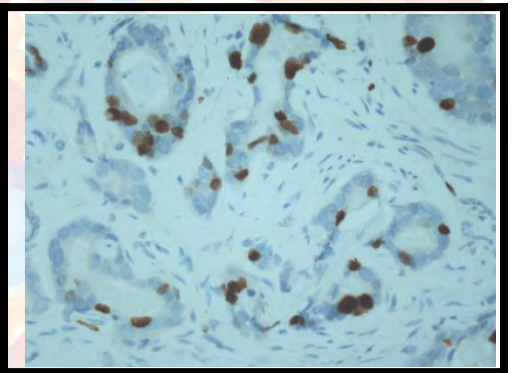
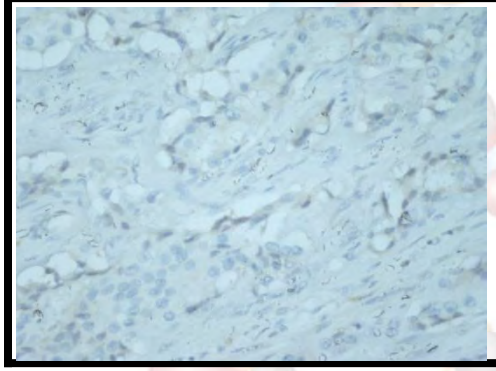
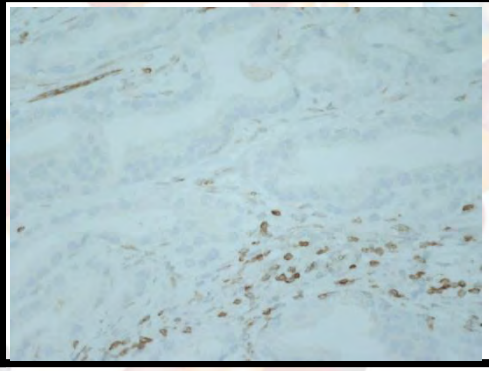
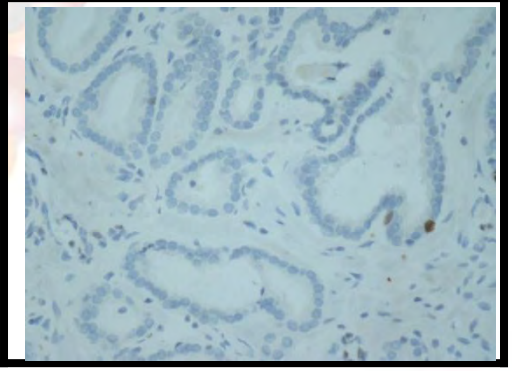
10 patients in this preliminary report

Medean age (min-max), ys	65 (52-74)
PSA (min-max), ng/ml	17.0 (4.47-41)
Gleason Score biopsy specimens (min-max)	8.5 (7-10)
Clinical stage	
cT2b	2 cases
cT3a	8 cases
cN0	8 cases
cN1	2 cases

Human Pathology:
Immunohistochemistry protocols

Human Anatomy:
Immunofluorescence

Results – 1

	p-53	Bcl-2	ki-67
+			
-			

Kluth M. Clinical significance of different types of p53 gene alteration in surgically treated prostate cancer. IJC 2014
Asmarinah A. Expression of the Bcl-2 family genes and complexes involved in the prostate mitochondrial transport. IJO 2014
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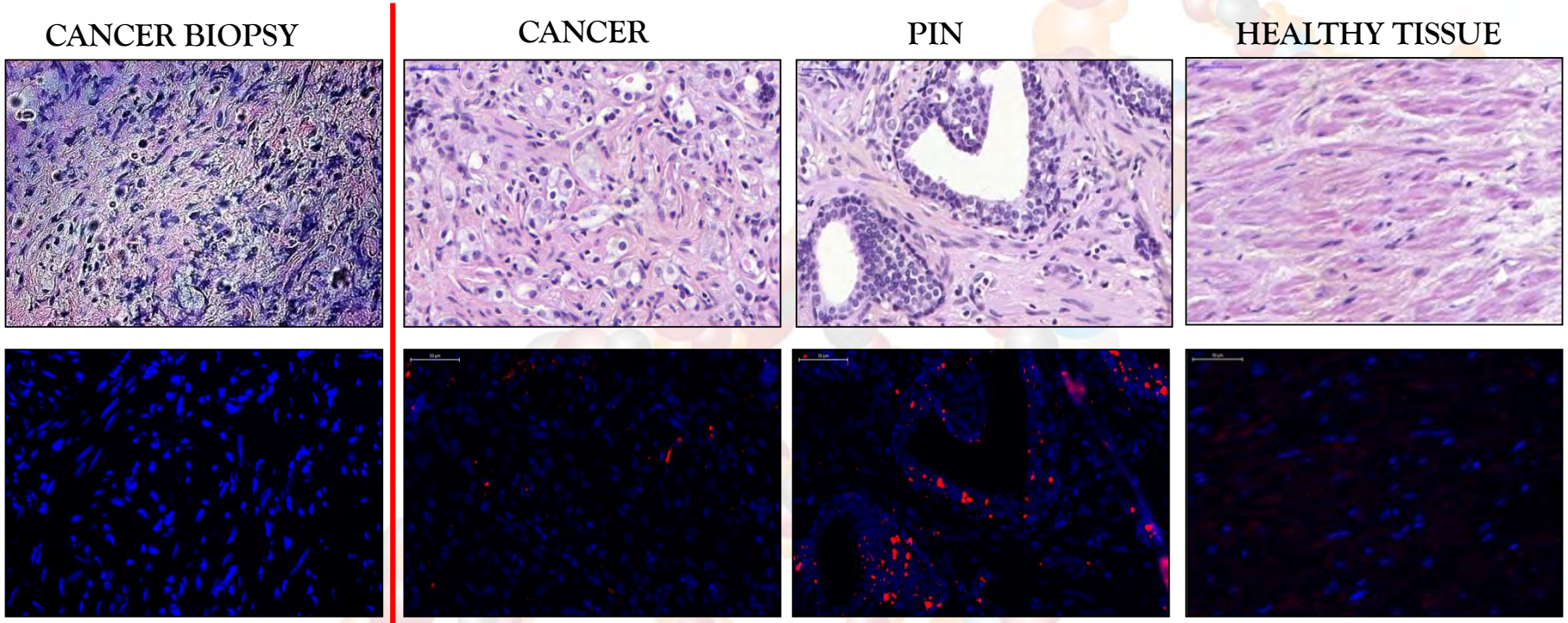
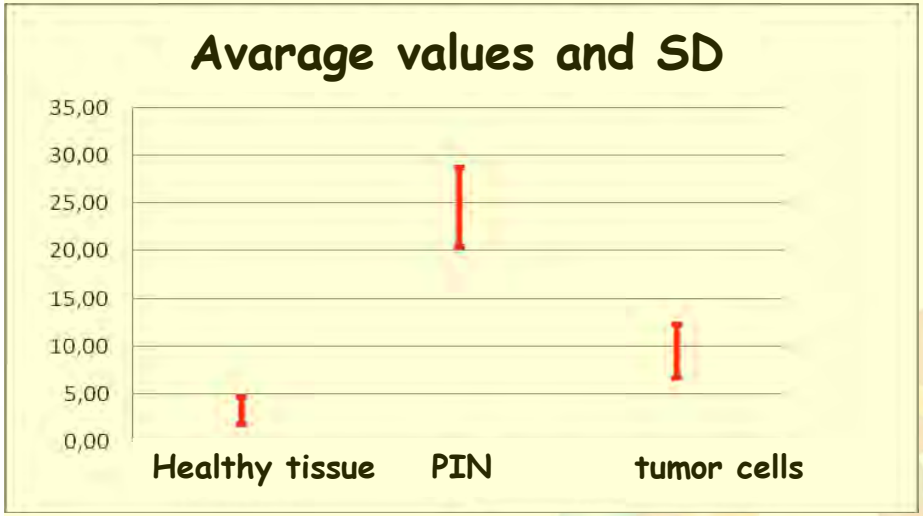
Results - 2



Avarage ± SD

1.66 ± 1.30	7.77 ± 4.60	21.51 ± 7.29	2.89 ± 1.86

Results - Bax



Tumor, PIN and healthy tissue post-IORT

	t-Student test
Haelthy tissue vs PIN	**p<0.0001**
Healthy tissue vs tumor	**p=0.0060**
Tumor vs PIN	**p=0.0001**

Before and after 12 Gy

	t-Student test
Healthy tissue vs biopsy	p=0.1035
Biopsy vs PIN	p=0.0001
Biopsy vs tumor cells	p=0.0008

"Preliminary" conclusions

- On biopsy specimens: the pro-apoptotic protein **Bax** is significantly less expressed than PIN cells and neoplastic areas after IORT → **before single high dose NO apoptosis**

- After 12 Gy, the pro-apoptotic protein Bax is significantly over-expressed in PIN cells ($p<0.0001$) and neoplastic areas ($p=0.0060$), while it is no expressed differently in healthy tissue → **selectivity in radio - induced damage even for irradiation in one shot, with sparing of healthy tissue**

Within 90-120' single shot, RT would activate mitochondrial apoptosis in tumor and PIN cells.

In our sample, PIN cells seem to be more sensitive to irradiation, in fact, PIN expresses Bax higher than the healthy tissue ($p < 0.0001$), and neoplastic areas ($p = 0.001$)

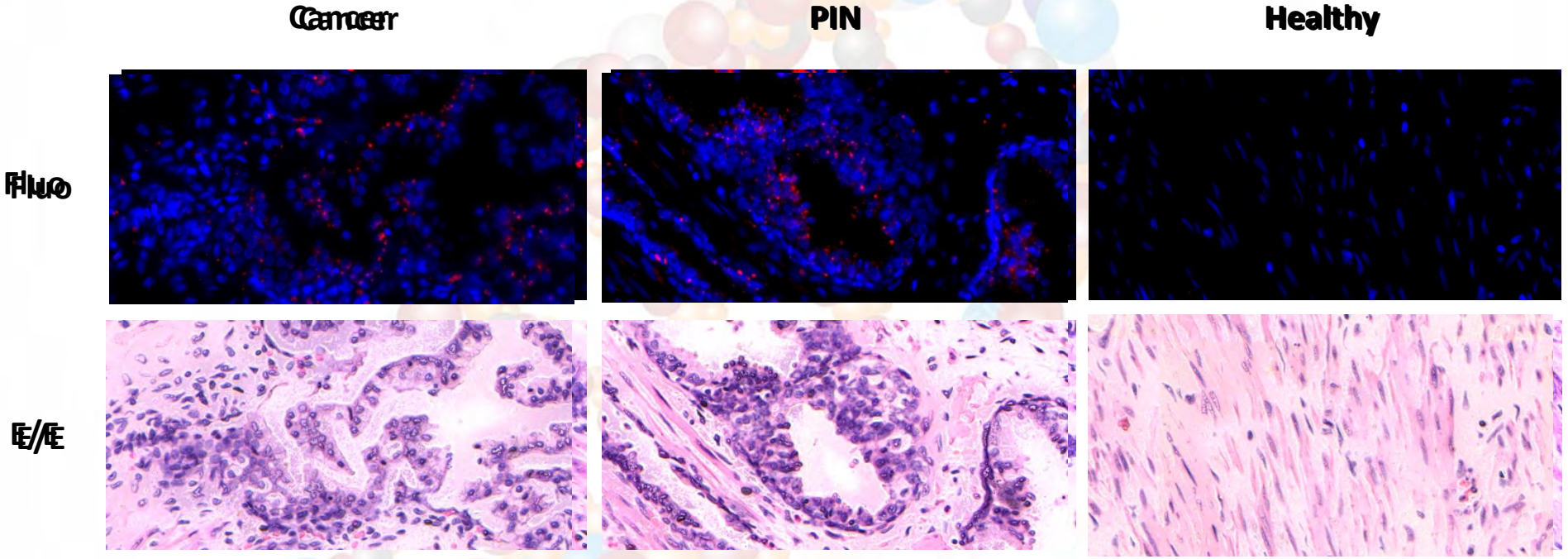
In animal model, it has been demonstrated that pre-neoplastic cells iper-expressed Bax protein.
Overexpression of pro-apoptotic proteins has been explained by the increased turnover in potentially malignant "cells."
However, neoplastic cells ipo-expressed apoptotic proteins because they have acquired "genetic resistance profile"

Xie W. The Prostate 2000

Future elements

Until now, we demonstrated the in vivo mitochondrial apoptosis activation by Bax.

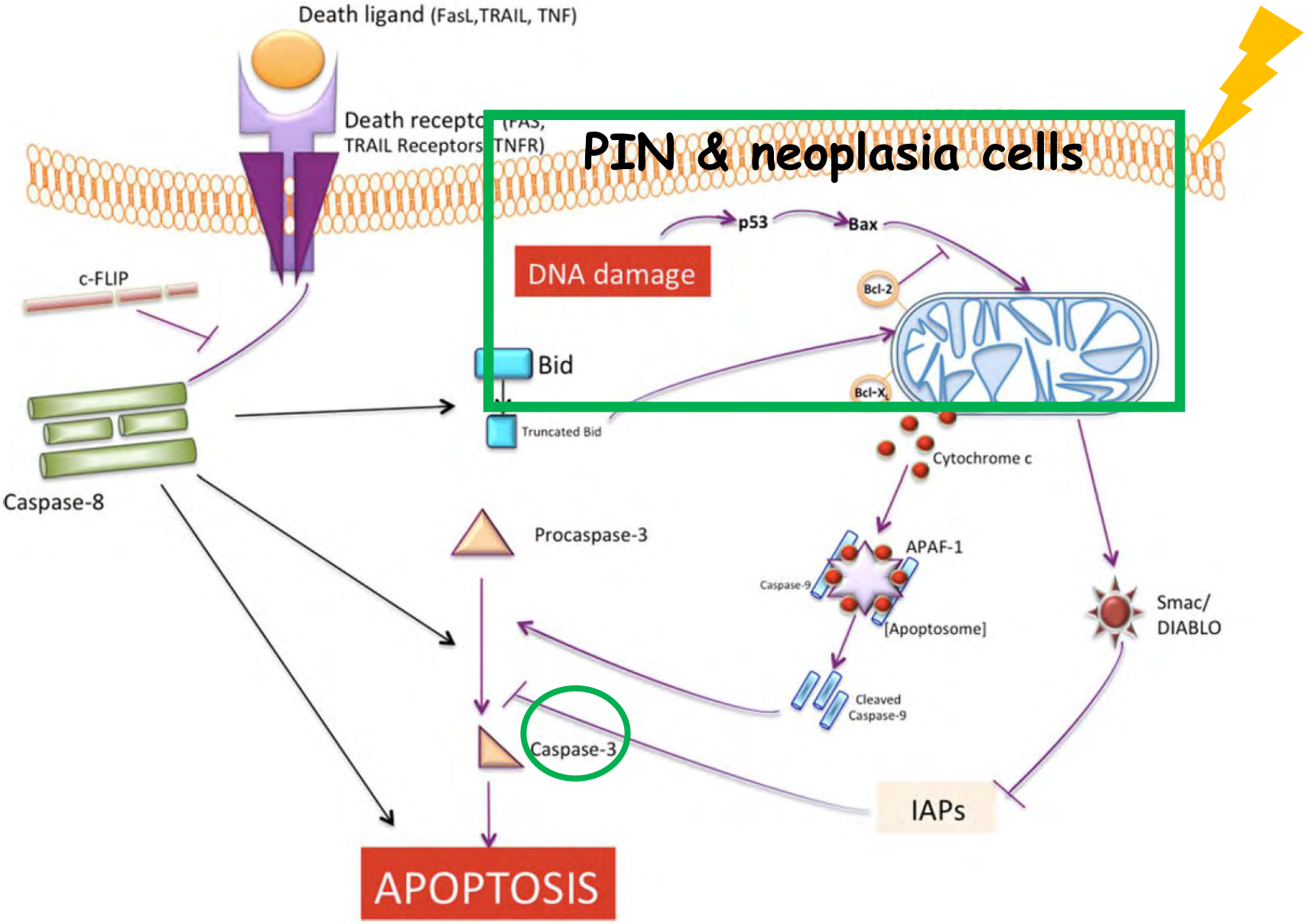
The next step is the evaluation of caspases (3 and 9) pathway.



Preliminary data show as the pathway of caspases is significantly expressed in cancer cells and in the areas of PIN after single shot

Single shot RT & apoptosis: in vivo radiobiological model

12 Gy



INTRAOPERATIVE RADIOTERAPY (IORT) IN THE MULTIMODALITY TREATMENT OF LOCALLY ADVANCED PROSTATE CANCER.

A. Volpe[1], D. Beldì[2], G. Marchioro[1], E. Ferrara[2], M. Billia[1], G. Loi[3], M. Krengli[2]

[1]Urology, [2]Radiotherapy, [3]Medical Physics, University Hospital "Maggiore della Carità", Novara, Italy

PURPOSE: The treatment for locally advanced prostate cancer is still a controversial issue and multimodality approaches can lead to treatment optimization. The aim of this study is to describe technical feasibility and clinical results of intra-operative radiotherapy (IORT) in patients with locally advanced prostate cancer.

MATERIAL /METHODS: A total of 120 patients have been enrolled in the present study thus far. The statistical analysis was performed in 97 patients with follow up > 12 months. Inclusion criteria were patients age < 76 years, KPS > 90 and at least 2 of the following preoperative risk factor: initial PSA (iPSA) > 10 ng/ml, Gleason Score ≥ 7, clinical staging ≥ cT2c according with TNM, probability of organ-confined disease < 25% according to MSKCC nomogram. Median age was 66.9 years (range 51-83), median iPSA was 14.8 ng/ml (range 2.0-154) and median Gleason Score (GS) was 8 (range 4-10). After surgical exposure of the prostate, IORT was delivered by a dedicated linear accelerator (Mobetron, Intraop, Sunnyvale, CA) with 30° beveled collimator, using an electron beam of 9 or 12 MeV to a total dose of 12 Gy. IORT was followed by radical prostatectomy and regional lymph node dissection. Rectal dose was measured "in vivo" by radio-chromic films placed on a rectal probe. All cases with pathological staging≥ pT3a, positive margins (R1) or metastatic lymph nodes (N1) received postoperative external beam radiotherapy (EBRT), delivered to surgical bed with 3D conformal technique or intensity modulated radiation therapy to a total dose of 46-50 Gy (2Gy/fraction). Patients with pT3 or pT4 disease and/or N1 received adjuvant hormonal therapy.

RESULTS: IORT procedure lasted in average 30 minutes (range 15-50). No major intra- or post-operative complication occurred. Median dose to the anterior rectal wall was 4.32 Gy (range 0.06-11.3). Pathological stage was: 30 pT2, 62 pT3, 5 pT4. 59/97 (60,8%) patients were R1 and 38/97 (39,2%) patients were N1. Median post operative PSA was 0.09 ng/ml (range 0-5.05). Post-operative radiotherapy was delivered to 76/97 patients (78.3%) with pathological staging ≥ pT3a or R1. Hormone therapy was prescribed to 63/97 patients (64.9%). Acute toxicity was: 16 G2 (9 GU; 7 GI), 2 G3 (1 GU; 1 GI). Late toxicity was: 11 G2 (5 GU, 6 GI), 4 G3 (2 GU; 2 GI). No G4 acute or late toxicity was observed. Twelve patients died of prostate cancer. With a median follow-up of 70 months (range 12-126), 35/97 patients experienced biochemical failure. Actuarial overall biochemical free survival (BFS) was 60% at 5 years; according to NCCN classification, 5-year BFS was 81% and 55 % in high and very high risk classes, respectively. Of note, no macroscopic failure in the prostate surgical bed was observed.

CONCLUSIONS: IORT during radical prostatectomy is a feasible procedure and allows to deliver safely post-operative EBRT to surgical bed without a significant increase of toxicity. With a median follow-up of 70 months, biochemical control seems to be favourable in particular for high risk patients.

Multi-Institution Phase II Trial of Intraoperative Electron Beam Radiotherapy Boost at the Time of Breast Conserving Surgery with Oncoplastic Reconstruction in Women with Early-Stage Breast Cancer

Jose G. Bazan

Ohio State University

June 25, 2016

Background

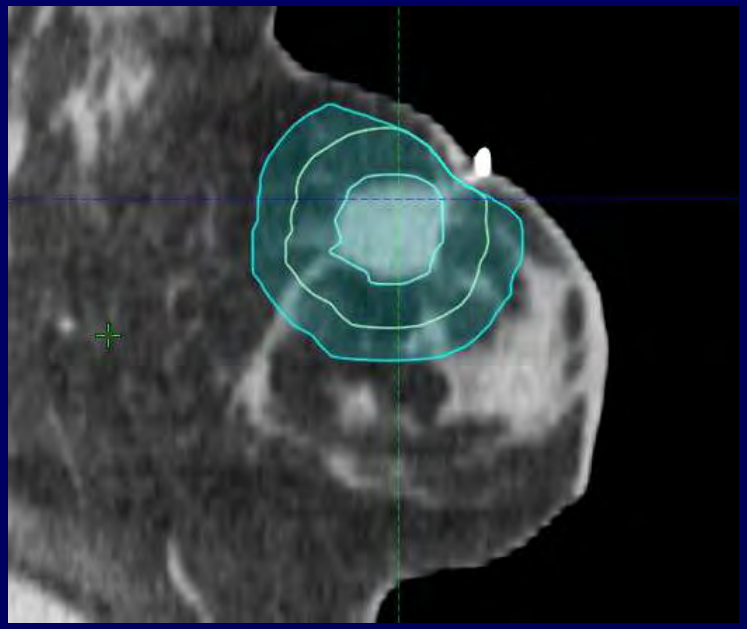
- Randomized trials have demonstrated that lumpectomy cavity boost helps to significantly reduce the risk of ipsilateral breast tumor recurrence

- There remains controversy regarding the exact definition of the boost target volume from an external beam radiotherapy technical planning perspective
  - Contemporary trials define the boost target volume as a 1.7 cm isometric expansion on the lumpectomy cavity

- Delineation of the lumpectomy cavity on CT can be challenging

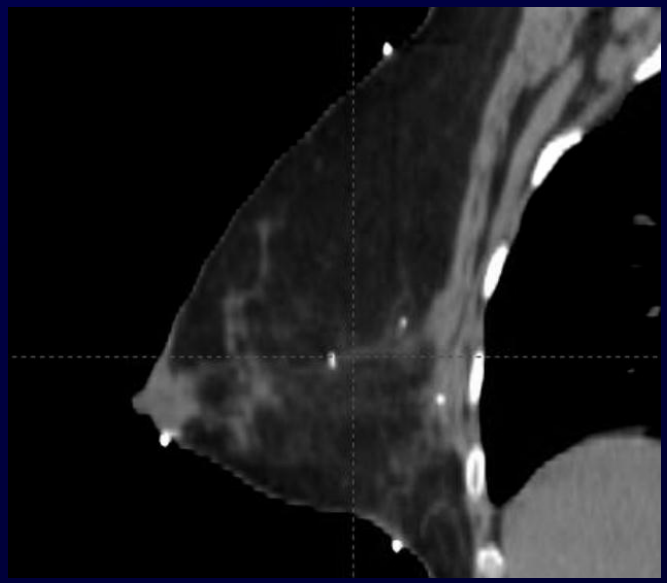
Background

- Oncoplastic techniques are increasingly being used in breast conserving surgery
- Oncoplastic techniques are used to prevent the poor cosmetic results that can occur when a large volume of breast tissue is resected
- In these cases, additional breast tissue is resected and/or rearranged to help provide an esthetically improved breast shape
  - Lumpectomy cavity may be incised and separated with different portions ending up in different quadrants of the resected breast



Standard post-lumpectomy case with well-defined cavity

Patient that underwent oncoplastic reconstruction



Rationale

- Intraoperative radiation (IORT) at the time of lumpectomy but just prior to oncoplastic reconstruction is one strategy to overcome the problem of lumpectomy cavity delineation
  - Allows direct visualization of the surgical cavity
  - Spares the skin of radiation
  - Reduces treatment time by 1-2 weeks

- Retrospective studies have demonstrated extremely low rates of local recurrence using IORT as a boost prior to standard whole breast radiation

- Use of an IORT boost prior to oncoplastic reconstruction are limited to case reports and small series underscoring the need for a prospective clinical trial

Rationale

- IORT boost dose chosen for this protocol is based on biologic effective dose

EBRT	BED3		IORT	BED3
2 Gy x 5	16.7 Gy		6 Gy x 1	18 Gy
2 Gy x 6	20 Gy		7 Gy x 1	26.7 Gy
2 Gy x 7	23.7 Gy		8 Gy x 1	29.3 Gy
2 Gy x 8	26.7 Gy		10 Gy x1	43.3 Gy

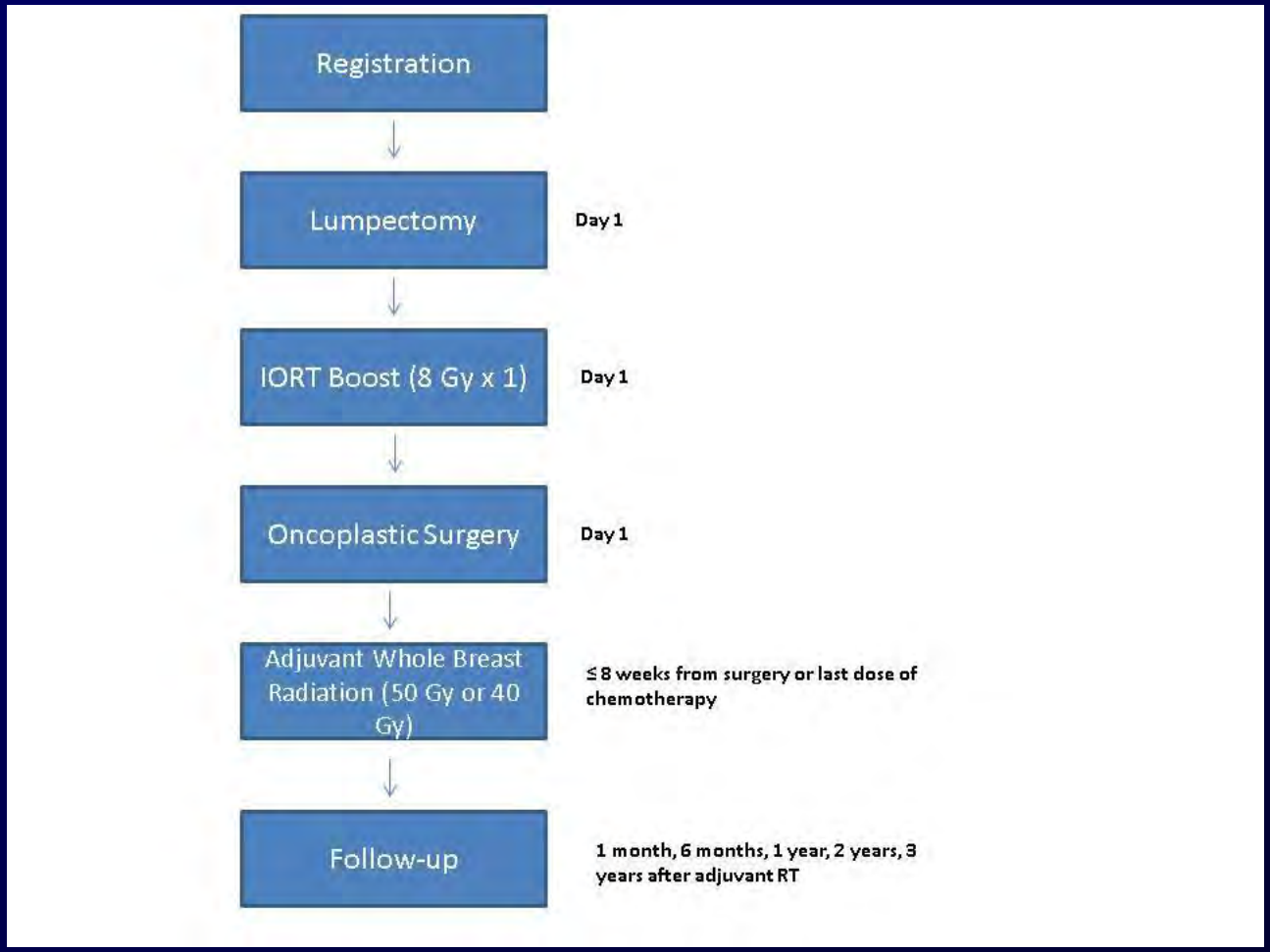
Chosen for protocol

Reported in literature

Hypothesis

- The rate of grade 3 fibrosis in women receiving IORT boost followed by whole breast radiotherapy will be ≤5% at 1 year from the end of treatment

Study Schema



Endpoints

- Primary Objectives
  - To determine the rate of grade 3 breast fibrosis at 1 year in women undergoing lumpectomy with oncoplastic reconstruction and immediate IORT boost followed by adjuvant whole breast radiation therapy

LENT SOMA Scale for Breast Fibrosis

Grade 1: Barely palpable, increased density

Grade 2: Definite increased density and firmness

Grade 3: Very marked density, retraction and fixation

Endpoints

- Secondary Objectives
  - To determine the rate of 5 year ispilateral breast tumor recurrence rate
  - To determine the change in self-reported cosmesis using the BCTOS cosmesis scale
  - To determine the change in physician-reported cosmesis

BCTOS Scale (PRO)

	Difference between treated and untreated breast and area			
	None	Slight	Moderate	Large
1. Breast size.....	1	2	3	4
2. Breast texture (hardening)	1	2	3	4
3. Arm heaviness.....	1	2	3	4
4. Nipple appearance.....	1	2	3	4
5. Shoulder movement	1	2	3	4
6. Arm movement	1	2	3	4
7. Breast pain.....	1	2	3	4
8. Ability to lift objects.....	1	2	3	4
9. Fit of shirt sleeve.....	1	2	3	4
10. Breast tenderness.....	1	2	3	4
11. Shoulder stiffness.....	1	2	3	4
12. Breast shape.....	1	2	3	4
13. Breast elevation (how high the breast is).....	1	2	3	4
14. Scar tissue.....	1	2	3	4
15. Shoulder pain.....	1	2	3	4
16. Arm pain.....	1	2	3	4
17. Arm swelling.....	1	2	3	4
18. Breast swelling.....	1	2	3	4
19. Arm stiffness.....	1	2	3	4
20. Fit of bra.....	1	2	3	4
21. Breast sensitivity.....	1	2	3	4
22. Fit of clothing.....	1	2	3	4

Harvard Breast Cosmesis Scale

1. Excellent	When compared to the untreated breast, there is minimal or no difference in the size or shape of the treated breast. The way the breast feels (its texture) is the same or slightly different. There may be thickening, scar tissue, or fluid accumulation within the breast, but not enough to change the appearance.
2. Good	There is a slight difference in the size or shape of the treated breast as compared to the opposite breast or the original appearance of the treated breast. There may be some mild reddening or darkening of the breast. The thickening or scar tissue within the breast causes only a mild change in the shape or size.
3. Fair	Obvious difference in the size and shape of the treated breast. This change involves one-quarter or less of the breast. There can be moderate thickening or scar tissue of the skin and the breast, and there may be obvious color changes.
4. Poor	Marked change in the appearance of the treated breast involving more than one-quarter of the breast tissue. The skin changes may be obvious and detract from the appearance of the breast. Severe scarring and thickening of the breast, which clearly alters the appearance of the breast, may be found.

Key Eligibility Criteria

- Women aged ≥ 18 yrs AND ≤60 yrs (women routinely boosted)
- Stage I or II
- Multifocal disease is allowed if intent is to undergo resection through a single lumpectomy incision

Key Ineligibility Criteria

- T4, N2 or N3, M1 or pathologic stage III/IV breast cancer
- DCIS only
- Intention to administer neoadjuvant chemotherapy prior to resection
- Prior radiotherapy to the breast or prior radiation to the region of the ipsilateral breast that would result in overlap of radiation fields

Safety/Feasibility Component

- First 30 patients will be used to determine the safety
  - Evaluated by the rate of surgical complications necessitating hospital admission or return to the operating room within 30 days of surgery+IORT
  - Greater than 15% incidence rate will be considered unacceptable

Halt if Number of Complications is equal or more than	Total Patients Treated
4	10
7	20
9	30

Sample Size Determination for Primary Endpoint

- Primary endpoint of the study is grade 3 fibrosis at 1 year with a hypothesis that the rate will be ≤ 5%
- A rate of 9% or more will be considered unacceptable

Non-inferiority proportion	Actual Proportion	Target alpha	Actual Alpha	Sample Size	Power
9%	3%	0.05	0.0474	100	82%
9%	4%	0.05	0.0479	158	82%
9%	5%	0.05	0.0496	266	82%

Assuming 10% dropout rate, sample size is 176 patients

Accrual

- Estimated accrual is projected to be 8 per month (in the multi-institutional setting) with a ramp up period in the first 6 months
- Estimated time to complete accrual is approximately 24 months

Study Calendar

Assessments	At or Prior to Study Entry – Pre IORTb/Surgery (Registration)	Prior to Start of Adjuvant RT (Post IORTb/Surgery)	Last Day of Adjuvant RT	1 Month After RT Completion	6 Months After RT Completion	1 year After RT Completion Then Annually x 5 years
History&Physical, Zubrod, weight documentation	X[1]	X[4]	X	X	X	X
Breast examination	X[1]	X[4]	X	X	X	X
Right and Left mammogram	X[1]					X
Performance Status	X[1]	X[4]	X	X	X	X
CBC with diff & ANC	X[1]					
Chemistry Panel	X[1]					
Serum or Urine Pregnancy Test (if applicable)	X[2]	X[2]				
Bone Scan	X[3]					
PET/CT or CT chest/abdomen/pelvis	X[3]					
Adverse Event Evaluation		X[4]	X	X	X	X
Doctor cosmetic assessment (questionnaire and photos)	X	X[4]				X (year 1 and year 3)
Patient questionnaire (BCTOS)	X	X[4]		X	X	X (for 3 years)

Participating Centers

Ohio State University

UNC-Chapel Hill

Scripps Hospital (California)

Avera Hospital (South Dakota)

St. Luke's Hospital (Iowa)

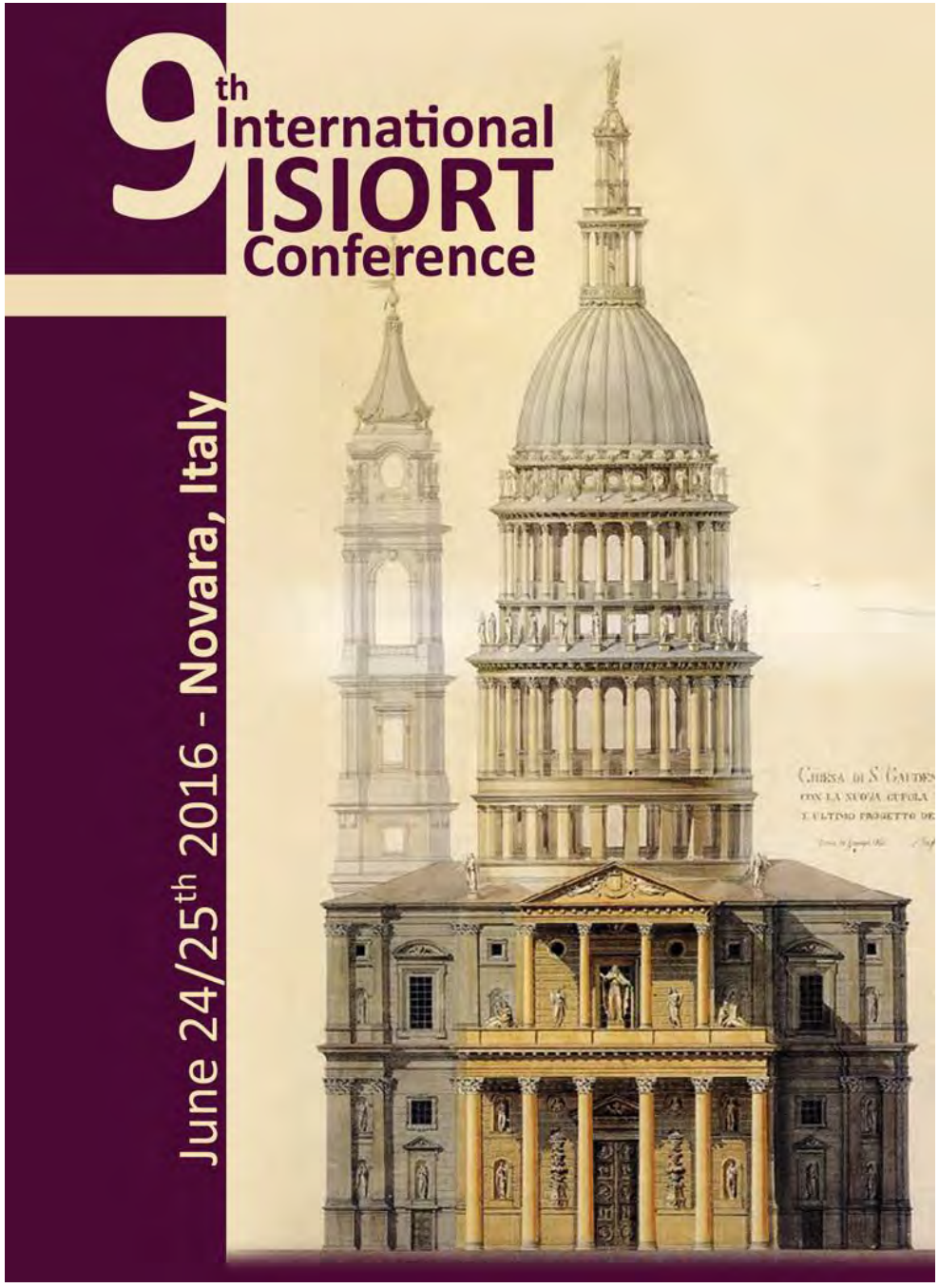
St. Joseph's Hospital (California)

Acknowledgements

Derek DeScioli

Julia White

Don Goer



UNIVERSITÀ DEL PIEMONTE ORIENTALE

University of Piemonte Orientale
Maggiore della Carità Hospital
Novara, Italy

IORT IN HIGH RISK PROSTATE CANCER

M. Billia, MD, FEBU
Consultant Urological Surgeon
Department of Urology

DISCLOSURE

- Nothing to disclose
- No conflict of interest

BACKGROUND

High risk, locally advanced

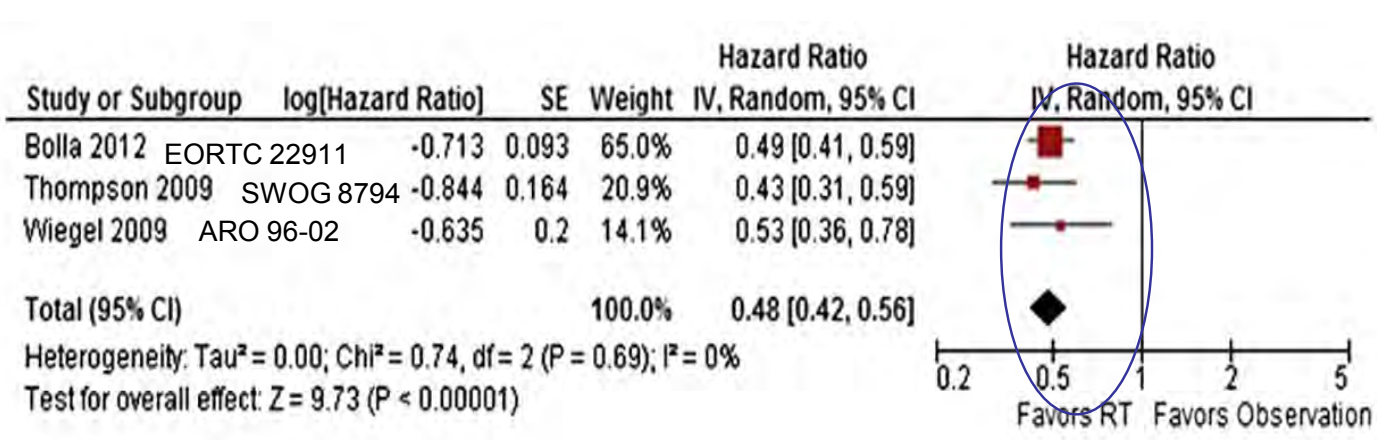
Conventional treatment (S/EBRT/HT):

37-62% Relapse-Free Survival @ 5 yrs

40% Local Failure after radical prostatectomy

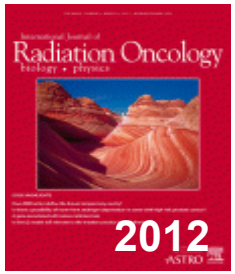
Randomized Trials with adjuvant EBRT in case of risk factors:
T3a/b and R+

Advantage in terms of bRFS



NCCN GL, v 3.2016
EAU GL,2015
Morgans et al, R&O 2008
Valicenti et al, IJROBP 2013

RATIONAL OF HYPOFRACTIONED RT OF PCa



CLINICAL INVESTIGATION **Genitourinary Cancer**

DOSE-FRACTIONATION SENSITIVITY OF PROSTATE CANCER DEDUCED FROM RADIOTHERAPY OUTCOMES OF 5,969 PATIENTS IN SEVEN INTERNATIONAL INSTITUTIONAL DATASETS: α/β = 1.4 (0.9–2.2) GY

RAYMOND MIRALBELL, M.D.,*† STEPHEN A. ROBERTS, PH.D.,‡ EDUARDO ZUBIZARRETA, M.D.,§ AND JOLYON H. HENDRY, PH.D.‖

ANTICANCER RESEARCH *33*: 1009-1012 (2013)

Is the α/β Ratio for Prostate Tumours Really Low and Does It Vary with the Level of Risk at Diagnosis?

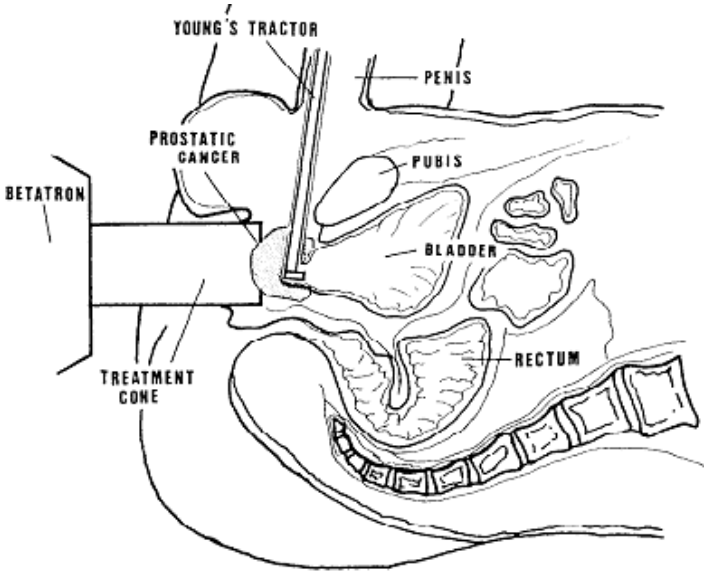
JACK F. FOWLER[1], IULIANA TOMA-DASU[2] and ALEXANDRU DASU[3]

α/β: 1.55

Low α/β → sensitivity to high dose/fraction: rationale for single dose and hypofractionation

Potential advantage on local control

HISTORY OF IORT OF PROSTATE CANCER



Int. J. Radiation Oncology Biol. Phys., Vol 11, pp. 147–151
Printed in the U.S.A.

INTRAOPERATIVE RADIOTHERAPY IN THE DEFINITIVE TREATMENT OF LOCALIZED CARCINOMA OF THE PROSTATE

MASAJI TAKAHASHI, M.D.,* KENICHIRO OKADA, M.D.,† YUHTA SHIBAMOTO, M.D.,*
MITSUYUKI ABE, M.D.* AND OSAMU YOSHIDA, M.D.‡

Kyoto University School of Medicine, Sakyoku, Kyoto 606, Japan

Lithotomy position
Perineal access
No RP
IORT as a boost, followed by EBRT

● *Original Contribution*

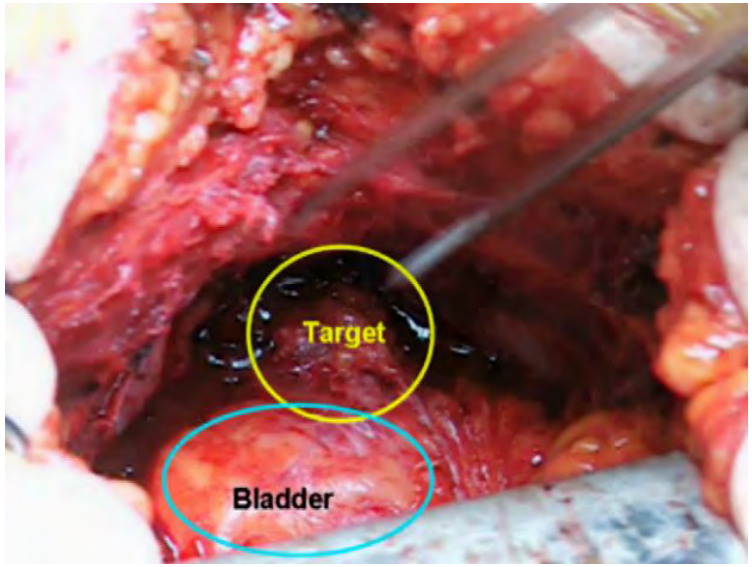
INTRAOPERATIVE RADIOTHERAPY: THE JAPANESE EXPERIENCE

MITSUYUKI ABE, M.D. AND MASAJI TAKAHASHI, M.D.

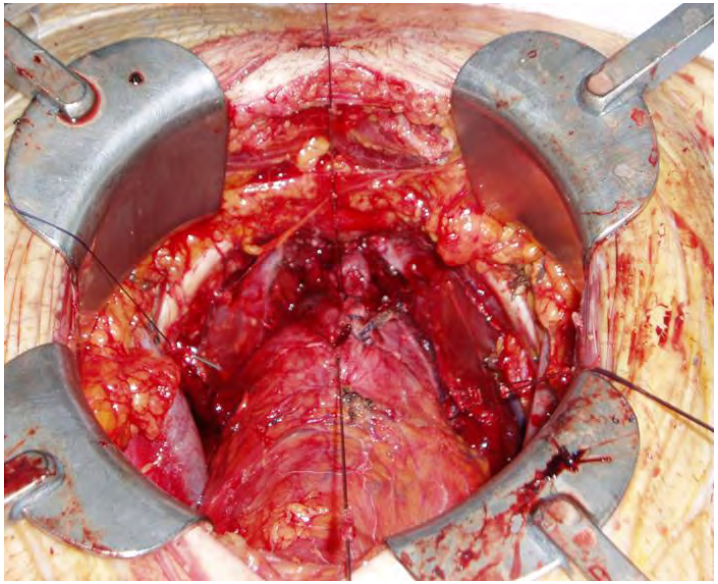
Int. J. Radiation Oncology Biol. Phys., Vol. 7, pp. 863–868
Printed in the U.S.A.

IORT DURING RADICAL PROSTATECTOMY

Author	#	Patients' selection	Surgical approach	IORT Energy / Dose	EBRT
Orecchia 2007	11	Interm.-high risk	Retropubic IORT-RP	8-10 MeV / 12 Gy	45 Gy, 1.8 Gy/fx
Saracino 2008	34	Interm. risk	Retropubic RP-IORT	7-9 MeV / 16-22 Gy (dose escalation)	no
Rocco 2009	33	Interm.-high risk	Retropubic IORT-RP	8-10 MeV / 12 Gy	45 Gy, 1.8 Gy/fx
Krengli 2010	38	Interm.-high risk	Retropubic IORT-RP	9-12 MeV / 10-12 Gy	46-50 Gy, 2 Gy/fx



(Saracino, 2008)



(courtesy of R. Orecchia)

FEASIBILITY STUDY

CLINICAL INVESTIGATION Prostate

INTRAOPERATIVE RADIOTHERAPY DURING RADICAL PROSTATECTOMY FOR LOCALLY ADVANCED PROSTATE CANCER: TECHNICAL AND DOSIMETRIC ASPECTS

MARCO KRENGLI, M.D.,* CARLO TERRONE, M.D.,† ANDREA BALLARÈ, M.D.,* GIANFRANCO LOI, PH.D.,‡ ROBERTO TARABUZZI, M.D.,† GIANSILVIO MARCHIORO, M.D.,† DEBORA BELDÌ, M.D.,* ELEONORA MONES, PH.D.,‡ CESARE BOLCHINI, R.T.,* ALESSANDRO VOLPE, M.D.,† AND BRUNO FREA, M.D.§

Departments of *Radiotherapy, †Urology, ‡Medical Physics, University Hospital Maggiore della Carità, Novara, Italy; and §Department of Urology, Hospital S. Maria della Misericordia, Udine, Italy

Table 1. Preoperative characteristics of study patients

No. of patients	38
Age, y, median (range)	67 (56–76)
Karnofsky performance status, mean	90
Initial PSA (ng/ml), median (range)	39.5 (2.9-63.9)
Biopsy Gleason score	
<7	5 (15%)
≥7	33 (85%)
Clinical stage* (TNM 2002 classification)	
≤T2c	11 (29%)
>T2c	27 (71%)
Neoadjuvant hormone therapy	11 (29%)

* Based on digital rectal examination, transrectal ultrasound, and abdominal computed tomography.

Table 3. Acute toxicity after postoperative external beam radiotherapy according to the Radiation Therapy Oncology Group scale (13)

Toxicity	G0 patients, *n* (%)	G1 patients, *n* (%)	G2 patients, *n* (%)
Gastrointestinal toxicity	22/27 (81.5%)	2/27 (7.5%)	3/27 (11%)
Genitourinary toxicity	25/27 (93%)	1/27 (3.5%)	1/27 (3.5%)

IOERT, electrons of 9 to 12 MeV
Total dose of 10-12 Gy.
Rectal dose measured in vivo by radiochromic films placed on a rectal probe (Mean 3.9 Gy).

No major intra- or postoperative complications oc- curred. Minor complications were observed in 10/33 (30%) of cases.

IORT DURING RADICAL PROSTATECTOMY

STUDY DESIGN

Phase II, non randomized, single arm trial
July 2005 – ongoing
Tertiary referral academic center
Joint team of radiation oncologists and urologists

Inclusion criteria

- High/very high risk Pca patients according NCCN
- Age $\leq$76y
- Primary Bx Gleason Score $\geq$ 4
- Presenting PSA>20 ng/ml
- Probability of organ confined tumour<25% (MSKCC nomogram)

Exclusion criteria

- unfit for surgery
- ASA score>3
- History of BID
- Previous prostate EBRT /BRT
- bone and/or visceral mets

TECHNIQUE

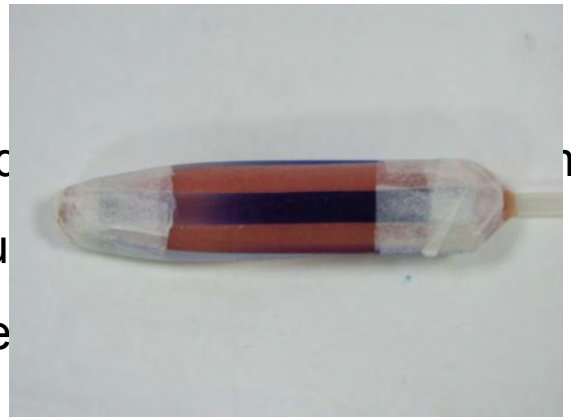
Rectal probe (12 cm, diam. 2.5 cm)

4 radio-chromic films positioned on the surface

ec

cu

se



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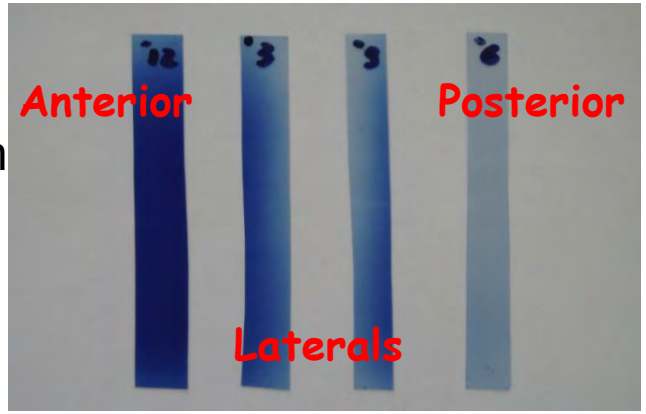
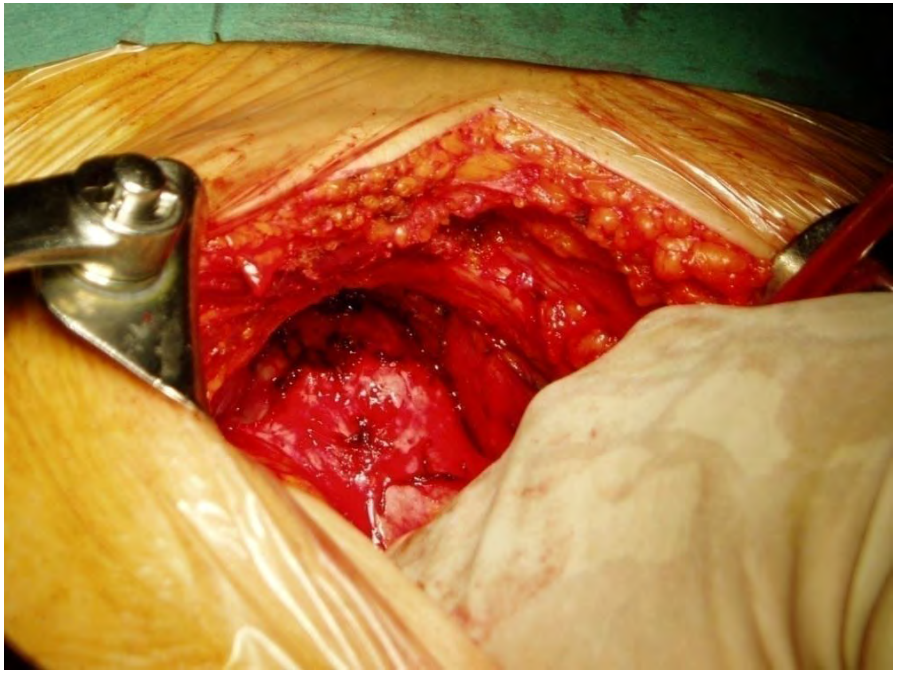
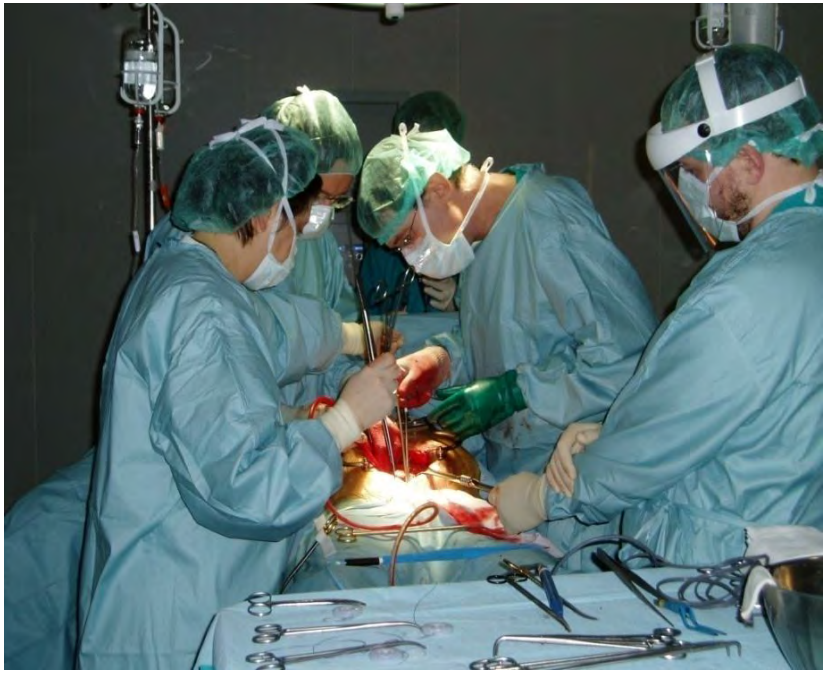
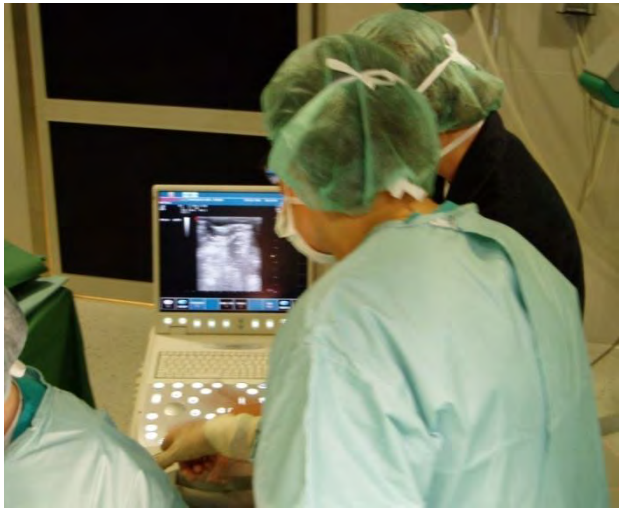


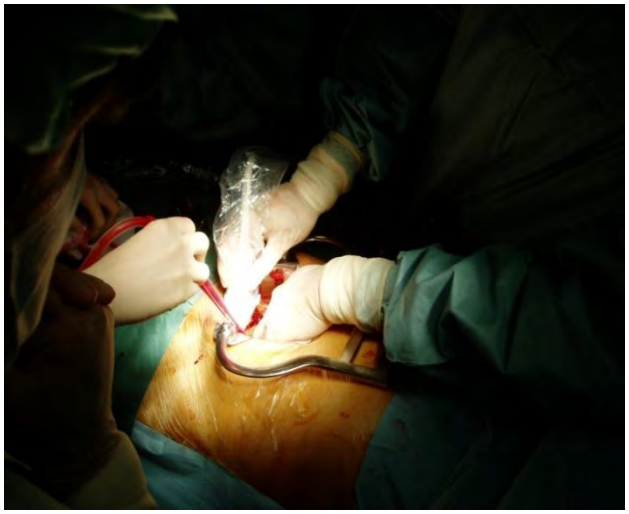


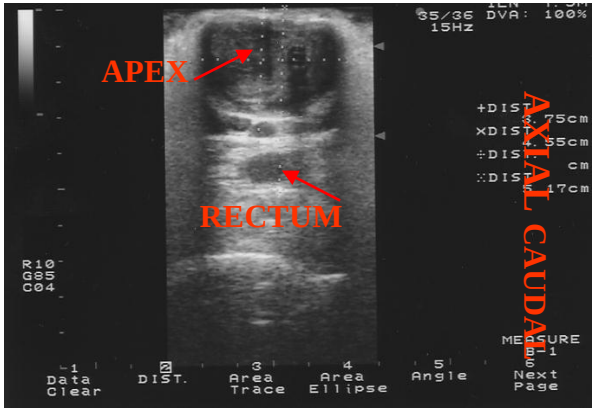


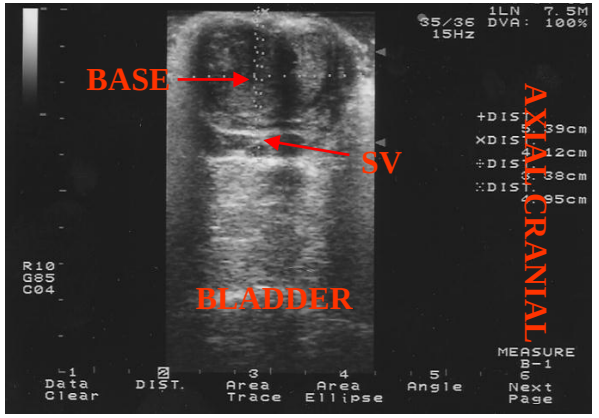
IORT TECHNIQUE

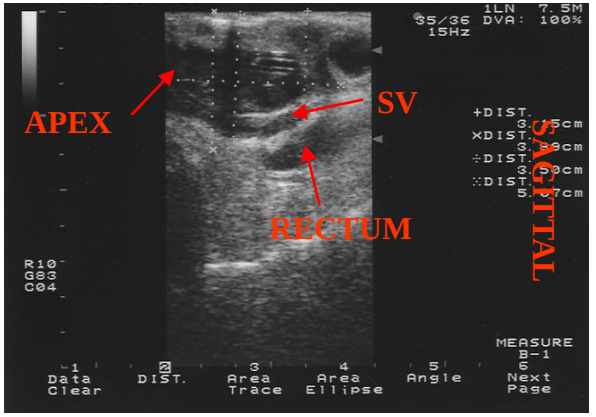
Intraoperative ultrasound







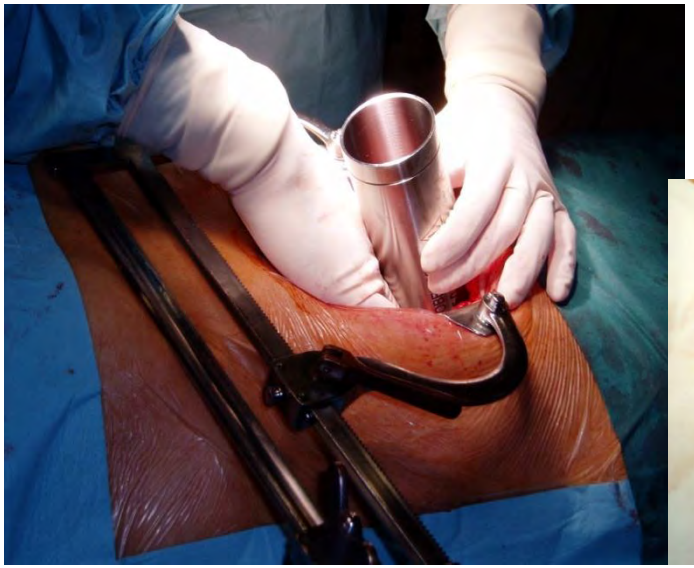


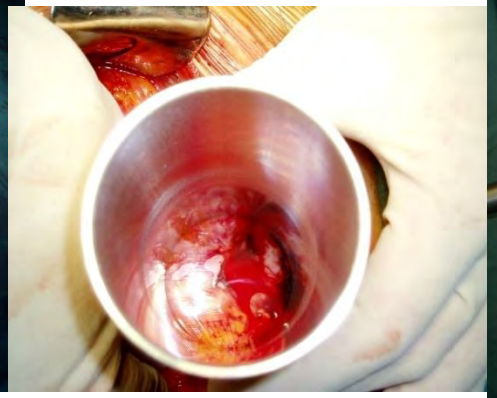


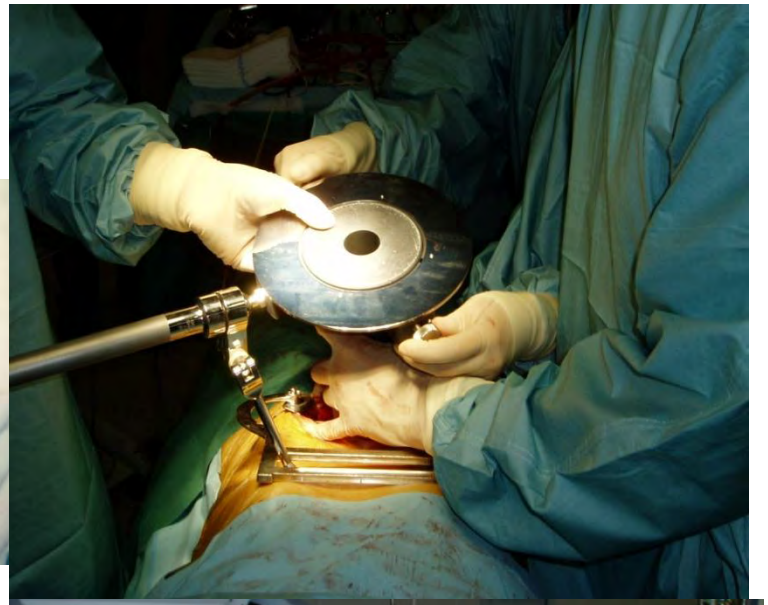
Ultrasound is mandatory to choose delivered beam energy

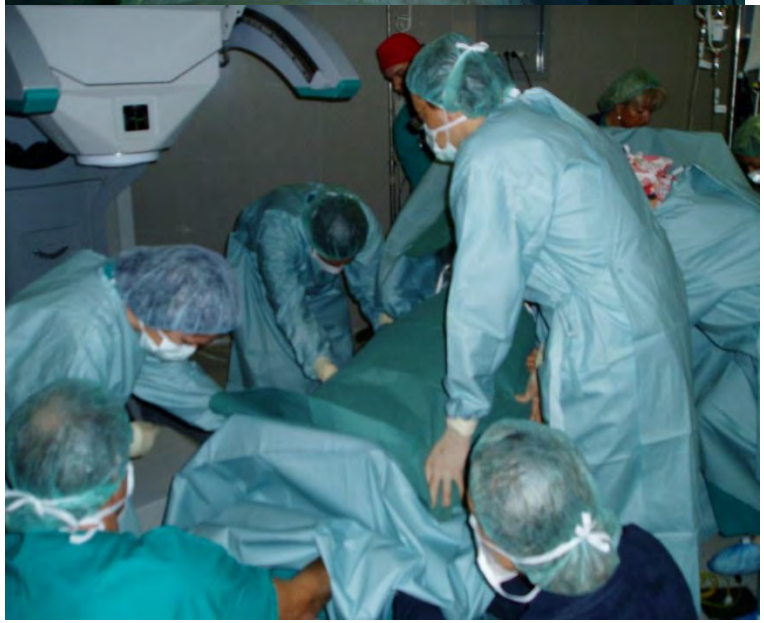
- 9 MeV (47%)
- 12 MeV (53%)

IORT TECHNIQUE





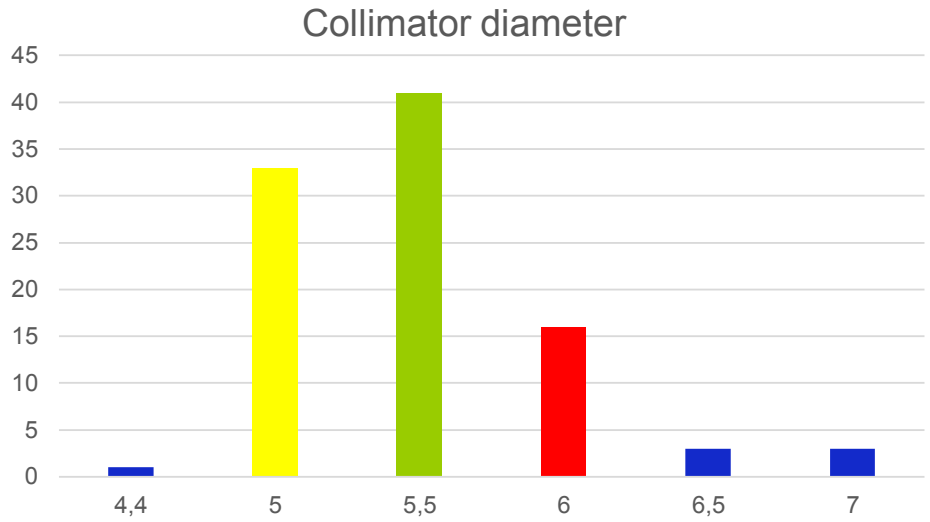




IORT target:

Prostate *plus* a surrounding margin of 0.5-1 cm

IORT



Collimator angulation:

30° (97%); 15° (3%)

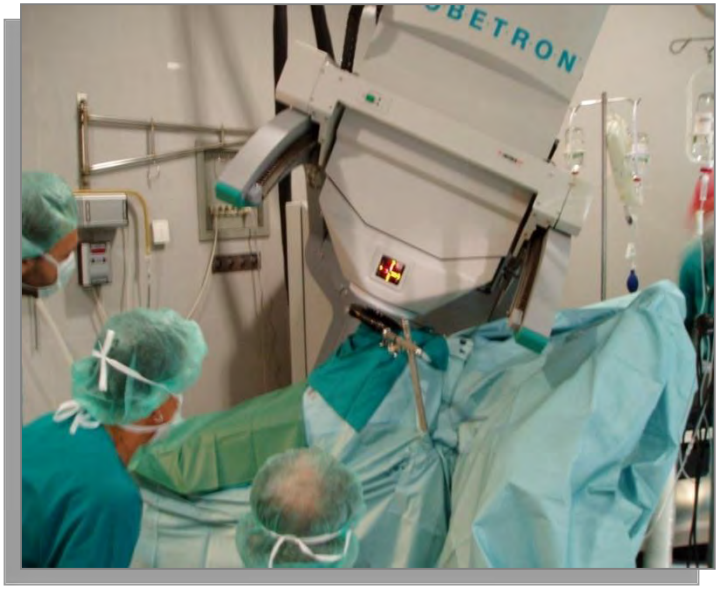
Mobile Linac: Mobetron, Intraop

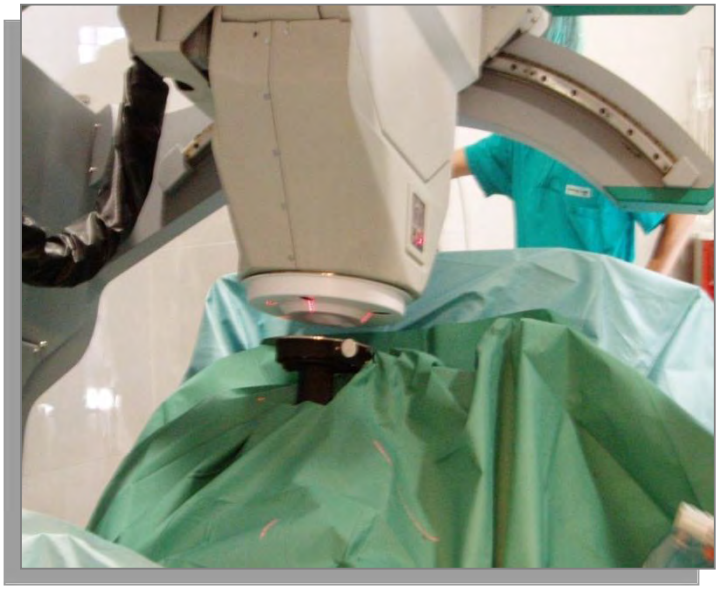
Energy: 9 MeV (47%) - 12 MeV (53%)

Target Dose: 12 Gy (90% isodose)

Median IORT time is 30 min (range 15-40 mins)

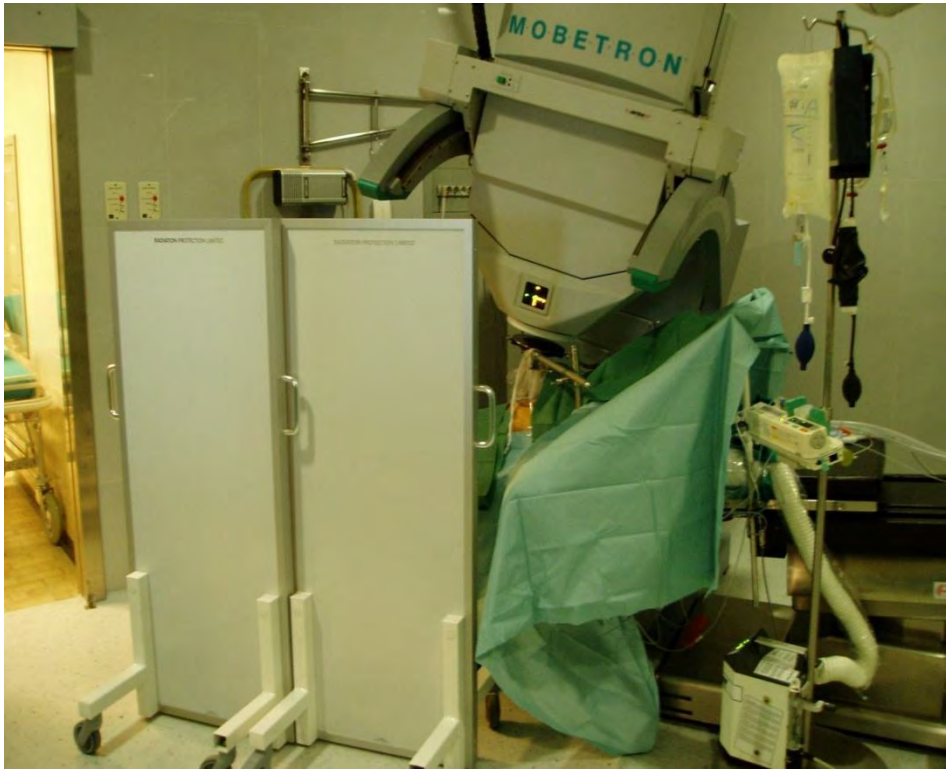
IORT – SOFT DOCKING





An air gap is maintained between collimator and nozzle

The bladder is outside the target avoiding the risk of traumatizing the tissues with movements of the machine



RESULTS

- 122 patients enrolled
- 97 patients with minimum follow-up of 12 mo

BASELINE CHARACTERISTICS

PARAMETER	VALUE
Age (years)	66.9 (51-83)
PSA at Bx (ng/ml)	14.8 (2.0-154)
Gleason Score sum Bx	8 (6-10)
Positive cores (n)	10/12 (8-12)
Prior ADT - Bicalutmide 150 mg - LHRH agonist	31/97 (32%) 90.3% 9.7%

RESULTS

PATHOLOGY

Median Bioptical GS → 8

Range (4-10)

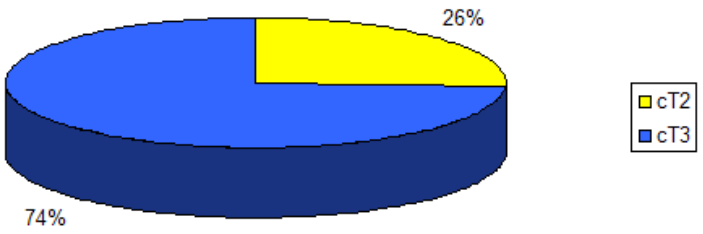
→

Median Patological GS → 9

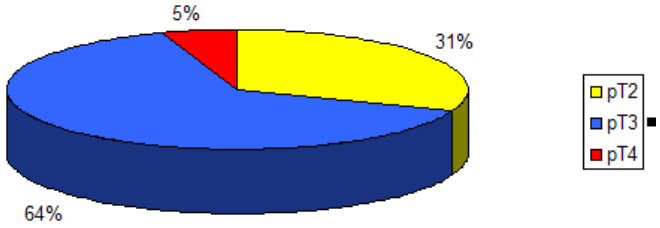
Range (6-10)

Clinical Stage cT3: 72/97 74 %
cT2: 25/97 26 %

Patological stage 30/97 pT2 (31 %)
62/97 pT3 (64 %)
5/97 pT4 (5 %)



→



R+: 59/97 (60,8%)
pN+: 38/97 (39,2%)
pT3/4: 67/97 (69%)

→

EBRT

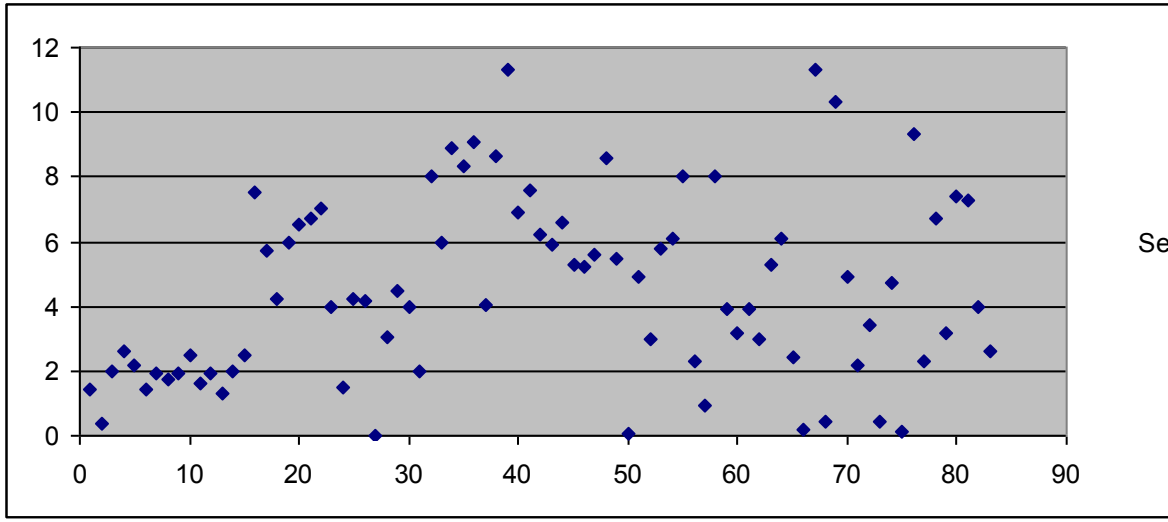
76/97 pts (78.3%)

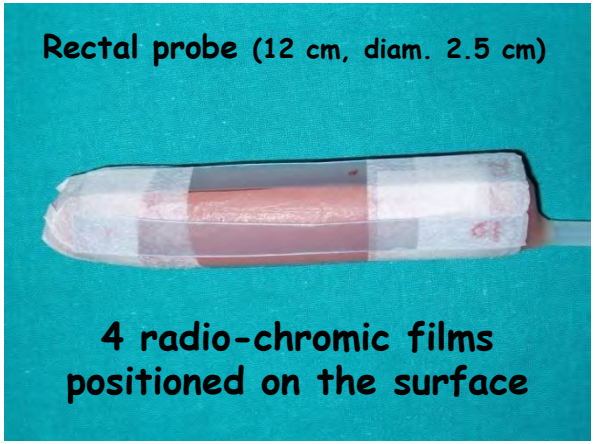
Adjuvant ADT prescribed to 63/97 patients (64.9%). (pT3/4 N1)

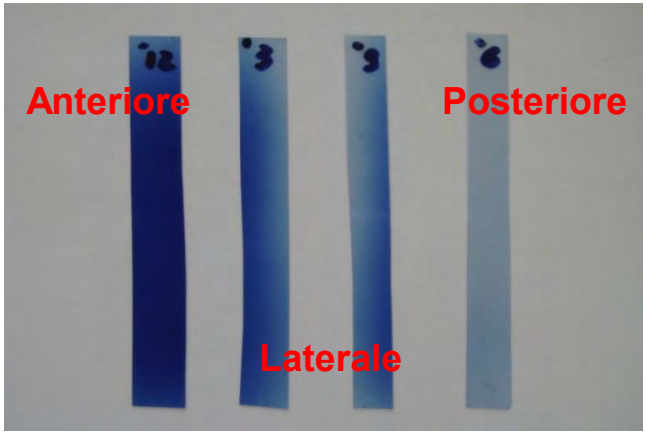
IN VIVO DOSIMETRY

Median dose to rectal wall **4.35 Gy**

(range: 0.06-11.3 Gy)







PERIOPERATIVE SURGICAL OUTCOMES (30 days)

Mean operative time was 167 mins (range 140-195 mins)

Event	n;%	Management	Clavien grade
Lymphocele	8 (8%)	Observation	I
Arythmia	1 (1%)	ITU care + monitoring	IVa
OVERALL	94 (100%)		

At a median follow-up of 70 mo (range 12-126)

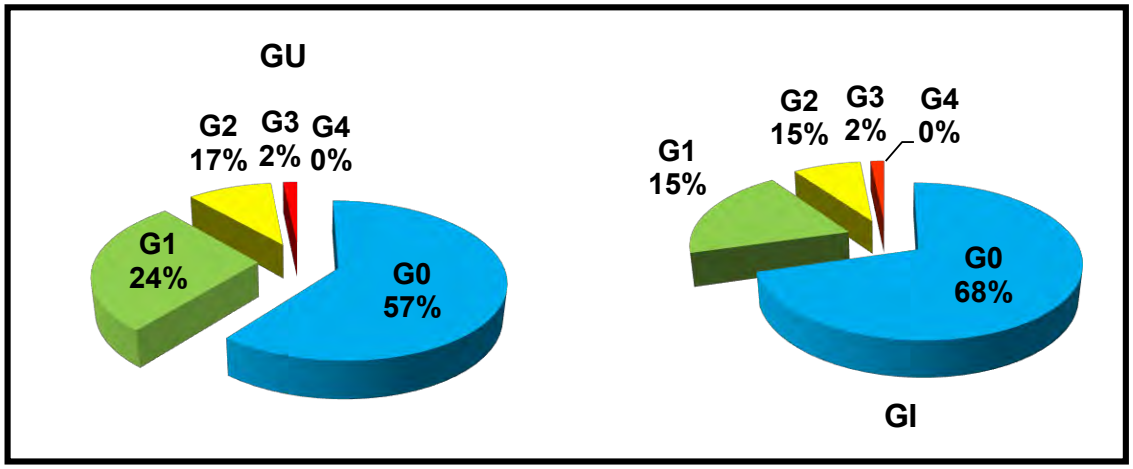
- 75% pts are continent (0-1 safety pad)
- 21% mild-moderate incontinence
- 4% severe incontinence

No acute rectal or bladder toxicity related to IORT

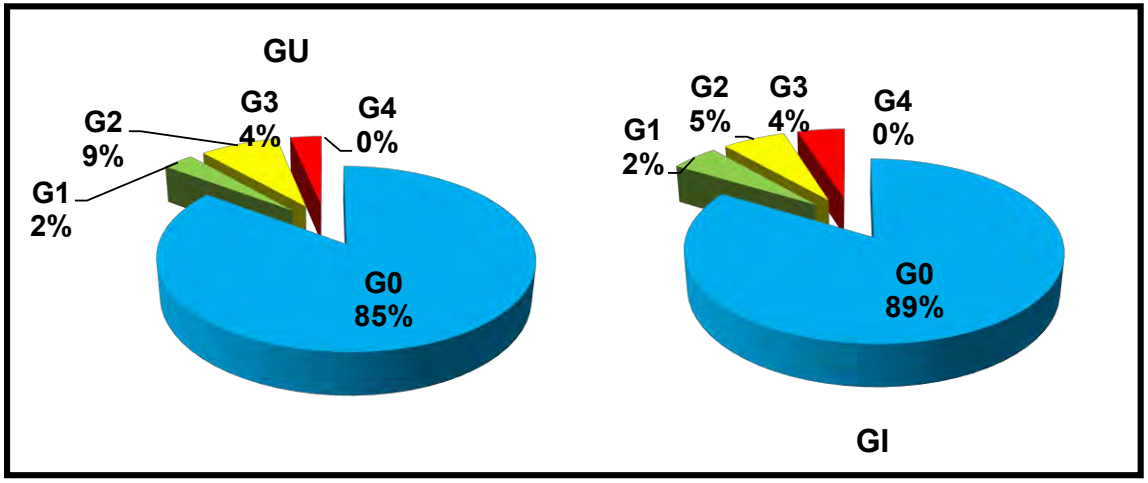
Dindo D. Ann Surg 2004

POSTOPERATIVE EBRT OUTCOMES (76/97 pts – 78.3%)

Early

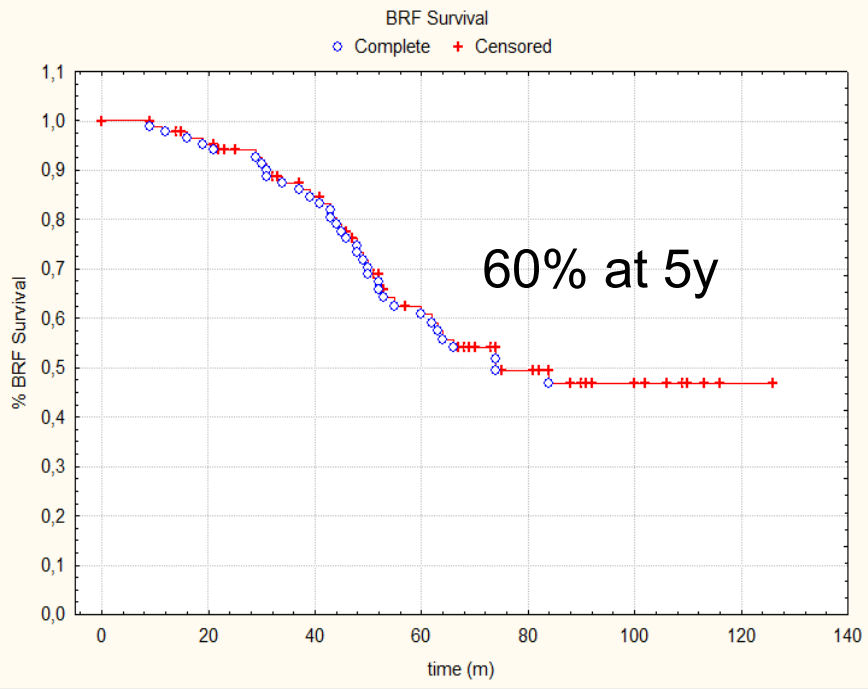


Late



ONCOLOGICAL OUTCOMES: BRFS

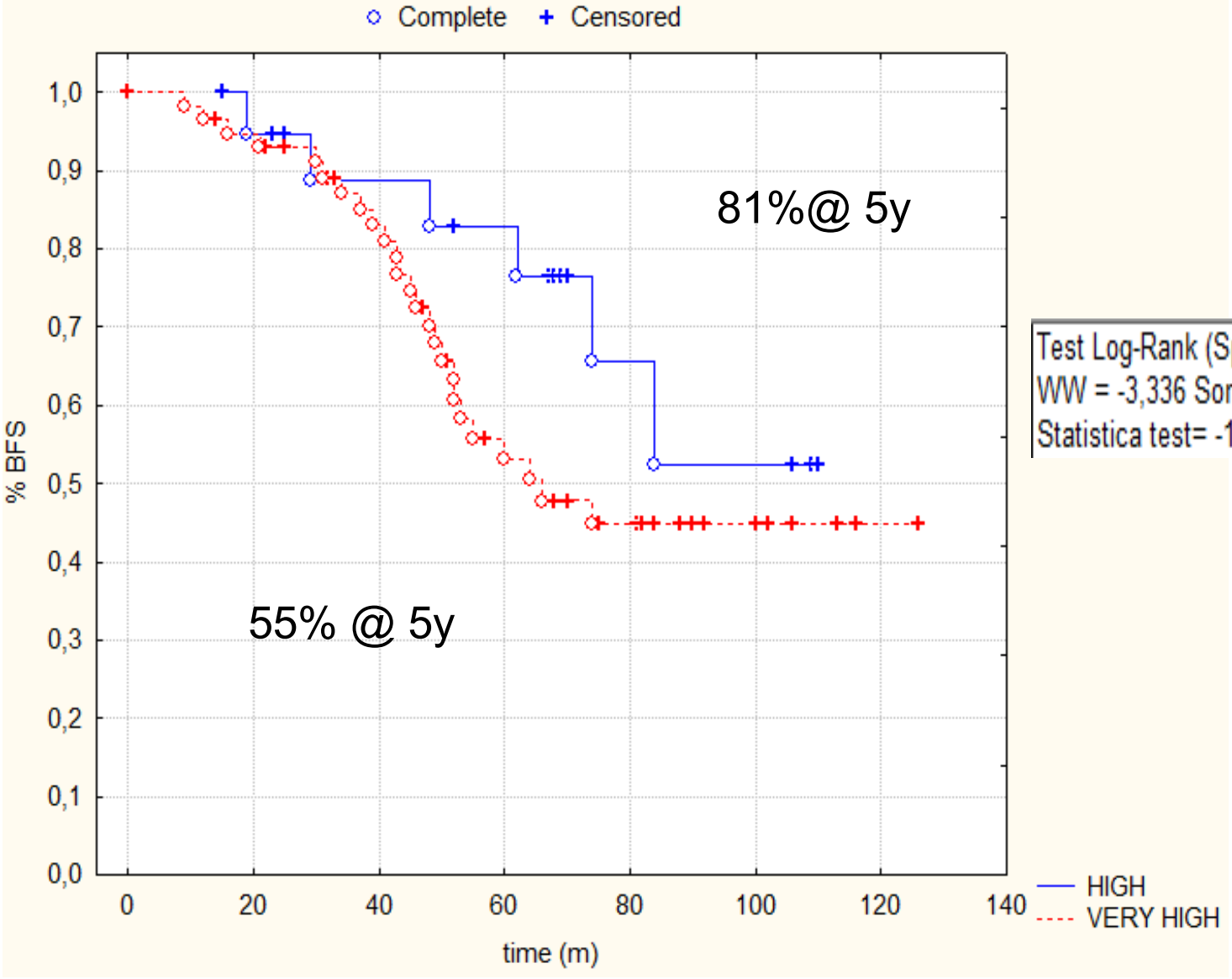
Biochemical failure: PSA ≥ 0.2 ng/ml



Median follow-up 70 months
(range 12-126)

	N° (%)
Lymph node recurrence	6/35 (17.2%)
Bone M+	2/35 (5.7%)
Lung M+	1/35 (2.8%)
Brain M+	1/35 (2.8%)

OS according to NCCN risk categories



CONCLUSIONS

∞ Radiobiological data (low **alfa/beta**) are supporting the use of high dose per fraction

∞RP and IORT **is feasible**, with relatively low morbidity (no acute rectal toxicity IORT-related)

∞ Study strenghts: largest reported series with prospective clinical and oncological outcomes

∞ Study limitations: median follow-up is <10y, a few patients received preoperative ADT, local staging with MRI is missing in early cases

∞ Open issues:

- Improved patient selection
- IORT as a single therapy vs boost prior to EBRT
- What adjuvant EBRT regimen? Hypofractionation?


DeAGOSTINI

UNIVERSITY HOSPITAL
UNIKLINIKUM
SALZBURG

Hypofractionated WBI plus IOERT-boost in early stage breast cancer (HIOB): Updated results of a prospective trial

Fastner G[1] Reitsamer R[2,3], Fussl C[1], Kopp P[1], Zehentmayr F[1], Milecki P[4], Karzcewska A[4], Murawa D[5], Hager E[6], Ciabattoni A[7], Budach W[8], Matuschek C[8], Brimmer R[9], Reiland J[10], Schumacher C[11], Ricke A[11], Ricardi U[12], Fusco V[13], Vidali C[14], Ivaldi GB[15], Alessandro M[16], Geinitz H [17], Bräutigam E [17], Fischer Th[2,3], Sedlmayer F[1]

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[14] Radioterapia, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Triest, Italy
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[17]Dep. for Radio-Oncology, Hospital Barmherzige Schwestern, Linz,Austria

Background

- **HIOB: IOERT 11 Gy + 15 x 2.7 Gy WBI**

- *Rationale for Hypofractionation:*
  Canadian and START-Trials (UK)
- *Rationale for IOERT Boost (10 Gy):*
  European Pooled Analysis (BIO-Boost): LRR 0.13 % / Jahr [Radiotherapy Oncology 2013]

Design:

- Sequential probability ratio test, SPRT
- One armed, multicentric, prospective trial

Primary Endpoint: „Local Control“

Superiority/equality of HIOB in comparison to „Gold Standard“:

Matching/exceeding the best published results for LR rates in 3 different age groups after *5 year observation* in terms of an

- ***upper limit*** *(exceeding = inferiority) and a*
- ***lower limit*** *(undershooting = superiority/equality).*

Sequiential probability Ratio Test - SPRT

	annual rate %	5-year rate %	
▪ ***Age > 50 :***	**0.7**	**3.5 (Bartelink)**	→ **upper limit (tolerated)**
	0.4	**2.0 (START B)**	→ **lower limit (best published)**
▪ ***Age 41-50 :***	**1.2**	**6 (Bartelink)**	
	0.72	**3.6 (Whelan)**	
▪ ***Age 35-40:***	**2**	**10 (Bartelink)**	
	0,72	**3.6 (Whelan)**	

Further Endpoints

Secondary Endpoints

- Disease free survival

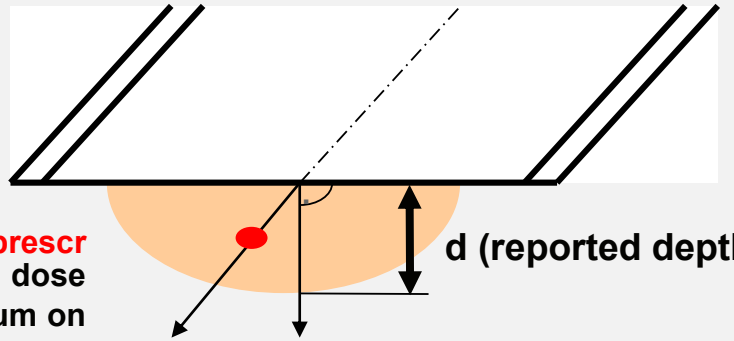
Tertiary Endpoints:

- acute toxicity : CTC-Sxcoring system
- late toxicity: LENT-SOMA
- Cosmesis: 5-Point-Scoring System (van Limbergen)

Inclusion criteria

- Inv. breast Carcinoma
- Age: ≥ 35
- T-status: T1-2
- N-status: N0-1
- R0-Resection
- All Grade G1-G3, all HR and Her-2 status
- Neoadjuvant/adjuvant therapy: No limits

IOERT



(Central beam axis –geometric tube axis)

- **PTV-Definition:**

  3D Volume of at least 2 cm beyond the former macroscopic tumor edge. ***Procedure:*** Without skin, “dose-limit” at rib-surface: 5 (-7) Gy

- **IOERT Dose: 11.1 Gy Dmax** on the central axis
- **PTV encompassed by 90%** of the prescribed dose (i.e. **10 Gy**)

WBI and Start of treatment

Day 36-56 post OP

- Adjuvant Chemotherapy:
  Up to 9 mths

WBI only (no RNI)

- **2.7 Gy (ICRU) x 15 (5 Fx/week)**

Status: 10/15 (Start: 13.01.2011)

Recruiting centres: 15

- **Austria:** UC Paracelsus Medical University/Landeskrankenhaus ***Salzburg***
  General Hospital ***Klagenfurt***
  Hospital BHS ***Linz***
- **Poland:** Wielkopolska Cancer Centre, ***Poznań***
- **USA:** Avera McKennan Hospital and University Health Center, ***Sioux Falls***
  St. Luke's Hospital ,***Cedar Rapids, IA***
- **Italy**: San-Felippo Neri***, Rom***
  A.U.O San Giovanni Battista, ***Turin***
  IRCCS-CROB Reference Cancer Center, ***Basilicata***
  Fondazione Salvatore Maugeri, ***Pavia***
  Azienda Ospedaliero-Universitaria "Ospedali Reuniti", ***Triest***
  IRCCS-CROB Reference Cancer Center Baslilicata, ***Rionero in Vulture***
  S.C. Radiotherapia Aziendale
- ***Germany:*** University Clinic ***Düsseldorf***
  St. Elisabeth-Hospital***, Köln-Hohenlind***

Recruited patients per 10/15

- Recruited active Patients: **799**
- **Age groups**: 35 - 40: 23 **3 %**
  41 – 50: 162 **20 %**
  > 50: 614 **77 %**

Patients in FUP: **695**

- 1/2 year: 639
- **1 year: 526 76 %**
- 2 years: 338
- **3 years: 159 23 %**
- 4 years: 50 6 %
- FUP (Months): Median **16 (0.13 – 51)**

Patient age (y)	n
35-40	23
41-50	162
> 50	614
T-Stage	
1	687
2	111
x	1
N- Stage	
0	689
1	108
X	2
Resection-status	
R0	799
Margin	Med 5 mm (0.1-30)
Multifocality	
no	692
yes	107

Histology	n
IDC	612
ILC	77
mixed	66
mucinous	9
tubular	30
medullary	2
metaplastic	3
EIC-status	
negative	693
positive	106
Grade	
G1	210
G2	460
G3	129
HER2-status	
neg	701
pos	98
HR- status	
neg	58
pos	741

Patient age (y)	n
35-40	23
41-50	162
> 50	614
T-Stage	
1	687
2	111
x	1
N- Stage	
0	689
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G1	210
G2	460
G3	129
HER2-status	
neg	701
pos	98
HR- status	
neg	58
pos	741

Acute Toxicity

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FUP (Months): : Med. 16 (0.13-51)

Evaluation:	*712*	*692*
CTC	*WBI – End*	*4 weeks post WBI*
CTC 0 (no reaction):	10.8 %	36.5%
CTC I (faint reaction):	80 %	56.3%
CTC II (moderate):	8.7 %	6.8%
CTC III(moist desquamation):	0.3 %	0.15%
ND	0.2 %	0.25%
∑ CTC 0/I	91%	93%

Subacute / “early“ late toxicity *(LENT-SOMA)*

4/5 Mon post WBI: 639 pats
13 Mon post WBI: 526 pats
24 Mon post WBI: 338 pats
36 Mon post WBI: 159 pats
48 Mon post WBI: 50 pats

***LENT-SOMA* G0/1**	**4-5 Mon**	**13 Mon**	**24 Mon**	**36 Mon**	**48 Mon**	**∑ mean**
Fibrosis	90 %	94 %	94 %	92 %	92 %	92 %
Edema	96 %	97 %	98 %	99 %	98 %	98 %
Teleangiectasia	98 %	99 %	97 %	96 %	94 %	97 %
Retraction	97 %	95 %	95 %	95 %	88 %	94 %
∑ mean	95 %	96 %	96 %	95 %	93 %	**95 %**

Cosmesis evaluation:

Rep. Photodocumentation, Double evaluation: Doctor/Patient

Qualitative 5-Point-Score Van Limbergen E 1989 & Harris JR 1979

E_0: Excellent

E_1: Good

E_2: Moderate

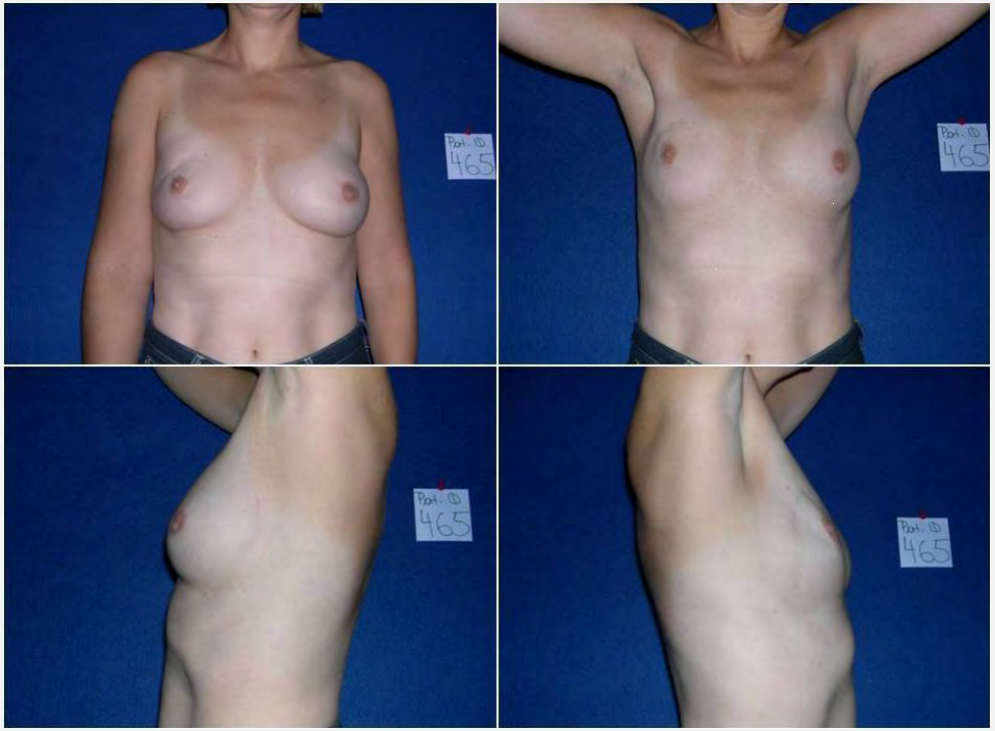
E_3: Bad

E_4: Complications

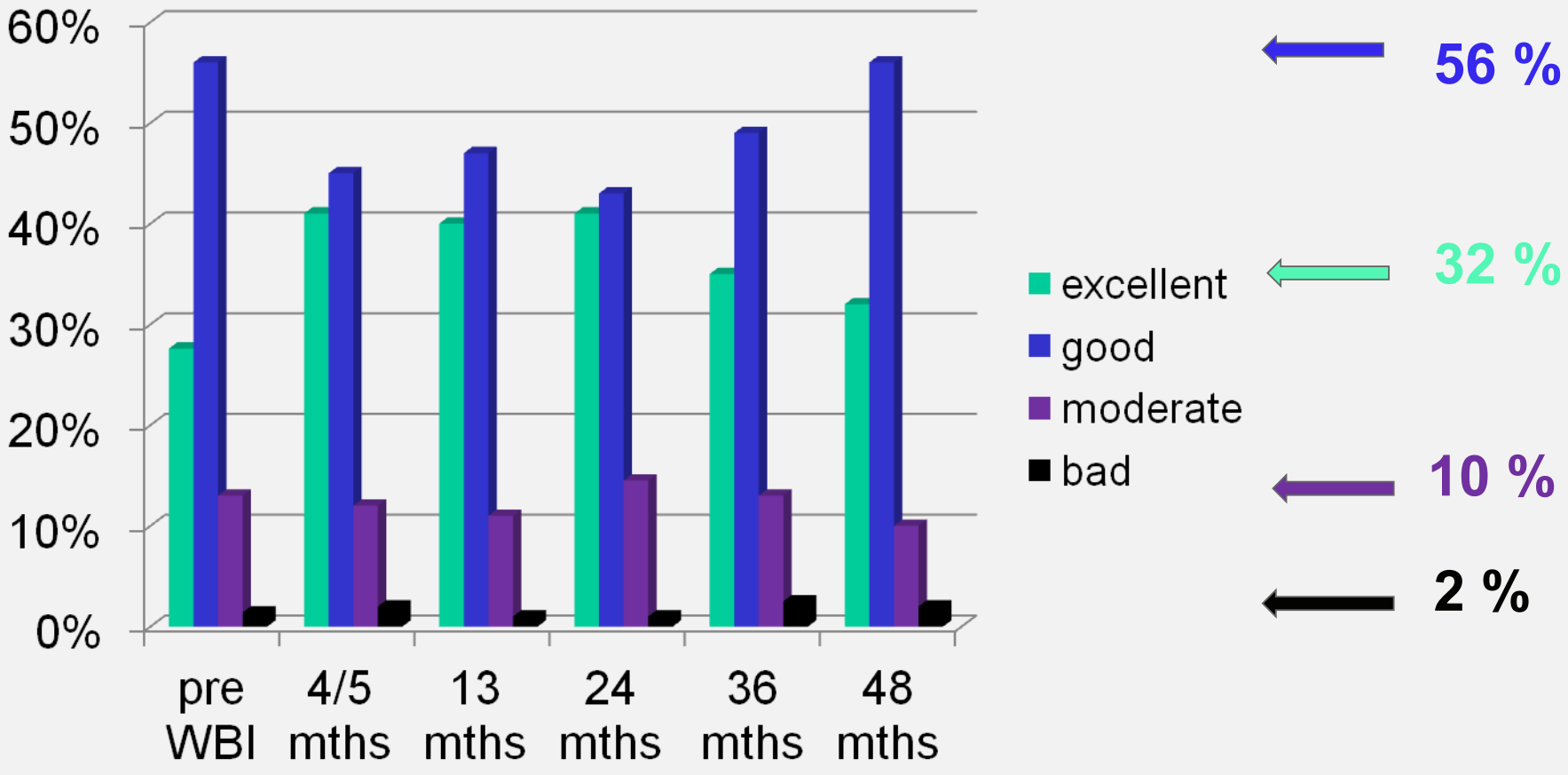
E_0-E_1: Satisfactory

E_0-E_2: Acceptable

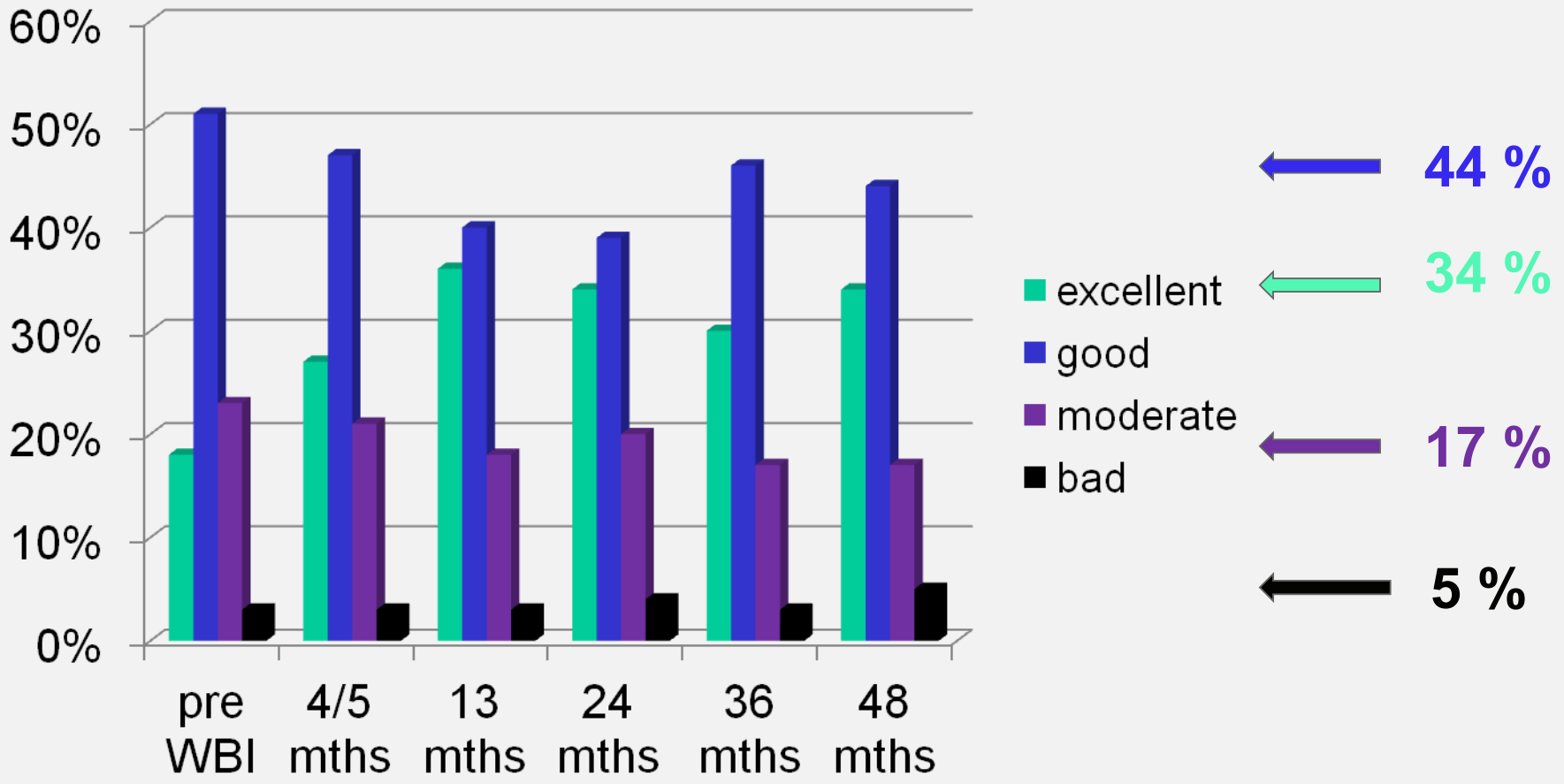
E_3-E_4: Unacceptable



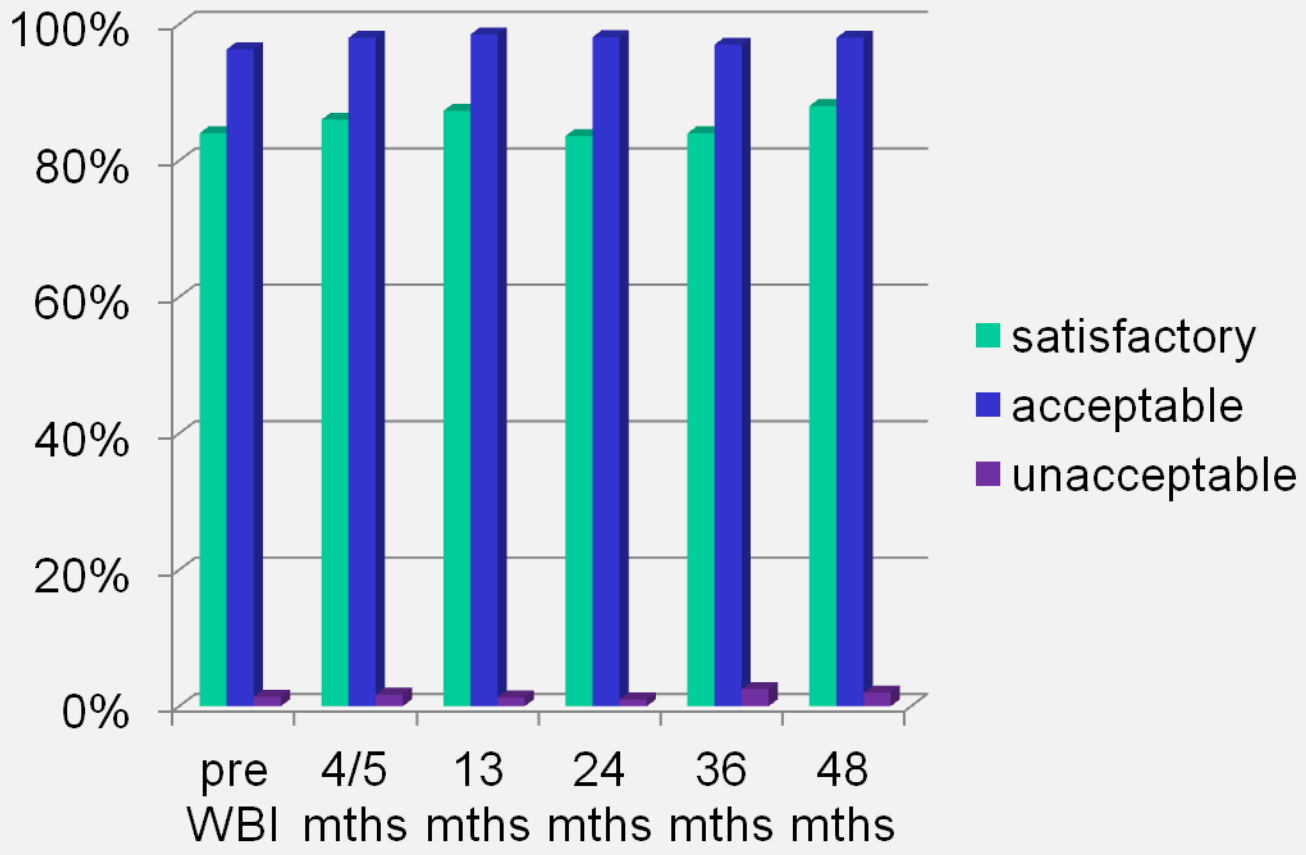
Cosmetic outcome „subjective“



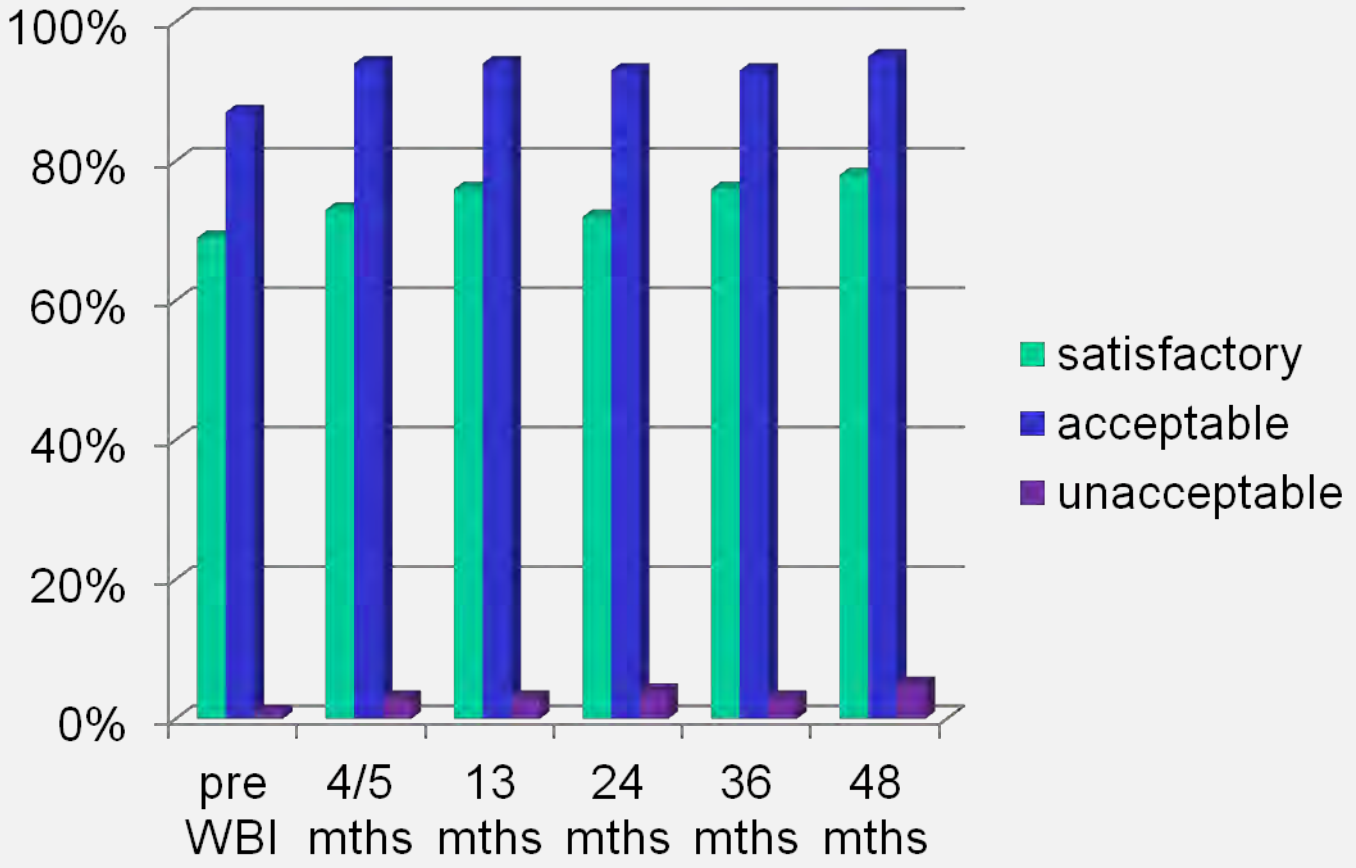
Cosmetic outcome „objective“



Cosmetic outcome „subjective“



Cosmetic outcome „objective“



95 %

78 %

5 %

Clinical Results:

FUP (Months): : Med. 16 (0.13-51)

No regional or In Breast rcurrence

2 patients with metastases

2 deaths

Conclusion

- *Hypofractionated WBI (START B) with IOERT:*

- **shows low acute and late toxicity**
- **(very) satisfactory cosmesis after short-time FUP**
- **High patient acceptance (shortened treatment duration)**

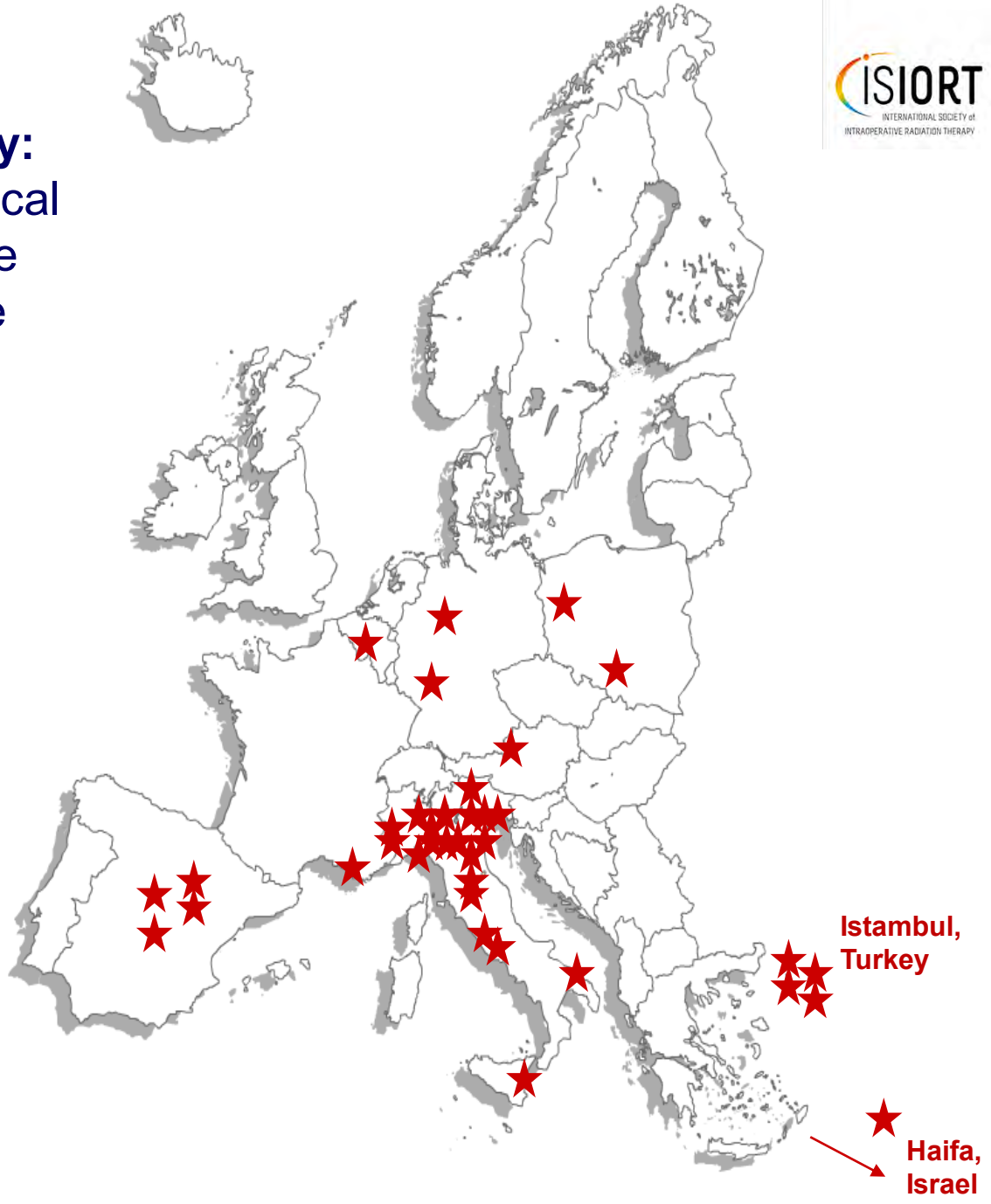
ISIORT pooled analysis 2016 update:

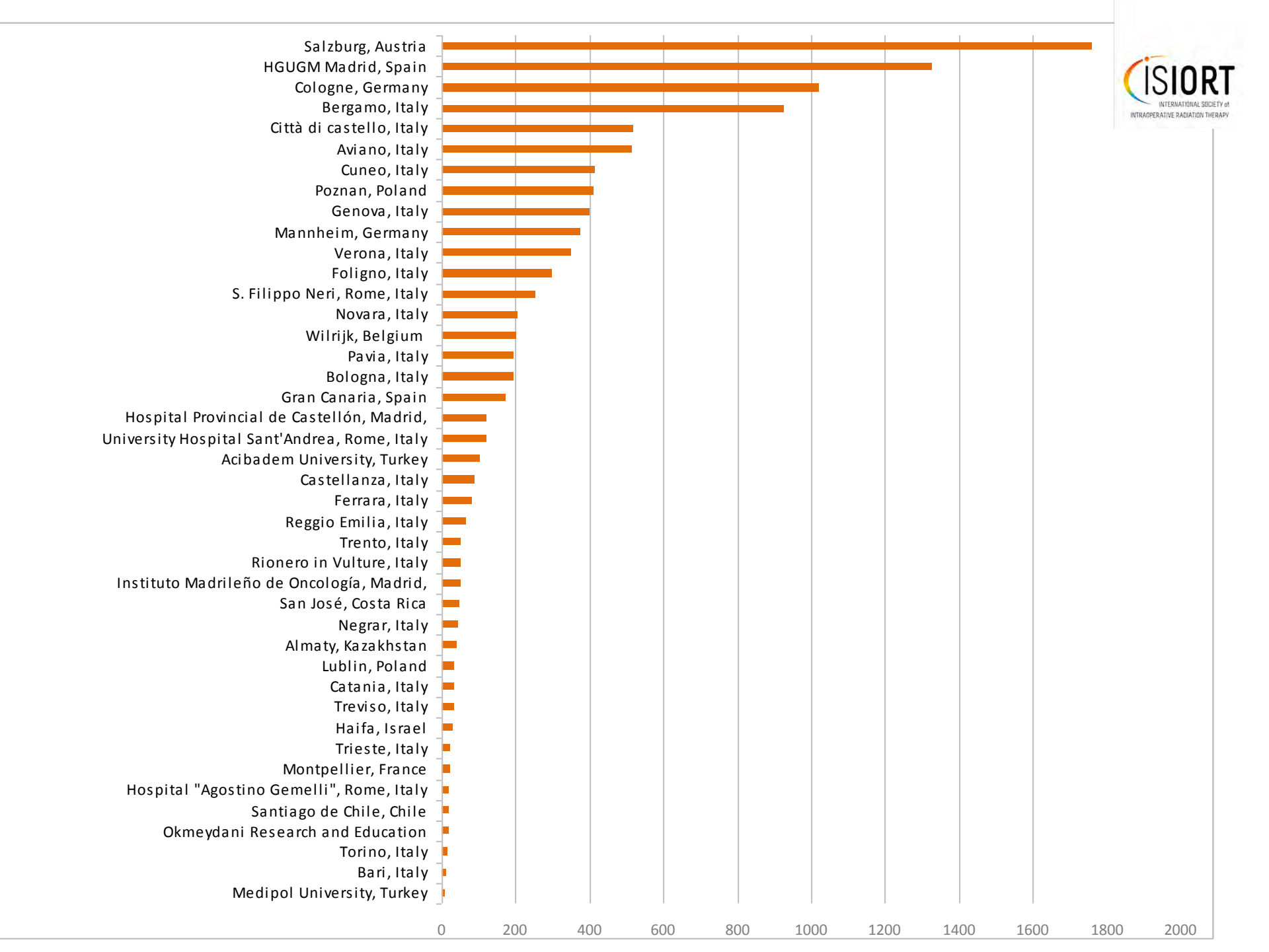
clinical and technical characteristics of intraoperative radiotherapy in 10,675 patients

M Krengli, FA Calvo, F Sedlmayer, C Schumacher, F Cazzaniga, M Alessandro, A De Paoli, E Russi, M Kruszyna, R Corvò, F Wenz, R Mazzarotto, F Fusconi, A Ciabattoni, R Weytjens, G Ivaldi , A Baldissera, C Pisani, V Morillo, P Lara, MF Osti, N Bese, G Catalano, A Stefanelli, C Iotti, L Tomio, V Fusco, I Azinovic, M Aguilar, F Richetti, N Kirsanova, W Polkowski, A Di Grazia, A Gava, L Abdach, C Vidali, JB Dubois, V Valentini, L Badinez, A Altinok, U Ricardi, A Milella, O Alan, P Lara.

Aim of the ISIORT Registry:
To collect technical and clinical data that could represent the basis for future collaborative clinical trials.

10,675 cases from 42 collaborating centres




Salzburg, Austria
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Cologne, Germany
Bergamo, Italy
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Aviano, Italy
Cuneo, Italy
Poznan, Poland
Genova, Italy
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Instituto Madrileño de Oncología, Madrid,
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Santiago de Chile, Chile
Okmeydani Research and Education
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Bari, Italy
Medipol University, Turkey
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ISIORT
INTERNATIONAL SOCIETY of
INTRAOPERATIVE RADIATION THERAPY

- HOME
- FUTURE EVENTS
- PAST EVENTS
- BOARD
- MEMBERS/SUPPORTERS
- ISIORT REGISTRY
- ONGOING TRIALS
- HISTORY

ʻation and Call for Abstracts Registr

Isiort Registry

We invite all ISIORT members to contribute to the **ISIORT Registry,** that is currently the largest collection of treatment data of IORT procedures. This registry has so far collected about 9000 cases from 36 collaborating centres, also serving to identify partners for future collaborative clinical trials. Updates are repeatedly published, with all contributing centers in authorship!

Do not hesitate to fill in your data send them to krengli@med.unipmn.it

Krengli ISIORT 2015 pooled analysis
ISIORT Europa Example
ISIORT Europe Registry

Anonimyzed data base
Excel file to be filled in

Articles reporting ISIORT Registry results

Strahlenther Onkol 2013 · 189:729–737

Clinical and technical characteristics of intraoperative radiotherapy

Analysis of the ISIORT-Europe database

M. Krengli · F.A. Calvo · F. Sedlmayer · C.V. Sole · G. Fastner · M. Alessandro · S. Maluta · R. Corvò · E. Sperk · M. Litoborski · C. Pisani · C. Fillini · F. Fusconi · M.F. Osti · L. Tomio · H. Marsiglia · A. Ciabattoni · W. Polkowski · A. Di Grazia · A. Gava · A. Kuten · C. Iotti · C. Gonzalez · M. Sallabanda · J.-B. Dubois · G. Catalano · V. Valentini

Transl Cancer Res 2014;3(1):48-58

ISIORT pooled analysis 2013 update: clinical and technical characteristics of intraoperative radiotherapy

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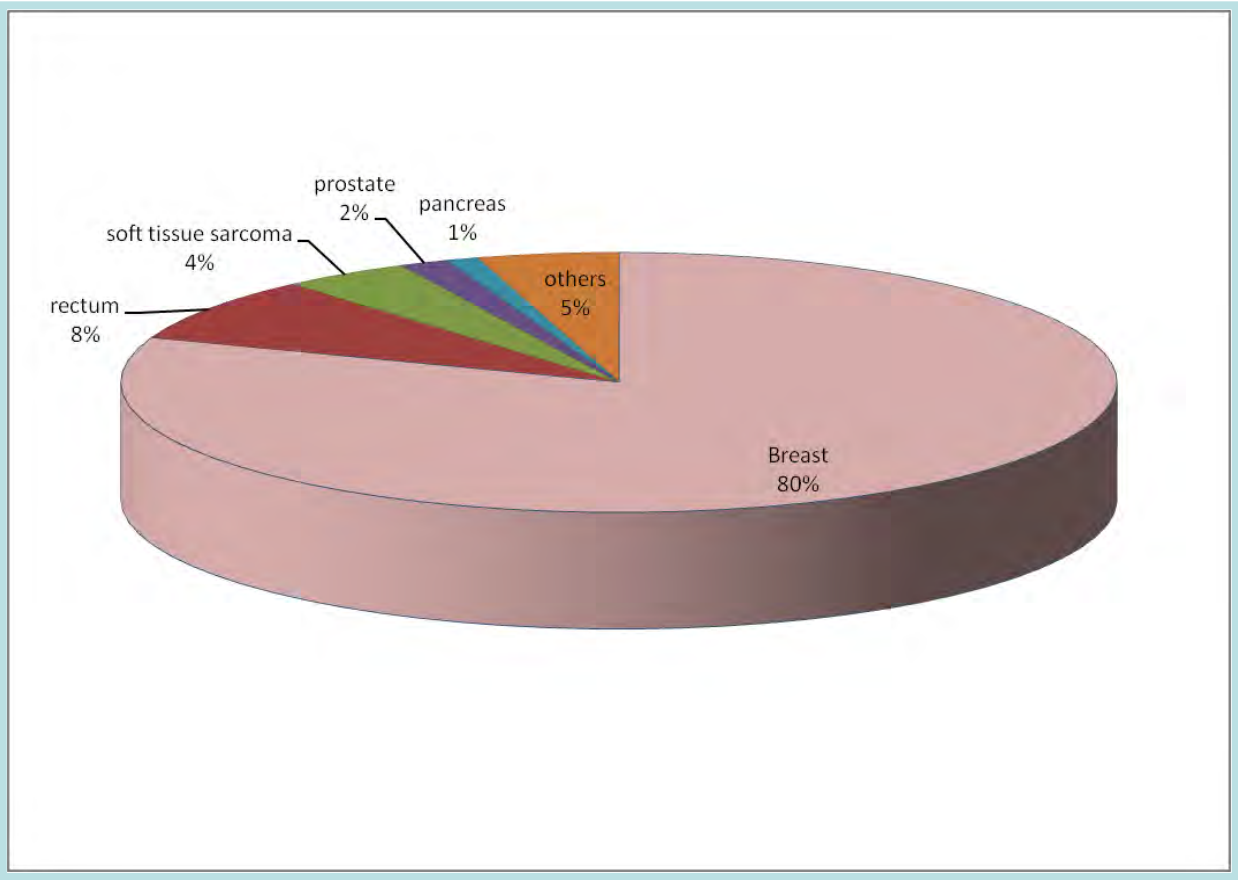
Aoknowledgements

Morena Sallabanda, University Hospital Gregorio Maranon, Madrid, Spain; Bernhard Mitterlechner, University Hospital of the Paracelsus Medical University, Salzburg, Austria; Franco Checcaglini and Fabrizio Fusconi, Hospital, Città di Castello, Italy; Sergio Maluta, Hospital, Verona, Italy; Renzo Corvò, University Hospital and Cancer Centre, Genova, Italy; Sebastian Adamczyk, Greater Poland Cancer Centre, Poznan, Poland; Elvio Russi and Claudia Fillini, Hospital Santa Croce e Carle, Cuneo, Italy; Fabrizio Fusconi, Hospital San Giovanni Battista, Foligno, Italy; Riccardo Maurizi Enrici and Mattia Osti, University Hospital Sant'Andrea, Rome, Italy; Luigi Tomio, Hospital Santa Chiara, Trento, Italy; Hugo Marsiglia and Ignazio Azinovic, Instituto Madrileño de Oncologia, Madrid, Spain; Antonella Ciabattoni, Hospital San Filippo Neri, Rome, Italy; Wojciech Polkowski, UniversityHospital, Lublin, Poland; Alfio Di Grazia, IOM Catania, Italy; Alessandro Gava Hospital, Treviso, Italy; Abraham Kuten, Rambam Health Care Campus, Haifa, Israel; Cinzia Iotti, Hospital Santa Maria Nuova, Reggio Emilia, Italy; Jean-Bernard Dubois, Centre Régional de Lutte contre le Cancer Val d'Aurelle Montpellier, France; Gianpiero Catalano, Hospital Multimedica, Castellanza, Italy; Franco Cazzaniga, Ospedale San Giovanni XXIII, Bergamo, Italy; Claudia Schumacher, St. Elisabeth-Krankenhaus, Koln, Germany; Reinhilde Weytjens, Sint Augustinus Hospital Wilrijk, Belgium; Bellaria, Antonella Baldissera, Hospital Bellaria, Bologna, Italy; Carlos Ferrer, Virginia Morillo, Juan Lopez-Tarjuelo Hospital Provincial of Castellon, Spain; Francesco Richetti, Hospital Sacro Cuore, Negrar, Italy; Vincenzo Fusco, IRCCS-CROB, Rionero in Vulture, Italy; Leonardo Badinez, Fundacion Arturo Lopez Perez, Santiago de Chile, Chile.

An overview of the 10,675 cases



Others (5%):

Tumor sites	#
Esophagus	53
Stomach	65
Brain	34
Cervix-vagina	29
Head and neck	28
Uterine body	17
Ovary	16
Bowel	12
Lymphnodes	9
Kidney	8
Abdominal	8
Biliary tract	8
Lung - lung apex	6
Sacrum	6
Adrenal glands	6
Bladder	5
Spine	2
Testis	2
Anus	1
Chordoma	1
Colangiocarcinoma	1
Liver	1
Ear	1
Vulva	1

Breast cancer (n = 8,075 cases)
Patients & Tumour characteristics

Median age: 61.1 yrs (16 – 90)

♀ 99.6%

⚷ 0.4%

T1: 81.8% - T2: 16.1%

Ductal carcinoma:96.5%

Lobular carcinoma: 3.5%

99.5% treatments with "curative intent"

113 cases: recurrent (previously EBRT → re-treatment with IORT)

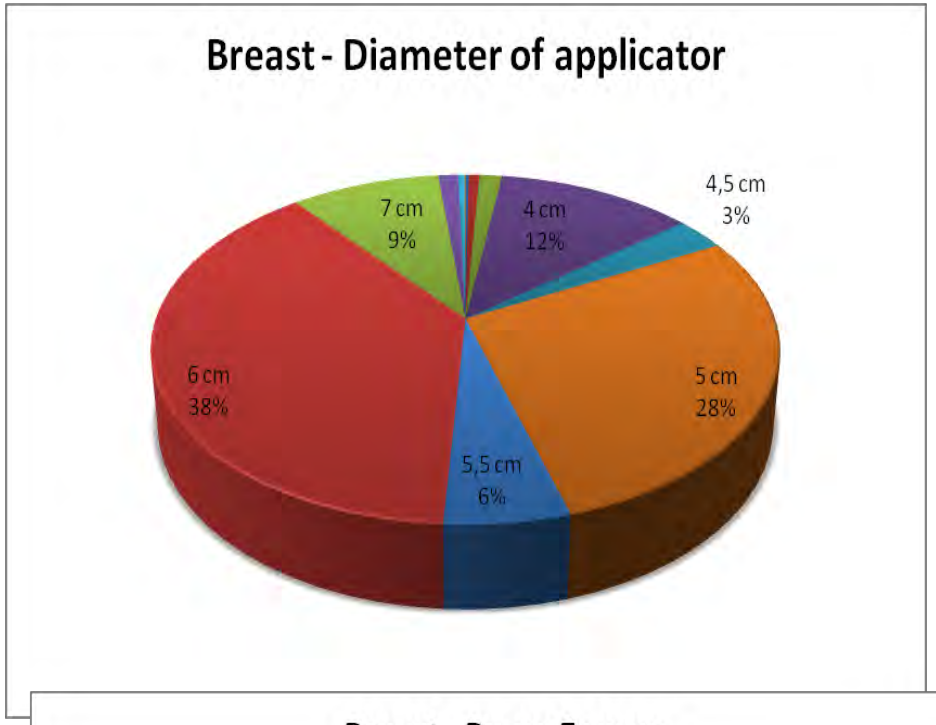
37 cases: R+ surgery

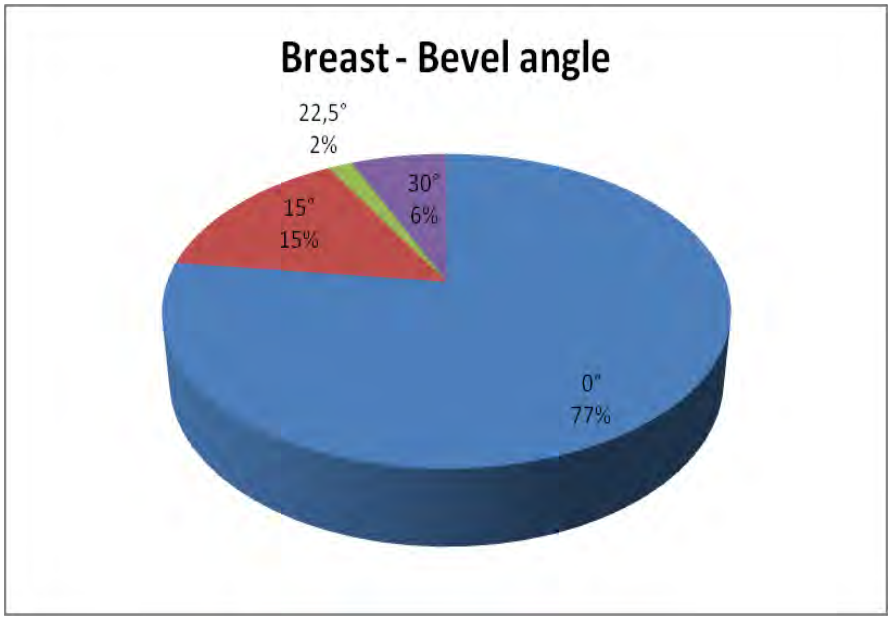
52.2% surgery + IORT

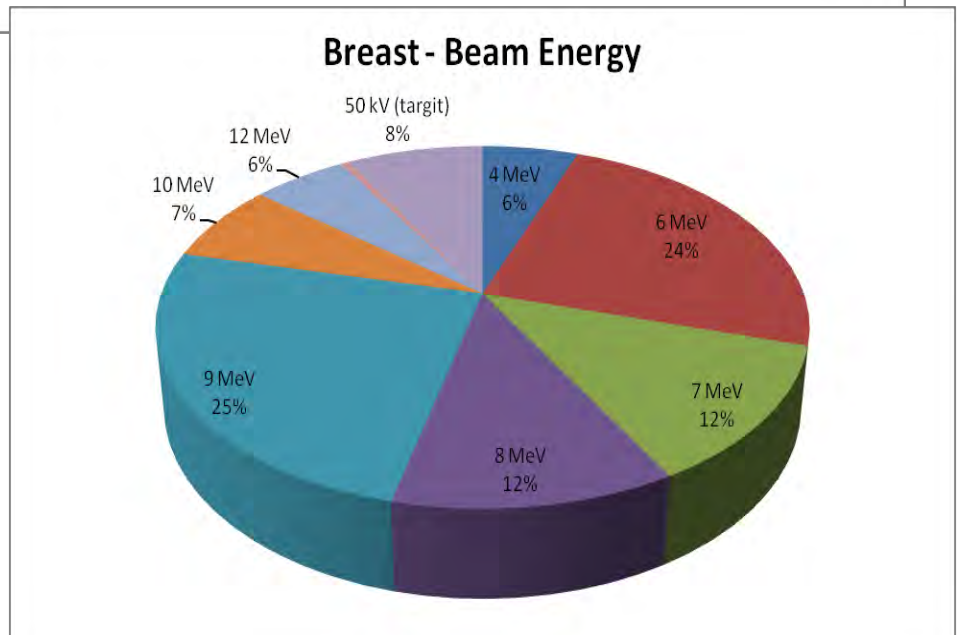
47.8% surgery + IORT + EBRT

13.2% surgery + IORT ±EBRT + chemo

Breast cancer (n = 8,075)







Breast IORT: TRENDS OVER TIME

60.3% cases in trials from 32 centres

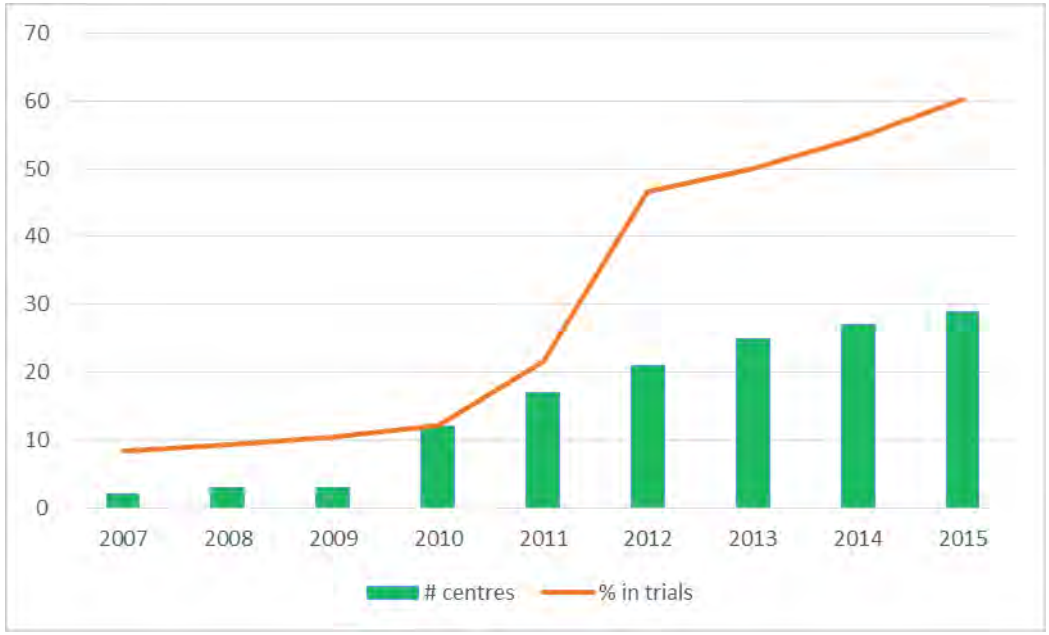
43.8% single shot

56.2% boost

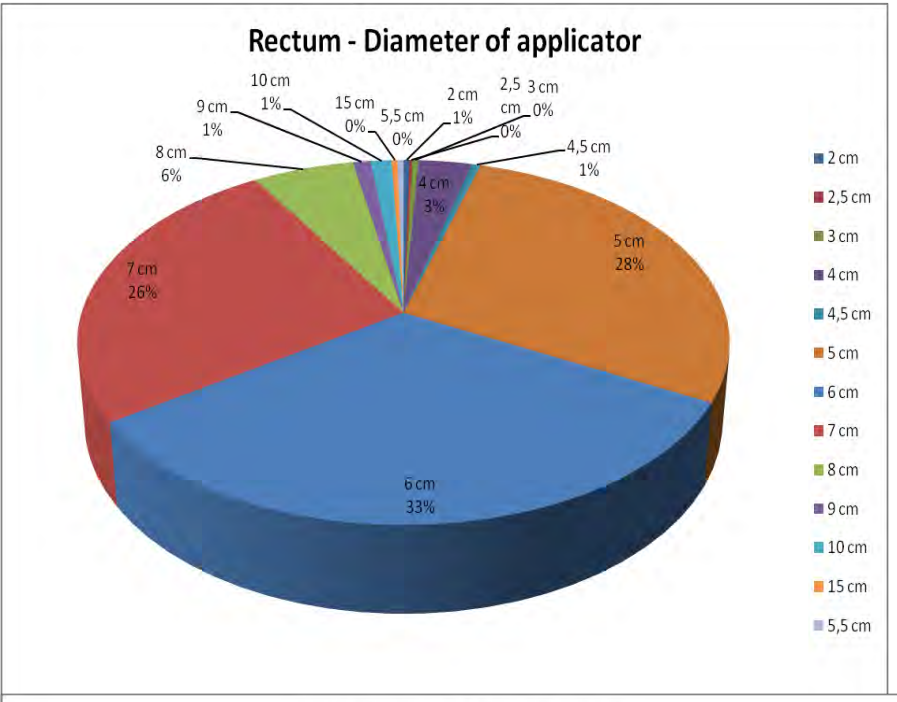
39.7% cases out of trials

37.8% single shot

62.3% boost



Rectal cancer (n = 913)

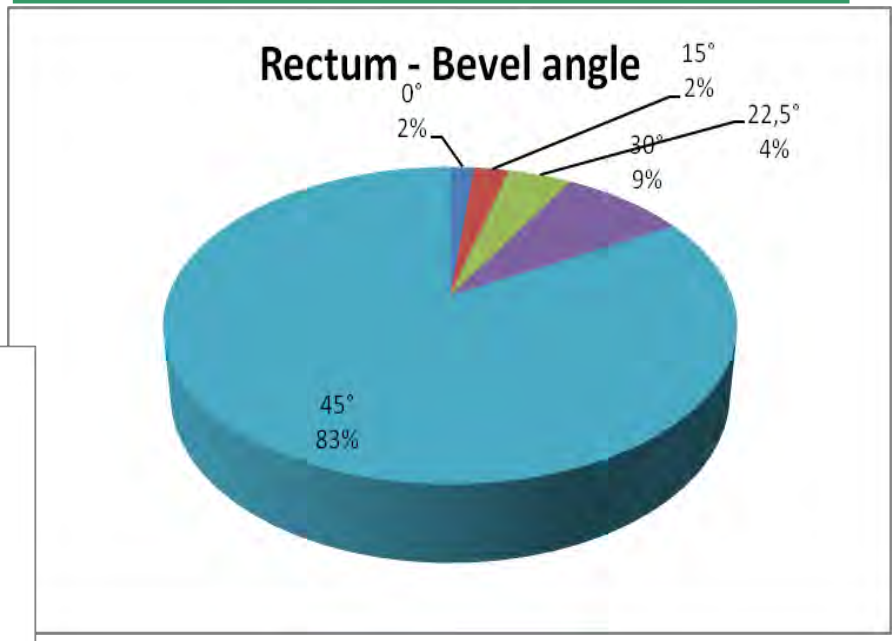


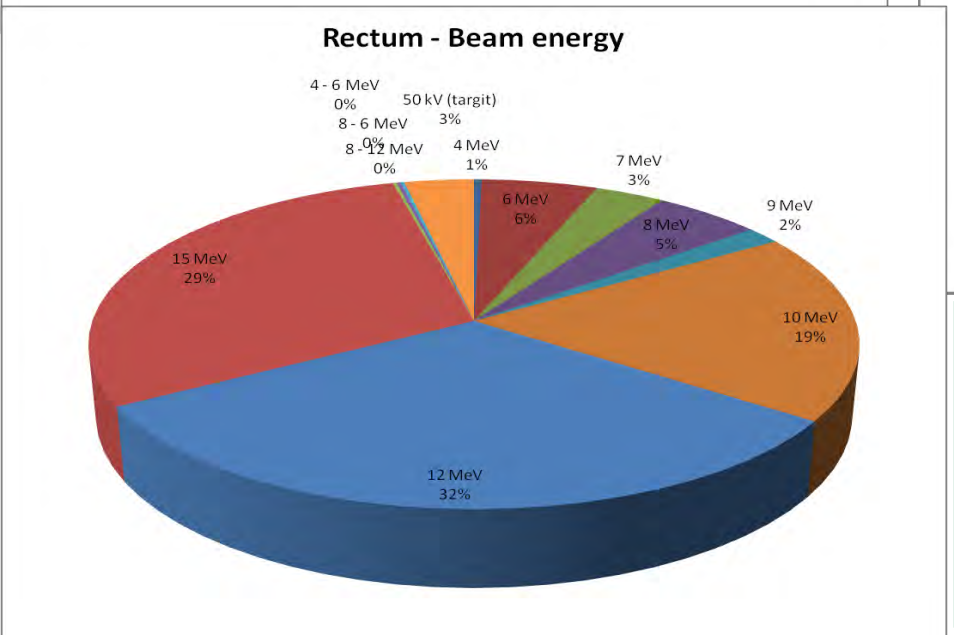
Median age: 62.9 yrs (26 – 94)

Primary: 86%

T2: 57.1%; T3: 16.4%; T4: 13.6%

Recurrent: 14%



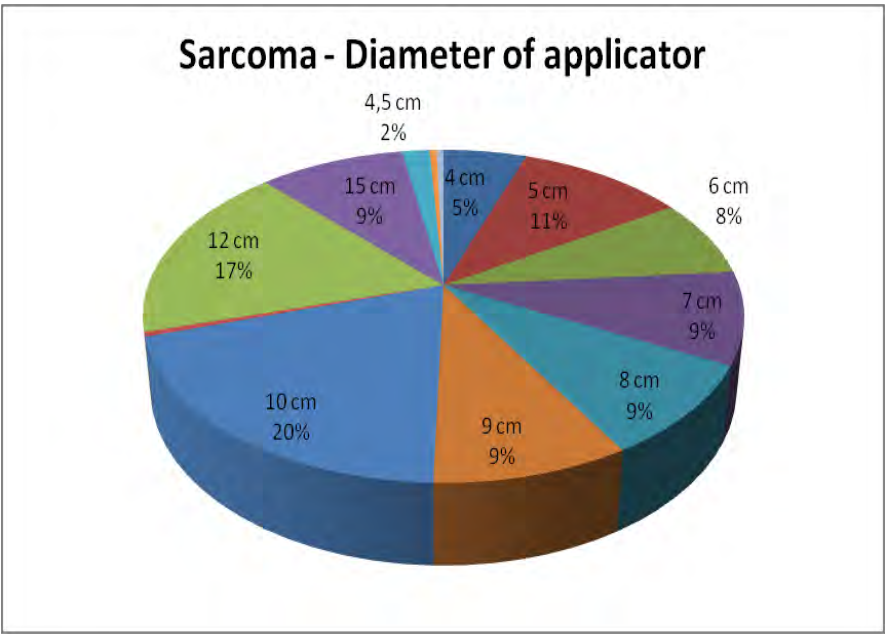


Doses:

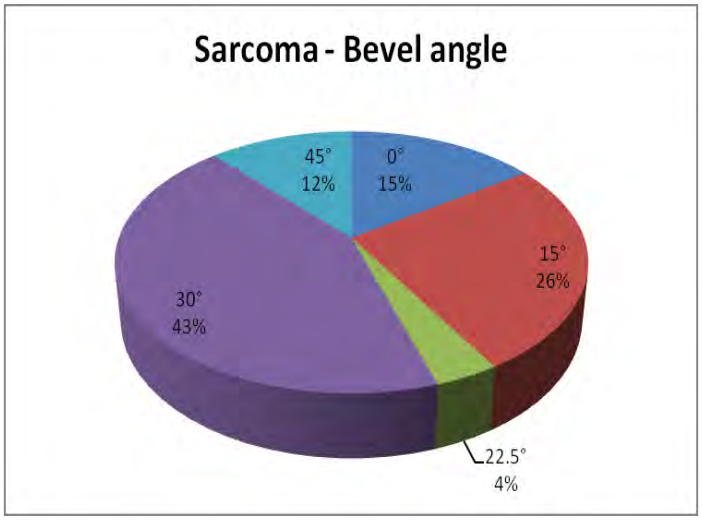
8 Gy (2%), 10 Gy (28%),

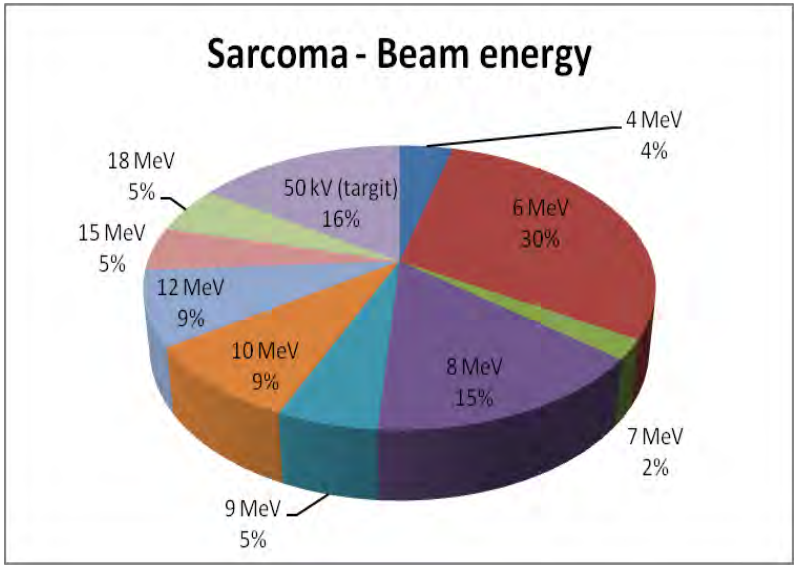
12.5 Gy (59%), 15 Gy (6%)

Soft tissue sarcomas (n = 345)



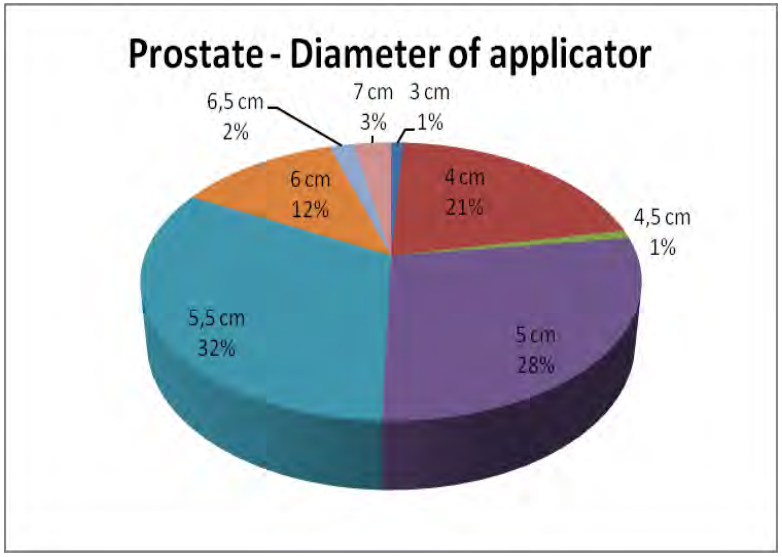
Median age: 50 yrs (5 months – 88 yrs)
Primary: 57.8%
Recurrent: 42.2%
Histology: liposarcoma: 50%
Ewing: 14%
leiomiosarcoma: 16%
chondrosarcoma: 5%
fibrohistiocitoma: 15%



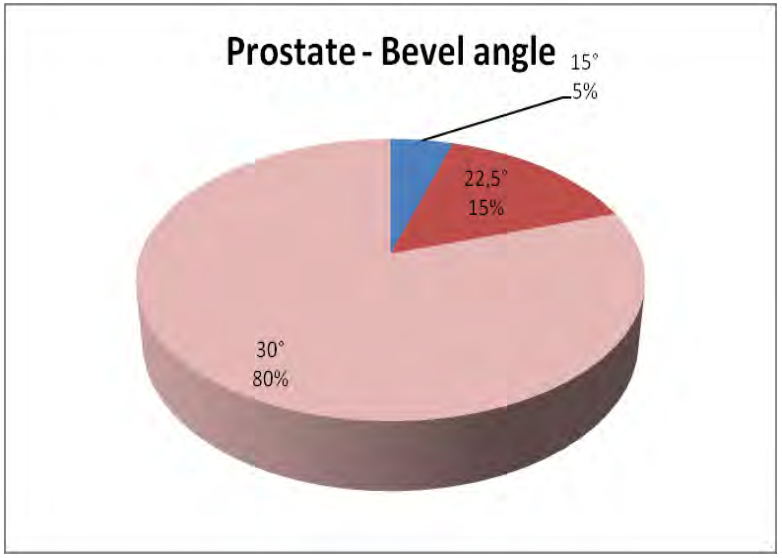


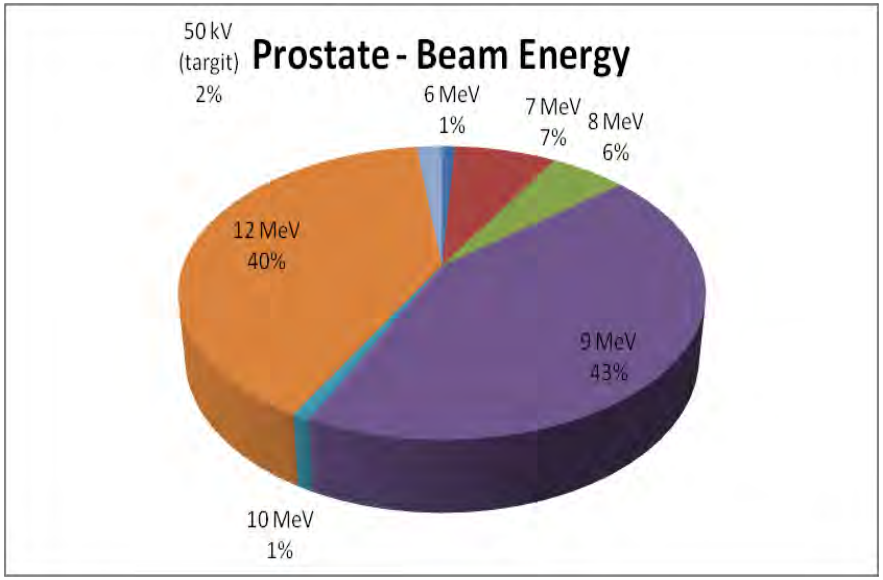
Doses:
10 Gy (40%), 12.5 Gy (32%), 15 Gy (12%), 12 Gy (10%)

Prostate cancer (n = 164)



Median age: 67.5 yrs (51 – 86)
Primary: 94.5% **Curative: 100%**
Histology: adenocarcinoma: 96.8%
sarcoma: 3.2%
Stage: T2c 26% T3a 42.8%





Doses:
IORT as boost 8 - 15 Gy
IORT as single shoot 18 - 21 Gy
72.6% enrolled in protocols

Perspectives

• The number of collaborating centers increased over time from 3 in 2007 to 21 in 2011, to 34 in 2014 and to 42 in 2016.

• These data are a report on a large clinical experience of patients treated with IORT worldwide and gives an overview on practice oriented patients selection.

• Further data analysis could focus on single tumor types and highlight specific clinical and technical issues. F/U data could also be included to analyze survival outcome

• The collected data could serve as a basis for designing prospective clinical trials in an effort to define the contribution of IORT in tailored multimodality approach.

ISIORT pooled analysis 2016 update: clinical and technical characteristics of intraoperative radiotherapy in 10,675 patients

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1 Novara, Italy; 2 Gregorio Maranon, Madrid, Spain; 3 Salzburg, Austria; 4 Cologne, Germany; 5 Bergamo, Italy; 6 Città di Castello, Italy; 7 Aviano, Italy; 8 Cuneo, Italy; 9 Poznan, Poland; 10 Genova, Italy; 11 Mannheim, Germany; 12 Verona, Italy; 13 Foligno, Italy; 14 San Filippo Neri, Rome, Italy; 15 Wilrijk, Belgium 16 Pavia, Italy; 17 Bologna, Italy; 18 Castellon, Spain; 19 Sant'Andrea, Rome, Italy; 20 Acibadem Maslak Hospital Istanbul, Turkey; 21 Castellanza, Italy; 22 Ferrara, Italy; 23 Reggio Emilia, Italy; 24 Trento, Italy; 25 Rionero in Vulture, Italy; 26 Istituto Madrileño de Oncologia, Madrid, Spain; 27 San José, Costa Rica; 28 Negrar, Italy; 29 Almaty, Kazakhstan; 30 Lublin, Poland; 31 Catania, Italy; 32 Treviso, Italy; 33 Haifa, Israel; 34 Trieste, Italy; 35 Montpellier, France; 36 Gemelli, Rome, Italy; 37 Santiago de Chile, Chile; 38 Medipol University, Istanbul, Turkey; 39 Torino, Italy; 40 Bari, Italy; 41 Okmeydani Research and Education Hospital, Istanbul, Turkey; 42 Gran Canaria, Spain.

Purpose:
Data from centres active in intraoperative radiotherapy (IORT) were collected within the International Society of Intraoperative Radiotherapy (ISIORT) program. The purpose of the present analysis was to analyse and report the main clinical and technical variables of IORT performed by the participating centres.

Materials and Methods:
In 2007, the ISIORT-Europe centres were invited to record demographic, clinical and technical data relating to their IORT procedures in a joint online database.

Results:
The numbers of centres increased from 3 centres in 2007 to 42 centres and 10,675 IORT procedures have been recorded until May, 2016. Median age of patients was 55.2 years (range: 5 months – 89 years). Gender was female in 80.2% of cases and male in 19.8%. Treatments were curative in 10,482 cases (98.2%) and 2,545 (23.8%) cases were included in study protocols. The most frequent tumour was breast cancer with 8,075 cases (75.6%) followed by rectal cancer with 913 cases (8.6%), soft tissue and bone sarcomas with 345 cases (3.2%), prostate cancer with 164 cases (1.5%), gastric cancer with 120 cases (1.1%) and pancreatic cancer with 117 cases (1.1%).

Conclusion:
Treatment chronology shows how IORT number of recorded cases increased according with the interest in this ISIORT project. This survey gives an overview of worldwide use of IORT including patient selection criteria and treatment modalities and could represent a basis to design future clinical trials.

Multidisciplinary Management of Spine Metastasis (V_IORT)

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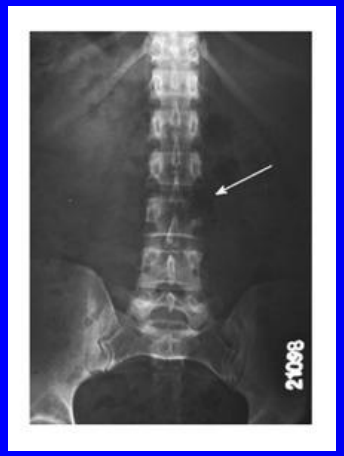
9 th ISIORT
Novara, 25 th June, 2016

Spine Metastasis

- **Metastatic tumors are the most common (97%) tumors of the spine, because the spine is well vascularized and has close relationship with regional lymphatic and venous drainage systems (especially Batson's venous plexus)**
- **The percentage of cancer patients who have had bone metastasis before death is between 50% and 70%, and in case of breast cancer this percentage rose up to 85%**
- **Other most frequent tumors metastatising in the spine are adenocarcinomas from the lung, prostate, kidney, gastrointestinal tract and thyroid**
- **The most common (70%) sites for spine metastasis are thoracic and thoracolumbar spine, and lumbar spine and sacrum have more than 20% of metastatic lesions. Cervical spine is a less frequent metastasis site**



Skeletal conseguences

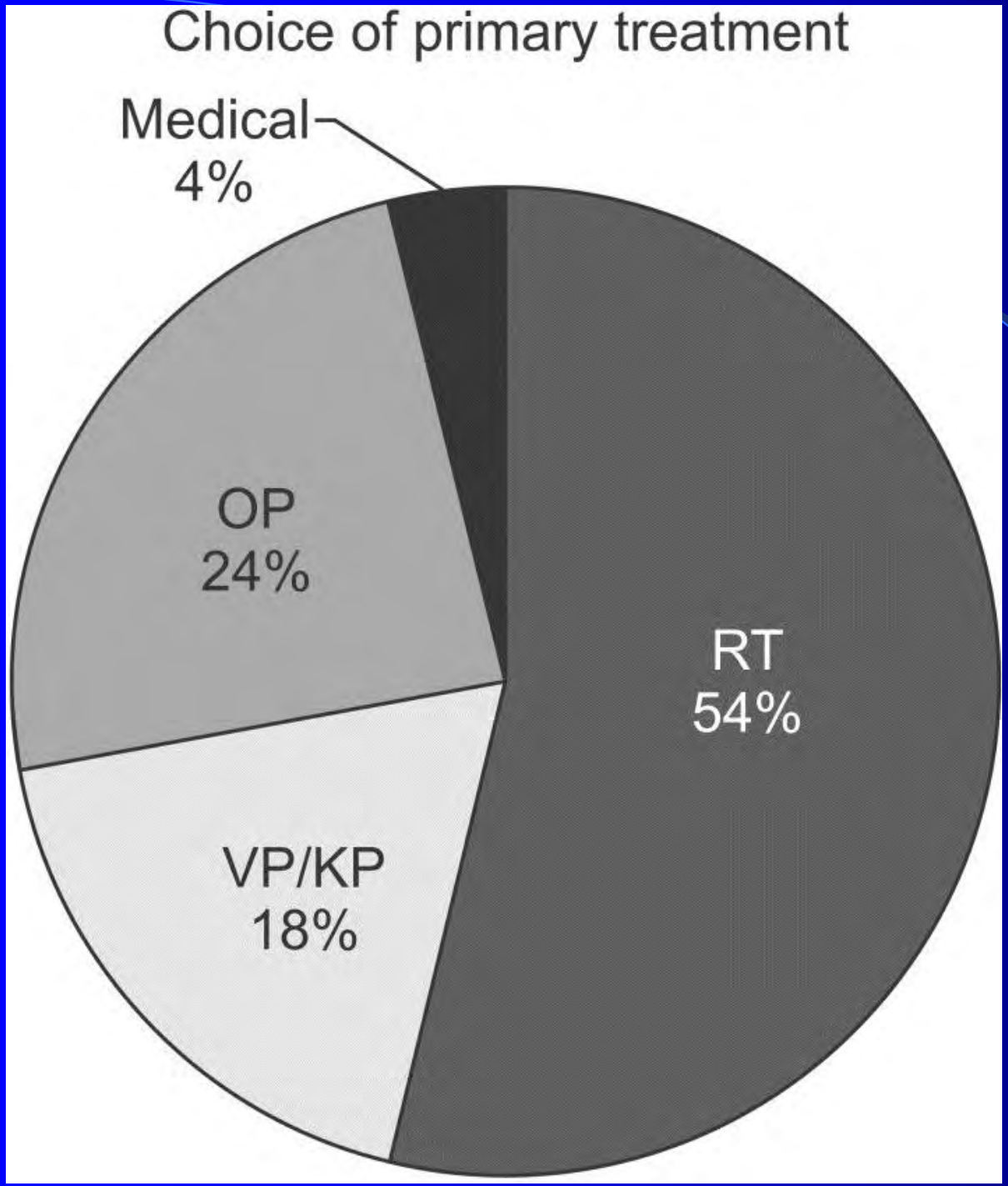
Consequences to functional independence and QoL

Spine metastasis

- Fracture
- SCC or vertebral collapse
- Hypercalcemia
- Surgery to bone

- Loss of autonomy
- Pain
- Anxiety and depression

SCC = Spinal cord compression
QoL = Quality of life

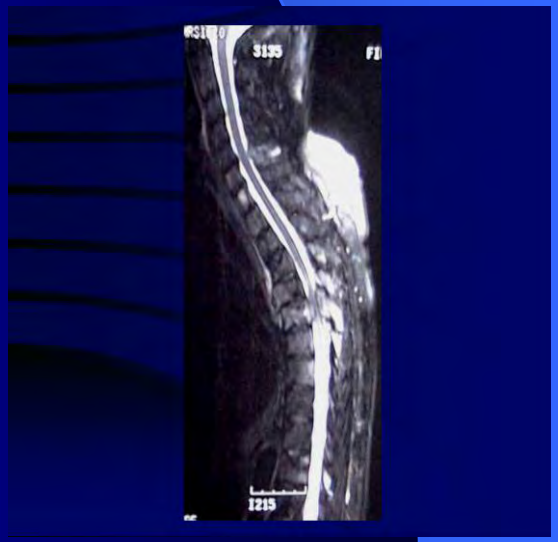


- RT is the most common primary choice
- OP can be considered for the relief of neurologic symptoms
- VP or KP can be considered for the short-term control of localized pain
- **Multidisciplinary guidelines are required**

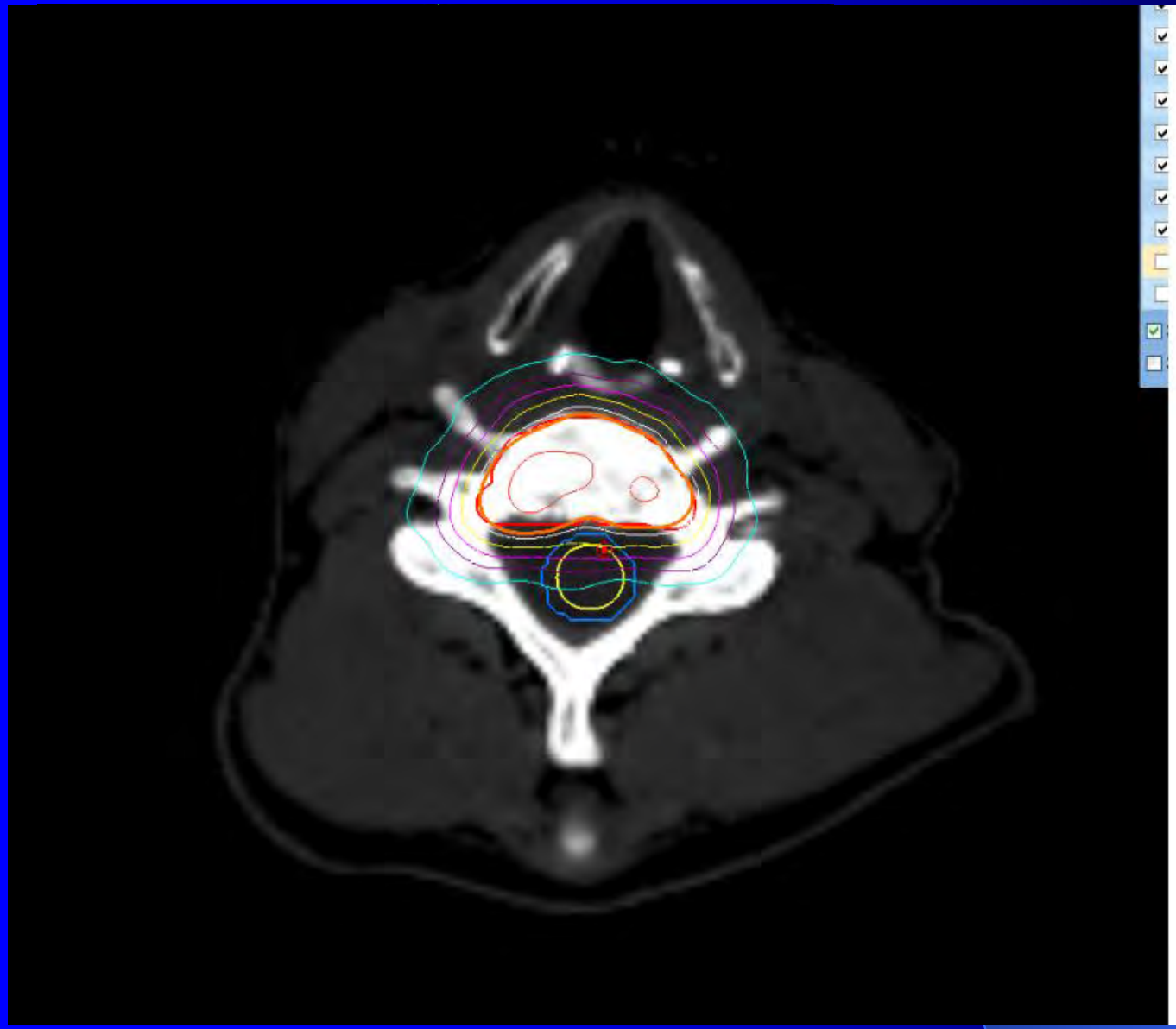
Cho JH et al,
Clin Orthop Surg 2015

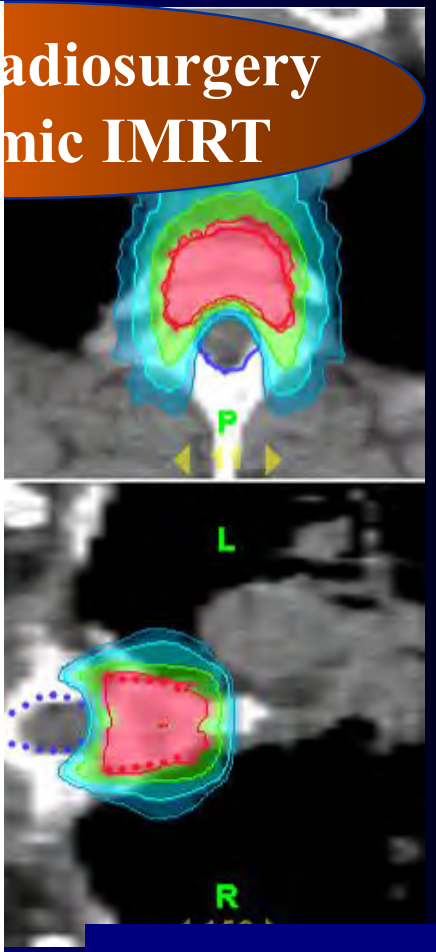
Spine Metastasis

- RT is effective in reducing pain on most of the patients (more than 80%)
- RT avoid spinal cord compression if the patient at risk is treated soon
- RT improves motor function in 45% to 60% of the cases with impaired functions



adiosurgery
mic IMRT





Lane Rosen,
Shreveport Cancer Center

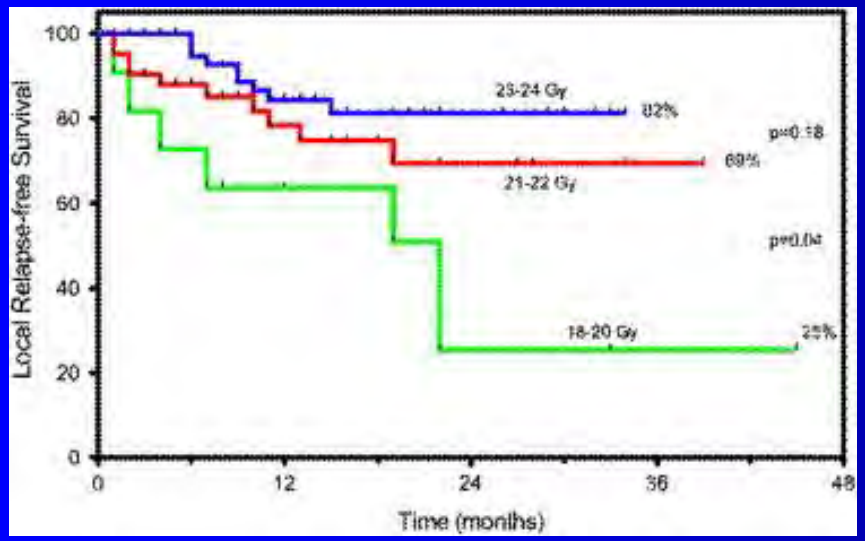
SBRT Spine Plan Comparison

IEO Arc

Vertebral Compression Fracture

VCF after conventional radiotherapy: < 5%

VCF after SBRT: from 11% to 39%



Greco C et al, IJROB 2012, 79: 1151-7

Zelefsky M et al, IJROBP 2012, 82: 1744-8

Spine Metastasis

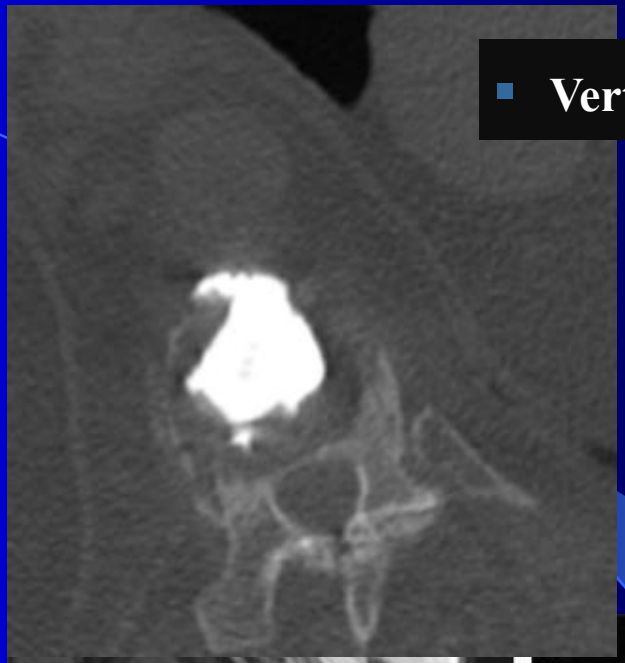
- Percoutaneous VertebroPlasty (PVP) and Percoutaneous KyphoPlasty (PKP) increase bone strenght and alleviate pain by mechanical stabilization

- A systemic meta-analysis comparing PVP and PKP demostrates that both are safe and effective procedures

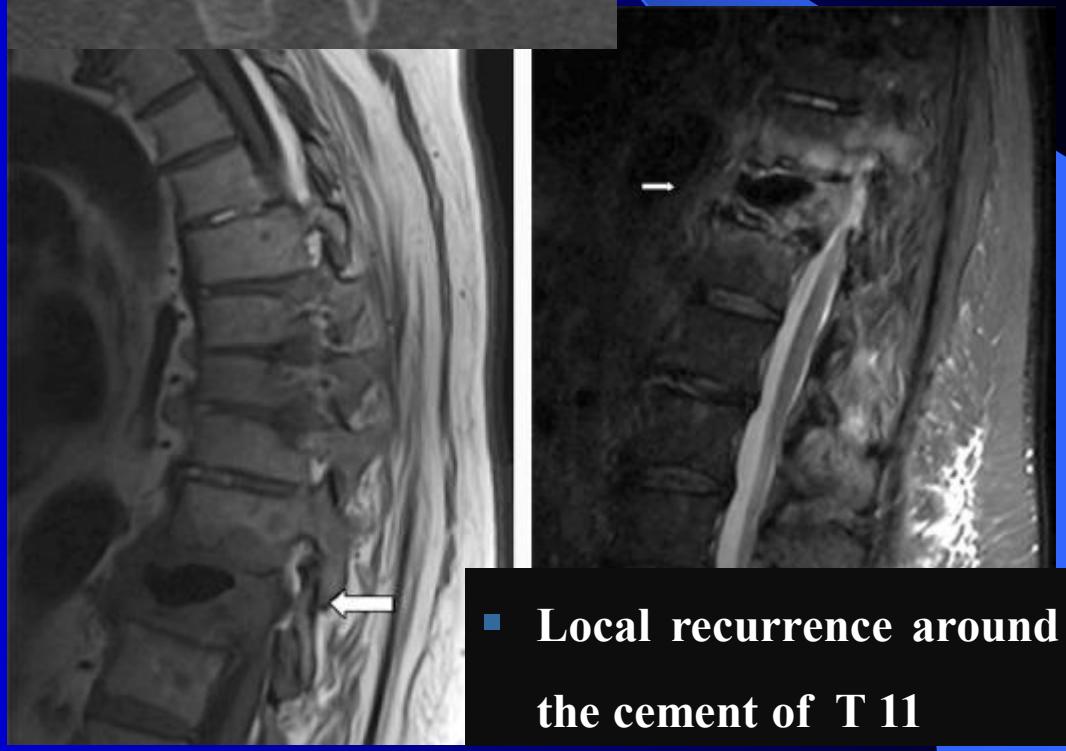
  (Hua wang et al, Pain Physician 2015)

- Vertebroplasty or Kyphoplasty are not antitumoral treatments by themselves
- A combination of these techniques with an antitumoral treatment should be considered
- RT is effective in preventing local relapse and could be the best option for the combined approach

Brahimi Y et al,
Cancer/Radiothérapie 2016



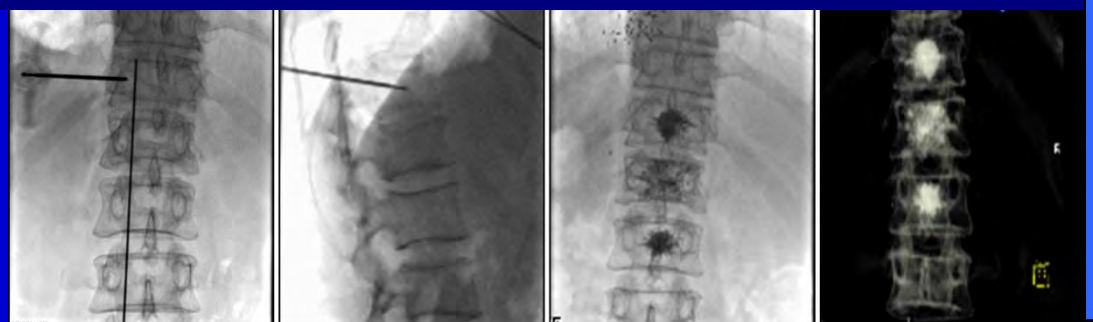
- Vertebroplasty of T 11



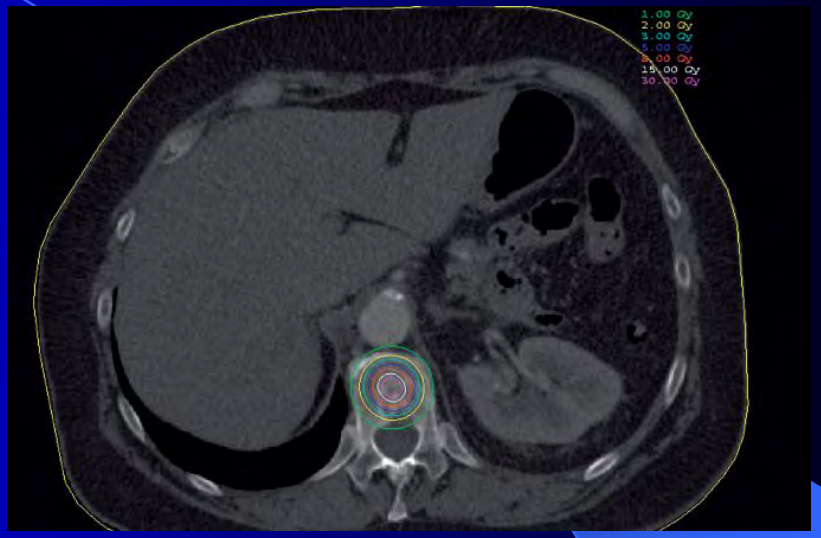
- Local recurrence around the cement of T 11

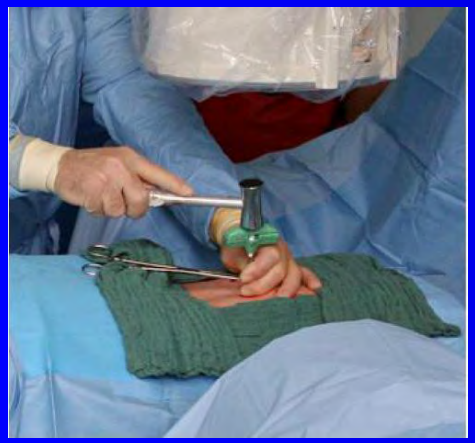
Combined treatment

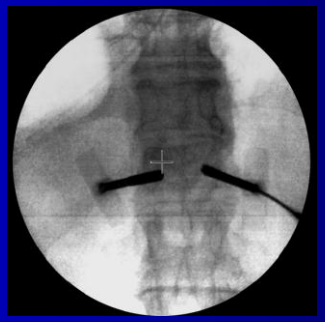
- With EBRT (two steps)
- With I-125 implantation (one step)
- With IORT (one step)

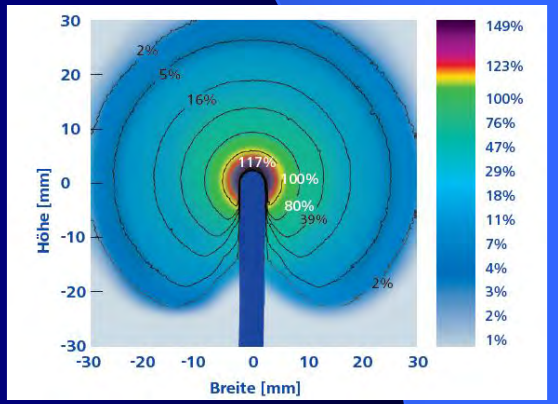


Kypho-IORT









Wenz F et al. Radiation Oncology 2010

Kypho-IORT

Part I: Irradiation

Vertebral body containing a bone metastasis

Step 1: A minimal invasive access is created

Step 2: Radiation (<5 min) of the bone metastasis at its precise location

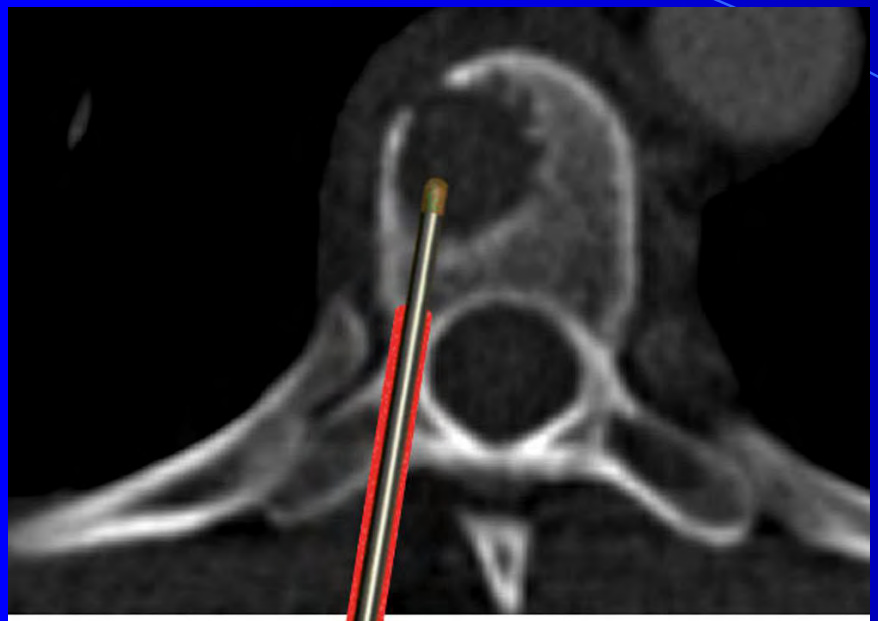
Part II: Stabilization

Step 3: A balloon is inserted in the vertebral body containing the lesion

Step 4: The balloon is carefully inflated, returning the vertebral body to its normal position

Step 5: The cavity created by the balloon is filled with bone cement for stabilization

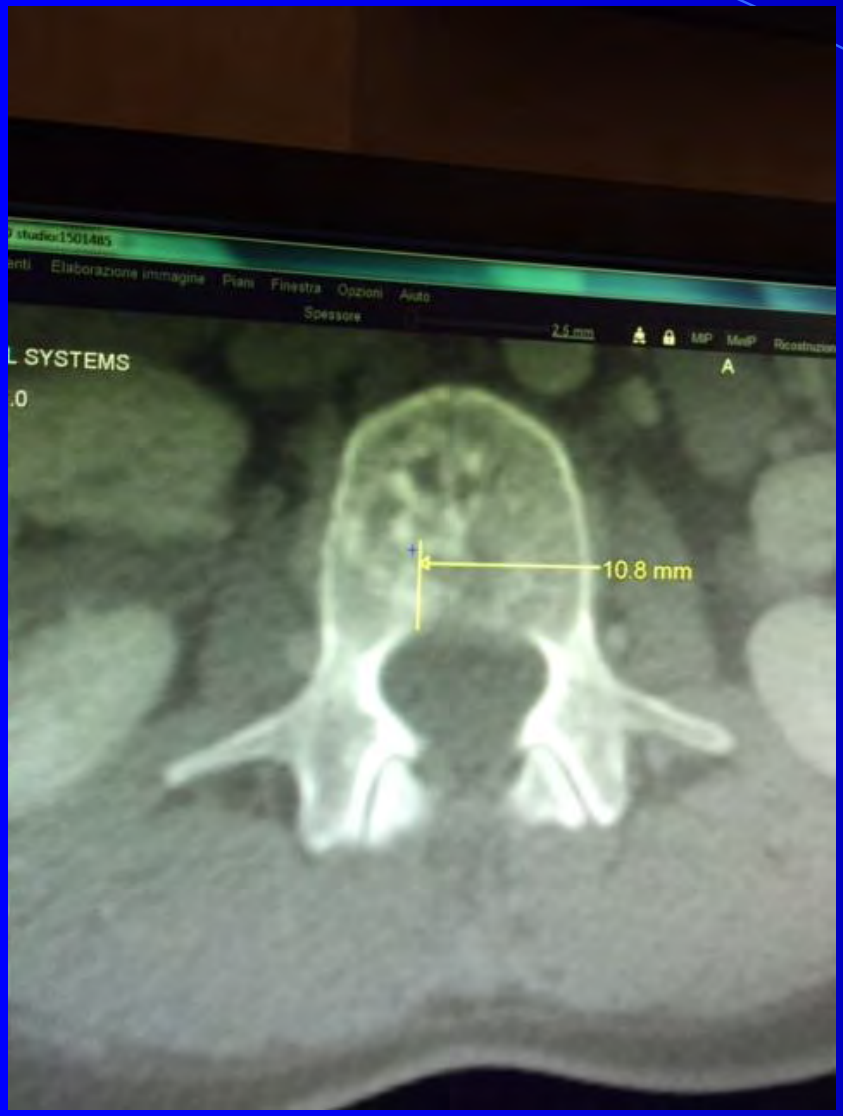
Kypho-IORT



- Age ≥50 year
- Spinal mets (≤2 cm)
- Caudal to T 3
- PFS at 3, 6 and 12 months of 97.5%, 93.8% and 91.2%
- Significant pain reduction median VAS 5/10 before to 2/10 after, mantained on the time
- Dose-escalation study, from 8 Gy in 8 mm (isocenter), to 8 Gy in 10 mm, and to 8 Gy in 13 mm (MTD)

Bludau T et al. Radiologe 2015
Reis T et al, 3rd ESTRO Forum 2015

V-IORT at IEO

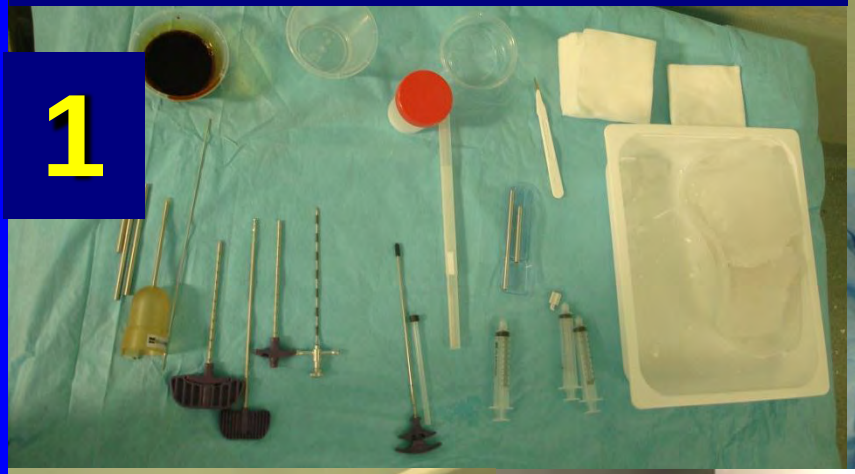


- Dedicated staff
- Training
- Multidisciplinary evaluation
- Patients
- Learning curve
- Treatment time

IEO
Arc Advanced Radiotherapy Center

V-IORT at IEO

1



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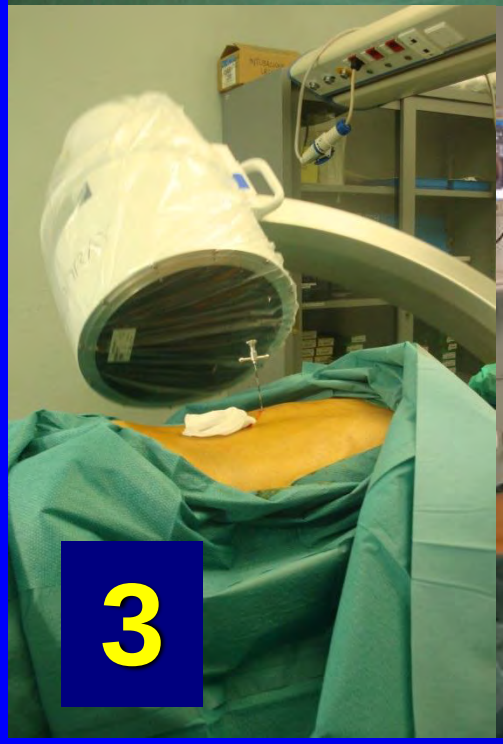

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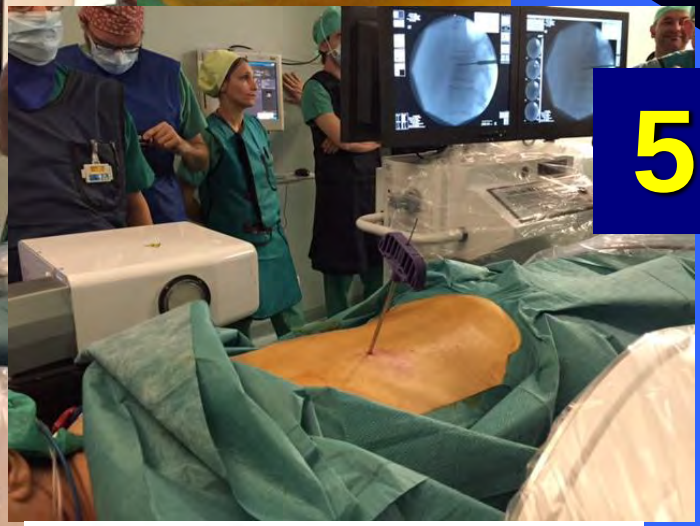

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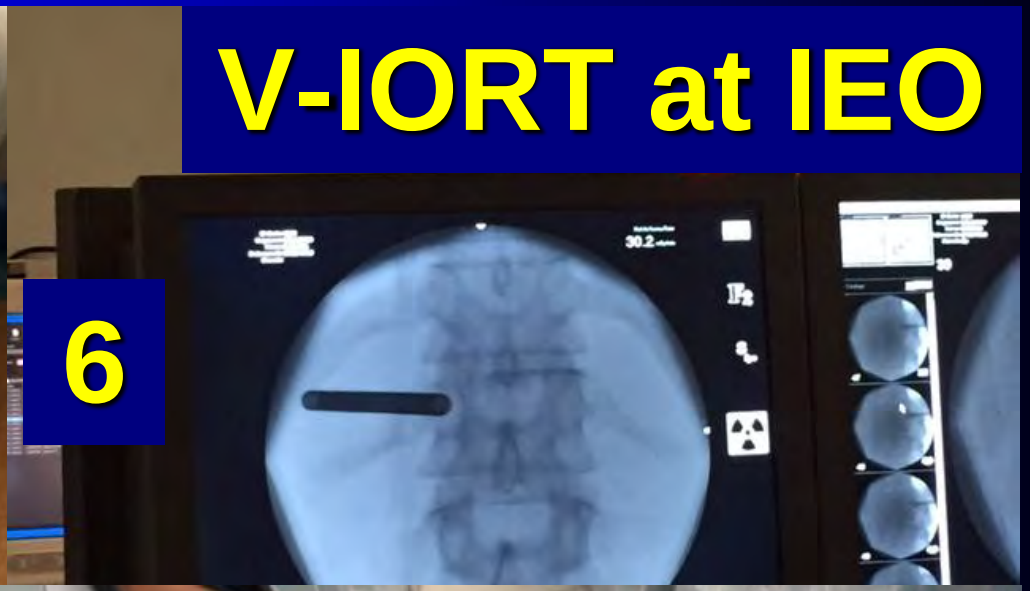
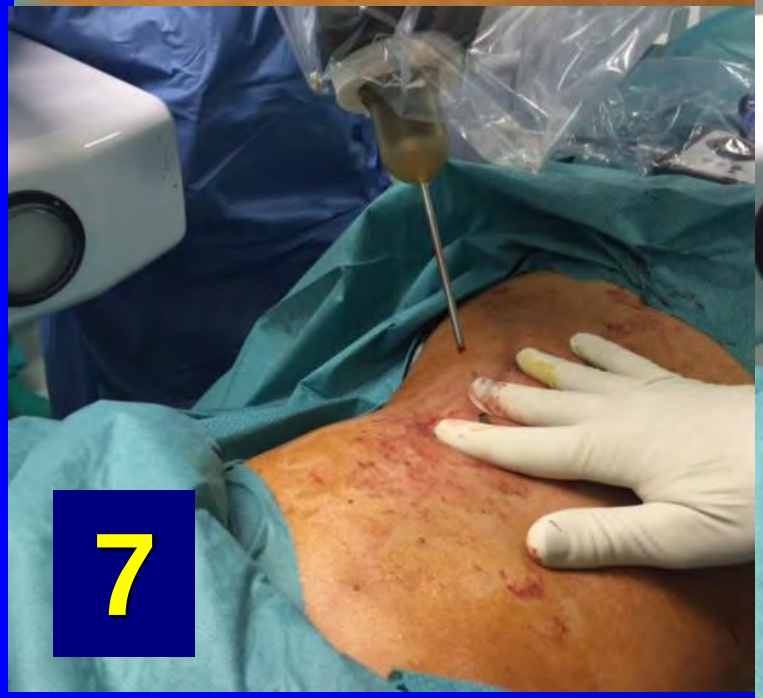
V-IORT at IEO





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V-IORT at IEO

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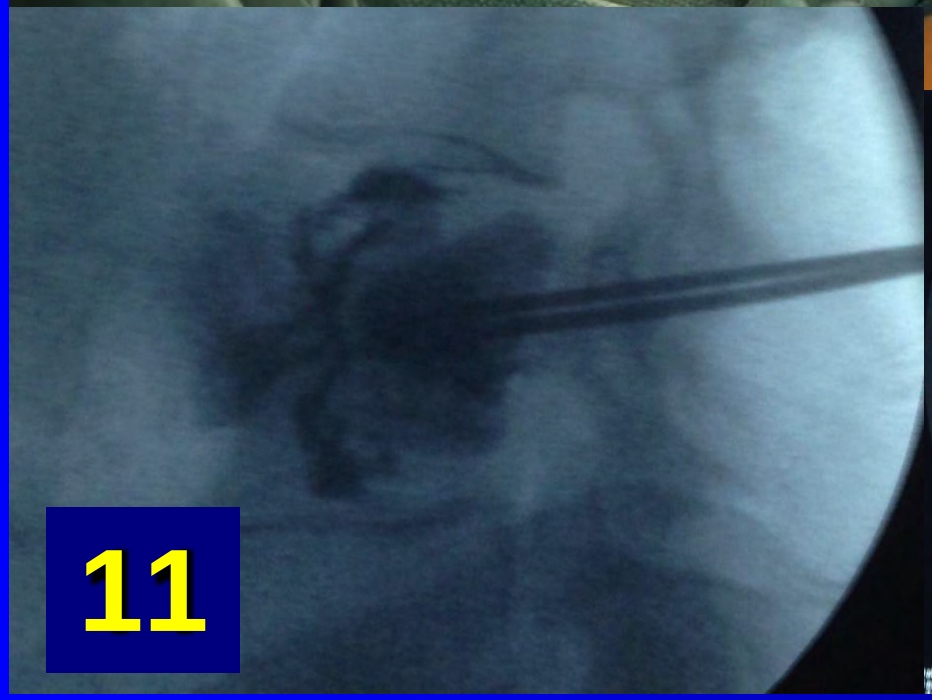

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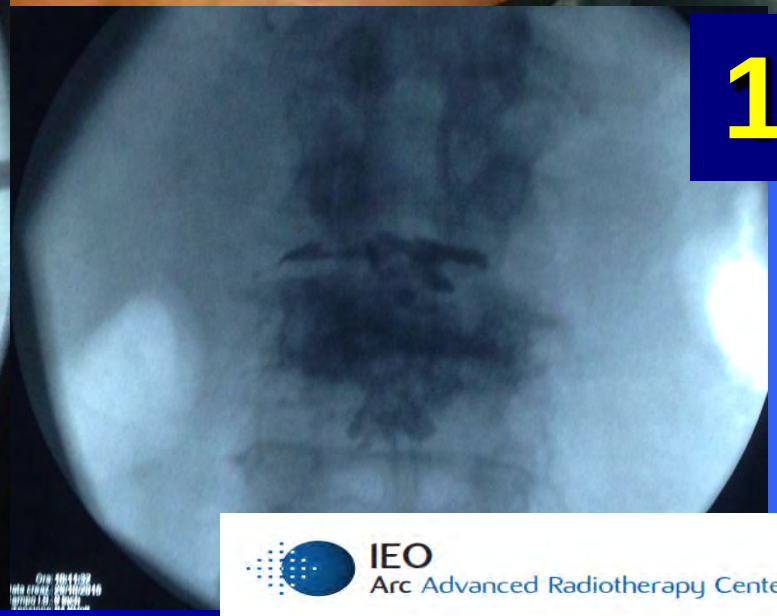

12

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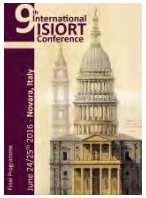
Take Home Message (I)

- The bone is the third most frequent site for metastasis, with the focus in the spine
- RT is often the main choice of therapy, also combined with surgery for patients who require metastasis resection and stabilization
- Less invasive techniques, such as VP and KP, have shown their effectiveness in reducing pain, and stabilize the column

Take Home Message (II)

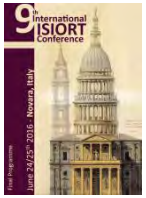
- The combination of VP/KP with high single dose of RT (IORT) has potential benefits in term of pain and tumor control, and prophylactic stabilization
- The combined procedure is feasible, without any additional risks, and fast
- Further studies are strongly recommended for definitive evaluation of this very promising approach



Status and Future Directions

ISIORT
INTERNATIONAL SOCIETY of INTRAOPERATIVE RADIATION THERAPY

- ISIORT is under renew



Status and Future Directions

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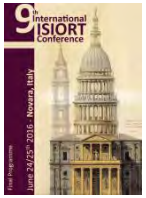
- ISIORT is under renew
- Development in new Countries



Status and Future Directions

ISIORT
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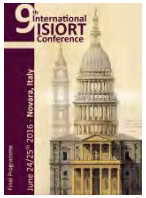
- ISIORT is under renew
- Development in new Countries
- Solid data on breast with appropriate patient selection



Status and Future Directions

ISIORT
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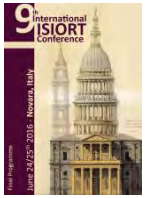
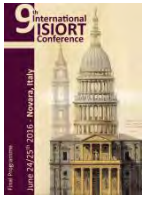
- ISIORT is under renew
- Development in new Countries
- Solid data on breast with appropriate patient selection
- Need for collaborative prospective trials in other tumours



Status and Future Directions

- ISIORT is under renew
- Development in new Countries
- Solid data on breast with appropriate patient selection
- Need for collaborative prospective trials in other tumours
- Technological developments ongoing



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- Development in new Countries
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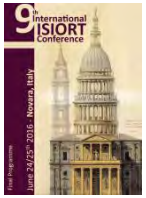
- Need for collaborative prospective trials in other tumours
- Technological developments ongoing
- Interesting new perspectives: immunotherapy, new clinical indications (kypho-IORT), model for biology studies (microenvironment), interactive scientific clinical platform



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- Interesting new perspectives: immunotherapy, new clinical indications (kypho-IORT), model for biology studies (microenvironment), interactive scientific clinical platform
- Strategic collaboration with ESTRO (Task Force)