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History and Future of IORT

Donald Goer, PhD
Scientist (retired)
IntraOp Medical Corporation

THE HISTORY AND FUTURE OF IORT

DISCLOSURES

- IP Consultant to IntraOp Medical
- Founder and former CEO of IntraOp Medical
- Founder of Accuray

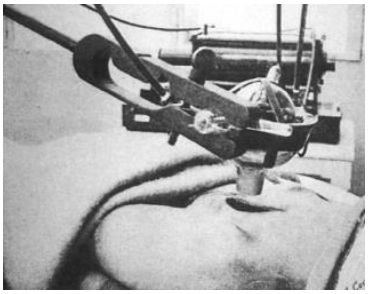
HISTORY

- IORT Treatment
  - Methods and Equipment
- Professional and Society Developments
- Non-IORT Treatment Advancements
  - Surgery
    - TME, Laparoscopic, Robotic
  - EBRT
    - MLC, IMRT, IGRT, VMAT
  - Medical Oncology
    - New CT agents
    - Timing of CT delivery (neo, concurrent, adjuvant)

Earliest treatment with IORT

-1905 Intraoperative "Roentgen Therapy" used in a patient with cervical cancer undergoing TAH, node dissection and partial cystectomy

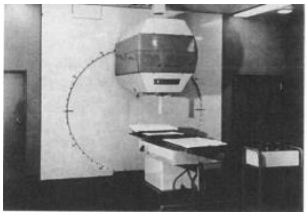
-1915 Unresectable gastric cancer irradiated intraoperatively after exposure with gastrojejunostomy



Orthovoltage IORT was used at some institutions in the 1930's through the 1950's to treat abdominal, thoracic, and head and neck tumors.

The Emergence of Electron Beams for IORT

- Abe at U. of Kyoto implemented electron IORT through patient transportation in 1964
  - Surgery was conducted in the OT
  - After tumor removal, patient was transported on a gurney to the Radiotherapy department
  - Electron IORT was delivered in the radiation bunker
  - After radiation, patient was transported back to the OT to complete the surgery
- **IORT Strategy was to deliver all of the radiation in a single dose of 25-40 Gy**



Toshiba 32 MeV Betatron at Kyoto

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- This is the start of the transport process
- – the patient is moved to a mobile stretcher

- Into the corridor in **the OT area**

Change floors using elevators

- … and down another corridor to the radiation therapy bunker

Treatment with conventional unit after patient transportation

MGH IORT STRATEGY: IORT as a Boost and integration into aggressive combined modality programs of EBRT, chemo and surgery **(Herman Suit 1978)**

Varian Clinac 35 at MGH

Era of IORT by Patient Transportation

(1970's through early 1980's)

More than 150 centers in Japan, Europe, and the United States did IORT by patient transportation. Some used Abe's single dose approach; some used a boost approach

BUT IORT by Patient Transportation has Problems

- **Inefficient use of OT and Linac in RT department**
- **Transportation Added 1-2 hours to the surgical procedure**
  - **Prolonged anesthesia**
  - **Risk of infection during transport**
  - **RT room needed to be shut down for the day or afternoon to prepare for the IORT**
  - **Personnel Intensive**
- **These issues generally limited IORT use to one patient per week, or less.**

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Era of the Dedicated IORT Linac
(early 1980s to mid-1990s)

- This led to the development of dedicated linacs for the OT.
  - Siemens ME (Heidelberg, Essen, Munich, Freiburg, MDACC, OSU, MGH)
  - Modified Varian Clinac (Mayo Clinic)
  - Modified Philips (Eindhoven, Salzburg)
- A conventional or modified linac unit in the OT eliminated the problems associated with patient transportation. However substantial shielding (50+ tons) and structural support must be added to the OT, which made it costly and/or impractical for most hospitals.
- While effective for increasing the volume of IORT, other less costly approaches were also considered.

Dedicated IORT units on the ground floor within the OT department and OT built in the RT department

- Modest incremental cost when implemented for new construction (Lyon, Essen)
- Some built an OT adjacent to or in the RT department to shorten path of patient transportation (TJU, Salzburg)

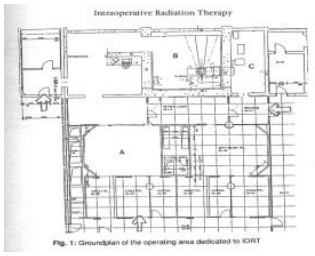

Fig. 1: Groundplan of the operating area dedicated to IORT

Other IORT Approaches

- Howard University (1975) equipped an RT room as an OT. Performed the entire surgery in the RT room.
- Eindhoven (before getting a dedicated linac in their OT) equipped part of one of the RT rooms as an OT and scheduled 2 days per week for IORT.
- Mayo Clinic (1981) (before getting a dedicated linac in their OT) did the surgery in the OT but re-opened for IORT in a room equipped for that in the RT department
- National Cancer Institute (1979) determined maximum IORT dose based on tissue toxicity for IORT combined with EBRT in the dog model. The NCI also conducted the first randomized IORT trial in RPS and gastric cancer. IORT had significantly improved LC but no survival advantage.
- MCOH (1983) surgery suite outside the RT room.

Orthovoltage IORT in the OT department

- Shielding costs much more practical that with electron IORT.
- X-ray unit usually suspended from the ceiling and on tracks that could positioned the unit over patient
- Did not become popular
  - Poor dose distribution
  - Higher bone absorption

X-ray units installed at Stanford, New England Deaconess Hospital

HDR-IORT also developed in the 1990's

HDR-IORT for recurrent RPS

HDR-IORT

- Requires a shielded room, though far less shielding than electron IORT
  - Some have created a small shielded room in the OT just to deliver the HDR
- Flexible applicator adapts to conform to curved surfaces (e.g., pelvic brim)
- Initially, treatment planning required substantial time, but now many centers have generated a "Library of plans" and select the one closest to the anatomic situation.
- Treatment delivery does take a long time, especially for large tumors.

Centers using HDR-IORT

Rotterdam
MSKCC
MDACC
Duke
Beth Israel (NYC)
Mayo (also has electron IORT)
John Hopkins
OSU (also has electron IORT)

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THE ERA OF MOBILE ELECTRON IORT (Late 1997 to the Present)

Mobetron

S.I.T Linacs

Different mobile electron IORT approaches

Mobetron

- Unit is Self-shielded ➡unit is heavy
- Soft Docking ….Now auto-docking
- QA applicator and phantom
- Applicators in 5 mm increments
- Large field applicators

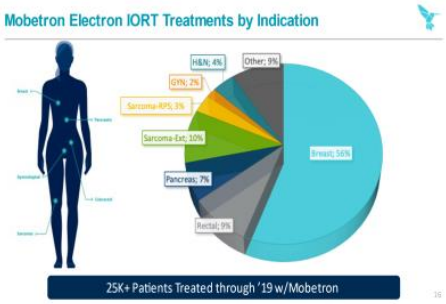
Novac, Liac, S.I.T

- Lighter unit but with mobile shields that need to be positioned about and under the surgical before treatment.
- Hard-docking
- Variable field-shaper

There are now more than 200 mobile electron IORT systems in more than 30 countries throughout the world

Mobile IORT Improvements

- Data management systems that connect to hospital data base
- IORT Treatment planning
- OT based CT systems compatible with IORT unit
- Improvements in moving the systems within the OT



Interest in Breast IORT created opportunity for new IORT equipment—50 kV devices

- IORT volume shifted between 2000 and 2020 from locally advanced and recurrent disease for which there were little alternative approaches, to early-stage breast cancer.
- Breast IORT focused on either breast boost, to improve the accuracy of the boost while eliminating a week of EBRT boost treatment, or…
- IORT APBI, in which for suitable low risk women, a single IORT treatment replaces all of the EBRT treatments.
- This focus on breast cancer, led to the emergence of new IORT devices to meet this demand.

INTRABEAM®

- Originally designed to treat brain cancer with 50 kV x-rays using a miniature x-ray tube inserted directly into the brain.
- Developed applicators to treat breast and skin. Applicators range from 1-5 cm spheres.
- Most Intrabeam® patients have been treated for breast cancer, but have also treated brain, rectal, spinal mets, and pelvic disease.
- A randomized trial and several single center and a large registry trial has been published.

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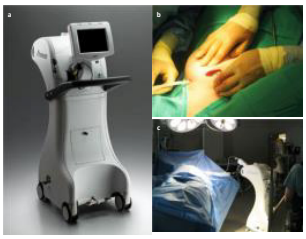
XOFT-AXXENT SYSTEM



- Originally designed to provide an electronic brachytherapy approach for Mammosite.
- The thin and flexible x-ray tube is used in conjunction with a double lumen catheter
- Xoft has also been used in conjunction with oncoplastic reconstruction in APBI. A large study[1] of 1400 tumors had a 5-year LR of 5.25% but a 5-year BCSS of 99.9% and OS of 96.3% as patients could be salvaged if they recurred.

[1] Silverstein M, et al., Recurrence and Survival Rates for 1400 Early Breast Tumors Treated with Intraoperative Radiation Therapy (IORT) Ann Surg Oncol (2022); 29(6):3726-3736

Papillon

- Designed to treat Anal Cancer with 50 kV administered by endocavitary radiation with the goal of organ preservation.
- A randomized trial[1] has shown that endocavitary boost with 50 kV x-rays combined with neo adjuvant chemo radiotherapy for cT2-T3 < 5cm :
  - Significantly increases the rate of Clinical complete response (64% vs 92%).
  - Significantly increases the 3-year rate of organ preservation especially for T < 3cm (63% vs 97%).
- Also have applicators for breast and skin cancer.

[1] Gerard, J-P, et al., Contact X-Ray Brachytherapy with Chemoradiotherapy is Improving Organ Preservation in Early cT2-T3 Rectal Adenocarcinoma. Three-year Results of the phase 3 Randomized OPERA Trial (NCT02505750).

Improvements in Non-IORT Treatment

SURGERY

- TME—impacted IORT for rectal cancer
- Laparoscopic Surgery—to avoid open surgery: IORT is possible
- Robotic Surgery: Not yet routinely possible, but technically feasible
- Oncoplastic Breast Surgery

Radiotherapy advancements

- MLC
- IMRT
- IGRT
- VMAT
- Monte Carlo based TPS
- Improved positioning systems
- Hypofractionation—converted 7- week breast treatment to 1 week

Medical Oncology Improvements

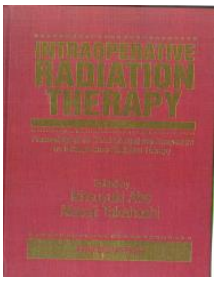
- **5 FU**
- **Capcitabine**
- **Gemcitabine**
- **FOLFOX**
- **FOLFIRINOX**

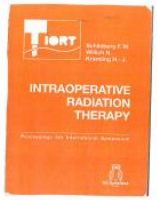
Radiation sensitizing chemo to make EBRT more effective

- **HT**
- **Immunotherapy**

EG Junction ACA - Laparoscopic Resection + IOERT

Professional and Society Developments





Beginning in 1988 in Toledo Ohio, IORT Meetings were held on an Ad Hoc basis approximately every 2 years---Kyoto, Munich, Lyon. At the 1996 San Francisco Meeting, it was decided to create a professional IORT society called the ISIORT.

- Membership open to surgeons and radoncs
- Plan was to alternate meetings between the US and Europe every two years
- 1st ISIORT Meeting in Pamplona Spain in 1998
  - 2000 Boston
  - 2002 Aachen
  - 2005 Miami
  - 2008 Madrid
  - 2010 Scottsdale
  - 2012 Baveno/Milan
  - 2014 Cologne
  - 2016 Novara
  - 2018 Mannheim
  - 2020 Salzburg
  - **2022 Columbus**
- Web Site (www.ISIORT.org)
- Early attempts at International IORT trials were unsuccessful.

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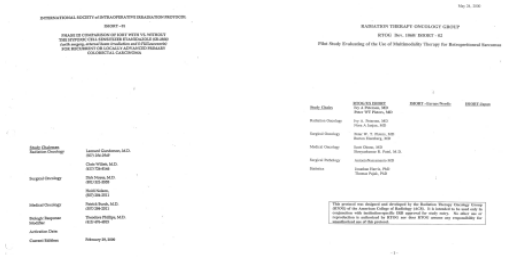
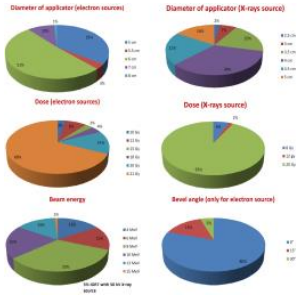
ISIORT Proposed Protocols
Never Implemented



ISIORT-EUROPE

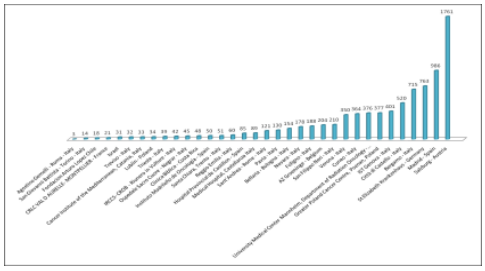
In 2005, the European ISIORT centers formed ISIORT-Europe. They would have a one-day meeting in conjunction with the GEC-ESTRO in years that the ISIORT dis not meet. Have met in Montpellier, Porto, London, Geneva, and Barcelona.

- Initiated a European Registry
- Conducted Pooled analyses
  - Pancreas-270 patients from 5 centers in 2009
  - Colorectal-605 patients from 4 centers in 2010
  - Extremity Sarcoma-259 patients from 3 centers in 2015



2013 Registry Results: 31 European centers; 7196 IORT cases; 95.4% are electron treatments. 4.6% are kilovoltage

ISIORT-EUROPE



2014 Update: 8,164 IORT treatments from 34 countries (31 in Europe Plus Israel, Cuba, and Chile. A number of key European centers are not yet participating

Accelerating Research and Collaboration
Prospective Trials

- **HIOB Trial: IORT Boost + 3 weeks WBI**
  - **Over 1,000 Patients and 14 institutions**
    - **Have demonstrated that IORT boost is superior in all age groups above 40 years old. Still waiting results for 35-40**
- **Ohio State University: IORT Boost with Oncoplastic Reconstruction**
  - **U.S Multi-Institutional Study opened April 2017**
- **Pacer Trial: IORT boost after neoadjuvant FOLFIRINOX and CRT for unresectable pancreatic cancer**
  - **U.S Multi-Institutional Study opened 2020**
- **Pancfort trial (Verona IT): Electron IORT combined with total neoadjuvant therapy in borderline pancreatic cancer**

Accelerating Research and Collaboration
Prospective Trials (Continued)

- **IOPANCA-IGET (Image Guided Electron Therapy) for resectable PDAC (Freiburg)**
- **Cosmopolitan Trial – breast quality of life comparing IORT with EBRT (Heidelberg)**
- **ELECTRA Trial: IOERT for locally advanced and locally recurrent rectal cancer (Southampton)**
- **HNSALV-Combining immunotherapy with salvage surgery and IORT for persistent and recurrent H&N Cancer (Ohio State).**
- **FLASH**
  - **Impulse – multi-resistant melanoma with dose escalation (Lausanne)**
  - **Lance--NMSC randomized phase II trial for BCC and SCC (Lausanne)**

Accelerating Research and Collaboration
U.S Registries

- **U.S Breast IORT Registry: IRB Approved. No longer enrolling patients, but continuing follow-up.**
- **EU Breast IORT Registry: IRB Approved, enrolling patients**
- **Locally Advanced Registries: Pending**
  - **RPS, Extermity Sarcoma, GYN**

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Future of IORT—some Possibilities

FUTURE of IORT: IORT combined with FLASH

If the FLASH effect works, the natural extension would be to combine FLASH with IORT.

Why?

- IORT dose is sometimes limited due to unaccepted toxicity
- Despite resection with negative margins, some IORT sites still have higher recurrence rates than would be desired.
- With FLASH, one can increase the IORT field size to capture any microscopic disease outside the original planned field since FLASH has little or no impact on any normal tissue that might receive FLASH radiation.

Some Possible FLASH/IORT sites

- Head and neck after salvage surgery
- Recurrent Rectal or GYN
- RPS
- Pancreas

FUTURE of IORT: IORT Boost for Breast due to increasing use of Oncoplastic procedures

Background

- Breast surgeons are increasingly using oncoplastic reconstruction in surgery for early-stage breast cancer.
- It is not possible to target the boost site with EBRT after oncoplastic reconstruction.
- HIOB has shown that electron IORT boost provides the best LC in all aged groups above the age of 40 years.
- Boost is needed to reduce recurrences in women < 60 years.

Prediction

IOERT Boost will be used at major breast centers as oncoplastic reconstruction becomes the standard of care.

SPECULATIVE OPPORTUNITIES ?

CAN IORT REPLACE HT IN WOMEN > 70 WITH BREAST CANCER?

Background

- CALGB 9343 established that in women 70 years and older, after surgical removal of the tumor, Tamoxifen RT results in 98% local control vs. 90% LC for just Tamoxifen. The 10-year OS are the same at 67% and 66%, respectively.
- Both the Florence APBI Trial and data from Bordet's 1000 IOERT patients treated to daye, show a poor adherence to HT therapy yet have fairly good results.
- The Europa Trial is testing whether APBI with EBRT alone vs. endocrine therapy alone is equivalent for low-risk women with breast cancer.

Prediction

IORT will be the ultimate APBI should the Europa Trial prove positive.

CONCLUSIONS

- IORT will continue to play an important role in cancer treatment for locally advanced and recurrent disease. Too this end, trials currently underway like PACER, Pancfort, ELECTRA, IOPANCA-IGET, and HNSALV, will validate the role of IOERT in these diseases.
- As oncoplastic surgery in conjunction with early breast cancer becomes the standard of care, women $\leq$ 60 years, who we know benefit from a boost, will be candidates for IORT boost. (Note that HIOB Trial has already proven IORT boost is superior to EBRT boost in women $\geq$ 40 years).
- New demand for IORT will emerge with the establishment of FLASH IORT.
- If the EUROPA Trial is successful, IORT will be the APBI treatment of choice to replace hormonal therapy in elderly women.

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ACKNOWLEDGEMENTS

Thanks to Len Gunderson and Felix Sedlmayer for providing me with some important information regarding the dates and locations of some of the early IORT Meetings