History and Future of IORT

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

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DISCLOSURES

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

EarlieSatheathreathwitht with **IORT IORT**

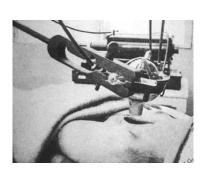
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-1915 Unresectable gastric cancer irradiated intraoperatively after exposure with gastrojejunostomy

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

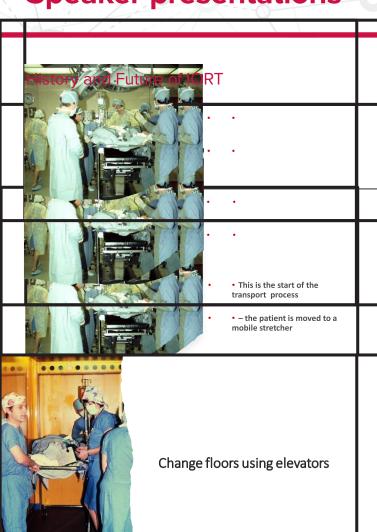


The Emergence of Electron Beams for IORT

- 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



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 - IORT Striate EvStwar





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



Varian Clinac 35 at MGH



the OT











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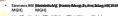
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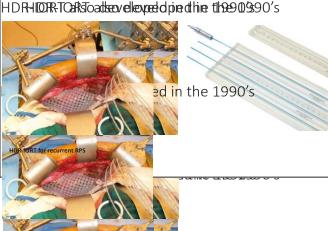
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- Modest incremental cost when implemented for new construction (Lyon, Essen)
- · Some built an OT adjacent to or in the RT department to shorten path of patient transportation (TJU, Salzburg)



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- over patient

Orthopyoitage IORT in the OT

- Higher bone absorption
- · Shielding costs much more practical that with
- 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 Hospita



New England Deaconess Hospita

- Higher broige erbson et information

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

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

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History and Future of IORT

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- Soft Docking Now autored liking
- QA applicator and phantom
- Applicators in 5 mm increments
- Large field applicators
- 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

Mobetron Electron IORT Treatments by Indication

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- Breast IORT focused on either breast boost, to improve the accuracy of the boost while eliminating a week of EBRT boost treatment, or...
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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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- Most livitoab tratmato patrienta tienes have been the attention of a storman ser, doubter, but have also vereisted the attention, beatal, rectal,

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- cavitary 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

-rest Repulso of the phase 3 Randomined OP RA Trial (NC 102 505 573). EG J**EGC LUGIO: TRAGITÀ A CLÀ palags a ropsic o pais e Patris ancticlo ERO** ERT

EG Junction ACA - Laparoscopic Resection + IOERT





- 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

2008 Madrid

• 2020 Salzburg

- 2002 Aachen 2010 Scottsdale
- 2014 Cologne
 - 2016 Novara
 - 2022 Columbus
- Web Site (<u>www.ISIORT.org</u>)
- Early attempts at International IORT trials were unsuccessful.
 - 2014 Cologne
- 2016 No2011a6 Novara
 - 2018 MaloulaeiMannheim

2005 Miami

2012 Baveno/Milan

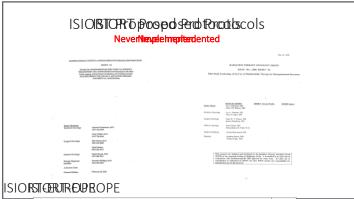
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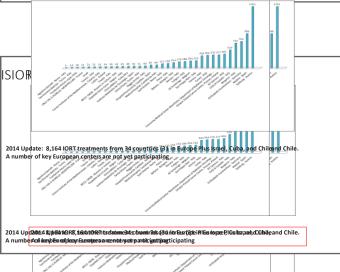
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History and Future of IORT

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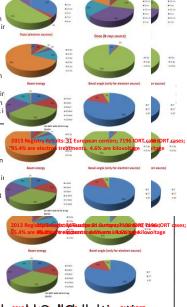
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- Initiated a European Registry
- · Conducted Pooled analyses
 - · Pancreas-270 patients from 5 centers in 2009
 - Colorectal-605 patients from 4 centers in
 - · Extremity Sarcoma-259 patients from 3



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- Ohio State University: IORT Boost with Oncoplastic Reconstruction
- Will institutional Study Research and Collaboration
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 U.S. Multi-institutional Study opened 2020
- HIOB Trial: | ORT Boost + 3 weeks WBI
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- 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
 - U.S Multi-Institutional Study opened 2020
- · Pancfort trial (Verona IT): Electron IORT combined with total neoadjuvant therapy in borderline

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Accelerating Research and Collaboration **U.S Registries**

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

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History and Future of IORT

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

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Why?

- > Pancreas Pancreas
 > 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

SPECULATIVE OPPORTUNITIES?

SPECULATIVE OPPORTUNITIES?

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 ≤ 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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History and Future of IORT

ACKNOWLEDGEMENTS

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