The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute

2022 International Society of Intraoperative Radiation Therapy (ISIORT) Conference

The James Cancer Hospital and Solove Research Institute

Thursday, Oct. 20
Friday, Oct. 21

The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

cancer.osu.edu

Welcome

Dear Colleagues,

On behalf of the International Society of Intraoperative Radiation Therapy (ISIORT), we are pleased to welcome you to the 11th annual ISIORT Conference.

Our conference features experts from several nations – Germany, Austria, Italy, the United Kingdom, Spain, Belgium and the United States. Our speakers' presentations will help promote research, education and treatment of patients with cancer by intraoperative radiation therapy (IORT), including orthovoltage, electron beam or HDR brachytherapy. The conference is also designed to foster liaisons among medical specialists and allied scientists who treat patients via IORT.

Our sincere thank you to our speakers and Platinum Sponsors: IntraOp Medical Corporation and The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute (OSUCCC – James). Without your participation, this conference would not be possible.

We hope the scientific scope of this year's conference will provide you with an informative and rewarding experience that widens your collective perspectives on current and future IORT applications in clinical practice.

Sincerely,

John Grecula, MD, FACR
ISIORT President
Professor, Department of Radiation Oncology
The Ohio State University

Dukagjin Blakaj, MD, PhD
ISIORT Conference Co-Director
Associate Professor, Department of Radiation Oncology
The Ohio State University

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The Ohio State University
Comprehensive Cancer Center

IntraOp

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John C. Grecula, MD, FACR
President, ISIORT
Professor
Department of Radiation Oncology
The Ohio State University
Columbus, Ohio, United States

8:30 a.m. **History and Future of IORT**
Donald Goer, PhD
Scientist (retired)
IntraOp Medical Corporation
Sunnyvale, California, United States

9 a.m. **Radiobiological Aspects of IORT/FLASH**
Jessica Fleming, PhD
Radiobiologist and Senior Research Associate
Department of Radiation Oncology
The Ohio State University
Columbus, Ohio, United States

9:20 a.m. **Clinical Perspective on the Present State and New Developments in Electron-Based IORT; FLASH**
Falk Röder, MD
Professor
Department of Radiation Oncology
Paracelsus Medical University Clinics
Salzburg, Austria

9:50 a.m. **Physicist's Perspective on the Present State and New Developments in Electron-Based IORT**
Markus Stana, PhD
Medical Physicist
Department of Radiation Oncology
Paracelsus Medical University Clinics
Salzburg, Austria

10:10 a.m. **Coffee Break and Visit Exhibits**

10:30 a.m. **Physics in FLASH Radiotherapy**
Ahmet Ayan, PhD
Medical Physicist
Department of Radiation Oncology
The Ohio State University
Columbus, Ohio, United States

10:50 a.m. **CT Imaging in Electron Based IORT – Current Status and Future Perspectives**
Christoph Gaisberger, PhD
Medical Physicist
Radiation Oncology
Paracelsus Medical University Clinics
Salzburg, Austria

11:10 a.m. **Quality Assurance in Intraoperative Radiotherapy**
Antonella Ciabattoni, MD
Radiation Oncologist
UOC Radiotherapy
San Filippo Neri Hospital, Rome, Italy

11:30 a.m. **Physics Abstracts**

Noon **Lunch and Visit Exhibits (ISIORT Board Meeting)**

1 p.m. **The Evolution of Pancreatic Cancer Treatment**
Cristina Ferrone, MD
Director, Liver Surgery Program
Department of Surgical Oncology
Massachusetts General Hospital
Boston, Massachusetts, United States

1:20 p.m. **IORT in Pancreatic Carcinoma**
Eric Miller, MD, PhD
Associate Professor
Department of Radiation Oncology
The Ohio State University
Columbus, Ohio, United States

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1:40 p.m. **IORT in Rectal Carcinoma**
Alex Mirnezami, MD
Professor
Department of Surgical Oncology
University of Southampton, England

2 p.m. **Mayo Experience of IORT in Rectal Carcinoma**
Michael Haddock, MD
Professor
Department of Radiation Oncology
Mayo Clinic
Rochester, Minnesota, United States

2:20 p.m. **GI Abstract Presentations**

2:50 p.m. **Coffee Break and Visit Exhibits**

3:10 p.m. **IORT in Head & Neck Cancers**
Mauricio Gamez Haro, MD
Radiation Oncologist
Mayo Clinic
Rochester, Minnesota, United States

3:30 p.m. **Combining Immunotherapy with Salvage Surgery and IORT for Treatment of Persistent/Recurrent Head and Neck Cancers**
Dukagjin Blakaj, MD, PhD
Associate Professor
Department of Radiation Oncology
The Ohio State University
Columbus, Ohio, United States

3:50 p.m. **Head and Neck Abstract Presentations**

6:30 p.m. **ISIORT Society Dinner**
Ohio Stadium VIP Suite

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8:00 a.m. **Breakfast and Visit Exhibits**

9 a.m. **HIOB Trial: Hypofractionated Whole Breast Irradiation and Electron IORT Boost in Early-stage Breast Cancer**
Gerd Fastner, MD
Professor
Paracelsus Medical University Clinics
Salzburg, Austria

9:20 a.m. **TARGIT A, C, and E Trials in Breast Cancer (pre-recorded)**
Elena Sperk, MD
Professor
Department of Radiation Oncology
University Medical Center
Mannheim, Germany

9:40 a.m. **IOERT Versus External Beam Electrons for Boost Radiotherapy in Stage I/II Breast Cancer: 10-Year Results of a Phase III Randomized Study**
Antonella Ciabattoni, MD
Radiation Oncologist
UOC Radiotherapy
San Filippo Neri Hospital, Rome, Italy

10 a.m. **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, MD
Associate Professor
Department of Radiation Oncology
The Ohio State University
Columbus, Ohio, United States

10:20 a.m. **Surgical Considerations in Incorporating IORT for Patients with Breast Cancer (pre-recorded)**
Kelsey Larson, MD, FACS
Assistant Professor
Department of Surgical Oncology
University of Kansas
Kansas City, Kansas, United States

10:40 a.m. **Coffee Break and Visit Exhibits**

11 a.m. **Changes in Peripheral Immune Cells After Intraoperative Radiation Therapy in Low-Risk Breast Cancer**
Ferran Guedea, MD
Chair
Department of Radiation Oncology
Institut Català d'Oncologia
Barcelona University
Barcelona, Spain

11:20 a.m. **Single Treatment Electron IORT for Breast Cancer; The Jules Bordet Institute Experience**
Catherine Philippson, MD
Department of Radiation Oncology
Institut Jules Bordet
Brussels, Belgium

11:40 a.m. **ELIOT and POLO Trials in Breast Cancer (pre-recorded)**
Cristina Leonardi, MD
Division of Radiation Oncology
European Institute of Oncology
Milan, Italy

Noon **Lunch and Visit Exhibits**

1 p.m. **IORT in Sarcomas**
Steve Braunstein, MD
Associate Professor
Department of Radiation Oncology
University of California San Francisco
San Francisco, California, United States

1:20 p.m. **Breast Carcinoma and Sarcoma Abstracts**

2:05 p.m. **Summary of ISIORT 2022**
John Grecula, MD, FACR
President, ISIORT
Professor
Department of Radiation Oncology
The Ohio State University
Columbus, Ohio, United States

2:20 p.m. **Adjourn**

Speaker biographies

Ahmet Ayan, PhD

Medical Physicist
Department of Radiation Oncology
The Ohio State University
Columbus, Ohio, United States

Ahmet S. Ayan, PhD, is a medical physicist and associate professor in the Department of Radiation Oncology at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute. He received his Bachelor of Science and Master of Science degrees in physics at Middle East Technical University, Ankara, Turkey, and doctorate degree in experimental high energy physics at the University of Iowa, United States, followed by postdoctoral research at the University of Pennsylvania (UPenn) Department of Radiology on SPECT and PET imaging (2005-09). He completed his therapeutic medical physics residency training program in the Department of Radiation Oncology at UPenn. His current research interests are centered on normal tissue toxicity modeling in radiotherapy, use of image informatics for medical linear accelerator imaging systems quality assurance and ultra-high-dose-rate radiotherapy focusing on improving the efficiency, dosimetric, spatial and temporal accuracy and safety in radiotherapy treatment delivery. He has been at The Ohio State University since 2011.

Jose Bazan, MD

Associate Professor
Department of Radiation Oncology
The Ohio State University
Columbus, Ohio, United States

Dr. Jose Bazan is a radiation oncologist with clinical expertise in treating non-small cell carcinomas of the lung and a variety of breast carcinomas, such as ductal, intraductal and hereditary. He also treats ovarian cancer and male breast cancer. He came to Ohio State in 2013 following the completion of medical school and his residency at Stanford University School of Medicine. Dr. Bazan has been honored to present his research findings at dozens of professional conferences since 2006, and he has been published in many medical journals such as International Journal of Radiation Oncology, Practical Radiation Oncology, Journal of Nuclear Medicine and Clinical Lung Cancer. He served as principal investigator for several clinical trials, including his most current research at Ohio State (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).

Speaker biographies

Dukagjin Blakaj, MD, PhD

Associate Professor
Department of Radiation Oncology
The Ohio State University
Columbus, Ohio, United States

Dr. Dukagjin Blakai's combination of experience and extensive training in translational research, direct involvement in clinical trials and service at the national level make him highly suited to contribute to this conference. Dr. Blakai serves as the director and associate clinical director of the Head and Neck/Skull Base and Radiation Oncology departments, respectively, at The Ohio State University Wexner Medical Center and the OSUCCC – James. He will become director of the Radiology Oncology Department within the next year. From a clinical standpoint, Dr. Blakai leads a skilled head and neck team that treats over 450 head and neck cancer patients per year, with 50-70 patients actively receiving treatment at any given time. In addition, Dr. Blakai leads the intra-operative radiation therapy (IORT) program, for which he has an active Intent-to-Treat (IIT) currently looking into primary and adaptive radiation resistance mechanisms in the presence of immunotherapy, conventional and stereotactic radiation therapy dosing.

Under Dr. Blakai's leadership during the past eight years, researchers at the OSUCCC – James have made major advances in recruiting participants to head and neck/skull base clinical trials with the cancer clinical trial matching service. Multiple trials in head and neck cancer, both local and cooperative, are currently being recruited here. In addition to his administrative roles and active clinical oncology practice, Dr. Blakai is actively involved in translational aspects of treatment resistance in head and neck squamous cell carcinoma (HNSCC). In particular, he has been working on predictive clinical and molecular markers of immunotherapy response within the locally recurrent metastatic head and neck cancer patient population. The team has identified four genes and clinical information that help predict the rates of response for a patient population that needs advances, is working on identifying molecular markers for rare skull base tumors and has provided initial evidence that a subset of sinonasal undifferentiated tumors may be neuronal in nature. The team is currently writing both projects for R01 applications.

Nationally, Dr. Blakai is a member of the NCI Head and Neck Previously Untreated Locally Advanced Task Force, the NRG Oncology Head and Neck Core Committee and ECOG-ACRIN Head and Neck Committee.

Steve Braunstein, MD

Associate Professor
Department of Radiation Oncology
University of California San Francisco (UCSF)
San Francisco, California, United States

Steve Braunstein is associate professor and vice chair of Radiation Oncology at the University of California San Francisco, specializing in the treatment of central nervous system treatment and soft tissue malignancies in the adult and pediatric patient populations. He serves as co-director of the UCSF Radiosurgery program and program director for the resident and fellowship training program. Dr. Braunstein's clinical research portfolio includes multiple projects examining the evolving outcomes of patients undergoing radiotherapy for high-grade glioma with advanced imaging approaches and the use of stereotactic radiosurgery in brain metastases as administered in combination with targeted and immunotherapies. In addition, he is a member of the NRG CNS Core Committee and UCSF Brain Tumor Research Center and Children Oncology Group investigator with a focus on translational research protocols. Dr. Braunstein is a frequent collaborator with the Orthopedic Oncology division as a champion of intra-operative radiotherapy in management of patients with primary and recurrent soft tissue sarcoma.

Speaker biographies

Antonella Ciabattoni, MD

Radiation Oncologist
UOC Radiotherapy
San Filippo Neri Hospital, Rome, Italy

Gerd Fastner, MD

Professor
Paracelsus Medical University Clinics
Salzburg, Austria

Cristina Ferrone, MD

Director, Liver Surgery Program
Department of Surgical Oncology
Massachusetts General Hospital
Boston, Massachusetts, United States

Jessica Fleming, PhD

Radiobiologist and Senior Research Associate
Department of Of Radiation Oncology
The Ohio State University
Columbus, Ohio, United States

Jessica Fleming, PhD, is a radiobiologist in the Department of Radiation Oncology at the OSUCCC – James. She earned a bachelor's degree in biology from Ashland University (2006) and a doctorate in molecular, cellular and developmental biology (2012) from The Ohio State University. Dr. Fleming currently serves on the Head Start 4/NEXT Consortium Trial Scientific Committee and the Advances in Radiation Oncology editorial board. Dr. Fleming has received the Best of ASTRO Award for Basic/Translational Science and the Columbus CEO Future 50 Award and was selected for the Leadership Columbus signature program. She is highly involved with the translational research program for the NRG Oncology cooperative group and serves as co-investigator on four CTEP protocols. Her research focuses on identifying prognostic and predictive biomarkers in adult and pediatric brain tumor patients and studying mechanisms of treatment response, resistance and toxicity using in vitro and in vivo models. Additionally, for the past two years, she has been leading the radiobiology pre-clinical studies in the OSU FLASH program.

Speaker biographies

Christoph Gaisberger, PhD

Medical Physicist
Paracelsus Medical University Clinics
Salzburg, Austria

Dr. DI Christoph Gaisberger, PhD, is a medical physics expert, the head of Medical Physics at the Institute for Radiotherapy and Radio-Onkology in Salzburg, Austria, and a member of the board from the Austrian Federation of Medical Physicists. In 2005, he started his career in radiation therapy in Salzburg, where he completed master's and doctorate degrees. Gaisberger's PhD thesis addressed surface scanning and gating applications. From the idea of software and hardware development to the clinical application, he published an article about an in hose-developed surface scanning system for accurate positioning breast cancer patients (2013). In Salzburg, over 4,800 patients have been treated with IOeRT since 1997.

Gaisberger heads the project for the reorganization and renovation of the IOeRT in the new operating theatre. In 2022, the organization expanded its global leadership in technology development in IORT imaging with a mobile CBCT system combined with an 3D IORT treatment planning system. Since 2019, he has been the head of medical physics on the Institute for Radiotherapy and Radio-Oncology in Salzburg.

Mauricio Gamez Haro, MD

Radiation Oncologist
Mayo Clinic
Rochester, Minnesota, United States

Donald Goer, PhD

Scientist (retired)
IntraOp Medical Inc.
Sunnyvale, California, United States

Donald A. Goer, PhD, received his doctorate in physics in 1973 from The Ohio State University. He is a recognized expert on linear accelerator technology and the author of many articles on the subject, including the chapter on radiation therapy linear accelerators in the Encyclopedia of Medical Devices and Instrumentation. After post-doctoral study in metallurgical engineering, Dr. Goer joined Varian Associates. Dr. Goer has more than 40 years of experience in the sales, marketing and product development of linear accelerators. From 1977-85, Dr. Goer was responsible for the product development of Varian's cancer therapy equipment. Five new cancer treatment units were successfully introduced to the market during this period, resulting in the sale of more than 700 treatment systems. Between 1985 and 1990, Dr. Goer was responsible for market development and strategic planning at Varian. Dr. Goer's final position at Varian was manager of sales operations with principal responsibilities in the international market. In 1991, Dr. Goer joined Schonberg Radiation Corporation as president, for which he helped apply X-band accelerator technology to medical applications. In 1991, Dr. Goer assisted in founding Accuray Inc., a medical company providing dedicated accelerators for radiosurgery, and in 1993, he co-founded Intraop Medical Corporation – the developer and manufacturer of the Mobetron, the world's only mobile and self-shielded linear accelerator designed for intraoperative radiotherapy treatment (IORT). Dr. Goer served as president from 1993-2007 and later as the company's chief scientist. He served on several IORT Quality Assurance committees, helped develop IORT protocols and was a corporate liaison to both the International Society of IORT and the American Society of Therapeutic Radiation Oncology. He has authored a chapter on the use of IORT for breast cancer in Breast Disease: Comprehensive Management and a textbook on breast cancer and has authored or co-authored several peer-reviewed articles on IORT.

Speaker biographies

John Grecula, MD, FACR

President, ISIORT
Professor
Department of Radiation Oncology
The Ohio State University
Columbus, Ohio, United States

John C. Grecula, MD, FACR, is a tenured professor of radiation oncology at The Ohio State University and current president of ISIORT. His subspecialties include head and neck carcinomas and brain malignancies. Dr. Grecula is the director of Gamma Knife radiosurgery. His research interests include radiation modifiers and advanced MR imaging, which have been funded by the National Comprehensive Network and the National Cancer Institute. He is co-chair of the publications committee at the Alliance for Clinical Trials in Oncology and was appointed by Gov. Mike DeWine to the Ohio Radiation Advisory Council for the state of Ohio.

Ferran Guedea, MD

Chair
Department of Radiation Oncology
Institut Catala d'Oncologia
Barcelona University
Barcelona, Spain

Dr. Ferran Guedea has master's and doctorate degrees in medicine and surgery from the Universidad Autónoma de Barcelona (UAB, 1983 and 1988). He is currently director of radiotherapy oncology at the Institut Català d'Oncologia (ICO) and professor at the Universidad de Barcelona (UB). Dr. Guedea is president of the technical committee at the Asociación contra el Cáncer (ACC) in Barcelona and corresponding academician of the Real Academia de Medicina de Cataluña (RAMC).

Dr. Guedea has participated in 320 scientific meetings, symposia and congresses. He has 138 publications and has participated in 18 research projects. He is also head of the radiobiology and cancer group at the Instituto de Investigación Biomédica de Bellvitge (IDIBELL), recognized by the Agencia de Ayudas Universitarias y de Investigación (AGAUR) as a consolidated research group.

His main lines of research are quality of life in patients with prostate cancer, new technologies in brachytherapy and external radiotherapy, intraoperative radiotherapy and predictive radiosensitivity tests.

Speaker biographies

Michael Haddock, MD

Professor
Department of Radiation Oncology
Mayo Clinic
Rochester, Minnesota, United States

Michael G. Haddock, MD, is a professor of radiation oncology at the Mayo Clinic in Rochester, Minnesota. He leads the gastrointestinal radiation oncology practice and actively treats gastrointestinal and gynecologic malignancies, soft tissue and bone sarcoma. He is an experienced brachytherapist and has extensive IORT experience treating primary and recurrent colorectal cancers, gynecologic cancers and soft tissue sarcomas. Dr. Haddock earned his bachelor's degree in mathematics from Brigham Young University (1985), his Doctor of Medicine from the University of Washington (1989) and completed residency training at the Mayo Clinic in 1994. He has served as past president of ISIORT and a member of the ISIORT Board of Governors. Dr. Haddock has been involved in numerous cooperative group research trials through North Central Cancer Treatment Group, Radiation Therapy Oncology Group, Alliance for Clinical Trials in Oncology and NRG Oncology and currently serves as co-PI at the Mayo Clinic. He has published over 180 research articles during 28 years as a Mayo Clinic faculty member.

Kelsey Larson, MD, FACS

Assistant Professor
Department of Surgical Oncology
University of Kansas
Kansas City, Kansas, United States

Dr. Larson is a breast surgical oncologist from the University of Kansas in Kansas City. Her practice is dedicated to breast surgery patients, particularly those with breast cancer or those who are at high risk for breast cancer. She has extensive fellowship-level training in advanced surgical techniques, including oncoplastic surgery and nipple-sparing mastectomy. In addition, she has an interest in clinical research and clinical education. Dr. Larson is certified by the American Board of Surgery and has earned both FACS and FSSO designations. She is the immediate past president of the Kansas Chapter of the American College of Surgeons, chair of the surgery research committee for the Department of Surgery, National Accreditation Program for Breast Centers Committee chair for KU Cancer Center and program director for the Society of Surgical Oncology-approved Breast Surgical Oncology Fellowship. She is also the surgeon leader for lintra-operative radiation therapy for breast cancer at the University of Kansas Cancer Center.

Cristina Leonardi, MD

Division of Radiation Oncology
European Institute of Oncology
Milan, Italy

Dr. Maria Cristina Leonardi was born in Camerino (MC), Italy, in 1965 and graduated in Medicine at the University of Milan in 1992 and completed her specialization in radiation oncology in 1996 at the University of Milan. Today, she is a clinician working as a radiation oncologist at the European Institute of Oncology (IEO), IEO IRCCS (Milan, Italy) since 1997. Dr. Leonardi has participated in training programs, such as training programs and a master course on breast cancer (2001-02) at the University of Milan, a training course on methodology in clinical research (2007), a fellowship at Royal Marsden Hospital in Sutton, London, UK, from 2009-10 and refresher courses on good clinical practice (2010 and 2014).

Speaker biographies

Eric Miller, MD, PhD

Associate Professor
Department of Radiation Oncology
The Ohio State University
Columbus, Ohio, United States

Dr. Eric Miller is an associate professor in the Department of Radiation Oncology at the OSUCCC – James, specializing in the treatment of gastrointestinal malignancies. He completed his PhD in biomedical engineering at Carnegie Mellon University prior to pursuing his MD at Indiana University in 2012. Dr. Miller finished residency in the Department of Radiation Oncology at The Ohio State University in 2017 and started as a faculty member in August 2017. His research efforts are focused on developing clinical trials which incorporate novel radiosensitizers for the treatment of gastrointestinal malignancies, utilizing functional imaging technologies such as MRI and PET to develop novel biomarkers to predict patient treatment response and developing strategies for mitigation of radiation toxicity with a focus on cardiotoxicity. Nationally, he serves on the National Cancer Institute Rectal Anal Task Force, the NRG Oncology Colorectal and Non-Colorectal Core Committees and the Alliance Gastrointestinal Committee, and he aids in developing national guidelines as part of the NCCN Colon/Rectal/Anal/Small Bowel Cancers Guidelines Panel.

Alex Mirnezami, MD

Professor
Department of Surgical Oncology
University of Southhampton, England

Catherine Philippson, MD

Department of Radiation Oncology
Institut Jules Bordet
Brussels, Belgium

Falk Roder, MD

Professor
Department of Radiation Oncology
Paracelsus Medical University Clinics
Salzburg, Austria

Speaker biographies

Elana Sperk, MD

Professor
Department of Radiation Oncology
University Medical Center
Mannhein, Germany

Dr. Elena Sperk is an assistant professor of radiation oncology at the Medical Faculty of the University of Heidelberg in Germany and currently works as CEO of the Mannheim Cancer Center Clinical Trials Unit at the University Medical Center Mannheim. She has been conducting research in the field of IORT since 2007 in the group of Prof. Frederik Wenz and has been a major contributor to the TARGIT trials of IORT in breast cancer in Germany. Dr. Sperk is also principal investigator of the TARGIT C, E, BQR studies and also in the international European Union-funded research project REQUITE. Her main focus is translational research regarding radiation toxicity.

Markus Stana, PhD

Medical Physicist
Radiation Oncology
Parcelsus Medical University Clinics
Salzburg, Austria

Mag.Dr. Markus Stana, MSc, is medical physics expert in the Department of Radiation Oncology, SALK, Salzburg, Austria. After receiving his PhD in solid-state physics and a short post-doc fellowship, Dr. Stana left the world of fundamental research to find a new home in the applied field of medical physics. Now at the university hospital in Salzburg, he can merge both, his previous and recent experience in medical research. His main scientific is lung cancer and intraoperative radiation therapy. In the latter field, he is responsible for QA of the Mobetron and the optimization of workflow and components encompassing it.

Speaker presentations

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

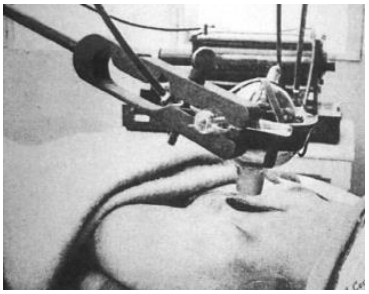
HISTORY

- 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

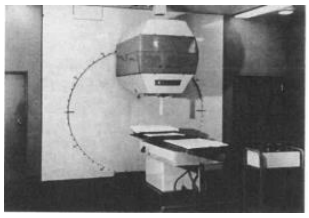
-1915 Unresectable gastric cancer irradiated intraoperatively after exposure with gastrojejunostomy



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

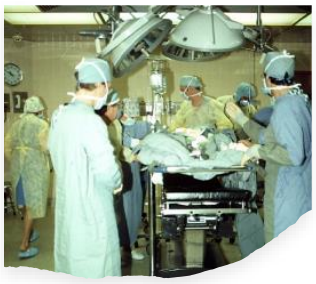
- Abe at U. of Kyoto implemented electron IORT through patient transportation in 1964
  - Surgery was conducted in the OT
  - After tumor removal, patient was transported on a gurney to the Radiotherapy department
  - Electron IORT was delivered in the radiation bunker
  - After radiation, patient was 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**



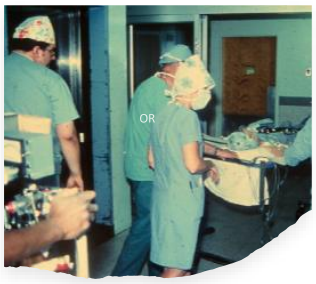
Toshiba 32 MeV Betatron at Kyoto

Speaker presentations

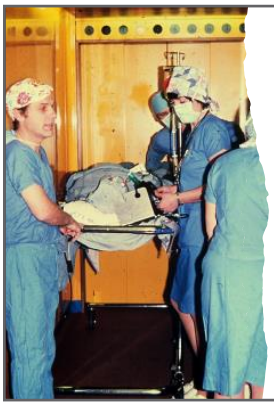
History and Future of IORT



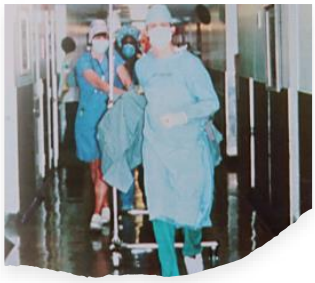
- This is the start of the transport process
- – the patient is moved to a mobile stretcher



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



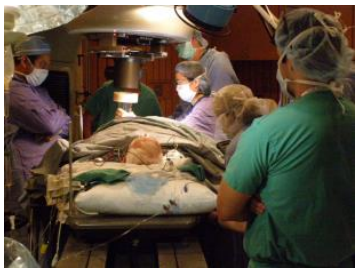
Change floors using elevators



- … 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.**

Speaker presentations

History and Future of IORT

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)

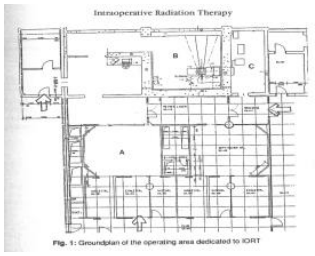


Fig. 1: Groundplan of the operating area dedicated to IORT

Other IORT Approaches

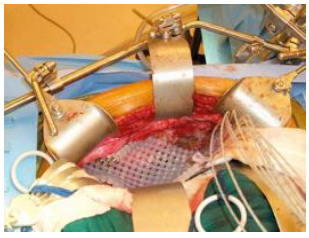
- Howard University (1975) equipped an RT room as an OT. Performed the entire surgery in the RT room.
- Eindhoven (before getting a dedicated linac in their OT) equipped part of one of the RT rooms as an OT and scheduled 2 days per week for IORT.
- Mayo Clinic (1981) (before getting a dedicated linac 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.

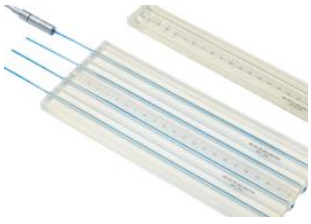
Orthovoltage IORT in the OT department

- 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

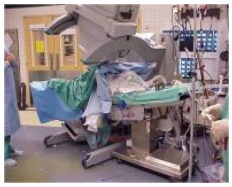
Rotterdam
MSKCC
MDACC
Duke
Beth Israel (NYC)
Mayo (also has electron IORT)
John Hopkins
OSU (also has electron IORT)

Speaker presentations

History and Future of IORT

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

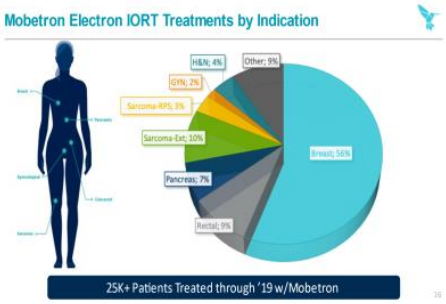
Novac, Liac, S.I.T

- 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

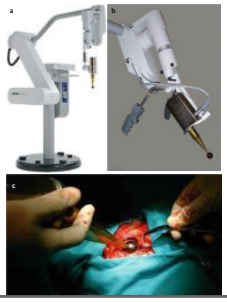
- Data management systems that connect to hospital data base
- IORT Treatment planning
- OT based CT systems compatible with IORT unit
- Improvements in moving the systems within the OT



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®

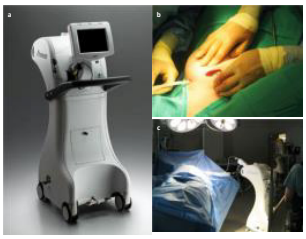


- Originally designed to treat brain cancer with 50 kV x-rays using a miniature x-ray tube inserted directly into the brain.
- Developed applicators to treat breast and skin. Applicators range from 1-5 cm spheres.
- Most Intrabeam® patients have been treated for breast cancer, but have also treated brain,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

Speaker presentations

History and Future of IORT

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

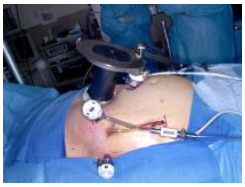
Medical Oncology Improvements

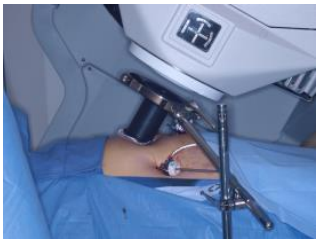
- **5 FU**
- **Capcitabine**
- **Gemcitabine**
- **FOLFOX**
- **FOLFIRINOX**

Radiation sensitizing chemo to make EBRT more effective

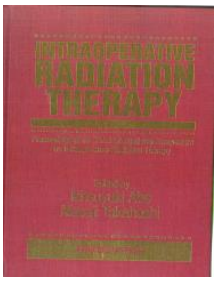
- **HT**
- **Immunotherapy**

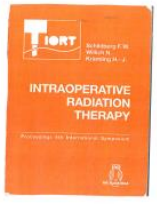
EG Junction ACA - Laparoscopic Resection + IOERT





Professional and Society Developments





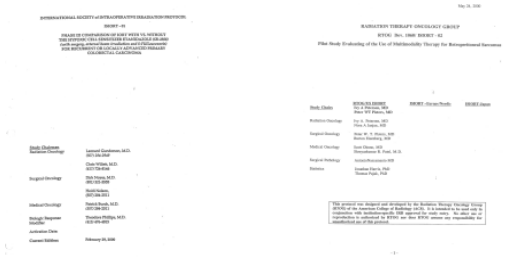
Beginning in 1988 in Toledo Ohio, IORT Meetings were held on an Ad Hoc basis approximately every 2 years---Kyoto, Munich, Lyon. At the 1996 San Francisco Meeting, it was decided to create a professional IORT society called the ISIORT.

- 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.

Speaker presentations

History and Future of IORT

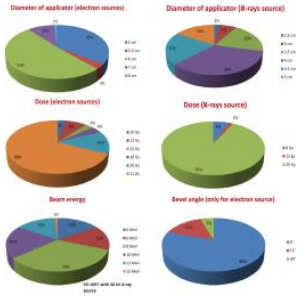
ISIORT Proposed Protocols
Never Implemented



ISIORT-EUROPE

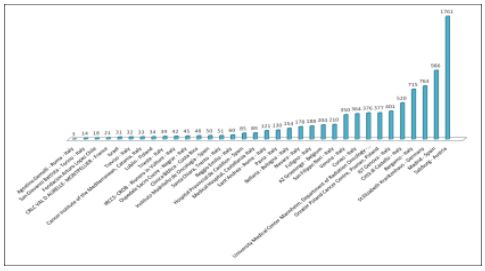
In 2005, the European ISIORT centers formed ISIORT-Europe. They would have a one-day meeting in conjunction with the GEC-ESTRO in years that the ISIORT dis not meet. Have met in Montpellier, Porto, London, Geneva, and Barcelona.

- 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**

Speaker presentations

History and Future of IORT

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

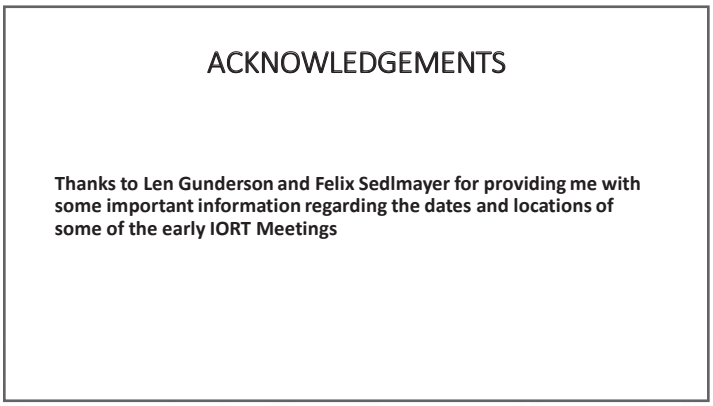
IORT will be the ultimate APBI should the Europa Trial prove positive.

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 ≤ 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 ≥ 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.

Speaker presentations

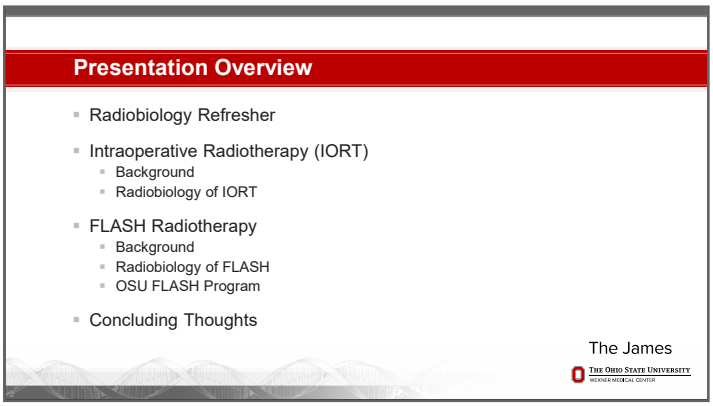
History and Future of IORT

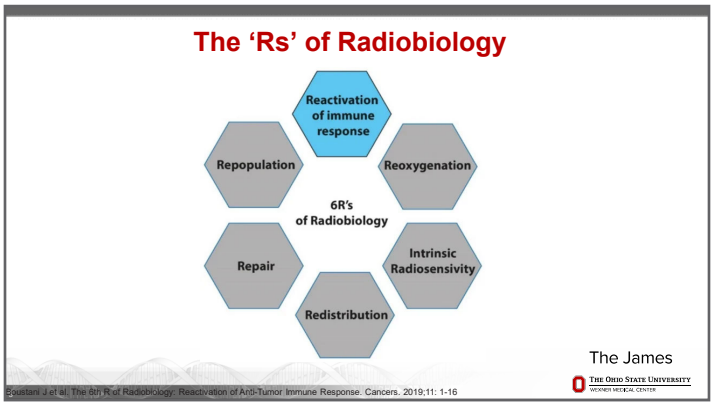


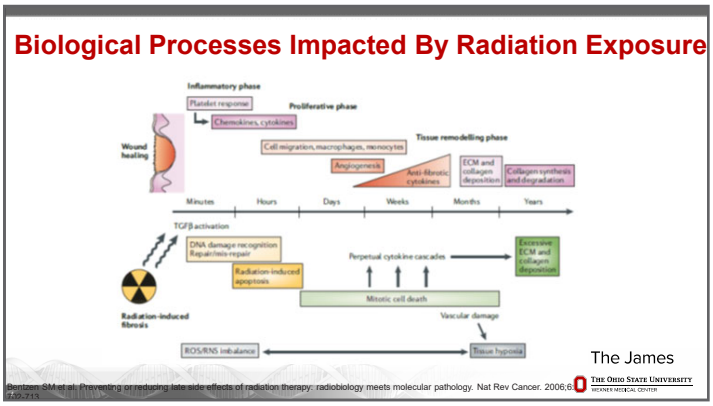
Speaker presentations

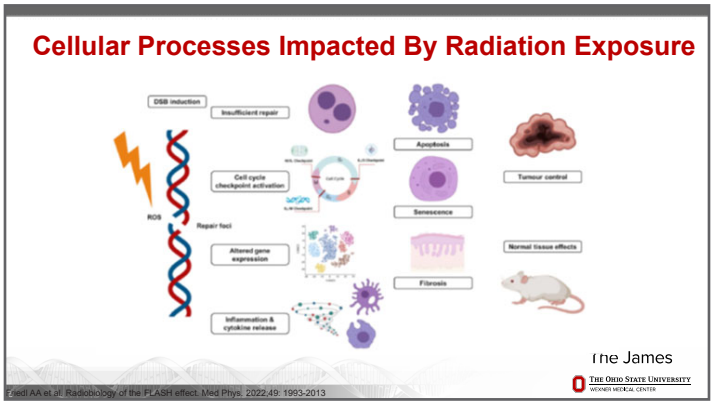
Radiobiological Aspects of IORT/FLASH

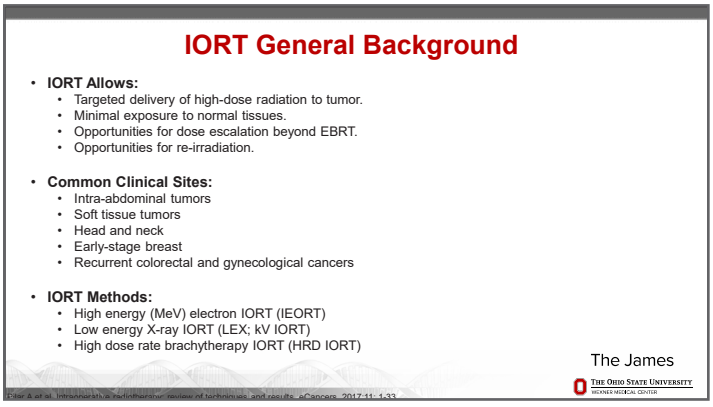
Jessica Fleming, PhD
Radiobiologist and Senior Research Associate
Department of Radiation Oncology
The Ohio State University
Columbus, Ohio, United States











Speaker presentations

Radiobiological Aspects of IORT/FLASH

Radiobiology of IORT General Background

Radiation quality	5 R's	Special effects ?	Irradiated volume
RBE	Reassortment Repair / chrom. instab. Reoxygenation Repopulation: eliminated Radiosensitivity	Cytokines Vascular Immune	S.o.E. Late NT effects

The James

Herskind C et al. Biology of high single doses of IORT: RBE, 5R's, and other biological aspects. eCancers. 2017;12: 1-13

Radiation Quality

- Linear energy transfer (LET): Rate at which energy is transferred per unit path length.
- Relative biological effectiveness (RBE): Dose ratio of the reference (MV X-rays) and test radiations producing the same biological effect:

$$RBE = \frac{D_{ref}}{D_{test}}$$

20-50 kV X-rays	3-12 MeV Electron	α-particles/Heavy ions
Low LET	Low LET	High LET
RBE > 1	RBE < 1	RBE >10

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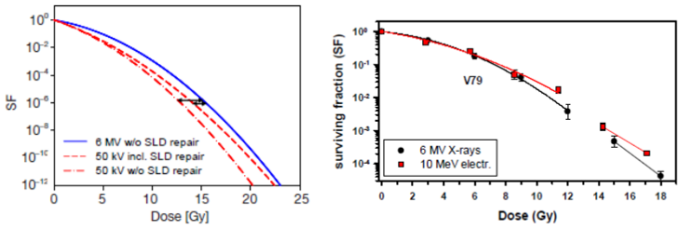
Herskind C et al. Biology of high single doses of IORT: RBE, 5R's, and other biological aspects. eCancers. 2017;12: 1-13

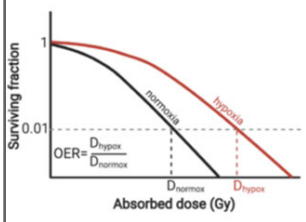
Radiation Quality

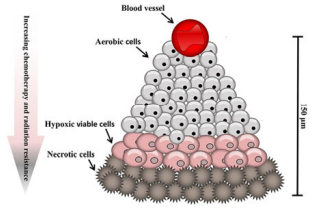


The James

Herskind C et al. Biology of high single doses of IORT: RBE, 5R's, and other biological aspects. eCancers. 2017;12: 1-13
Herskind C et al. Radiobiological aspects of intraoperative tumour-bed irradiation with low-energy X-rays (LEX-IORT). Transl Cancer Res. 2014;3: 5-17

Reoxygenation



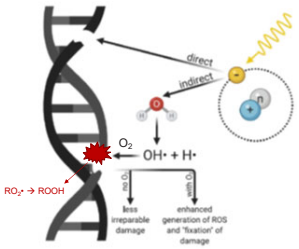


With IORT, remaining tumor cells are well-oxygenated.

The James

Tameemi WA et al. Hypoxia-Modified Cancer Cell Metabolism. Front. Cell Dev. Biol. 2019; 29: 1-15

Reoxygenation

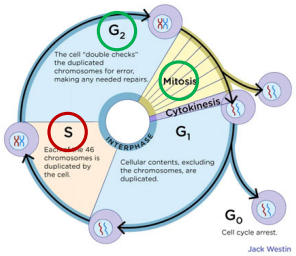


- Radiation exposure depletes O_2 through radiolysis
- Fractionated RT allows for reoxygenation between doses.
- For single high doses of RT, reoxygenation is not a factor.

The James

Tellarovic I et al. Interfering with Tumor Hypoxia for Radiotherapy Optimization. J. Exp. Clin. Cancer Res. 2021; 40: 1-26

Redistribution/Reassortment



- Cellular radiosensitivity varies through the cell cycle.
- Radioresistant population enriched after RT.
- In fractionated RT cells will redistribute across phases of cell cycle between daily fractions.
- Reassortment does not play a role in IORT with a single dose.
- At single high doses of radiation, cell survival curves show little evidence of a resistant population.

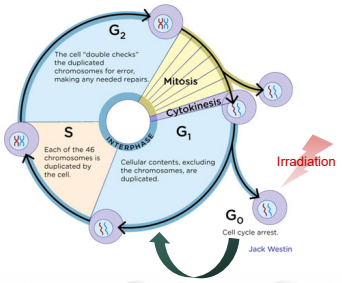
The James

Herskind C et al. Biology of high single doses of IORT: RBE, 5R's, and other biological aspects. eCancers. 2017;12: 1-13

Speaker presentations

Radiobiological Aspects of IORT/FLASH

Repopulation



2 Phases of Repopulation:

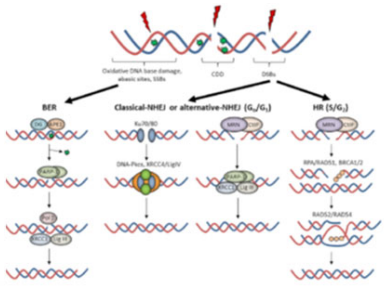
1. After surgery
   - Prior to RT
2. After radiation
   - Resting cells (G_0) enter the cell cycle in order to compensate for cells killed by RT.

Major advantage of IORT is the elimination of repopulation by the extreme shortening of the overall treatment time.

The James
The Ohio State University Wexner Medical Center

Herskind C et al. Biology of high single doses of IORT: RBE, 5R's, and other biological aspects. eCancers. 2017;12: 1-13

Repair



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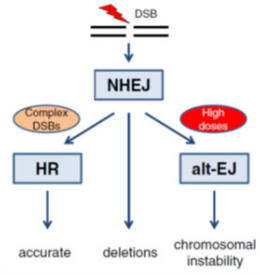
The Ohio State University Wexner Medical Center

Fabbrizi MR et al. Radiotherapy and the cellular DNA damage response: current and future perspectives on head and neck cancer treatment. Cancer Drug Resist 2020;3:775-90

Radiosensitivity



Higher doses of RT:

1. Saturates HR and overloads the NHEJ pathway.
2. Increases chromosomal instability.
3. Influences number and properties of surviving cells.

The James
The Ohio State University Wexner Medical Center

Herskind C et al. Biology of high single doses of IORT: RBE, 5R's, and other biological aspects. eCancers. 2017;12: 1-13

Additional Factors to Consider

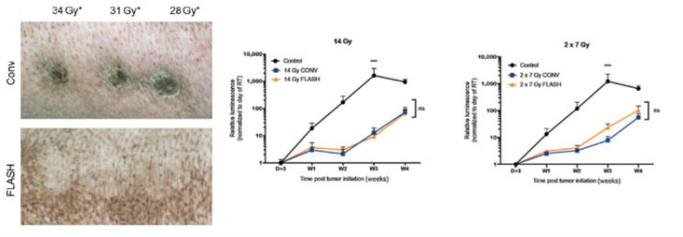
- Vasculature:
  - Increased endothelial cell apoptosis.
- Inflammatory/immune response:
  - Increased tumor cell necrosis and antigen presentation.
  - Recruitment of T-cells to irradiated and distant unirradiated tumors.
- Irradiated volume, local control, and normal-tissue reaction.
  - Dose distribution.
  - Distance between applicator and target.

The James
The Ohio State University Wexner Medical Center

Herskind C et al. Biology of high single doses of IORT: RBE, 5R's, and other biological aspects. eCancers. 2017;12: 1-13

FLASH Radiotherapy

Ultra-high dose rate (> 40 Gy/sec) radiation delivered in a very short period of time that produces a damaging effect in tumor tissue while sparing surrounding normal tissues.



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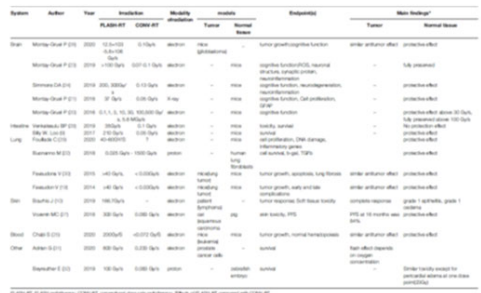
The Ohio State University Wexner Medical Center

Vozenin MC et al. The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients. Clin Cancer Res. 2019;25: 35-42
Montay-Gruel P et al. Hypofractionated FLASH-RT as an Effective Treatment against Glioblastoma that Reduces Neurocognitive Side Effects in Mice. Clin Cancer Res. 2021;27:775-84

FLASH Radiotherapy



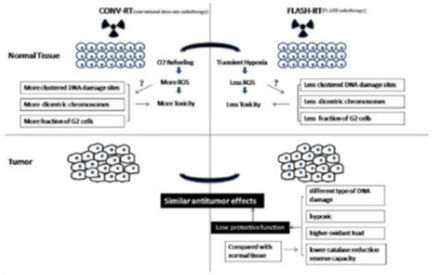
The James
The Ohio State University Wexner Medical Center

Liu B et al. FLASH Radiotherapy: History and Future. Front Oncol. 2021;11: 644400

Speaker presentations

Radiobiological Aspects of IORT/FLASH

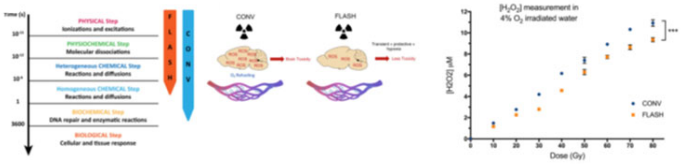
Biological Responses to FLASH Versus CONV Radiotherapy



The James

Liu B et al. FLASH Radiotherapy: History and Future. Front Oncol. 2021;11: 644400

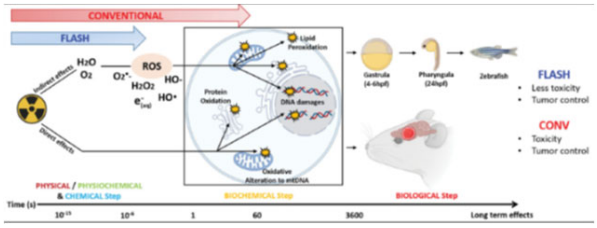
Understanding the FLASH Effect Mechanism: Rapid Oxygen Depletion-Reduced ROS



The James

Montay-Gruel, P et al. Long-term neurocognitive benefits of FLASH radiotherapy driven by reduced reactive oxygen species.. 2019; Proc Natl Acad Sci USA. 116: 10943-10951

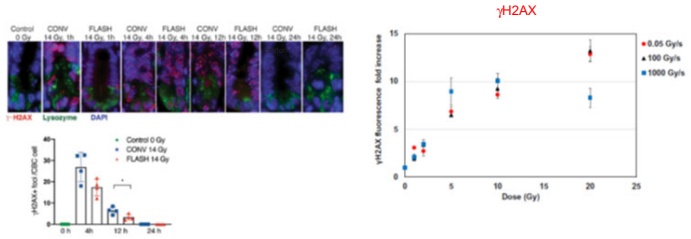
Understanding the FLASH Effect Mechanism: Reduced ROS = Less Indirect DNA Damage



The James

Kacem H et al. Understanding the FLASH effect to unravel the potential of ultra-high dose rate irradiation. 2022; Int J Radiat Biol: 98: 506-516

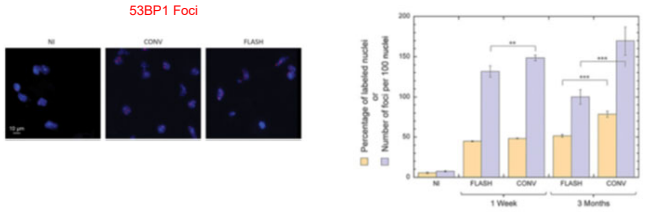
Understanding the FLASH Effect Mechanism: Rapid Oxygen Depletion-Reduced DNA Damage



The James

Fouillade C et al. FLASH Irradiation Spares Lung Progenitor Cells and Limits the Incidence of Radio-induced Senescence. Clin Cancer Res. 2020; 26: 1497-1506
Buonanno M et al. Biological effects in normal cells exposed to FLASH dose rate protons. Radiother & Oncol. 2019; 139: 51–55
Levy K et al. Abdominal FLASH irradiation reduces radiation-induced gastrointestinal toxicity for the treatment of ovarian cancer in mice. Sci Rep. 2020; 10:21600

Understanding the FLASH Effect Mechanism: Rapid Oxygen Depletion-Reduced DNA Damage



The James

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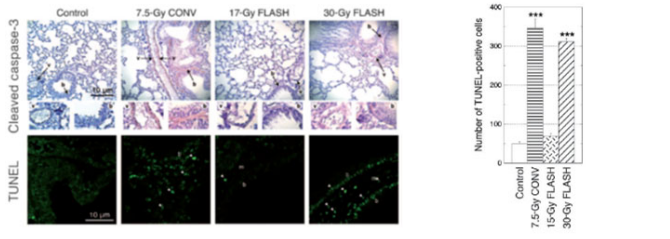
Levy K et al. Abdominal FLASH irradiation reduces radiation-induced gastrointestinal toxicity for the treatment of ovarian cancer in mice. Sci Rep. 2020; 10:21600

Understanding FLASH Effect Mechanism: Apoptosis



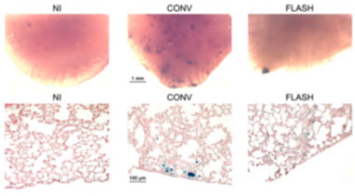
The James

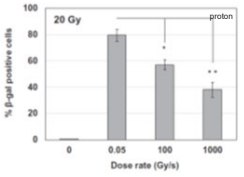
Favaudon V et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Sci Transl Med. 2014; 6: 245ra93

Speaker presentations

Radiobiological Aspects of IORT/FLASH

Understanding the FLASH Effect Mechanism: Limits Senescence





The James

Fouillade C et al. FLASH Irradiation Spares Lung Progenitor Cells and Limits the Incidence of Radio-induced Senescence. Clin Cancer Res. 2020; 26: 1497-1506
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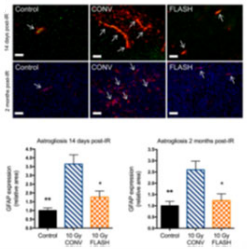
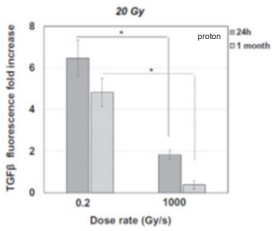
Understanding the FLASH Effect Mechanism: Reduced Inflammation





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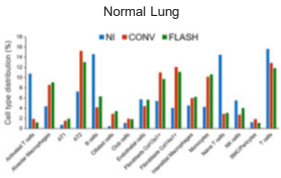
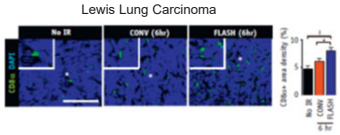
Montay-Gruel, P et al. Long-term neurocognitive benefits of FLASH radiotherapy driven by reduced reactive oxygen species.. 2019; Proc Natl Acad Sci USA; 116: 10943-10951

Understanding FLASH Effect Mechanism: Immune Modulation

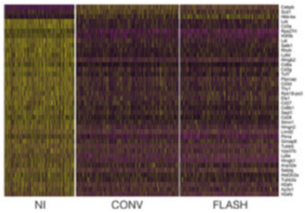


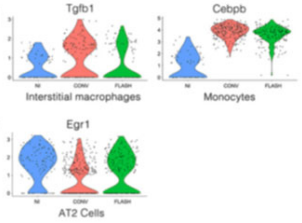


The James

Fouillade C et al. FLASH Irradiation Spares Lung Progenitor Cells and Limits the Incidence of Radio-induced Senescence. Clin Cancer Res. 2020; 26: 1497-1506
Kim YE et al. Effects of Ultra-high doserate FLASH Irradiation on the Tumor Microenvironment in Lewis Lung Carcinoma: Role of Myosin Light Chain. Int J Radiat Oncol Biol Phys. 2020; 109: 1440-1453

Differential Gene Expression: FLASH Versus CONV RT





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Fouillade C et al. FLASH Irradiation Spares Lung Progenitor Cells and Limits the Incidence of Radio-induced Senescence. Clin Cancer Res. 2020; 26: 1497-1506

Limitations With FLASH Radiotherapy

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FLASH Radiotherapy + IORT

OSU Received The Very First FLASH-IntraOp® Mobetron® In North America

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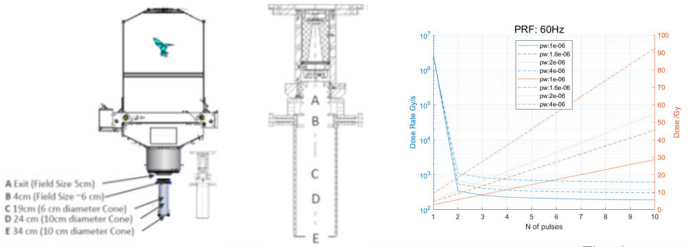
Speaker presentations

Radiobiological Aspects of IORT/FLASH

IntraOp® Mobetron® Is Capable Of Achieving Dose Rates >1000 Gy/sec



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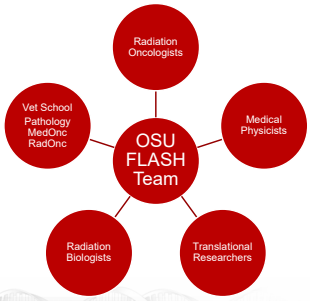
Multidisciplinary OSU FLASH Team



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OSU FLASH Team

Unique Resources At OSU

- Designated OSU FLASH Team
- FLASH Capable IntraOp Mobetron
- FLASH Capable Varian CLINAC
- FLASH Capable Proton Center
- OSU Veterinary School
- Human Clinical Trials Pipeline
- Molecular Biology Expertise And Shared Resources
- Drug Development Institute

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OSU FLASH Team Pre-Clinical Strategy

Disease sites:
- GI/GU
- CNS
- Skin
- Breast
- Lung
- H&N

Understand impact of:
- Dose rate
- Total dose
- Pulse structure
- Fractionation
- Treatment volume
- SSD/cone size
- Machine
- Radiation modality

Measurable outcomes:
- Tumor control
- Normal tissue toxicity
  - Acute
  - Late
- Secondary malignancies

Characterization:
- Histopathological
- Morphological
- Molecular
  - Genomic
  - Epigenomic
  - Transcriptomic
  - Proteomic
  - Metabolomic
  - mFISH

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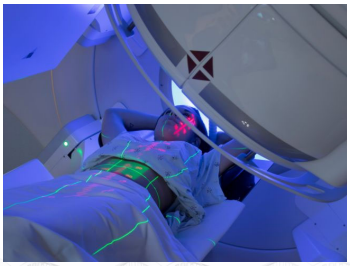
Future Perspectives

IORT and FLASH radiotherapy have the potential to revolutionize the way we treat cancer patients.



Work towards:

- Understanding the biological mechanisms underlying the FLASH effect and IORT.
- Head-to-head biological comparisons of IORT and EBRT.
- Additional FLASH studies necessary before moving into human clinical trials!
- Development of biomarker driven treatment plans.

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Speaker presentations

Radiobiological Aspects of IORT/FLASH

Speaker presentations

Physicist's Perspective on the Present State and New Developments in Electron-Based IORT

Markus Stana, PhD
Medical Physicist
Radiation Oncology
Paracelsus Medical University Clinics
Salzburg, Austria

UNIKLINIKUM SALZBURG

Physicist's perspective on the present state and new developments in electron-based IORT

Markus Stana, Christoph Gaisberger, Brane Grambozov, Falk Röder and Gerd Fastner

Universitätsklinik für Radiotherapie und Radio-Onkologie
Gemeinnützige Salzburger Landeskliniken Betriebsgesellschaft mbH
Müllner Hauptstr. 48
A-5020 Salzburg

October 20, 2022

Old vs. new vs. next?

Elekta® SL 18

IntraOp® Mobetron®

M. Stana IOeRT - what's new from a Φ's view? October 20th, 2022 2 / 12

Old vs. new vs. next?

Elekta® SL 18

IntraOp® Mobetron®

FLASH therapy

M. Stana IOeRT - what's new from a Φ's view? October 20th, 2022 2 / 12

New demands for components

Same quality, more versatility:

- new technical components
  - tubes must be transparent for diagnostic X-rays but not for electrons and bremsstrahlung
  - couch and other treatment aids must fit multi-purpose
- well chosen dosimetry equipment
  - new challenges with new machines (high pulse dose, less energy pre-filtering)
  - ALARA also in QA

M. Stana IOeRT - what's new from a Φ's view? October 20th, 2022 3 / 12

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M. Stana IOeRT - what's new from a Φ's view? October 20th, 2022 3 / 12

New demands for components

More work, same time:

- fast and flexible interchangeability of technical components like actual operation setup, linac, imaging system etc.
- fast imaging
- fast linac
  - more compact linac
  - faster docking procedures (autodocking)
  - high dose rate
- fast and precise planning
  - treatment planning systems
  - fast data transfer between components (imaging to TPS, TPS to linac)

M. Stana IOeRT - what's new from a Φ's view? October 20th, 2022 3 / 12

Physicist's Perspective on the Present State and New Developments in Electron-Based IORT

New demands for components

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New technical components - POM-C tubes

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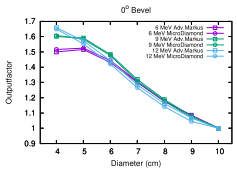
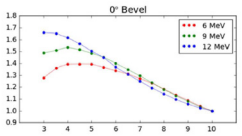
Comparison of POM-C and aluminum tubes - **output factors**





Aluminum tubes
measured by Landon et. al 2000

New technical components - POM-C tubes

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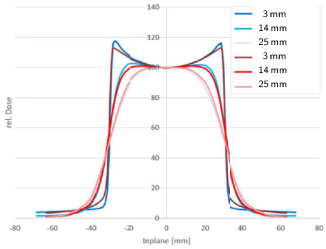
Comparison of POM-C and aluminum tubes - **flatness of profiles**



New technical components - POM-C tubes

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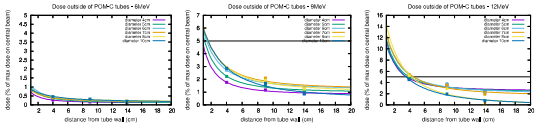
Dose outside POM-C tubes

6 MeV 9 MeV 12 MeV



Choice of dosimetry equipment

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	Roos Electron Chamber	Advanced Markus Electron Chamber
Type of Product	vented plane parallel ionization chamber	
Nominal Sensitive Volume	0.35 cm^3 radius 7.8 mm depth 2 mm	0.02 cm^3 radius 2.5 mm depth 1 mm
Reference Point	chamber center, 1.12 mm below surface	chamber center on entrance foil, or 1.3 mm below surface of protection cap
Nominal Response	12 nC/Gy	0.67 nC/Gy
Long-term Stability	$<$ 0.5% per year	$<$ 1% per year
Chamber Voltage	200 V nominal $\pm$400 V max.	300 V nominal $\pm$400 V max.
Polarity Effect	$<$0.5%	$<$ 1% for electrons $>$ 9 MeV
h **window (water-equiv.)**	1.3 mm	1.06 mm (protection cap included)
Guard ring width	4 mm	2 mm
Ion collection time	125 μs	22 μs
Max. dose rate for		
$>$ **99.5 % saturation**	5.2 Gy/s	187 Gy/s
$>$ **99.0 % saturation**	10.4 Gy/s	375 Gy/s
Max. dose per pulse for		
$>$ **99.5 % saturation**	0.46 mGy	2.78 mGy
$>$ **99.0 % saturation**	0.93 mGy	5.56 mGy
Useful ranges:		
Chamber voltage	$\pm$50 to 300 V	$\pm$50 to 300 V
Radiation quality	2 - 45 MeV electrons	2 - 45 MeV electrons
Field size	4$\times$4 cm^2 to 40$\times$40 cm^2	3$\times$3 cm^2 to 40$\times$40 cm^2
Temperature	10° - 40° C	
Humidity	10 - 80 % rel.	
Air pressure	700 - 1060 hPa	

Choice of dosimetry equipment

UNIKLINIKUM SALZBURG

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Temperature	10° - 40° C	
Humidity	10 - 80 % rel.	
Air pressure	700 - 1060 hPa	

Speaker presentations

Physicist's Perspective on the Present State and New Developments in Electron-Based IORT

Choice of dosimetry equipment

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Mobetron®:

- pulse repetition frequency (PRF) = 30 Hz
- 30 pulses per second
- recommended dose rate = 10 Gy/min = 166.7 mGy/s
- dose per pulse = 5.56 mGy

Choice of dosimetry equipment

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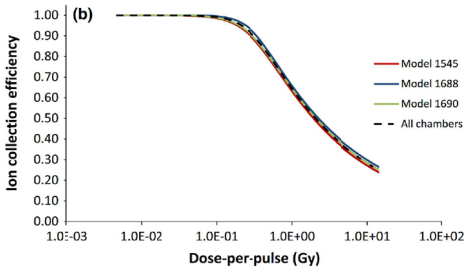

Petersson, et al. (2017). *Medical physics, 44(3),* 1157–1167.

Choice of dosimetry equipment

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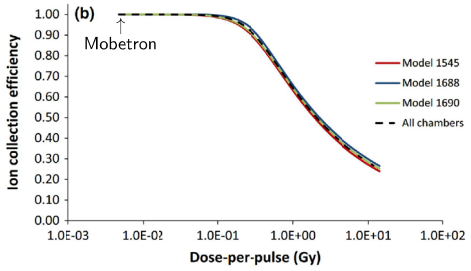

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Choice of dosimetry equipment

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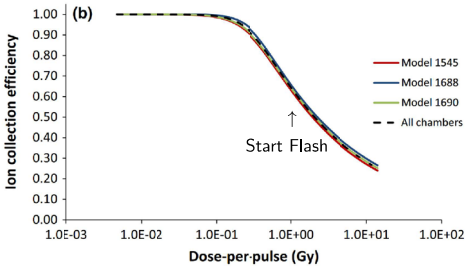

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Choice of dosimetry equipment

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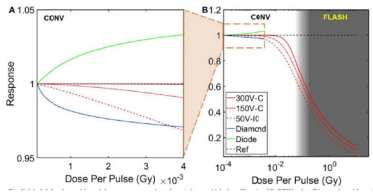

FIGURE 5 | Model for charged based detector response based on Advanced Markus Chamber IC, PTW microDiamond, and Isorad Gold (n-type) diode detectors. Dose per pulse dependency of detector response are shown for **(A)** conventional beams and **(B)** FLASH beams. Advanced Markus Chamber IC response (charge collection efficiency) was calculated for three different bias voltages and the only charge-based detector to be tested in FLASH dose rates [48]. Model for diamond detector response (charge collection efficiency) and diode detector response (sensitivity) were only tested at conventional dose rates [45, 50].

Ashraf, et al. (2020). *Frontiers in Physics, 8,* 328.

Choice of dosimetry equipment

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TABLE 1 | Dosimeters and their capabilities rated for potential FLASH dose measurement of key parameters.

Response	Detectors	Measurement type	FLASH study	Instantaneous dose-rate/dose per pulse (D_p) dependesce	Spatial resolution	Time-resolution	Energy dependence
Luminescence	TLD/OSLD	1D, 3D	e [15, 37, 71]	Independent (~10^6 Gy/s) [80, 137]	~ 1 mm	Passive	Tissue-equivalent
	Scintillators	1D, 2D, 3D	p [13, 18]	Independent (~10^6 Gy/s) [29]	~ 1 mm	~ns	Tissue-equivalent
	Cherenkov	1D, 2D, 3D	e [29]	Independent (~10^6 Gy/s) [29]	~ 1 mm	~ps	Energy dependent
	INTD	2D	NA	Independent (~10^6 Gy/s) [80]	~ 1 µm	Passive	Energy dependent
Charge	Ionization chambers	1D, 2D	p [13, 18, 19] e [15, 37, 71] ph [18, 17]	Dependent on D_p [48, 82] (>1 Gy/pulse),	~3–5 mm	~ms	Energy dependence shows up > 2 MeV
	Diamonds	1D	p [18]	Dependent on D_p (> 1mGy/pulse) [89]	~ 1 mm	~µs	Tissue-equivalent
	Si diode	1D, 2D	NA	Dependent on D_p [54] (independent ~0.2 Gy/s) [139]	~ 1 mm	~ms	Energy dependent
Chemical	Alanine pellets	1D	e [12, 15, 37, 139]	Independent (10^3 Gy/s) [69]	~ 5 mm	Passive	Tissue-equivalent
	Methyl viologen/fricke	1D	e [29, 48]	Depends on the decay rate and diffusion of radiation induced species	~ 2 mm	~ns	Tissue-equivalent
	Radiochromic film	2D	p [18, 19] e [10–12, 15, 33, 37, 71, 140] ph [18]	Independent (10^3 Gy/s) [70, 71]	~ 1 µm	Passive	Tissue-equivalent
	Gel dosimeters	3D	NA	Strong dependence below 0.001 Gy/s [141] and above 0.100Gy/s [142]	~1 mm	Passive	Tissue-equivalent

Ashraf, et al. (2020). *Frontiers in Physics, 8,* 328.

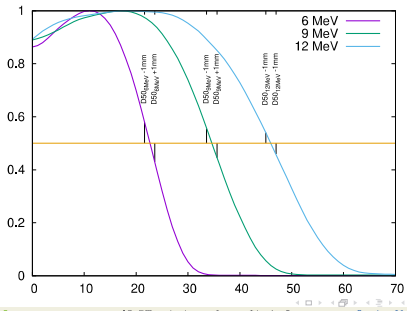
Speaker presentations

Physicist's Perspective on the Present State and New Developments in Electron-Based IORT

Choice of dosimetry equipment

UNIKLINIKUM SALZBURG

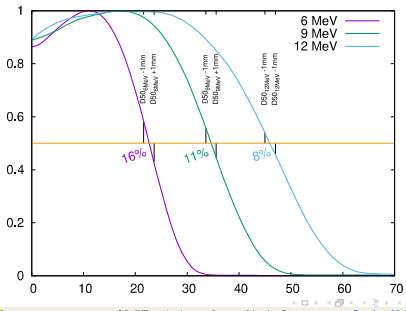
PDDs for 6 cm tube with 0°:



Choice of dosimetry equipment

UNIKLINIKUM SALZBURG

PDDs for 6 cm tube with 0°:



Choice of dosimetry equipment

UNIKLINIKUM SALZBURG

AAPM Report No. 092:

B. Quality assurance for mobile electron accelerators

When adapting these recommendations to mobile accelerators, the clinical physicist needs to deal with some conflicting considerations. These units are partially disassembled and transported each day of use. They forgo adjustable collimator jaws and eliminate bending magnets to reduce weight and radiation leakage. These design elements simplify the system, but they make the electron beam energy more dependent on variations in rf power generation and coupling to the accelerator. Therefore, on one hand, there are reasons to perform more frequent beam measurements than with conventional installations. On the other hand, the equipment is used in ORs with little or no added shielding, so radiation safety considerations argue for limiting the beam time for QA as much as possible. These competing concerns can be partially resolved by developing an efficient QA process, but they do present an ongoing challenge.

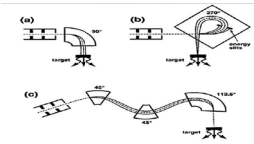
Output and energy can be checked efficiently with the use of a dedicated solid phantom in which a dosimeter can be

Choice of dosimetry equipment

UNIKLINIKUM SALZBURG

AAPM Report No. 092:

Bending magnets



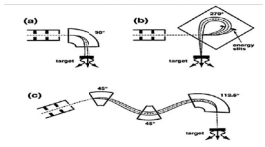
Van Dyk, J. (1999). *Madison, WI: Medical Physics Publishing*, 437-479.

Choice of dosimetry equipment

UNIKLINIKUM SALZBURG

AAPM Report No. 092:

Bending magnets



Van Dyk, J. (1999). *Madison, WI: Medical Physics Publishing*, 437-479.

Mobetron beam guide

source: IntraOp® Mobetron® demonstration video

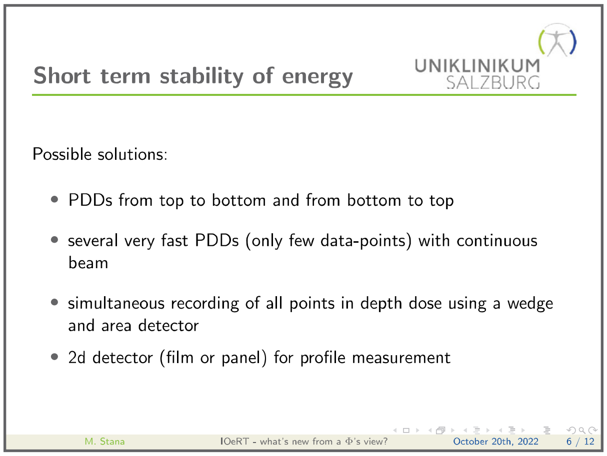
Short term stability of energy

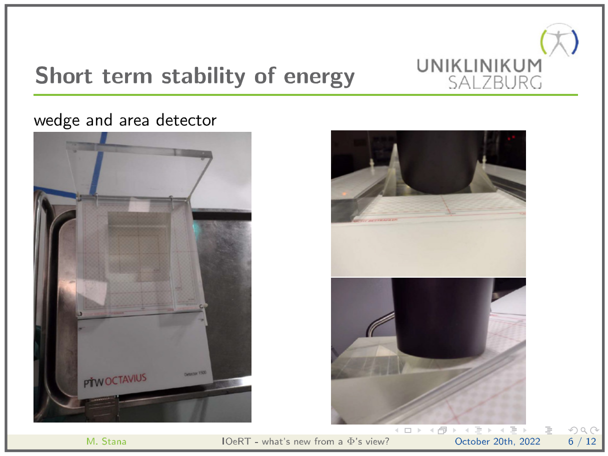
UNIKLINIKUM SALZBURG

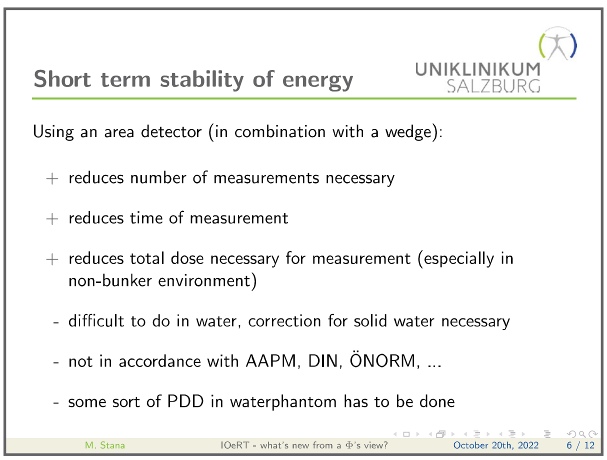
A swaying or drifting energy results in:

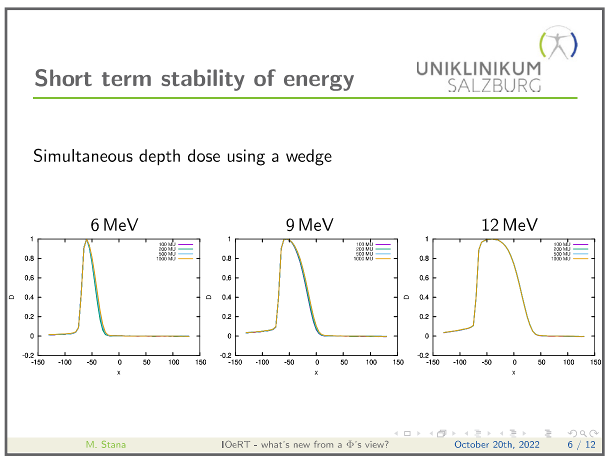
- scanned PDD is a set of points taken from slightly different PDDs
- scanned profile can show asymmetry due to increase or decrease in energy for a perfectly symmetric beam

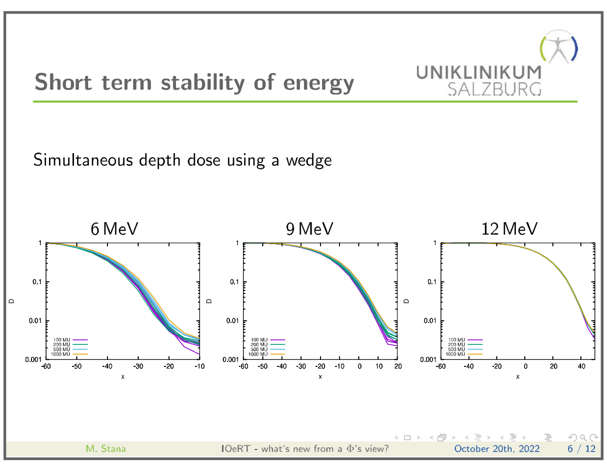
Physicist's Perspective on the Present State and New Developments in Electron-Based IORT

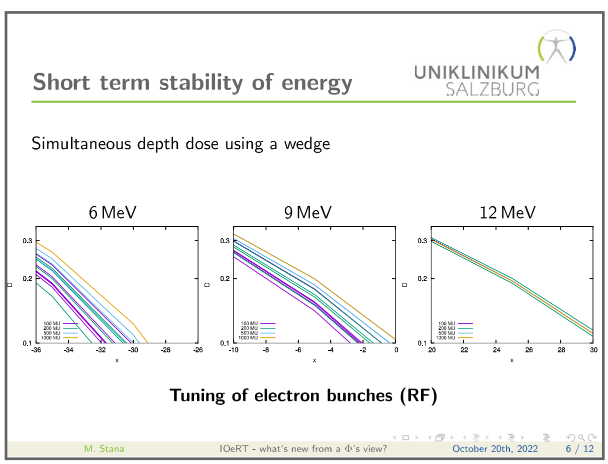












Speaker presentations

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Long term stability

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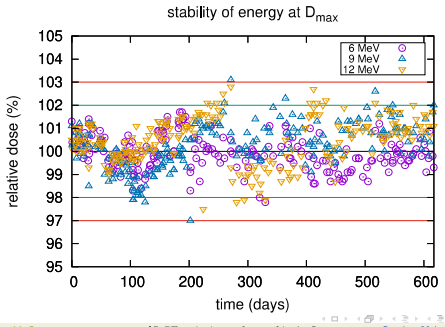

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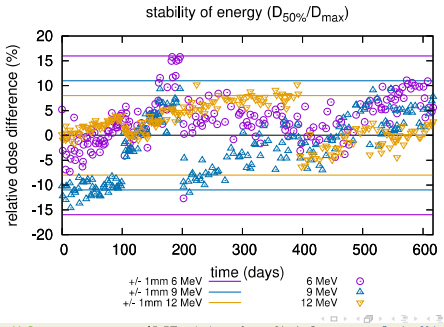
Long term stability

UNIKLINIKUM SALZBURG



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New advantages - dose profiles

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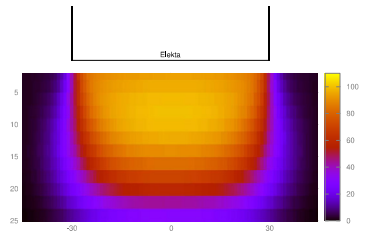
Tube diameter 6 cm, 0° bevel, 6 MeV, Elekta SL 18:



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New advantages - dose profiles

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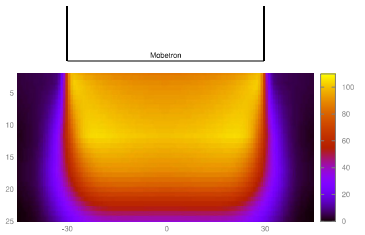
Tube diameter 6 cm, 0° bevel, 6 MeV, IntraOp Mobetron:



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New advantages - dose profiles

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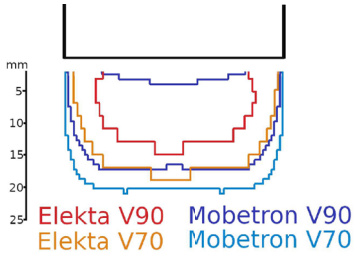
Tube diameter 6 cm, 0° bevel, 6 MeV:



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Automatic soft docking

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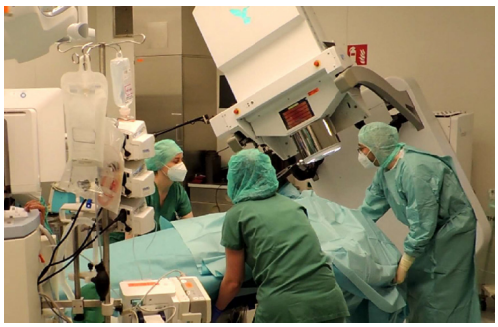

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Speaker presentations

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Automatic soft docking

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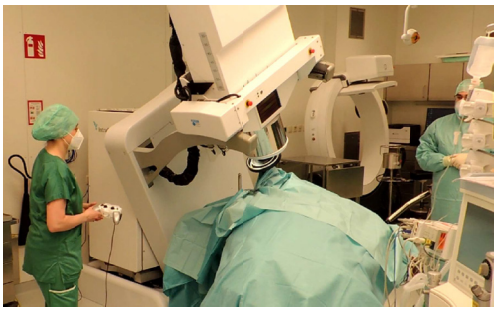

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Automatic soft docking

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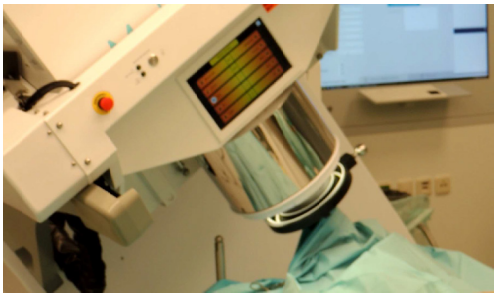

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Automatic soft docking

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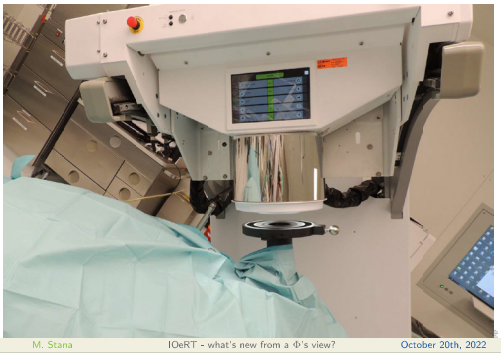

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Automatic soft docking

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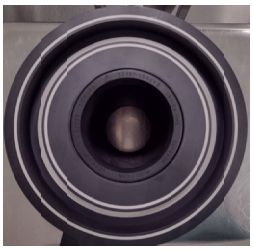

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Automatic soft docking

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Automatic soft docking

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- setup time: patient travel + pre-align + auto-align ≈ 5-10 min
- separation along beam axis: 40.0±0.5 mm
- accuracy in both axes normal to beam: ±0.5 mm
- accuracy in axis alignment: ±0.5°

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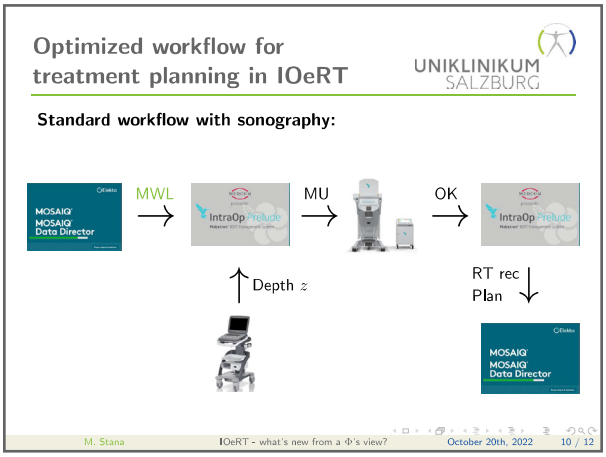
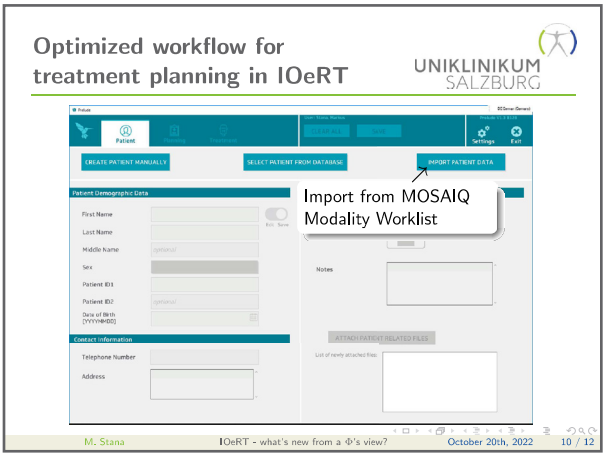
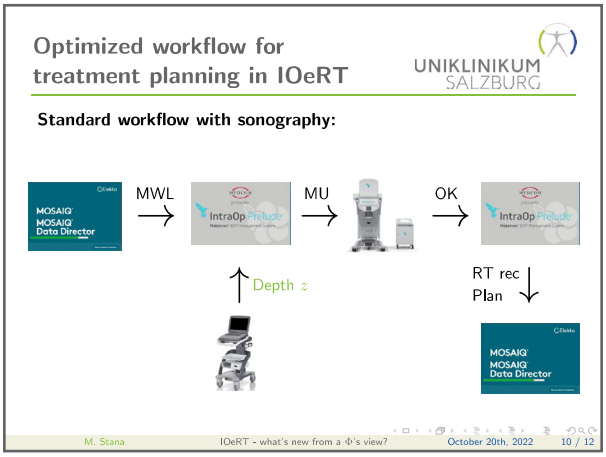
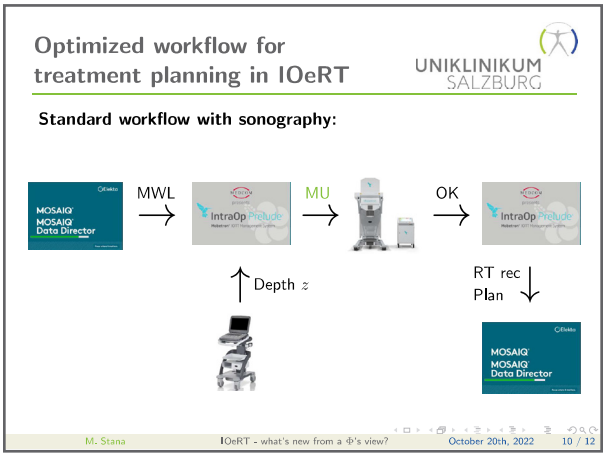
Speaker presentations

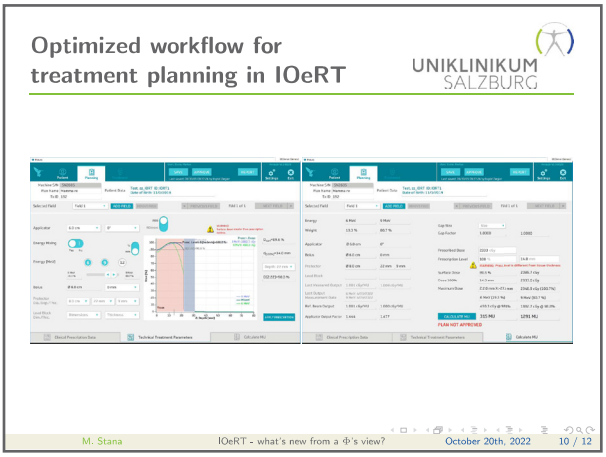
Physicist's Perspective on the Present State and New Developments in Electron-Based IORT



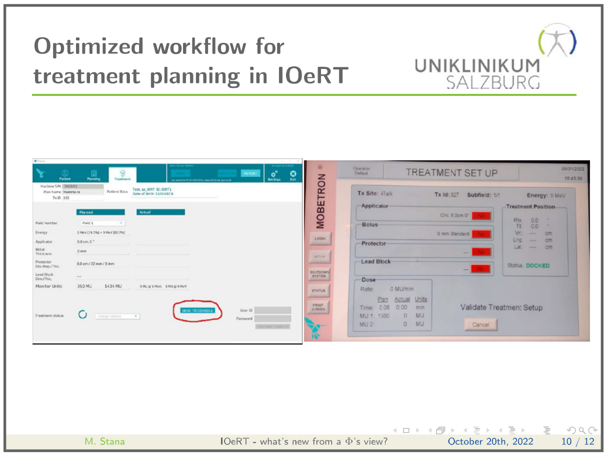


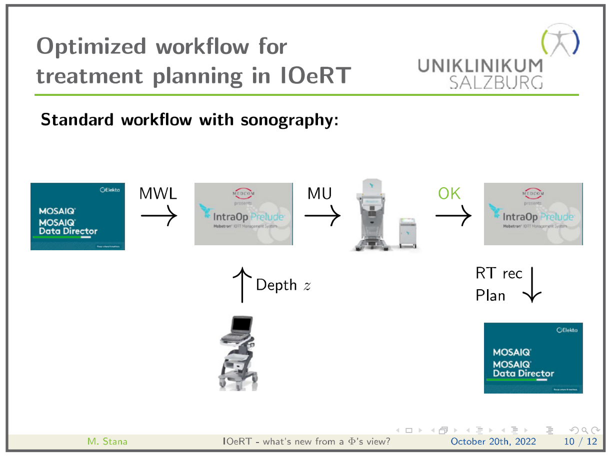


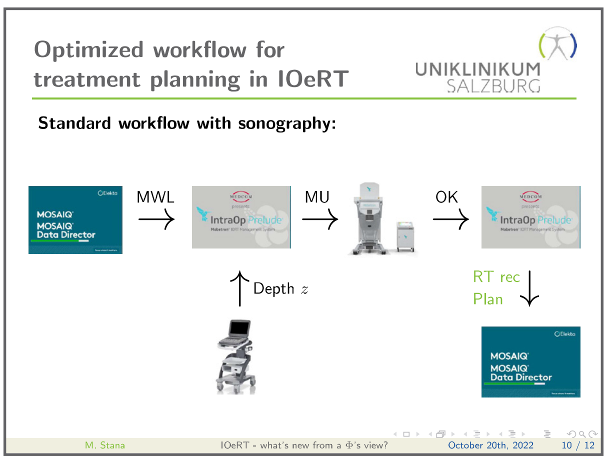


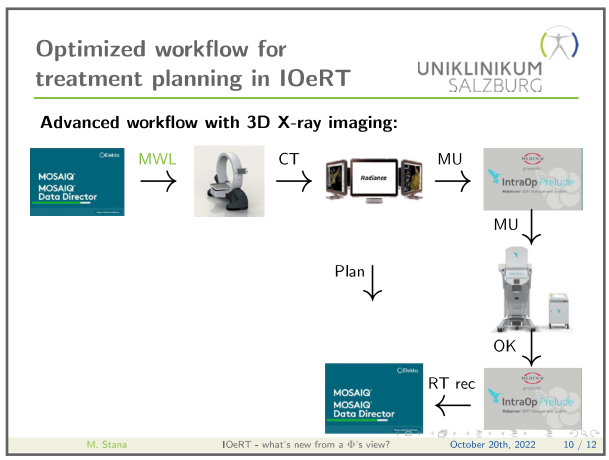


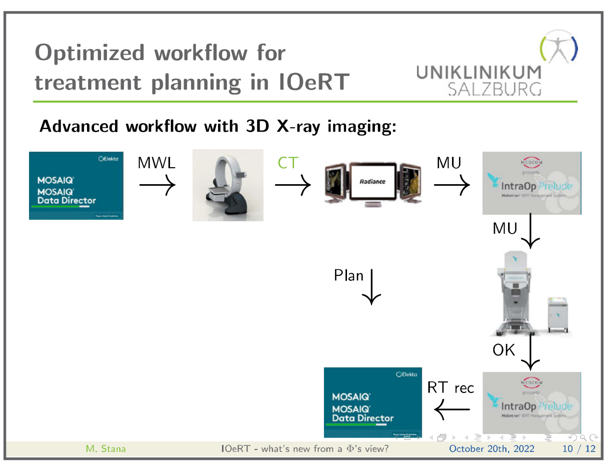
Physicist's Perspective on the Present State and New Developments in Electron-Based IORT

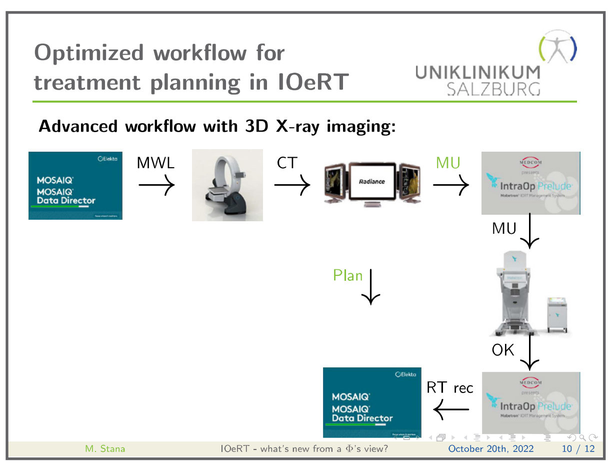




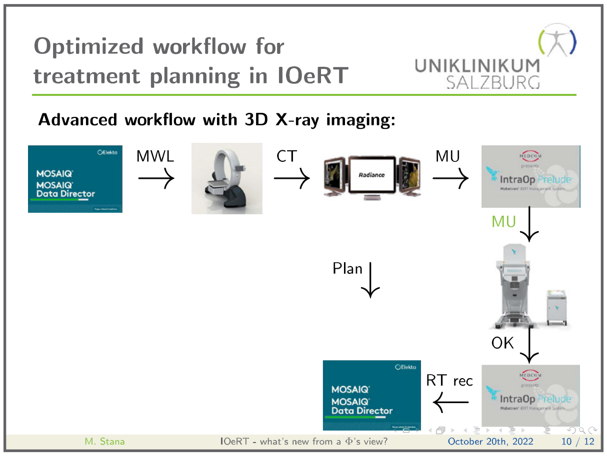


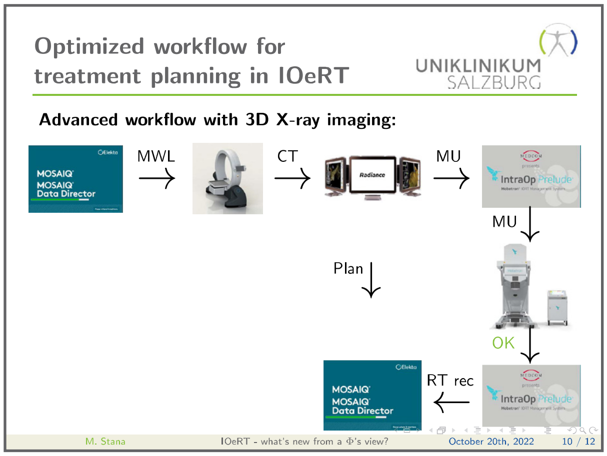


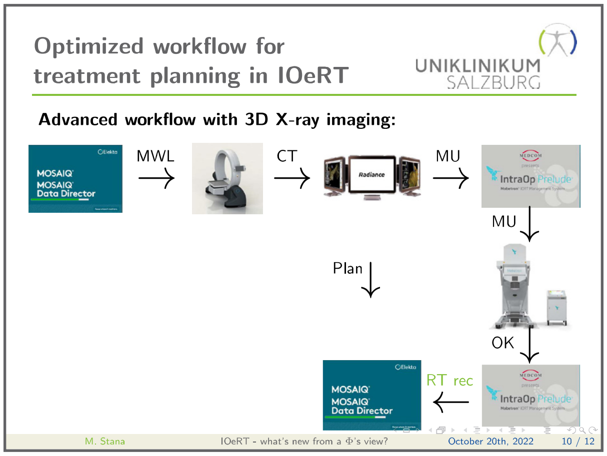


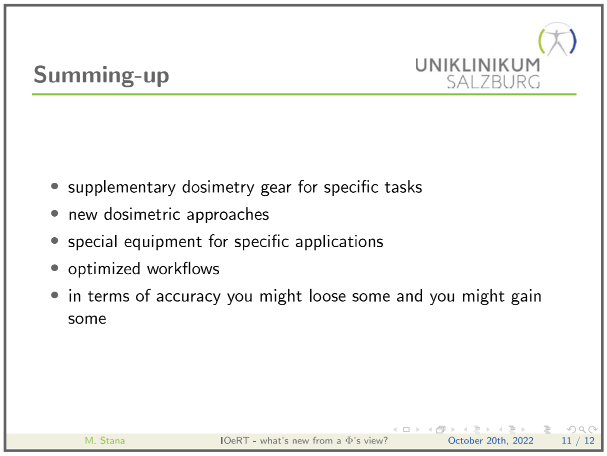


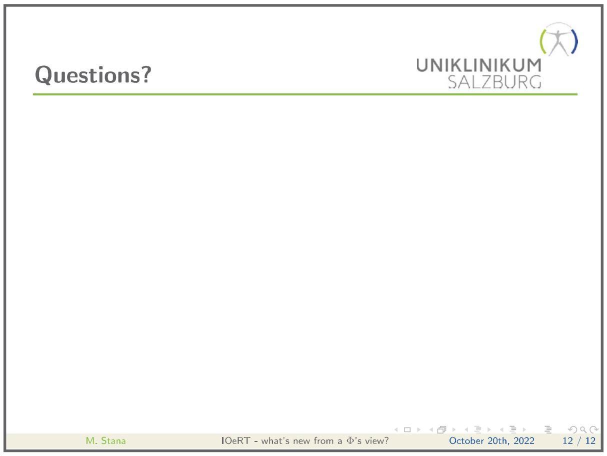
Physicist's Perspective on the Present State and New Developments in Electron-Based IORT











Speaker presentations

Physics in FLASH Radiotherapy

Ahmet Ayan, PhD
Medical Physicist
Department of Radiation Oncology
The Ohio State University
Columbus, Ohio, United States

(Challenges with) Physics in FLASH Radiotherapy

Ahmet S. Ayan, PhD
Radiation Oncology
The Ohio State University

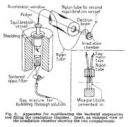
Outline

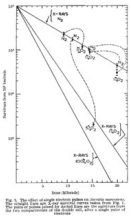
- A (historical) review of UHD beams used in radiotherapy and radiobiology
- (Challenges with) Characterization of Dose and Dose rate
- Shielding considerations with FLASH RT
- What does future look like?

A (*historical*) review of UHD beams used in radiotherapy and radiobiology

D. L. Dewey and J.W. Boag, "*Modification of the Oxygen Effect when Bacteria are given Large Pulses of Radiation*", Nature, Vol 83, p1450-1451, **1959**

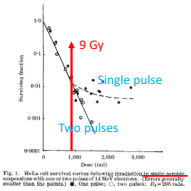
- Serratia marcescens bacteria cells show enhanced sensitivity to radiation & oxygen effect
- 1.5MV x-rays with conventional dose rates ~600 rads/min
- Same accelerator could deliver a pulsed **electron beam** of doses of 10-20 krad delivered in 2μs
  - ➔100-200 Gy/pulse
  - ➔0.5-1 x10^{10} rad/s = 0.5-1 x 10^{8} Gy/s
- "… when large single pulse is used, the same bacteria saturated with the same oxygen-nitrogen mixture show the lower sensitivity corresponding to anaerobic irradiation".

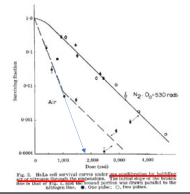




C.D. Town," *Effect of High Dose Rates on Survival of Mammalian Cells*" Nature, Vol 125, p847-848, **1967**

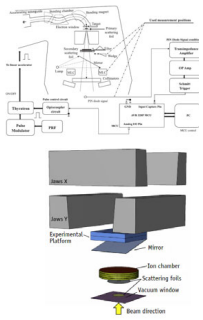
- 14 MeV **electron beam** of 1.3 μs pulses of 4500 rad/pulse
  - 45 Gy/pulse, 3.5x10^{7} Gy/s in pulse dose rate
  - Two pulses delivered with 400Hz
- Dosimetry was performed with TLDs
- Output of the accelerator was kept constant, different doses obtained by placing samples at different distances, hence the irradiation time was constant
- "… biphasic nature of the single pulse survival curve is thought to be caused by the removal of oxygen from the relevant site within the cell by its reaction with the radical intermediates formed during the irradiation"
- "…for irradiation in hypoxic conditions the single and double pulse data both follow the same line which has a slope approximately 2·5 times smaller than that of the line for air. In this case too, the single pulse curve for air changes in slope after a dose of about 1,000 rads."





Modified medical linacs for Ultra-High-Dose-Rates

- Lempart et al. [Radiotherapy and Oncology 139 (2019) 40–45] modified an ELEKTA Precise linac
  - 10 MeV electron beam
  - Pulse-to-pulse control of the linac was achieved with an external trigger circuit
  - Dose rates of greater than 30, 80, and 300 Gy/s were achieved at different locations in the linac head
- Schuler et al [Int J Radiation Oncol Biol Phys, Vol. 97, No. 1, pp. 195e203, 2017], modified a Varian Clinac 21EX
  - Achieved a dose rate of ~900 (70) Gy/s within the linac head (at the level of inner jaws) with 20MeV electron beam



Speaker presentations

Physics in FLASH Radiotherapy

Custom built linear accelerators

- Oriatron eRT6 was custom built for the Lausanne University Hospital (Switzerland) by a commercial company of the ALCEN Group
- Jaccard et al [Med. Phys. 45 (2), February 2018] published the machine characterization
- Nominal electron beam energies of 5 and 6 MeV with dose rates up to 200 Gy/s

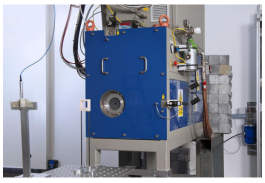
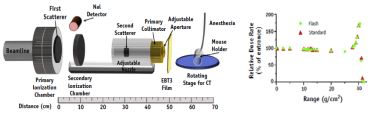


TABLE I. Parameter definitions and corresponding dose-rates (at a SSD of 1 m and at the depth of dose maximum in water) of the Flash and Conv functioning modes of the eRT6.

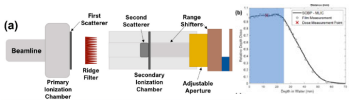
	Flash	Conv
GT (V)	300	100
w (μs)	2.2	1.0
f (Hz)	200	10
$\dot{D}_{av}$ (Gy/s)	200	0.05
$\dot{D}_p$ (Gy/s)	4.5×10^3	4.9×10^3

UHDR with Proton beams

- UPenn IBA Proteus Plus with 230 MeV fixed proton beam line [Diffenderfer et al., Int J Radiation Oncol Biol Phys, Vol. 106, No. 2, pp. 440e448, 2020]
- *Double scattered* beam with achieved dose rate of 94 Gy/s

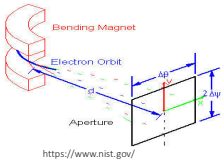


- UPenn also created a *SOBP* beam [Kim et al., Cancers 2021, 13, 4244] with a ridge filter
- Achieved dose rate of 108 Gy/s in the SOBP



UHDR with Photon beams

- **European Synchrotron Research Facility (ESRF)** is based on the spatial fractionation of the incident X-ray beam into wafers of parallel microbeams which are a few tens of μm wide and separated by a few hundred μm
  - Photons of median energy of 100 keV
  - As high as 16000 Gy/s in slice (Mean dose rate of 37Gy/s reported in experiments by Montay-Gruel et al [Radiotherapy and Oncology 129 (2018) 582–588])
- **Imaging and Medical Beamline (IMBL) of the Australian Synchrotron** 3 GeV e⁻ storage ring with 200mA beam current [J. Synchrotron Rad. (2017). 24, 110–141]
  - Up to 700 Gy/s dose rates (@ 2cm depth)
  - Photon energies of 60-500 keV are possible with a field size of 30 x 2 mm²

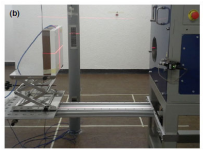


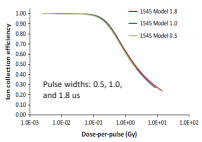
https://www.nist.gov/

(Challenges with) Characterization of Dose and Dose rate

Challenges with UHDR beam measurements with IC

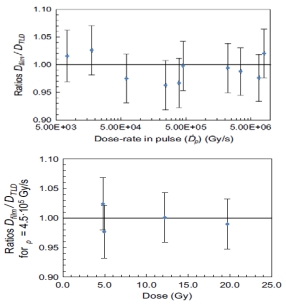
- Beam characterization is essential for an accurate dosimetry in pre-clinical and clinical UHDR irradiations
  - Absolute dose and dose rate
  - Beam depth-dose curves
  - Beam profiles
- *Ion chambers for absolute and relative dose measurements are rendered useless due to high ion recombination effects*
- Petersson et al [Medical Physics, 44 (3), March 2017] studied the ion recombination characteristics of the Advanced Markus Chambers (PTW) with UHDR electron beam
- Ion collection efficiency of the Advanced Markus chamber decreases for measurements in electron beams with increasing dose-per-pulse





UHDR beam measurement with GafChromic film

- Jaccard et al. [Med. Phys. 2017 Feb;44(2):725-735] studied energy and $\dot{D}$ dependency of GafChromic (EBT3) with e⁻ beams of (4, 8, 12 MeV)
- Benchmarked against TLD (known to be independent of dose rate)
- Demonstrated to be dose-rate independent up to the 8x10⁶ Gy/s
- Demonstrated to be energy independent for 4, 8, and 12 MeV e⁻ beams

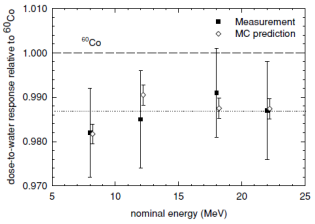


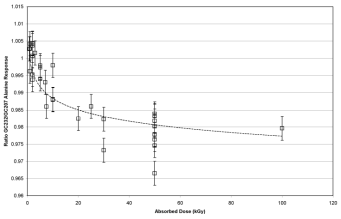
Speaker presentations

Physics in FLASH Radiotherapy

UHDR beam measurement with Alenine

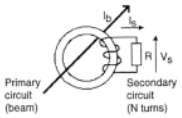
- A study by Zeng et al., [Phys. Med. Biol. 50 (2005) 1119–1129]
  - found no significant change (< 0.6%) in alanine/EPR response to absorbed dose-to-water over the e- beam of range 8–22 MeV
  - 1.3% (±0.2) reduction in the Alenine response compared to 60Co gamma rays
- A study by Desrosiers et al., [Journal of Research of the National Institute of Standards and Technology, 113, 2, 2008.] showed no $\dot{D}$ dependence for doses up to 5 kGy.





Beam time signatures monitoring with Current Transformer

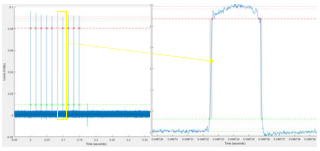
- An independent (other than machine reported) measurement & verification is an essential part of QA program
- Time signature of the pulsed beam is of utmost critical importance (others are: N and Dpp)
- Operating Principle:
  - Pulsed charged beam primary beam current induces a signal at the secondary proportional to the beam current
- Several institutions and linac manufacturer employed a non-destructive monitoring technology, current transformer,
- Has been in use in particle beam accelerator diagnostics for many years

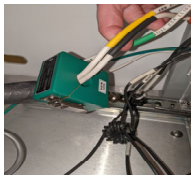


1994, Beam instrumentation CERN lectured Notes

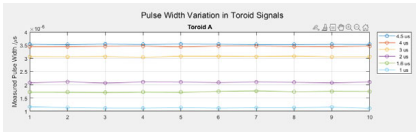
Beam time signatures monitoring with Current Transformer

- We monitor
  - electron gun pulses (below) and
  - electron pulses after they exit the accelerating waveguide read out by a digital oscilloscope (4ns sampling)



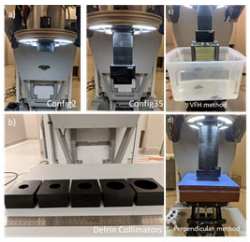


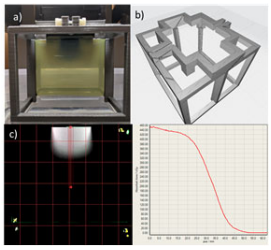
Monitoring e-gun pulses



(For detailed pulse-to-pulse analysis, see our paper @ FRPT 2022)

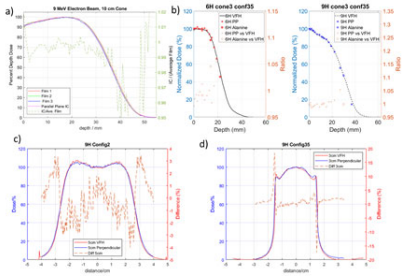
Using Gafchromic film dosimetry for UHDR linac commissioning





Jain et al., "Commissioning Measurements for Ultra High Dose Rate Electron Beams using a Novel Device", Submitted to JCAMP.

Using Gafchromic film dosimetry for UHDR linac commissioning



Jain et al., "Commissioning Measurements for Ultra High Dose Rate Electron Beams using a Novel Device", Submitted to JCAMP.

Time signature of UHDR beams and impact on Dose Rate

- With electrons, to calculate $Dose\ rate = \frac{Dose}{time}$, one needs to know the time signature of the delivered beam:

$$Dose\ rate = \frac{N \times D_{pp}}{[(N-1)\times PRF + pw]}$$

- With protons, may not be so trivial:
  - Depends on the accelerator type (cyclotron, synchrotron) delivery technique: i.e., whether as Passively Scattered, PBS (hence scan speed), single energy, multi-energy (hence time required energy change) using Bragg peak, beam current at nozzle
  - If PBS, it depend on how one accounts for time dose is deposited to a given voxel (scan pattern, speed)
  - ➔ A lot of activity is ongoing in this domain with vendors and various institutions

Electron linear accelerator	
Pulse length	a few µs
Pulse Repetition Frequency	10 - 200 Hz
Pulses arrive at every 100 - 5 ms	

Proton (ex: Isochronous cyclotron)	
Pulse width [pw]	~1-2 ns
RF Freq	~70 MHz
Pulses arrive at every ~14 ns, so, practically a continuous beam	

Speaker presentations

Physics in FLASH Radiotherapy

IntraOp Mobetron Electron Beam Linear Accelerator

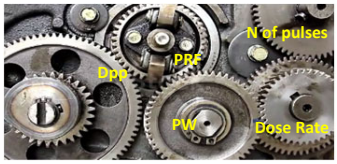
- For the high-dose-rates beam, we can program/select
  - Nominal Pulse Widths / µs ∈{ 1, 1.6, 2, 3, 4 }
  - PRF ∈ {10, 20, 30, 45, 60} Hz
  - # of pulses ∈ {1, 2, .. 200}
- Of course, one can introduce SSD into the free parameters to choose from

Our radiobiologists & physicians would like to prescribe

RX DOSE

RX DOSE RATE

This is what we have



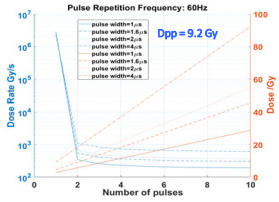
Pulsed electron beam: D vs $\dot{D}$ vs N

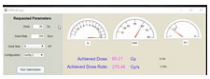
- If N=1, the dose rate is dominated by the pulse width
- If N>1, the dose rate is dominated by the PRF
- Different collimation and irradiation setup & geometries will most likely require different D_{pp}

$$min\left\{\left(\frac{D_{achieved}}{D_{Rx}}-1\right)^2+\left(\frac{\dot{D}_{achieved}}{\dot{D}_{Rx}}-1\right)^2\right\}$$

$$\text{s.t.}\begin{cases} PRF \in [10,20,30,45,60]\ Hz \\ pw \in [1,1.6,2,3,4]\ \mu s \quad \text{where} \\ N \in \mathbb{Z} \end{cases}$$

$$D = D_{pp} \times N, \dot{D} = \frac{D}{\left(\frac{(N-1)}{PRF}+pw\right)}$$





Shielding considerations with FLASH RT

Implications of UHDR on shielding

- USNRC Federal limit for instantaneous dose rate in uncontrolled areas: < 0.02 mSv (20 µSv) in any hour
  - This is NOT equivalent to measured dose rate, i.e., not 20 µSv/hr
- Standard linac vaults (designed for 18X) may not be enough
- Potential concerns are
  - Bremsstrahlung photons
  - Neutron activation

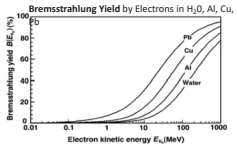


Fig 5.7 in Podgorsak, Radiation Physics for Medical Physicists

- **Bremsstrahlung yield** of a charged particle with KE (EK_0) striking an absorber is defined as that fraction of the initial kinetic energy that is emitted as Bremsstrahlung radiation in the absorber

Implications on shielding by 16 MeV UHDR electron beam in a vault designed for 18MV photon beam

- At UHDRs, dose rate from bremsstrahlung photons is an order of magnitude higher than that from an 18 MV beam
- Poirier et al [Medical Physics. 2021;48:5396–5405] investigated the shielding by radiation survey results from 16 MeV UHDR electron beam in a vault designed for 18MV photon beam
- Radiation surveys were performed using a survey meter (Fluke 451P) and Wendi-2 neutron detectors
- To exceed USNRC limit (20 µSv in any 1h) in uncontrolled areas, 92 sec. continuous run needed w/ G180
- neutron activation of linac components can reach 25 µSv/h near the isocenter following FLASH-RT delivery, but dissipates within minutes, and total doses within an hour are below 20 µSv.

TABLE 2 Radiation survey results

	Instantaneous ambient dose equivalent rate (µSv/h)					
	Door		Console		Uncontrolled area	
Energy	Photons	Neutrons	Photons	Neutrons	Photons	Neutrons
18 MV photons	28	36	1.6	2	6.0	83
16 MeV e⁻–clinical	0.4	*Not detectable*	0.2	*Not detectable*	0.2	*Not detectable*
16 MeV e⁻–FLASH (G180°"biology mode")	65	45	3.0	4.0	430	350
16 MeV e⁻–FLASH (G0°"physics mode")	31	38	2.0	8.0	1.0	0.3

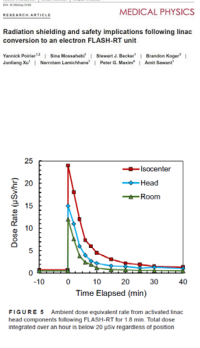
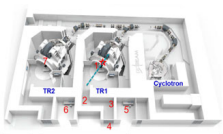


FIGURE 5 Ambient dose equivalent rate from activated linac head components following FLASH-RT for 1.8 min. Total dose integrated over an hour is below 20 µSv regardless of position

Shielding considerations for proton UHDR beams

- Xiao et al [Med Phys. Sept 2022, https://doi.org/10.1002/mp.15964] investigated the validity of their proton vault shielding in UHDR irradiation conditions
- They measured using Wendi-II neutron detector with 244 MeV p beam, 7x20 cm² delivering 8Gy @ isocenter with a beam current of ~10 nA
- They scaled the measured values to nominal UHDR proton irradiation beam currents of ~170 nA
- Assuming a workload of 200Gy/hr, they measured ≤ 0.4 mSv/yr at the treatment room door
- They concluded that *"conventionally shielded proton rotating gantry rooms result in acceptable occupational and public doses when the transmission FLASH beams delivered at four cardinal gantry angles based on 200 Gy/hr workload assumption"*



Locations	No.	Description	Distance from TR1 Isocenter
Inside TR1	1	On the floor of TR1, 1 m off the beam axis	~ 2 m straight length through air
	2	The end of maze from the TR1 entrance	~ 12 m diffusion length through air
	3	The first turn of maze from the TR1 entrance	~ 17 m diffusion length through air
	4	The entrance door of TR1	~ 22 m diffusion length through air
Control Areas	5	The control room of TR1	~11 m straight line through air and concrete
	6	The control room of TR2	~13 m straight line through air and concrete
	7	Isocenter of TR2	~15 m straight line through air and concrete

Speaker presentations

Physics in FLASH Radiotherapy

Future outlook

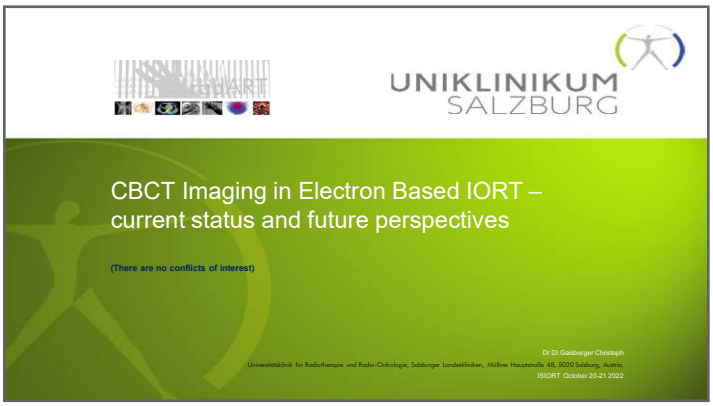
- Currently FLASH dose rates are limited to small treatment volumes
  - Small field sizes with FLASH dose rates: Current pre-clinical practice is limited to small animals and cell cultures
  - Beam energies are suitable for mostly superficial depths in larger animals. Deep seated tumors may not be feasible yet
  - Large fields have implications on $\dot{D}$
- Under development
  - Detectors working at FLASH dose rates for *real-time absolute dose* measurements
  - FLASH with photon linacs (ex: PHASER)
  - FLASH with very-high-energy-electron (VHEE) beams (> 100 MeV)

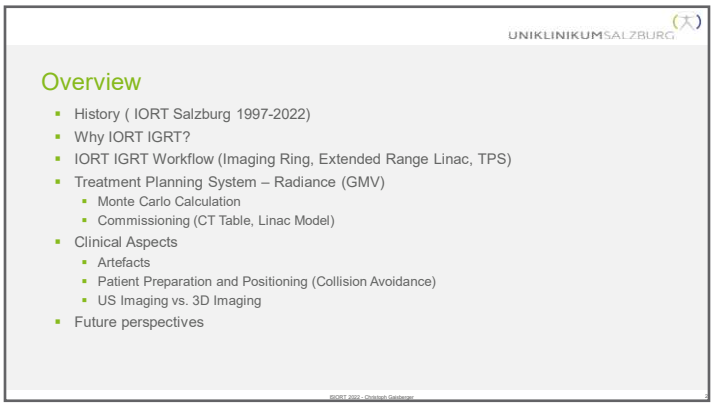
Thank you for your attention

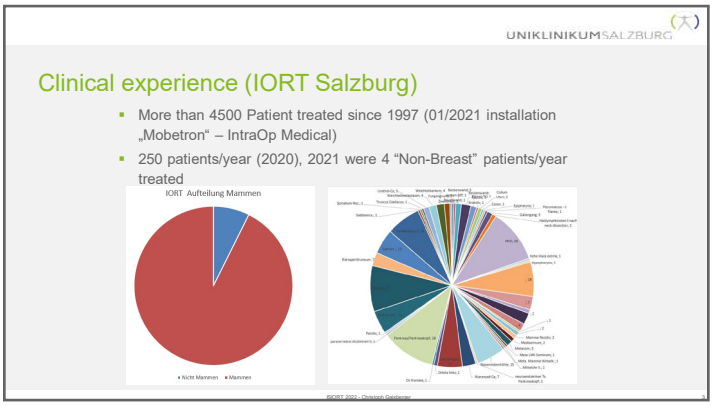
Speaker presentations

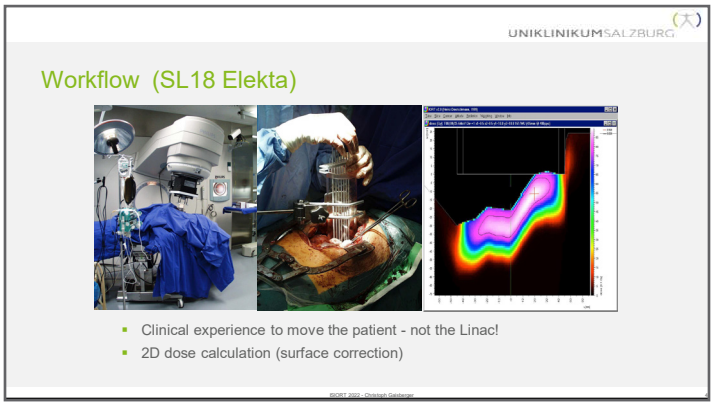
CT Imaging in Electron Based IORT – Current Status and Future Perspectives

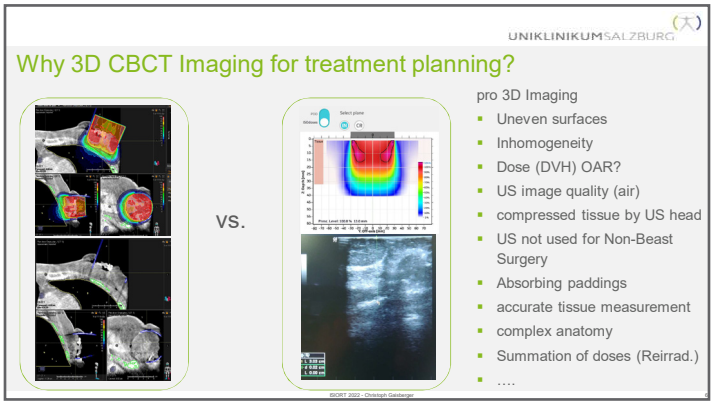
Christoph Gaisberger, PhD
Medical Physicist
Radiation Oncology
Paracelsus Medical University Clinics
Salzburg, Austria











Speaker presentations

CT Imaging in Electron Based IORT – Current Status and Future Perspectives

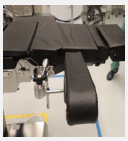
UNIKLINIKUMSALZBURG

Elements for new 3D Imaging Workflow

Clinical operational:

- Mobetron – Extended Range Addendum (extended DOF, no beamstoper)
- Radiolucent IORT tubes (Ø 4-10, 0°, 30°)
- Radiolucent tube holder
- Radiolucent treatment couch
- mobile CBCT imaging System
- IORT 3D Tretment planning system (radiance, GMV)
- virtualized software modules

Mobetron (IntraOp Medical) - Extended Range Addendum



IRm (MedPhoton)

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Imaging Ring mobile (Irm) - MedPhoton

- 120cm clearance
- HU values for treatment planning (patient specific, histogram opimized)
- mobile (x/y/z7Rot)
- metal artefact correction
- **TOF – Laser bases collision avoidance**
- independent moveable tube and detector
- Energie 40kV-120kV (150kV)
- Detector 25cmx25cm (Large FOV mode)
- high resolution panel
- integrated optical cameras
- automated filterweel
- weight 517kg
- variable non-isocentric Field of View
- wearable remote control panel
- ....

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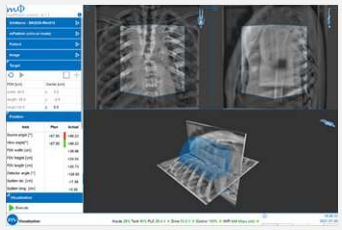
Imaging Procedure



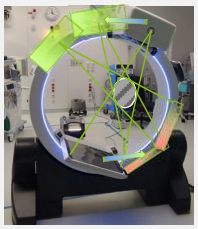


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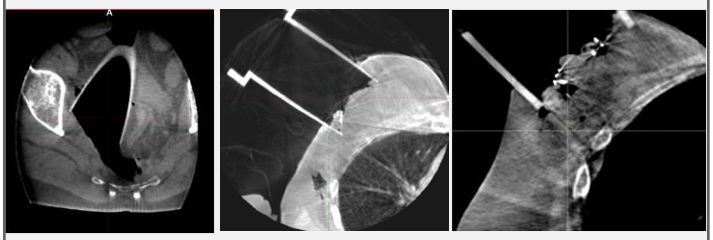
Image Quality – CBCT Imaging



UNIKLINIKUMSALZBURG

Current status - Operating Theater (2022)

1. mobile anesthesia system
2. Linac – Mobetron
3. mobile treatment couch
4. mobile CBCT
5. virtualized Software (Prelude, Radiance)
6. mobile US

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OP Logistic

- mobile couch
- automated IRm parking/treatment position
- mobile anesthesia equipment
- virtual available software (TPS, Irm, Radiance)

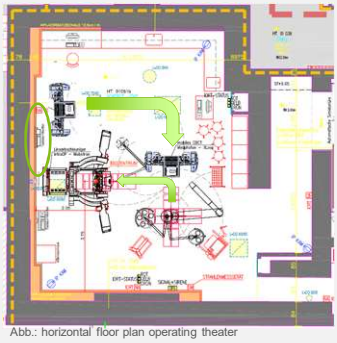
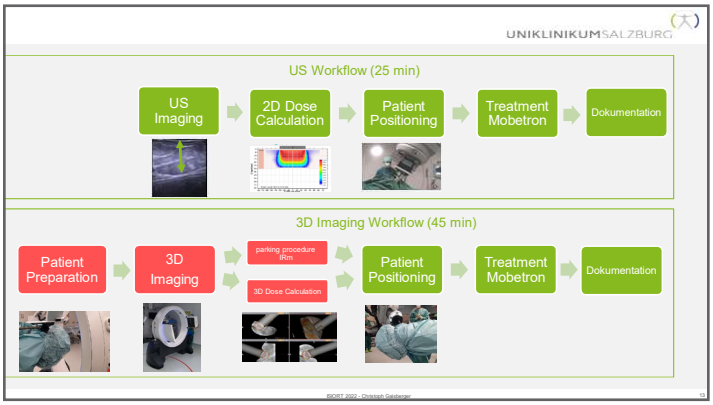
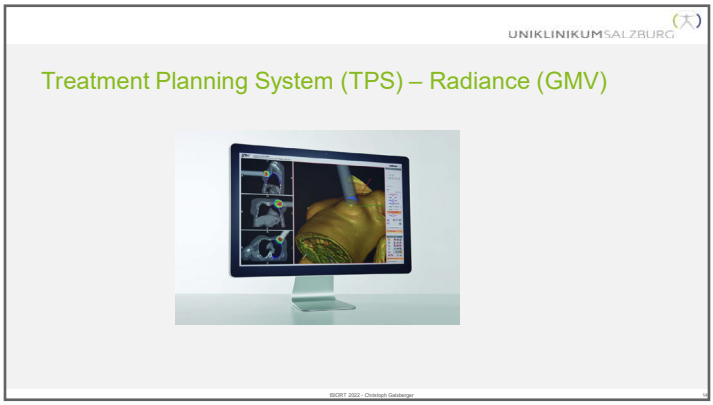


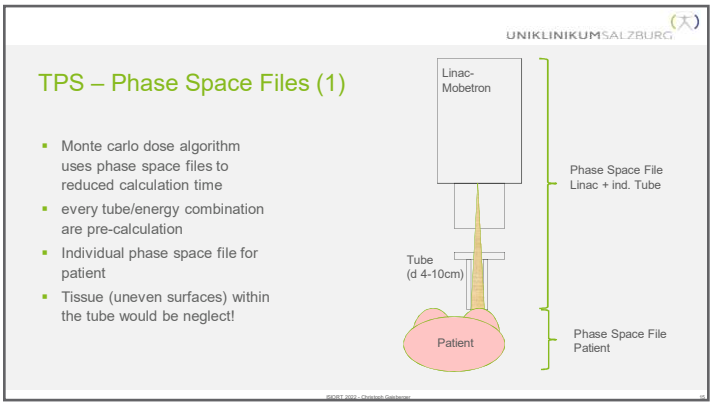
Abb.: horizontal floor plan operating theater

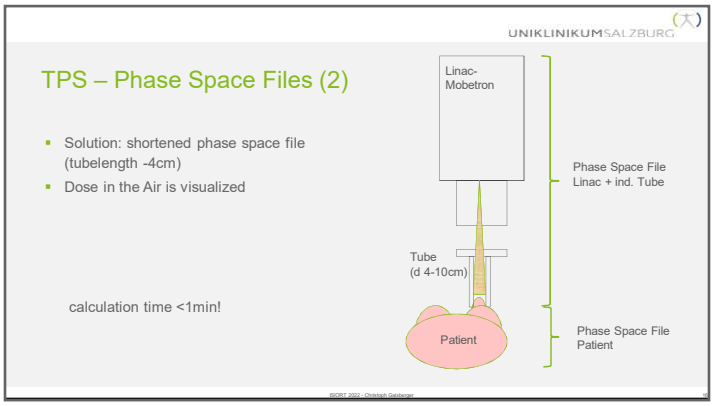
Speaker presentations

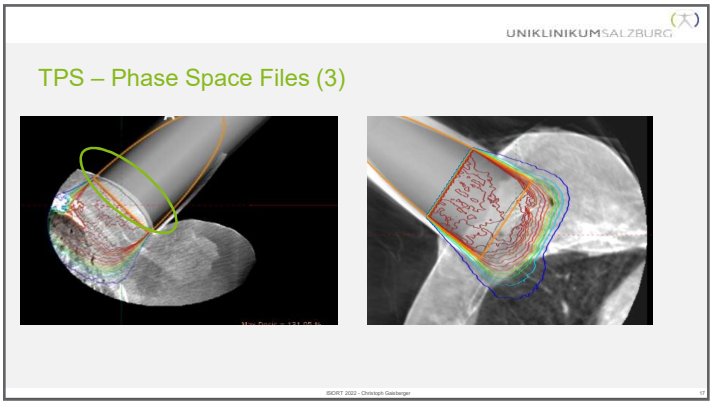
CT Imaging in Electron Based IORT – Current Status and Future Perspectives











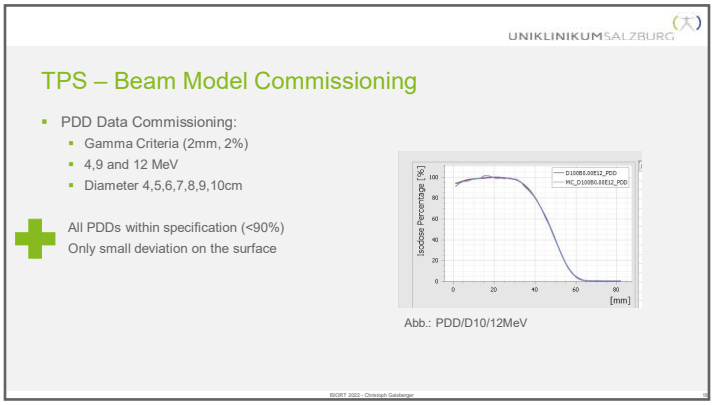


Abb.: PDD/D10/12MeV

Speaker presentations

CT Imaging in Electron Based IORT – Current Status and Future Perspectives

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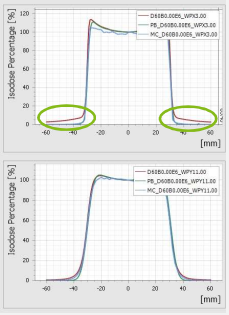
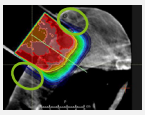
TPS – Beam Model Commissioning

- Profiles (CP/IP) Data Commissioning:
  - Gamma Criteria (2mm, 2%)
  - 4,9 and 12 MeV
  - Diameter 4,5,6,7,8,9,10cm



The verification shows deviations outside the beam.

Small deviation at the surface profiles, deeper profiles are within specifications



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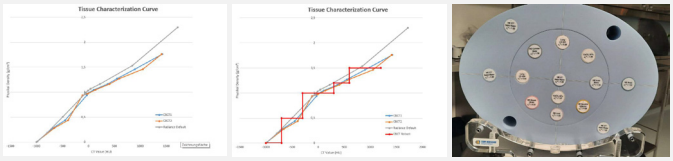
TPS – CT

- CT Conversation Table (CBCT)
  - HU Density Correction (Based on histograms, depends on imaging volume, FOV and energy)
  - Electron Density Correction - clinical used presets measured
  - Discrete CT Table (example) for tissue characterization



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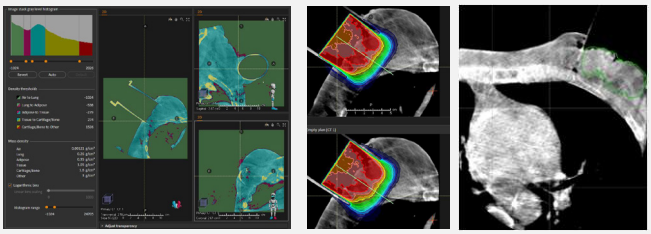
TPS – CBCT discrete HU Table



- Clinically measured HU values (breast tissue, 90% Dose Volume)
- Patient A (HUAvg = -38HU) Patient B (HUAvg = -80HU)

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Clinical Aspekts

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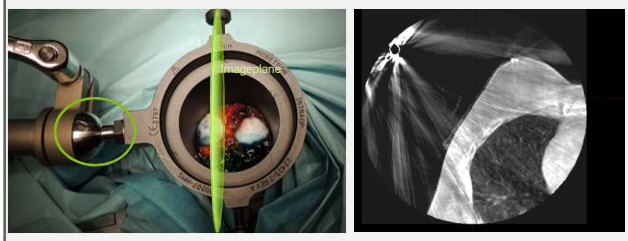
Clinical Aspekts: Metal Artefacts



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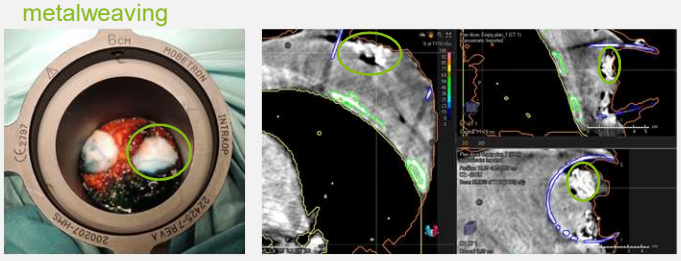
Clinical Aspekts: Metal Artefacts – paddings with metalweaving



Speaker presentations

CT Imaging in Electron Based IORT – Current Status and Future Perspectives

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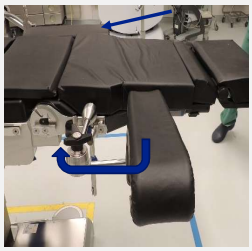
Clinical Aspekts: Patient Positioning - Armholder

- flexible arm holder (metal components)
- Radiolucent table components



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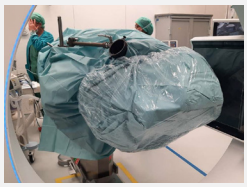
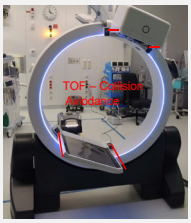
Clinical Aspekts: Collision Avoidance – sterile drapes





TOF Laser detect every obstacle (soft drapes)

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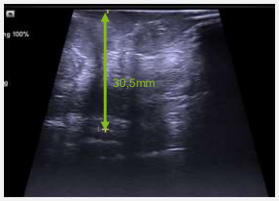
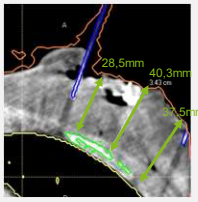
Clinical Aspekts: Comparison US vs. 3D Measurement





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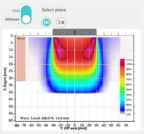
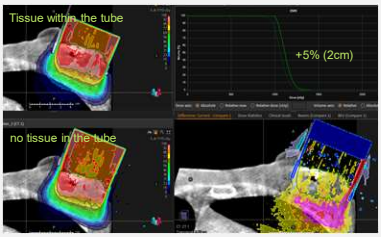
Clinical Aspekts: Tissue within the tube





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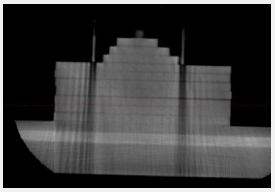
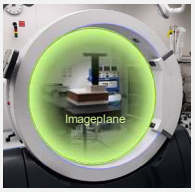
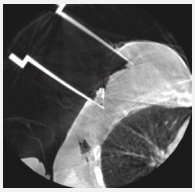
Clinical Aspekts: Artefacs - Tubes







- Short Tubes – reduced absorbing material results in reduced artefacts
- FOV located near the isocenter
- tube axis not parallel to the image plane

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Future Perspectives

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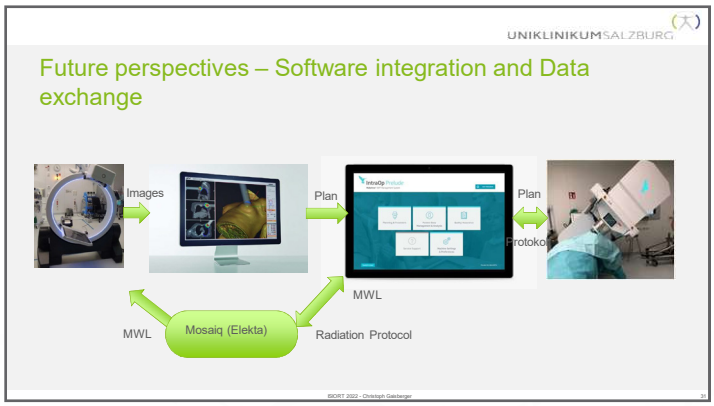
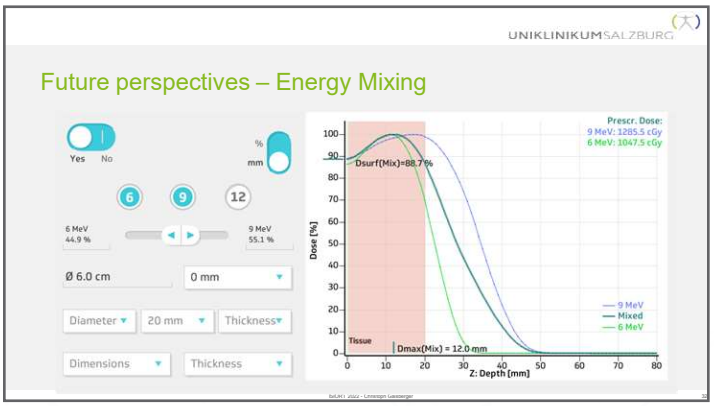
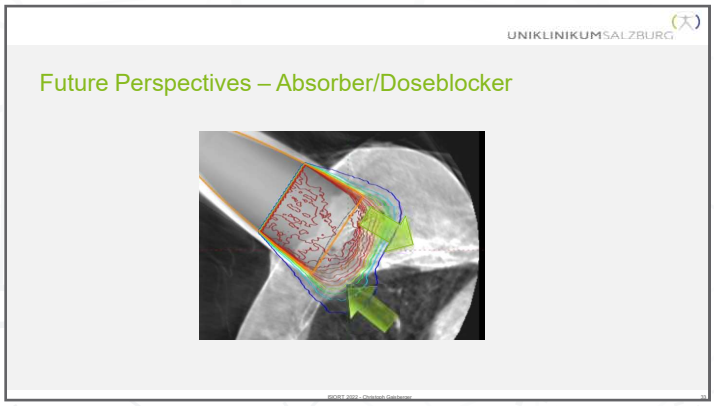
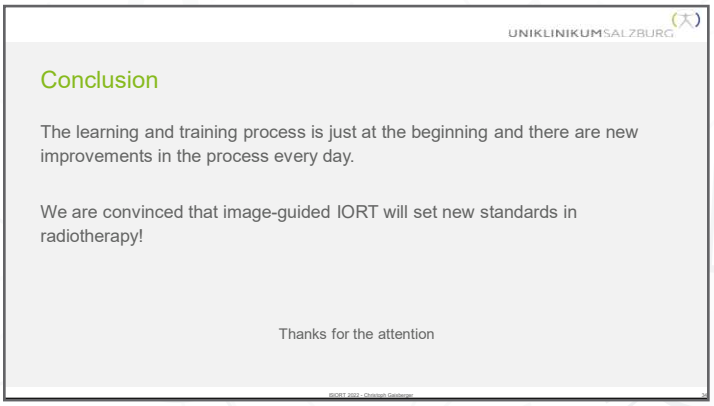
Speaker presentations

CT Imaging in Electron Based IORT – Current Status and Future Perspectives









Speaker presentations

Quality Assurance in Intraoperative Radiotherapy

Antonella Ciabattoni, MD
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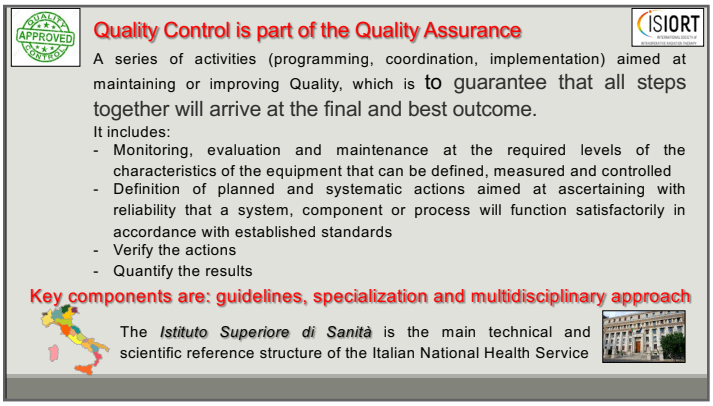
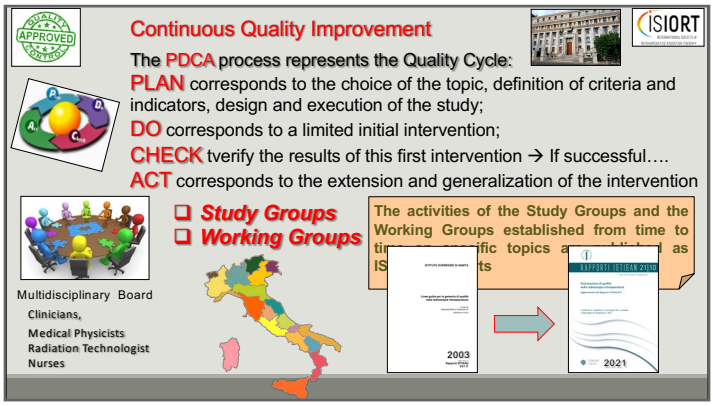
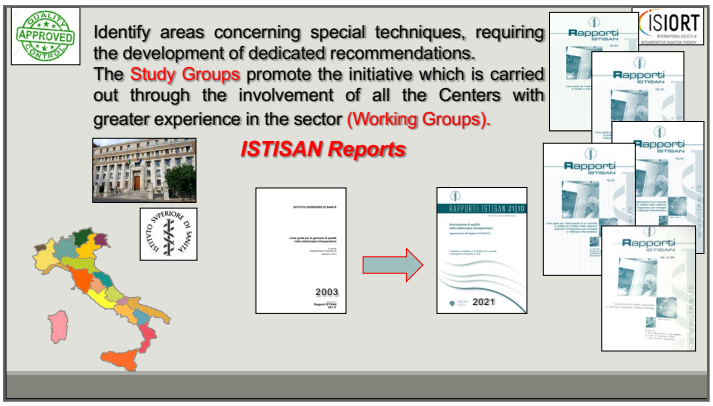
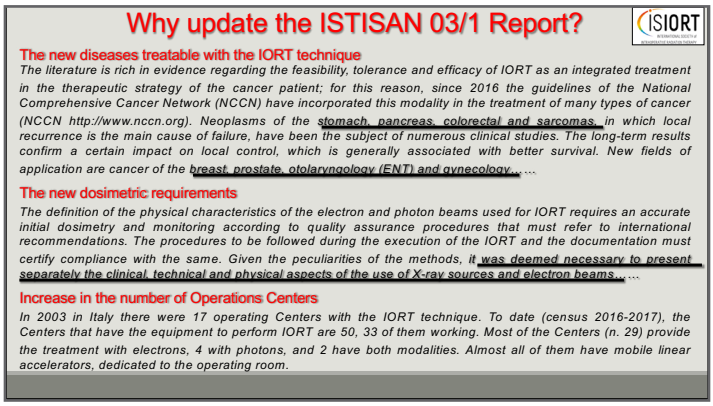
San Filippo Neri Hospital, Rome, Italy



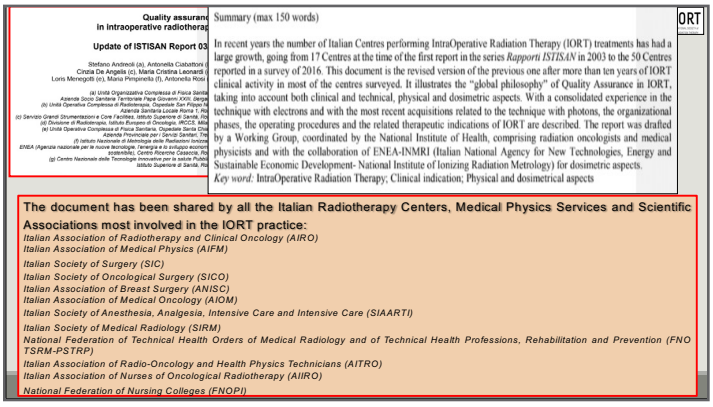






Speaker presentations

Quality Assurance in Intraoperative Radiotherapy



Quality assuranc
in Intraoperative radiotherap

Update of ISTISAN Report 03

Stefano Andreoli (a), Antonella Ciabattoni (
Cinzia De Angelis (c), Maria Cristina Leonardi (
Loris Menegoti (e), Maria Pimpinella (f), Antonella Rosi

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Azienda Sociо Sanitaria Territoriale Papa Giovanni XXIII, Bergo
(b) Unità Operativa Complessa di Radioterapia, Ospedale San Filippo N
(c) Servizio Grandi Strumentazioni e Core Facilities, Istituto Superiore di Sanità, Ro
(d) Divisione di Radioterapia, Istituto Europeo di Oncologia, IRCCS, Mila
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Summary (max 150 words)

In recent years the number of Italian Centres performing IntraOperative Radiation Therapy (IORT) treatments has had a large growth, going from 17 Centres at the time of the first report in the series *Rapporti ISTISAN* in 2003 to the 50 Centres reported in a survey of 2016. This document is the revised version of the previous one after more than ten years of IORT clinical activity in most of the centres surveyed. It illustrates the "global philosophy" of Quality Assurance in IORT, taking into account both clinical and technical, physical and dosimetric aspects. With a consolidated experience in the technique with electrons and with the most recent acquisitions related to the technique with photons, the organizational phases, the operating procedures and the related therapeutic indications of IORT are described. The report was drafted by a Working Group, coordinated by the National Institute of Health, comprising radiation oncologists and medical physicists and with the collaboration of ENEA-INMRI (Italian National Agency for New Technologies, Energy and Sustainable Economic Development- National Institute of Ionizing Radiation Metrology) for dosimetric aspects.

Key word: IntraOperative Radiation Therapy; Clinical indication; Physical and dosimetrical aspects

The document has been shared by all the Italian Radiotherapy Centers, Medical Physics Services and Scientific Associations most involved in the IORT practice:

Italian Association of Radiotherapy and Clinical Oncology (AIRO)
Italian Association of Medical Physics (AIFM)
Italian Society of Surgery (SIC)
Italian Society of Oncological Surgery (SICO)
Italian Association of Breast Surgery (ANISC)
Italian Association of Medical Oncology (AIOM)
Italian Society of Anesthesia, Analgesia, Intensive Care and Intensive Care (SIAARTI)
Italian Society of Medical Radiology (SIRM)
National Federation of Technical Health Orders of Medical Radiology and of Technical Health Professions, Rehabilitation and Prevention (FNO TSRM-PSTRP)
Italian Association of Radio-Oncology and Health Physics Technicians (AITRO)
Italian Association of Nurses of Oncological Radiotherapy (AIIRO)
National Federation of Nursing Colleges (FNOPI)

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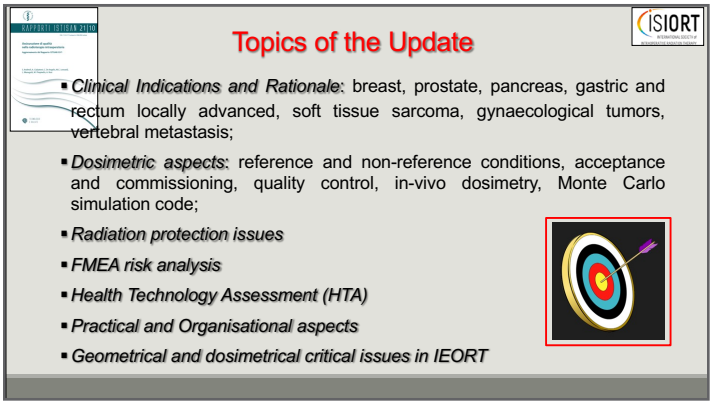
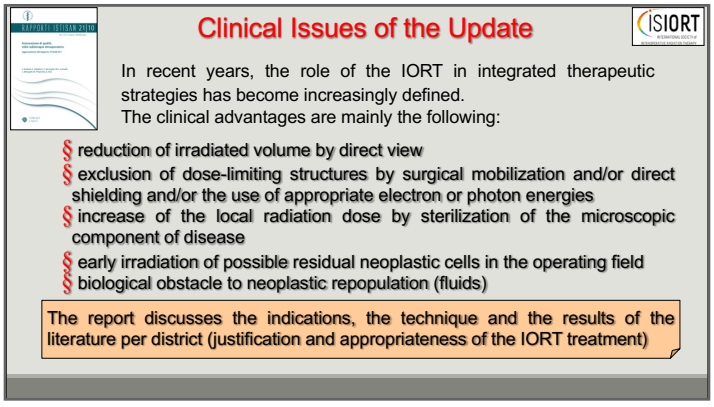


Topics of the Update

- *Clinical Indications and Rationale*: breast, prostate, pancreas, gastric and rectum locally advanced, soft tissue sarcoma, gynaecological tumors, vertebral metastasis;
- *Dosimetric aspects*: reference and non-reference conditions, acceptance and commissioning, quality control, in-vivo dosimetry, Monte Carlo simulation code;
- *Radiation protection issues*
- *FMEA risk analysis*
- *Health Technology Assessment (HTA)*
- *Practical and Organisational aspects*
- *Geometrical and dosimetrical critical issues in IEORT*

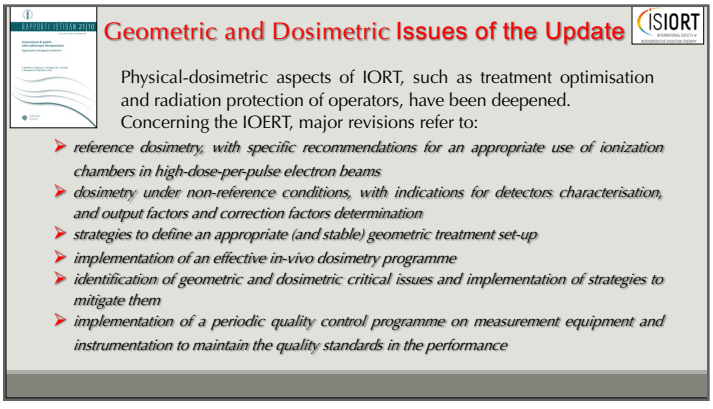


Clinical Issues of the Update

In recent years, the role of the IORT in integrated therapeutic strategies has become increasingly defined.
The clinical advantages are mainly the following:

- reduction of irradiated volume by direct view
- exclusion of dose-limiting structures by surgical mobilization and/or direct shielding and/or the use of appropriate electron or photon energies
- increase of the local radiation dose by sterilization of the microscopic component of disease
- early irradiation of possible residual neoplastic cells in the operating field
- biological obstacle to neoplastic repopulation (fluids)

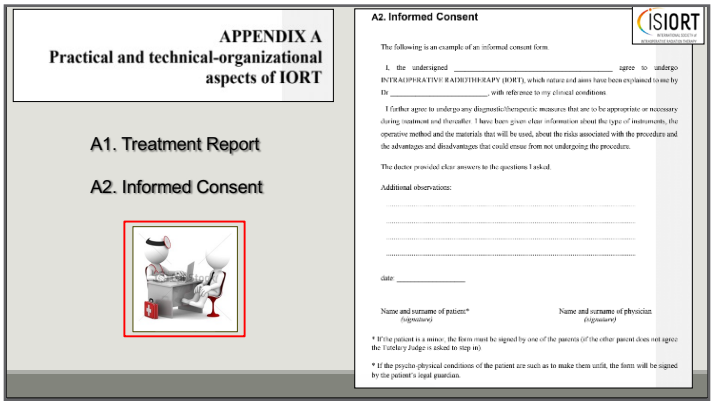
The report discusses the indications, the technique and the results of the literature per district (justification and appropriateness of the IORT treatment)



Geometric and Dosimetric Issues of the Update

Physical-dosimetric aspects of IORT, such as treatment optimisation and radiation protection of operators, have been deepened.
Concerning the IOERT, major revisions refer to:

- *reference dosimetry, with specific recommendations for an appropriate use of ionization chambers in high-dose-per-pulse electron beams*
- *dosimetry under non-reference conditions, with indications for detectors characterisation, and output factors and correction factors determination*
- *strategies to define an appropriate (and stable) geometric treatment set-up*
- *implementation of an effective in-vivo dosimetry programme*
- *identification of geometric and dosimetric critical issues and implementation of strategies to mitigate them*
- *implementation of a periodic quality control programme on measurement equipment and instrumentation to maintain the quality standards in the performance*



APPENDIX A
Practical and technical-organizational aspects of IORT

A1. Treatment Report

A2. Informed Consent

A2. Informed Consent

The following is an example of an informed consent form.

I, the undersigned _____ agree to undergo INTRAOPERATIVE RADIOTHERAPY (IORT), which nature and aims have been explained to me by Dr _____ with reference to my clinical conditions.

I further agree to undergo any diagnostic/therapeutic measures that are to be appropriate or necessary during treatment and thereafter. I have been given clear information about the type of instruments, the operative method and the materials that will be used, about the risks associated with the procedure and the advantages and disadvantages that could ensue from not undergoing the procedure.

The doctor provided clear answers to the questions I asked.

Additional observations:

date: _____

Name and surname of patient* (signature) | Name and surname of physician (signature)

* If the patient is a minor, the form must be signed by one of the parents (if the other parent does not agree the Tutelary Judge is asked to step in)

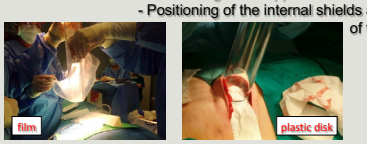
* If the psycho-physical conditions of the patient are such as to make them unfit, the form will be signed by the patient's legal guardian.

Speaker presentations

Quality Assurance in Intraoperative Radiotherapy

APPENDIX A
Practical and technical-organizational aspects of IORT

A3. Critical issues and considerations on Electron Beam IORT
A3.1 Geometric critical issues:
- Positioning of the applicator
- Positioning of the internal shields and evaluation of target volume thickness



By courtesy of S. Andreoli

APPENDIX A
Practical and technical-organizational aspects of IORT

A3. Critical issues and considerations on Electron Beam IORT
A3.2 Dosimetric critical issues:

- High doses delivered in a single session
- High doses per pulse generated by some types of dedicated accelerators
- Treatment beam energy selection
- Use of applicators that must mantain the same physical characteristics over time
- Use of internal shields having a high atomic number
- Output reproducibility on the day of the treatment
- In vivo dosimetric verification

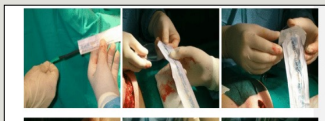


Figure A3.10. Procedure for treatment set-up and positioning of a micromosfet detector for entrance dose measurement in a breast treatment (note the disk between the applicator and the target surface and the micromosfet placed between the disk and the target surface)(photos by S.Andreoli)

By courtesy of S. Andreoli

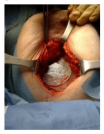
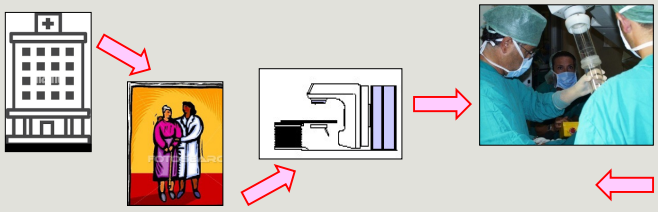


Figura A3.11. Positioning of a radiochromic film for exit dose measurement and applicator-target-disk alignmentverification in the case of breast treatment (photo by M. Severgnini)

By courtesy of M. Severgnini

APPENDIX A
Practical and technical-organizational aspects of IORT

A4. PHYSICAL AND DOSIMETRIC OPTIMIZATION OF ELECTRON BEAM IORT
A4.1 Technical aspects
A4.2 Organizational and Management aspects



B Appendix

Main indications for quality assurance in electron and photon IORT treatments

Main indications for quality assurance in electron and photon IORT treatments

B1. CLINICAL ASPECTS

- Organization
- Treatment Planning
- Radiotherapy Treatment Procedure
- Anaesthesia
- Surgical Procedure
- Management of Emergencies
- Follow-up:
  Gathering and Classifying Side Effects / Adverse Events

B Appendix
Main indications for quality assurance in electron and photon IORT treatments

B1: INDICATIONS FOR TREATMENT WITH ELECTRONS AND PHOTONS

Clinical, histological, biomolecular and radiological criteria for the main diseases

BREAST
- single dose. Refer to national and international guidelines (AIRO, ASTRO, ESTRO);
- boosts have broader indications because they include external beam radiation therapy.

PROSTATE
- exclusive treatment without prostatectomy or combined with pelvic lymphadenectomy and/or pelvic RT with external beams;
- "exclusive" adjuvant treatment after radical prostatectomy with pelvic lymphadenectomy;
- treatment of relapses with or without external beam pelvic RT.

PANCREAS
- anticipated boost in resectable carcinoma with external beam RT with or without chemotherapy;
- additional boost after preoperative radio-chemotherapy in borderline carcinoma;
- single dose with a symptomatic-palliative objective in unresectable carcinoma.

RECTUM
- additional boost in advanced carcinoma/relapses after preoperative radio-chemotherapy;
- additional boost in advanced carcinoma in the presence of R1-R2;
- re-treatment after previous RT with external beams in multimodal re-treatment programs with or without chemotherapy.

B Appendix
Main indications for quality assurance in electron and photon IORT treatments

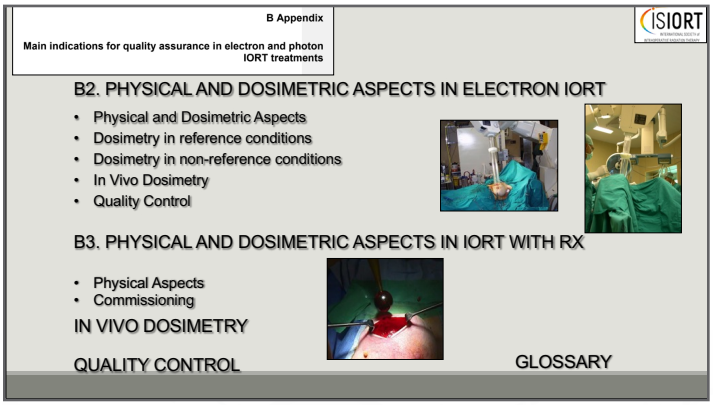
B1: INDICATIONS FOR TREATMENT WITH ELECTRONS AND PHOTONS

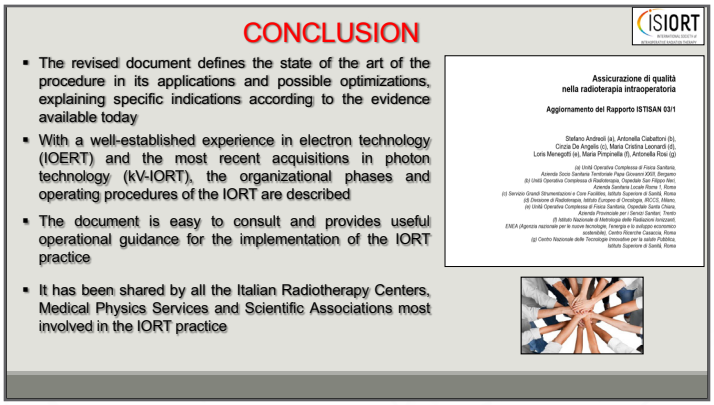
Clinical, histological, biomolecular and radiological criteria for the main disease

SARCOMAS of SOFT TISSUES
Boosts
additional *boost* in programs with pre- or postoperative RT with or without chemotherapy both for the limbs and for the retroperitoneum.
STOMACH
Boosts
additional *boost* in programs with pre- (less common) or postoperative RT with or without chemotherapy
GYNAECOLOGY
additional *boost* in locally advanced/relapsing cervical cancer after pre-operative radio-chemotherapy;
re-treatment (adjuvant or exclusive) after previous external beam RT in multi-modal retreatment programs with or without chemotherapy.
BONE METASTASES
KYPHO IORT (only photons).
SPECIAL SITUATIONS
IORT in pregnancy (in the case of treatment with electrons)
Feasible in selected cases in the second trimester of pregnancy, estimating beforehand the dose to the foetus and and performing an in vivo dose assessment.
IORT in the presence of CIED
Feasible in selected cases estimating beforehand the dose to the device, planning a treatment set-up such as to maintain the minimum safe distance between the field edge and the device, and then making an in vivo dose assessment, if any.

Speaker presentations

Quality Assurance in Intraoperative Radiotherapy





Speaker presentations

IORT in Pancreatic Carcinoma

Eric Miller, MD, PhD
Associate Professor
Department of Radiation Oncology
The Ohio State University
Columbus, Ohio, United States

IORT in Pancreatic Carcinoma

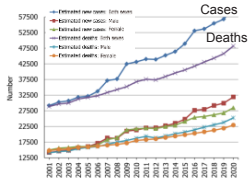
Eric Miller, MD, PhD
Associate Professor
Department of Radiation Oncology

Outline

- Challenges in treating pancreatic cancer
  - Role of RT
- RT dose escalation in pancreatic cancer
- IORT in pancreatic cancer
  - Early experience with IORT
  - IORT in resectable disease
  - IORT in unresectable disease
- PACER
- Conclusions

Challenges in Treatment of Pancreatic Cancer

- Incidence of pancreatic cancer is on the rise:
  - Globally, the number of deaths and cases have more than doubled from 1990-2017.
- 4th leading cause of cancer-related death in the U.S.
- For all stages combined, pancreas has the lowest 5-year survival rate.

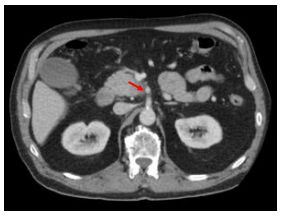


- Surgical resection remains the only curative modality:
  - Most patients (~80%) present with locally advanced disease where resection is not possible or have metastatic disease.

Pourshams et al. Lancet Gastro 2019;4:934.
Siegel et al. CA Cancer J Clin 2022;72:7.
Patel et al. Ann Surg Oncol 2021;28:4101.
Hu et al. World J Gastro 2021;27:4298.

Treatment of Borderline Resectable or Locally Advanced Disease

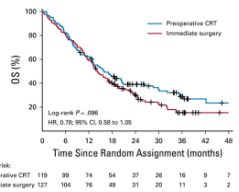
- Neoadjuvant chemotherapy is the mainstay:
  - Facilitate margin negative resection.
  - Early treatment of potential micrometastatic disease.
- Consider RT for those with an inadequate response to initial chemotherapy.



Suker et al. Lancet Oncol 2016;17:801.
Janssen et al. Front Oncol 2020;10:41.
Murphy et al. JAMA Oncol 2018;4:963.

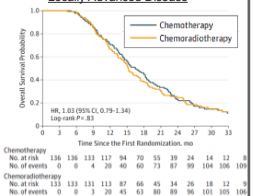
Treatment of Borderline Resectable or Locally Advanced Disease

PREOPANC Trial:
Resectable/Borderline Resectable



- No difference in OS by ITT.
- Preop CRT arm showed:
  - Improved R0 resection rate (71% vs. 40%, *P*<.001).
  - OS benefit in those w/ resection who received adjuvant chemo (35.2 vs. 19.8 m, *P*=.029).

LAP07 Trial:
Locally Advanced Disease

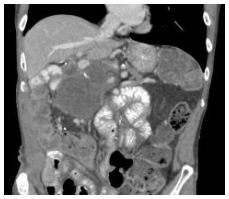


- No difference in OS by ITT.
- CRT arm showed:
  - Reduced locoregional progression (32% vs. 46%, *P*=.03).
  - Longer delay to treatment restart (7.0 vs. 3.7 m, *P*=.02).

Versteijne et al. JCO 2020;38:1763.
Hammel et al. JAMA 2016;315:1844.

Local Control Remains a Challenge

- Rate of conversion from unresectable to resectable disease remains low.
  - Unresectable disease and margin-positive resection both associated with poor prognosis.
- Locally destructive disease may be the direct cause of death in up to 30% of patients based on autopsy series.



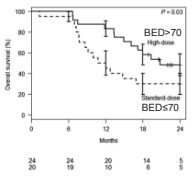
Konstantinidis et al. Ann Surg 2013;257:731.
Iacobuzio-Donahue et al. JCO 2009;27:1806.

Speaker presentations

IORT in Pancreatic Carcinoma

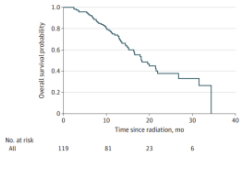
RT Dose Escalation for Locally Advanced PDAC May Result in Improved Outcomes

MRI Linac:
BED_{10} > 70 Gy



- High-dose showed improved OS compared to low-dose (49% vs. 30%, *P*=0.03).
- Trend for improvement in 2-year freedom from local failure in the high-dose group vs. the low-dose group (77% vs. 57%, *P*=0.15).

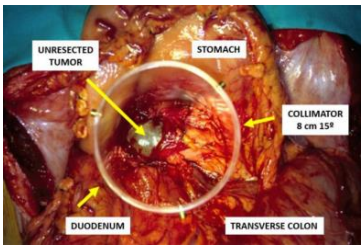
Hypofractionated Ablative RT:
BED_{10} = 98 Gy



- Median OS from RT was 18.4 months.
- 24-month cumulative incidence of locoregional failure was 32.8%.

Rudra et al. Cancer Medicine 2019;8:2123.
Reyngold et al. JAMA Oncol 2021;7:735.

IORT - Optimal Method for Dose Escalation in PDAC

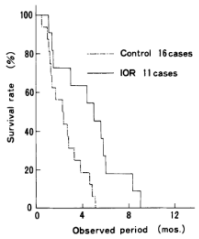


Calvo et al. Radio & Oncol 2020;148:57.

Early Experience with IORT in PDAC

- Nishimura et al:
  - 70 patients treated with multimodality therapy for PDAC:
    - 33 received IORT:
      - 20.1-40 Gy with 8-25 MeV electrons.
  - Of those with pain, 70% experienced improvement.
  - Improved OS observed in those with Stage IV disease treated with IORT (4.6 months) vs. control (2.5 months), *P*<0.05.

Stage IV PDAC

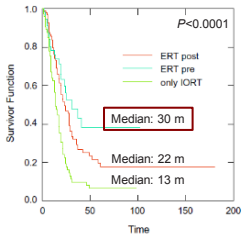


Nishimura et al. Cancer 1984;54:2375.

IORT in Resectable Pancreatic Cancer

- Valentini et al. ISIORT-Europe Experience:
  - 270 patients treated with surgery + IORT (7.5-25 Gy):
    - 24% received pre-op EBRT.
    - 40% received post-op EBRT.
    - 36% received IORT alone.
  - 47% of patients underwent R1 or R2 resection.
  - 5-year local control (LC) was 23.3% with median LC of 15 months.
  - 5-year OS was 18% with median OS of 19 months.
  - No grade 3 toxicities reported.

Overall Survival

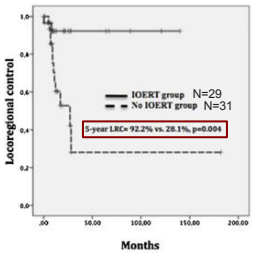


Valentini et al. Radio and Onc 2009;91:54.

IORT in Resectable Pancreatic Cancer

- Calvo et al:
  - 60 patients treated with chemoradiation + surgery ± IORT (10-15 Gy):
    - 68% received post-op CRT.
    - R1 resection performed in ~40% of both groups, *P*=0.77.
  - 5-year OS was 20%.
  - 5-year locoregional control was 58%.
  - On MVA, margin resection status (HR=3.0, *P*=0.05) and no IORT (HR=6.75, *P*=0.01) were associated with higher locoregional recurrence.
  - Perioperative complications were similar in IORT and non-IORT groups, ~43% grade ≥3.

Locoregional Control

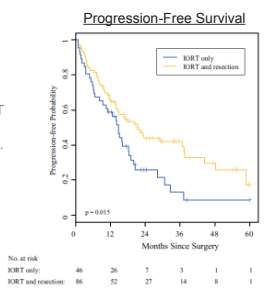


Calvo et al. Pancreatology 2013;13:576.

IORT in Resectable Pancreatic Cancer

- Harrison et al. MGH Experience with borderline resectable and locally advanced PDAC:
  - 86 patients treated with neoadjuvant FOLFIRINOX→RT →Surgery+IORT (10 Gy).
  - Local recurrence rate of 12.7%.
  - Median PFS was 21.5 months.
  - Median OS was **46.7 months**.
  - Overall postoperative complication rate was ~25%; major (Clavien-Dindo III/IV) complication rate of 13%.

Progression-Free Survival

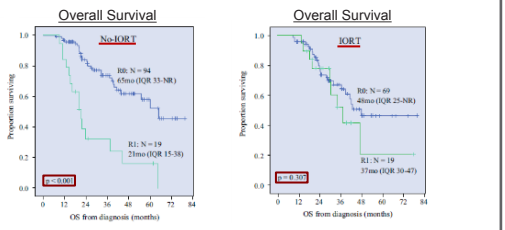


Harrison et al. Ann Surg Onc 2020;27:1400.

Speaker presentations

IORT in Pancreatic Carcinoma

IORT Mitigates R1 Resection



- MGH: 201 patients with borderline/locally advanced PDAC treated with FOLFIRINOX→RT→Surgery±IORT.
- For patients with an R1 resection, receipt of IORT showed a trend for significance for improved OS (37 months vs. 21 months, *P*=0.064).

Sekigami et al. Ann Surg Onc 2021;28:4592.

IORT in Resectable Pancreatic Cancer

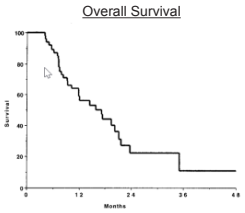
Study	Patient Number (N)	IORT Dose Range (Gy)	EBRT Dose Range (Gy)	Systemic Therapy	Local Control	Median Overall Survival
Valentini (ISIORT-Europe)	270 (169 IORT+EBRT, 95 IORT alone)	7.5-25	18-61	11.8% concurrent with EBRT	Median local control 15 months	19 months
Showalter (Jefferson)	37 (23 IORT+EBRT)	10-20	45-50.4	70% adjuvant	23% locoregional recurrence	19.2 months
Ogawa (JROSG)	210 (62 IORT+EBRT, 148 IORT alone)	20-30	20-60	19% concurrent with EBRT; 46% adjuvant	2-year local control 83.7%	19.1 months
Calvo	29	10-15	45-50.4	100% concurrent with EBRT; 62% adjuvant	5-year locoregional control 92.2%	5-year 20% for all patients (including no IORT)
Harrison (MGH)	86 (all treated with EBRT+IORT)	10.2 (mean)	50.4-58.8 or SBRT	100% received neoadjuvant treatment	12.7% local recurrence rate	46.7 months

Abbreviations: EBRT, external beam radiation therapy; Gy, gray; IORT, intraoperative radiation therapy; SBRT, stereotactic body radiation therapy

Valentini et al. Radio and Onc 2009;91:54.
Showalter et al. Ann Surg Onc 2009;16:2116.
Ogawa et al. IJROBP 2010;77:734.
Calvo et al. Pancreatology 2013;13:576.
Harrison et al. Ann Surg Onc 2020;27:1400.

IORT in Unresectable Pancreatic Cancer

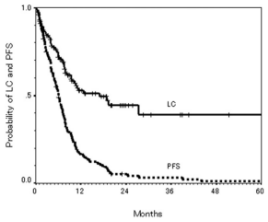
- Mohiuddin et al. (Jefferson):
  - 49 patients treated with surgery+IORT→CRT→5-FU maintenance.
    - IORT: 15-20 Gy
    - EBRT: 40-55 Gy
  - Median OS of 16 months; 2-year OS of 22%.
  - Freedom from local progression achieved in **71%** of patients.
  - Early G3/4 toxicity in 14%, late G3/4 toxicity in 19% of patients.



Mohiuddin et al. JCO 1995;13:2764.

IORT in Unresectable Pancreatic Cancer

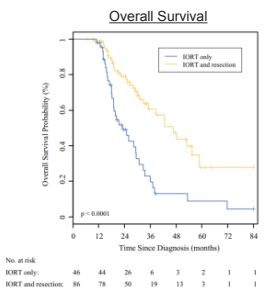
- Ogawa et al. (JROSG):
  - 144 patients treated with IORT (median 25 Gy) ± EBRT (median 45 Gy):
    - 79% received IORT+EBRT.
    - 45% received adjuvant chemotherapy.
  - 2-year local control rate in all patients was 44.6%.
  - Improved 2-year local control observed in patients receiving IORT+EBRT vs. IORT alone (50.9% vs. 17.5%, *P*=0.0004).
  - The median OS for all patients was 10.5 months; 2-year OS of 14.7%.
  - Late grade 3 GI toxicity was reported in 1.4% of patients.



Ogawa et al. IJROBP 2011;80:111.

IORT in Unresectable Pancreatic Cancer

- Harrison et al. MGH Experience with BR and LA PDAC:
  - 46 patients treated with FOLFIRINOX→RT→IORT alone (15-20 Gy).
  - Local progression in 15% of patients.
  - Median PFS was 14.7 months.
  - Median OS was **23 months**.
  - Overall postoperative complication rate was ~20%; major (Clavien-Dindo III/IV) complication rate of 4.7%.



Harrison et al. Ann Surg Onc 2020;27:1400.

IORT in Unresectable Pancreatic Cancer

Study	Patient Number	IORT Dose Range (Gy)	EBRT Dose Range (Gy)	Systemic Therapy	Local Control	Median Overall Survival
Tepper (RTOG-8505)	51	15-20	50.4	100% concurrent with EBRT; no adjuvant	Not evaluated	9.0 months
Mohiuddin (Jefferson)	49	15-20	40-55	100% concurrent with EBRT; 100% adjuvant	31% local recurrence rate	16.0 months
Ogawa (JROSG)	144 (113 IORT+EBRT, 31 IORT alone)	12-35	14-50.8	69% concurrent with EBRT; 45% adjuvant	2-year local control rate 44.6%	10.5 months
Chen	247 (90 IORT+EBRT, 157 IORT alone)	10-20	36-40	32% concurrent with EBRT; 35% adjuvant	2-year local PFS rate of 40.1%	9.0 months
Harrison (MGH)	46 (all treated with EBRT+IORT)	15 (mean)	50.4-58.8 or SBRT	100% received neoadjuvant treatment	15% local recurrence rate	23.0 months

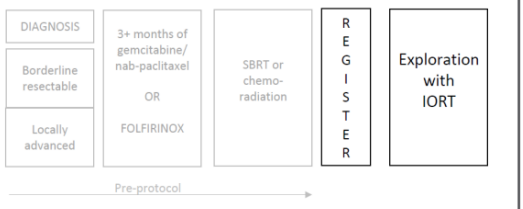
Abbreviations: EBRT, external beam radiation therapy; Gy, gray; IORT, intraoperative radiation therapy; PFS, progression-free survival; SBRT, stereotactic body radiation therapy

Tepper et al. IJROBP 1991;21:1145.
Mohiuddin et al. JCO 1995;13:2764.
Ogawa et al. IJROBP 2011;80:111.
Chen et al. Medicine(Baltimore) 2016;95:e4861.
Harrison et al. Ann Surg Onc 2020;27:1400.

Speaker presentations

IORT in Pancreatic Carcinoma

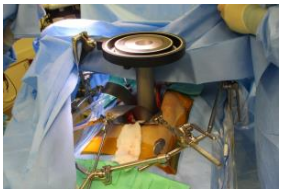
PACER (Pancreatic AdenoCarcinoma with Electron Intraoperative Radiation Therapy)



- PI: Ted Hong, MD; 7 sites – Georgetown, MGH, Mayo (MN,FL), OSU, UCI, UNC.
- Primary Endpoint: 2-year OS post-IORT.
- Planned for 100 borderline resectable patients; 100 locally advanced patients.

Conclusions

- Local control remains a problem in pancreatic cancer:
  - Systemic therapy continues to improve resulting in better control of distant disease.
  - Local progression can result in substantial morbidity/mortality.
- Current data suggests that RT dose escalation results in improved local control and may improve OS in patients with locally advanced disease.
- IORT is an effective method of delivering a higher dose to the tumor or post-op bed while minimizing dose to adjacent normal tissues.
  - For resectable disease, data suggests that IORT may improve local control and mitigate an R1 resection.
  - For unresectable disease, data suggests that IORT may help prevent local progression and potentially impact OS.
- PACER continues to enroll – we need additional prospective clinical trials!



Thank you!

wexnermedical.osu.edu

Eric.Miller@osumc.edu

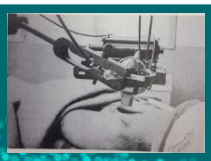
Speaker presentations

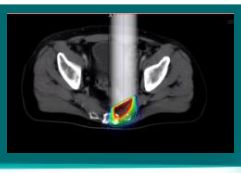
Mayo Experience of IORT in Rectal Carcinoma

Michael Haddock, MD
Professor
Department of Radiation Oncology
Mayo Clinic
Rochester, Minnesota, United States

MAYO CLINIC

IORT for Rectal Cancer: Mayo Clinic Experience





Michael G. Haddock, M.D.
ISIORT Oct 20,2022, Columbus, Ohio

Disclosures

- None

Learning Objectives

- Discuss Mayo Experience with IORT for colorectal cancer
  - Indications and rationale
  - Techniques
  - Outcomes and toxicities
  - Future directions

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

Stanford, 1937

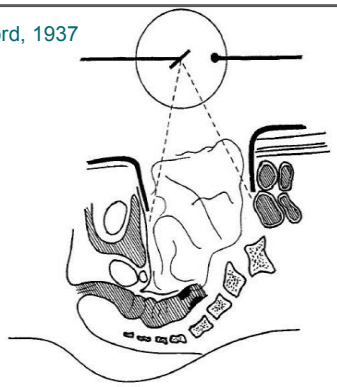


FIG. 1.—Irradiation of cancer of sigmoid (abdominal approach).

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 depends on the number of clonogens and may not be achievable in all cases with acceptable normal tissue effects

Speaker presentations

Mayo Experience of IORT in Rectal Carcinoma

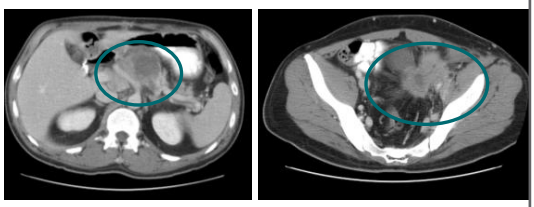
Radiation Dose Problem

- Dose needed for local control:
  - Complete resection: 50 Gy
  - Microscopic disease: > 60 Gy
  - Gross disease: > 70 Gy
- Small bowel tolerance: 100 cc
  - Ulcer, stricture, perforation, obstruction
  - 45 – 50 Gy: 1-5% risk at 5 years
  - 55 Gy: 25-50% risk at 5 years

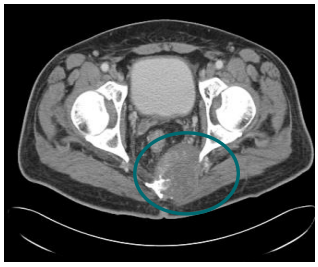
IORT
General Rationale

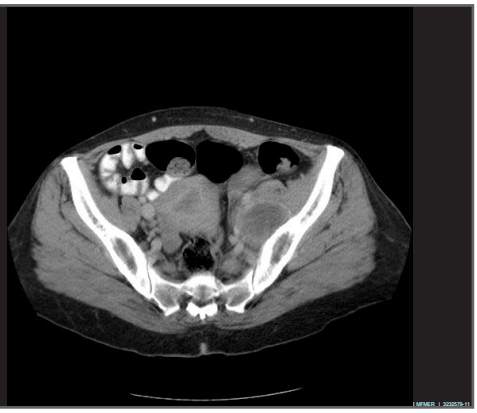
- able to treat small volume of tissue within IORT boost field
- can limit dose to sensitive normal organs such as small bowel
- can increase effective radiation dose

"Unresectable" Cancers
(i.e.fixation to critical structures)



"Unresectable" Colorectal Cancer





Microvascular Radiation Effects

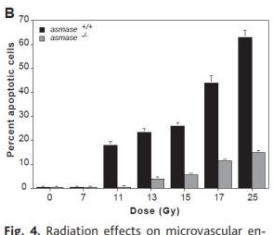


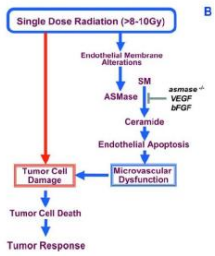
Fig. 4. Radiation effects on microvascular endothelial apoptosis. Radiation induces microvascular endothelial apoptosis in tissue explants from *asmase*$^{+/+}$ but not *asmase*$^{-/-}$ mice harboring MCA/129 fibrosarcomas. (**A**) Tumors

Garcia-Barros, Science 2003;300;1155-1159

Speaker presentations

Mayo Experience of IORT in Rectal Carcinoma

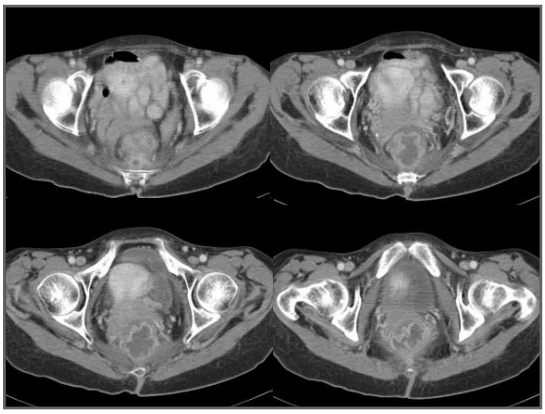
Vascular component of XRT response

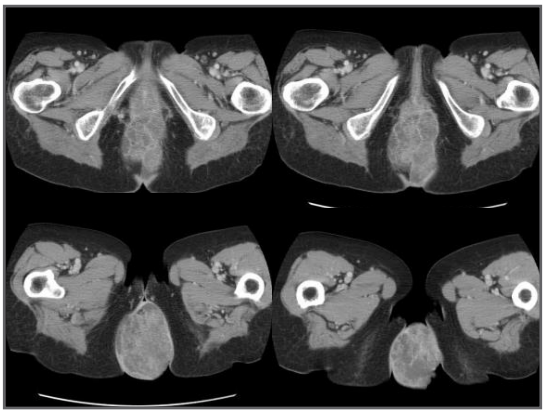


Fuks, Cancer Cell 2005;8:89-91

Recurrent Rectal Cancer
Flap Recurrence

- 54 yof fixed rectal cancer
  - 5580 cGy: unresectable
  - To Mayo: resection + IORT 15 Gy
  - Rectus abdominus flap
- 14 months later: recurrence in flap





Mayo Clinic IORT Program

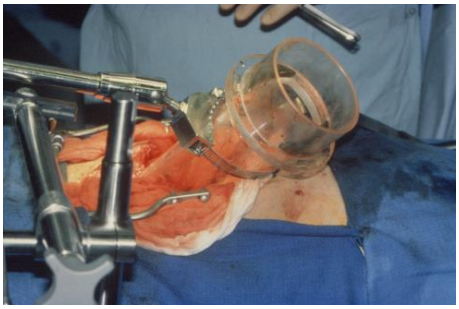
- Rochester
  - 1981: IORT in rad onc department
  - 1988: dedicated OR suite with refurbished linac
  - 2022: 2nd IORT (mobile electron unit)
- Phoenix: mobile electron unit in OR
- Jacksonville: mobile electron unit OR

IOERT - Mayo
Treatment Applicators

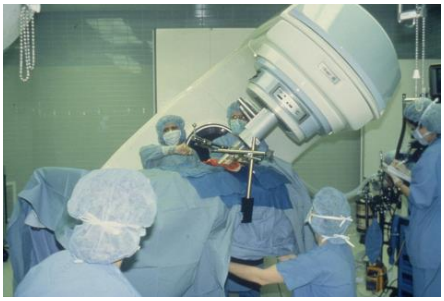
Speaker presentations

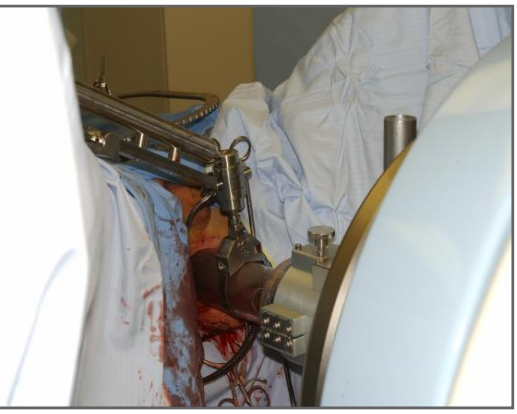
Mayo Experience of IORT in Rectal Carcinoma

IOERT - Mayo
Applicator Fixation



IOERT - Mayo
Linac – Hard docking system





IOERT Cases – Mayo Rochester
April 1981 – Sept, 2022

Site	Primary	Recurrent	Total
GI	494	1087	1581
Soft tissue/bone	583	379	962
GYN	46	276	322
GU	15	65	80
Head and Neck	14	33	47
Miscellaneous	14	20	34
Total	1166	1860	3026

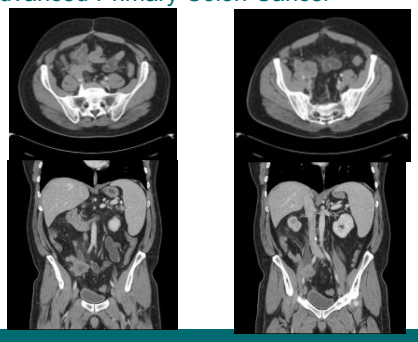
IOERT Cases – Mayo Rochester
April 1981 – Sept, 2022

Site	Primary	Recurrent	Total
Esophogogastric	43	17	60
Small bowel	33	13	46
Hepatobiliary	26	7	33
Pancreas	130	14	144
Colon	55	261	316
Rectum	214	740	954
Anus	17	41	58
Total	494	1087	1581

Speaker presentations

Mayo Experience of IORT in Rectal Carcinoma

Advanced Primary Colon Cancer

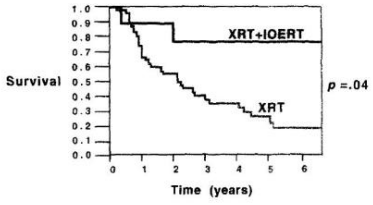


Locally Advanced Colon Cancer
Mayo Clinic Results

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

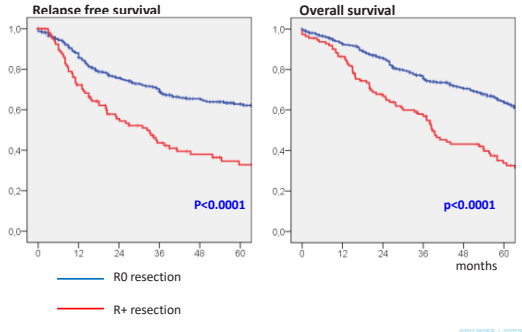


Schild, Red journal 37:51, 1997

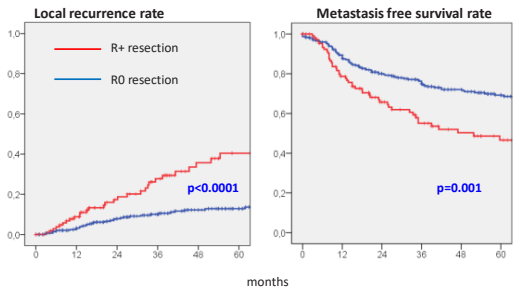
Locally Advanced Rectal Cancer
Selected Series

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

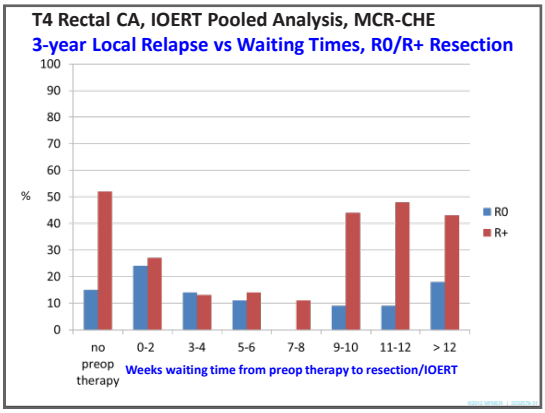


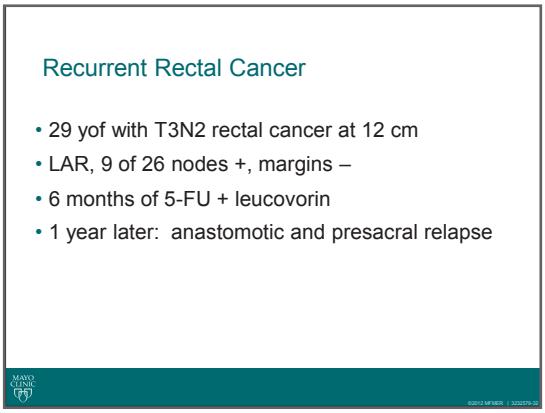
T4 Rectal CA – IOERT Pooled Analysis, MCR-CHE
Relapse Outcomes vs Radicality of Resection – 417 pts

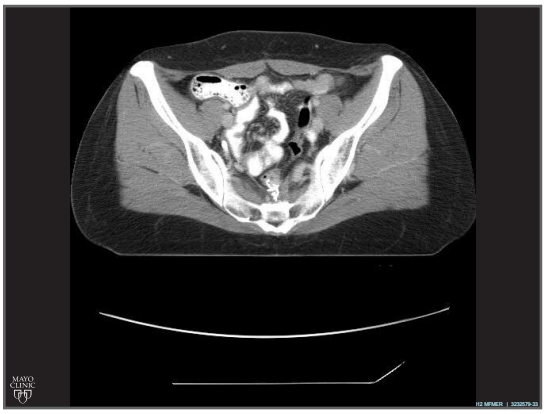


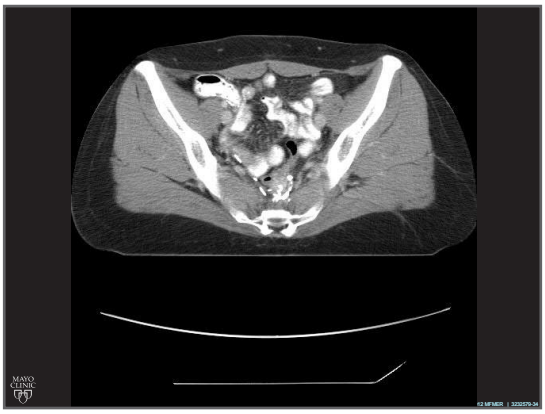
Speaker presentations

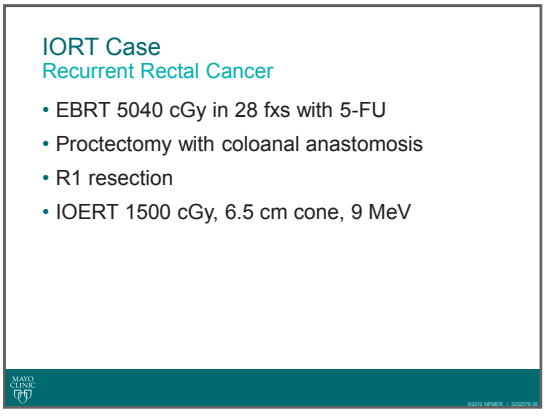
Mayo Experience of IORT in Rectal Carcinoma

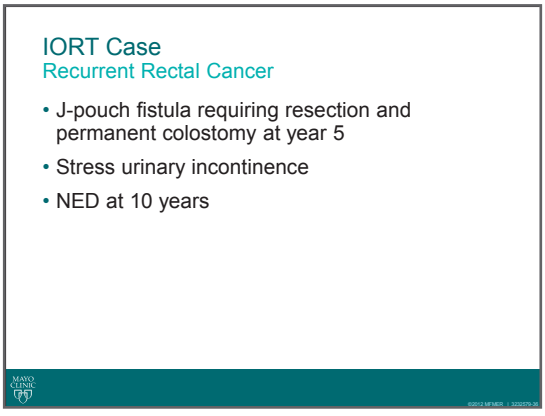








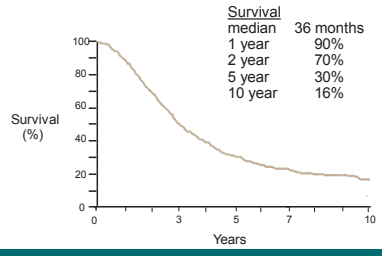




Speaker presentations

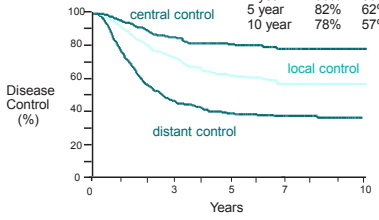
Mayo Experience of IORT in Rectal Carcinoma

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 – Recurrent Colorectal Ca 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 – Recurrent Colorectal Ca R1 resection

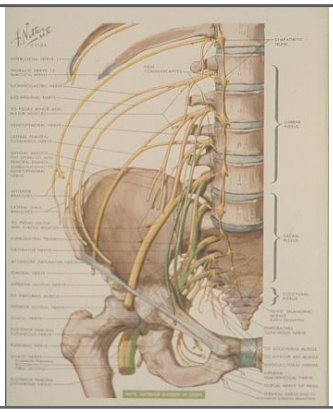
Study	# Pts	EBRT dose, Gy	IORT dose, Gy	IORT technique	5-year LC	5-yr DM	5-yr OS
Alektiar, MSKCC	21	50.4*	10-18	IOHDR	26%	-	11%
Wiig, Norway	29	46-50	15-20	IOERT	50%	-	20%
Eble, Heidelberg**	9	41.4	10-20	IOERT	67%	33%	33%^
Dresen, Eindhoven***	34	50.4^^	12.5	IOERT	29%	69%	27%
Haddock, Mayo Clinic	224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



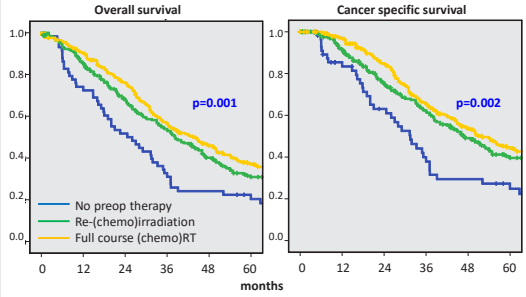
Speaker presentations

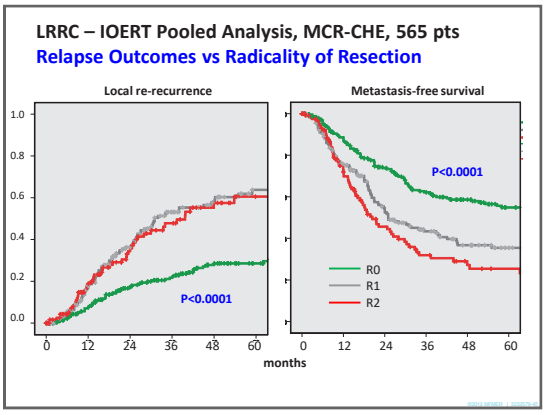
Mayo Experience of IORT in Rectal Carcinoma

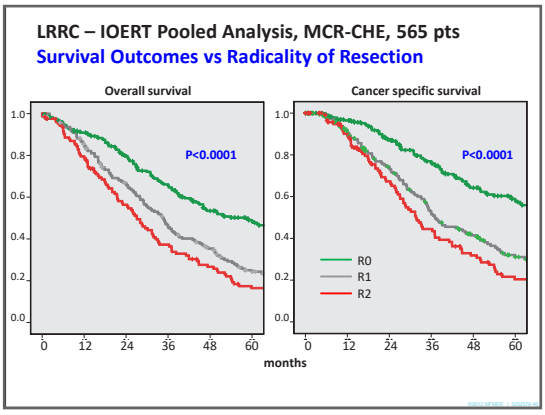
IOERT Related Neuropathy
Recurrent Colorectal Cancer

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

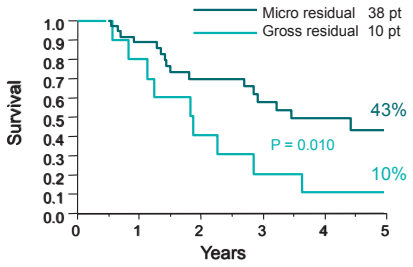
P = 0.0003



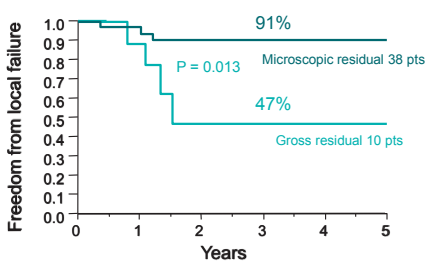




IOERT for Colorectal Nodal Mets
Survival by amount of residual



IOERT for Colorectal Nodal Mets
Local control by residual

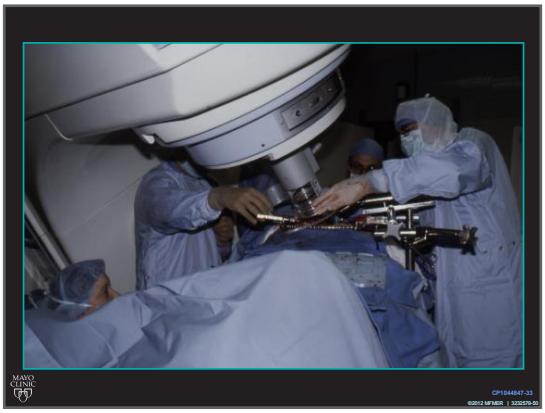


Speaker presentations

Mayo Experience of IORT in Rectal Carcinoma

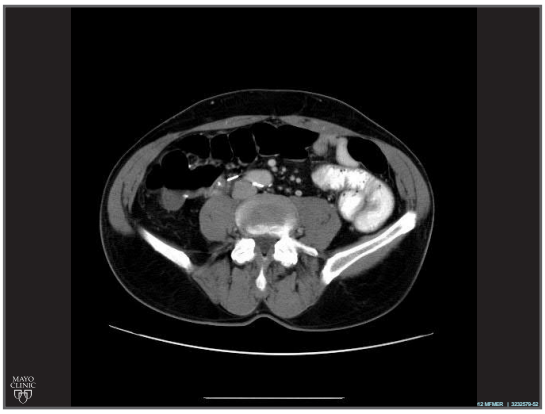
IORT for Colorectal Cancer
Conclusions

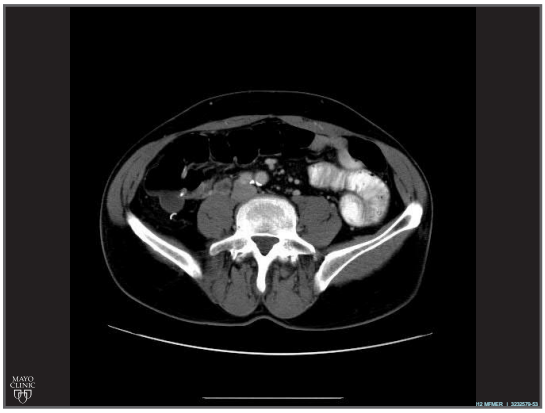
- IORT associated with improved disease control in patients with locally advanced primary and recurrent colorectal cancer
- IORT likely has tumoricidal and vascular effects
- Gross total resection is key prognostic factor
- IORT dose ≥ 15 Gy associated with more frequent and more severe neuropathy
- Resection within 8 weeks of EBRT is best
- Systemic therapy is key component of treatment



Case #1

- 70 yom with T4N0 cecal cancer
- Resection with positive radial margin
- No adjuvant therapy
- Tumor bed relapse one year later



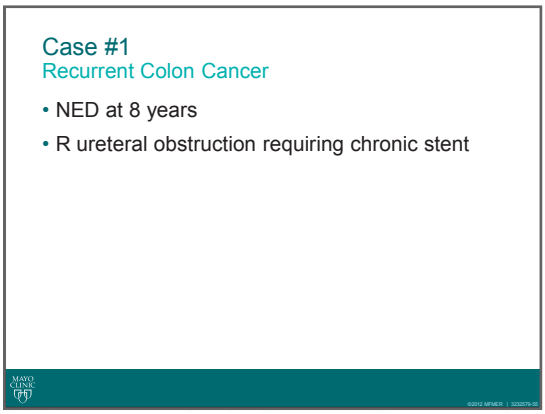


Case #1
Recurrent Colon Cancer

- 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

Speaker presentations

Mayo Experience of IORT in Rectal Carcinoma



Speaker presentations

Combining Immunotherapy with Salvage Surgery and IORT for Treatment of Persistent/Recurrent Head and Neck Cancers

Dukagjin Blakaj, MD, PhD
Associate Professor
Department of Radiation Oncology
The Ohio State University

HNSALV Trial: Combining Immunotherapy with Salvage Surgery and IORT for Treatment of Persistent/Recurrent Head and Neck Cancers

Dukagjin M. Blakaj, MD PhD
Associate Professor
Associate Director of Clinical Operations
Director of H&N/Skull Base Division
Director of CNS/Peds & H&N IORT Fellowships
Department of Radiation Oncology

THE OHIO STATE UNIVERSITY WEXNER MEDICAL CENTER

Background

- Standard of care for locoregionally recurrent head/neck cancer is surgical resection with adjuvant therapy.
- Local control after surgery alone is unacceptably low. Post-op chemoradiation has been shown to improve LC and PFS.
- Local failure remains the primary site of recurrence and overall prognosis is very poor.
- IORT may play a role in improving local control and decreasing toxicity for these patients.

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Randomized Trial of Postoperative Reirradiation Combined With Chemotherapy After Salvage Surgery Compared With Salvage Surgery Alone in Head and Neck Carcinoma

François Janot, Dominique de Raucours, Ellen Benhamou, Christophe Ferron, Gilles Doliver, René-Jean Bensadoun, Marc Hamoir, Bernard Géry, Morbize Julieron, Marine Castaing, Etienne Bardet, Vincent Grégoire, and Jean Bourhis

- 130 previously radiated patients with recurrent head/neck cancer
- Randomized to surgery followed by:
  - Observation
  - Chemoradiation
    - 60 Gy with concurrent 5-FU and Hydroxyurea

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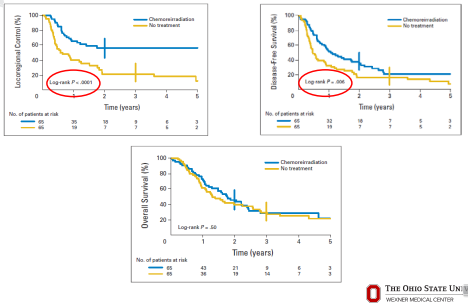
Results



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Toxicity

Table 3. Late Toxicity at 1 and 2 Years After Random Assignment

Toxicity	RT Arm (n = 42; 1 missing) No.	%	WS Arm (n = 33; 3 missing) No.	%
Toxicity at 12 and 12.5 months after random assignment, RTOG grade ≥ 3				
Mucositis	4	10	1	3
Skin	0	0	0	0
Subcutaneous tissues	6	14	3	9
Larynx	0	0	0	0
Osteoradionecrosis	1	2		
Trismus	3	7	2	6
Pharyngeal stenosis	1	2	0	0
No. of patients	11	26	3	9
Toxicity at 24 months after random assignment, RTOG grade ≥ 3*				
Mucositis	1	6	0	0
Skin	1	6	0	0
Subcutaneous tissues	4	22	1	5
Larynx	1	6	0	0
Trismus	5	28	2	10
Osteoradionecrosis	3	17	0	0
Pharyngeal stenosis	1	6	0	0
No. of patients	7	39	2	11

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Purposes of study

1. Conduct a retrospective review of our clinical outcomes using IORT for recurrent head/neck cancer.
2. Compare our outcomes to historical controls.
3. Determine if surgical margin status has a significant impact on LRC, PFS, and OS.

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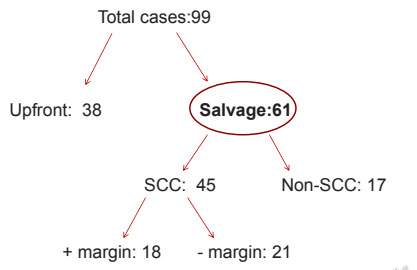
Speaker presentations

Combining Immunotherapy with Salvage Surgery and IORT for Treatment of Persistent/Recurrent Head and Neck Cancers

Case Breakdown at The Ohio State University from 2004-2015



Patient Characteristics

- 55 (90%) had recurrence, 6 (10%) had persistent disease

Age	Median 58 (range 26 – 86)
Gender	
Male	39 (64)
Female	22 (36)
Primary disease site	
Oropharynx	15 (25)
Oral cavity	10 (16)
Sinonasal	10 (16)
Larynx	9 (15)
Salivary	7 (11)
Unknown primary	5 (8)
Skin	3 (5)
Hypopharynx	1 (2)
Neck	1 (2)
IORT treatment site	
Primary	41 (67)
Neck	20 (33)

	n (%)
Histology	
Squamous	45 (74)
Adenoid Cystic	5 (8)
Carcinoma	4 (7)
Sarcoma	3 (5)
Mucoepidermoid	2 (3)
Ex pleomorphic adenoma	1 (2)
Adenocarcinoma	1 (2)
Margins	
Positive	28 (46)
Negative	27 (44)
Unknown	6 (10)
Perineural invasion	
Present	32 (52)
Not present	7 (11)
Unknown	22 (36)
Lymphovascular invasion	
Present	13 (21)
Not present	13 (21)
Unknown	35 (58)

Prior therapy

	n	Details
Surgery	44	Median # of surgeries: 1 Average # of surgeries: 1.8 Range: 1 – 7
EBRT (one course)	54	Median: 66 Gy Range: 25 – 70.2 Gy
EBRT (two courses)	2	72 Gy + 66 Gy 40 Gy + 52 Gy
EBRT + IOERT	2	60 Gy + 15 Gy 50.4 Gy + 10 Gy

IORT Prescriptions

- Median dose was 12.5 Gy (range 10 – 17.5 Gy)

	n (%)
Dose (Gy)	
10	29 (48)
12.5	12 (20)
15	17 (28)
17.5	3 (5)
Energy (MeV)	
6	58 (95)
9	2 (3)
12	1 (2)
Isodose level (%)	
90	59 (97)
100	2 (3)
Bevel diameter (cm)	
3	3 (5)
4	7 (11)
5	20 (33)
6	17 (28)
7	6 (10
8	5 (8)
9	2 (3)
10	1 (2)

Additional treatment

	n	Regimen
No post-op EBRT Post-op EBRT	38 23	N/A Median 45 Gy; Range 25 –56 Gy
No post-op chemo Post-op chemo	52 9	N/A Carboplatin/Paclitaxel (4) Cisplatin (4) Carboplatin (1)

~62 % of patients only had surgery and IORT

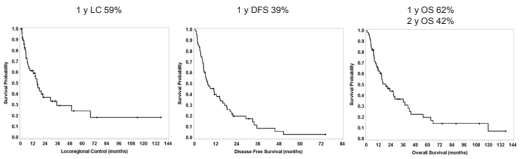
Results

	N	Median LRC (months)	1 yr LRC	Median PFS (months)	1 yr PFS	Median OS (months)	1 yr OS	2 yr OS
All histologies	61	16.6	59%	9.8	39%	19.1	62%	42%
Squamous cell	45	14.5	55%	6.2	28%	13.0	60%	32%
Non-squamous cell	16	18.4		18.1		37.7		
		p = 0.30		p = 0.09		p = 0.03		
SCC - Positive margin	18	5.2	42%	4.5	17%	9.6	44%	27%
SCC - Negative margin	21	14.5	60%	7.4	40%	16.1	75%	42%
		p = 0.31		p = 0.09		p = 0.06		
Post-op EBRT	23	16.8		6.5		13.1		
No post-op EBRT	38	15.9		8.9		26.3		
		p = 0.68		p = 0.38		p = 0.26		

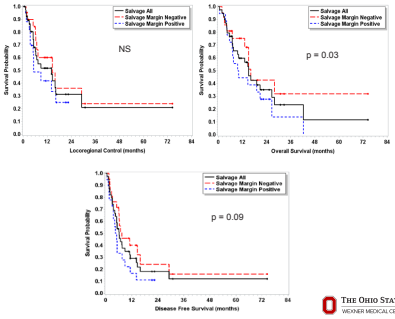
Speaker presentations

Combining Immunotherapy with Salvage Surgery and IORT for Treatment of Persistent/Recurrent Head and Neck Cancers

Salvage – All histologies



Salvage - SCC



Grade 5 toxicity

- Carotid blowout
  - 18 days after surgery
  - Within IORT treatment field
  - Patient had split thickness skin graft placed over carotid at time of surgery

Other significant toxicities

- ORN (2)
- Wound dehiscence (1)
- PC fistula (1)
- TE fistula (1)

Conclusions

- In a population of previously radiated recurrent H&N cancer patients, IORT achieved 1 and 2 year OS rates comparable to the French trial, despite only ~40% receiving post-operative RT and ~15% receiving post-op chemotherapy.
- Advantages of IORT may include decreased toxicity, decrease duration of post-op treatment.

ORIGINAL ARTICLE

Intraoperative electron beam radiotherapy for locoregionally persistent or recurrent head and neck cancer

Patrick Wald MD[1] | John Grecula MD[1] | Steve Walston DO[1] | Lai Wei PhD[2] | Aashish Bhatt MD[3] | Douglas Martin MD[1] | Marcelo Bonomi MD[4] | James Rocco MD[5] | Matthew Old MD[5] | Theodoros Teknos MD[3] | Dukagjin Blakaj MD, PhD[1]

Head & Neck. 2019;1–6. wileyonlinelibrary.com/journal/hed

Speaker presentations

Combining Immunotherapy with Salvage Surgery and IORT for Treatment of Persistent/Recurrent Head and Neck Cancers

Future Directions

- Pool H&N salvage IORT data with other institutions to increase our numbers
- Prospective protocol looking at the safety and efficacy of salvage surgery/IORT with and followed by immune therapy.
  - Hypothesis: Adding IO and pre op RT to IORT will improve upon our LC and PFS outcomes

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Future Directions

- Emerging data is revealing that HNSCC display an enriched immune landscape with key immunological implications.
- Both HPV+ and HPV– HNSCC tumors are found to display among the most prominent immune-infiltrate, with highest levels of CD8+ T cells and activated NK cells, paralleled by a marked expression of regulatory pathways in-cluding regulatory T cells (Treg) and related immune checkpoints like CTLA-4, GITR, ICOS, IDO, KIR, TIGIT, 4-1BB and VEGFA, in addition to PD-1.
- HNSCC has strong immunogenic features needing comparable immunosuppressive pressure to be nullified in most progressing patients.
- Can we provide new antigens with radiation therapy or 'jump start' the immune system in the recurrent/persistent H&N cancer patients?
- Radiation therapy may increase the capability of the immune system to exert its function through an increase in tumor neoantigens, due to the mutagenic activity of radiation, boost in antigen presentation, enhanced killing by CD8+ T-cells and improved cytokines production triggering a acute proinflamatory cascade. Irradiation induces upregulation of PD-L1,which could reduce the immune response of effector T-cells but at the same time potentiate the activity of PD-1 blockers.

Mandal R, et al. The head and neck cancer immune landscape and its immunotherapeutic implications. JCI Insight 1(17).
Cavalieri S, et al. Immuno-Oncology in head and neck squamous cell cancers: News from clinical trials, emerging predictive factors and unmet needs. Cancer treatment reviews 2018

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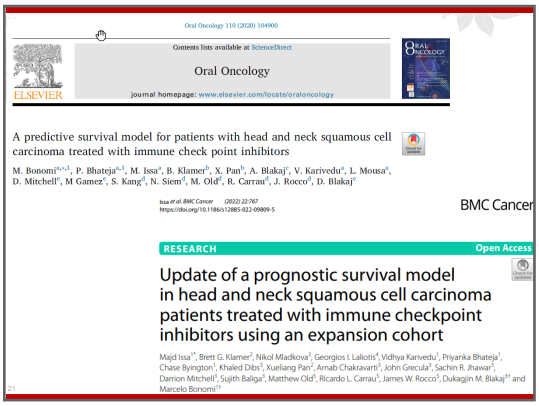

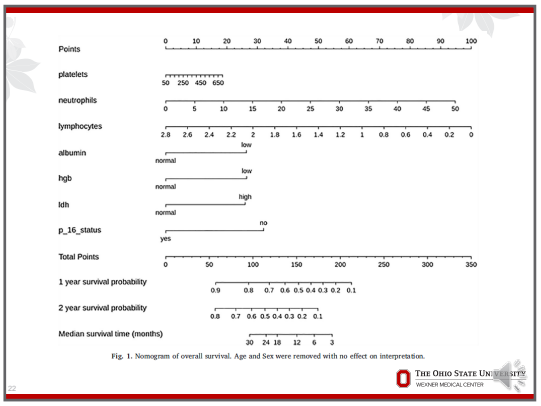

Fig. 1. Nomogram of overall survival. Age and Sex were removed with no effect on interpretation.

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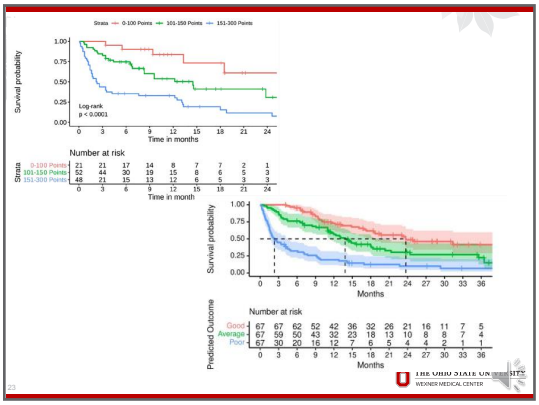

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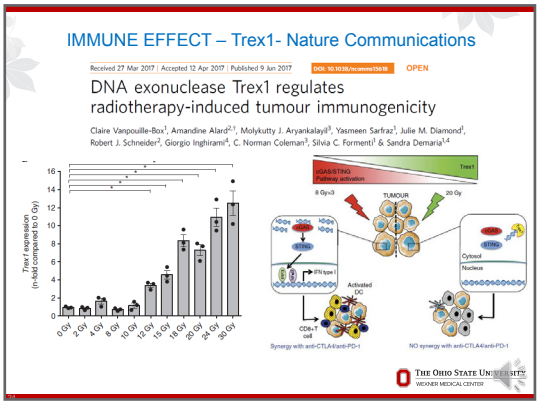
IMMUNE EFFECT – Trex1- Nature Communications



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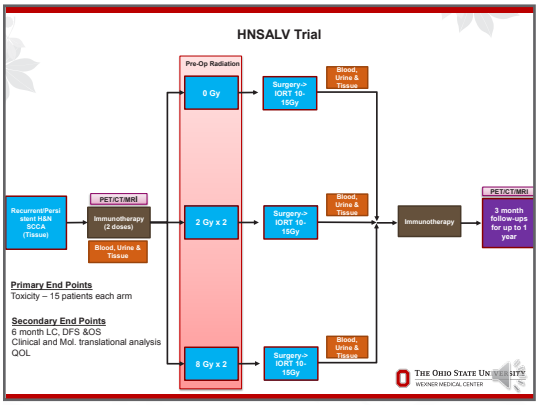
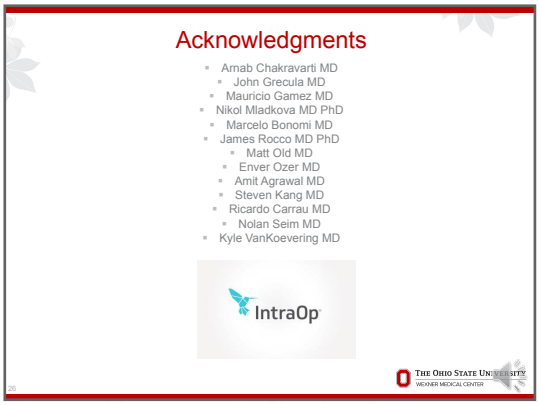
Speaker presentations

Combining Immunotherapy with Salvage Surgery and IORT for Treatment of Persistent/Recurrent Head and Neck Cancers

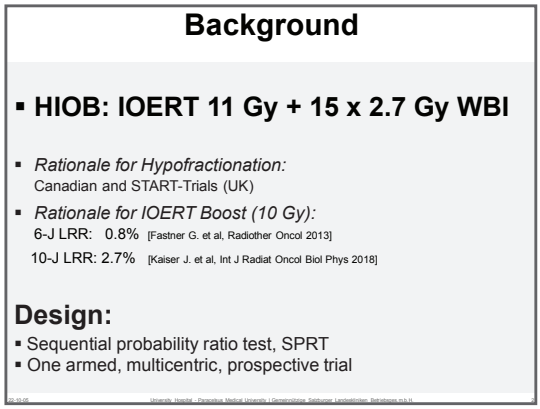


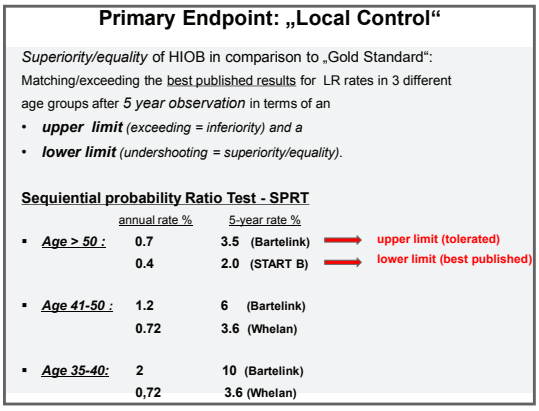


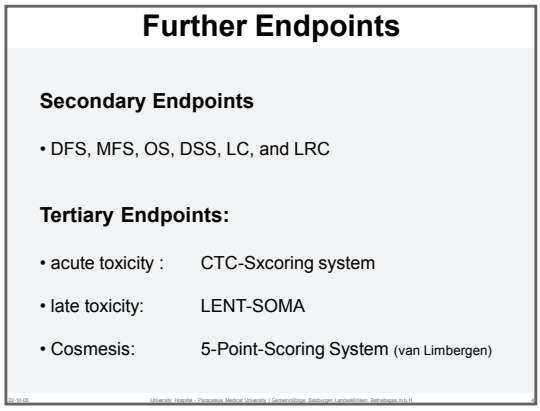
Speaker presentations

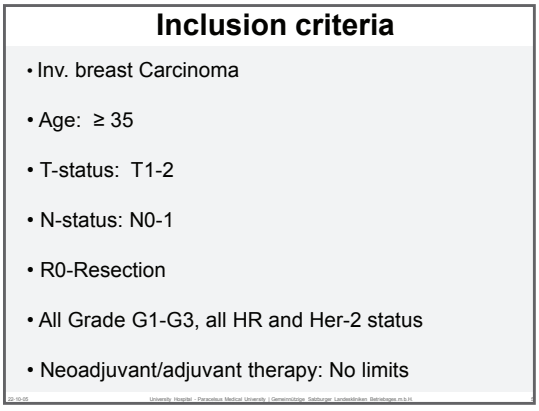
HIOB Trial: Hypofractionated Whole Breast Irradiation and Electron IORT Boost in Early-Stage Breast Cancer

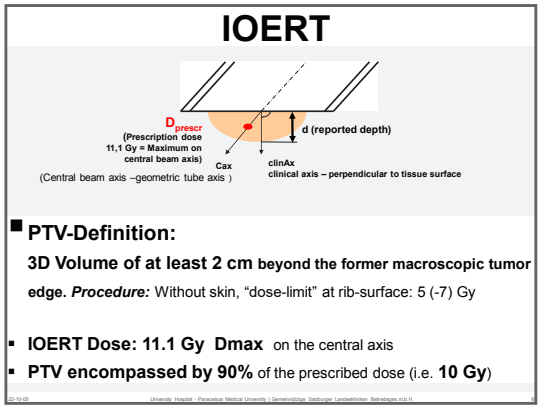
Gerd Fastner, MD
Professor
Paracelsus Medical University Clinics
Salzburg, Austria











Speaker presentations

HIOB Trial: Hypofractionated Whole Breast Irradiation and Electron IORT Boost in Early-Stage Breast Cancer

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)**

CONSORT-diagram:

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Eligible patients: N= 1445

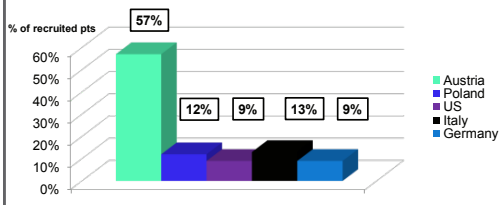
Excluded: N= 326

Analysis (04/20): N= 1119

- „per protocol“: N=758
- „ITT-criteria“: N=361

Recruiting centres: 18

- **Austria:** 3
- **Poland:** 1
- **USA:** 2
- **Italy:** 9
- ***Germany:*** 3



Patients and FUP: N= 1119

- **Age groups**: 35 - 40: n=45 4%
  41 – 50: n=285 **26%**
  > 50: n=789 70%

Patients in FUP: **n=1104**

- 1 year: 1049 95 %
- 3 years: 863 78 %
- **5 years: 518 47 %**
- **6 years: 348 31 %**
- 7 years: 98 9 %
- 8 years: 33 3 %
- 9 years: 1
- FUP (Months): **Median 50 (0.7 – 104)**

Age (y)	n (%)	Histology	n
35-40	45 (4)	IDC/NST	870 (78)
41-50	285 (26)	ILC	103 (9)
> 50	789 (70)	mixed	88 (8)
T-Stage		others	58 (5)
1	949 (85)	EIC-Status	
2	145 (13)	negative	970 (87)
x	5 (0.5)	positive	149 (13)
0	20 (1.5)	Grading	
		G1	268 (24)
N- Stage		G2	629 (56)
0	984 (88)	G3	168 (15)
1	130 (11.5)	Gx	54 (5)
X	5 (0.5)	HER2-Status	
R-Status (mm)	5 (0.1-80)	neg	961 (85.9)
KI67 (%)		pos	157 (14)
<20	487 (44)	ns	1 (0.1)
≥ 20	494 (44)	HR- Status	
ns	138 (12)	neg	98 (8.9)
Multifocality		pos	1020 (91)
no	979 (87)	ns	1 (0.1)
yes	140 (13)		

Age (y)	n (%)	Histology	n
35-40	45 (4)	IDC/NST	870 (78)
41-50	285 (26)	ILC	103 (9)
> 50	789 (70)	mixed	88 (8)
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KI67 (%)		pos	157 (14)
<20	487 (44)	ns	1 (0.1)
≥ 20	494 (44)	HR- Status	
ns	138 (12)	neg	98 (8.9)
Multifocality		pos	1020 (91)
no	979 (87)	ns	1 (0.1)
yes	140 (13)		

Speaker presentations

HIOB Trial: Hypofractionated Whole Breast Irradiation and Electron IORT Boost in Early-Stage Breast Cancer

Systemic treatment / IOERT parameters

ET:	N=983, 88%
adj.CT +/- Tra +/- Per:	N=213, 21%
NACT +/- Tra +/- Per:	N=53, 5%
ET/CT:	N=183 (16%)
Tra/+-Per:	N=61 (5.5%)

Tube diameter cm:	Med. 6 cm (4-8)
Lead shielding:	yes: n=268 (24%) no: n=851 (76%)
Electron energy MeV:	Med. 9 (4-15)
V 90 ml:	Med.44 (4-104)
Breast volume (PTV) ml:	Med. 1350 (233-2457)

Clinical Results:

- ***2 (0.2%) In-Breast recurrences (IQ): > 50 y***
- ***1 (0.1%) Reg. recurrences: 1 (Scl)***

➢ ***Metastases: n=23 (2%)***
- *Breast cancer: n=17 (1.5%)*
- *Secondary cancer: n= 6 (0.5%)*

➢ ***Died: n=25 (2%)***
- *Breast cancer: n=6 (0,5%)*
- *Secondary cancer: n=8 (0.5%)*
- *others: n=11 (1%)*

➢ ***Secondary cancers: 49 (4%)***
- *contralateral breast cancer: n=17 (1.5%)*
- *others: n=32 (3%)*

Treatment tolerance

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Acute toxicity

Evaluation:	*n=1118*	*n=1103*
CTC	*WBI – End*	*4 weeks post WBI*
CTC 0/I (no/faint reaction):	99.7 %	99.3%
CTC II/III(moderate/moist desquamation):	0.3 %	0.7%

CTC III	**WBI-End**	**4 weeks post WBI**
Pats	1	0
CTC IV	0	1*

*: prolonged wound healing ipsilat. axilla (not in the IORT field)

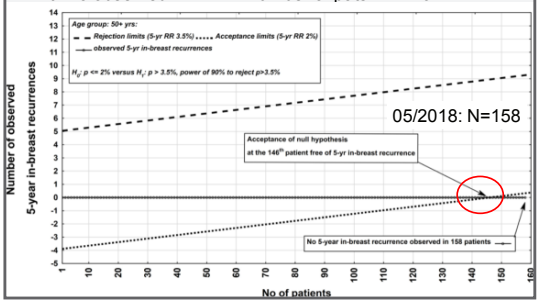
Late toxicity (since months 4/5, annually): Mean values (ranges)

G0/2:	99.6% (99.3-100)
G3/4**:	0.3% (0-1.9)

**:3 patients with pain G4:
Pat.1: until year 2
Pat.2: In the course of metastases
Pat. 3: G3 fibrosis – lost to FUP

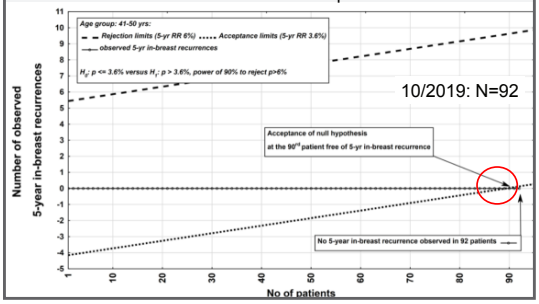
LRR: Age group > 50 years

5-year LRR-assumptions (SPRT): Upper benchmark 3.5% (EORTC-Boost-trial), lower benchmark 2.0% (START B)
- With no observed LR: Min. number of pats: N=146



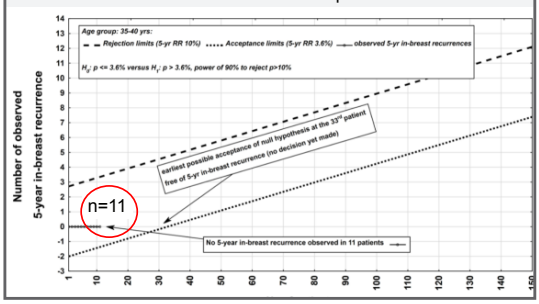
LRR: Age group 41 - 50 years

5-year LRR-assumptions (SPRT): Upper benchmark 6% (EORTC-Boost-trial), lower benchmark 3.6% (Whelan et al)
- With no observed LR: Min. number of pats: N=90



LRR: Age group 35 - 40 years

5-year LRR-assumptions (SPRT): Upper benchmark 10% (EORTC-Boost-trial), lower benchmark 3.6% (Whelan et al)
- With no observed LR: Min. number of pats: N=33



Speaker presentations

HIOB Trial: Hypofractionated Whole Breast Irradiation and Electron IORT Boost in Early-Stage Breast Cancer

Secondary endpoints

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Act. 4-year rates (95% CI)

DFS: 97.8% (96.9-98.8)

MFS: 98.1% (97.2-99)
DSS: 99.4% (98.8-99.9)
OS: 97.9% (96.6-98.9)
LC: 100%
LRC: 99.7% (99.4-100)

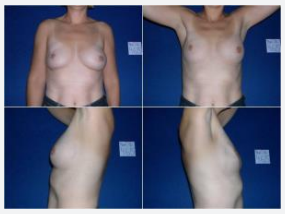
Cosmesis evaluation:

Rep. Photodocumentation, Double evaluation: Doctor/Patient

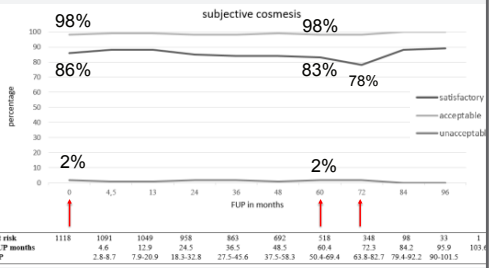
Qualitative 5-Point-Score Van Limbergen E 1989

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

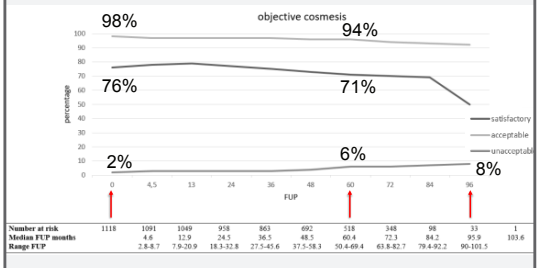


„Subjective“ breast cosmesis



Number at risk	1118	1091	1049	958	863	692	518	348	98	33	1
Median FUP months		4.6	12.9	24.5	36.5	48.5	60.4	72.3	84.2	95.9	103.6
Range FUP		2.8-8.7	7.9-20.9	18.3-32.8	27.5-45.6	37.5-58.3	50.4-69.4	63.8-82.7	79.4-92.2	90-101.5	

„Objective“ breast cosmesis

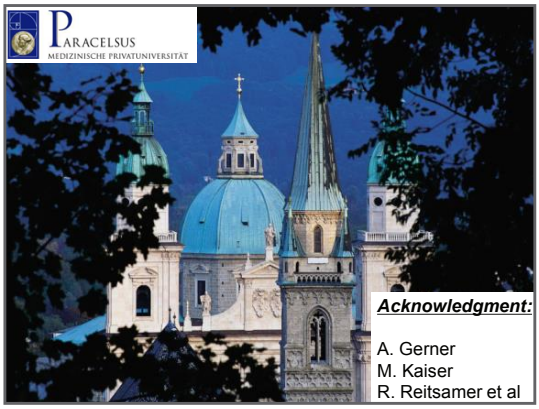


Number at risk	1118	1091	1049	958	863	692	518	348	98	33	1
Median FUP months		4.6	12.9	24.5	36.5	48.5	60.4	72.3	84.2	95.9	103.6
Range FUP		2.8-8.7	7.9-20.9	18.3-32.8	27.5-45.6	37.5-58.3	50.4-69.4	63.8-82.7	79.4-92.2	90-101.5	

Conclusion

- Prim. endpoint 5-year-LRR:
  - *Superiority for **AG 41-50, > 50 J***
  - *No decision AG 35-40 J*
- Acute- and late toxicity: low
- (very) acceptable (subj./obj.) Breast cosmesis

PARACELSUS MEDIZINISCHE PRIVATUNIVERSITÄT



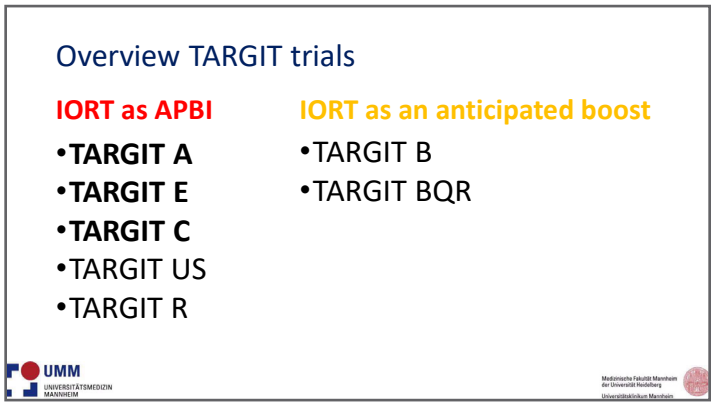
Acknowledgment:

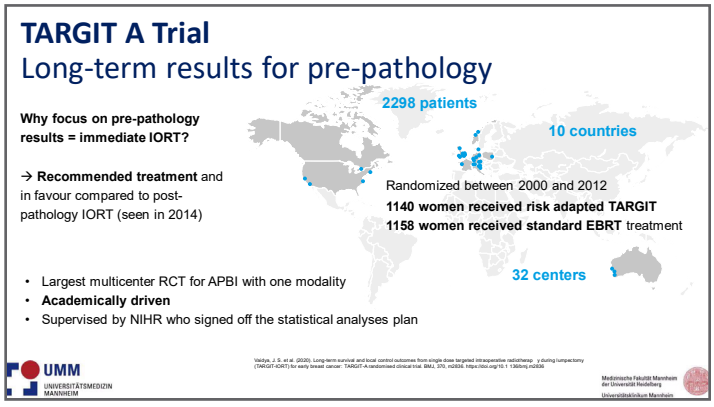
A. Gerner
M. Kaiser
R. Reitsamer et al

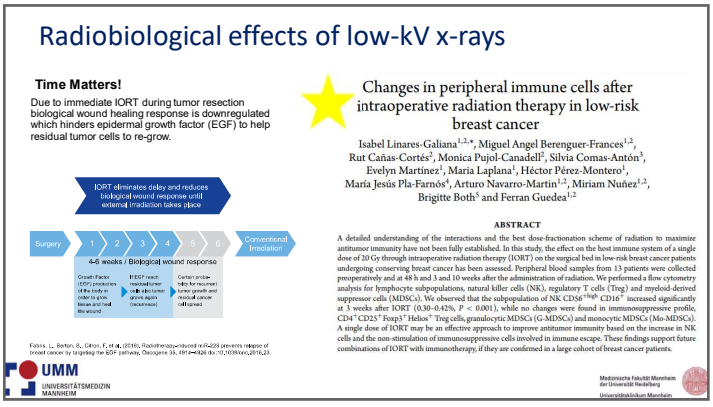
Speaker presentations

TARGIT A, C, and E Trials in Breast Cancer (pre-recorded)

Elena Sperk, MD
Professor
Department of Radiation Oncology
University Medical Center
Mannheim, Germany







Speaker presentations

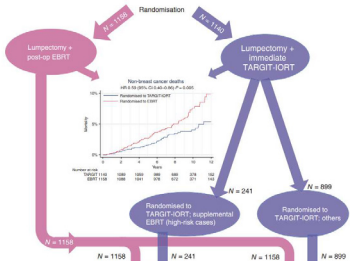
TARGIT A, C, and E Trials in Breast Cancer (pre-recorded)

TARGIT A Trial

Experimental arm:

IORT n=899
IORT + EBRT n=241 27%

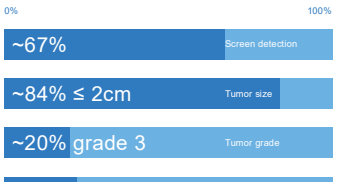
→ Planned risk adapted treatment based on final histopathology
→ **Safety:** No risk for patient or physician because same dose for APBI and boost (20Gy)



Vaidya J et al 2021 Br J Cancer – New clinical and biological insights from the international TARGIT-A randomised trial of targeted intraoperative radiotherapy during lumpectomy for breast cancer

TARGIT A Trial
Long-term results

Patient Characteristics



Vaidya, J. S. et al. (2020). Long-term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial. BMJ, 370, m2836. https://doi.org/10.1136/bmj.m2836

TARGIT A Trial
Long-term results

Non-inferiority in terms of local control

Primary Outcome:

Local recurrence rate @ 5 years

Local recurrence rates at 5 years complete follow up:

TARGIT-IORT	EBRT
2.11%	0.95%

Difference **1.16%** (90% CI 0.32 to 1.99)

Difference was less than **2.5%** (pre-specified non-inferiority margin)

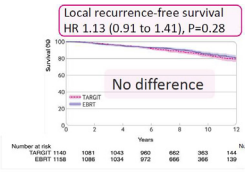
Non-inferiority of TARGIT-IORT to EBRT confirmed

Vaidya J et al 2020 BMJ – Long-term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT –A randomised clinical trial

TARGIT A Trial

Results

Long-term outcomes of the TARGIT-A trial



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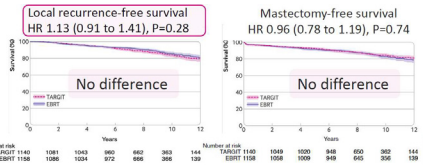
TARGIT A Trial

Results

Long-term outcomes of the TARGIT-A trial



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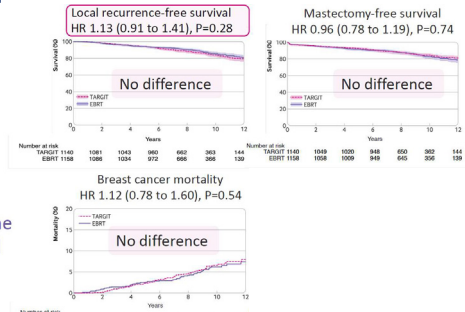
TARGIT A Trial

Results

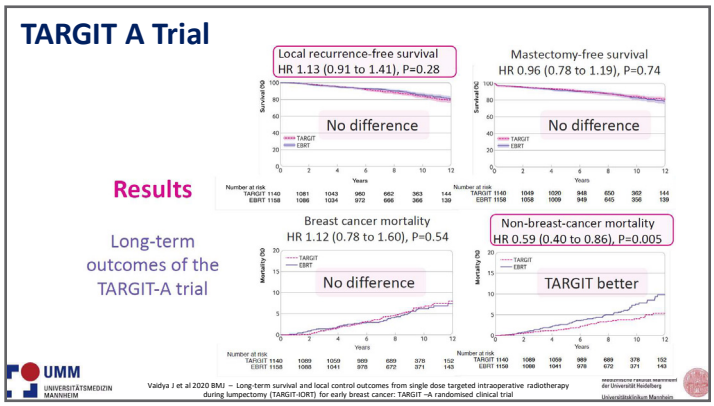
Long-term outcomes of the TARGIT-A trial

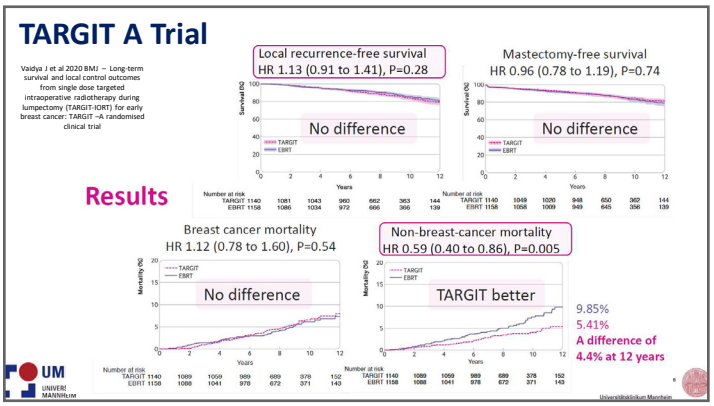


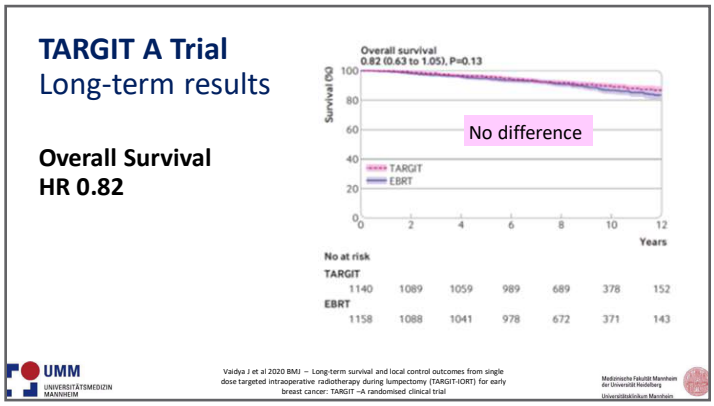
Vaidya J et al 2020 BMJ – Long-term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT –A randomised clinical trial

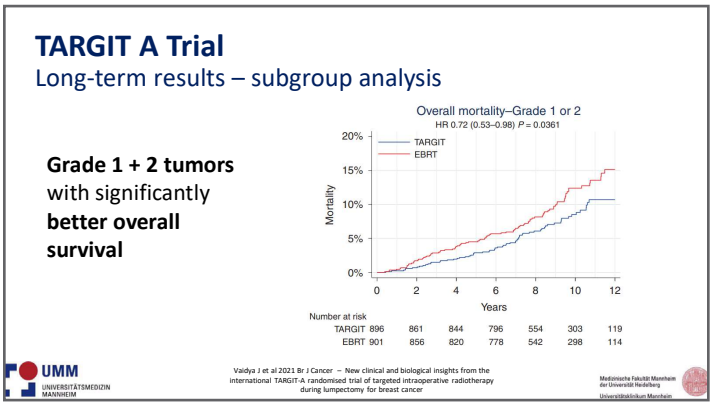
Speaker presentations

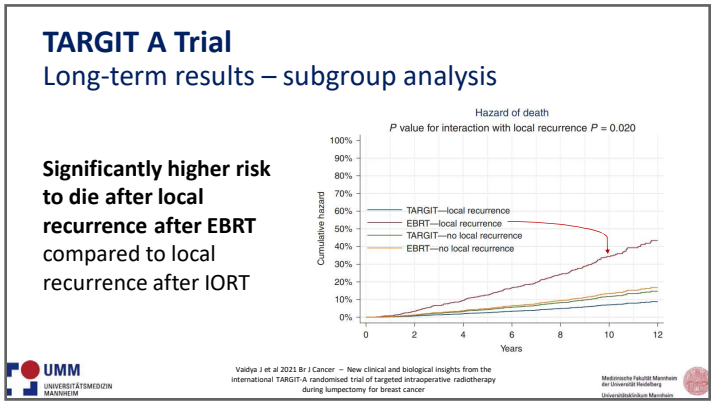
TARGIT A, C, and E Trials in Breast Cancer (pre-recorded)

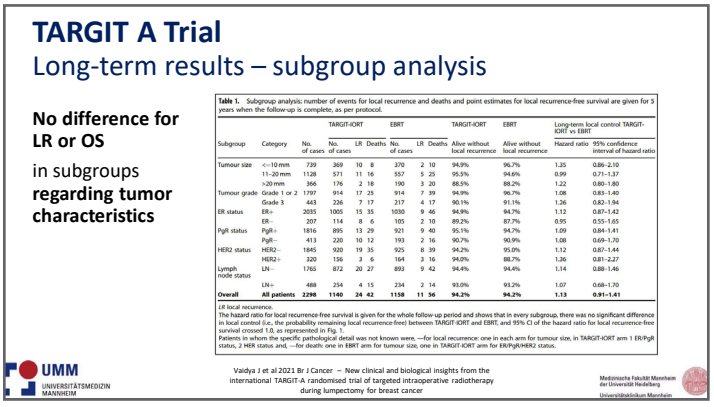












TARGIT A, C, and E Trials in Breast Cancer (pre-recorded)

TARGIT A Trial
Long-term results – subgroup analysis

No difference for LR or OS

in subgroups **regarding RT modality**

Table 2. Total number of patients, total numbers in each arm and proportion of patients receiving supplemental EBRT among those randomised to receive TARGIT-IORT.

	Total no.	Allocated TARGIT-IORT	IORT + EBRT	IORT		Allocated EBRT
		Characteristics of 1140 patients in the TARGIT arm	Characteristics of 241 patients allocated TARGIT who received supplemental EBRT	Characteristics of 899 patients allocated TARGIT who did not receive supplemental EBRT	Proportion (%) in TARGIT arm receiving supplemental EBRT	Characteristics of 1158 patients in the EBRT arm
Overall	**2298**	**1140**	**241**	**899**		**1158**
Local recurrences (invasive/DCIS/ unknown) cumulative incidence		15/6/3 1.3%/0.5%/0.3%	2/1/0 0.8%/0.4%/0%	13/5/3 1.4%/0.6%/0.3%	–	9/1/1 0.8%/0.1%/0.1%
Cumulative incidence of any type of local recurrence		24 2.11%	3 1.24%	21 2.35%		11 0.95%
Deaths (cumulative incidence)		42 (3.7%)	14 (5.8%)	28 (3.1%)	–	56 (4.8%)
Alive without local recurrence		94.15% (92.6–95.4)	93.46% (89.4–96.0)	94.33% (92.6–95.7)	–	94.19% (92.6–94.4)

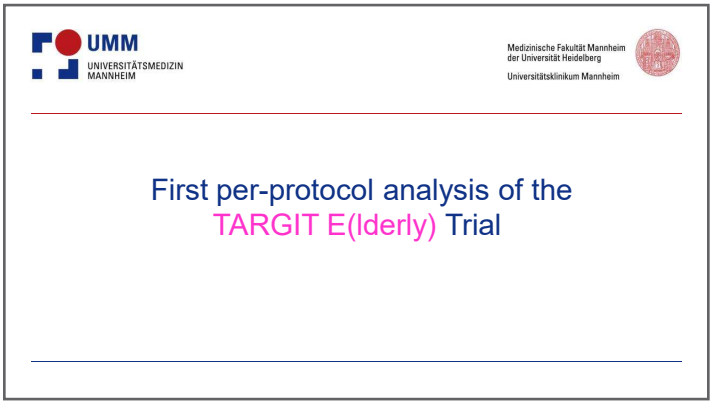
LRFS local recurrence-free survival.
Of the 1140 randomised to TARGIT-IORT, 241 received supplemental EBRT after TARGIT-IORT during lumpectomy. The local recurrence and mortality and local control values are at complete follow-up of 5 years.

Vaidya J et al 2021 Br J Cancer – New clinical and biological insights from the international TARGIT-A randomised trial of targeted intraoperative radiotherapy during lumpectomy for breast cancer

TARGIT A and other APBI trials

Trial name	Patient Characteristics	Follow-up (months)	PBI Treatment Technique	Local Recurrence (PBI vs. WBI)	Overall Survival (PBI vs. WBI)
Florence[1,2,4] n = 520	Grade 3 = 11.4% N0 = 85.6%	128.4	IMRT 5 fractions	3.7% vs. 2.5%	91.9% vs. 91.9%
Budapest[1,2] n = 258	Grade 3 = 0% N0 = 94.6%	122.4	Brachytherapy (HDR) 7 fractions	5.9% vs. 5.1%	82% vs. 80%
B-39 (NSBAP)[1,2] n = 4216	Grade 3 = NR pN0 = 65.0%	122	3D-Radiotherapy, Brachytherapy (HDR) Mammosite Balloon 10 fractions or 5-10 days	4.6% vs. 3.9%	90.6% vs. 91.3%
TARGIT-A[1,2,3] n = 2298	**Grade 3 = 20.1% N0 = 83.9%**	**102**	**IORT (50kV) 1 fraction**	**2.11% vs. 0.95%**	**92.0% vs. 90.0%**
GEC-ESTRO[1,2] n = 1184	Grade 3 = 8.4% N0 = 99.2%	79.2	Brachytherapy (HDR) ~8 fractions	1.4% vs. 0.9%	97.3% vs. 95.5%
IMPORT-LOW[1,2] n = 1343	Grade 3 = 9.5% N0 = 97.0%	72.2	IMRT 15 fractions	0.5% vs. 1.1%	94% vs. 94%
ELIOT[1,2] n = 1305	Grade 3 = 21.7% N0 = 73.4%	69.6	IOERT 1 fraction	4.4% vs. 0.4%	98.8% vs. 96.9%

1 Strnad, V., et al. (2020). DEGRO practical guideline for partial-breast irradiation. Strahlenther Onkol 196, 749–763. https:/ doi.org/10.1007/s00066-020-01610-z
2 Kocsis, Y., et al. (2019). Toxicity and clinical outcomes of partial breast irradiation compared to whole breast irradiation for early-stage breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat 175, 531–545. https://doi.org/10 .1007/s10549-019-05209-9
3 Vaidya, J. S. et al. (2020). Long-term survival and local control outcomes from single dose targeted intraoperative radiother apy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial. BMJ, 370, m2836. https://doi.o rg/10.1136/bmj.m2836
4 Meattini, I., et al. (2020). Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast C ancer: Long-Term Results of the Randomized Phase III APBI-IMPORT Fornence Trial

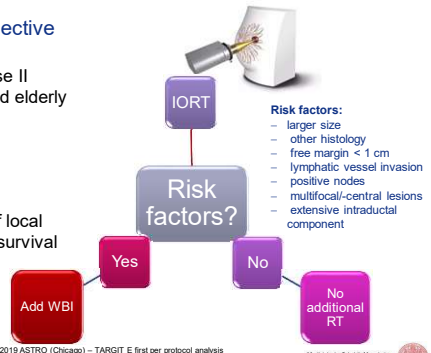


TARGIT E: Purpose/Objective

Single arm prospective phase II study to test APBI in selected elderly patients

Risk-adapted approach

First per protocol analysis of local recurrence rate and overall survival



Sperk et al 2019 ASTRO (Chicago) – TARGIT E first per protocol analysis
Priv.-Doz. Dr. med. Elena Sperk
22

TARGIT E: Inclusion/Exclusion criteria

Inclusion criteria
- ≥70 years
- cT1/2 (< 3.5 cm)
- cN0
- cM0
- invasive carcinoma (ductal)
- Informed consent

Exclusion criteria
- Extensive intraductal component

Sperk et al 2019 ASTRO (Chicago) – TARGIT E first per protocol analysis
Priv.-Doz. Dr. med. Elena Sperk
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TARGIT E: Materials/Methods

Number of centers: n=28 (Germany, France, Denmark, Switzerland)
Enrollment: February 2011 – September 2014
Treatment:
IORT with low-energy x-rays (INTRABEAM®) with 20Gy
+/- whole breast irradiation with a standard dose of 46-50Gy

Primary outcome: **local recurrence rate** measured at 2.5,5 and 7.5 years using the Kaplan-Meier method. Termination due to futility was deemed necessary in case local relapse rates exceeded 3/4/6% at 2.5/5/7.5 years.

Secondary outcome: overall survival

Sperk et al 2019 ASTRO (Chicago) – TARGIT E first per protocol analysis
Priv.-Doz. Dr. med. Elena Sperk
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Speaker presentations

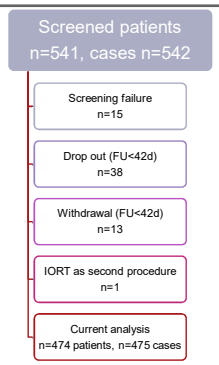
TARGIT A, C, and E Trials in Breast Cancer (pre-recorded)

TARGIT E: Results

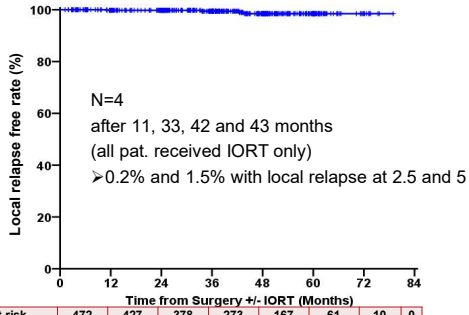
Applied radiation:
73% IORT only
21% IORT + WBI
5% WBI only
1% surgery only/no radiation

Median follow-up: 3 years (range 2 – 79 months)
Median age: 74 years

Risk factors:
N+: 14.6%, >T1: 9.7%, G3: 10.1%, R1: 5%



TARGIT E: Primary outcome



N=4
after 11, 33, 42 and 43 months
(all pat. received IORT only)
➢0.2% and 1.5% with local relapse at 2.5 and 5 years

At risk	472	427	378	273	167	61	10	0
%	100	99.8	99.8	99.4	98.5	98.5	98.5	-

TARGIT E: Patient characteristics with local recurrence

Patient	Age at enrollment	Side of primary	Clear margins	Adjuvant Chemother. (all Her2neu negative)	Adjuvant Endocrine therapy	Tumour size	Multifocal/ -centric	Intra-ductal	Lymph vessel invasion	Grade	EIC	Positive nodes
1	84	Left	Yes	Unknown	**No (negative)**	14	No	Yes	No	**3**	No	No
2	75	Left	Yes	No	Yes	8	No	Yes	No	2	Unknown	**Yes**
3	71	Right	**No**	No	Yes	**24**	Unknown	Yes	No	2	Unknown	Unknown
4	70	Left	Yes	No	**No (negative)**	7	No	Yes	No	**3**	No	No

All patients with IORT as APBI with 20 Gy

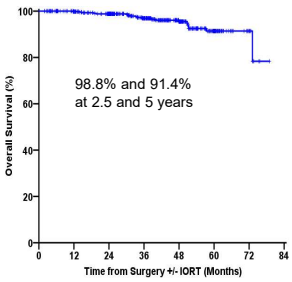
TARGIT E: Secondary outcome

Overall survival

N=20

3 breast-cancer-related deaths

17 non-breast-cancer-related deaths



At risk	475	433	384	279	175	61	11	0
%	100	99.8	98.8	96.9	95.5	91.4	91.4	-

TARGIT E: Conclusion

- The first per protocol analysis of the prospective TARGIT E trial shows that **local relapse rates of 0.2% at 2.5 years (1.5% at 5 years) are far below the predefined stopping rules** (3/4/6% at 2.5/5/7.5 years)
- The current results therefore support the **risk-adapted approach of accelerated partial breast radiotherapy (APBI) in selected patients**

UMM UNIVERSITÄTSMEDIZIN MANNHEIM

Medizinische Fakultät Mannheim der Universität Heidelberg
Universitätsklinikum Mannheim

First per-protocol analysis of the TARGIT C(onsolidation) Trial

Speaker presentations

TARGIT A, C, and E Trials in Breast Cancer (pre-recorded)

TARGIT C: Purpose/Objective

Single arm prospective phase IV study to test APBI in selected patients

Risk-adapted approach

First per-protocol analysis after
100 included patients

TARGIT C: Inclusion/Exclusion criteria

Inclusion criteria

- ≥50 years
- cT1 (< / = 2 cm)
- cN0
- cM0
- invasive carcinoma (ductal)
- Positive hormone receptors
- Informed consent

Exclusion criteria

- Multifocal lesions
- Extensive intraductal component

TARGIT C – Current state

Number of centers: n=5
(**Germany**: Mannheim & Kassel, **France**: Montpellier, Lyon & Toulouse)
Enrollment: October 2014 – March 2021, n=388
Treatment: IORT with low-energy x-rays (INTRABEAM®) with 20Gy
+/- whole breast irradiation with a standard dose of 46-50Gy
Primary outcome: **local recurrence free rate** using the Kaplan-Meier method

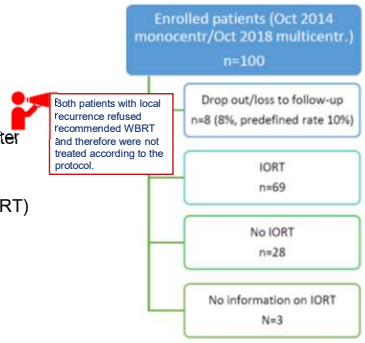
Predefined parameter for first safety analysis was a local relapse free rate of at least 98.45% after 12 months with a lower confidence interval of 97%.

Secondary outcome: overall survival, other oncological outcome, toxicity

TARGIT C: Results

Median follow-up:
12 months (range 0 – 60 months)

→ n=1 local recurrence (17 months after IORT)
→ n=1 synchronous contralateral and local recurrence (3 months after IORT)
→ no ipsilateral in-breast recurrences
→ no metastasis
→ no deaths
→ no grade IV/V toxicities



TARGIT C: Conclusion/Summary

Actuarial local relapse free rate was 98.9% at 12 months in all included patients and 100% in patients treated according to the protocol.

The first per protocol analysis of the prospective TARGIT C trial shows that local relapse free rate at 12 months is within the predefined range, especially for patients treated according to the protocol. The current results therefore support the risk-adapted approach of accelerated partial breast radiotherapy (APBI) in selected patients.

Summary

- Very low recurrence rates in elderly patients (**TARGIT E**)
- First per-protocol analysis of the first 100 patients in **TARGIT C** show good local control within the range
- Long-term outcome from **TARGIT A** confirm non-inferiority of risk-adapted TARGIT –IORT in early breast cancer patients and show better OS

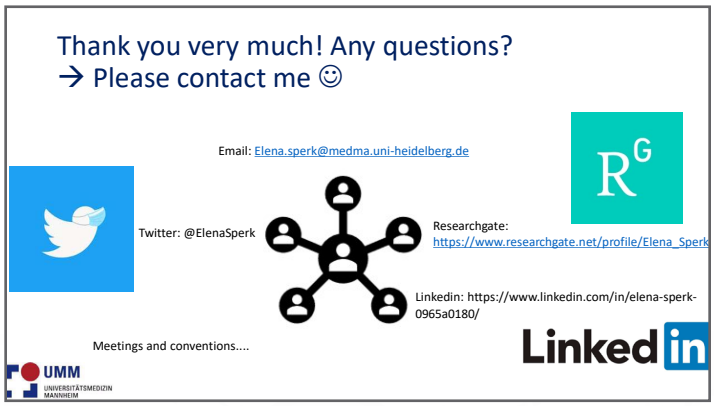
….. and Conclusion

TARGIT-IORT means

- having **only as much RT as needed based on final histopathology** and
- **being longer alive**

Speaker presentations

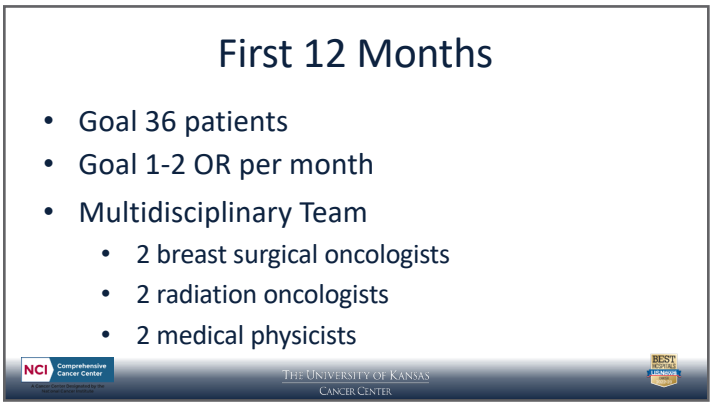
TARGIT A, C, and E Trials in Breast Cancer (pre-recorded)

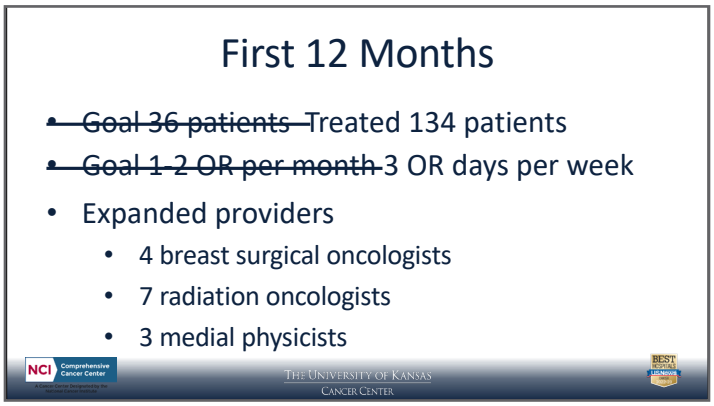


Speaker presentations

Surgical Considerations in Incorporating IORT for Patients with Breast Cancer (pre-recorded)

Kelsey Larson, MD, FACS
Assistant Professor
Department of Surgical Oncology
University of Kansas
Kansas City, Kansas, United States





Speaker presentations

Surgical Considerations in Incorporating IORT for Patients with Breast Cancer (pre-recorded)

Starting Program

Multidisciplinary Champions

Narrow Focus

Defined Vision

Starting Program & Gaining Momentum

- Approach 1st level Stakeholders
  - Chairs, cancer center leadership, patient advisory board/advocates
- Encourage Buy-In Clinical Team
- Patient focus, clinical outcomes, financials

Gaining Momentum - Center

- Develop center policy
  - Patient selection criteria & provider credentialing requirements
- Radiation Safety Officer
- Prior Authorization, Billing/Coding, Reimbursement Leadership

Gaining Momentum – Provider Team

- Everyone learned every role
- Assign who will own each role
  - Physicist – Move machine, QA, sources
  - R/O – Prescription, timeout, paperwork
  - Surgeon – Probes, ultrasound

Gaining Momentum - OR

- Anesthesia team education!
- Special shielding?
- Storage?
- SPD handling equipment?
- Training approach?

Preoperative Consultation

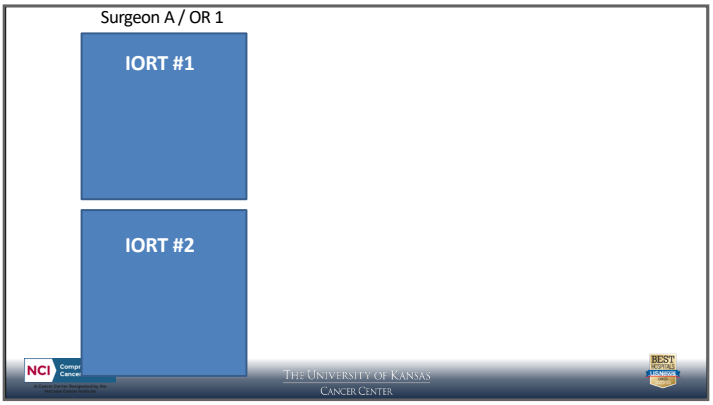
- Surgical oncologists screen (policy is key!)
  - Consent: Preparation of cavity for IORT
- Radiation oncology officially offer via consult
  - Consent: Administration of IORT treatment
  - Multidisciplinary Clinic *or* Save Consults
- Prior Authorization following radiation oncology consultation
  - Questions to radiation oncology

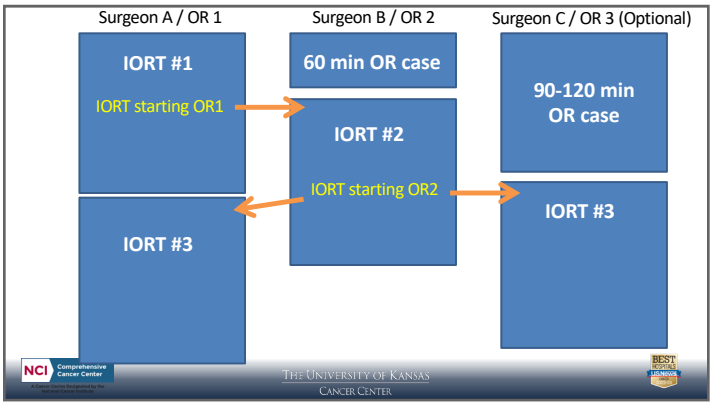
Speaker presentations

Surgical Considerations in Incorporating IORT for Patients with Breast Cancer (pre-recorded)

OR Scheduling

- Aim for 2-3 cases per day
  - Best: 2-3 surgeons in 2-3 OR
  - 1st case of the day
- Set days of the week/month
- Add 1 hour OR time / case initially
  - Drop to 30 min OR time / case with experience





Best Practices in OR

- Buddy in each role 1-2 cases
- Team introductions
- No students
- No breaks during case (90 min)
- Reminder sterility practices non-surgeons

Surgical Approach

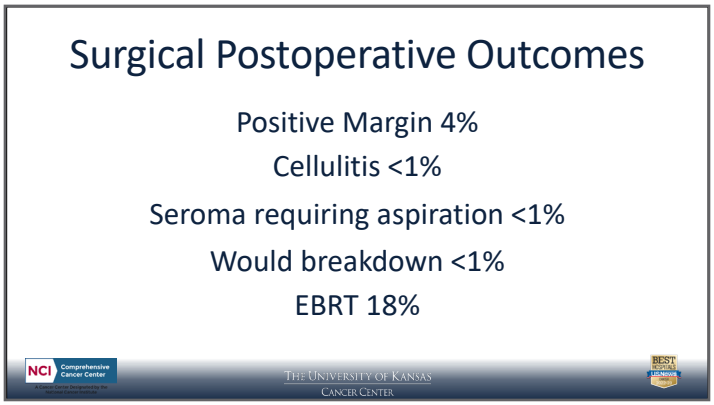
- Precise localization
- Incision planning
  - Tunnel distance versus device reach
  - Distance under skin / to chest wall
- Controlling cavity size

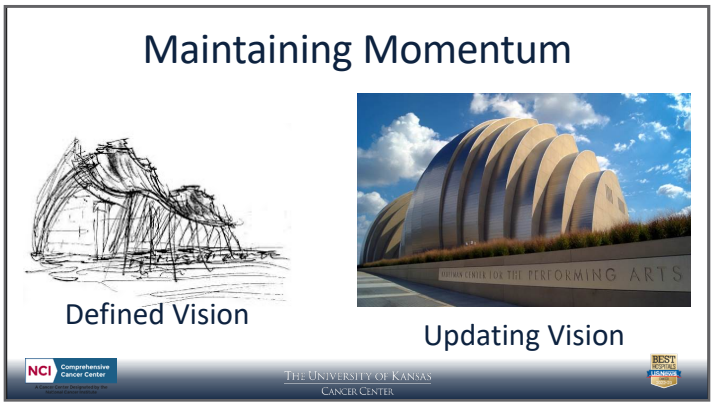
OR Workflow

- Intraoperative Pathology
  - SLN frozen?
  - Routine shave margins?
  - Gross margin evaluation?
- Strict timeouts
  - Pre-incision + probe selection + confirm probe selection + everyone out of room + prior to starting radiation treatment

Speaker presentations

Surgical Considerations in Incorporating IORT for Patients with Breast Cancer (pre-recorded)

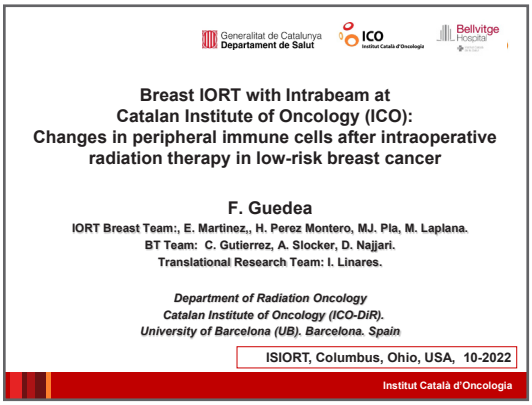


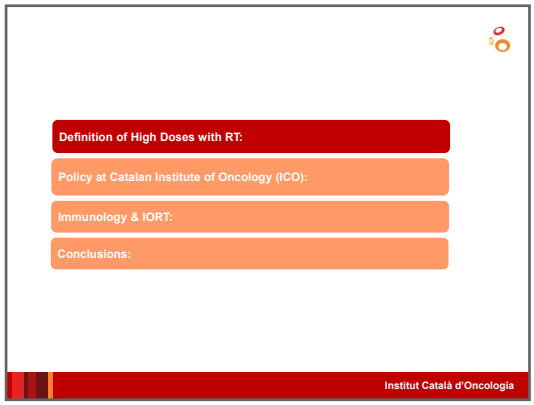


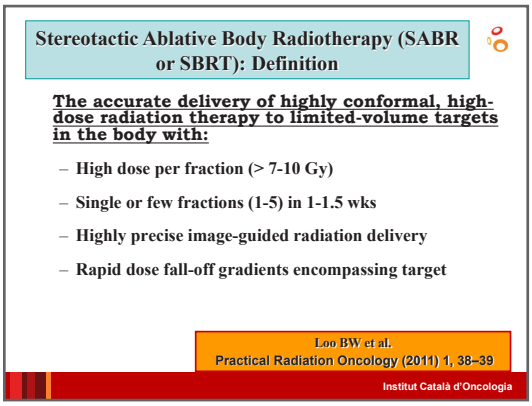
Speaker presentations

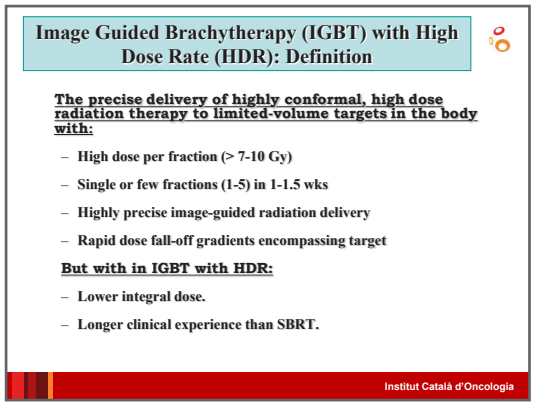
Changes in Peripheral Immune Cells After Intraoperative Radiation Therapy in Low-Risk Breast Cancer

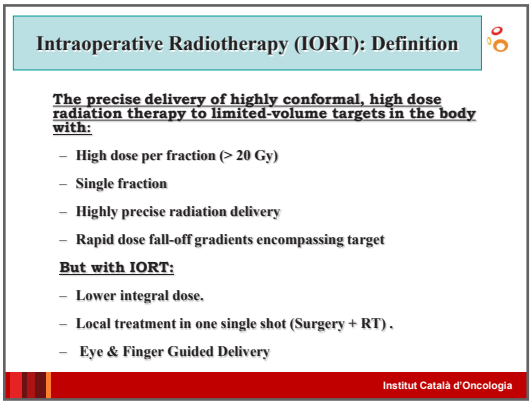
Ferran Guedea, MD
Chair
Department of Radiation Oncology
Institut Català d'Oncologia
Barcelona University
Barcelona, Spain

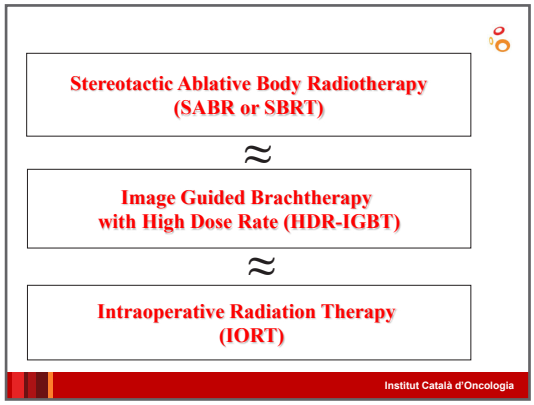






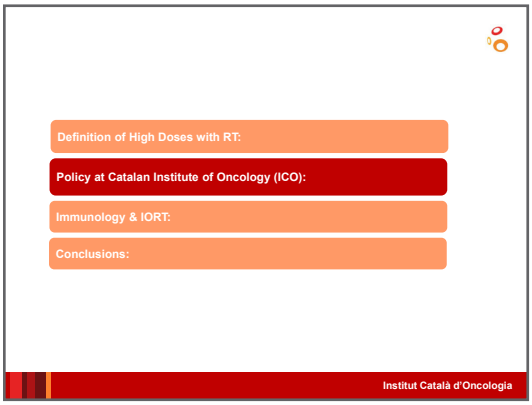


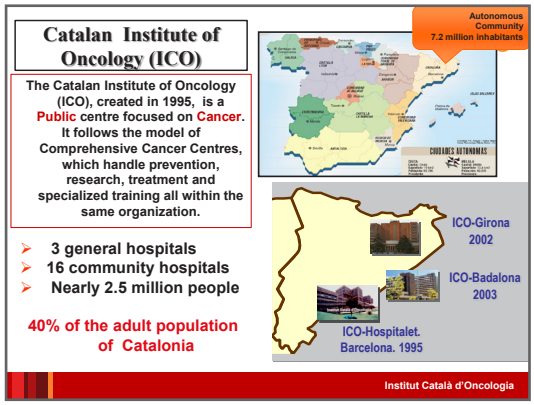


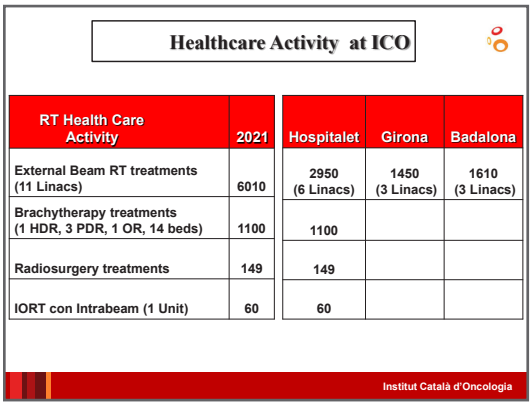


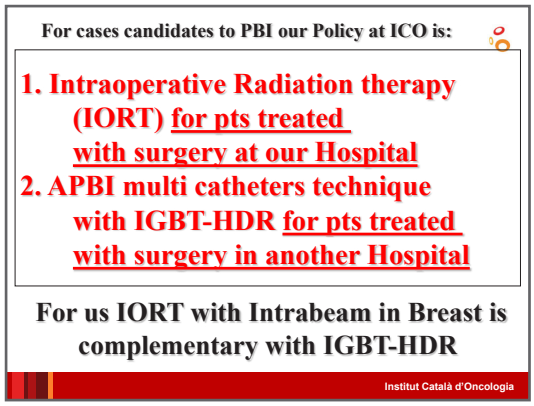
Speaker presentations

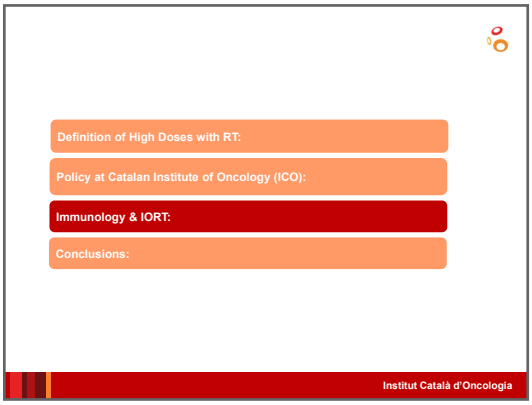
Changes in Peripheral Immune Cells After Intraoperative Radiation Therapy in Low-Risk Breast Cancer

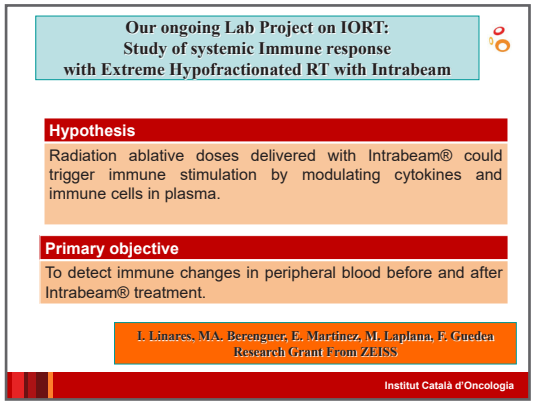






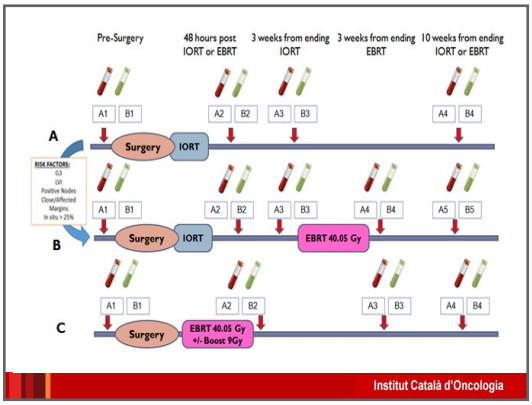


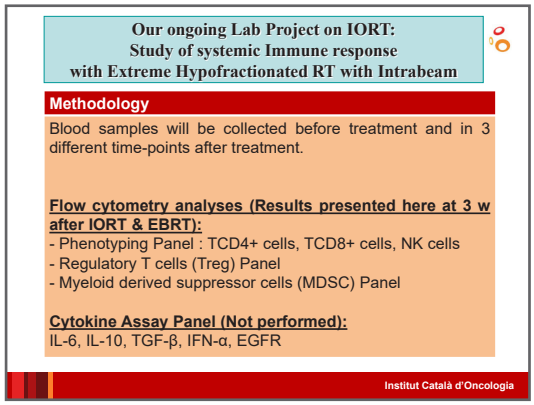


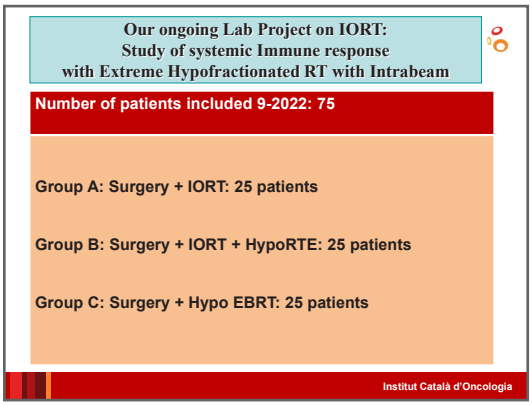


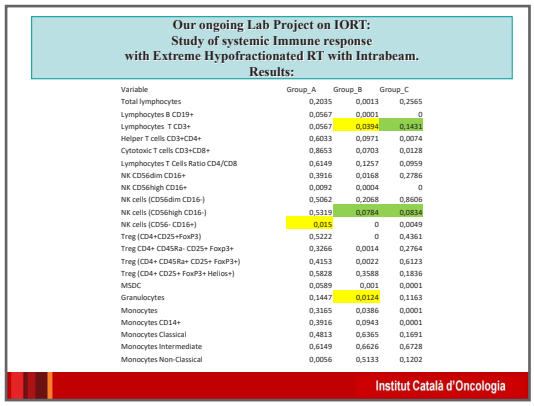
Speaker presentations

Changes in Peripheral Immune Cells After Intraoperative Radiation Therapy in Low-Risk Breast Cancer

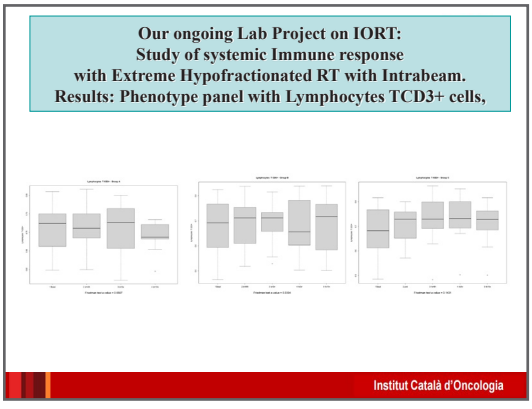


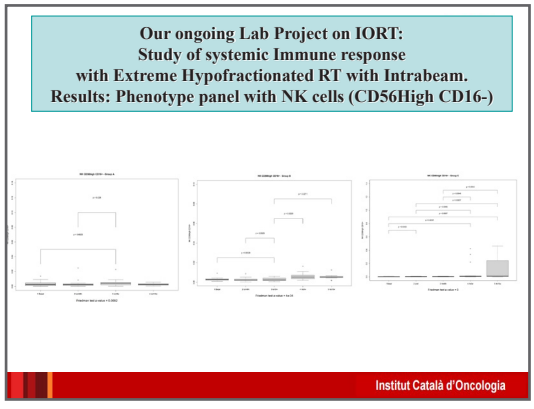






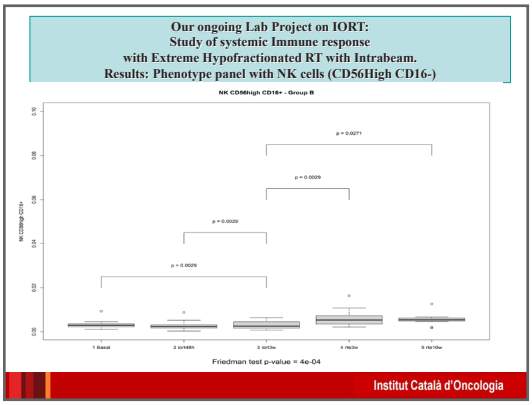
Variable	Group_A	Group_B	Group_C
Total lymphocytes	0,2035	0,0013	0,2565
Lymphocytes B CD19+	0,0567	0,0001	0
Lymphocytes T CD3+	0,0567	0,0394	0,1431
Helper T cells CD3+CD4+	0,6033	0,0971	0,0074
Cytotoxic T cells CD3+CD8+	0,8653	0,0703	0,0128
Lymphocytes T Cells Ratio CD4/CD8	0,6149	0,1257	0,0959
NK CD56dim CD16+	0,3916	0,0168	0,2786
NK CD56high CD16+	0,0092	0,0004	0
NK cells (CD56dim CD16-)	0,5062	0,2068	0,8606
NK cells (CD56high CD16-)	0,5319	0,0784	0,0834
NK cells (CD56- CD16+)	0,015	0	0,0049
Treg (CD4+CD25+FoxP3)	0,5222	0	0,4361
Treg CD4+ CD45Ra- CD25+ Foxp3+	0,3266	0,0014	0,2764
Treg (CD4+ CD45Ra+ CD25+ FoxP3+)	0,4153	0,0022	0,6123
Treg (CD4+ CD25+ FoxP3+ Helios+)	0,5828	0,3588	0,1836
MSDC	0,0589	0,001	0,0001
Granulocytes	0,1447	0,0124	0,1163
Monocytes	0,3165	0,0386	0,0001
Monocytes CD14+	0,3916	0,0943	0,0001
Monocytes Classical	0,4813	0,6365	0,1691
Monocytes Intermediate	0,6149	0,6626	0,6728
Monocytes Non-Classical	0,0056	0,5133	0,1202

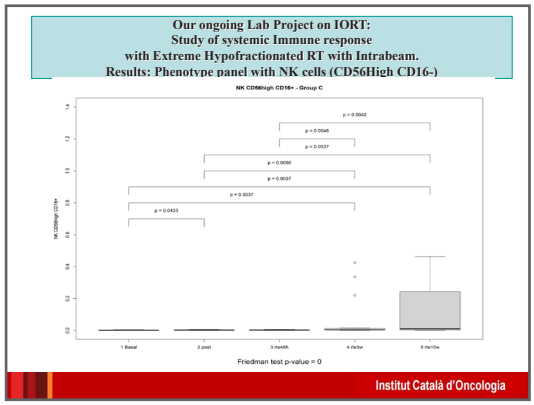


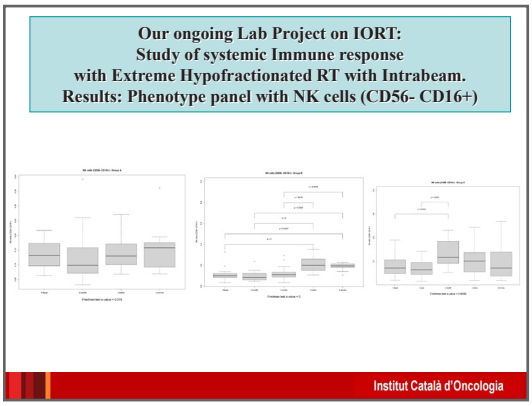


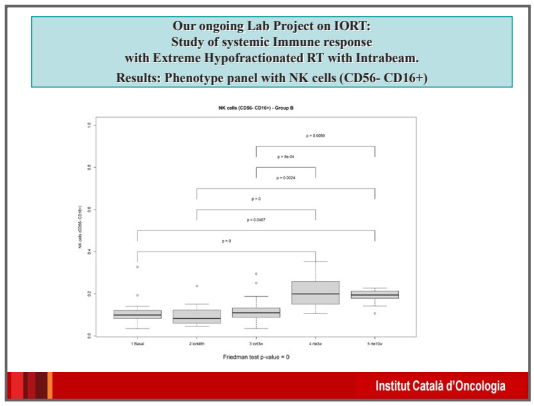
Speaker presentations

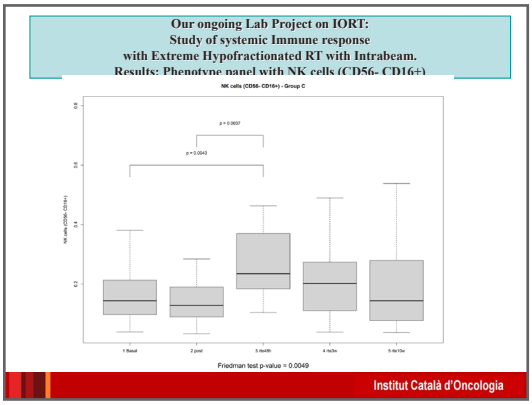
Changes in Peripheral Immune Cells After Intraoperative Radiation Therapy in Low-Risk Breast Cancer

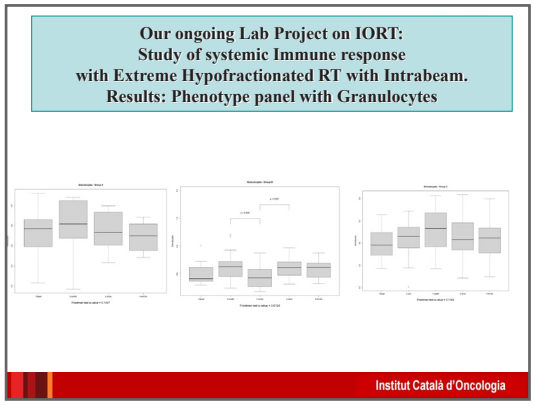






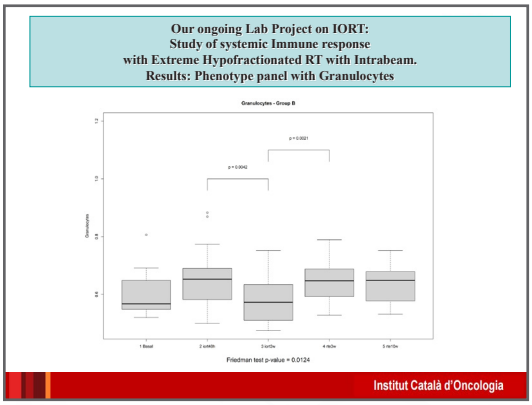


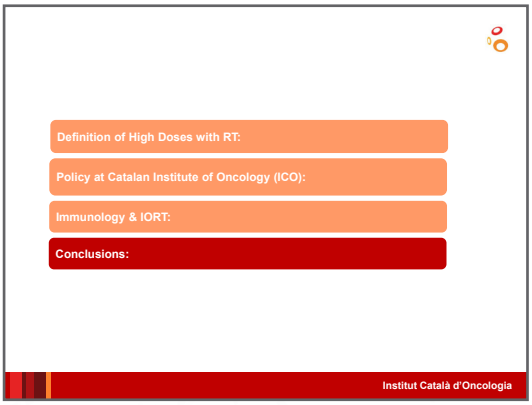


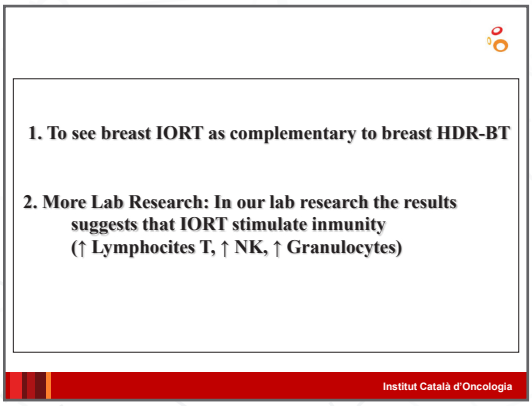


Speaker presentations

Changes in Peripheral Immune Cells After Intraoperative Radiation Therapy in Low-Risk Breast Cancer



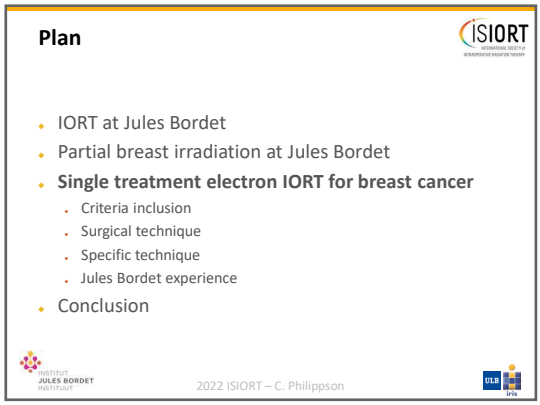


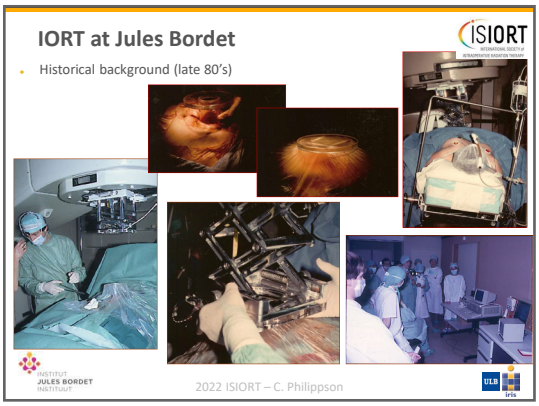


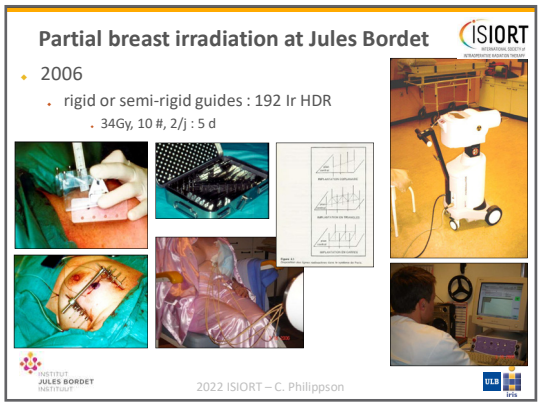
Speaker presentations

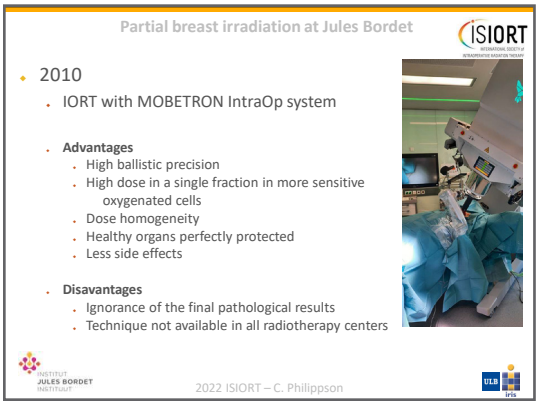
Single Treatment Electron IORT for Breast Cancer; The Jules Bordet Institute Experience

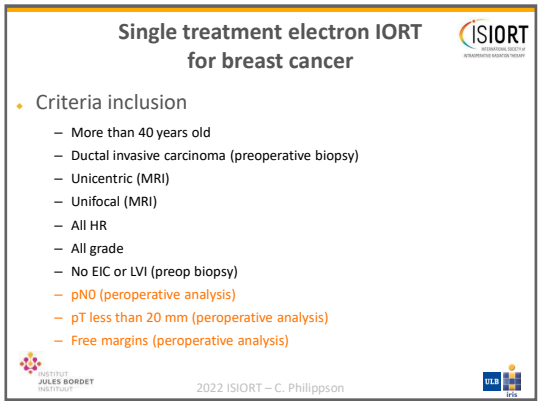
Catherine Philippson, MD
Department of Radiation Oncology
Institut Jules Bordet
Brussels, Belgium





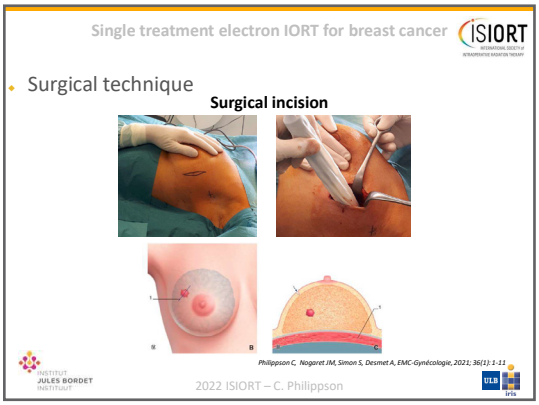


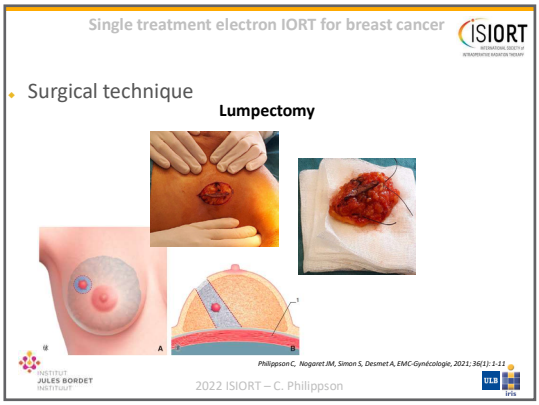


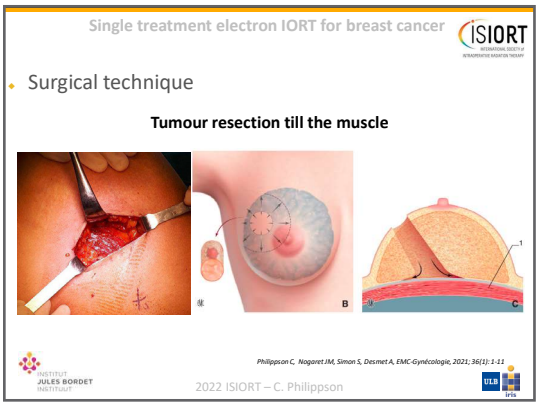


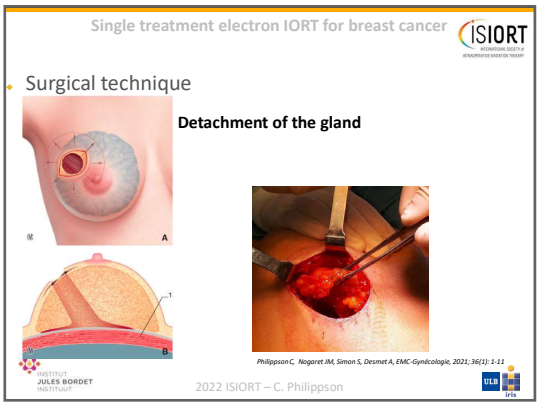
Speaker presentations

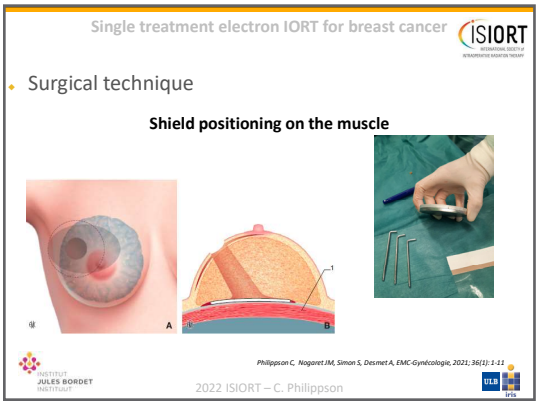
Single Treatment Electron IORT for Breast Cancer; The Jules Bordet Institute Experience

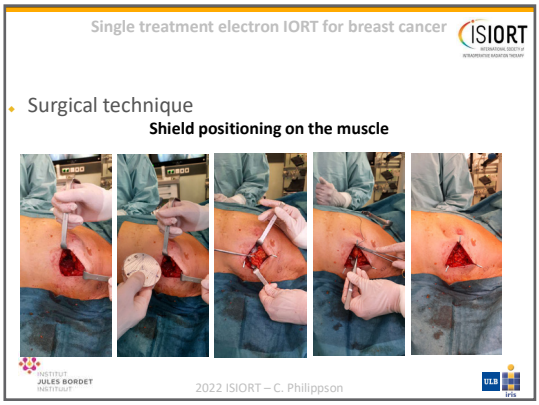






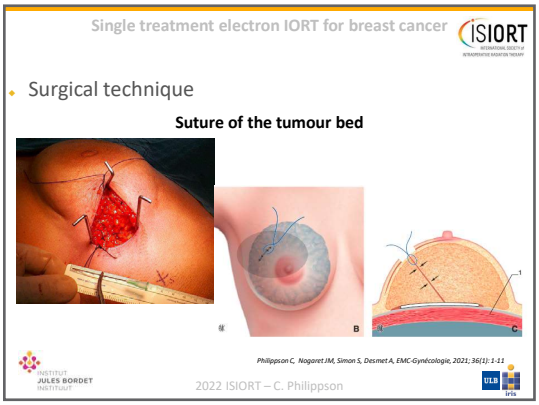


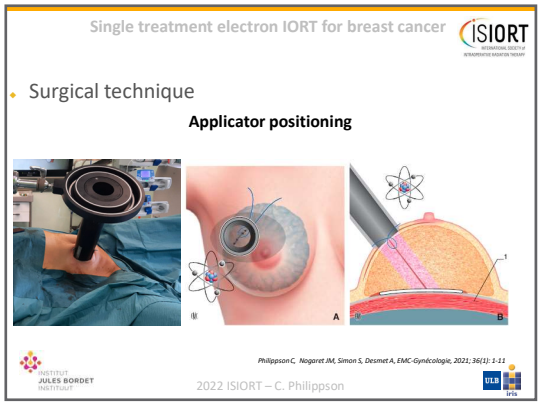


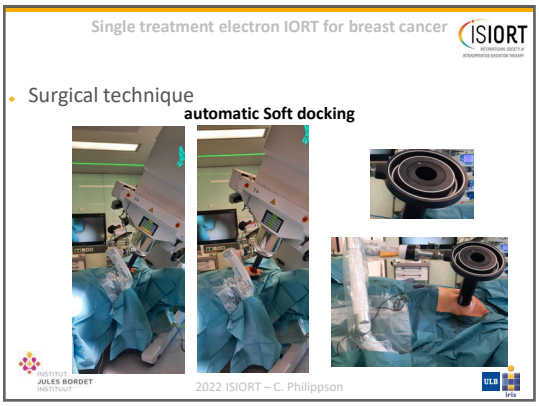


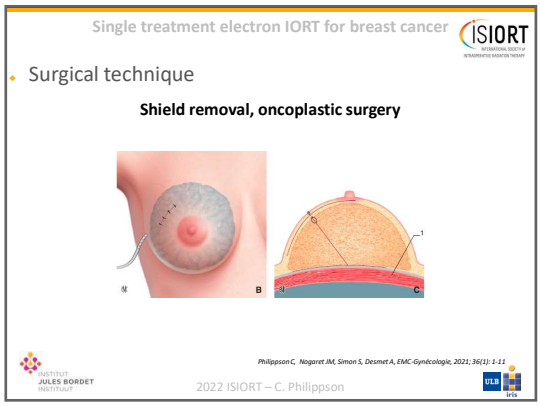
Speaker presentations

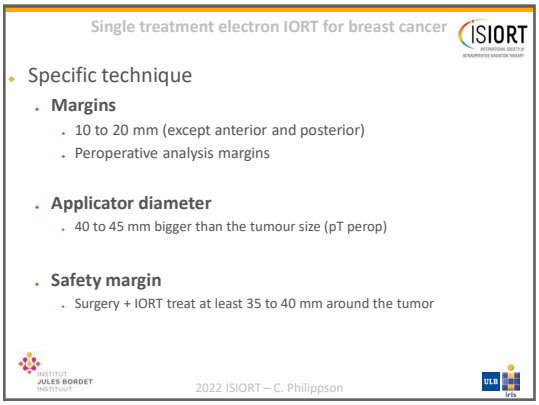
Single Treatment Electron IORT for Breast Cancer; The Jules Bordet Institute Experience

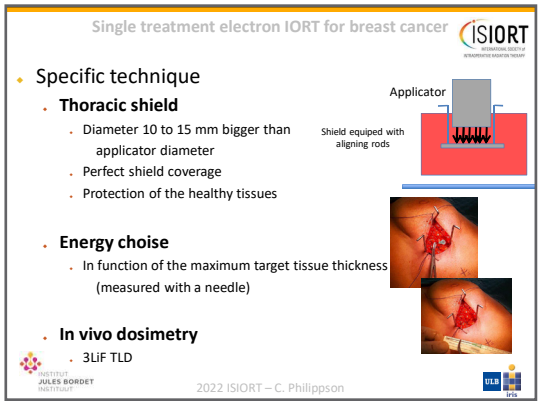






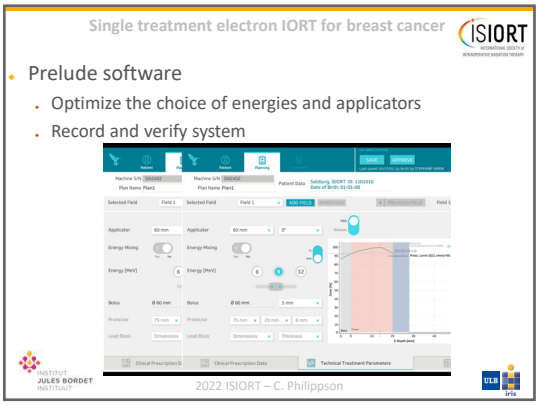


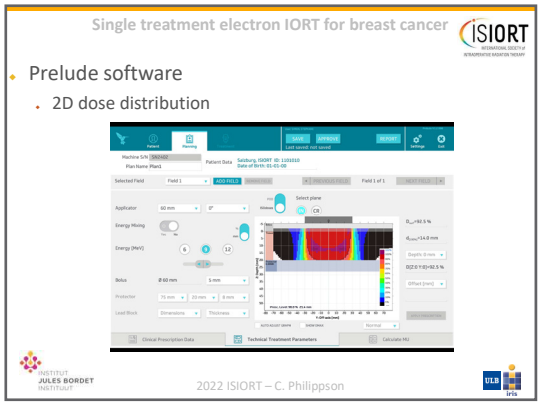


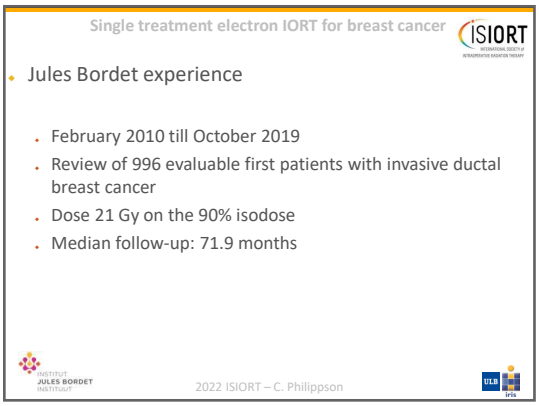


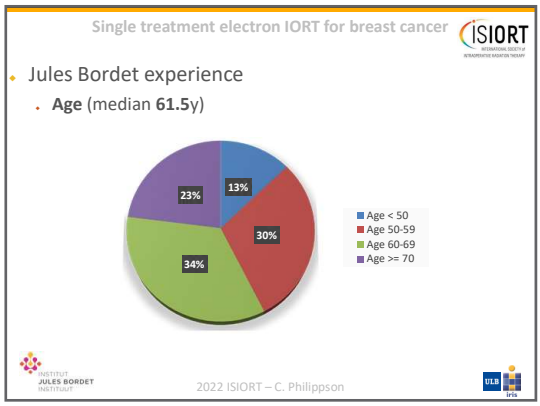
Speaker presentations

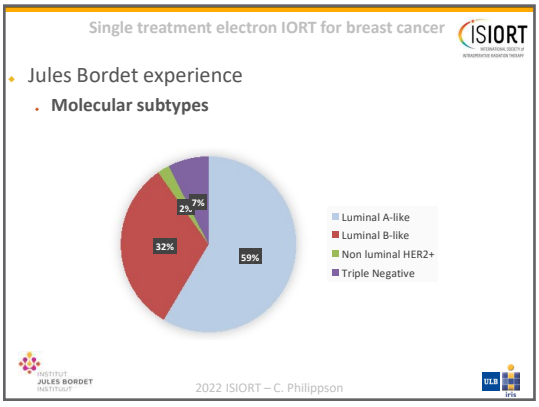
Single Treatment Electron IORT for Breast Cancer; The Jules Bordet Institute Experience

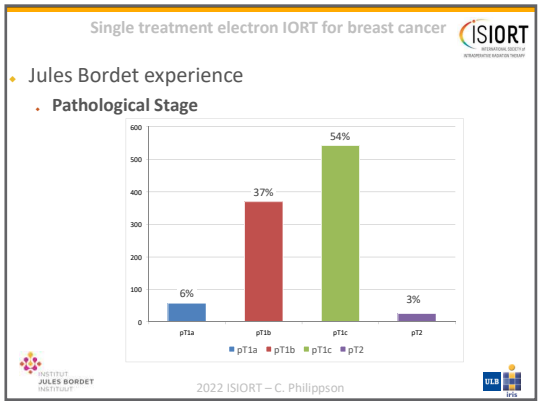






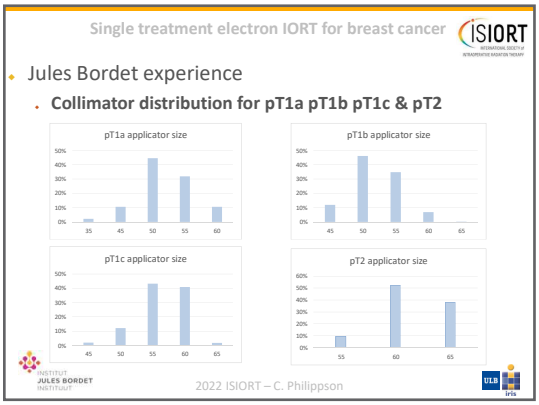


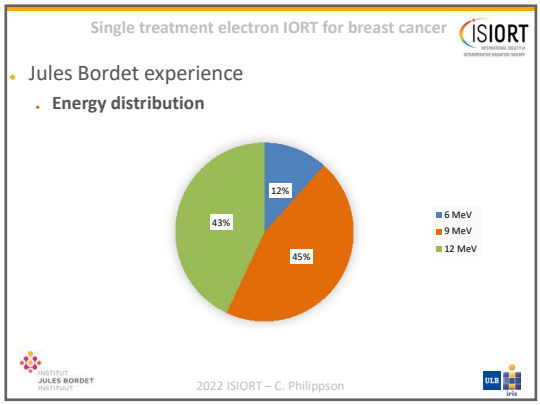


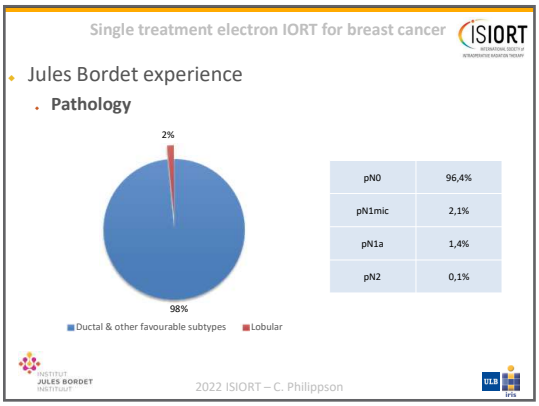


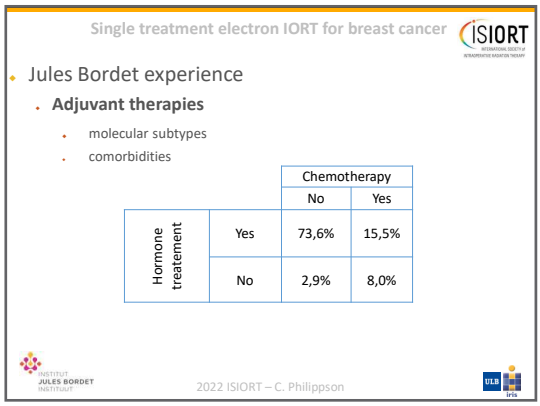
Speaker presentations

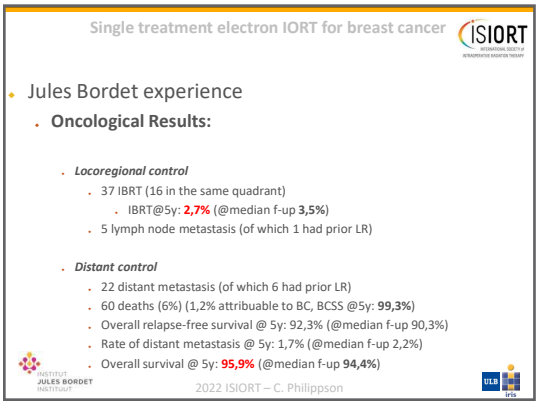
Single Treatment Electron IORT for Breast Cancer; The Jules Bordet Institute Experience

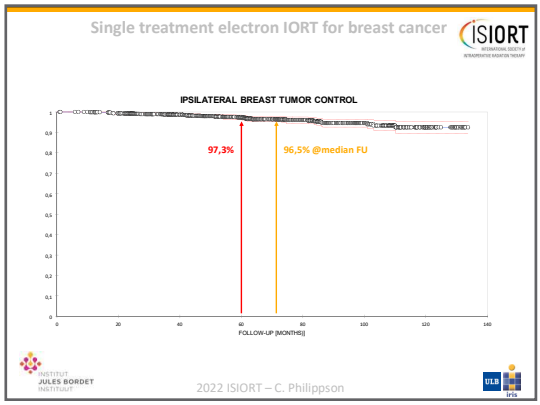






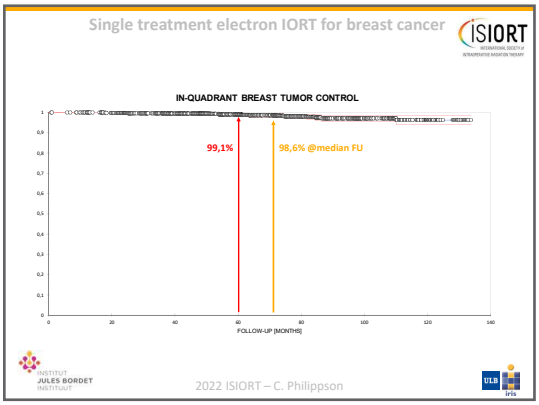


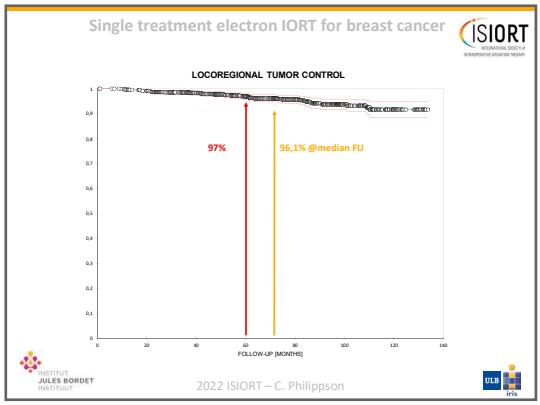


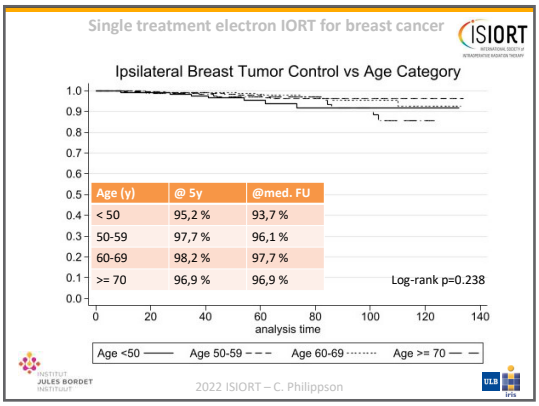


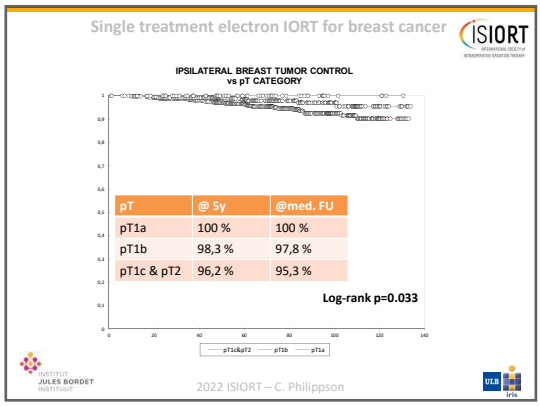
Speaker presentations

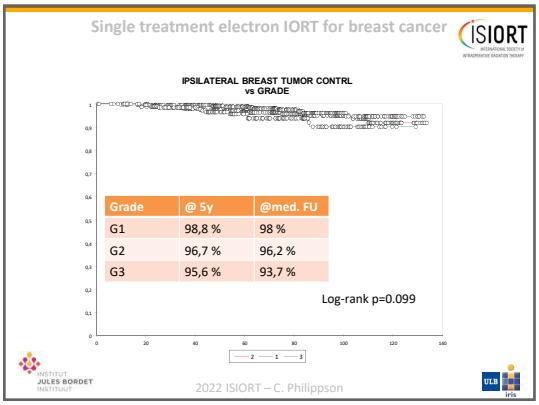
Single Treatment Electron IORT for Breast Cancer; The Jules Bordet Institute Experience

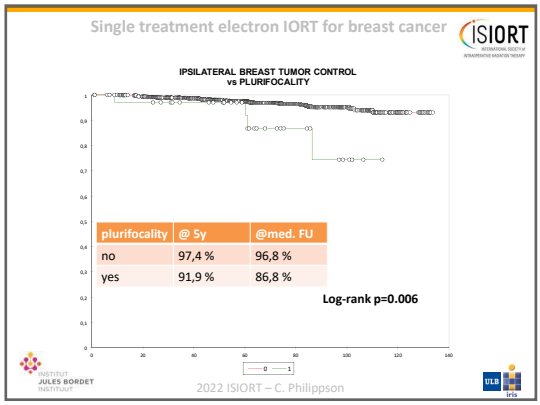






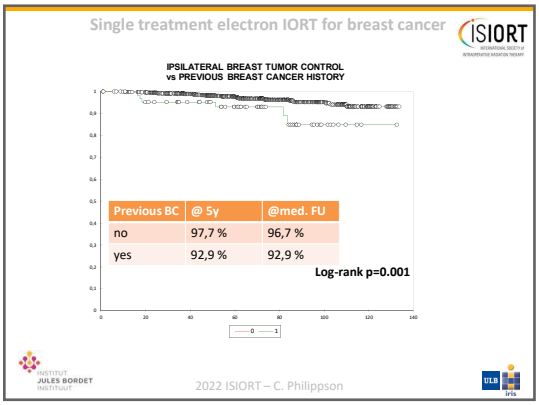


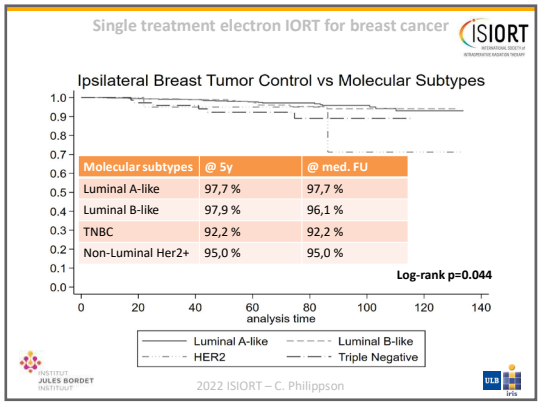


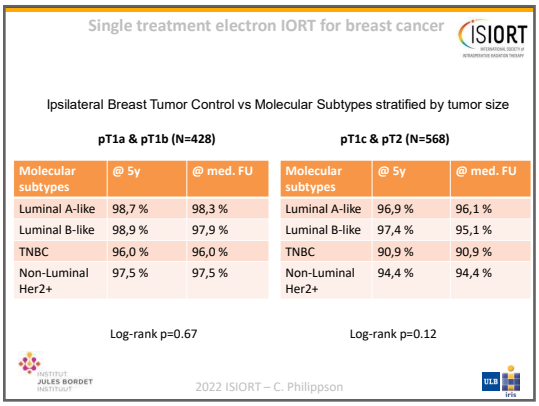


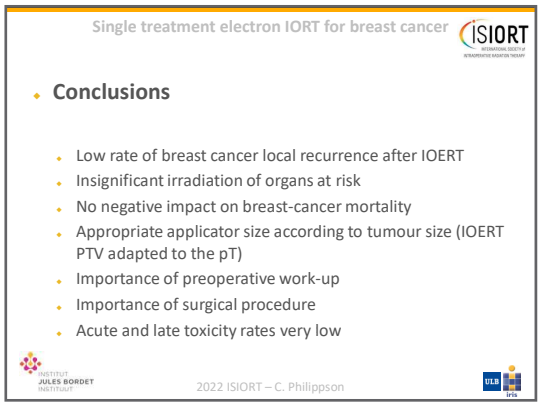
Speaker presentations

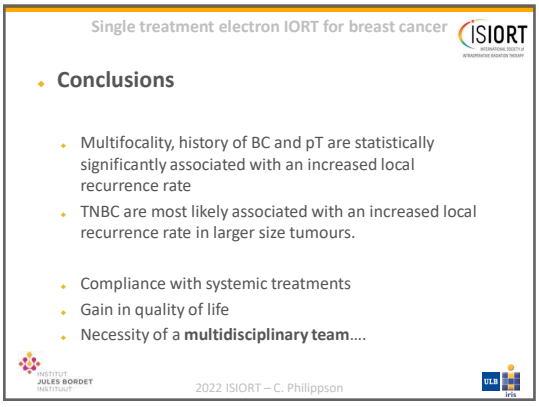
Single Treatment Electron IORT for Breast Cancer; The Jules Bordet Institute Experience

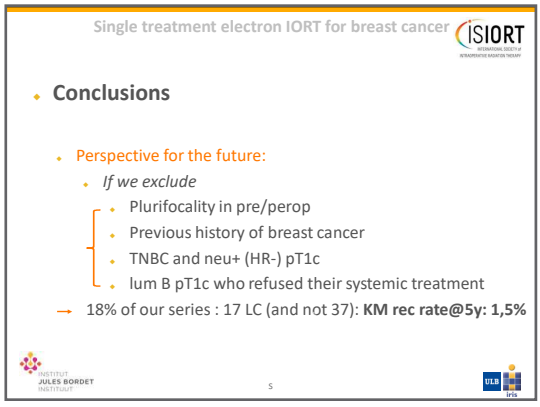












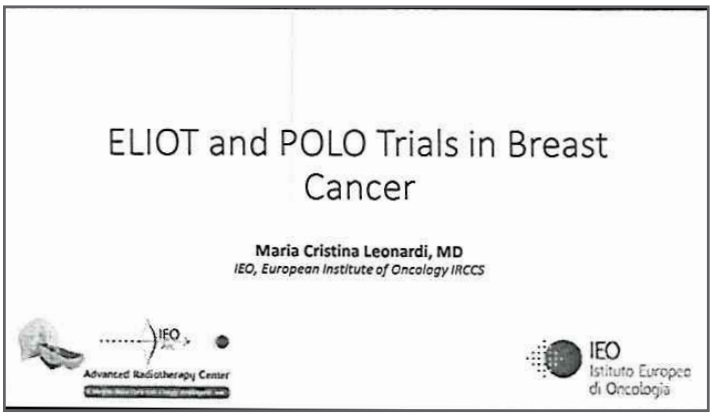
Speaker presentations

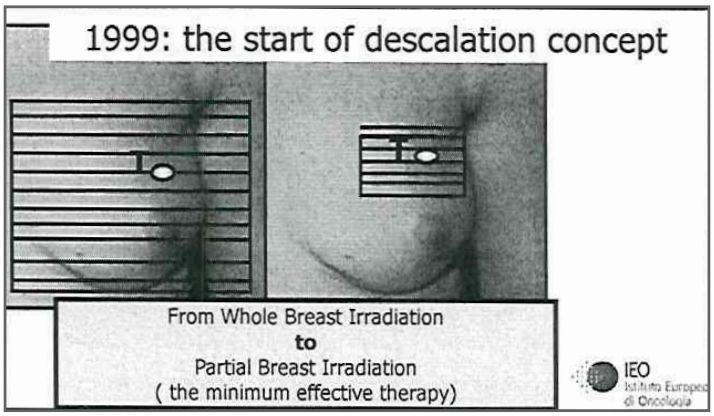
Single Treatment Electron IORT for Breast Cancer; The Jules Bordet Institute Experience

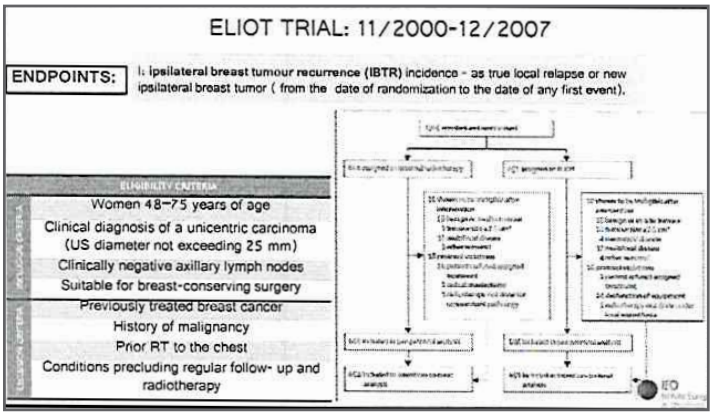
Speaker presentations

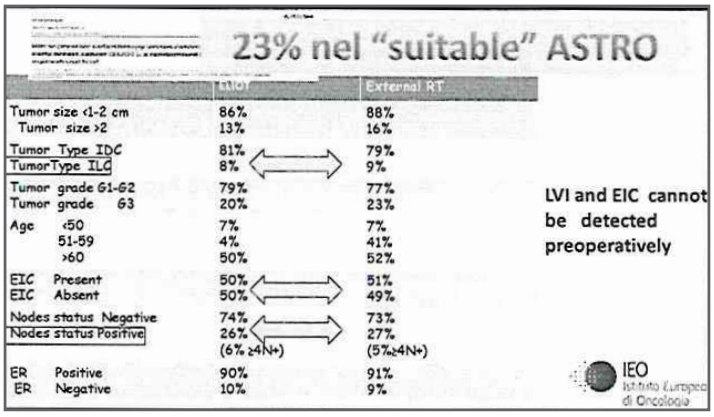
ELIOT and POLO Trials in Breast Cancer (pre-recorded)

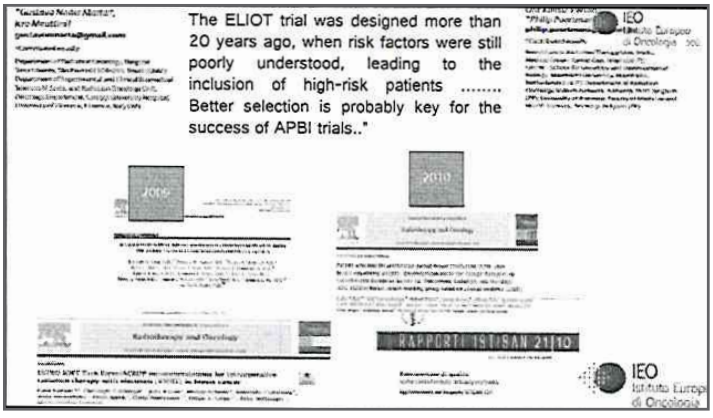
Cristina Leonardi, MD
Division of Radiation Oncology
European Institute of Oncology
Milan, Italy

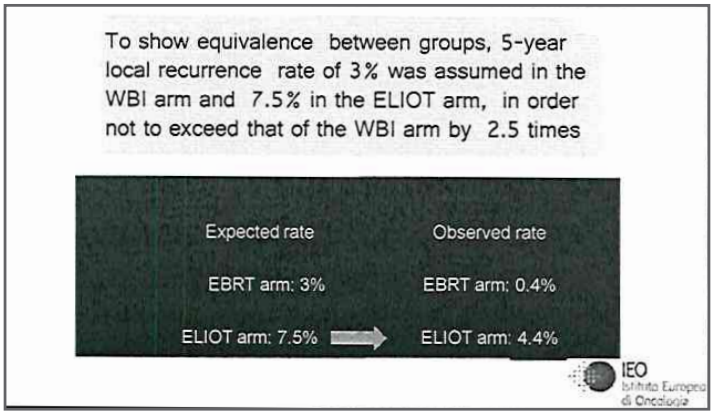






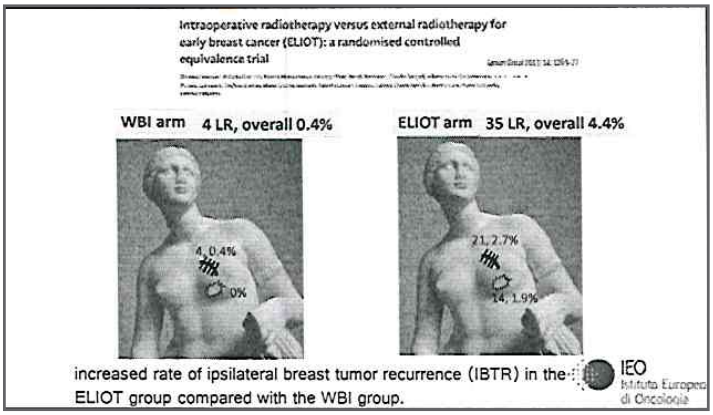


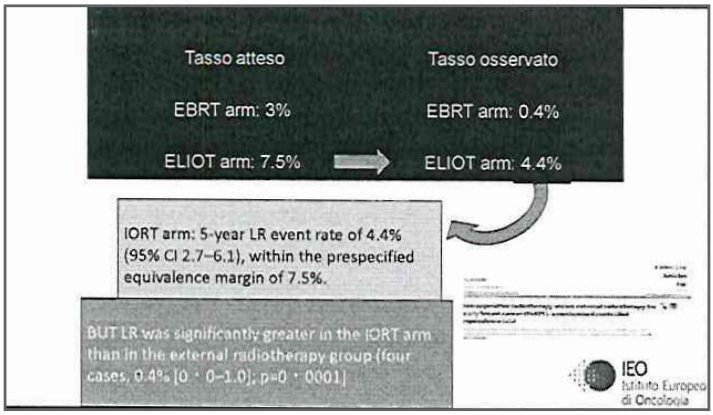


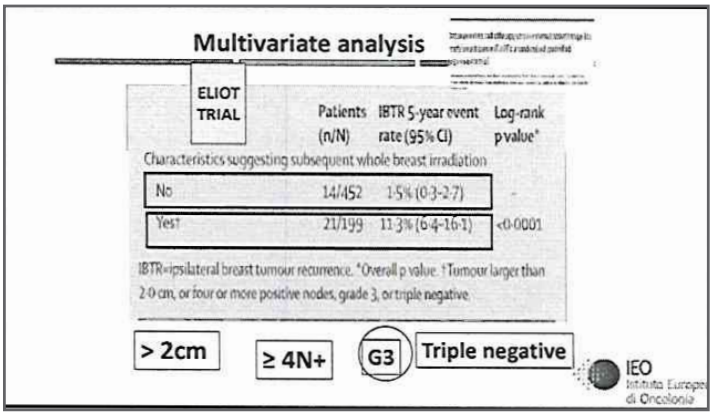


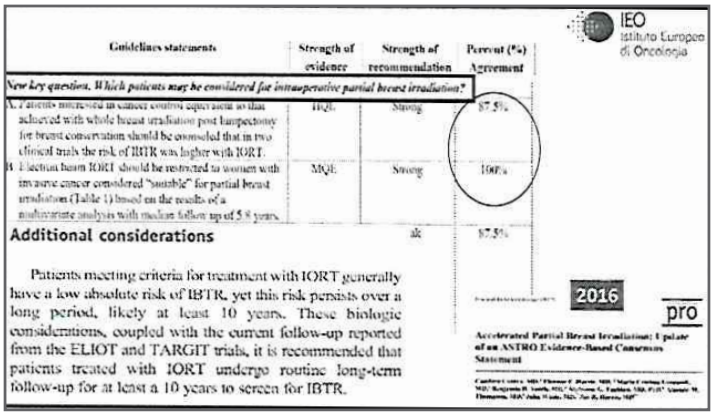
Speaker presentations

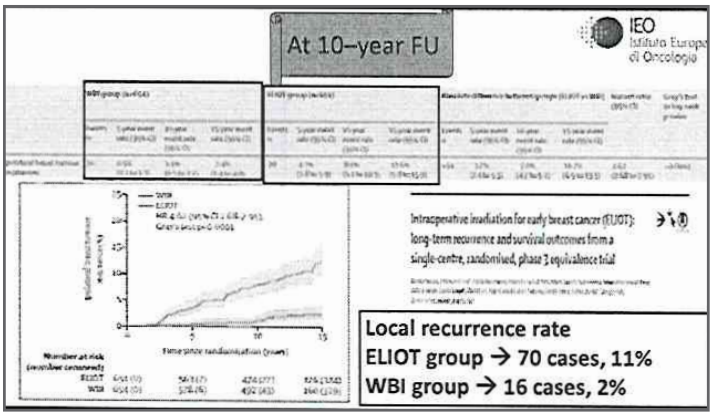
ELIOT and POLO Trials in Breast Cancer (pre-recorded)

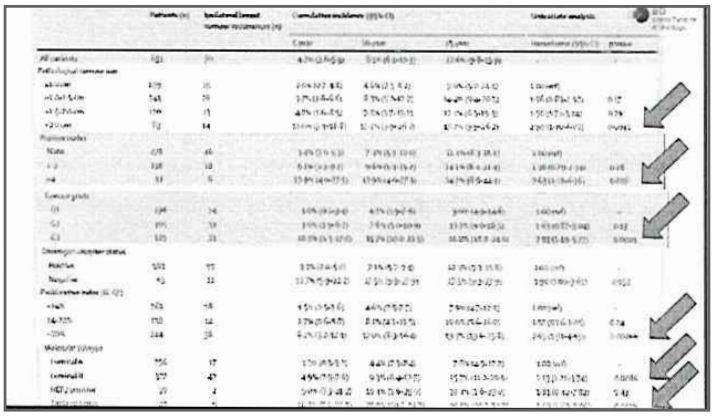






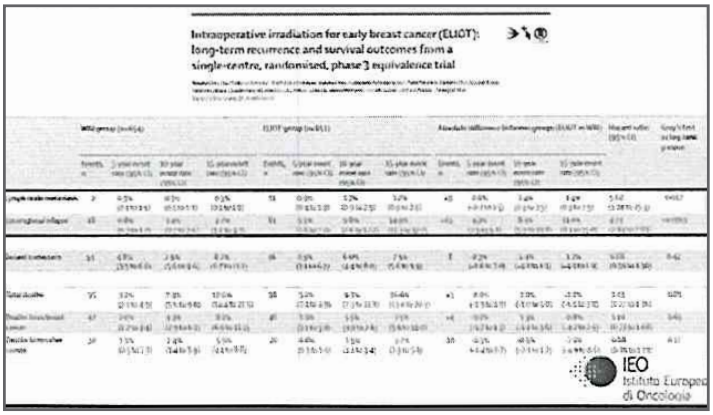


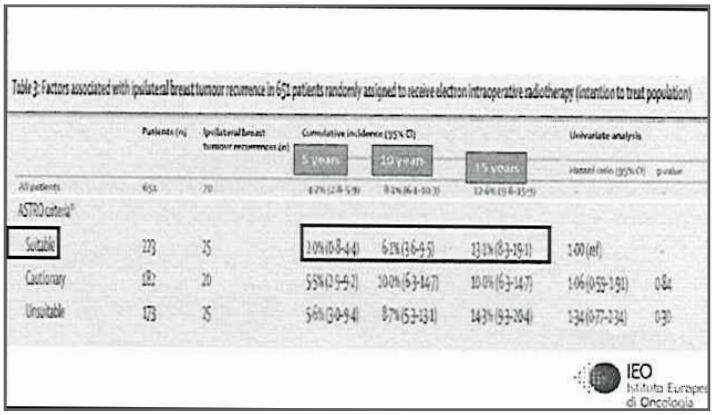


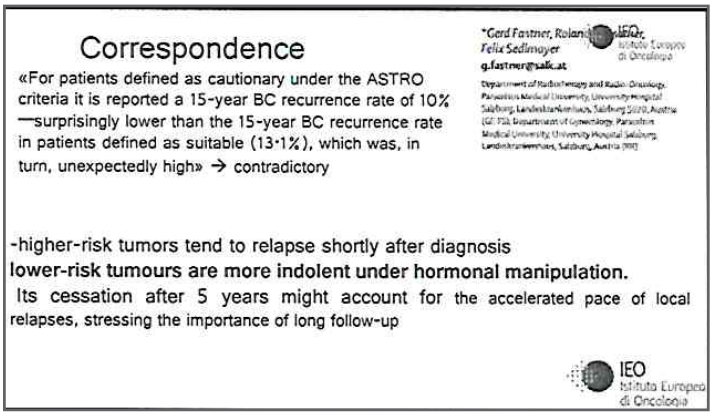


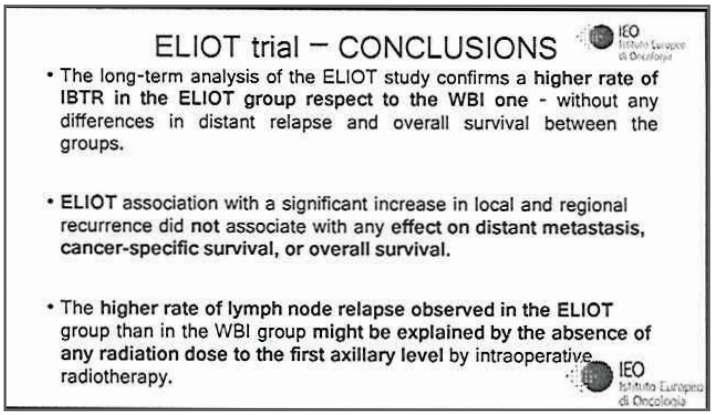
Speaker presentations

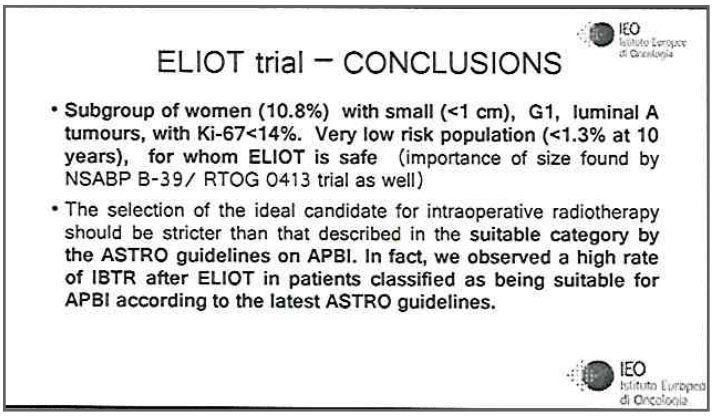
ELIOT and POLO Trials in Breast Cancer (pre-recorded)

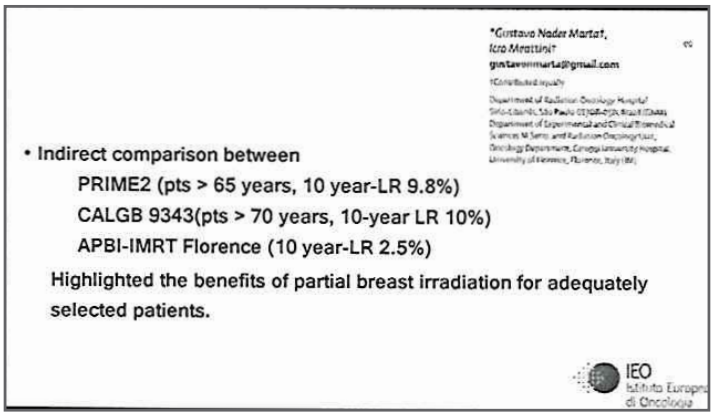












Speaker presentations

ELIOT and POLO Trials in Breast Cancer (pre-recorded)

«Question of whether target volumes were sufficiently encompassed by tumouricidal doses of 21 Gy ..... Appropriate target volumes with IORT are generally achieved by use of the correct sizes of tube diameters and electron energies.... their first publication (2013), the authors also reported the use of smaller-sized tubes, which might lead to insufficient coverage ... a sub-group analysis for these results has not been provided with the latest Article»

*Gerd Fastner, Roland [illegible], Felix Sedlmayer
g.fastner@salk.at
Department of Radiation Therapy and Radio-Oncology, Paracelsus Medical University (University Hospital Salzburg), Landeskrankenhaus, Salzburg (LKH), Austria (GF, FS); Department of Gynecology, Paracelsus Medical University, University Hospital Salzburg, Landeskrankenhaus, Salzburg, Austria (RR)

Unlike in the first publication of ELIOT, we did not want to categorise LR according to the tumour site. We **believe that the true value of any APBI lies in the potential for control of the disease across the whole breast.**

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Management and significance of IOERT local relapse

Different prognostic and therapeutic implications?

Inadeguate CTV coverage **Tumor biology**

Undetected distant tumor foci

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Type of salvage treatment across the studies

Salvage therapy	ELIOT trial (Orecchia 2021)		Hungarian trial (Polgár 2020)		Mammosite Registry (Shah 2012)	William Beaumont H (Shah 2012)
	PBI	WBI	PBI	WBI	PBI	PBI
2ndBCS	35/70	8/16	6/10	3/8	9/38	4/18
2ndBCS+RT	NS	NS	4/6 (WBI 45-50.4 Gy)	-		4/18 (2nd PBI)
mastectomy	24/70	5/16	4/10	4/8	28/38	13/18
Mastectomy + RT	NS	NS	-	-	-	2/18
Palliative/refusal	2/70		-	1/8	13	1/18
missing	9/70	3/16	-	-	-	-

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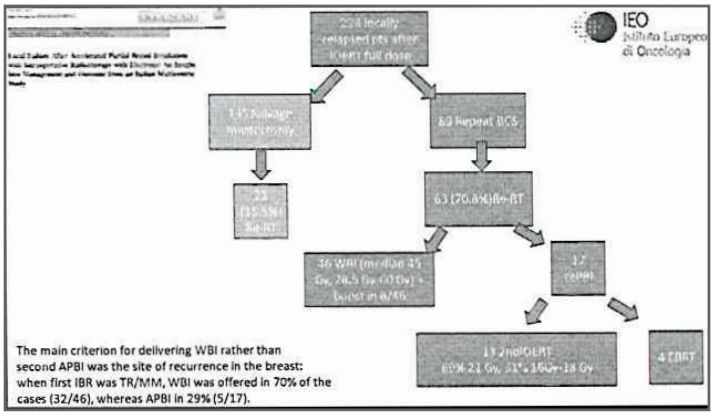

The main criterion for delivering WBI rather than second APBI was the site of recurrence in the breast: when first IBR was TR/MM, WBI was offered in 70% of the cases (32/46), whereas APBI in 29% (5/17).

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Outcome	All pts	SM (n 135)	2nd BCS alone (n 26)	2ndBCS+re-RT (n 63)	Hazard ratio, p
5-y LR	8.4%	7.4%	25.5%	3.7%	
HR SM vs 2ndBCS+re-RT					1.41 p=0.5
HR 2ndBCS alone vs. 2ndBCS+ re-RT					5.63 p=0.006
5-y OS	89.3%	86.4%	86.1%	96%	
HR SM vs 2ndBCS+re-RT					3.27 p=0.06
HR 2ndBCS alone vs. 2ndBCS+ re-RT					4.38 p=0.04
5 y DFS	67.4%	61.9%	52.9%	83.3%	
HR SM vs 2ndBCS+re-RT					2.13 p=0.01
HR 2ndBCS alone vs BCS+ re-RT					3.21 p=0.003

A match-paired subanalysis of T1N0-1 LRs showed no difference inlocal control nd DFS between SM and 2ndBCS+ re-RT

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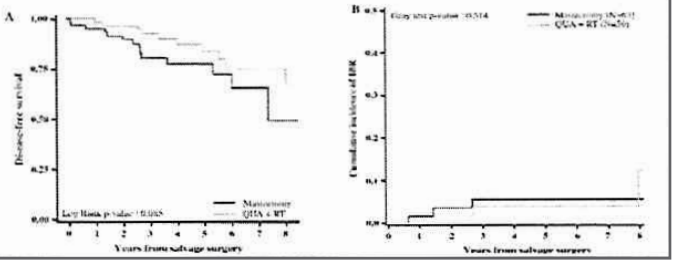

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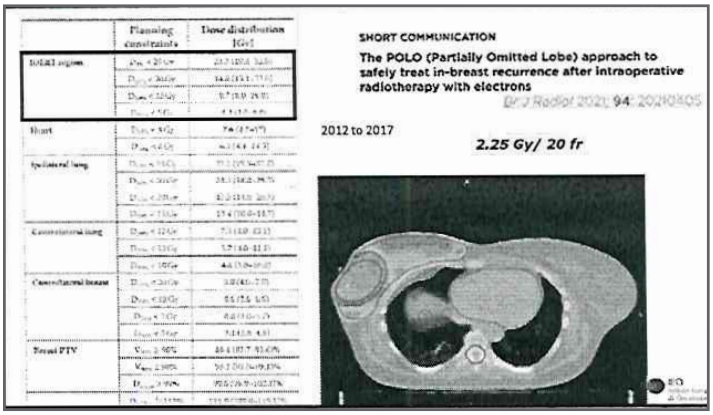
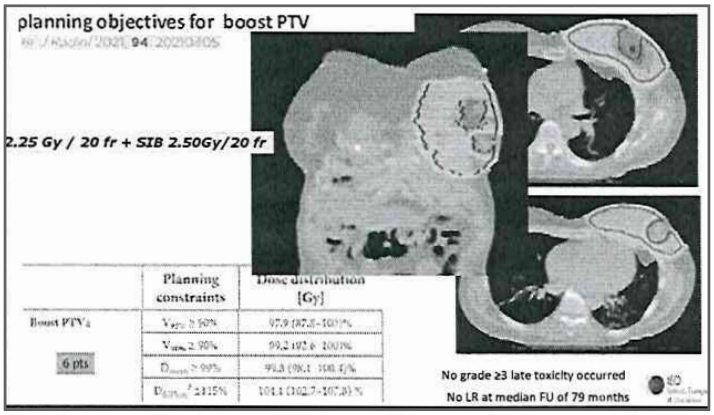
ELIOT and POLO Trials in Breast Cancer (pre-recorded)





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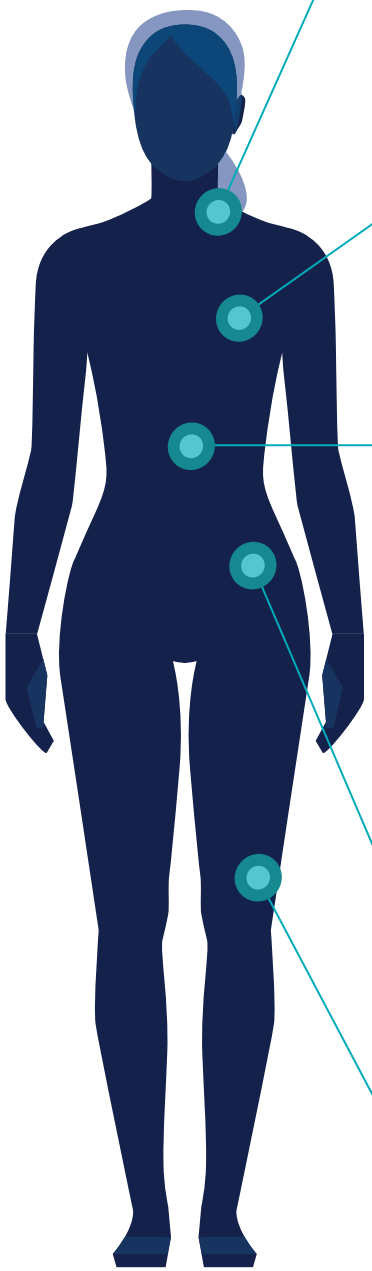

HEAD & NECK

Combining Immunotherapy with Salvage Surgery and IORT for Treatment of Persistent /Recurrent Head and Neck Cancers
Dukagjin Blakaj, M.D, Ph.D, *Assoc. Professor*
Ohio State University, *Columbus, OH, USA*
Thursday, Oct. 20, 3:30 pm

BREAST

HIOB trial: Hypofractionated whole breast irradiation and electron IORT boost in early-stage breast cancer
Gerd Fastner, M.D., *Professor*
Paracelsus Medical University Clinics, *Salzburg, Austria*
Friday, Oct. 21, 9:00 am

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, M.D., *Assoc. Professor*
The Ohio State University, *Columbus, OH, USA*
Friday, Oct. 21, 10:00 am

Single Treatment Electron IORT for Breast Cancer; The Jules Bordet Institute Experience
Catherine Philippson, M.D.
Institut Jules Bordet
Brussels, Belgium
Friday, Oct. 21, 11:20 am

PANCREATIC

The Evolution of Pancreatic Cancer Treatment
Cristina Ferrone, M.D., *Director*
Liver Surgery Program, Massachusetts General Hospital, *Boston, MA, USA*
Thursday, Oct. 20, 1:00 pm

IORT in Pancreatic Carcinoma
Eric Miller, M.D., Ph.D., *Assoc. Professor*
Ohio State University, *Columbus, OH, USA*
Thursday, Oct. 20, 1:20 pm

COLORECTAL

IORT in Rectal Carcinoma
Alex Mirnezami, M.D., *Professor*
University of Southampton, *Southampton, UK*
Thursday, Oct. 20, 1:40 pm

Mayo Experience of IORT in Rectal Carcinoma
Michael Haddock, M.D., *Professor*
Mayo Clinic, *Rochester, MN, USA*
Thursday, Oct. 20, 2:00 pm

SARCOMAS

IORT in Sarcomas
Steve Braunstein, M.D., *Assoc. Professor*
University of California San Francisco, *San Francisco, CA, USA*
Friday, Oct. 21, 1:00 pm

Latest advancements in image-guided **IORT** and the clinical translation of **FLASH** radiotherapy

History and Future of IORT
Don Goer, Ph.D., *Scientist*
IntraOp Medical Corporation
Thursday, Oct. 20, 8:30 am

Radiobiological Aspects of IORT/FLASH
Jessica Fleming, Ph.D., *Radiobiologist*
The Ohio State University, *Columbus, OH*
Thursday, Oct. 20, 9:00 am

Clinical perspective on the present state and new developments in electron-based IORT; FLASH
Falk Röder, M.D., *Professor*
Paracelsus Medical University Clinics, *Salzburg, Austria*
Thursday, Oct. 20, 9:20 am

Physicist's perspective on the present state and new developments in electron-based IORT
Markus Stana, Ph.D., *Medical Physicist*
Paracelsus Medical University Clinics
Salzburg, Austria
Thursday, Oct. 20, 9:50 am

Physics in FLASH Radiotherapy
Ahmet Ayan, Ph.D., *Medical Physicist*
The Ohio State University, *Columbus, OH*
Thursday, Oct. 20, 10:30 am

CT Imaging in Electron Based IORT – current status and future perspectives
Christoph Gaisberger, Ph.D, *Med. Physicist*
Paracelsus Medical University Clinics, *Salzburg, Austria*
Thursday, Oct. 20, 10:50 am