Quality assurance in intraoperative radiotherapy

Update of Rapporto ISTISAN 03/1
English version of Rapporto ISTISAN 21/10

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Quality assurance in intra-operative radiation therapy. Update of the Rapporto ISTISAN 03/1.
Stefano Andreoli, Antonella Ciabattoni, Cinzia De Angelis, Maria Cristina Leonardi, Loris Menegotti, Maria Pimpinella, Antonella Rosi
2022, xii, 189 p. Rapporti ISTISAN 21/10 (in Italian)

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 words: IntraOperative Radiation Therapy; Clinical indication; Physical and dosimetrical aspects

Istituto Superiore di Sanità
Assicurazione di qualità nella radioterapia intraoperatoria. Aggiornamento del Rapporto ISTISAN 03/1.
Stefano Andreoli, Antonella Ciabattoni, Cinzia De Angelis, Maria Cristina Leonardi, Loris Menegotti, Maria Pimpinella, Antonella Rosi
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Il numero di Centri italiani che effettuano trattamenti di radioterapia intraoperatoria (*Intra-Operative RadioTherapy*, IORT) è cresciuto molto in questi ultimi anni passando dai 17 Centri all'uscita del primo documento pubblicato nella serie *Rapporti ISTISAN* del 2003 ai 50 Centri risultati operativi sul territorio italiano in una *survey* del 2016. Questo documento costituisce la revisione della precedente versione dopo oltre 10 dieci anni dall'avvio dell'attività nella maggior parte dei Centri censiti e illustra la "filosofia globale" della garanzia di qualità nella IORT, considerando sia gli aspetti clinici, sia quelli tecnici e fisico-dosimetrici. Con un'esperienza ormai consolidata per la tecnica con elettroni e con le acquisizioni più recenti relative alla tecnica con fotoni, vengono descritte le fasi organizzative, le procedure operative e le relative indicazioni terapeutiche della IORT. Il rapporto è stato redatto, attraverso il coordinamento dell'Istituto Superiore di Sanità, da un Gruppo di Lavoro costituito da radioterapisti oncologi e specialisti in fisica medica con la collaborazione dell'ENEA-INMRI (Agenzia nazionale per le nuove tecnologie, l'energia e lo sviluppo economico sostenibile-Istituto Nazionale di Metrologia delle Radiazioni Ionizzanti) per gli aspetti dosimetrici.
Parole chiave: Radioterapia intraoperatoria; Indicazioni cliniche; Aspetti fisici e dosimetrici

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We would like to thank the Scientific Societies AIRO (Italian Association of Oncological Radiotherapy) and AIFM (Italian Association of Medical Physics) the International Society for IORT (ISIORT) and the Intraop Medical Corporation for supporting the English translation of the ISTISAN 21/10 Report. We thank Dr Sandra Salinetti for her valuable contribution in the editorial revision of the document.

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ACRONYMS

CTV	Clinical Tumor Volume
EBRT	External Beam Radiation Therapy
EGS	Electron Gamma Shower
EORTC	European Organization for Research and Treatment of Cancer
FLUKA	FLUcturiendeKAScade
FMEA	Failure Mode and Effects Analysis
GEANT4	Geometry ANDTrack
HDR	High Dose Rate
HTA	Health Technology Assessment
IOERT	IntraOperative Electron Radiation Therapy
IORT	IntraOperative Radiation Therapy
ISIORT	International Society IntraOperative Radiation Therapy
kV-IORT	kiloVolt IORT
kypho-IORT	Kypho is a minimally invasive surgery-IORT
LAGC	Locally Advanced Gastric Carcinoma
LARC	Locally Advanced Rectal Carcinoma
LINAC	LINear ACcelerator
LRRC	Locally Recurrent Rectal Carcinoma
OF	Output Factor
PDD	Percentage Depth Dose
PTV	Planning Target Volume
RCT	RadioChemoTherapy
RTOG	scala per tossicità acuta e tardiva elaborata dal *Radiation Therapy Oncology Group*
SOMA-LENT	*Subjective, Objective, Management and Analytic - Late Effects on Normal Tissues*
TC	Tomografia Computerizzata
TPS	Treatment Planning System
US	ultrasounds
MD	Ministerial decree

PREFACE

The Council Directive 2013/59/Euratom of 5 December 2013 (1) and its transposition into Italian Legislative Decree 101 of 31 July 2020 (2) establishes basic safety standards for protection against the dangers deriving from exposure to ionizing radiation and repeals Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom. The current legislation promotes the implementation of quality assurance programs for optimizing the clinical use of radiation with a view to the radiation protection of patients. The Istituto Superiore di Sanità (ISS, the National Institute of Health in Italy) has for years been involved in Quality Assurance activities in radiological sciences through the coordination of multidisciplinary working groups for the development of technical and clinical recommendations for the use of ionizing radiation. The documents drawn up by the Working Groups are published as reports in the series *Rapporti ISTISAN* and are updated periodically to take into account the clinical and technological developments in the field.

A first document on special radiotherapy techniques, in particular on the Intra Operative Radiation Therapy (IORT) technique was drawn up in 2003 (3). IORT involves the administration of a dose of radiation, delivered with (high-energy) electrons or low-energy photons, during surgery, before or after the removal of a tumour. In 2003, in Italy there were 17 Centres that used the IORT technique. To date, the Italian Centres that have the equipment to perform IORT are 50, of which 33 are operational according to a survey (2016-2017). Most of the Centres (n. 29) provide treatment using electrons, 4 using photons while 2 have both modalities. Almost all of them have mobile linear accelerators dedicated to the operating room.

In light of such developments along with the clinical indications for an increasing number of pathologies, and the development of new dosimetry systems, a revision of the document *Rapporto ISTISAN* 03/1 has become necessary.

This document updates the *Rapporto ISTISAN* 03/1 after more than ten years since activities were started in most of the operating Centres and it illustrates the “global philosophy” of quality assurance in IORT, considering not only the clinical aspects but also the technical, physical and dosimetric aspects of IORT. The organizational steps, the operating procedures and related therapeutic indications for IORT are described against a background of consolidated experience with the electron-based technique and with the more recent acquisitions of the technique that uses photons.

The purpose of this document is to provide a common framework for the operators involved in the organization and execution of IORT. Tthis document defines the state of the art of the IORT procedure in its various applications and possible optimizations, providing specific evidence-based indications for use in the various neoplastic pathologies.

This document was drawn up, under the coordination of the ISS, by radiation oncologists and medical physicists with proven experience in the field, in agreement with their respective associations, namely: the Italian Association of Radiotherapy and Clinical Oncology (AIRO) and the Italian Association of Medical and Health Physics (AIFM).

Many of the professionals involved in performing the IORT procedure also participated in the final review through the Presidents of the Scientific Associations to which they belong: the Italian Society of Surgery (Società Italiana di Chirurgia, SIC); the Italian Society of Oncological Surgery (Società Italiana di Chirurgia Oncologica, SICO); the Italian Association of Breast Surgery (Associazione Italiana di Chirurgia Senologica, ANISC); the Italian Association of Medical Oncology (Associazione Italiana di Oncologia Medica, AIOM); the Italian Society of Anaesthesia, Analgesia, Critical Care Resuscitation and Intensive Care (Società Italiana di

Anestesia, Analgesia, Rianimazione e Terapia Intensiva, SIAARTI); the Italian Society of Medical Radiology (Società Italiana di Radiologia Medica, SIRM); the National Federation of Technical Health Orders of Medical Radiology and of the Technical Health Professions, Rehabilitation and Prevention (Federazione Nazionale Ordini Tecnici Sanitari di Radiologia Medica e delle Professioni Sanitarie Tecniche, Riabilitative e della Prevenzione, FNO TSRM-PSTRP); the Italian Association of Oncological Radiotherapy and Health Physics Technicians (Associazione Italiana Tecnici di Radioterapia Oncologica e Fisica Sanitaria, AITRO); the Italian Association of Radiation Oncology Nurses (Associazione Italiana Infermieri di Radioterapia Oncologica, AIIRO); and the National Federation of Professional Nursing Orders (Federazione Nazionale Collegi Infermieri, FNOPI).

The document has also been approved by all the Italian Radiotherapy Centres and Medical Physics Services that provide IORT treatments, and it therefore sets the stage for creating a working synergy that will contribute to making the best possible use of this radiotherapy technique and to defining shared procedures that will help reduce potential risks.

As in the previous edition, these recommendations have a modular structure to facilitate future revisions and updates.

INTRODUCTION

Intra Operative Radiation Therapy (IORT) is an alternative to and/or supplementary technique of External Beam Radiation Therapy (EBRT) which involves the precise delivery of a single dose of radiation directly to the tumour or to the tumour bed during surgery. IORT can be either preceded or followed by EBRT when used to deliver a selective boost to the tumour, or it may be used as single adjuvant radiotherapy treatment in the early stages of a tumour, or in non-resectable tumours for palliative purposes. The main purpose of IORT is to deliver a high dose of radiation directly to the target, thus enhancing local disease control, and sparing all the surrounding structures and organs. In the last 20 years the use of IORT for the treatment of a large number of malignant tumours has increased worldwide thanks to studies that have proven the safety and efficacy of this treatment. Historically, the possibility of using ionizing radiation directly in the operating room dates back to the early twentieth century, but actual use was limited by the availability of only X-rays or high-energy γ radiation. It was only in 1960 that, thanks to linear accelerators, electron beams with high energy and dose homogeneity could be used on "target" tissues. Even today IORT can be performed using electrons produced by linear accelerators which are usually intended for EBRT. In this case, the patient can undergo surgery and receive radiation treatment in a dedicated bunker (the operating room can be set up in a radiation therapy bunker and for the IORT treatment the patient is placed under the accelerator to be irradiated) or the patient is transported to the radiotherapy bunker after surgical exposure of the area to be irradiated. After radiation treatment the patient is returned to the operating room for completion of the surgery (treatment of outpatient patients is interrupted for the time required to prepare the room and execute the treatment, usually 1-2 hours).

To facilitate the preparation of treatment set-up, the use of a radiotherapy treatment table having multiple degrees of freedom is recommended. In the case of treatment with a non-dedicated accelerator, the use of a treatment table suitable for both patient transfer and treatment is recommended.

However, there have been limited clinical indications to the use of IORT due to the difficulties in transporting patients, under general anaesthesia, during surgery, from the operating room to the bunker (4) in aseptic and safe conditions. But these organizational disadvantages have been overcome thanks to the availability of mobile electron accelerators, conceived exclusively for intraoperative treatment, which can be placed in the operating room, without the need for special radioprotection requirements. Hence, the patient does not need to be moved from the surgical table. The mobile treatment unit is brought up to the tumour bed for the execution of the treatment and can therefore be used in multiple adjacent rooms. However, the simplification of the procedure has increased the complexity of the dosimetry problems. In recent years, besides the mobile linear accelerator, new equipment with miniaturized low-energy X-ray sources has been introduced. The IORT mode may also include the use of high dose-rate radioactive sources which are conveyed by means of implants introduced intraoperatively, with the source loading and dose administering during the operation itself. On the contrary, the intraoperative placement of vectors for brachytherapy, which are loaded after the restoration of the anatomy and closure of the surgical breach, is not included in the IORT modality. In fact, in these cases one of the fundamental requirements of the IORT is missing, namely delivery of the radiation after displacement of the healthy tissues located between the radiation source and the tumour. For sake of uniformity of the text, it was decided to deal separately with the technical methods, clinical indications and physical and dosimetric aspects of IORT carried out with electrons (Intra Operative Electron Radiation Therapy, IOERT) and

with photons (kV-IORT). Issues related to treatment with high dose rate radioactive sources (High Dose Rate - Intra Operative Radiation Therapy, HDR-IORT), more directly associated with the general topics of brachytherapy, are not a subject of this document.

Given the separate treatment of IOERT and kV-IORT in this document, for sake of simplicity the term IORT will always be used, unless the method of delivery needs to be specified.

Based on the radiobiological characteristics of some tumours, the single intraoperative session (extreme hypofractionation) has unquestionable advantages in terms of dose intensification and possible increase in local disease control, as well as optimal integration with systemic therapies.

It also has a significant impact on the patient's quality of life thanks to the reduction or elimination of the EBRT sessions, shorter waiting lists due to the shorter duration of the EBRT and lower cost of treatment. Indeed, according to several studies (5), single dose IORT is the strategy with the best cost-benefit ratio and with lower costs compared to EBRT.

The therapeutic goal of IORT can be reached through:

- direct visualization of the area to be irradiated, with precise identification of the target thus allowing to reduce the margins of the radiation field, and with a potential reduction in toxicity to the surrounding tissues;
- high biological efficacy of the single fraction, administered as a boost or as a single dose. According to the radiobiological models of reference, the equivalent dose with IORT is higher than that administered with EBRT, with a potential improvement in local control;
- total or partial sparing of healthy structures and organs, which can be displaced away from the radiation field or shielded; this makes IORT particularly interesting in clinical situations in which the target volume is close to radiosensitive tissues (ureters, kidneys, spinal cord, lung) and in all cases of re-treatment for recurrence of the disease;
- administration of the treatment during surgery, which prevents the repopulation of neoplastic cell clones in the interval between surgery and EBRT, with an undeniable radiobiological advantage.

Thanks to these characteristics, IORT fits the modern definition of "precision oncology", based on a multidisciplinary approach that includes knowledge of tumour biology, of diagnostic techniques, clinical strategy and therapeutic innovation (6), thus providing a comprehensive vision for the personalized treatment of the patient.

The literature is rich in evidence regarding the feasibility, tolerance and efficacy of IORT as combination treatment in the therapeutic strategy of cancer patients; for this reason, since 2016 the guidelines of the National Comprehensive Cancer Network (NCCN) have incorporated this modality into the treatment of many types of cancer (7). Based on radio-sensitivity and tolerance studies, the recommended doses are of the order of 20-25 Gy for the single dose or 9-15 Gy for the boost, preceded or followed by EBRT.

According to the published papers on IORT treatment of various tumours, local control has always been shown to be very high and toxicity very low. Stomach, pancreas, colorectal tumours and sarcomas, for which local recurrence is the main cause of failure, have been the subject of numerous clinical studies. The long-term results confirm an undeniable impact on local control, which is generally associated with better survival. New fields of application are the prostate, head and neck, and gynaecology tumours (8). However, the reported experiences almost always refer to single institutions and this represents the main limit for the validation of the method. In fact, there is a need for phase III randomized cooperative studies, in order to confirm the contribution of IORT to combined treatment. The possibility of involving multiple Centres, thanks to the greater availability of mobile equipment, may be an interesting opportunity to obtain a higher level of clinical evidence and therefore overcome the cited

limitations. In prescribing IORT, the clinical indications reported in the literature, referring to consolidated experience, must therefore be taken into account and distinguished from those of a more innovative nature, so that treatment may be carried out in compliance with the indications of good clinical practice.

The treatment of breast cancer using IORT deserves to be dealt with separately since in the last 15 years this pathology has represented the field of greatest interest for the IORT technique. Based on the assumption that the majority of breast relapses after conservative surgery occur in the originally affected quadrant, partial irradiation of the tumour bed only, or a higher dose at that site, could be a valid approach for local disease control. As already pointed out, IORT can be performed in either of two ways: as an anticipated boost, with the intention of administering a biologically effective dose at time zero on the real site of the disease, or as a single treatment (single dose) instead of postoperative EBRT.

IORT toxicity is generally related to the dose and to the type of anatomical structures involved in the treated area and is mainly of the late type (9-12). The procedures to ensure sterility of the operating field are consolidated and easy to perform, and any increase in the operating risk due to the lengthening of the duration of surgery can be estimated in advance by the anaesthesiologist. The late toxicity most frequently described in the literature, due to the volumes and doses usually used for various tumours, involves the peripheral nerves and the ureter, where these structures fall inside the treatment area. Collapses due to degeneration of the vertebral bodies, bleeding from the rupture of large vessels and cerebral demyelination are rarely described (9-11). In all these situations toxicity is due not only to IORT, but also to the surgical manipulation and to the infiltration of the tumour (13). It is a common observation that single doses in excess of 20-25 Gy are significantly correlated with a higher incidence of late toxicity (14). Evaluation of the incidence of toxicity requires the use of international scoring scales.

There are many aspects that contribute to the success of treatment with IORT which can be enhanced by a quality assurance program.

The dose prescription must specify the dosimetry reference point used and must take into account that the radiation dose is delivered in a single fraction. The clinical significance of a single high dose is still a controversial issue. In an attempt to give a value comparable to conventional fractional radiotherapy, radiobiological models such as the linear quadratic model are applied (15). However, it is worth mentioning that extrapolations of the meaning of the dose outside the theoretical limits of the model used as reference are not recommended, and therefore in clinical practice, the doses advocated in the literature should be adhered to.

The radiation oncologist has full clinical responsibility for the prescription and execution of the treatment, but the entire procedure necessarily requires multidisciplinary collaboration with the other figures involved in patient care/patient management: the surgeon, the anaesthesiologist, the medical physicist, the therapeutic radiographers (Tr), and the nursing staff. The surgeon, in particular, is involved in the removal of the tumour mass, in identifying the tumour bed and in the procedure itself, in synergy with the radiation oncologist. The need for close collaboration further sensitizes the surgical team to the possible indications of IORT and calls for greater multidisciplinary integration and the possibility of implementing specific protocols.

The definition of the physical characteristics of the electron and photon beams used for IORT requires an accurate initial dosimetry and monitoring according to quality assurance procedures that are to comply with international recommendations. The identification of the procedures to be followed during the execution of the IORT treatments and the documentation certifying compliance with such procedures are essential for optimizing the quality assurance

program of this treatment. Given the peculiarities of the methods, the clinical, technical and physical aspects of the use of X-ray sources and of the electron beams are presented separately.

All the practical and technical-organizational details of IORT are shown in Appendix A, while Appendix B contains summary sheets on the main quality assurance indications in IORT with electrons and photons.

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Chapter 1
IORT TECHNIQUE: PROFESSIONAL FIGURES AND METHODS OF DELIVERY

1.1. Professionals involved in intraoperative radiotherapy: the regulatory framework of reference

Patient health protection is dealt with in Title XIII of Italian Legislative Decree 101/2020 (1) which lays down the safety objectives for patients that are pursued also through the identification of specific professional figures, the definition of the activities to be carried out and the ensuing attribution of roles, functions and responsibilities. A fundamental requirement laid down in the legislation is the adequate training of the health professionals responsible for ensuring patient radiation protection.

The professional figures, their roles and their functions underlying the system of responsibility envisaged by Title XIII are indicated in the following, with special reference to those involved in intraoperative radiotherapy.

In the following, unless specifically indicated, the Articles mentioned are to be understood as referring to Legislative Decree 101/2020 (1).

Each Centre should set up two working groups: a Quality Group, with strategic and organizational tasks, and an Operational Group, essential to facilitate the multidisciplinary integration that characterizes this procedure and to define and monitor the quality assurance programs for the different treatment strategies.

1.1.1. Quality Group and Operational Group

The Quality Group is of fundamental importance in the initial phase of the IORT program and maintains its importance throughout the activity, ensuring that quality standards are monitored and maintained.

The group, coordinated by the Health Director, includes professionals from the following Units: Oncological Radiotherapy, Specialized Surgery, Health Physics/Medical Physics, Anaesthesia and Critical Care Resuscitation/ Intensive Care, Department of Health and Social Professions, Technical Division.

The tasks of the group are aimed at the Quality Assurance of the IORT program. In particular the tasks are to:

- identify treatment targets, estimate workloads and assess the resources needed;
- identify the nominal characteristics of the radiological system to be used for the treatment, including related accessories;
- plan masonry, plant and radioprotection work, if any;
- take care of paperwork and documentary aspects (description of the procedure, treatment and anaesthesiology protocols and traceability via the anaesthesia card for procedures outside the operating room, forms, etc.);
- check conformity between the research and treatment proposals according to clinical evidence;

- verify that the envisaged quality procedures (scheduled maintenance, periodic quality checks, evaluation of indicators, etc.) are carried out systematically;
- provide a permanent training program for the professionals involved in IORT procedures;
- keep an archive of the treatment protocols under way and of the main scientific publications;
- define the patient's follow-up procedures.

The Operational Group is made up of a Radiation Oncologist, a Surgeon, a Medical Physicist, an Anaesthesiologist, a Radiation Technologist and Nursing staff. Its constitution is essential to promote the multidisciplinary integration that characterizes IORT treatment.

In the start-up phase of the IORT program, it must address the organizational aspects, in accordance with the indications of the Quality Group, defining the time schedule and needs for the implementation of the method.

Once the IORT program has started, it must comply with the quality standards and promptly report any critical issues to the Quality Group.

The professional figures of the Operational Group, their roles and responsibilities according to Legislative Decree 101/2020 (1) are reported and described below.

1.1.1.1. Radiation oncologist

IORT is a radiotherapy technique for which the radiation oncology specialist has full clinical responsibility (prescription and execution of the treatment), as set forth in Legislative Decree 101 2020 (1). In accordance with Legislative Decree 101/2020 (1) and with Article 4 of Law 341 of 19 November 1990 (2), the medical specialist (in the case of radiotherapy: the radiation oncologist) is defined as the surgeon (or dentist) who has the qualifications to assume clinical responsibility for individual medical actions pursuant to this decree and who after graduating from university obtained a university specialization diploma qualifying him as specialist in radiotherapy or the equivalent qualification of specialist in oncological radiotherapy (which therefore authorizes him to use ionizing radiation for therapeutic purposes), or surgeons without specialization but who have worked for at least 5 years in the corresponding specialty on the date of entry into force of the aforementioned decree (3).

In the case of IORT, in particular, the radiation oncologist:

- proposes the clinical research protocols that pertain to the IORT program;
- is responsible for the selection of patients eligible for treatment and for the ensuing treatment plan;
- is responsible for the management of the treatment equipment;
- discusses, in the assessment of the patient's eligibility for IORT, the surgical procedure with the surgeon; together they define the area to be irradiated;
- participates, during surgery, in the assessment of the extent of the tumour and its relationship with adjacent structures;
- decides jointly with the surgeon on the technical feasibility of the treatment for which he has full responsibility;
- is responsible for the definition of the area to be irradiated (Clinical Tumour Volume (CTV)) and for the Planning Target Volume (PTV) and he cooperates with the surgeon in making this assessment (assessment of suspect areas of infiltration, possible intraoperative frozen section diagnosis of the resection margin, mobilization and displacement of healthy structures);
- is responsible for prescribing the irradiation dosage, for the choice of the applicators to be used and for the energy of the electron beams required; he makes the latter assessment in collaboration with the medical physicist;

– is responsible, during the treatment phase, for the procedure that provides for the positioning of the applicator on the area to be irradiated and for the correct coupling between the lower and upper part of the applicator (he does this in collaboration with the surgeon, the physicist and the radiotherapy technical staff);
– is responsible, at the end of treatment, for the description of the procedure which is to be reported in a specific form;
– is responsible together with the surgeon for the organization and execution of the follow-up of patients who have received IORT treatment.

Prescribing and reporting guidelines are provided in Appendix A1.

1.1.1.2. Surgeon

The surgeon discusses clinical research protocols and the indications for treatment of individual patients with the radiation oncologist. Furthermore, the surgeon:

– is responsible for the indication for surgery, the surgical procedure and patient management in the postoperative course;
– discusses the surgical procedure with the radiation oncologist before surgery, contributing to the definition of the area to be irradiated and the structures to be shielded, and plan any changes to the intervention to facilitate the feasibility of the IORT;
– performs the surgical procedure for the removal or exposure of the tumour, on the basis of what has been agreed with the radiation oncologist and of what is technically feasible;
– assesses, during surgery, together with the radiation oncologist, the extent of the tumour and the presence or absence of a macroscopic residual after resection, specifying its location, relationship and size; in this regard, the surgeon may take samples for intraoperative frozen section analyses;
– helps the radiation oncologist to define the area to be irradiated and is jointly responsible for its optimal exposure and in particular for the mobilization, protection and dislocation of the surrounding healthy structures;
– is responsible for the surgical exposure of the area to be irradiated;
– verifies, upon completion of the treatment, that no injuries have been caused;
– is responsible, as part of the multidisciplinary follow-up, together with the radiation oncologist, for the monitoring and management of possible side effects resulting from the IORT treatment.

In case of IORT with a non-dedicated LINAC (LINear ACcelerator), the surgeon:

– is responsible for any temporary suturing of the surgical wound and for ensuring it remains sterile;
– follows the patient during transfer, if any, to the radiotherapy bunker and is present during the delivery of the treatment for any surgical emergencies.

1.1.1.3. Anaesthesiologist

The anaesthesiologist is responsible for the anaesthetic procedure and for monitoring the patient during surgery, during transport (in case of non-dedicated LINAC), during irradiation and in the awakening phase. In all these phases the anaesthesiologist is assisted by the nursing staff.

In case of IORT with a non-dedicated LINAC, the anaesthesiologist is responsible:

– for the preparation of the anaesthesiological instrumentation and check of its functioning, for the preparation of the anaesthetic drugs, and for the prevention and management of the anaesthetic emergencies also in the radiotherapy bunker;
– for the transport of intubated, ventilated and sedated patients;

– for the preparation of the portable instrumentation required to ensure adequate ventilation and monitoring of vital parameters during transport.

The anaesthesiologist is also responsible for:

– the multiparameter monitoring (through an internal television circuit or through a repeater monitor connected to the control unit) of the patient's vital parameters during the IORT treatment (including temperature and depth of the anaesthesia using appropriate instruments) (4). If necessary, it must be possible to immediately interrupt the treatment to ensure immediate assistance to the patient;
– the prevention and management of any anaesthetic emergency ensuring that the necessary instrumentation and pharmacological support are available; they must also verify that continuity of care complies with the clinical safety criteria, in collaboration with the intensive-care team, also after the IORT;
– training of radiotherapy nurses to support the IORT procedures.

With regard to the operating room, these responsibilities remain unchanged even where treatment is provided through a dedicated accelerator, with a preliminary assessment being made of any extension of the duration of anaesthesia in order to complete the IORT procedures.

1.1.1.4. Medical physicist

The medical physicist is a physics graduate with a specialization diploma in Medical Physics or Health Physics and, consequently, they are expected to have the knowledge, training and experience required to operate or to express opinions on issues concerning radiation physics applied to medical exposures (Article 7, definition 148, Legislative Decree 101/2020) (1).

These qualifications, as well as registration with the Italian Order of Chemists and Physicists, are a necessary condition for carrying out the activities of medical physicist in the specific field of application of Legislative Decree 101/2020 (Article 159, paragraph 11) (1).

The decree does not introduce any new transitional forms but confirms those introduced in the previous regulatory framework (Article 159 paragraph 16) according to which university graduates in Physics, Chemistry and Engineering, without specialization, who can provide proof of having carried out the activity of medical physicist pursuant to Article 7 paragraph 5 of Legislative Decree 187/2000 (5), can go on carrying out their previous activity subject to:

– registration with the relevant Professional Order;
– informing the supervisory body competent for the area that they are carrying out that activity;
– providing the supervisory body with certificates demonstrating the completion of periodic professional training, which must be equivalent to what is required for the medical physicist in Article 162 paragraph 3.

As regards intraoperative radiotherapy, the medical physicist:

– participates in the optimization process, within the scope of their competences, in accordance with the procedures defined by the guidelines referred to in Article 161 paragraph 1 (Article 159 paragraph 8);
– provides specialist advice, having sole responsibility for the measurement and assessment of the doses absorbed by patients in the context of the exposures referred to in Article 156 paragraph 2, as well as for the selection of the instrumentation to be used for patient dosimetry, and for the quality checks to be carried out on the medical-radiological equipment (Article 160 paragraph 1);
– carries out the acceptance testing and performance testing of the medical-radiological equipment, respectively for the purposes of technical testing and after any relevant maintenance intervention (Article 160, paragraph 2, letter a);

- helps to define and carry out quality assurance programs aimed at implementing the optimization principle (Article 160 paragraph 2, letter b);
- contributes to ensuring surveillance of the medical-radiological equipment also through adequate quality control (Article 160 paragraph 2, letter c);
- defines protocols for the performance of functional tests on the medical radiological equipment (Article 160 paragraph 2, letter d);
- carries out the dosimetric treatment planning in compliance with the therapeutic prescriptions by the specialist doctor and ensures that the dosimetry checks are carried out (Article 160 paragraph 2, letter e);
- contributes to the prevention and analysis of accidental and incorrect exposures referred to in Article 167 (Article 160 paragraph 2, letter f);
- contributes to the training of the health professionals involved in medical exposures with a view to protecting patients (Article 160 paragraph 2, letter g);
- expresses his opinion on the technical quality of the medical-radiological equipment (Article 163 paragraph 5);
- keeps track of the European and international recommendations and indications regarding quality assurance programs and the acceptability criteria of the radiological equipment used (Article 163 paragraph 11);
- ensures, within the scope of their competence, that the work-up, treatment with ionizing radiation and relevant technical parameters are recorded individually on an IT medium (Article 168 paragraph 1).

1.1.1.5. Therapeutic radiographer

The professional activities of a Therapeutic radiographers (Tr) can be carried out only by graduates in Medical Radiology Techniques for Imaging and Radiotherapy, or by professionals holding an equivalent qualification, in accordance with the Decree of the Ministry of Health of 27 July 2000, published in *Official Gazette* no. 190 of 16 August 2000 (5), and registered with the relevant Order of Radiology Technologists, Technical Health Professionals of Rehabilitation and Prevention (Article 159 paragraph 12) of Legislative Decree 101/2020).

In particular, where the radiation technologist is a member of the Radiology team, within the scope of their competences they

- participate in the optimization process (Article 159 paragraph 8), in accordance with the procedures defined by the guidelines referred to in Article 161 paragraph 1);
- are responsible for the practical aspects of carrying out the medical-radiological procedure (or part of it), governed by the guidelines referred to in Article 161 paragraph 1 (Article 159 paragraph 3);
- participates in the performance of quality control, on the basis of the indications and of the execution protocol prepared by the medical physicist (Article 163 paragraph 7).
- promptly notifies the Manager who is in charge of the Quality Assurance of radiological procedures according to the methods defined by the Manager, of any circumstances, even if only potential, of accidental or undue exposure (Article 167 paragraph 3);
- ensures that the workup, treatments with ionizing radiation and the main technical parameters relating to them are recorded individually on a computerized medium, also for the purpose of preparing the data referred to in (3 and comparing them with the Diagnostic Reference Levels (DRL), where applicable (Article 168 paragraph 1).

With regard to IORT, the Tr is responsible for carrying out the technical procedure and for the correct use of all the equipment entrusted to them; as member of the team they cooperate with the radiation oncologist and with the medical physicist in preparing the treatment set-up and is responsible for the operational procedure for managing the control console of the

radiological system and for carrying out the treatment, in compliance with the indications of the radiation oncologist and the medical physicist.

1.1.1.6. Nursing staff

The nursing profession is regulated by the professional profile (MD 14 September no. 739/1994). Nursing is open to individuals who have obtained a qualification diploma and to those in possession of a degree in Nursing pertaining to class no. 1 of the university degrees of the Major in Health Professions provided for in MD of 2 April 2001. To practice as a nurse, individuals need to be enrolled in one of the registers run by the Provincial Orders of the Nursing Professions (OPI). Nurses are responsible for general nursing care, and contribute to identifying the health needs of the individual and of the community. Nurses work jointly with the multidisciplinary team and they manage and evaluate the nursing care to be delivered to patients for which they are entirely responsible.

During IORT the nurse guarantees the safety and continuity of patient management before and during the procedure. In particular, the nurse:

- guarantees patient safety by not asking leading questions;
- sets up the operating room, with the help of the support staff, making sure that all the instruments for patient care and for carrying out the operation/treatment are available;
- guarantees a safe environment for the patient and for the entire team by contributing to ensuring compliance with radiation protection procedures;
- collaborates with the entire surgical team, monitoring vital parameters, verifying the safety positions, ensuring the sterility of the operating/treatment field and the administration of the prescribed therapy;
- is co-responsible for compliance with the differentiated entrance and exit pathways and with the buffer zone, in order to ensure sterility of the operating field;
- supervises and monitors the possible side effects deriving from surgical procedures, guaranteeing prompt treatment in case of urgency/emergency;

When IORT is delivered without a dedicated LINAC, in addition to shouldering the responsibilities described above, the nurse:

- receives the patient, makes an assessment of care needed, provides health information to the patient and to their caregivers and carries out the risk management activities required by the Hospital Management;
- makes sure the environment within the bunker area is safe, in compliance with radiation protection standards;
- guarantees continuity of care (information, management and relationships) among the various professionals and operational contexts.

1.1.1.7. Medical Director

The Medical Director coordinates the activities of the Quality Group.

The duties and skills of the Medical Director are defined by Legislative Decree 502/1992 (6), by Legislative Decree 517/1993 (7) and by the Regional Accreditation Regulations.

The job description of a Medical Director includes multidisciplinary skills. In particular, their tasks can be summarized as follows (8):

- strategic development (governing the planning, programming and innovation of activities);
- ensuring that services provided comply with the service standards;
- operational management (resource optimization);
- enhancement of human resources;

– guarantee and supervisory functions.

1.1.1.8. Technical Department

The task of the Technical Department is to:
– draw up the technical document containing the requirements to be included in tender or purchase order documents;
– coordinate the modifications that are necessary so that the radiology system can be used in the operating room or bunker, in accordance with current legislation;
– oversee the installation and technical-administrative testing of the radiology system including its accessories, as well as of any structural changes to be made to the operating room or to the bunker;
– define the technical aspects of the best route to be followed, where necessary, for transporting the patient (lifts with uninterruptible power supply, cordoning off the route, etc.) to the bunker, making sure that it works;
– contribute to the definition of the procedures to be adopted in case of failures and emergencies.

1.2. Delivery of IORT (IOERT or kV-IORT)

1.2.1. IOERT

The use of electron IORT (IOERT) is historically the most reported in the literature. The first treatments were carried out by adapting conventional accelerators to the IORT modality. Subsequently, dedicated mobile accelerators were introduced to be used directly in the operating room. This chapter describes the different types of equipment available today. The equipment used for treatment may be associated with dedicated or non-dedicated accelerators.

1.2.1.1. Non-dedicated accelerators

1.2.1.1.1. Characteristics of the accelerator

The non-dedicated LINAC may be used for IORT without requiring any structural and/or functional changes (electron beam production system, energy range and dose rate).

However, the IORT procedure requires the use of beam collimation accessories that are different from conventional electron applicators used for EBRT. These accessories are characterized by the type of beam collimation system chosen (hard-docking or soft-docking).

Accessories

The accessories required for IORT treatment are:
– main adapter to be fixed to the LINAC head;
– docking adapter connected to the main adapter which may be fixed or telescopic;
– set of applicators for IORT treatment of different sections and different shapes;
– set of applicators for simulating the treatment to be performed in the operating room which are to be the same as those used for the real treatment;

– visualization and verification system of the surgical cavity to be irradiated after completion of the docking, with a periscope equipped with a moving mirror or an optical fibre periscope, generally applied to the adapter, as well as an image recording system;
– camera in the LINAC control room to view the monitoring systems of the patient's vital parameters.

1.2.1.2. Dedicated accelerators

These are electron accelerators that can be used in the operating room without any specific adaptation or structural changes.

They have been designed to emit a low level of diffused radiation.

They are mobile and can be moved within the operating room and from one surgery room to another.

They are mobile and flexible so that they can assume all the positions necessary to perform the treatment, from macro-movements for approaching the bed down to micro-movements to facilitate alignment and docking with the applicator. There are two different ways of positioning the applicator for treatment: hard-docking and soft-docking, which make sure that the correct position of the applicator during the coupling procedure is maintained. In hard-docking, the applicator is divided into two parts: a lower part (terminal) placed directly in contact with the tumour bed and an upper part, which is attached to the head. The two parts are physically coupled. In the case of soft-docking, the applicator is supported by surgical elements and the coupling is of the optical type.

The mobile electron accelerators currently in use are the NOVAC7 (no longer marketed), the NOVAC11 and the LIAC (in different versions) produced by SIT, and the Mobetron produced by IntraOp. The characteristics of the accelerators currently on the market are presented in the following.

1.2.1.2.1. NOVAC 11 accelerator

The NOVAC 11 accelerator is an upgrade of the NOVAC7 accelerator, from which it differs for the applicator length, maximum energy and dose per pulse values.

The NOVAC11 mobile unit is 235 cm long, 95 cm wide and has a minimum height of 235 cm. It weighs approximately 630 kg.

The nominal energies available vary in the 4 MeV - 10 MeV range.

The dose rate for the reference applicator is within the 4-30 Gy/min range; the pulse frequency is 9 Hz, and the dose per pulse is between 7 and 56 mGy.

Adjustments are made at the company site during the acceptance test; Subsequently, minor variations around the set values can be made.

The level of scattered radiation measured at the machine plane at a distance of 3 m is less than 0.3 μSv for each Gy of delivered dose at z_{max}.

For treatment, the applicator positioning is done in hard-docking mode.

Accessories

The NOVAC 11 accelerator is equipped with a set of PolyMethylMetaAcrylate (PMMA) applicators with a diameter between 3 and 10 cm. The applicators are supplied with different bevel angles (0°, 15°, 22.5°, 30° and 45°) so that they can be positioned according to the inclination of the surface of the target volume. The distance between the source and the treatment surface is determined by the length of the applicators (80 cm for the reference applicator and 65 cm for all other applicators).

Mobile radiation protection shields and a horizontal beam absorber are optionally provided: the latter can be tailor-made based on the specific radiation protection needs of each installation.

For the protection of the organs and tissues located downstream of the target, the manufacturer can supply discs made of PolyTetraFluoroethylene (PTFE) and steel. The manufacturer can also supply a Monte Carlo simulation software, which facilitates the commissioning and the dosimetric characterization of the beams, i.e. depth dose curves (Percentage Depth Dose, PDD), transversal dose profiles at fixed depth, isodose curves and OF (Output Factor).

The accelerator has a Treatment Planning System (TPS) with three-dimensional (3D) ultrasound (US) / Computed Tomography (CT) imaging. Once the planning has been approved, the integrated optical tracking system provides information to the user regarding the correct positioning of the applicator onto the target surface. Then, based on the real position of the applicator, the TPS recalculates the final treatment plan.

Compliance with the DICOM standard allows the user to load and export data into typical *Record & Verify* information systems.

1.2.1.2.2. LIAC Accelerator (in LIAC and LIAC HWL versions)

The mobile unit is 210 cm long, 76 cm wide and has a minimum height of 180 cm. The weight of the LIAC is 400 kg while the LIAC HWL weighs 570 kg.

The nominal energies available vary in the 6 MeV-12 MeV range, depending on the model of the accelerator.

The dose rate for the reference applicator is within the range from 3 to 20 Gy/min for the LIAC and 10 to 30 Gy/min for the LIAC HWL; with the adjustable pulse frequency for both accelerators being between 5 and 50 Hz, the dose per pulse is between 3 and 33 mGy for the LIAC and between 8 and 50 mGy for the LIAC HWL.

Adjustments are made at the company site during the acceptance test; subsequently, minor variations around the set values can be made.

The level of scattered radiation measured at the machine plane at a distance of 3 m is less than 0.6 μSv for the LIAC and 0.2 μSv for the LIAC HWL for each Gy of delivered dose at z_{max}.

For treatment, the applicator positioning is done in hard-docking mode.

Accessories

The LIAC and LIAC HWL accelerators are equipped with a set of applicators in PMMA with a diameter between 3 and 10 cm. The applicators are supplied with different bevel angles (0°, 15°, 30° and 45°) so that they can be positioned according to the inclination of the surface of the surgical volume to be treated. The distance between the source and the treatment surface is determined by the length of the applicators (71.3 cm for the LIAC with 60 cm applicators and 64.5 cm for the LIAC HWL with 40 cm applicators).

Mobile radiation protection shields and a horizontal beam absorber are optionally provided: the latter can be tailor-made based on the specific radiation protection needs of each installation.

For the protection of the organs and tissues located downstream of the target, the manufacturer can supply discs made of PolyTetraFluoroEthylene (PTFE) and steel. The manufacturer can also supply a Monte Carlo simulation software, which facilitates the commissioning and the dosimetric characterization of the beams (i.e., PDDs, transversal dose profiles at fixed depth, isodose curves and OFs). The accelerator features a TPS with three-dimensional (3D) US/CT imaging. Once the planning has been approved, the integrated optical tracking system provides information to the user regarding the correct positioning of the

applicator on the target surface. Then, based on the real position of the applicator, the TPS recalculates the final treatment plan.

Compliance with the DICOM standard allows the user to load and export data into typical *Record & Verify* information systems.

1.2.1.2.3. Mobetron Accelerator

The mobile unit is 223 cm long, 109 cm wide and has a minimum height of 198 cm. Its weight is approximately 1400 kg, including an integrated beam absorber, which automatically tracks the movements of the head and includes interlocks to block the delivery of the beam in the event that it is not aligned with the beam.

Nominal energies vary in the 6 MeV-12 MeV range. Furthermore, the proprietary management software offers the possibility of combining beams with different nominal energies thus offering great flexibility in defining the depth of penetration of the combined beam.

The dose rate for the reference applicator is 10 Gy/min, even though it can be provided at a nominal dose rate starting from 3Gy/min, with a dose per pulse that is lower than 6 mGy.

The level of scattered radiation measured at the machine plane at a distance of 3 m is less than 0.3 μSv for each Gy of delivered dose at z_{max}.

For treatment, the applicator positioning is done in soft-docking mode.

Accessories

The Mobetron accelerator is equipped with a set of applicators having a diameter between 3 and 10 cm, with 0.5 cm increments. The applicators are supplied with different bevel angles (0°, 15°, 30° and 45°) in order to allow their positioning according to the inclination of the surface of the target volume. There are also rectangular and elliptical applicators that allow to deliver uniform doses of radiation over relatively large volumes. For each applicator and bevel angle, a plastic bolus of 5 and 10 mm thickness is provided, to create a build-up effect while it also minimizes the irregularities of the surface of the tissue.

The accelerator has proprietary management software, equipped with planning, quality control and DICOM connectivity tools in a single platform and TPS with three-dimensional (3D) CT imaging.

Compliance with the DICOM standard allows the user to load and export data into typical *Record & Verify* information systems.

1.2.2. kV-IORT

In the last 15-20 years, at both national and international levels, there has been a huge increase in the use of mobile devices for IORT that produce low-energy photons (typically X-rays ≤ 50 kV).

Numerous papers in the literature have examined the various aspects of this method from a clinical, radiobiological physical and dosimetric point of view. This scientific evidence has given kV-IORT an important role in the treatment of oncological diseases.

The X-ray generator delivers a high dose of X-rays directly to the tumour bed immediately after the surgical excision of the tumour. This treatment modality has some peculiar aspects. First, the dose delivered to the tumour bed decreases sharply in a manner that is approximately proportional to the inverse of the cube of the distance from the applicator; a second important aspect is the fact that the relative biological effectiveness (RBE) of low-energy photons is greater than that of high-energy photons.

In addition to the normal procedures aimed at ensuring the sterility of the surgical field, as described in (6.3 with regard to radiation protection, the operating room does not need special shielding. In any case, before installing the device, a study of the distribution of spaces in the operating room and adjacent rooms is recommended, as well as an evaluation of the transit pathways. Based on these considerations, mobile shields may be adopted, where necessary.

The mobile photon systems in use today are Intrabeam, Xoft System, ioRT-50 System and Papillon^{+TM}. The characteristics of the systems currently on the market are shown below.

1.2.2.1. Intrabeam

The Intrabeam system (Zeiss) is a specific device for intraoperative radiation treatment developed to be inserted in direct contact with the tumour bed through the surgical breach after macroscopic resection of the tumour, in any part of the body. It includes a stand, a miniature accelerator, specific applicators for various uses and a trolley equipped with a touchpad terminal, control unit, dosimeter and other components necessary for quality control and treatment (9). The stand consists of a base on which a mechanical arm with six degrees of freedom is installed endowed with a weight balance system and magnetic brakes that keep the accelerator still so that it can maintain its position during irradiation of the target area. The radiation source is mounted at the end of the mechanical arm. Overall, the weight of the device does not exceed 160 kg and it has a footprint of approximately 1 x 2 x 1 m (DxWxH); Intrabeam is endowed with a Floor Stand having six degrees of freedom, rollers and electromagnetic brakes which make it easy to move within the operating room and from one room to another.

The radiation source (XRS 4 X-ray Source), mobile and miniaturized, is composed of an internal radiation monitor (IRM), an emission cathode, an accelerator section, an electron beam deflector, a probe and a thin gold target (Figure 1).

The electron beam accelerated with a maximum potential difference of 50 kV across the probe (100 mm long and 3.2 mm in diameter) reaches the gold target producing low-energy X-rays. The IRM detects part of the X-rays delivered in the direction of the cathode and records the dose rate in real time. The result is reproduced on the treatment screen of the control unit and therefore allows continuous control of the dose released during the entire treatment.

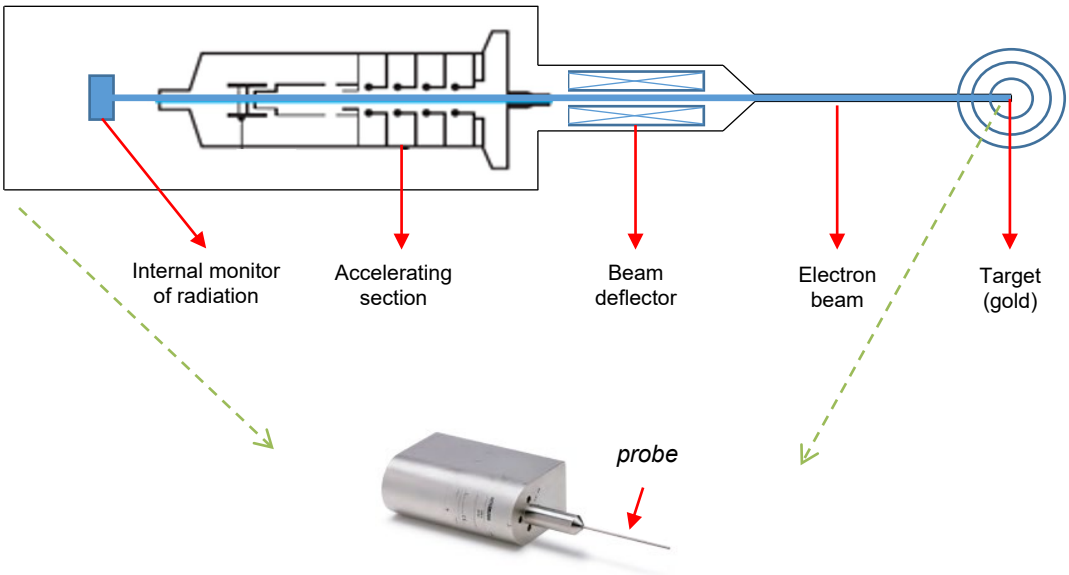

Figure 1. Radiation source (XRS 4 *X-ray Source*) and *probe*

The spot emission of photons provides an almost spherical distribution of the dose around the isocentre, with good isotropy between -130° and + 130° with respect to the rotation axis of the probe itself; the positioning precision of the delivered dose is of ± 1 mm at 40 mm in diameter from the isocentre. Depending on the clinical application, applicators of various types and different sizes can be attached to the radiation source.

1.2.2.2. Xoft

The Xoft (Axxent) system is designed to deliver brachytherapy and kV-IORT treatment. It includes a controller, the X-ray source, and a set of source cooling tubes. The controller moves the X-ray source in a linear step-by-step mode through the applicator, based on the time and position data entered by the operator. The source is a miniaturized X-ray tube, operating at 50 kV, located on the tip of a refrigerated catheter, which releases the radiation in linear step mode to deliver conformational doses through the applicator directly to the tissue. The X-ray source is a non-sterile disposable device. The life of a source varies depending on the frequency of use. On average it is replaced every month.

1.2.2.3. ioRT-50

The ioRT-50 (WOmed) unit consists of an X-ray tube that delivers photons, at multiple energy configurations up to 70kV (e.g., 30kV - 50kV - 70kV depending on clinical needs). The system is mounted on a mobile trolley, which can be operated via a touch-screen panel or remotely with a tablet PC. The head is mounted on a movable arm capable of rotating on two axes. An anchoring mechanism allows the patient to maintain a stable treatment position in any position, from standing to lying down. The delivery of the dose is homogeneous around the spherical surface of the applicators. The high dose rate ensures short treatment times.

1.2.2.4. Papillon^{+TM}

The Papillon system (Ariane Medical System Ltd), initially developed for contact radiotherapy treatment with low-energy X-rays, has spherical applicators to deliver IORT treatment to breast cancer since 2016. The system consists of an X-ray generator operating at 30 or 50 kV, various applicators and a terminal for remote control. The electrons emitted by the cathode are accelerated and electrostatically focused on an inner copper tube about 20 cm long, they then strike a rhenium plate producing a beam of X-rays having a symmetric radial distribution. An external steel cylinder contains the acceleration structure, a beryllium window for removing the electrons from the radiation beam, an oil cooling system, a homogenizing aluminium filter, an ionization chamber for monitoring the radiation beam and an exit window in polycarbonate. Clinical applicators are mounted on the outer cylinder. The beam has an aperture of 140°; at a distance of 20 mm the field has a diameter of 25 mm and the dose rate produced is 30 Gy/min. An advantage of the Papillon system is its ability to deliver high dose rates compared to other low-energy X-ray systems, thus reducing the IORT treatment times to a few minutes (10).

1.2.2.5. Accessories

The kV-IORT applicators come in various shapes and sizes, such that they can be used for the treatment of various tumours in different clinical situations (Figure 2).

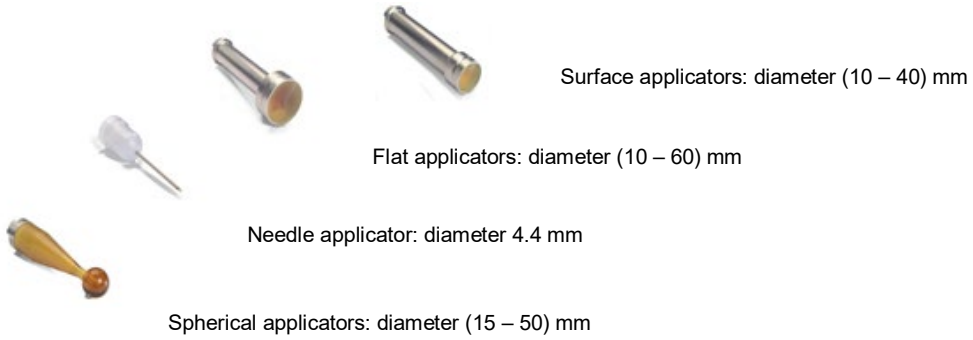

Figure 2. Examples of applicators for kV-IORT and their typical sizes

The types of applicators available include:
- spherical and needle applicators whose emission geometry is "almost spherical";
- flat applicators and applicators for surface therapy with a flat emission geometry;
- cylindrical applicators that allow the positioning of the source along the longitudinal axis of a slide inside the applicator, in order to produce an "almost" cylindrical emission geometry.

All applicators can be sterilized and reused.

The spherical applicators that the Intrabeam, Xoft, ioRT-50 and Papillon$^{+\ TM}$ systems are equipped with are used for intracavity treatment of the tumour bed, for example for breast-conserving surgery or for the treatment of brain tumours; they are inserted into the cavity created by removing the tumour. They generally vary in diameter from 1.5 to 6 cm, and are made from plastic material with high resistance to radiation damage. The choice of applicator size is made on the basis of the size of the tumour cavity size.

Some of these systems are also equipped with applicators of other forms, including: the needle applicator that can be used for the treatment of vertebral metastases, superficial applicators for the treatment of skin cancer, cylindrical applicators for the treatment of gynaecological tumours and flat applicators (flat) for the treatment of ellipsoidal gastro-enteric tumours.

1.2.2.5.1. Treatment table

The treatment table corresponds to the surgery table in the operating room, where the IORT device is located. No movement of the table is necessary during treatment because the system is equipped with a mechanical arm that allows maximum flexibility.

1.2.2.5.2. Anaesthesiological procedure

The anaesthesia used is that normally adopted for surgical procedures. The additional anaesthesia time when performing IORT varies from 20 to 50 minutes, with a variable depending mainly on the diameter of the applicator used. The entire clinical procedure takes place with sedation-narcosis at the discretion of the anaesthesiologist, based on the characteristics of the patient and the type of treatment. Whatever the anaesthetic procedure

chosen, it must comply with the safety standards required for general anaesthesia in terms of equipment, monitoring and dedicated personnel (11).

1.2.3. General remarks

Some general aspects need to be assessed irrespective of the type of accelerator/system used, for instance, protection of the organs and tissues downstream of the target, the cleaning and sterilization of the applicators and accessories used, the choice of the system for assessing the thickness of the target, and the treatment bed.

To protect the tissues underlying the target (essentially in the case of IOERT), shields made of composite material (high and low atomic number) or plastic are normally used, with a diameter slightly larger (about 2 cm) than that of the applicator. In the case of shields having a high atomic number, the transmitted dose and the backscattered dose need to be carefully assessed.

It is necessary to have at least two sets of internal shields (if they are used) and applicators of all diameters and angles and at least three sets of the most commonly used applicators

The applicators and accessories (in general, all the material that comes into contact with the patient) must be washed and sterilized after use, according to the indications given in the manufacturer's technical data sheet and stored in an easily accessible location for retrieval for the IORT procedure. Expiration dates of sterilization must be recorded as well as the number of sterilizations of the applicators, shields and various accessories, so as to keep track of the wear of the material in accordance with the indications provided in the technical data sheets.

Assessment of target thickness can be made using a graduated needle, ultrasound probe, or X-ray imaging.

To facilitate the preparation of the treatment set-up, it is advisable, in the case of IOERT, to use treatment tables with many degrees of freedom. For treatment with a non-dedicated accelerator, the use of a single treatment table is recommended, suitable for both patient transfer and treatment.

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Chapter 2
CLINICAL INDICATIONS AND RATIONALE

In recent years, the role of IORT in the context of combined therapeutic strategies has been increasingly better defined (1, 2).

The main clinical advantages are the following:

- reduction of the irradiated volume by means the direct visualization of the tumour;
- exclusion of dose-limiting structures through surgical mobilization or direct shielding and by using appropriate electron or photon energies;
- increase in the "effective" dose delivered to the tumour and sterilization of the microscopic component of the disease;
- immediate irradiation of any residual tumour cells in the operative field thus offsetting any possible tumour cell repopulation.

Furthermore, the overall reduction in the time required to complete the radiation treatment allows the radiotherapy workload to be optimized while saving the patient's social time (fewer absences from the family and/or work, reduction of logistical inconvenience due to travel).

Since the IORT is performed during the surgery, the radiation treatment is always administered in a single fraction. Although its radiobiological efficacy has not been fully clarified, the single dose administered by IORT is estimated to probably have a cell-killing power that is equivalent to twice or three times the dose delivered by conventional fractionated treatments. Therefore, by administering a boost of 10 Gy through IORT, followed or preceded by an EBRT of 45-50 Gy, an overall dose biologically equivalent to about 65-80 Gy is delivered with a higher probability of eliminating any residual disease and a possibly increasing local control (3).

From a technical point of view, during surgery, after resection of the tumour, metal clips placed in the tumour bed accurately map the site of the primary tumour and location of the resection margins, especially after surgical tissue remodeling. Thanks to the presence of these clips the dose distribution of EBRT in combined radiotherapy treatments can be optimized thus avoiding over/underdosing in the IORT field (4). Furthermore, in case of recurrence, the clips identify the site of the recurrence with respect to the IORT field (infield or outfield recurrence) and contribute to verifying whether the conditions exist for further radiotherapy (retreatment).

The indications for use, technique and results of the studies by anatomical areas are illustrated below.

2.1. Breast carcinoma

2.1.1. Introduction and background information

Intra-operative radiotherapy of the breast delivers a dose of radiation directly to the tumour bed immediately after tumour resection, during conservative surgery, either as exclusive radiotherapy (Accelerated Partial Breast Irradiation, APBI) or as a boost. The rationale of APBI is based on the observation that after conservative surgery, most recurrences occur at or near the site of the primary tumour (5). In Holland's study, 90% of residual neoplastic foci were confined within 3 cm of the primary tumour (6), supporting the effectiveness of APBI in increasing local control. APBI has progressively established since the early 2000s hence

introducing the concept of partial irradiation for low-risk cases in the international guidelines (7). IORT represents a modality of APBI with theoretical and practical advantages and a favourable cost/benefit ratio (8), in case eligible patients are carefully selected. The IORT treatment can be delivered with electrons (IOERT) or with low energy photons (kV-IORT). Both modes have been tested in dedicated studies with experiences dating back to the late 1990s.

The Milan experience has made a fundamental contribution to the development and implementation of the single dose IOERT, with the design and execution of phase I trials to establish the optimal dose, of phase II trials to evaluate acute and intermediate toxicity (9), and of a phase III trial to investigate the efficacy of IOERT at a dose of 21 Gy compared to EBRT on the whole breast at a dose of 50 Gy, followed by a boost of 10 Gy, using an equivalence design. Based on the ELIOT randomized trial published in 2013 (10), the guidelines on APBI, updated by ASTRO (American Society for Radiation Oncology) have recognized the role of IOERT as single treatment in tumours whose biomolecular and histopathological characteristics fall into the category of tumours with the best prognosis (2.11). In the revision of the ASTRO guidelines, there are still indications that patients to be treated with kV-IORT should be included in controlled clinical trials, given the fact that at the time when the guidelines were drafted, the follow-up of the phase III TARGIT-A trial (TARGet Intraoperative radioTherapy) was too short (12). Unlike the IOERT, the TARGIT trial uses a spherical applicator of suitable sizes which houses the photon source in its centre. This configuration allows for a three-dimensional delivery of the radiation dose in an isocentric manner to the tumour cavity (13).

The IORT boost to the tumour bed, which can be delivered with both IOERT and kV-IORT, offers the advantages of easier identification of the tumour bed, of early irradiation with potential radiobiological benefits, of carrying out an oncoplasty procedure if required, and of avoiding problems related to the identification of the boost site in the postoperative context. To date, the IORT boost has shown excellent results in terms of tolerance (14) and good local control. In the current HIOB (Hypofractionated IntraOperative Boost) study, both acute and chronic toxicity were found to be very low (2).

The selection criteria, the treatment technique, the indications and a review of the literature in this regard have been described in the published ESTRO-ACROP guidelines (2).

2.1.2. Multidisciplinary pre-surgical assessment

In order to correctly define whether the IORT treatment is indicated or not in light of the criteria laid down in national and international documents, the following assessments are considered mandatory before prescribing the method:

- *clinical evaluation*: the surgeon and the radiation oncologist must evaluate the feasibility of the method, considering the clinical factors indicated above, the volume of the breast and the site of the tumour. Lesions of the inframammary sulcus and very peripheral lesions may represent a limitation due to the difficulty in reconstructing a volume (CTV) suitable for the operation;
- *instrumental evaluation*: a mammogram and ultrasound (also extended to lymph node stations) are the best-suited exams for staging, while magnetic resonance is reserved for particular situations (e.g., a dense breast that cannot be assessed with the methods indicated above, discrepancy greater than 1 cm between mammographic findings and ultrasound; possible multifocality);
- *anatomopathological evaluation*: a pre-surgical evaluation with core biopsy is indicated, with definition of the histotype and grade, receptor status, HER 2 receptor, and Ki67.

2.1.3. IOERT

2.1.3.1. Indications and patient selection

On the basis of the ASTRO and ESTRO consensus documents on APBI (2, 11, 15) and of the literature data (16), it is suggested that patients presenting the following features could be candidate for exclusive IOERT treatment, even outside clinical trials:

- age over 50;
- unifocal disease;
- tumour smaller than or equal to 2 cm (in accordance with the ASTRO guidelines) on a preoperative core biopsy;
- negative surgical margins, preferably greater than 2 mm on intra-operative radiological examination possibly confirmed by intraoperative extemporaneous macroscopic examination, absence of metastases on preoperative ultrasound, possibly confirmed by intraoperative analysis of the sentinel lymph node;
- non-lobular invasive histotype on preoperative core biopsy;
- positive hormone receptors (in accordance with the ASTRO guidelines);
- absence of lymph node metastases.

Based on the multivariate analysis of the ELIOT randomized trial, the single-dose IOERT should not be performed in the presence of:

- tumour greater than 2 cm;
- Grade 3;
- ≥ 4 positive lymph nodes;
- triple negative molecular subtype.

Based on unplanned analyses within the population of the ELIOT randomized trial (10), no differences in whole breast local control were found between IOERT and EBRT for the molecular group with the Luminal A phenotype (low proliferation index, positive hormone receptors, negative HER 2). If all the criteria for optimal APBI candidacy established by the ASTRO and ESTRO guidelines (11, 15) are not met, the execution of IOERT requires a careful risk/benefit analysis which also includes the complete evaluation of the patient (assessment of comorbidities, psychiatric conditions, advanced age or logistical difficulties in accessing radiotherapy centres, etc.) in a multidisciplinary context. The final clinical decision must be shared with the patient who is to be adequately informed. In case of recurrence after conservative quadrantectomy, partial re-irradiation may be proposed after a multidisciplinary discussion and the signed patient's informed consent. A possible model of informed consent is shown in Appendix A2. IOERT may be one of the possible partial re-irradiation techniques (re-irradiation after previous radiotherapy) (17).

Similarly, in the case of cancer arising after a previous thoracic radiotherapy for another pathology (e.g., for lymphoma), IORT irradiation may be proposed, considering the criticalities of irradiation of the wholebreast. Planning of the treatment must include detailed knowledge of the doses and volumes of the previous radiotherapy treatment and the patient needs to be given correct and thorough information.

2.1.3.2 Treatment technique

The surgical technique involves a skin incision along the mammary tension lines or radial, in the quadrant where the neoplastic lesion is located. Then, once the skin flaps have been prepared, a large resection of the glandular parenchyma including the nodule is carried out, widening the resection from the surface towards the deep plane down to the pectoral muscle fascia. Separately, or from the same incision, the axillary cavity is accessed to remove the

sentinel lymph node, previously identified generally by lymphoscintigraphy and sent for extemporaneous testing in accordance with the ASTRO / ESTRO guidelines on partial breast irradiation (11, 15). At the discretion of the Centre, the removal of the sentinel lymph node can be anticipated and performed before the quadrantectomy, even on an outpatient regimen (18-20).

According to the procedures followed by the individual Centres, the adequacy of the resection is assessed by histological frozen section analysis (with definition of the margins and analysis of the sentinel lymph nodes), or with radiological control of the surgical sample in accordance with the ASTRO and ESTRO guidelines on partial breast irradiation (11, 15).

After removal of the tumour and after the sentinel lymph node biopsy, having ascertained the presence of the criteria that make the patient eligible, a CTV is prepared for irradiation of the peritumoural tissues and protection of the healthy organs (21).

After completing the irradiation, it may be useful to place clips on the tumour bed (before or after removal of the applicator respectively in the case of kV-IORT or IOERT), with the aim to define the boundaries of the irradiated area.

2.1.3.3 Preparation of the CTV

The glandular flaps around the tumour bed are moved away from the skin and from the thoracic wall (Figure 3), drawn together and appropriately sutured, albeit temporarily, above the shielding disc positioned at the bottom of the tumour bed at the level of the fascia to protect the underlying lung, and on the left breast to protect the heart (22).

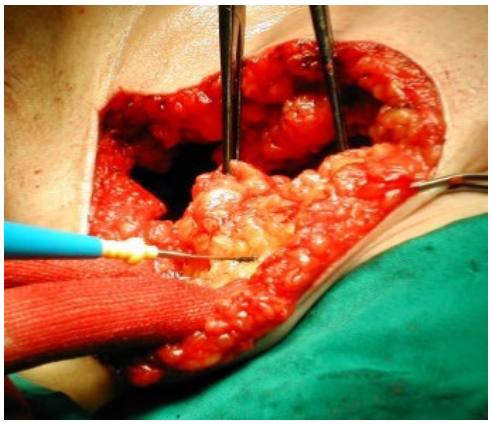

Figure 3. Preparation of the tumour bed for treatment of breast carcinoma with IOERT (photo by A. Ciabattoni)

The thickness of the CTV must be as uniform as possible, in order to avoid tissue herniations in the applicator and air gaps that could cause inhomogeneity in the dose delivery, with significant lower/higher doses to the target.

2.1.3.4. Selection and positioning of the applicator

Applicators with a diameter of ≥ 4 cm should be used, while applicators with a diameter of ≥ 5 cm should preferably be used in the case of exclusive treatment, also considering the diameter of the tumour, its location in the breast and the characteristics of the beam. Where possible, flat applicators are to be preferred, especially in the vertical position.

In the case of treatment with contact applicators, care must be taken to avoid herniation of the glandular tissue inside the applicator. This problem can be limited by paying special attention to the preparation of the area to be irradiated, which should be as flat and as homogeneous as possible, and by positioning the applicator, without excessive compression, at an angle perpendicular to the anatomical plane obtained after removal of the surgical sample. Various technical solutions can be adopted to avoid this problem; for example, a sterile plastic wrap can be applied to the terminal part of the applicator, or plastic discs (approximately 2 cm larger than the applicator) can be interposed between the end of the applicator and the gland (Figure 4) (23-25).

For details, see Appendix A3

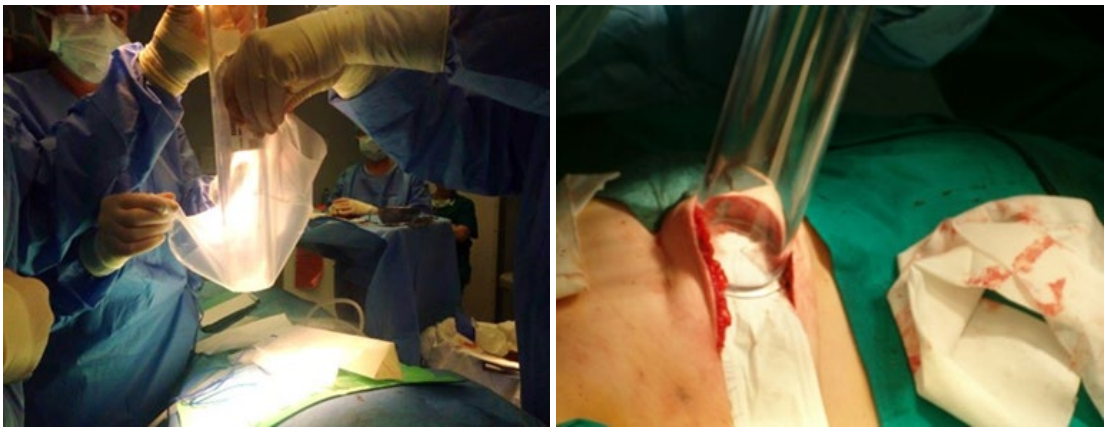

Figure 4. Breast cancer treatment: positioning of the applicator with possible technical solutions to avoid herniation of the tissue: plastic sterile wrap (left) or plastic disk (right)
(photo by S. Andreoli)

A plastic sterile wrap or plastic disk are also indicated in case of treatment with non-contact applicators to correctly evaluate the treatment distance.

2.1.3.5. Selection of the electron energy and irradiation

The energy is selected based on the thickness of the tissue to be irradiated, taking into account the geometric set-up of the treatment. Target thickness can be assessed with a graduated needle, ultrasound probe, or with CT imaging.

The prescribed dose is generally 21 Gy at 90% isodose for the exclusive treatment, and 10 Gy (range 9-12 Gy) at 90% isodose for the boost.

The duration of the irradiation phase is around 1-2 minutes.

2.1.3.6. Clinical results

2.1.3.6.1. Exclusive IOERT

For exclusive treatment, the dose that is mostly used is 21 Gy prescribed at the reference isodose (mainly 90%). In some trials the single dose treatment has also been proposed to young patients, starting from the age of 45 (26-28). Based on data from the ELIOT randomized trial, tumour size greater than 2 cm was an independent prognostic indicator/predictor of recurrence, therefore it is recommended not to treat tumours larger than 2 cm with full dose IORT (10). Some authors argue that the size of the applicator is to be adapted to the size of the tumour (29),

and hence its diameter should be proportionately increased. In most of the studies in the literature, IOERT was administered after tumour removal (2). The only published experience of IOERT before tumour excision at a dose of 15 Gy comes from the University of North Carolina group (30, 31). Grade 3, estrogen and progesterone receptor status have generally not been considered among the eligibility criteria in published studies. Histology other than non-special histotype (NST) was included in some studies, with no evidence of statistically significant differences in local control (29, 32, 33).

The absence of positive axillary lymph nodes was a requirement of most of the studies. In fact, minimal lymph node involvement, such as microscopically positive lymph nodes (34) or no more than 2-3 affected lymph nodes (10, 35), causes a loss, albeit insignificant, of local control.

In addition to the T dimension greater than 2 cm, the multivariate analysis of the randomized ELIOT trial (36) identified some factors associated with a high risk of local recurrence: 4 or more positive axillary lymph nodes, grade 3 and triple-negative molecular subtype. A description of the main published single dose studies is shown in Table 1.

Table 1. Main parameters in the treatment of breast cancer with single-dose IOERT technique in major international studies

1° Author, year (rif.), *trial*	Pazients (no.)	FU (months)	Eligibility criteria	IOERT in Gy (isodose, %)	LR (%)	OS (%)
Mussari, 2006 (33)	47	48	>45 yrs, T_{size} ≤2 cm, G1-2, ER^+, N0	20-24 (100)	0	NR
VanderWalde, 2013 (31)	71	69	>48 yrs, T_{size} ≤3 cm, cN0, IDC	14-24 (90)	15	94.4 at 6 yrs
Lemanski, 2010 (27) Lemanski, 2013 (28)	42	72	>65 yrs, T_{size} ≤2 cm, IDC, ER^+,N0	21 (90)	9.5	100 a 5t yrs
Veronesi, 2010 (36)	1822	36	≥33 yrs, T_{size} ≤5.5 cm, any lynph node state	16-21 (90)	3.6	89.7 at 10 yrs
Maluta, 2012 (26) Maluta 2014 (35)	226	62	≥50 yrs, T_{size}, ≤3 cm, IDC, no EIC	21 (100)	1,8	100 at 4 yrs
Osti, 2013 (32)	110	27	>48 yrs, T_{size}<2.5 cm, no EIC, cN0	21 (100-90)	2.7	97.3 at 3 yrs
Veronesi, 2020 (37) ELIOT	651	70	>48 yrs, T_{size} ≤2.5 cm, cN0	21 (90)	4.4	96.8 at 5 yrs
Barros, 2014 (38)	187	51	>40 yrs, T_{size} <3 cm, IDC, cN0	21 (90)	3.7	97.8 at 5 yrs
Cedolini, 2014 (34)	77	77	>48 yrs, T_{size} <3 cm, cN0	21 (90)	2.0	98.7 at 6 yrs
Philippson, 2014 (29)	200	23	>40 yrs, T_{size} ≤2 cm, IDC, N0, 1 mi	21 (90)	0.5	98.9 at 2 yrs
Kawamura, 2020 (39)	38	72	>50 yrs, T_{size} <2.5 cm, cN0	21 (90)	0	97 at 6 yrs
Takanen, 2017 (24)	758	62	Category groups	19-21 (90)	1.3* 13.5**	99*, 90.8** at 5 yrs

Year: year of publication**; FU:** median follow-up in months**; IOERT:** dose in Gy for intraoperative electron radiotherapy at the reference isodose; **LR:** local recurrence in %; **OS:** overall survival rate in %**; yrs:** years**; T_{size}:** tumor size**; EIC:** Extensive Intraductal Component; **IDC:** Invasive Ductal Carcinoma**; NR:** not reported**; *(low risk); **(high risk); ER+:** estrogen receptor positive**; N0:** lymph node negative**; cN0:** clinical lymph node negative**; mi:** microscopic involvement

Regarding side effects, data from the literature show relatively low and acceptable acute and chronic toxicity (40). Postoperative complications include oedema, haematoma, seroma, mild/moderate pain, dehiscence or delayed wound healing, and infection. Clinical liponecrosis

was observed in 2-15.5% of cases, while radiological liponecrosis was more frequent – up to 70% of cases – and affected elderly patients more frequently because of the greater amount of breast adipose tissue (10, 28, 32, 33). The cosmetic outcome was considered good/excellent in most cases (29, 32, 33, 40). The most frequent side effect was tumour bed fibrosis. The intensity of fibrosis was described using different toxicity scales. Severe grade 3 fibrosis according to the SOMA LENT scale (*Subjective, Objective, Management and Analytic - Late Effects on Normal Tissues*) was rarely found (2-6%) (29, 41), while grade II fibrosis affected as many as 32 % of cases (33, 41).

2.1.3.6.2. IOERT as *a boost*

In breast cancer, the *Salzburg Concept of IOERT* established that the primary goal of the IORT-boost was to reduce the rate of local recurrences (42). In a paper published by the Austrian group in 2004 (43), a higher local control of disease was observed with the IORT-boost treatment compared to the local control secured with the external beam boost administered with conventional fractionation. The median follow-up was 55.3 months for the 12 Gy IORT-boost group (group 1) and 25.8 months for the 9 Gy IORT-boost group (group 2), and local recurrence rates were 4.3% and 0.0% respectively in group 1 and in group 2.

IOERT, delivered in doses from 9 to 12 Gy, was followed by whole-breast EBRT. The time interval between IOERT and EBRT was not well defined and was strictly dependent on the state of the surgical wound and on systemic therapy, if any. The literature reports a minimum time of 3-4 weeks and up to several months. The pooled analysis of ISIORT (International Society of IntraOperative Radiation Therapy) showed no differences in terms of local recurrence between the EBRT delivered before 70 days or 140 days after the IOERT boost (44). In the literature, the EBRT schemes contemplate either conventional fractionation between 45 and 50 Gy or hypofractionation in 13-15 sessions of 2.85-2.67 Gy per fraction. A list of the main studies with IOERT including information on the irradiation patterns is shown in Table 2.

A retrospective multicentre analysis of the ISIORT group (44) performed on a sample of 1109 patients, showed, for all risk classes, surprising results in terms of local disease control, which had not been shown before by any other trial with similar sample and similar follow-up: the annual rate of local breast cancer recurrence in patients aged <40 years, between 40-49 years, 50-59 years and > 60 years was 0.64%, 0.34 %, 0.21% and 0.16% respectively. Interesting results with good disease control were also reported in a retrospective analysis of a sample of 71 patients with negative triple breast cancer, therefore at high risk of local and late recurrence (15,45): at 8 years, local disease control, metastasis-free survival, and overall survival rates were 89%, 75%, and 69%, respectively. The long-term outcomes for an unselected population of 770 patients, undergoing 10 Gy IOERT followed by external beam radiotherapy on the whole breast with a median dose of 54 Gy, showed local control and a 10-year survival rate of 97.2% and 85.7% respectively (15). Also, for acute and late toxicity and cosmetic appearance, no differences emerged with the combined EBRT IORT-boost compared to standard radiotherapy treatment (27, 46-49).

Two prospective multicentre trials are ongoing, both aimed to verify the equivalence or superiority on local control of the anticipated boost followed by EBRT on the whole breast compared to EBRT alone: the HIOB trial (50), where the anticipated boost with IORT (10 Gy) is followed by moderate hypofractionation (40.5 Gy in 2.7 Gy per fraction), and the TARGIT-B trial (51) which includes about 20 Centres worldwide.

Table 2. Main parameters in treatment of breast cancer with IOERT technique as boost followed by whole breast radiotherapy in major international studies

1° author, year (ref.) trial	Patients (no.)	FU (months)	Stage	IOERT in Gy (isodose %)	+WBI (Gy)	LC (%)	OS (%)
Merrick, 1997 (52)	21	71	I-II	10-15 (100)	45-50	100 crude	90.5 crude
Dubois 1997 (46)	102	minimum 24	I-II	10 (90)	45	100 crude	
Lemanski, 2010 (27)	50	109	I-II	9-20 (90)	50	96 crude	NR
Ciabattoni, 2004 (53)	234	NR	I-II	10 (100)	50	100 crude	
Reitsamer, 2006 (42)	190 (IOERT)	51	I-II	9 (100)	51-56	100 act. at 5 yrs	NR
	118 (EBRT)	81		12 (EBRT)		95.7 act. at 5 yrs	
Ivaldi, 2008 (49)	204	8.9	I-III	13,3 (100)	37.05	100 act. at 9 mths	
Fastner 2013 (44) ISIORT	1109	72.4	I-III	6-15 (100)	50-54	99.2 act. at 6 yrs	91.4 act. at 6 yrs
Fastner, 2015 (54)	83 (IOERT)	59	II-III (Neoadjuvant chemotherapy)	9 (100)	51-57	98.5 act. at 6 yrs	86.4 act. at 6 yrs
	26 (EBRT)	67.5		12 (EBRT)		88.1 act. at 6 yrs	92 act. at 6 yrs
Fastner, 2016 (45)	71	97	I-II	7-12 (100)	54 med	89 act. at 8 yrs	75 act. at 8 yrs
Kaiser, 2018 (14)	770	121	I-III	5-12 (100)	54 med	97.2 act. at 10 yrs	85.7 act. at 10yrs
Ciabattoni 2021 (47)	133	144 (range120-192)	I-II	10 (90)	50	5 yrs 4.7 10 yrs 7.9	10 yrs 91.6 95 (CI 84.9-95.4)
Ciabattoni 2022 (48)	797	57 (range 12-109)	I-III	9-12 (90-100)	40.5-50	In field LR 0.8	5 ys 98.6 95 (CI 97.2-99.3)

year: year of publication; **FU**: median follow-up in months; **EBRT**: external beam radiation therapy; **IOERT**: dose in Gy for intraoperative electron radiotherapy at the reference isodose; **WBI**: dose in Gy for whole breast irradiation; **yrs**: years; **LC**: local disease control in %; **OS**: overall survival rate in %; **act**: actuarial expected; **crude**: actual observed value; **med**: median value; **NR**: not reported.

2.1.4. kV-IORT

2.1.4.1. Indications and patient selection

For kV-IORT as single treatment, the eligibility criteria provided by the TARGIT A trial are substantially comparable to those used for IOERT.

Lymphovascular invasion, an extensive in situ component and lobular histology are considered criteria for either exclusion or completion with whole-breast EBRT.

The maximum tumour size of 3.5 cm depends on the largest spherical applicator has a diameter of 5 cm. Tumours larger than 3.5 cm can lead to the creation of a surgical cavity greater than 5 cm, whose walls would not adhere properly to the spherical applicator.

To use kV-IORT as a boost, the tumour size criterion must always be respected and must not exceed 3.5 cm.

kV-IORT has also been used in the treatment of recurrences after a previous quadrantectomy and radiotherapy; in these cases, a further quadrantectomy is performed as part of partial breast re-irradiation (55, 56).

2.1.4.2. Treatment technique

After the radical resection of the tumour, which takes place according to standard procedures, and the intraoperative evaluation of sentinel lymph nodes, the surgical flaps are not brought together, so as to maintain the surgical cavity that will house the spherical applicator (of various diameters).

2.1.4.3. Creation of the CTV

In order to prepare the tumour bed for the insertion of the applicator, due to the rapid drop in dose of the low-energy X-rays, particular care must be taken to maintain haemostasis and to avoid the pooling of serum and blood inside the surgical cavity. The liquid around the applicator would in fact significantly reduce the thickness of the tissue receiving the planned dose.

Once the surgical cavity has been prepared, the surgeon makes a tobacco pouch, suitable for accommodating the spherical applicator (Figure 5), thanks to which the radiation will be isotropic.

Figure 5. Breast cancer treatment with kV-IORT: tumour detection (left), surgical resection (centre), positioning of the Intrabeam applicator (right)

2.1.4.4. Selection and positioning of the applicator

The size of the applicator is selected on the basis of the size of the surgical cavity so that the sphere adheres tightly to the tumour bed as a result of the surface tension that is created at the applicator/tissue interface. The surrounding skin is retracted with a clamp from the irradiation field and the pouch is closed around the applicator itself with a suture for perfect adherence to the source of the tissue delimiting the operating cavity, which is the target.

The applicators vary in diameter from 1.5 to 5 cm, they can be sterilized and are reusable. The distribution of the dose is isotropic and the target tissue, represented by the walls constituting the surgical cavity, is irradiated uniformly. In general, the applicators used have a diameter of 4 to 5 cm.

In order to avoid skin radionecrosis, the skin is displaced by at least one centimeter, if necessary, by interposing sterile gauze soaked in physiological solution.

Due to the rapid drop in dose downstream of the target, shielding at the base of the surgical cavity is not required to protect the heart and lung.

2.1.4.5. Dose and irradiation

For exclusive treatment and for boost the prescribed dose is 20 Gy at the applicator surface, which is attenuated to 5-7 Gy at a depth of one cm and is equivalent, in terms of Biologically Effective Dose (BED), to approximately 50 Gy of conventional fractionation calculated at a depth of 5 mm from the surface of the spherical applicator (57). Beyond this depth, the delivered dose drops very quickly, thus sparing the surrounding tissues. In fact, the physical characteristics of low-energy photons are such as to reduce the dose already at a distance of a few millimeters from the isocentre, with undisputed advantages for two very important elements in oncological radiotherapy: preservation of organs at risk from acute and late side effects and radiation protection (13).

The dose rate is approximately 0.5-2 Gy/min at the applicator surface. The duration of irradiation varies from 20 to 50 minutes; the time variability depends, for the same dose, on the diameter of the applicator used (the greater the diameter of the applicator, the longer the irradiation time).

As for the boost, the 20 Gy dose is followed by whole-breast EBRT. The scheme can consist of either mild hypofractionation (e.g., 2.67 Gy x 15 fractions) or what in the past was considered conventional fractionation (1.8-2 Gy) with a total dose between 45 Gy and 50.4 Gy. Recently, guidelines from Meattini et al (58) reported that 25 fraction are not still considered as conventional fractionation.

2.1.5. Clinical results

2.1.5.1. Exclusive kV-IORT

More than 35 publications providing results on the use of kV-IORT are available in the literature. Follow-up varies between 12 and 40 months and the incidence of local recurrences is between 0 and 3.3% (Table 3).

The TARGIT-A trial was a non-inferiority trial in which patients were randomized between whole breast radiotherapy arm and partial irradiation arm with Intrabeam (12, 59). Inclusion criteria included age 45 years or older, tumour size up to 3.5 cm and N0-N1 lymph node status, unifocal cancer and ductal histology. If tumour aggressiveness appeared in the final histological examination, the patient could be referred for completion of irradiation with radiotherapy in 5 weeks, at discretion of the recruiting centre.

The study population was broken down into postpathology and prepathology groups, to identify patients who received partial irradiation respectively in the 30 days after resection of the primary tumour or directly during surgery to remove the tumour. 21.6% of the prepathology group subsequently received whole breast irradiation. Severe complications were significantly reduced in the partial irradiation arm, with no difference in terms of lymph node recurrence.

In an early analysis, at 29 months of follow-up, the local recurrence rate was 1.3% in the EBRT arm and 3.3% in the kV-IORT arm (p 0.042). Trial update with a longer follow-up (complete at 5 years and a median of 9 years) showed a local recurrence rate of 2.2% in the TARGIT-IORT arm and of 0.95% in the EBRT arm. (59), with a difference of 1.16% which falls within the non-inferiority margin of 2.5%, thus confirming the non-inferiority of the APBI with low-energy photons (60). It should be emphasized that in accordance with the study design,

about 23% of patients in the TARGIT arm also received EBRT due to the presence of unfavourable factors emerging from the final histological analysis.

Table 3. Main parameters in the treatment of breast cancer with single-dose kV-IORT technique in major international studies

1° Author, year (ref.) trial	Pazients (no.)	FU (months)	Eligibility criteria	kV-IORT (Gy)	LR (%)	M (%) or OS %
Vajda, 2020 (59) TARGIT-A	3451	median: 9 yrs; minimum: 5 yrs	>45 yrs, IDC, T_{size} ≤3.5 cm, cN0, local criteria	20 (15% WBI)	pre-pathology (2298 pz): 2.2 (TARGIT) *vs.* 0.95 (WBI)	M: 5.9 (TARGIT) *vs.* 6.5 (WBI)
					post-pathology (1153 pz): 3.96 (TARGIT) *vs.* 1.05 (WBI)	OS: 88.60 (TARGIT) Kaplan Meier *vs.* 87.7 (WBI) at 5 yrs
Valente, 2016 (60) TARGIT-R	935	23	T_{size} ≤2 cm, cN0, ER^+	20 (31% WBI)	2.3	M:1.6
Abbott, 2017 (61)	686	12	TARGIT-R, R0, pN0	20 (WBI: 29% <70 yrs; 11% >70 yrs)	0.73 (0.94<70 yrs, 0.38>70 yrs)	NR
Sperk, 2012 (62) TARGIT-A	305	40	109 pts TARGIT-A	20 (37% WBI) TARGIT-A	0 TARGIT-A	M: 0 TARGIT-A
			196 pts IORT *boost* off	71% WBI	2 IORT *boost* off	M: 7 IORT *boost* off
Barrou, 2018 (63)	287	30	T1N0	20 (46% WBI)	1.07	M: 0
Rakhra, 2017 (64)	113	40	≥50 yrs, T1, ER^+, G1-2, IDC	20 (13% WBI)	0.9	NR
Abbott, 2015 (65)	100	24	≥50 yrs, IDC, T_{size} ≤3 cm	20 (17% WBI)	0<70 yrs, 2.8 ≥ 70 yrs	NR
Grobmyer, 2013 (66)	78	12,5	heterogeneous	20 (1.3% WBI)	0	M: 0
Key, 2017 (67)	71	39	≥50yrs, IDC, T_{size} ≤3 cm, G1-2, ER^+, $HER2^-$, Ki67<30%	20 (42% WBI)	0	M: 1.4
Elliott, 2011 (68)	67	28	≥50 yrs, IDC, T_{size} ≤3.5 cm	5 at 1 cm (16% WBI)	0	M: 3
Merdad, 2013 (69)	45	18	IDC, T_{size} ≤3.5 cm, cN0	20 (36% WBI)	0	NR
Rivera, 2016 (70)	35	36	DCIS ≤4 cm	20	5.7	M: 0

year: year of publication; **FU:** median follow-up in months; **kV-IORT:** dose in Gy for intraoperative photon radiation therapy; **WBI** dose in Gy fort whole breast irradiation; **LR:** local recurrence in %; **M:** mortality rate in %; **OS**: overall survival rate in %; **yrs:** years; **T_{size}:** tumor size; **pre:** preoperative; **post:** postoperative; **IDC:** Invasive Ductal Carcinoma; **G1-2:** low and intermediate tumor grade; **N0:** negative lymph nodes; **cN0:** clinically negative lymph nodes; **Ki67:** proliferative activity**; pN0:** pathologically negative lymph nodes; **ER+**: estrogen receptor positive; **HER2-:** human epidermal growth factor receptor 2; **DCIS:** ductal carcinoma in situ, **NR:** not reported; **IDC:** Invasive Ductal Carcinoma

In further sub-analyses, local recurrence was 2.1% in the prepathology group and 5.7% in the postpathology group.

Recurrences in the postpathology group exceeded the non-inferiority margin set at 2.5% (5.4% *vs.* 1.7%, p 0.069), unlike the prepathology group (2.1 *vs.* 1.1%, p = 0.31).

Negative results in terms of local control in the postpathology group were confirmed by the subsequent follow-up update at five years (71), which showed a difference with the EBRT arm of 2.9% (3.96% *vs.* 1.05%), without affecting survival (59). The researchers therefore concluded that kV-IORT treatment should be administered at the time of resection of the primary tumour. Breast cancer mortality was similar in the two arms, while patients undergoing partial irradiation showed a significant reduction in non-cancer-related deaths, mainly due to a reduction in death for cardiovascular disorders and second primary tumours. In the entire population, overall mortality was lower among patients treated with kV-IORT than among patients in the conventional arm (1.3% *vs.* 4.4%, p 0.016). Vaidya's meta-analysis (12) confirms overall survival is better when APBI is used, due to the decrease in non-cancer-related deaths. This finding was also noted in other meta-analyses (72) without however documenting an impact on overall survival. The TARGIT-E trial included only patients over the age of 70 and with cT1-T2 disease ≤ 3.5 cm, cN0. It reported interesting results, with local control greater than 99% at 2.5 years and an overall survival of 98.6% (73, 74).

2.1.5.2. kV-IORT as boost

Studies where kV-IORT is delivered as boost report an incidence of local recurrences in the range between 0% and 9.9% with a follow-up from 3 to 80 months (Table 4). The most commonly used boost dose is 20 Gy, followed by 45-50 Gy with EBRT on the whole breast. In the published studies, tumour diameter in case of boost was subject to some variation. A list of the main studies is shown in Table 4.

Table 4. Main parameters in the treatment of breast cancer with kV-IORT technique as boost followed by whole breast irradiation in major international studies

1° Author, year (ref.)	Pazients (no.)	FU (months)	Eligibility criteria	Dose (Gy)	LR (%)	Mortality (%)
Vaidya, 2010 (75) Vajda 2011 (76)	300	1-60.5	invasive, T_{size} ≤ 3.5 cm	20+ 45-50 WBI	1.7	NR
Blank, 2010 (77)	197	37	invasive, T_{size}≤ 4.5 cm	20+ 46-50 WBI	2.5	8.7
Kraus-Tiefenbacher, 2010 (78)	157	2	invasive, DCIS, T_{size} <4.5 cm	20+ 46 WBI	NR	NR
Wenz, 2010 (79)	155	34	invasive, T_{size} <4.5 cm	20+ 46-50 WBI	1.3	6.5
Ebner, 2016 (80)	152	20.4	invasive, T_{size} <3 cm, cN0	9+ WBI*	NR	NR
Malter, 2014 (81)	149	1	Oncoplastic surgery	20+ WBI*	NR	NR
Kraus-Tiefenbacher, 2006 (82)	137	1-6	invasive, T_{size} <4.5 cm	20+ 46 WBI	NR	NR
Kolberg, 2017 (83)	116	49	Neoadjuvant chemotherapy	20+ 50 WBI	9.9% (*vs.* 8.3% EBRT)	3.3% (*vs.* 8.3% EBRT)
Chang, 2014 (84)	55	40	invasive, T_{size} <3 cm	5 (at 1 cm)+ 46 WBI	0%	0%
Wasser, 2007 (85)	54	≤ 24	invasive, T_{size} <4.5 cm	20+ 46 WBI	0%	NR

Year: year of publication; **FU:** median follow-up in months; **Dose:** dose in Gy for intraoperative photon radiotherapy**; LR:** local recurrence in %; *** WBI** : dose for whole breast irradiation; not specified ; **WBI**: whole breast irradation; **NR:** not reported; **DCIS:** ductal carcinoma in situ**; cN0:** clinically negative lymph nodes.

As regards the side effects of the kV-IORT treatment, seromas and hematomas are the most frequent complications (86, 87), with an incidence that may be as high as 90%. In the study conducted by Globle et al. (87), seromas persisted at 12 months in 31% of patients. In the TARGIT-A trial, repeated seroma aspirations were much more frequent in the APBI arm than in the external beam radiotherapy arm (59).

Acute dermal toxicity with very low incidence and intensity was reported (82,88,89). The rate of postoperative infections was similar to the arm that did not receive kV-IORT (90).

Fibrosis is a very frequent side effect in patients treated with kV-IORT, while skin discolouration and telangiectasias are rarely reported (62). The increase in side effects was found to be due mainly to the diameter of the applicator (64). In an analysis of 48 patients, Wenz et al. (91) observed an increase in chronic toxicity (fibrosis, telangiectasias, hyperpigmentation, pain) in the population for whom the time period between the IORT boost and the delivery of external beam radiotherapy was shorter (29.5 days *vs.* 39.5 days). The authors therefore decided to adopt a time interval of 5-6 weeks.

The impact of the boost on the cosmetic result is good for some authors (82,89), while for others it is detrimental (82).

2.1.6. Conclusions

Intraoperative partial irradiation after conservative surgery may be indicated in low-risk cases, but requires a careful preoperative and intra-operative evaluation with the aim of adequately select patients. However, it should be emphasized that the full application of the ASTRO and ESTRO guidelines (11,15) for partial irradiation is difficult when using intraoperative methods, since complete histopathological data are not always available at the time of the therapeutic decision. In any case, it is essential to obtain all possible information on the tumour and on the lymph node status in the preoperative phase (through true-cut and core biopsy) and in the intraoperative phase (frozen specimen). Treatment with kV-IORT allows for adaptive radiotherapy, i.e. the possibility of converting the single dose into a boost dose on the basis of the risk factors involved. The use of IORT as boost strategy in the treatment of breast cancer with both electrons and photons may be indicated in all cases of irradiation in which a higher dose is deemed necessary.

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2.2. Prostate cancer

2.2.1. Introduction and background information

Clinical outcomes of treatment in prostate cancer are quite favourable for low-risk patients (1,2), with recurrence-free survival rates of 80-92% at 5 years and 76-92% at 10 years after radical prostatectomy or exclusive radiotherapy. Results on the local control of the disease, on the other hand, are less satisfactory for patients having intermediate risk and even less satisfactory for high/very high-risk patients. In these patient groups, combined treatments with hormone therapy, radiation therapy and/or surgery may only achieve 37-62% and 44% or less in terms of local control at 5 and 10 years, respectively. Insufficient loco-regional control occurs in over 40% of patients with locally advanced disease after radical prostatectomy and in 24-72% with biochemical recurrence after radiotherapy and hormone therapy. The rationale for using IORT in prostate cancer is associated with the role of dose escalation, with the dose-response relationship and with the low α / β value according to the linear quadratic model (3).

The peculiarity of the pathology associated with the limited number of patients included in single-institution case series explains the growing interest in ISIORT, which allows for the collection of cases from the Centres participating in the project. 16.1% of the centres that provide IORT treated at least one patient with prostate cancer with this method and 72.6% of the patients treated were included in a research protocol.

Patient selection varies widely in the various studies and in the various Centres. The Japanese series, for example, included both early and advanced diseases, treated with curative or palliative intent (4,5). This heterogeneity in patient selection has always represented a limitation in subsequent analyses.

Italian studies, on the other hand, involved locally advanced or high-risk cases.

2.2.2. Indications and patient selection

2.2.2.1. Exclusive treatment without prostatectomy or combined with lymphadenectomy and/or pelvic EBRT

IOERT was used at Kyoto University and at the Saitama Cancer Centre in Japan as exclusive treatment (without surgery) or combined with lymphadenectomy and/or EBRT at the pelvic lymph nodes level. The perineal approach was used and the delivered dose was 25-35 Gy in single fraction (8-14 MeV electrons). The dose of IOERT was reduced to 20-25 Gy when combined with EBRT (5-7).

A different approach was adopted by three Italian Centres (European Institute of Oncology, Milan; Ospedale Maggiore della Carità, Novara; Regina Elena National Cancer Institute, Rome) which selected high-risk patients based on initial PSA, Gleason Score and clinical staging.

2.2.2.2. Exclusive treatment for radical pre- or post-prostatectomy and pelvic lymphadenectomy in high-risk patients based on initial PSA, Gleason Score and clinical staging

In the Italian Centres, IOERT was combined with radical retropubic prostatectomy and pelvic lymphadenectomy. Saracino et al. (8) described 34 cases treated after radical prostatectomy with IOERT at a dose of 16-22 Gy and 7-9 MeV electron beams. EBRT was not used in any of these cases; rectal and urethral dosimetry was performed in all cases (8, 9). Other authors (10, 11) reported a single-institution series of 11 and 38 patients, treated with IOERT before prostate resection, with total doses of 10-12 Gy and using 9-12 MeV electron beams.

2.2.2.3. Treatment of recurrences, with and without EBRT

As at 2013, in the ISIORT database there were 128 cases of prostate tumours treated in various European centres with the IORT technique. This represents the first non single-institution case series on prostate cancer. In 5.5% of cases, intraoperative treatment was performed on loco-regional recurrences.

The dose administered was 8-15 Gy, if used as a boost, and 18-21 Gy in case of sole treatment not supplemented by EBRT. Treatment was delivered with IOERT, with the exception of 6 cases (4.7%) of tumour recurrences that were treated with kV-IORT and 5.6-8 cm spherical applicators at a single dose of 5-8 Gy (12) .

2.2.3. Treatment technique

This section describes only the IOERT procedure, since kV-IORT is less frequently used; furthermore, reference is made only to the treatment modality which involves irradiation before prostatectomy.

The first surgical step consists of a sub-navel-pubic incision which allows adequate exposure of the structures, then the prevesical space is prepared. The endopelvic fascia are incised bilaterally and the puboprostatic ligaments are dissected. The Santorini venous plexus is then ligated and dissected to expose the prostate apex and the urethra. The anterior surface of the gland is therefore exposed and mobilized; finally, a a stitch was placed as a marker of the bladder neck which allows for moderate traction and better exposure of the gland (Figure 6).

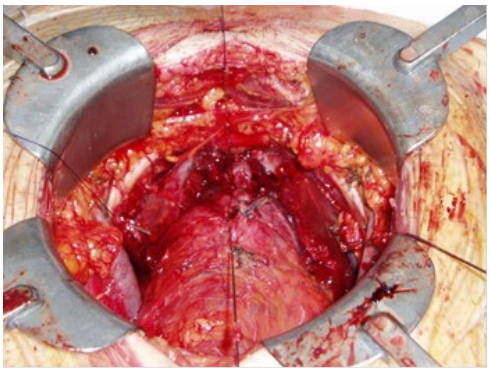

Figure 6. Surgical Exposure of the gland with repere on the neck of the bladder (photo by M.Krengli)

The next step is the assessment of the antero-posterior diameter of the gland and of the distance between the prostatic surface and the anterior wall of the rectum, both measured by intraoperative ultrasound.

An applicator and energy beam of appropriate sizes are chosen on the basis of clinical and ultrasound data and are to be such as to include the prostate and surrounding soft tissues, with a compatible margin for subclinical disease of 0.5-1 cm (Figures 7 and 8). The electron beam energy used is usually between 9 MeV and 12 MeV. The dose is prescribed at 90% of the isodose.

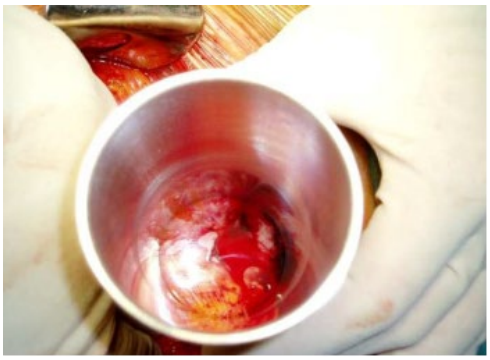

Figure 7. Applicator positioning before treatment delivery (photo by M.Krengli)

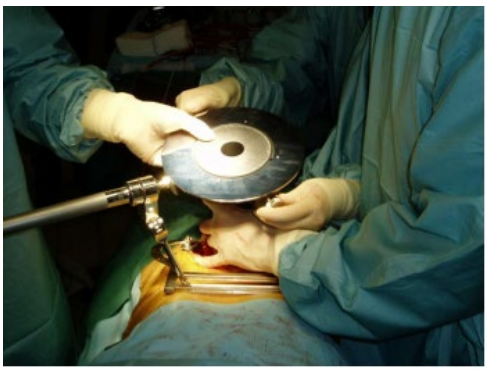

Figure 8. *Soft-docking*: applicator is rigidly clamped to the operating table which is then positioned under the accelerator (Mobetron) (photo by M.Krengli)

The dose received by the rectum can be measured in vivo using a rectal probe inserted into the cavity at the beginning of the surgical procedure. Four radiochromic films applied to the surface of the rectal probe can be used to evaluate the dose received by the anterior, posterior and lateral walls of the rectum.

After the IOERT procedure, the applicator and the rectal probe are removed and radical prostatectomy and pelvic lymphadenectomy are performed.

2.2.4. Clinical results

The Japanese case series reported in the literature consist mainly of pilot and feasibility studies with relatively small numbers of patients. Local control was obtained in over 80% of cases without prostatectomy, and overall survival rates were between 43% and 72% at 5 years. Local control and survival exceeded 90% in cases with a more favourable preoperative staging. No acute and/or late gastro-enteric toxicities > G3 emerged from these series. Cases of haematuria, chronic cystitis and urethral stenosis were reported. Over the years, the authors have preferred to switch from a perineal to a retropubic approach so as to minimize rectal damage during surgery, performing the lymphadenectomy simultaneously so as to reduce discomfort to the patient who, after the perineal approach, could not maintain the seated position for a few days (6, 7).

The Italian case studies report a relatively low rate of toxicity; most of the complications are related to the surgical procedure rather than the radiotherapy itself and consist mainly of lymphoceles, hematomas and anastomotic changes (10, 11).

Favourable results in terms of local control and biochemical recurrence-free survival were observed in the Saracino study after a median follow-up of 41 months (8). In this series, the poor prognostic factors for recurrence were: cancer stage ≥T3, PSA at diagnosis > 10 ng / mL, and positive surgical margins. The pT2 stage was found in 53% of cases in the Saracino series (8), in 36% of cases in the Orecchia series (10) and in 37% of cases in the Krengli series (11). In all of these cases, postoperative radiotherapy was not performed. The treatment characteristics of the main studies are described in Table 5. In terms of early and late post-surgical side effects, the toxicity profile that emerges from the literature is quite good (Table 6).

Table 5. Main parameters in the treatment of prostate cancer with IOERT technique in major international studies

1° Author, year (ref.)	Pazients (no.)	Access	Surgery	IOERT Energy (MeV)	Dose (Gy)	
					IOERT	EBRT
Takahashi, 1985 (5)	14	perineal	no prostatectomy	10-14	28-35 (single dose); 20-25 (combined)	50 pelvis
Abe, 1991 (4)	21	perineal	no prostatectomy	8-14	28-35 (single dose); 20-25 (combined)	50 pelvis
Kojima, 1988 (7)	30	perineal/ retropubic	lymphadenoctopathy/ no prostatectomy	NR	NR	NR
Higashi, 1998 (6)	35	NR	no prostatectomy	NR	25-30	30
Rocco, 2009 (9) Orecchia 2007(10)	11	retropubic	pre-prostatectomy	8-10	12	45
Saracino, 2008 (8)	34	retropubic	post-prostatectomy	7-9	16-22	NO
Krengli, 2010 (11)	38	retropubic	pre-prostatectomy	9-12	10-12	46-50

Year: year of publication; **IOERT:** dose in Gy and Energy (MeV) for intraoperative electron radiotherapy**; EBRT:** external beam radiotherapy; **NR:** not reported.

Table 6. Main parameters in the treatment of prostate cancer with IOERT technique in major international studies

1° Author, year (ref.)	LC (%)	Survival (%)	Acute toxicity	Late toxicity	Prognostic factors
Takahashi, 1985 (5)	86	NR	None > G2	None	NR
Abe, 1991 (4)	81	72 (OS at 5 yrs)	100% hematuria 10% pollakiuria	1 pt chronic cystitis 1 pt urethral stenosis	NR
Kojima, 1988 (7)	NR	43	NR	NR	NR
Higashi, 1998 (6)	NR	92 (stage pT2) 87 (stage pT3) (OS act. at 5 yrs)	None > G2	None	NR
Orecchia, 2007 (10)	NR	NR	1 pt lymphocele 3 pts anastomotic leakage	NR	NR
Saracino, 2008 (8)	91	77 (PFS at 3 yrs)	No toxicity	None	stage ≥ pT3; PSA>10; margins^{+}
Krengli, 2010 (11) Krengli, 2014 (12)	98	100 (OS at 18 months)	5 pts lymphocele 2 pts hematoma	6,8% bladder neck stenosis	NR

year: year of publication; **OS**: Overall survival in %; **LC**: local disease control in %; **PFS**: Progression Free Survival in %; **act**: actuarial; **G2**: toxicity value in RTOG scale; **PSA**: prostate-specific antigen; margins+: positive resection margins;pt(s): **patient**(s); **NR**: not reported.

2.2.5. Conclusions

Although the follow-up was relatively short, the results in terms of biochemical disease-free survival was promising, exceeding 70% in both the Japanese and the Italian series, also considering the locally advanced cases and cases with pelvic lymphonodes.

Clinical trials with a long follow-up are needed to evaluate the effectiveness of this treatment modality. The best candidates for IORT, possibly combined with EBRT, could be T3N0 patients with a high risk of positive margins.

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2.3. Pancreatic cancer

2.3.1. Introduction and background information

Pancreatic cancer is a tumour that at the present time still has a particularly unfavourable outcome. The mortality rate is close to the incidence rate and it is the fourth leading cause of cancer-related death in the world (1-4). Radical surgery remains the only potentially curative form of treatment. However, at diagnosis only 10-20% of patients present a localized, potentially resectable tumour. Indeed, at the first observation, most patients present a locally advanced unresectable disease (40%) or a disease in an advanced phase with distant metastases (40-50%) (5).

Even after radical surgery, however, the prognosis is still very poor, with survival at 5 years ranging from 10% to 20% (6, 7). Advances in surgical techniques and a more accurate selection of patients eligible for surgery using modern staging procedures have partially improved these results, but most of the operated patients still have loco-regional and/or distant recurrences. Indeed, radical resection with negative margins (R0) which is the most important prognostic factor in pancreatic cancer, is difficult to achieve due to the frequent microscopic vascular, lymphatic and neurological infiltration of this tumour even in the initial stages of the disease (8, 9).

Several clinical trials have shown a favourable impact of chemoradiotherapy and even of postoperative precautionary chemotherapy alone on local disease control and patient survival, compared to radical surgery alone (10-14). A comparison of the results of these studies is still subject to debate and both postoperative therapeutic options remain open in clinical practice. While the combination of chemotherapy and radiotherapy prevails in North American countries,

in European countries the indication for chemotherapy prevails as the only post-operative treatment (15-17). Within the framework of multidisciplinary therapeutic combination programs, IORT is of great interest in a dose escalation program selectively limited to the tumour both in operable pancreatic cancer and in locally advanced, borderline resectable and unresectable ones.

Several clinical trials are being carried out on new drugs and new irradiation modalities (intensity modulated radiotherapy, stereotaxis, IORT) and on new ways of combining chemotherapy and surgery in the adjuvant or neoadjuvant phase (18).

The procedures related to IORT treatment with electrons, the most documented in the literature, are presented in this section.

2.3.2. Indications and patient selection

Treatment of gastrointestinal malignancies with external beam radiation therapy (EBRT) is limited by the normal level of tissue tolerance of various abdominal and pelvic organs, including the stomach, intestine, liver, and kidneys. IOERT has the advantage of delivering a biologically significant dose of radiation followed by a rapid drop in dose and the ability to spare nearby organs at risk of normal complications.

In pancreatic cancer, the possible applications of IOERT are the multidisciplinary combined treatment for resectable tumours and selected cases of locally advanced unresectable disease (19, 20). After initial studies on the use of IOERT in some gastrointestinal malignancies reported in Japan in the early 1980s (21, 22), clinical research on IOERT in pancreatic cancer was promoted and developed in some North American centres as dose escalation in combination with EBRT, with and without chemotherapy, in unresectable locally advanced tumours (23, 24). These experiences demonstrated a clinical benefit of IOERT at a dose of 20 Gy, reporting pain remission in over 75% of treated patients and medium and long-term maintenance of remission in a significant proportion of cases. These studies also confirmed the feasibility of the treatment with acceptable risk of complications (25). On the basis of these experiences, the interest in IOERT in pancreatic cancer was promoted in various North American and European institutions, and its use was extended also to resectable tumours.

Retrospective studies and a prospective randomized trial on a limited series of patients support the indication of IOERT in resectable tumours for the possible improvement of local disease control (26-30) and, in some studies, survival (26-28). There are still no phase III trials that confirm these indications, which therefore remain in the context of personalized treatments (level III evidence).

The new imaging techniques currently make it possible to define a subgroup of patients with borderline resectable disease that present partial involvement of the vascular axis (vein and mesenteric artery and/or celiac trunk) where the resection of the tumour, even if technically feasible, would be marginal (R1) and therefore with a high risk of recurrence. Borderline resectable pancreatic cancer represents an area of intense clinical research with new combined chemoradiotherapy and/or preoperative chemotherapy programs that include new drugs and new irradiation modalities aimed at achieving radical R0 surgery and at improving the survival of patients (18, 31). In these innovative programs, IOERT is of great interest as a dose escalation program and phase I-II studies are currently underway (32, 33).

Its indication in borderline resectable tumours is currently still being explored.

In locally advanced unresectable disease, treatment is even more controversial. Even in this most unfavourable group of patients, chemoradiotherapy after induction chemotherapy demonstrated a favourable impact on local control compared to chemotherapy alone. However, in studies reported in the literature, this finding is not accompanied by a clear advantage in

terms of survival (18, 31). Also in these cases, the strength of the recommendation in clinical practice for chemoradiotherapy is currently weak and therefore the enrollment of patients in clinical research studies on new drugs and new irradiation modalities in innovative combination programs is strongly recommended (15-17).

In locally advanced cancer, several retrospective studies have documented the clinical benefit of IOERT on pain, but again there is a lack of higher levels of evidence and its indication remains limited as a possible option in selected patients.

2.3.3. Treatment technique

2.3.3.1. Resectable pancreatic cancer

The indication for IOERT, discussed in a multidisciplinary context, must be defined on the basis of the surgical radicality envisaged in the therapeutic treatment plan.

The details of the IOERT procedure must be discussed jointly by the radiation oncologist and the surgeon before surgery and they must define the area to be treated after the planned surgical resection (area at risk), based on staging/restaging imaging; they must also decide on the mode of access of the IOERT applicator and envisage possible changes to the procedure. The IOERT patient's set up will then be discussed with the medical physicist (location and prediction of the PTV) and with the therapeutic radiographers (Tr) (geometrical set up of the anatomical site, patient position, manoeuvers planned for bringing the LINAC closer to the patient and for the preparation of the treatment set-up).

In resectable pancreatic cancer, IOERT should be considered as an early boost in a dose escalation program combined with EBRT and chemotherapy. "The area at risk" (CTV) is to be defined during surgery by the radiation oncologist in collaboration with the surgeon on the basis of the surgical findings, after mobilization and resection of the tumour (duodenocephalopancreatectomy or total pancreatectomy depending on the site of the tumour) (Figure 9).

In borderline resectable pancreatic cancer, IOERT should be considered as dose escalation after preoperative chemoradiotherapy treatment. The CTV is defined during surgery, once resection of the tumour has been verified and performed (3).

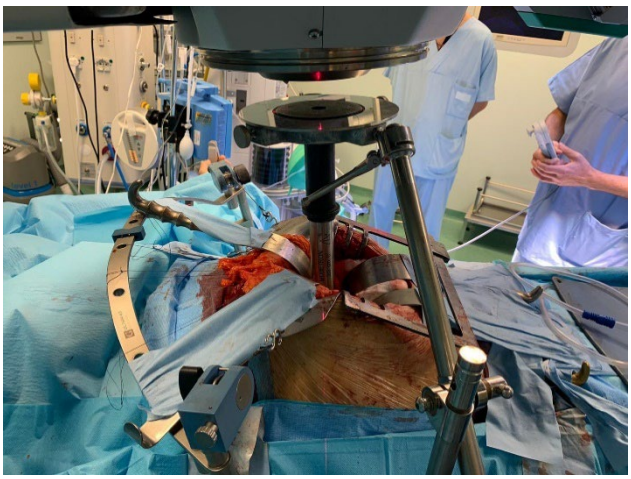

Figure 9. Patient preparation for treatment delivery of pancreas tumor (photo by Pancreas Institute of Verona)

After marginal resection of resectable or borderline resectable lesions, the tumour bed to be treated includes retroperitoneal soft tissues, vascular structures (portal vein, superior mesenteric artery and vein, aorta) and the prevertebral ligament (Figure 10). The dissected bile duct, the remaining pancreas, the colon and the stomach are excluded from the IOERT field; they must be under visual control and mechanically retracted. The upper pole of the right kidney can also be checked and shifted manually. Under conditions of appropriate haemostasis, intraoperative fluids do not represent a limiting factor for the selection of the electron beam energy, as long as the level covering the target is stable. The PTV should include the entire circumference of the aforementioned vascular structures and the residual retroperitoneal surface after resection with a safety margin, which can be adequately treated with low-energy electrons in the 9-12 MeV range. After resection, the radiation oncologist and the surgeon discuss the retroperitoneal area at risk of residual tumour and this volume must be within a field defined by the IOERT applicator with a safety margin of at least 1-2 cm on the sides, to adequately cover the PTV, including anatomical, dosimetric and geometric uncertainties; in depth, a margin of 0.1-0.5 cm should be sufficient to balance the uncertainties of beam penetration. The tumour bed after a pancreatectomy is generally well comprised within 7-10 cm applicators.

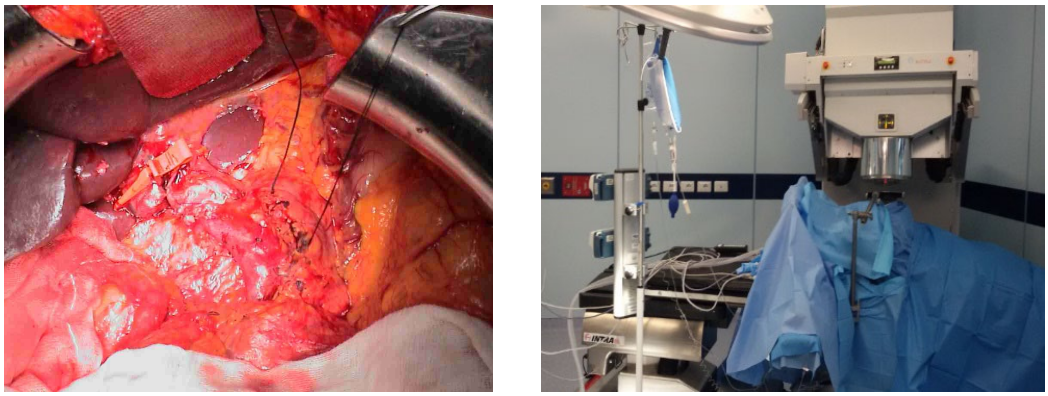

Figure 10.Tumor bed (retroperitoneal soft tissue, vascular structures, prevertebral ligament) identification after duodenocefalopancreasectomy (left) and irradiation phase after applicator positioning, its anchorage to the tumor bed and soft-doking) (photo by A. De Paoli)

The whole process can be summarized as follows:

1. define/evaluate the tumour bed, in terms of:
   - state of the surgical margin (inspection of the surgical field and of the posterior aspect of the surgical sample; the histopathological analysis on a frozen sample is optional);
   - characteristics of the perivascular tissue in borderline resectable lesions.
2. exclude healthy tissues and structures (mobilize and move away) not involved in the volume to be treated with IOERT: i.e. the bile duct dissected for subsequent biliary-pancreatic anastomosis, the pancreatic stump (dissected if it exists), the stomach, the colon, the small intestine, the liver and the upper pole of the right kidney.
3. include healthy tissue at risk in the PTV: i.e. the circumferential vascular structures (inferior vena cava; portal vein; superior mesenteric artery and vein, aorta; ligated left gastric artery), the soft tissues and lymphatic and retroperitoneal vessels and the prevertebral ligament (3).

2.3.3.2. Locally advanced, non-resectable pancreatic cancer

Also for unresectable pancreatic cancer, IOERT should be considered as an anticipated boost in a dose escalation program combined with EBRT, with and without chemotherapy (3). The area at risk (CTV) in this case is defined by the tumour with the contiguous structures involved (vessels, nerves) and is exposed by the surgeon at surgery. Contiguous unaffected structures (liver and biliary tract, stomach, intestines, kidneys) are mobilized and dislocated. The radiation oncologist, in collaboration with the surgeon, defines the PTV on the basis of the operative findings and preoperative imaging. The PTV must include the CTV with a radial margin of 0.5-1 cm (round applicators (7-8 cm diameter), with different bevel angles, as needed; the depth of the PTV is assessed at surgery, integrating preoperative imaging, and must include the tumour, the large vessels, the aorta and the vena cava (generally 3-4 cm).

Planning is completed in collaboration with the medical physicist with the choice of the most appropriate electron beam energy, size and bevel angle of the applicator, assessing the need for a bolus, evaluating any air gap (corrective factor) and the dose to critical structures if at risk and if included in the PTV, in particular for gastric carcinoma and nerve roots (dose limit 12.5 Gy). IOERT treatment must be performed before the reconstructive phase of surgery (biliodigestive anastomosis). The recommended dose is 15-18 Gy. If necessary, protective shielding discs can be used to protect non-target and non-displaceable nerve roots. The prescribed dose should be 90% of the reference isodose, along the central axis, with a ± 5% variability range.

2.3.4. Clinical results

2.3.4.1. Resectable pancreatic cancer

The first experience with IOERT after duodenocephalopacreatectomy was reported by the National Cancer Institute, Bethesda, USA in a randomized trial involving a series of 24 patients where IORT (20 Gy) plus postoperative radiotherapy was compared to postoperative radiotherapy alone. Despite the limitations due to the small size of the series, the study reported an improvement in local control and in the survival of the patients treated with IOERT (26).

Other studies on retrospective single-centre series were subsequently reported in North America and in Europe (27-29, 30, 34, 35) (Table 7).

Table 7. Main parameters in the treatment of pancreatic carcinoma with IOERT technique in major international studies

1° Author, year (ref.)	Pazients (no.)	Therapeutic approach	Dose IOERT (Gy)	EBRT (%)	MO (%)	CP (%)	RL (%)	OS (months)
Sindelar, 1999 (26)	12	S + EBRT	--	100	NR	NR	100	12
	12	S + IOERT + EBRT	20	100	NR	NR	33	18
Zerbi, 1994 (27)	47	S	--	--	2.1	23.4	56.4	12
	43	S+ IOERT	12.5-20	36	2.3	23.2	26	19
Alfieri, 2001(28)	20	S	--	--	8	43	71.2	10.8
	26	S + IOERT ± EBRT	10	67	9	57	41.6	14.3
Reni, 2001 (29)	76	S	--	--	4	45	11 mths§	12
	127	S + IOERT ± EBRT	10-25	28	5	39	14 mths§	15.5
Ogawa, 2010 (34)	210	S + IOERT ± EBRT	15-20	63	NR	NR	16.3	19.1
Valentini*, 2009 (35)	270	S + IOERT ± EBRT	7.5-25	63	NR	NR	15 mths§	19
Showalter**,	46	S ± EBRT	--	66	NR	40	39	19.2

2009 (30)	37	S ± IOERT ± EBRT	10-20	74	NR	46	21	21

year: year of publication; **IOERT**: dose in Gy forintraoperative radiotherapy (median value or range); **S:** Surgery; **EBRT:** external beam radiotherapy in %; **MO:** operative mortality rate in %; **CP:** perioperative complication rate in %; **RL:** local recurrence; **OS:** median overall survival in months; **§**actuarial estimate in months (mths) at the occurrence of local recurrence; *****Pooled analysis; ****** Propensity score analysis; **NR:** not reported.

In these experiences, IOERT was used as an anticipated boost (10-25 Gy) and associated in most cases (28% -74%) with postoperative radiotherapy (with and without chemotherapy). Albeit based on historical comparisons, these studies reported an improvement in local disease control and, in some series, also in survival compared to surgery alone (26, 28, 29). The incidence of local recurrence was 16% - 41%, compared to 39% -71% of patients who underwent surgery only, and median survival was 18-21 months compared to 11-19 months for patients who underwent surgery without IOERT.

A recent propensity score analysis of a retrospective single-centre series, however, did not confirm the improvement in local control and survival when the comparison between IOERT and surgery alone was adjusted for some potentially confounding factors (age, sex, stage, margins of resection, complications) (30). The limited number of patients studied, the higher incidence of advanced disease and the more frequent post-surgery positive margins in the group treated with IOERT, may however have influenced the comparative analysis, the conclusions of which require further evaluation. The most recent pooled analysis on clinical data from 5 European Centres with a total case series of 270 patients confirmed the improvement in local disease control with IOERT in resectable pancreatic cancer and the superiority of its combination with preoperative rather than postoperative radiotherapy, an element that represents the most innovative aspect of the combination (35).

Regarding the feasibility and safety of the treatment, in most of the reported experiences, IOERT was feasible, with an incidence of postoperative complications and perioperative mortality comparable to surgery alone (see Table 7).

2.3.4.2. Locally advanced non-resectable pancreatic cancer

Several studies have provided evidence of the safety of the treatment and of clinical benefits with regard to pain, with symptom remission in 75-85% of cases. In most studies, IOERT (15-25 Gy) was combined with pre- or post-IORT external radiotherapy (usually at 45-50.4 Gy), with and without 5-Fluoruracil (5-FU), with results that were superior to conventional EBRT alone (with and without 5-FU) (24,36-41) in terms of palliation and quality of life. The medium- and long-term results showed that symptom remission was maintained in a significant proportion of patients and, in some series, there was even a small fraction of long-term survivors at 5 and 10 years (37,38) (Table 8).

These results were the expression of retrospective analyses of single-centre experiences. RTOG 8505, a prospective multicentre study, has demonstrated the feasibility of IOERT even in a multi-institutional setting, but they do not confirm its superiority over conventional radiotherapy (36).

Table 8. Main parameters in the treatment of locally advanced, inoperable pancreatic carcinoma with IOERT technique in major international studies

1° Author, year (ref.)	Pazients (no.)	Therapeutic approach	Dose IOERT (Gy)	PL (%)	OS (months)
Roldan, 1988 (24)	122	EBRT	--	52	12.6
	37	EBRT+IOERT	20	18	13.4
Tepper*, 1984 (25)	51	EBRT+IEORT	20	NR	9

Willet, 2005 (37)	150	EBRT+IOERT	15-20	NR	13
Cai, 2013 (38)	194	EBRT+IOERT	15-25	59	12
Mohiuddin, 1995 (39)	49	EBRT+IOERT	10-20	29	16
Schuricht, 1998 (40)	29 76	EBRT EBRT+IOERT	-- 15-20	NR 30	18 20
Shibamoto, 1996 (41)	44 71	EBRT EBRT+IOERT	-- 10-20	NR	NR

year: year of publication; **IOERT:** dose in Gy for intraoperative electron radiotherapy (median or range); **EBRT: external beam radiation therapy; PL:** local disease progression rate in %; **OS:** median overall survival rate in months; *Multicenter prospective study, **NR:** not reported.

2.3.5. Conclusions

In resectable pancreatic cancer, IOERT as an anticipated boost in a dose escalation program within a combined treatment plan with external (postoperative) radiotherapy, with and without chemotherapy, has demonstrated possible improvements in local disease control and, in some selected series, also in survival. In most studies the incidence of postoperative complications and mortality after IOERT did not increase significantly (42), thus confirming its feasibility and safety. Even if recent pooled analyses confirm these indications, conclusive scientific validation is currently lacking.

There are two important phase II clinical trials currently underway that are expected to strengthen currently available evidence: the PACER trial, sponsored by the Massachusetts General Hospital (USA), on resectable and locally advanced borderline pancreatic cancer, which started in October 2018 (PACER NIH ClinicalTrials.gov), and the PancFORT trial, sponsored by the University of Verona, on borderline resectable pancreatic cancer, launched in September 2019 (PancFORT NIH ClinicalTrials.gov).

IOERT in resectable pancreatic cancer, therefore, is an option as part of a combined therapeutic strategy with level III evidence.

In unresectable pancreatic cancer, IOERT has demonstrated a palliative effect with remission of symptoms in most patients and maintenance of remission even in the medium and long term, but without a clear impact on local control. Therefore, in these cases, IOERT is a possible treatment option (level III evidence) in selected patients.

In borderline resectable cancer, IOERT combined with preoperative chemoradiotherapy in a dose escalation program, is an innovative approach of great interest. However, currently its role in this setting is still being investigated.

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2.4. Locally advanced gastric cancer

2.4.1. Introduction and background information

Over the past 30 years, Locally Advanced Gastric Cancer (LAGC) has been the second leading cause of cancer death in the world, although incidence and mortality have decreased in Western countries. In Europe, it is the sixth most frequent malignancy among males and females and the fifth in mortality with 8.4 deaths / 100,000 (1). In Italy, in terms of incidence it is ninth among men and tenth among women, while it is fifth in mortality (deaths in 2015 were 9,394) (2).

Radical surgery (total or subtotal gastrectomy with D2 lymphadenectomy) remains the only potentially curative therapeutic option, but only 35-40% of patients with gastric cancer are eligible for surgery. Most patients, in fact, already have an advanced unresectable or metastatic disease at diagnosis (3,4).

Even after radical surgery, however, the prognosis remains very poor, with a 5-year survival for 20-30% of patients (5-8) while loco-regional recurrence, alone or as a component of recurrence, still accounts for the most frequent cause of failure, even with the most advanced surgical approaches (5, 9-11).

The numerous randomized trials on post-operative chemotherapy after radical surgery published so far have not shown an unquestionable survival benefit; however, a significant, albeit limited, benefit was reported in the more recent meta-analyses (12, 13). In recent years, there has been growing interest in postoperative chemoradiotherapy following the publication of the results of the Intergroup Study 0116 (14) and subsequent experiences (15-18), and more recently also in perioperative chemotherapy (19, 20) and preoperative chemoradiotherapy (21-24). The significant advantage in terms of overall and disease-free survival for patients undergoing postoperative chemoradiotherapy or perioperative chemotherapy has stimulated growing interest in combined multidisciplinary treatment and has characterized research and

clinical practice, thus defining the role of radiotherapy in the treatment of gastric cancer. (25-27).

2.4.2. Indications and patient selection

IOERT in the treatment of gastric cancer is used as part of a combined approach that involves radical surgery with extensive dissection of the lymph nodes, in order to improve the prognosis of patients after gastrectomy. IOERT can be used both as single dose treatment and as boost in a combined program, with and without chemotherapy, in all cases of LAGC. The median dose of the boost is 12 Gy (10-17 Gy), while the median dose as single treatment is 20 Gy (15-30 Gy).

A recent meta-analysis of 8 selected studies (7 retrospective studies and one prospective randomized study) out of the 12 studies analysed, with more than 550 patients, demonstrated a statistically significant benefit of IOERT in combination with EBRT with and without chemotherapy after surgery in terms of increase in local disease control (28) (HR: 0.40; 95% Confidence Interval (95% CI) 0.26-0.62; p <0.011), while there was no significant impact on overall survival (HR: 0.97; 95% CI 0.75-1.26; p = 0.837) (Figures 11 and 12).

In gastric cancer, IOERT is indicated, within a dose escalation program combined with EBRT and chemotherapy, in operable locally advanced disease (stage T3-4 or N +, M0), with the aim of reducing the risk of local recurrence. A condition in which IORT can be of particular benefit is in the presence of massive lymph node localization in the region of the celiac tripod which is a critical site from the surgical point of view due to the risk of margin involvement (5).

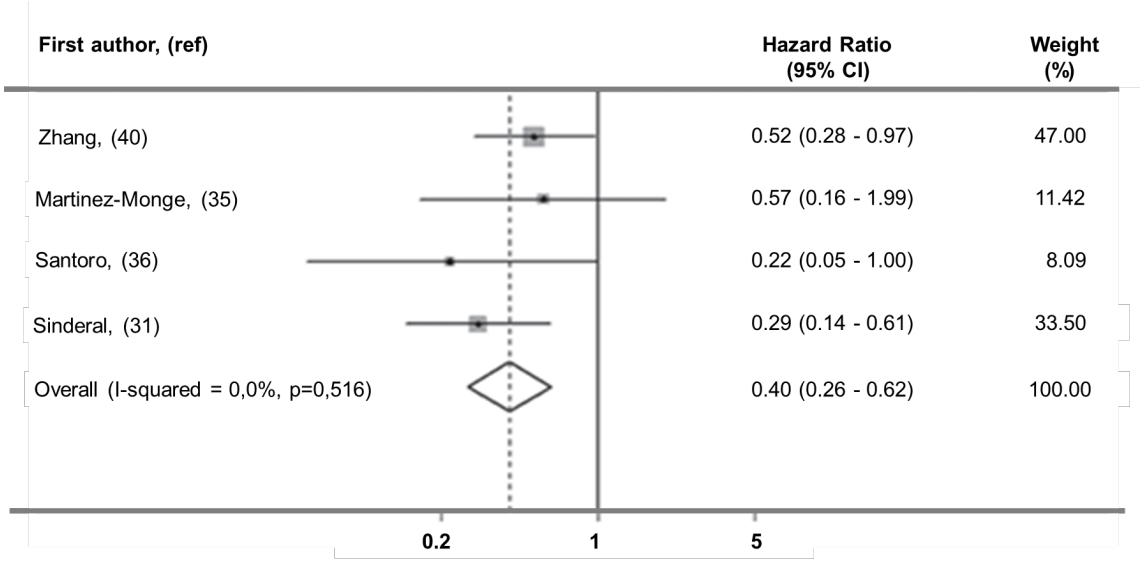

Figure 11. Meta-analysis at fixed effects of adjuvant IOERT on locoregional control. CI: Confidence interval (28)

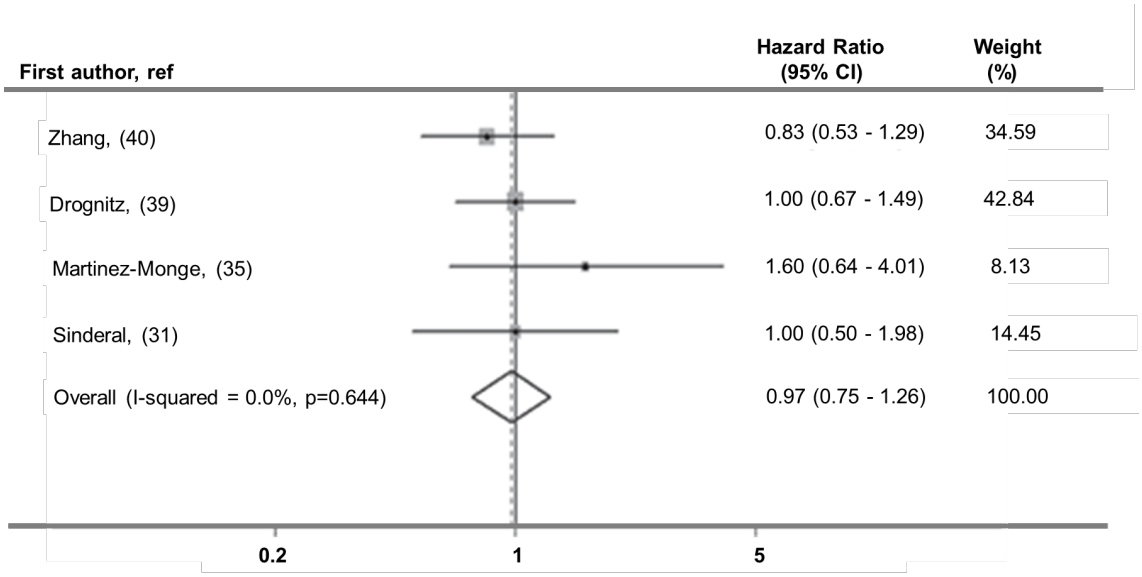

Figure 12. Meta-analysis at fixed effects of adjuvant IOERT on overall survival for all patients within 4 studies . CI: Confidence interval (28)

2.4.3. Treatment technique

The details of the IOERT procedure are to be discussed jointly by the radiation oncologist and the surgeon before surgery and they must define the area to be treated after the planned surgical resection (area at risk), based on staging/restaging imaging; they must also decide on the mode of access of the IOERT applicator and envisage possible changes to the procedure.

Patients should undergo gastrectomy with D2 lymph node dissection. The area at risk (CTV) is defined by the radiation oncologist in collaboration with the surgeon based on the surgical findings, location and extent of the primary tumour, the lymph nodes involved and on the basis of the previously discussed imaging. The CTV should include, after resection, the regional lymph node stations along the celiac tripod, the splenic artery, the common hepatic artery and the left gastric artery. Depending on the location of the tumour and extent of its diffusion, part of the pancreas body and, in the proximal localizations/gastroesophageal junction, the diaphragmatic pillars of the esophageal hiatus may also be included (29).

The tumour bed can be included in case of massive transmural disease (30).

After exposure of the area at risk and displacement of the unaffected surrounding tissues and organs (esophageal stump, duodenal stump, liver and gallbladder, colon and the small intestine,) the PTV is defined which must include the CTV with radial margins of 0.5-1 cm; the depth of the PTV is assessed at surgery, integrating preoperative imaging, and it must include the large vessels (generally 2-3 cm).

Planning is completed in collaboration with the medical physicist with the selection of the most appropriate electron beam energy, the size and bevel angle of the applicator, possible need for a bolus, evaluation of any air gap (corrective factor) and evaluation of the dose to be delivered to the critical structures included in the PTV, in particular the duodenum, the jejunum, the bilio-pancreatic tissues and the nerve roots (dose limit 12.5 Gy). If necessary, Pb shielding discs for non-displaceable healthy tissue can be used.

The IOERT dose generally used is 10 Gy in case of an R0 resection, 12.5 Gy in case of an R1 resection, and 15 Gy in case of an R2 resection. In some clinical studies of the 1990s and 2000s, doses even higher than 20 Gy were used.

The IOERT dose should be prescribed at 90% of the reference isodose, along the central axis, with a ± 5% variability range.

2.4.4. Clinical results

Gastric cancer was one of the first malignancies in which the clinical application of IOERT was tested (31). The dose limits of EBRT that can be safely used in the abdominal area had prompted interest in the application of IOERT, initially exclusively as treatment after gastrectomy and subsequently in a dose-escalation treatment plan, in association with EBRT, with and without chemotherapy. The comparison between IOERT treatment (20-35 Gy) and postoperative EBRT alone (50 Gy / 25-28 fractions) was reported in a limited series of patients in a randomized study in the early 1990s. Although the study was negative in terms of overall and disease-free survival, a significant advantage was reported on locoregional control (100% *vs.* 70%), without an increase in postoperative complications (32).

In terms of feasibility and advantage over local control these results were confirmed, albeit without a clear impact on survival, in two other trials one of which also included preoperative radiotherapy (33, 34) (Table 9).

Table 9. Main parameters in the treatment of locally advanced gastric cancer with IOERT technique in major international randomized trials

1° Author, year (ref.)	Pazients (no.)	Therapeutic approach	Dose (Gy)		OS at 5yrs (%)	LC at 5 yrs (%)
			IOERT	EBRT		
Sindelar, 1993 (31)	16	S+IOERT	20	--	NS	56
	25	S+EBRT	--	50		8
Kramling, 1997 (32)	51	S+IOERT	20-35	--	29 (3yrs)	NR
	64	S	--	--	31 (3yrs)	
Skoropad, 2000 (33)	59	Pre-op RT+S+IOERT	20	20	50	NR
	53	S	--	--	52	

year: year of publication; **S:** Surgery; **OS at 5yrs**: 5-year overall survival rate if not otherwise specified (in %); **IOERT:** intraoperative electron radiation therapy; **EBRT**: external beam radiation therapy; **LC at 5yrs:** 5-year local control (in %); **NR:** not reported; **NS:** not significant difference. **Pre-op**: preoperative

In most of the reported experiences, IOERT was associated with postoperative EBRT (with and without chemotherapy) as an anticipated boost. In these studies, IOERT was found to have improved local disease control and, in some series, also survival compared to surgery alone and postoperative EBRT with and without chemotherapy. The median IOERT dose was 12 Gy (10-20 Gy) and the postoperative EBRT dose was 45-50.4 Gy with and without chemotherapy (5-FU-based) (30,35-40). The studies that retrospectively compared the results of treatments with and without IORT (with and without postoperative EBRT and with and without chemotherapy) are presented in Table 10. In the IORT series, local control and 5-year survival were 50-89% and 41-58%, respectively. In the series without IORT, local control and survival were 35-80% and 38-59%, respectively.

Table 10. Main parameters in the treatment of locally advanced gastric cancer with IOERT technique in major international nonrandomized studies

1° Author, year (rif.)	Pazients (no.)	Therapeutic approach	Dose (Gy)		OS at 5 yrs (%)	LC at 5 yrs (%)
			IOERT	EBRT		
Ogata, 1995 (34)	58 120	S+IOERT S	28-30 --	-- --	*55 *35	NR
Martinez-M., 1997 (35)	62	S+IOERT+EBRT±CT	15	40-46	38	80 at 91 mths
Santoro, 1998 (36)	59 341	S+IOERT S	27-30 --	-- --	38 39.8	8,7 13.9 (p0.05)
Lowy,§ 2001 (21)	24	S+IOERT+EBRT/CT	10	45	NR	NR
Glehen,§§ 2003 (37)	87	S+IOERT+EBRT± CT	12-23	46	44.8	78
Qin, 2006 (38)	106 441	S+IOERT S	10-30 --	-- --	5% Improvement with IOERT p<0.001	NR
Drognitz, 2008 (39)	84 61	S+IOERT S	15-25 --	-- --	58 59	NR
Zhang, 2012 (40)	46 51	S+IOERT+EBRT± CT S+EBRT±CT	12-15 --	39-45 39-45	NR	50 35

year: year of publication**; S:** Surgery; **OS at 5yrs:** 5-year overall survival rate unless otherwise specified in **%; LC:** local control in %; **IOERT:** dose in Gy for intraoperative electron radiation therapy**; mths:** months; **EBRT:** dose in Gyfor external beam radiotherapy; **§:** Phase II preoperative chemo-radiotherapy study (pathologic complete response 11%); **CT:** chemotherapy; ***** Stage III only; **§§**Stage N1-N2.

Also the incidence of reported postoperative complications was comparable in most of the series where IORT was compared to non-IORT. A significant increase in complications has been described only in some studies where IORT was the only treatment at doses of 20-25 Gy (32.40). The incidence of perioperative mortality was comparable in all the reported series.

2.4.5. Conclusions

For LAGC, studies have shown an improvement in local disease control with the use of IORT as part of a dose-escalation program, in combination with EBRT (postoperative) with and without chemotherapy. Based on retrospective studies and recent meta-analysis, IORT in locally advanced T3-4, N + M0, has level IIa evidence. In most of these studies, IORT was not associated with a significant increase in the incidence of postoperative complications confirming its feasibility and safety, especially when doses are increased by moderate amounts (10-15 Gy). No evidence was found in favour of improvement in survival.

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2.5. Locally advanced rectal carcinoma

2.5.1. Introduction and background information

Locally Advanced Rectal Cancer (LARC) is a leading cause of cancer-related morbidity and mortality, with approximately one million new cases diagnosed worldwide each year (1, 2). Rectal cancer represents about 30% of colorectal cancers and is characterized by a natural history and diagnostic and therapeutic complexity that set it apart from colon cancer. In the locally advanced stages, T3-4 and / or N0-2, long-course preoperative chemoradiotherapy or short-course preoperative radiotherapy followed by radical surgery with Total Mesorectal Excision (TME) represent the gold standard of treatment (3-7). Although improvements in surgical technique with TME and neoadjuvant therapy have significantly reduced the incidence of local recurrence to levels below 10%, the risk of distant metastases currently represents the main problem for these patients, 65-70% of whom are still alive at 5 years (8-11). However, even if systemic disease control is the most important goal and is the focus of current clinical research, the risk of local recurrence still remains a problem in some subgroups of patients (stage T4 or T3 with positive circumferential margins, distal localization of the tumour, N2), for whom new ways of intensifying the radiation dose representa great interest for the multidisciplinary approach to these tumours (12-14).

It is in this context of dose intensification, within a combined multimodal treatment approach, that IORT is considered to be the therapeutic modality of greatest interest in rectal cancer. This chapter presents the procedures related to IORT treatment with electrons since it is the modality that is most documented in the literature.

2.5.2. Indications and patient selection

In rectal tumours, the combined IOERT-EBRT treatment has been widely used both in locally advanced primary cancer and in local recurrences.

In primary rectal cancer, the selection of candidates for the IOERT boost is of fundamental importance. For example, patients diagnosed with primary T4 rectal cancer who would not obtain an R0 resection margin with surgery alone can benefit from local treatment with IOERT, preceded or followed by EBRT. A French multicentre phase III trial (15) randomized patients with T3-T4 rectal cancer, comparing standard EBRT versus preoperative EBRT with a dose of 40 Gy in 20 fractions followed by an IOERT boost of 18 Gy. There were no differences in the two groups in terms of local and distant disease control, nor of toxicity. Several studies have shown that patients at risk of subtotal resection and treated with neoadjuvant chemo-radiotherapy should be identified and selected preoperatively (16-19). The most commonly used regimen was the following: 45-50 Gy administered with conventional fractionated EBRT

concomitantly with 5-FU or capecitabine chemotherapy. Surgery was performed 4-8 weeks after the end of radiotherapy concomitantly with the IOERT boost at a dose of 10-20 Gy. Local control by IOERT was maintained in most patients even after an R2 margin resection (57% in the Massachusetts General Hospital analysis, Boston, USA, and 73% in the Mayo Clinic analysis) (20, 21), taking into account that positive resection margins are the most important factors related to the risk of locoregional recurrence and cancer-related death.

Even for the local recurrences of rectal tumours, the most important element associated with local disease control and overall survival was the type of surgical resection (22,23). In patients with R0 resection margins, IOERT was associated with a local control of 60-80% and an overall 5-year survival of 40-50%. In case of residual disease (R2) the local control rate dropped to 30-50%.

In Holman's analysis (24), with a median follow-up of 51 months, multidisciplinary treatment, which included surgery and IOERT preceded or followed by EBRT with and without chemotherapy, showed encouraging results in terms of local control and recurrence, especially in the subgroup of patients with positive resection margins.

The NCCN 6.2020 guidelines (25) insert IOERT as a boost (10-20 Gy) in case of *close* or positive margins after surgical resection, especially for patients with T4 or recurrent tumour.

In conclusion, the indications for the treatment of the rectum can be summarized as follows:

- T3 rectal adenocarcinoma with high risk of recurrence (evidence of pre-sacral/contact lymphangitis or infiltration of the mesorectal fascia on MRI, after multimodal neoadjuvant therapy);
- T4N0 / N +;
- pelvic recurrence of rectal adenocarcinoma subjected or not to previous radiotherapy;
- in all previous cases when surgery alone is insufficient to obtain R0 resections with a Circumferential Resection Margin (CRM) <1 mm, R1-2 resections, and where the tumour adheres to adjacent unresectable structures.

In order to perform the IOERT, the following conditions are required:

- technical feasibility of removing the lesion;
- possibility of mobilizing the organs and tissues at risk, displacing them away from the area to be irradiated;
- absence of distant or oligo-metastatic metastases;
- Performance Scale (PS) (Karnofsky) > 60%.

Relative or absolute contraindications are:

- collagen diseases in the active phase, inflammatory bowel diseases in the active phase, diverticula at risk of perforation in the irradiation area (also valid for pelvic EBRT);
- technical unfeasibility of pelvic access;
- impossibility to mobilize/protect the organs and tissues at risk outside the area to be irradiated;
- presence of multiple distant metastases;
- Performance Scale (PS) (Karnofsky) ≤ 60%.

2.5.3. Treatment technique

Intraoperative treatment does not differ significantly between advanced and recurrenced forms of carcinoma, except in the case of palliative treatment with macroscopic disease still in place. The area at risk (CTV) is defined during surgery on the basis of the surgical findings and previously discussed imaging.

Curative resection of rectal cancer requires thorough radicalization along four planes: the visceral plane of the pelvic fascia (surrounding the mesorectum and rectum), the parietal plane of the pelvic fascia (including the musculoskeletal boundaries of the pelvic lateral wall and pelvic autonomic nerves), the internal iliac vascular system and the extravascular spaces (obturators).

Intraoperative irradiation can be carried out after adequate resection, extemporaneous histological assessment to evaluate the state of the margins and haemostasis.

Generally, the areas at greatest risk are:

- the pre-sacral space (the most frequent site of pelvic recurrence, even after IOERT treatment) (22, 23);
- the parietal mesorectum: site of infiltration of the CRM or where the CRM is <1 mm (26);
- the lateral spaces: frequent site of microscopic spread of the disease;
- the sites of fixity/adhesion of the tumour to adjacent non-resectable structures.

The PTV is defined after exposure of the risk area and dislocation of the neighboring unaffected structures (intestinal loops, ureters, bladder, uterus, prostate) (Figure 13). The PTV must include the CTV with a 0.5-1 cm radial margin (circular applicators with different bevel angles, as needed and with a diameter of not less than 4 cm, compatibly with the possibility of being inserted into the pelvic cavity, in order to ensure a relatively homogeneous dose to the target volume) (Figure 14); the depth of the PTV is assessed during surgery, integrating direct visualization with preoperative imaging. Particular attention is paid to avoiding the collection of serum in the pre-sacral space to reduce dose attenuation. Planning is completed in collaboration with the medical physicist, with the selection of the most appropriate electron beam energy, the size and bevel angle of the applicator, the need for a bolus, and the evaluation of any air gap (corrective factor) (Figure 15).

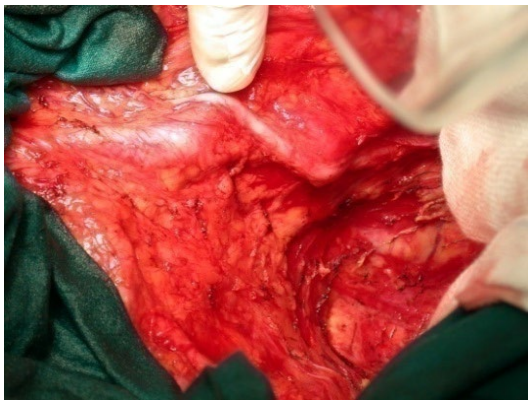

Figure 13. Pelvic cavity opening with ureter indication for proper displacement outside the field IOERT of irradiation (photo by A.Ciabattoni)

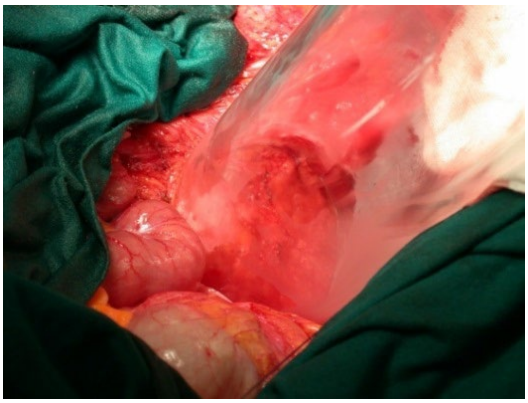

Figure 14. Applicator introduction in pelvic scavo to deliver treatment with IOERT (photo by A.Ciabattoni)

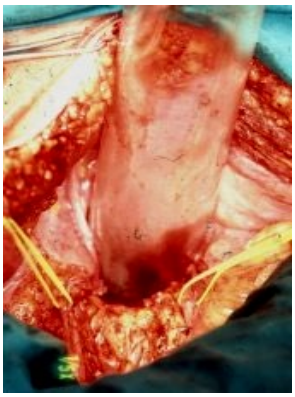

Figure 15. Applicator position for rectum carcinoma treatment with IOERT (photo by A.Ciabattoni)

Once the treatment has been performed, surgical clips should be placed along the margins of the irradiation field so as to identify the area that has already received a boost, and also as landmarks that can guide the setting phase of postoperative external radiotherapy, if any (and if neoadjuvant radiotherapy has not already been performed). When the resection is subtotal, the CTV is defined on the basis of clinical suspicion of infiltration or, in R2 cases, by direct observation of the macroscopic residue. Surgical clips are recommended also in these circumstances.

The dose limits for the main organs at risk (OAR) are 12.5 Gy for the peripheral nerves, while for the ureter, if not displaceable, a ureteral stent after surgery is recommended.

The recommended IORT dose is 10 Gy for R0 resection, 12.5 Gy for R1 and 15 Gy for R2. The IORT dose should be prescribed at 90% of the reference isodose.

2.5.4. Clinical results

2.5.4.1. Locally advanced rectal cancer (LARC) - IOERT

Currently available experience mostly consists of retrospective studies in which IORT in combination with preoperative external radiotherapy (with and without chemotherapy) has shown an improvement in local disease control and in the survival of treated patients compared to preoperative radiotherapy alone and surgery (16,17).

In these studies, the preoperative radiotherapy dose was 45-50.4 Gy/25-28 fractions followed by surgery and IORT with a median dose of 12.5 Gy (range 10-20 Gy). The results, in terms of local control and 5-year survival, were resepctively 57-100% and 4-75%, and 1% in the case of R2. These results are comparable with the 72% -84% local control rate reported in the non-IORT series with preoperative radiotherapy (with and without chemotherapy) and R0 surgery, while the benefit of IORT is significant in local control and survival in patients with R1-R2 resection who have an increased risk of local recurrence (Table 11) (15, 18-23, 25, 27, 28).

Even though these data are interesting in their assumptions and conclusions, they cannot be considered of general guidance since, both for the quality of the studies and for the heterogeneity of the treatments performed, they do not meet the criteria of clear evidence required by Evidence Based Medicine. The only two randomized trials that compared the combination of IORT treatment with the standard treatment of only external radiotherapy and chemotherapy did not demonstrate any significant benefits in terms of local control or survival. However, these studies had methodological limitations both in terms of the number of patients enrolled (27) and in their selection criteria (89% of favourable T3 R0 stages in the Dubois study) (15).

More indicative data were reported in the pooled analysis of the European group on a total of 605 patients (431 stage T3 and 174 stage T4) treated for rectal cancer in four reference centres which had significant experience with IORT (23). The treatment program in all of these cases consisted of preoperative chemo-radiotherapy followed by radical surgery with IORT (10-12.5 Gy) and adjuvant chemotherapy. The local recurrence, overall and 5-year cancer-specific survival rates of these patients were 12%, 67% and 74%, respectively, hence more favourable than the results reported in published studies of patients with the same disease presentation, same therapeutic programs, but without IORT. These authors also reported that 55% of patients with positive resection margins were free from local recurrence at 5 years, confirming the indications of historical data supporting the efficacy of dose escalation with IORT after preoperative chemoradiotherapy and R1 resection with positive circumferential margins (29-33).

Table 11. Main parameters in the treatment of locally advanced rectal cancer with IOERT technique in major international studies

1° Author year (ref.) trial	Pazients (no.)	Type of study	T4 (%)	IOERT Dose (Gy)	EBRT in % (Gy)	FU	LC at 5 yrs (%)	OS at 5 yrs (%)	Late toxicity grade 3+
Ratto, 2003 (19)	19 S+IOERT+EBRT 24 S	NRC	93	10-15	100	74	91 S+IOERT+EBRT 57 S p=0.035	61	NR
Sadahiro, 2004 (30)	99 S+IOERT+EBRT 68 S	NRC	12	15-25	100 (20)	67 83	98 S+IOERT 84 S p=0.002	79 S+IOERT 58 S p=0.002	NR
FerensSild, 2006 (18)	30 S+IORT+EBRT 93 S	NRC	25	10(HDR-IORT)	100	25	72 R0+IORT 71 R0 (NS) 58 R(+)+IORT 0 R(+) p=0.016	56 R0+IORT 66 R0:(NS) 38 R(+)+IORT 0 R+ p=0.026	NR

Roeder, 2007 (22)	243	RC	20	10-15	86	59	94 R0+IOERT 72 R(+)+IOERT	NR	total 10%: 8pts proctitis, 7pts fistula, 8pts stenosis
Mathis, 2008 (16)	146	PC	64	7.5-25	100	44	86	52	total 22%: 3*pts neuropathy, 23*pts GI/GU
Masaki, 2008 (26)	19 S+IOERT 25 S	RCT	0	18-20	No	34	9.,7 S+IOERT 95.5 S	p=0.344 NS	Bladder catheter: 29% 3%
Valentini, 2009 (19)	73 S+IOERT+EBRT 69 S	NRC	100	10-15	100	31	100 R0+IOERT 81 R0 p=0.014	NR	NR
Dubois, 2011 (15)	73 S+IOERT+EBRT 69 S	RCT	100	15-18	100	60	91.8 S+IOERT 92.8 S p=0-6018	69.8 S+IOERT 74.8 S p=0.25	no differences toxicity p=0.15
Kusters, 2010 (22)	605	PC pooled analysis	29	10-12.5	100		90.5 R0+IOERT 55 R(+)IOERT p<0.001	67	NR
Sole, 2014 (28)	335	PC	16	10-15	100	72.6	92	75	total10%: 19* pts GI, 8* pts GU, 7* pts neuropathy
Holman, 2016 (23)	417	PC pooled analysis	100	10-12.5	97	52	87 R0+IOERT 60 R1+IOERT 57R2+IOERT p<0.001	65 R0+IOERT 34 R1+IOERT 14 R2+IOERT p<0.001	NR

year: year of publication; **NRC:** non-randomized comparison; **S:** surgery; **IOERT:** intraoperative electron radiation therapy; **EBRT**: external beam radiation therapy **HDR-IORT:** high dose rate brachytherapy; **RCT:** randomized controlled**; PC:** prospective cohort; **RC:** retrospective cohort; **FU:** follow-up median value in months; **LC**: local disease control in %; **OS:** overall survival in %; **NR**: not reported**; NS:** non-significant difference; **R(+):** residual after surgery**; R0** no residual after surgery; **R1** microscopic residual (1mm); **R2:** macroscopic residual (>1mm); ; Late toxicity grade 3+ expressed according to RTOG scale; **GI:** Gastro-intestinal toxicity; **GU:** Genito-urinary toxicity.

A systematic review and meta-analysis of 29 published studies reported significant data supporting indications for IORT in rectal cancer (LARC) and in major evidence-based recurrences (34). This meta-analysis demonstrated a statistically significant benefit of IORT when combined with preoperative radiotherapy, with and without chemotherapy, plus surgery on all cancer endpoints (local control, global disease-free survival) without a significant increase in evaluated complications (urological and gastrointestinal) (Figure 16). In particular, of the 29 studies, 14 were prospective (2 randomized) and 15 retrospective, for a total of 3003 patients. The indication for IORT included 1792 patients with LARC and 1211 with recurrence of the disease. In 95% of patients, IORT was performed with IOERT. Even though it was difficult to clearly define the concept of "locally advanced" (heterogeneity of the local presentation of the disease and lymph node involvement) and also of the IORT dose which was between 7.5 and 25 Gy (generally between 10 and 15 Gy in the case of microscopic (R1) residual disease and 15-20 Gy for macroscopic (R2) disease), the categories of patients affected by LARC in whom IORT can currently be indicated were identified. IORT was reported to have significant benefits also on disease-free survival for the four comparative studies (18,26,30,35), (HR = 0.51; 95% CI 0.31-0.85; p = 0.009) (Figure 17).

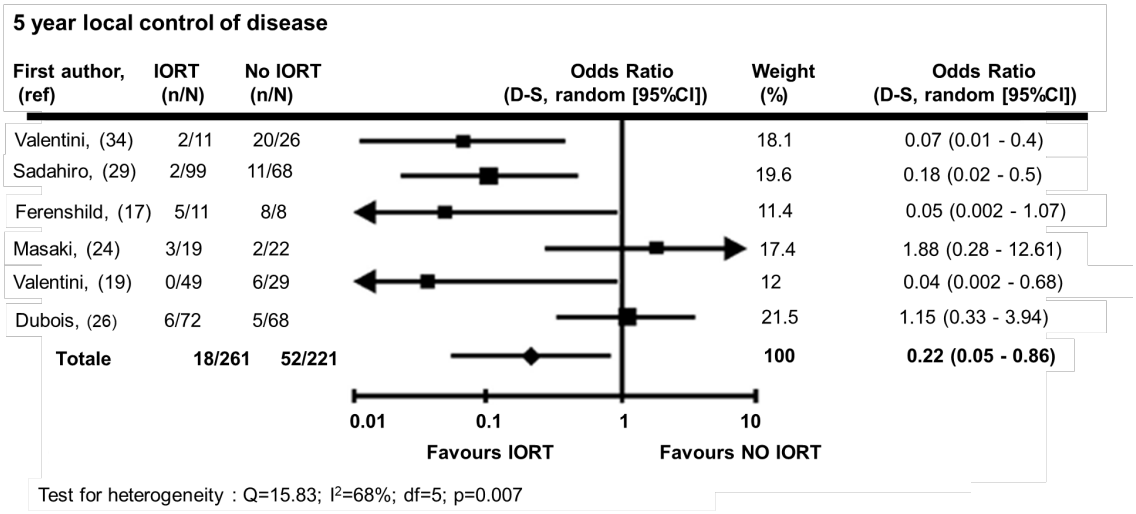

Figure 16. Systematic revision and meta-analysis studies related to local control of disease at 5 years (34)

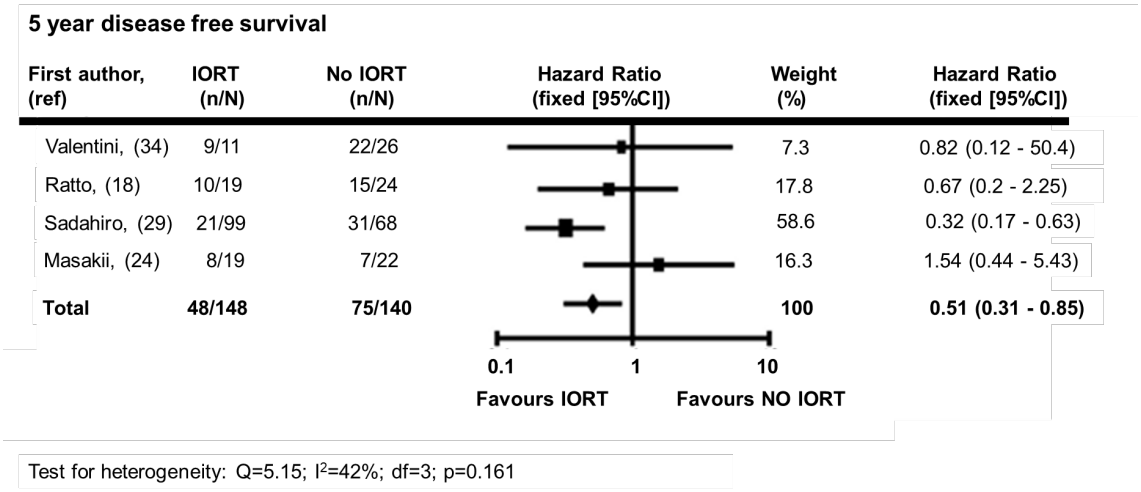

Figure 17. Systematic revision and meta-analysis studies related to survival free of disease at 5 years (34)

The benefit of IORT on survival was confirmed also by the 5 comparative studies examined (17, 26, 30, 35, 36) with an HR = 0.33 (95% CI 0.2-0.54; p = 0.001) (Figure 18). Finally, 4 studies provided comparative data on the impact of IORT on postoperative complications (27, 30, 36, 37). The pooled estimates did not demonstrate a significant increase in the total number of complications, neither urological nor intestinal, while a greater number of surgical wound complications were reported (OR = 1.86, 95% CI 1.03-3, 38, p = 0.049) (Figure 19).

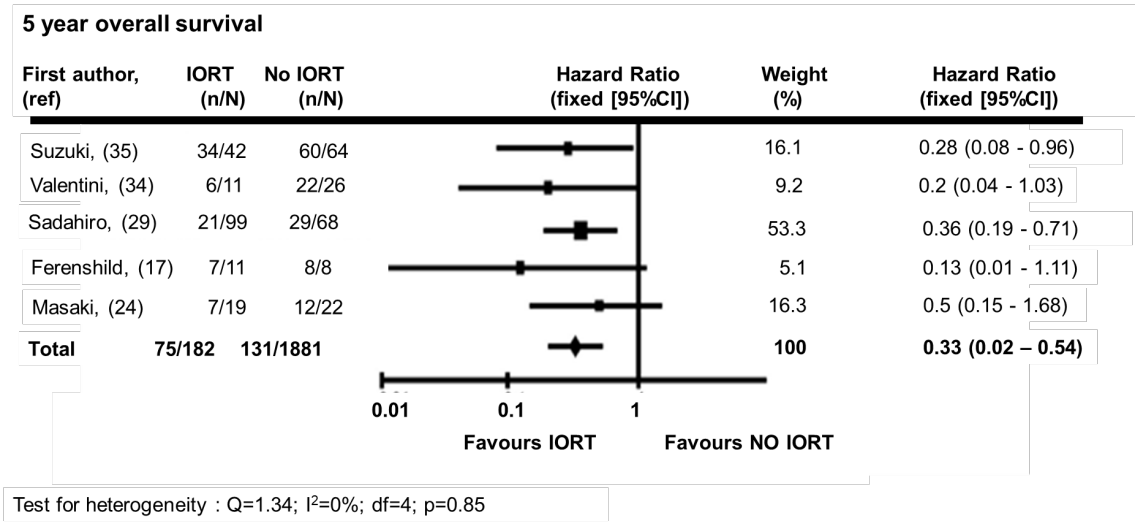

Figure 18. Systematic revision and meta-analysis studies related to the overall survival at 5 years (34)

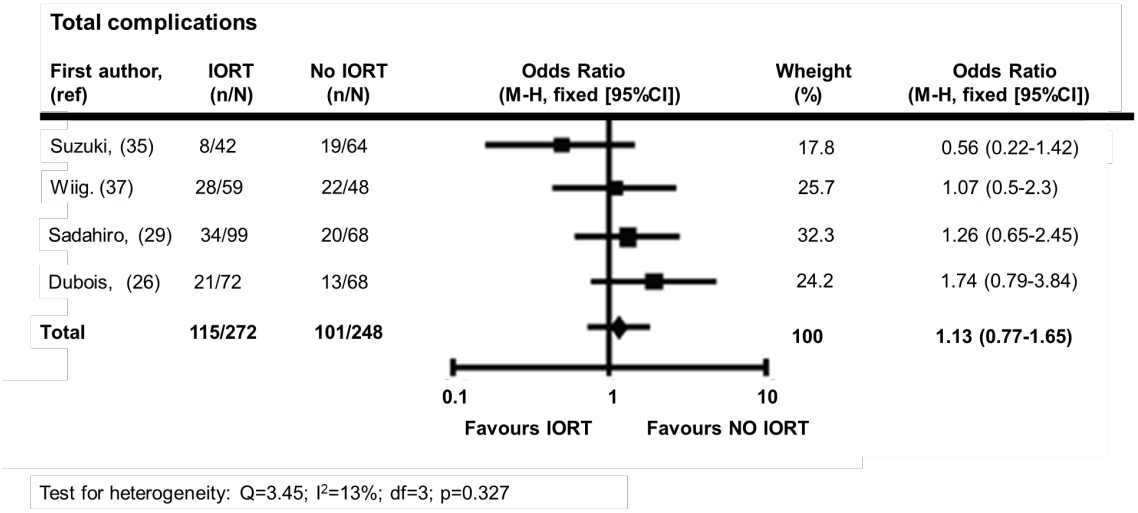

Figure 19. Systematic review and meta-analysis of toxicity studies at 5 years (34)

This meta-analysis, albeit with the limitations reported in the foregoing (mainly based on retrospective phase II studies), indicates that IORT may lead to better local disease control and survival through the multimodal treatment of selected patients with LARC after R1 (R2) resection and in patients with recurrence after R0 resection (level IIb evidence).

2.5.4.2. Rectal cancer recurrences

Locally Recurrrent Rectal Cancer (LRRC) presents a difficult clinical problem. Recurrence of the disease is often accompanied by pain, bleeding, urinary and rectal obstruction with a very poor quality of life for patients and the recurrence itself can cause death even in the absence of distant metastases. The therapeutic approach has gradually shifted from palliative treatment towards a curative intent in selected cases thanks to multimodal treatment with preoperative radiotherapy with and without chemotherapy and radical surgery. Consequently, the prognosis

of these patients has changed from a median survival of 8 months reported with palliative radiotherapy alone to a possible 5-year survival for 30-39% of patients with combined multimodal treatment (38).

The possibility of intensifying the dose of radiotherapy with IORT within a combined chemo-radiotherapy treatment plan has stimulated great interest in the treatment of recurrences from rectal cancer. Retrospective studies using IORT in combination with preoperative radiotherapy (with and without chemotherapy) and surgical resection have shown improved local control and survival, compared to historical comparisons with surgery and/or radiotherapy alone in patients with LRRC who did not receive pretreatment. Radical R0 surgery was the determining prognostic factor with local control and 5-year survival of 68% and 63%, respectively, compared to 19% and 11% in R1-2 resections. The preoperative radiotherapy dose was 45-50.4 Gy and the IORT dose was 10-20 Gy. The incidence of major acute toxicity (Grade 3+) occurred in 11% - 42% of cases while late Grade 3+ toxicity was described in 4% - 18% of patients (35-43) (Table 12).

Table 12. Main parameters in the treatment of recurrence of locally advanced rectal cancer with IOERT technique in major international studies

1° Author, year (ref.)	Pazients (no.)	Type of study	IOERT Dose (Gy)	Prior EBRT %	Adiuv EBRT %	FU (m)	LC at 5 yrs (%)	OS at 5 yrs (%)	Acute/late toxicity grade ≥ 3
Suzuki, 1995 (36)	42 S+IOERT 64 S	NRC	10-30	25	98	44	60 S+IOERT 7 at 3 yrs S	19 S+IOERT 7 S p=0.0006	36% total: 5% abscess, 9% GI/GU
Valentini, 1999 (35)	11 S+IOERT 14 S	NRC	10-15	28	100	80	80 S+IOERT 24 S p<0.05	41 S+IOERT 16 S NS	1pt hydrophrenosis 0*pts neuropathy
Wiig, 2002 (37)	59 S+IOERT 48 S	NRC	15-20	0	100	NR	50 S+IOERT 30 S NS	30 S+IOERT 30 S NS	NR late toxicity, NS acute complications
Dresen, 2008 (39)	147	RC	10-17.5	53	84	NR	69 R0+IOERT 29 R1+IOERT 28 R2+IOERT p<.,001(3yrs)	59 R0+IOERT 27 R1+IOERT 24 R2+IOERT p<0.001(3yrs)	16*pts neuropathy, 4*pts ureter stenosis
Haddock, 2011 (40)	606	PC	7.5-30	45	96	44	79 R0+IOERT 56 R1+IOERT 49 R2+IOERT p<0.001	46 R0+IOERT 27 R1+IOERT 16 R2+IOERT p<0.001	11% total: 42* pts wound, 18* pts neuropathy
Roeder, 2012 (41)	97	PC	10-20	44	52	33	82 R0+IOERT 41 R1+IOERT 18 R2+IOERT p<0.001 (3yrs)	80 R0+IOERT 37 R1+IOERT 35 R2+IOERT p<0.001 (3yrs)	acuta:16 pts abscess/late fistola: 8* pts neuropathy, 3*pts ureter stenosis
Calvo, 2013 (42)	60	PC	10-15	50	47	36	44 R0 vs R1 p=0.05	43 R0 vs R1 p=0.05	42% total: 4 pts fistola, 4* pts neuropathy, 4* pts GI
Holman, 2017 (43)	565	PC pooled analisi	10-20	46	95	40	72 R0+IOERT 36 R1+IOERT 39 R2+IOERT p<0.0001	48 R0+IOERT 25 R1+IOERT 17 R2+IOERT p<0.0001	

year: year of publication; **NRC:** Non-randomized Control Study; **Prior:** recurrence after previous RT treatment in %; **Adiuv:** post-operative EBRT in %; **FU:** median follow-up in months; **RCT:** Randomized Controlled Trial; **LC**: local disease control in %; **OS**: 5-year overall survival rate in %; **S:** Surgery; **IOERT: intraoperative radiation therapy PC:** Prospective Cohort; **RC:** Retrospective Cohort; **R (+):** residual after surgery; **R0:** no residual after surgery; **NR:** not reported; **NS:** non-significant differences**; R1**: microscopic residual; **R2**: macroscopic residual; **GU:** Genito-urinary toxicity; **GI:** Gastro-intestinal toxicity.

These data are in line with the results of a meta-analysis that included some series of patients with LRRC published in 2008 (26) (see Figures 17-19). Despite the limitations mentioned earlier, the meta-analysis indicates that, in selected patients with LRRC and subjected to R0 resection, the inclusion of IORT in a multimodal treatment plan can lead to better local disease control and improved survival (level IIb evidence).

The use of IORT as a single treatment modality after surgical resection has been explored in some series of patients with LRRC pretreated with radiotherapy. Most of these patients had undergone R2 resections and the results reported with IORT alone were disappointing in most cases (36, 44, 45). More recently, clinical studies on external re-irradiation with and without chemotherapy (23.4-40.8 Gy) were reported. The results were encouraging; clinical benefits were reported in the majority of patients and 33% - 75% of these underwent re-operation for curative purposes (46-48). In one of the reported experiences, IORT was also used in a dose-escalation treatment plan in a selected group of patients with R0 resection, with a dose of 10-15 Gy. Also in these cases, radical surgery was a determining factor and local control and 5-year survival were 69% and 67%, respectively (49).

As for the side effects of treatment, the incidence of complications reported with IORT in the treatment of LARC and of LRRC varied between 5% and 60% (see Table 12) and were generally higher for LRRC (48). In particular, possible complications were reported for the surgical wound and for the gastrointestinal tract. Gastrointestinal fistulas and ureteral structures had an incidence of between 2% and 12% and plexopathy and neuropathy were late toxicities of IORT in the pelvic area showing a dose-dependent relationship (14, 31). However, aggregated estimates in the previously reported meta-analysis did not demonstrate a significant increase in the total number of complications (urological or intestinal), while a greater number of scar-related problems occurred.

The recent publication of the ESTRO/ACROP recommendations on IOERT in the treatment of locally advanced rectal cancer (50) speaks in favour of the implementation of pelvic dose intensification strategies and the personalization of therapeutic choices for the promotion of local control, including treatment with the IORT.

In vivo dosimetry and intraoperative imaging can improve the accuracy, reproducibility and safety of combined treatments.

Data from the literature therefore indicate the feasibility of retreatment in a multimodal approach that may also include IORT in selected cases of patients with LRRC. The recurrence of rectal cancer in patients pretreated with radiotherapy is an emerging problem (currently they account for most of the cases) and hence there is great interest in a possible rescue therapeutic strategy that has curative purposes even in this very unfavourable patient population. However, experience with IORT in multimodal retreatment is still limited and hence this approach is still in the experimental stage and is reserved for Centres with proven experience.

2.5.5. Conclusions

Available evidence indicates that the inclusion of IORT in multimodal treatment plans with external radiotherapy, with and without chemotherapy, can lead to improved local control and survival in selected patients with LARC after R1-R2 resection and in patients with LRRC after R0 resection.

The lack of controlled prospective studies with large numbers of cases limits the possibility of drawing firm conclusions. However, the indications of the recent pooled analysis and the subsequent meta-analysis of available studies support its use in clinical practice in selected cases (level IIb evidence).

The indication for IORT in LARC was also confirmed at the consensus meeting on the multidisciplinary treatment of rectal cancer promoted by the European Registry of Cancer Care or European Cancer Audit (EURECCA) which includes the IORT option in high-risk patients (T3-4 N2 M0, MRF +) with persistent positive circumferential margins after preoperative chemoradiotherapy.

Finally, the use of IORT in multimodal retreatment programs with radiotherapy with and without chemotherapy in LRRC patients pretreated with radiotherapy has proven to be feasible with encouraging results.

However, this requires a further definition of the correlations between the biological calculation of the equivalent dose (BED), topographic models of recurrence and prognostic characteristics of patients. In these cases, IORT must still be considered experimental and subject to further clinical research (50).

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2.6. Soft tissue sarcomas

Soft Tissue Sarcomas (STSs) represent a heterogeneous group of rare tumours of mesenchymal origin that may occur ubiquitously throughout the body. The extremities and the walls of the trunk are the most frequent sites (60%) followed by the retroperitoneum (15%) and the cervico-facial area (10%), while the viscera (uterus) and the thorax are more rarely affected. Despite the small number of cases (5-7 cases/100,000 inhabitants/year, equal to about 4500 new cases every year in Italy), sarcomas have a wide histological variability, with at least fifty histological subtypes, often divided into different degrees of biological aggressiveness, and with natural histories and sensitivity to specific radiotherapy and chemotherapy (1-3).

The indication for IORT is generally established on the basis of surgical radicality as part of a multidisciplinary strategy. A systematic review of the literature regarding patient selection, integration of IORT into multimodal treatments, and technical details is contained in the ESTRO/ACROP recommendations for soft tissue sarcomas (4).

2.6.1. Sarcomas of the limbs and trunk

2.6.1.1. Introduction and background information

The treatment of limb and trunk sarcomas has changed significantly over the past few decades. The combination of conservative surgery (large resection) with pre- or postoperative

radiotherapy in the STSs of the limbs has progressively replaced the sole radical compartmental, often destructive (amputation) surgery, hence defining the reference standard in the multidisciplinary approach and emphasizing the essential role of radiotherapy in the conservative treatment of these tumours (3, 5, 6).

2.6.1.2. Indications and patient selection

IORT in the STSs of the limbs and trunk was delivered mainly as part of a dose-escalation plan (used as a boost dose) in the area of greatest risk of positivity of the surgical margin in the context of multimodal treatment with surgery, pre- or postoperative external beam radiotherapy, and possibly chemotherapy in high-risk disease (7).

The rationale for administering part of the radiotherapy intraoperatively lies in the possibility of displacing any sensitive structures away from the treatment bed; it is therefore possible to exploit the biological efficacy of the high dose/fraction without simultaneously increasing the risk of toxicity (4). IORT only as exclusive modality plus surgery was reported in some retrospective series in the 1980s and is currently rarely used due to the high risk of late toxicity.

Currently, exclusive IORT is indicated in selected cases of recurrence of the disease, after surgery and radiotherapy, as an option in salvage therapy with conservative surgery and re-irradiation as an alternative to major surgery (8). For sarcomas of the limbs, IOERT should be considered when planning resection with close or positive margins. Other factors that constitute an indication for IORT are: high degree of the tumour, size > 5 cm, deep localization, and recurrence (4).

2.6.1.3. Treatment technique

The details of the IOERT procedure must be discussed jointly by the radiation oncologist and the surgeon before surgery and they must define the area to be treated after the planned surgical resection (area at risk), based on staging/restaging imaging (MRI, or CT if MRI is contraindicated); they must also decide the best way for of the IOERT applicator to approach the target and envisage possible changes to the procedure if necessary. The IOERT plan will then be discussed with the medical physicist (location and prediction of the PTV) and with the Tr/RTT (anatomical site, patient position, manoeuvers planned for the LINAC-operating table).

The area at risk (CTV) is defined during surgery by the radiation oncologist in collaboration with the surgeon, based on the preoperative imaging and on the state of the resection margins after removal of the tumour (defined on the basis of the surgeon's opinion or of the histological examination on a frozen section). The CTV includes the tumour bed with a 1-2 cm margin, including partially resected muscles, bone (periosteum), and vascular and nerve structures considered at risk after their isolation from the tumour. Care must be taken to dislocate the skin away from the irradiation field. Healthy tissues not at risk of microscopic infiltration by the disease must be displaced as far away as possible from the irradiation field.

The PTV is defined after exposure of the risk area and dislocation of the unaffected neighboring structures; the PTV must include the CTV with a radial margin of 0.5-1 cm (circular applicators with different bevel angles); the depth of the PTV is assessed at surgery, integrating the preoperative imaging.

Planning is completed, in collaboration with the medical physicist, with the selection of the applicator (size and angle) and the most appropriate electron beam energy. In some cases, it may be necessary to place a bolus. If appropriate, Pb shielding discs can be used to protect non-displaceable healthy tissue.

The recommended IOERT dose, in combination with pre- or postoperative radiotherapy of 45-50 Gy, is 10 Gy in case of an R0 resection (negative margin), 12.5 Gy in case of an R1

resection, and 15 Gy in case of an R2 resection. The IOERT dose should be prescribed at 90% of the reference isodose, along the central axis, with a ± 5% variability range.

Particular attention should be paid to the dose that reaches the healthy organs at risk included in the treatment field, in particular peripheral nerves and bone.

The dose limit for peripheral nerves is 12.5 Gy. For the bone structures (femur, tibia-fibula) the unaffected cortex should be excluded as far as possible, attenuating the dose (<50%) with an appropriate selection of electron energy in order to minimize the risk of fracture.

An example of IOERT after radiotherapy and preoperative chemotherapy for a High Grade Pleomorphic Sarcoma (G3) of the thigh is shown in Figure 20.

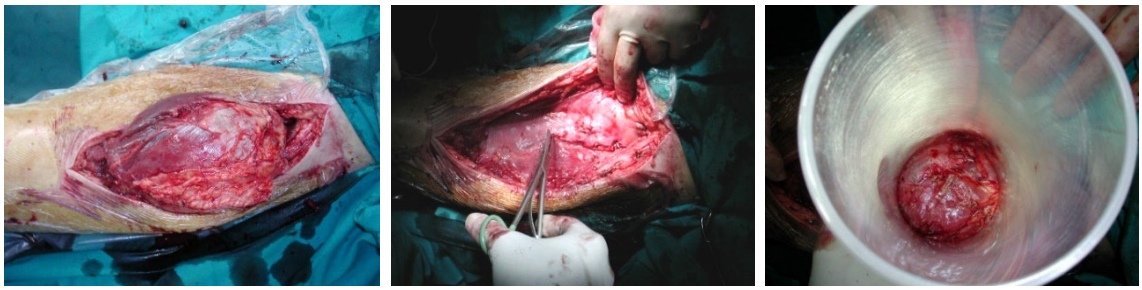

Figure 20. Wide resection of the tumor, exposure of the high risk area CTV (tumor bed, neurovascular structures) and applicator's postioning to define the PTV for IOERT treatment of pleomorphic sarcoma of the thigh, after chemotherapy and preoperative EBRT (photo by A. De Paoli)

2.6.1.4. Clinical results

In the STSs of the limbs, cingula and superficial trunk, the combination of IOERT with conservative surgery, EBRT and chemotherapy has been shown to be very effective, with a local control rate of 82-97% at 5 years (9-20).

These results are comparable to or even better than the 83-93% local control rate reported in the surgery plus EBRT cases alone, despite the fact that patients treated in the IOERT series had more unfavourable prognostic factors in most cases (incomplete surgical radicality, site, size and disease recurrence) (7). In all studies, IOERT was delivered at a dose of 10-15 Gy (based on the R0-R1-R2 residual tumour) and was preceded or followed by 46-50 Gy of EBRT, for an overall biologically equivalent dose of 60-75 Gy (21).

As regards toxicity, a recent review, which analyzed a number of studies in the literature, showed a low rate of acute and late toxicity, with a high percentage of limb function preservation (59-86%) (7) (Table 13).

The use of IORT did not influence the incidence of postoperative complications whose rate was between 5% and 20% in the combination case series with postoperative EBRT, and between 21% and 31% in those with preoperative EBRT (18, 20).

These data are comparable to both the incidence of surgical wound complications reported in the Canadian trial that compared postoperative EBRT *vs.* preoperative EBRT (17% *vs.* 35%), without IORT (22), and the results of the RTOG 0630 study on the use of Image Guided Radiation Therapy (IGRT) (23).

Some clinical studies have also shown that the association of IORT with adjuvant chemotherapy (with pre- or postoperative EBRT) does not lead to a significant increase in the incidence of postoperative complications compared to the cases treated without IORT, thus confirming the feasibility of the procedure also in high risk patients in whom the combination with chemotherapy is indicated (24, 25).

Table 13. Main parameters in the treatment of limb sarcomas with IOERT technique in major international studies

1° Author year (ref.)	Pazients (no.)	Type of study	FU (months)	R0	Dose (Gy)		LC at 5yrs (%)	OS at 5yrs (%)	LP (%)	FC (%)
					IOERT	EBRT				
Haddock, 1997 (27)	91	R,SC	34	NR	10–15	45–50	92[b]	76[b]	NR	NR
Edmonson, 2001 (10)	39	R,SC	70	62	10–20	45	90[a]	80	95	NR
Azinovic, 2003 (11)	45	R,SC	93	67	15	45–50	80[a]	64[a]	88	77
Kretzler, 2004 (12)	28	R,SC	52	61	12–15	50	84	66	100	59
Oertel, 2006 (13)	128[c]	R,SC	33	49	15	45	83	83	90	86
Llacer, 2006 (14)	79	R,SC	58	42	20(LDR)	45–50	90	69	100	NR
Roeder, 2018 (15)	53	R,SC	66	NR	7,5–12,5	NR	87	75	83	81
Sole, 2014 (16)	48	R,SC	20	83	10–15	50	83[b]	84[b]	NR	NR
Roeder, 2015 (28)	34	P,SC	43	88	10–15	40–50	97	79	94	81
Calvo, 2014 (18)	159	R,MC	67	84	12,5	45	82	72	94	NR
Roeder, 2015 (20)	183	R,SC	64	68	15	45	86	71	95	83
Roeder, 2015 (28)	259	R,MC	63	71	12	45	86	78	95	81

year: year of publication; type of study: **R**: restrospective; **P**:prospective; **SC**: single center; **MC**: multicenter; **FU**: median follow-up in months; **R0** rate of "microscopically complete resections" in %; **IOERT**: dose in Gy or intraoperative radiotherapy (median or range); **EBRT**: dose in Gy for external beam radiotherapy (median or range); **LC at 5yrs**: local control at 5 years; **OS at 5yrs**: 5-year overall survival rate in %; **LP**: rate in % of limb preservation; **FC**: rate in % of excellent/good functional outcome; **a**: crude rate in %; **b**: estimated rate at 3 years; **c**: excluding patients with distant metastases at the time of surgery; **NR**: not reported; **LDR** low dose rate brachytherapy.

Neuropathy represents dose-limiting late toxicity in IORT, that depends on the dose (10-20 Gy) and on the treatment volume. In the STSs of the limbs, the various series report an overall incidence between 3% and 12%, with peaks of up to 25% if the analysis is limited only to patients in whom the IORT volume includes the nerve structures (7). If the removal or shielding of peripheral nerves from the radiotherapy field is not technically feasible or if they are the target of treatment (contiguity-involvement by the disease), in order to contain the risk of neuropathy below 3%, the dose should be kept at < 12.5 Gy (8, 9), while the total dose deemed to be effective should be delivered by preoperative or postoperative EBRT.

The risk of fibrosis with possible functional outcomes (joint stiffness, motor deficits) in the reported series varies from 4% to 9% and is related to the volume and irradiation dose (11, 17, 26), while the risk of bone fractures is limited to values < 4% (11, 20, 26).

2.6.2. Retroperitoneal sarcomas

2.6.2.1. Introduction and background information

Unlike the STSs of the limbs and the superficial STSs of the trunk, disease control in retroperitoneal sarcomas is more difficult and the incidence of local recurrence after surgery is

higher due to the feasibility limits of radiotherapy in such sites. The anatomical complexity, the generally large dimensions of these tumours and the close anatomical contiguity with abdominal structures considerably restrain surgical radicality with the ensuing risk of local recurrence (28).

Even if multivisceral surgery seems to improve local disease control (29,30), the possible involvement of structures that are more difficult to resect, such as the large abdominal vessels, the structures of the cephalo-pancreatic region and the paravertebral structures, may limit also the radicality of this type of surgery (31, 32).

The possible impact of pre- or postoperative radiotherapy on survival and disease control in retroperitoneal sarcomas remains controversial. Compared to the sarcomas of the extremities, where the role of surgery combined with radiotherapy is well established, there is no high level evidence of its efficacy in the sarcomas of the retroperitoneum.

The IORT treatment is generally performed with a dedicated, mobile LINAC located in the operating room, with operational procedures specific to each Centre. The traditional IORT treatment with the patient being transported from the operating room to the radiotherapy room has been superseded by the new technological solutions and is still used only in a few Centres.

2.6.2.2. Indications and patient selection

Given the limited dose range (45-50 Gy) that can be safely administered to the abdominal area with EBRT, sarcomas of the retroperitoneum represent an area of great interest for the application of IORT in a dose escalation treatment plan (7). IORT should be considered as part of a combined approach with pre- or postoperative external radiotherapy, when complete resection, even multivisceral, but with narrow (*close*) or positive margins, can be performed. The risk generally occurs when the disease appears to infiltrate or is very close to unresectable abdominal structures (large vessels, vertebral bodies, nerve roots).

2.6.2.3. Treatment technique

The area at risk (CTV) is defined at the time of surgery by the radiation oncologist in collaboration with the surgeon, on the basis of the previously discussed preoperative imaging (MRI or CT if MRI is contraindicated) and on the basis of the surgical findings (state of the resection in the opinion of the surgeon and any extemporaneous histological examinations). Generally, the CTV includes the tumour bed with the bone, and the vascular and nerve structures considered at risk after the radical removal of the tumour. A safety margin of 1-2 cm is recommended. If coverage of the surgical bed is not possible with a single applicator, the use of adjacent (but not overlapping) fields can be considered.

If necessary, Pb shielding discs can be used to protect peripheral nerves, ureters, non-target biliary tract and other non-displaceable organs at risk. The PTV is defined after exposure of the risk area and the dislocation of the unaffected neighboring structures (intestinal loops, stomach, duodenum, pancreas, biliary tract, ureters, bladder); the PTV must include the CTV with a radial margin of 0.5-1 cm (dedicated circular and/or elliptical applicators, with different bevel angles); the depth of the PTV is assessed at surgery, also on the basis of the preoperative imaging.

Planning is completed, in collaboration with the medical physicist, with the choice of the most appropriate electron beam energy, the size and angle of the applicator, the bolus, if necessary, and with the assessment of the dose to critical structures included in the PTV, in particular, nerve structures and ureters.

The recommended IORT dose is 10 Gy for R0 resection (approximate negative margin), 12.5 Gy for R1 resection and 15-20 Gy for R2 resection.

The IORT dose should be prescribed at 90% of the reference isodose, along the central axis, with a variability range of ± 5%.

Placing a ureteral stent is recommended (preferably postoperatively), given the risk of post-radiotherapy stenosis (33). In addition to the ureter, it is strongly recommended to limit the dose also to the gastro-intestinal and bone structures.

As for sarcomas of the limbs, therefore, if nerve roots and peripheral nerves are included in the target volume (due to contiguity-involvement by the disease) the dose should be limited to values <12.5 Gy to contain the risk of neuropathy <3 % (9). This IORT dose constraint is compatible with the combination of IORT with preoperative radiotherapy (45-50.4 Gy) (4, 22).

2.6.2.4. Clinical results

The role of postoperative radiotherapy has been assessed in a small number of, mostly retrospective, clinical studies. Although none of these studies have demonstrated a clear benefit in terms of survival, a possible impact on local disease control was documented when adequate doses of radiotherapy (> 54 Gy) after complete R0 resection could be used with sufficient safety (34-38).

Other mostly retrospective clinical studies have reported more favourable results with preoperative radiotherapy (45-50.4 Gy) especially when combined with IORT (12-15 Gy) compared to the more traditional postoperative radiotherapy (45-55 Gy) with IORT (15 Gy), in terms of both local tumour control (51-83% *vs.* 40-60%) and, above all, the incidence of acute gastrointestinal, urological toxicity and major postoperative complications (6-12% *vs.* 10-40%) (33, 39-47).

Multivariate analyses have shown the most significant prognostic factors to be disease presentation (primary cancer *vs.* recurrence), surgery radicality (R0-R1 *vs.* R2), size and grade of the tumour (39-45, 48).

Table 14 shows the main studies on the use of IORT in retroperitoneal sarcomas. The results are comparable with those obtained with surgery and pre- or postoperative radiotherapy alone without IORT (34-38) and with surgery alone, even when performed with the multivisceral approach (29, 30).

In retroperitoneal sarcomas, the combined IORT-EBRT approach was the subject of a phase I / II trial of the University of Heidelberg (49) in which the treatment was preoperative intensity-modulated EBRT with simultaneous boost up to 50-56 Gy followed by surgery and IORT 10 - 12 Gy. The results of the interim analysis of the trial were updated in a subsequent publication in 2014 (17, 26) which reported an estimated 3-year local control rate of 72% and an estimated 3-year distant recurrence rate of 63%. The hystology of leiomyosarcoma was found to be the only negative prognostic factor that had a significant impact on the Progression-Free Survival (PFS). Acute toxicity was mainly haematological and gastrointestinal (CTCAE grade 3 in 15% of cases), while severe late toxicity (CTCAE G3 scale) was 6% at 1 year and 0% at 2 years.

The incidence of neuropathy in the reported series varies from 3% to 50% in relation to the IORT dose (10-20 Gy) and the treated volume.

Two studies based on data from the *Surveillance Epidemiology and Results Program of the National Cancer Institute* (SEER) aimed at assessing the benefit of postoperative radiotherapy on overall survival in retroperitoneal sarcomas have provided contrasting results (50,51). The National Cancer Data Base conducted two case-control propensity score-matched analyses, between postoperative radiotherapy and preoperative radiotherapy *vs.* surgery alone. The study included over 9,000 patients with retroperitoneal sarcoma treated from 2003 to 2011 and demonstrated that, in comparison with surgery alone, both pre- and postoperative radiotherapy had a favourable impact on survival (52). Although this was a retrospective study, thanks to the amount of data collected and the methodological rigor of the analyses performed, it supported the indication for the combination of surgery and radiotherapy in retroperitoneum sarcomas (Table 14). However, the recently published STRASS study (EORTC-STBSG), which

compared preoperative radiotherapy to surgery alone, as already reported in previous publications (53, 54), confirmed the superiority of preoperative radiotherapy in terms of survival and disease control only in the histological subset of liposarcoma (55). These results therefore confirm the possible benefit of preoperative radiotherapy for patients with retroperitoneum liposarcoma for which new dose-escalation programs can be developed with IOERT (4).

Table 14. Main parameters in the treatment of sarcoma of the retroperitoneum with IOERT technique in major international studies

1° Author year (ref.)	Pazients (no.)	Type of study	FU (months)	GTR (%)	EBRT			IOERT		LC at 5yrs (%)	OS at 5yrs (%)
					Pre (%)	Post (%)	Dose (Gy)	Pazients (%)	Dose (Gy)		
Sindelar, 1993 (48)	15	P,SC	96	100	--	100	35-40	100	20	60[1]	45[2]
	20	Rand		100	--	100	50-55	--	--	20[1]	52[2]
Gieschen, 2001 (39)	16	R,SC	38	100	100	--	45	100	10-20	83	74
	13	SC		100	100	--	45	--	--	61	30
Petersen, 2002 (56)	87	R,SC	42	83	75	28[b]	48	100	15	59	48
Krempien, 2006 (40)	67	R,SC	30	82	--	67	45	100	15	40[3]	64
Pierie, 2006 (41)	14	R,SC	27	100	100		40-50	100	10-20	--	77
	27			100	100		40-50	--	--	--	45
Pawlik, 2006 (42)	72	P,MC	40	75	100	--	45	47	15	60[4]	50
Ballo, 2007 (43)	18	R,SC	47	100	60	40	45-66	100	15	51	NR
	63		47	100			45-66	--	--	46	NR
Sweeting, 2013 (45)	18	R,SC	43	100	94	--	45	100	10-20	64	72
Gronchi, 2014 (46)	83	R,MC	58	84	88	--	50	17	12	63[1,5]	59
Roeder, 2014 (26)	27	P,SC	33	96	100	--	45-55	85	12	72	74

Year: year of publication; Type of study; R: restrospective; P: prospective; SC: single center; MC: multicenter; Rand: randomized; FU: median follow-up in months; GTR: % of patients with macroscopically complete resection; Pre: rate (in %) of patients treated before surgery with external beam radiotherapy; Post: rate (in %) of patients treated with external beam radiotherapy after surgery; EBRT: external-beam radiotherapy in Gy (median or range); IOERT: patients treated with intraoperative electron radiotherapy (in %); LC at 5yrs: 5-year local control (in % unless otherwise specified); OS at 5yrs: 5-year overall survival rate (in % unless otherwise specified); 1: crude rate in %; 2: median OS in months; 3: abdominal control; 4:in patients undergoing macroscopic resection; 5: in patients undergoing resection; NR: not reported.

The superiority of the combination of IORT (20 Gy) with postoperative radiotherapy (35-40 Gy) compared to postoperative radiotherapy alone (55 Gy) was reported in a randomized study in the early 1990s where the advantage over local control (60% *vs.* 20% at 5 years) was also accompanied by a lower incidence of gastrointestinal toxicity, while neuropathy, reported in 60% of cases, emerged as long-term dose-limiting IORT toxicity. The 5-year survival was similar in the two treatment arms (48).

2.6.3. Conclusions

All reported studies demonstrated potential improvements in local disease control with IORT as a dose-escalation program in the therapeutic combination with preoperative or postoperative radiotherapy with and without chemotherapy, for both limb sarcomas and retroperitoneum sarcomas. In these studies, IORT did not lead to a significant increase in the incidence of acute postoperative complications, thus confirming its feasibility and safety in the treatment of these tumours. The combination of IORT with preoperative radiotherapy appears to be the most favourable sequence, particularly in retroperitoneal sarcomas. The risk of long-term neuropathy represents the main late dose-related toxicity, so it is recommended that the dose of 12.5 Gy not be exceeded whenever possible.

In the absence of phase III studies, IORT is still of investigational interest. However, thanks to the increase in local control reported in numerous retrospective and prospective phase II studies, it has level IIa evidence according to the NCCN 2020 guidelines (5). Both in the case of limb/trunk and retroperitoneal sarcomas, the NCCN (NCCN 2020) considers the possibility of delivering a boost by IORT in the case of microscopically positive margins (10-12.5 Gy) or macroscopic residual tumour (15 Gy), after preoperative EBRT and surgery.

Based on available evidence, the Italian radiotherapy cancer community has expressed its consent to the use of IORT in soft tissue sarcomas of the limbs and retroperitoneum as a dose-escalation option within the therapeutic combination with preoperative or postoperative radiotherapy with and without chemotherapy, even outside clinical research studies (46).

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2.7. Gynaecological cancer

2.7.1. Introduction and background information

Although the first references to IORT in gynecological pathology date back to the early 1900s, publications grew in numbers between the 1960s and 1980s thanks to American and Japanese researchers. However, it was in the 1990s that IORT had the greatest development, thanks above all to the spread of dedicated accelerators installed directly in the operating room (1).

IORT can be used in all gynecological pathologies (cervical, endometrium, ovarian cancer), mainly in the context of recurrences (2), but also in a curative context (3, 4).

However, while in the treatment of recurrences the results are encouraging (5), in the curative setting they do not appear to show any improvement compared to the traditional treatment protocols, at least as regards cervical cancer. Since 2011, some researchers have explored the role of reirradiation with tumour-directed external beams before surgery and IORT, in a combined multidisciplinary perspective that aims at achieving maximum local disease control (4, 6).

2.7.2. Indications and patient selection

The following sections show the indications for IOERT treatment by location.

2.7.2.1. Uterine cervix

The experiences that have considered IORT in an exclusively curative perspective in recurrences are very few and disappointing (7). However, in selected cases (very elderly patients, concomitant pathologies) where EBRT radiation treatment after surgical treatment of the recurrence is not feasible, personalized treatment at the sites at greatest risk of further recurrence can be considered (for example: pelvic wall, groin region) (8).

In locally advanced disease, the current treatment standard is concomitant chemo-radiotherapy (9), but randomized trials involving the addition of neoadjuvant chemotherapy are underway. In very selected cases, that respond poorly to chemoradiotherapy, and when a higher dose with brachytherapy is not recommended or not feasible, it may be reasonable to consider the surgical option and propose IORT to consolidate it (10).

There is much greater experience with IORT treatment in the loco-regional recurrence of diseases that are candidates for salvage surgery.

In some studies, in the recurrence of disease in the pelvis, particularly when the lesion reaches the lateral pelvic wall, the addition of IORT to surgery seems to have a favourable impact on local disease control (5, 11, 12). Although data in the literature are scarce, even more

favourable results seem to be obtained if surgery and IORT are preceded by EBRT in patients not previously irradiated (13).

A careful interdisciplinary assessment of the radiological documentation, the potential and limits of neoadjuvant EBRT and a joint clinical assessment by the radiation oncologist and the surgeon are mandatory in the discussion of the therapeutic program.

2.7.2.2. Endometrium

Unlike the recurrences of cervical cancer, radiotherapy rarely plays a purely curative role in endometrial cancer.

In pelvic recurrences of the cancer, the salvage therapy is brachytherapy (with and without EBRT) or, alternatively, surgery (9), the latter with less satisfactory results. In very selected cases, debulking surgery associated with IORT may be considered when close or frankly positive margins exist or are expected (5, 14, 15).

Experience with uterine sarcomas is very poor and the results are modest given the poor prognosis of the disease in terms of survival and local control. Particular and well-selected cases can however be considered for IORT (9) (level III evidence).

2.7.2.3. Ovaries

There are sporadic experiences of IORT in recurrent ovarian cancer.

In adequately selected patients, a combined approach of cytoreductive surgery and IORT has acceptable toxicity and can contribute, as part of a broader therapeutic strategy, to improving local control and to providing palliation (16).

2.7.2.4. Vulva – vagina

Although cancer of the vulva and cancer of the vagina are different in terms of prognosis and therapy, recurrences make them comparable by location.

In these cases, IORT can be considered when the disease reaches the area of the pubic symphysis, which represents an obstacle to surgical radicality. However, this location also constitutes a limit to the technical feasibility of IORT itself (1).

2.7.2.5. Lymph node irradiation

IORT, possibly associated with EBRT pre- or post-surgery, can be considered for the sites of lymph nodes where radical surgery is not feasible (17).

2.7.3. Treatment technique

All the radiological staging images are to be available in the preoperative phase in order to predict the possible site of treatment and assess, in advance, the relationship with nearby structures. Likewise, all the iconographic documentation of any previous radiotherapy treatments performed are to be available or, at least, data on the doses delivered and the technique used need to be available.

During the surgery, the surgeon exposes the area susceptible to treatment and defines it if possible with a dermographic pencil (Figure 21), so as to make sure that the applicator, by adhering to the designed area, will correctly reach the desired target.

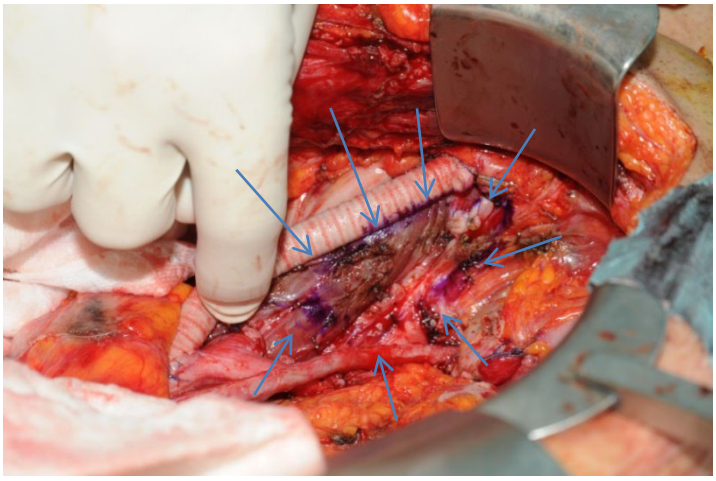

Figure 21. Preparation at surgery of tumor bed, marked with dermographic stencil (purple) with respect to surrounding tissues, paying attention to nerve and vascular structures (In the figure a vascular prosthesis can be observed) before proceeding with applicator positioning for irradiation (photo by R. Lazzari)

For macro or microscopic lesions of the pelvic wall, bevelled applicators are used, with an inclination of usually up to 30° and a diameter of 4 to 7 cm. If there is suspicion of microscopically infiltrated resection margins, the use of a wet gauze as a bolus is recommended to increase the dose on the surface. Since the gauze partially obscures the verification of the correct positioning of the applicator with respect to the target area, it is advisable to first check the collimation and adhesion of the applicator to the surface without the bolus (Figure 22) and then repeat the procedure with the bolus. Often, the biggest technical limit to the execution of the treatment is represented by the size of the abdominal surgical breach and by the anatomical conformation of the patient, which may not allow a sufficient angle for the coupling of the part of the applicator connected to the head of the accelerator with the part of the applicator positioned in the abdominal cavity.

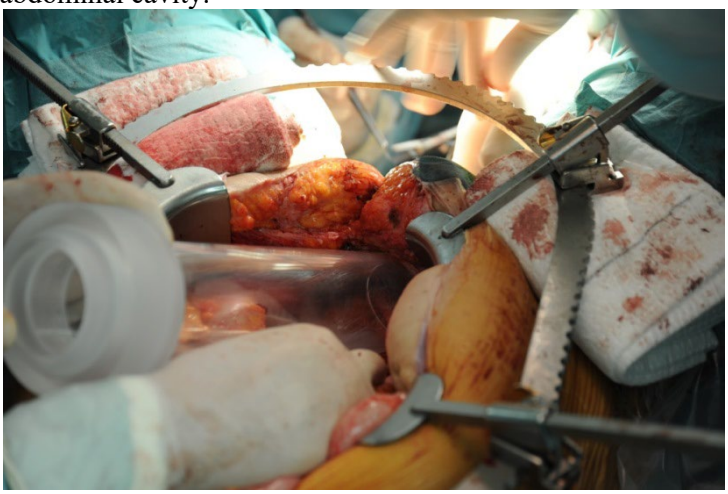

Figure 22. Pre-treatment verification of applicator placement in the pelvic excavation in relation to the width of the abdominal surgical breach and anatomical conformation of the patient, before proper attachment with the applicator part laced to the head of the accelerator (photo by R. Lazzari)

At times, for very low or retropubic lesions, a transperineal approach may be considered, if technically feasible. At the end of the procedure it is advisable to mark the treated area with surgical clips.

The selection of dose and energy to be used depend partially on the assessment of any previous treatments performed and partially on the site to be irradiated. Dose limiting factors are represented by the proximity of vessels and nerves (see Figure 21).

The vessels are considered resistant to high doses and, thanks to their easy visualization, they can generally be moved away from the irradiation field (Figure 23). Nerves are usually more sensitive to high doses per fraction and are located deeper than the irradiation plane and consequently require special attention at the point of prescription in order to minimize the risk of neurological damage (maximum recommended dose is 12 Gy).

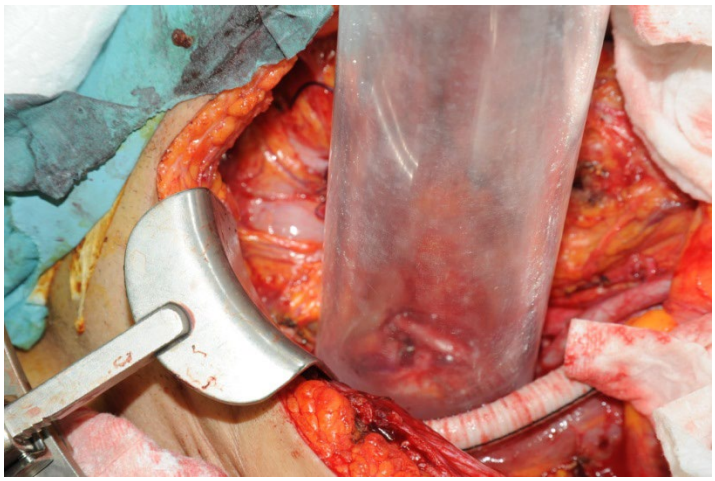

Figure 23. Exemple of applicator positioning into the pelvic cavity , prepared for gynecological tumor treatment. To note in the figure, vessels moved far from irradiation field and substituted vascular protheses (photo by R. Lazzari)

2.7.4. Clinical results

Published studies are mostly retrospective, they do not include a large number of cases and are conducted in single institutions.

Although the results are interesting, these methodological limitations prevent the identification of a clear role for IORT in the therapeutic strategy and point to the need for prospective collaborative studies. Table 15 shows the main series published in a recent review of the literature (18).

Table 15. Main parameters in the treatment of gynecological cancers with IOERT technique from case reports in the review by Krengli et al 2017

1st Author, year (ref.)	Pazients by site (no.)	prim/rec (%)	Dose (Gy)		FU (months)	LC (%)	OS (%)	Acute and/or late toxicity
			EBRT no. pts	IOERT				
Sole, 2014 (17)	18 Uterus 32 Cervix 11 other	57 pelvic rec , 43 paraortic rec	mean 31 (29-45)	R0:10-12.5 R1:15	42 (2-169)*	65 at 5 yrs	42 at 5 yrs	RTOG acute ≥ G3: 23pts RTOG late ≥ G3: GI 8pts, GU 3pts, 1pt neuropathy

Foley, 2016 (4)	21 Cervix 6 Uterus 5 other	81 pelvic rec , 19 prim	NA	mean 13.5 (10-22.5)	26 (3-196)*	R1: 73 at 5 yrs; R2: 71 at 5 yrs	70 at 5 yrs, R1: 77 at 5 yrs, R2: 55 at 5 yrs	RTOG≥G3 47%, 5pts depending on IOERT, 2pts GU, 1pt osteonecrosis, 2pts lymphedema
Backes, § 2015 (1)	21 Cervix 11 other	100 rec	6 pts: mean 26 (10-40)	mean 17.5 (10-20)	NA	mean PE+IORT 10 mths; LEER+IORT 9 mths; PE 33 mths	mean PE+IORT 10 mths LEER+IORT 17 mths PE 41 mths	NA
Barney, 2013 (11)	86 Cervix	85pelvic rec , 15 prim	61 pts: no preRT: mean 45, preRT: mean 39.6	mean 15 (6-25)	32 (1-306)*	62 at 3 yrs: 70% prim 61% rec	25 at 3 yrs	RTOG≥G3: 4pts 1 pt GI, GU, 1pt neuropathy, 4pts Other
Calvo, 2013 (19)	7 Uterus 20 Cervix 8 other	100 pelvic rec	16 pts: 45 no preRT, 30.6 preRT	R0: 10-12.5 R1: 15	46 (3-169)*	58 at 5 yrs	42 at 5 yrs	RTOG acute ≥G3: 14 pts RTOG late ≥G3: 5 pts GI, 2 pts GU 1pts neuropathy
Giorda, 2011 (10)	35 Cervix	100 prim	neoad 50.4	10-15	NR	89 a 2 yrs	49 a 5 yrs	peri/post-Ch 10pts GU
Tran, # 2007 (5)	17 Cervix 11 Uterus 8 Other	88 rec	18 pts mean 44	mean 11.5 (6-17.5)	50** (2-198)*	44 at 5 yrs: 45% Cervix 58% Uterus	42 at 5 yrs	RTOG ≥G3:10 pts
Dowdy, 2006 (15)	25 Uterus	100 rec	21 pts: 45	mean 15 (10-25 Gy)	34	84	R0: 71 at 5 yrs, R1: 47 at 5 yrs, R2: 0 at 5 yrs	8pts neuropathy, 5pts GU, 5pts fistula, 2pts bone fracture
Awtrey, 2006 (20)	27 Uterus	100 rec pelvic	12 pts: dose NR	NR	24 (5-84)*	NR	78 at 2 yrs	NR
Martinez-Monge, 2001 (13)	67 Cervix	54 pelvic rec, 46 prim	36 pts: 45	prim: mean 12 (10-25), rec: 15 (10-20)	prim 58 (8-144)* rec 19 (1-138)*	69 at 10yrs: 93% prim 47% rec	35 at 10 yrs; prim 58 rec 14	10 pts depending on IOERT
Gemignani #, 2001 (21)	9 Cervix, 7 Uterus, 1 Other	rec 100	2 pts: dose NR	mean 14 (12-15Gy)	20 (3-65)*	67	54	NA
DelCarmen, 2000 (22)	5 Cervix 3 Uterus 7 Other	93pelvic rec, 7 prim	NR	10-22.5	(3-36)*	54	74	4pts neuropathy, 3pts GU, lymphedema 2pts
Garton, 1997 (23)	22 Cervix, 10 Uterus 7 Other	92 pelvic rec, 8 prim	28 pts mean 45 (1-67)	mean 17.3 (10-25)	25 (6-125)*	67 at 5 yrs	32 at 5yrs	RTOG ≥G3 14pts, 6pts depending on IOERT
Mahè, 1996 (12)	70 Cervix	100 pelvic rec	30 pts (20-45)	R0 mean 18 (10-25); R1-biopsy mean 19 (10-30)	15** (2-69)*	21: 27% R0 11% R1-2	8 at 3yrs	10pts depending on IOERT , 1pt GI, 4pts GU, 5pts neuropathy
Stelzer, 1995 (24)	22 Cervix	100 pelvic rec	6 pts (26-50); 7 pts (45-62.4)	mean 22 (14-27.8)	minimum 15 months	48 at 5yrs	43 at 5yrs	7pts neuropathy

year: year of publication; **prim/rec:** primary tumor or recurrence; **FU:** median follow-up in months;*: range**;** **: mean**;** **type:** tumor type; **pt(s):** patient(s); **preRT:** previous radiotherapy; **EBRT:** external beam radiotherapy dose in Gy reported for n pts**;** **IOERT dose:** dose in Gy intraoperative radiation therapy; **LC:** local control in %; **OS:** overall survival

rate (in %); **yrs:** years; **NR:** not reported. **When not specified, the technique is IOERT (18 Krengli et al 2017); §:** HDR-IORT **; #:** Orthovoltage-IORT; **LEER:** laterally extended endopelvic resection ; **PE:** Pelvic exenteration**; RTOG:** scale for acute and late toxicity; **neoad:** neoadjuvant; **mths:** months; **GI:** Gastro-intestinal toxicity; **GU:** Genito-urinary toxicity;**R0**: no residual tumor; **R1:** microscopic residual; **R2**: macroscopic residual.

2.7.5. Conclusions

In this context IORT is mainly indicated in the recurrences of gynecological tumours that have already been irradiated, with postoperative adjuvant or exclusive/radical intent. Crucial factors for the feasibility of retreatment are the time elapsed since radiotherapy, the response to the radiotherapy and the doses delivered. Combination treatment of preoperative EBRT followed by an IORT boost finds application in pelvic recurrences from uterine sarcoma, an indication also recognized by the NCCN guidelines with level III evidence (9) in the case of isolated disease, and in recurrences from endometrial and cervical cancer. Even in locally advanced gynecological tumours, the combination of preoperative EBRT (with or without chemotherapy) with the IORT boost has given excellent results in terms of local control (13).

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2.8. Vertebral metastases

2.8.1. Introduction and background information

The Kypho-IORT method is mainly used in the treatment of vertebral metastases. The role of radiotherapy in bone metastases is consolidated especially in osteolytic lesions: in addition to an analgesic action, radiotherapy also results in bone recalcification, even if both effects are not immediate. For injuries where the risk of vertebral fracture or vertebral collapse is high, a procedure to restore the morphology of the vertebral body (vertebroplasty) followed by EBRT is indicated (1, 2). The Kypho-IORT procedure consists of irradiation followed by vertebroplasty which is performed using a balloon (Kyphoplasty) or with the direct injection of intravertebral cement (vertebroplasty) (3, 4). The use of the kV-IORT equipment makes it possible to combine the two procedures in a single treatment session, thus shortening the time the patient has painful symptoms compared to conventional radiotherapy alone, and it immediately stabilizes the vertebra. Often the resolution of pain occurs immediately after the execution of the procedure, although, as a result of the intravertebral manoeuvers, the pain may take a few days to dissipate.

The kV-IORT equipment is equipped with a dedicated applicator for intravertebral procedures. The irradiation is extremely selective and produces a high drop in dose within a few millimeters (5).

2.8.2. Indications and patient selection

Based on German experience, the therapeutic indication is reserved for lesions of the spine from T4 to L3 (6). The exclusion of the other vertebral tracts is due to the difficulty for the applicator to reach them since the applicator has a single predefined length. Injuries involving the vertebral peduncles and those that cause any interruption in the posterior wall of the vertebra are not eligible for the procedure since there is a risk of spinal cord damage due to the distribution of the dose by the linear applicator.

2.8.3. Treatment technique

The procedure is performed in conditions of mild or deep sedation, with the patient in the prone position, under local skin anesthesia. It involves a first intravertebral approach by the orthopaedist-radiologist-interventional radiologist, through the lateral pedicle(s) to create a tunnel in the bone through which the dedicated applicator can be inserted and subsequently, once the irradiation is complete, cement is injected to close the tunnel.

While the irradiation phase usually takes place through a single transpedicular approach, for vertebroplasty it is often useful to inject the cement also through the contralateral pedicle. In addition to the metal applicator that accommodates the radiation source and which will remain fixed throughout the procedure, the disposable kit provided by the parent company includes other metal vectors that are mounted in succession and according to a pre-ordered sequence and then removed. The instrumentation for creating the intraosseous tunnel is provided by the hospital or by the non-radiotherapist operator. A pre-treatment biopsy can be taken to confirm the neoplastic nature of the lesion (Figure 24). The manoeuvers are performed under fluoroscopic control.

Operationally, the metal vector which will subsequently hold the radiation source and which, as mentioned, will remain fixed throughout the irradiation, can be conventionally inserted at the level of the junction between the lateral pedicle and the vertebral body, in order to maintain the

distance between the tip of the radiation source and the posterior wall of the vertebra constant (considering the relationship between the distance of the tip of the intraosseous metal vector and the radiation source; when the prescription point is unvaried the dose to the marrow/cauda is zero). Otherwise, in a more personalized perspective, which takes into account the size and location of the lesion as well as any previous radiation treatments, it is possible to preoperatively define the most suitable positioning of the radiation source to cover the target, estimating the prescription point and the dose.

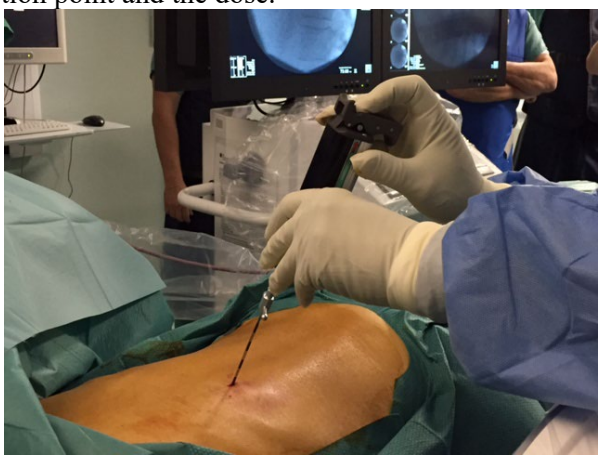

Figure 24. Bone biopsy performed before Khypho- IORT treatment to confirm the neoplastic nature of vertebral lesion (photo by R. Lazzari)

By performing a preoperative CT scan of the patient in the prone position, with thin-layer acquisitions of the vertebra, and the use of dedicated simulation software, a forecast can be made of the dose distribution that can be recalculated in a matter of minutes by modifying the technical parameters (total dose, point of prescription, access point and insertion angle of the applicator) (Figure 25).

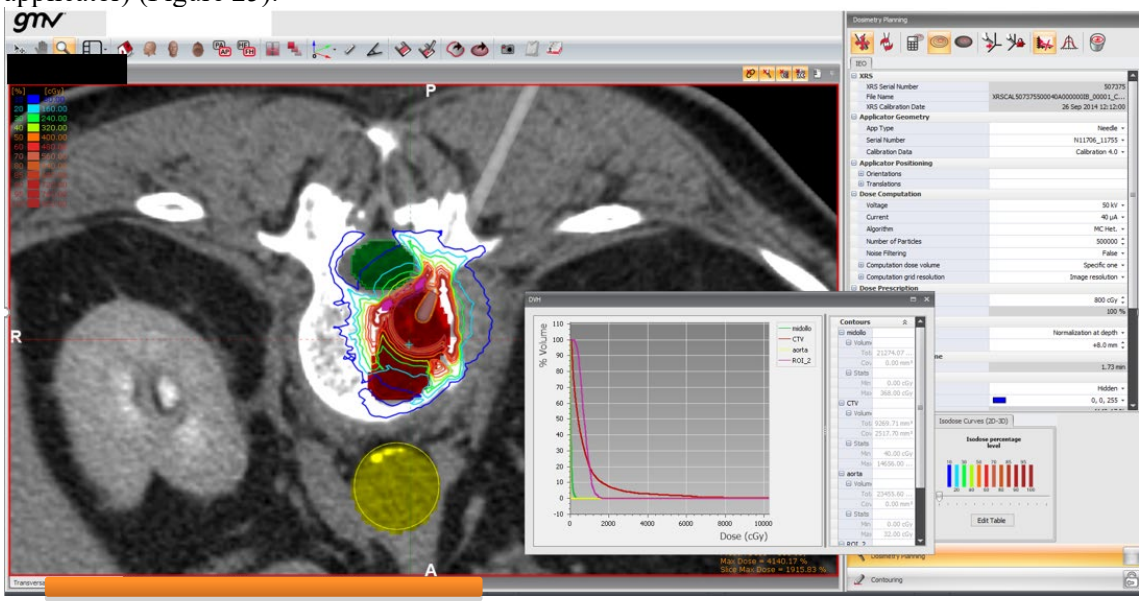

Figure 25. Isodose distribution on CT images acquired in prone position in previsional calculation related to the hypothetical irradiation source position, by using a dedicated software, in the pre-operative study relative to vertebral tumor treatment with Kv-IORT (photo by R.Lazzari)

With the source in position and before the delivery of the therapy, fluoroscopes can be used to acquire and view images in the 3 projections and provide a three-dimensional reconstruction of the vertebrae: this can help to confirm the adequacy of the positioning with respect to the forecast and to verify the distance between the source and the posterior wall or between the source and the anterior vertebral profile along the entire axis of the vertebra (Figure 26).

If the image acquisition systems can be connected to the dedicated software, an instant care plan can be obtained. With the applicator in position, the delivery of the treatment is checked and irradiation is carried out. The treatment time in the dose delivery phase is approximately 30-40 seconds, while the pre-delivery procedure depends on the operator and is closely related to the disease site and to the robustness of the vertebral body which may be such as to require several transpedicular approaches. There are initial experiences with multiple irradiation through multiple vectors or in sequence through the progressive displacement of the same access route along the longitudinal axis.

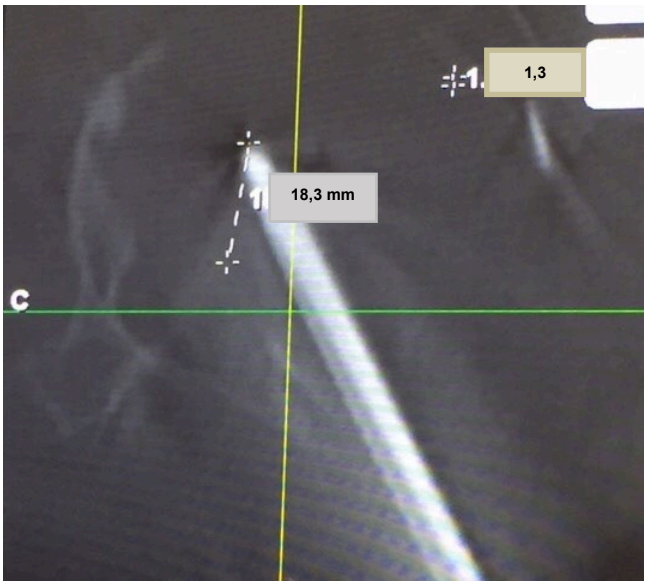

Figure 26. Measurement of distance between source and posterior vertebral wall under a fluoroscopic guidance, before therapy administration to verify source positioning with respect the forecasting in case of vertebral tumor treatments with Kypho-IORT

The suggested dose is 8-10 Gy; the point of prescription depends on the positioning of the metal vector, and therefore on the position of the radiation source, evaluated by considering the size and location of the lesion with respect to the vertebral body as a whole (for very anterior lesions consider the adjacent vascular structures) and to the posterior wall (for posterior lesions consider the marrow/cauda). At the end of the radiation procedure, vertebroplasty or Kyphoplasty is performed for the details of which the reader is referred to the specific literature.

2.8.4. Clinical results

There are only a small number of papers published in the literature since this is a niche procedure. The main studies are shown in Table 16 (6-8).

Table 16. Main parameters in the treatment of vertebral tumors with kypho-IORT technique from case histories reported in the review by Krengli et al 2017

1° Author, year (ref.)	Pazients (n.)	FU (months)	Kypho-IORT Dose in Gy	LC (%)	Relief of pain	OS (%)	PFS (%)	Patient selection
Bludau, 2018 (6)	9 phase I; 52 phase II	6.7	phase I: 8 (at 8, 11 and 13 mm); phase II: 8 (at 13 mm)	NR	Median pain score dropped from 5 to 2 after procedure; 69.8% reduction ≥3 points	76,9 (at 3 mths); 64.0 (mths); 48.4 (at 12 mths)	97.5 (a 3 mths); 93.8 (at 6 mths); 93.8 (at 12 mths)	≥50 yrs, oligometastic, D3 to L5 lesions, confined to vertebral body (maximum Ø 2 cm) PS according to Karnoski ≥60
Chen, 2017 (7)	40	12.5	9.2±3.6 (at 10.2±2.1 mm)	92,3	89.7%	NR	NR	NR
Reis, 2012 (8)	18	4.5	8 (at 5 mm)	93	100% at 6 weeks	NR	NR	NR

year: year of publication;mm: millimeters; **FU**: median follow-up in months; **LC**: local disease control in %; **OS**: overall survival rate in % evaluated to the number of months reported; **PFS**: Progression free Survival; **PS**: Performance Status; **NR**: not reported; **Ø**: diameter; mths: months; **pain scale**: 1 to 10.

2.8.5. Conclusions

Kypho-IORT represents an alternative method in the treatment of bone metastases which is particularly useful in the case of vertebral lesions with a non-negligible risk of structural failure as it combines stabilization and cancer treatment in a single procedure.

However, it is a complex method that requires particular expertise and organization. In fact, an accurate interdisciplinary assessment by the radiation oncologist, radiologist and / or orthopaedic and / or interventional radiologist, of the site and characteristics of the lesion is essential to identify the technical feasibility of the procedure. In fact, the accessibility of vectors for vertebroplasty and radiotherapy must be ascertained as well as the potential limits linked to the osteosclerotic or mixed features of the lesion, which may, in some cases, make intravertebral maneuvers uncomfortable or impossible.

To establish the role of Kypho-IORT, a Phase III trial (registered with ClinicalTrials.gov, number: NCT02773966) has been designed that will randomize patients into the experimental Kypho-IORT arm (8 Gy prescribed at 13 mm) and the control arm with EBRT (30 Gy in 10 fractions or 8 Gy in a single dose). The primary goal is to reduce pain by at least 3 points on the visual analogue scale (VAS) compared to baseline. The study will enroll 54 patients aged 50 years or older with up to 4 vertebral metastases and with a pain score of at least 3 out of 10 on the VAS scale (9).

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2.9. Special situations

Special situations may be represented, for example, by the use of IORT in pregnant women or in the presence of cardiac implantable electronic devices (CIED). In these cases, appropriate dedicated procedures are to be performed.

2.9.1. IORT and pregnancy

As yet there are few references in the literature to the problems related to radiotherapy in pregnancy. Doses below 100 mGy do not appear to lead to a significant increase in the risk of deterministic effects (prenatal death, malformation, growth retardation or mental retardation) compared to the baseline incidence of these phenomena, but they make stochastic effects possible (development of childhood cancers and germline mutations in oocytes) (1-3). Since the threshold of 100 mGy can easily be exceeded in radiation treatments (4,5), the evaluation of the dose to the fetus is essential to estimate the risks and benefits for the mother and the unborn child.

Due to the technical-dosimetric characteristics of IORT that lead to a reduction in the dose to the organs and tissues surrounding the irradiation site, its feasibility as adjuvant treatment in pregnant patients undergoing quadrantectomy for breast cancer was considered (6 Galimberti 2009, 7 Leonardi 2017). In vivo dosimetric measurements were performed in non-pregnant patients using thermoluminescent micro-rod dosimeters (TLD 100) inserted into sterile closed-tip catheters to estimate the potential dose to the fetus. The energy of the electrons used varied between 5 MeV and 10 MeV and the diameter of the applicators was between 4 cm and 6 cm.

In a first study (6) the doses were measured both at the subdiaphragmatic skin level and in utero in 15 patients, while subsequently (7) the doses were also analysed at the ovaries in

another 5 patients. A shielding apron (2 mm of lead equivalent) was placed on the abdomen of the patients in order to block most of the electrons diffused by the machine.

The results of the first study (6) were as follows: the average dose to the skin in the subdiaphragmatic position was 3.7 ± 2.4 mGy; the mean dose to the suprapubic skin was equal to 0.9 ± 0.5 mGy; the mean intrauterine dose, on the other hand, was 1.7 ± 0.8 mGy. From these data it can be inferred that the intrauterine dose is about half that to the skin in the more cranial position (closer to the radiation field) and about double the dose to the skin in the more caudal position. These results suggest that the dose to the skin measured in the subdiaphragmatic position can be considered as the upper limit of the absorbed dose to the fetus. The second study (7) showed that the average dose to the skin at the right and left ovaries is less than 1 mGy.

Overall, the measured doses seem independent of the size of the applicator, the energy of the beam and the irradiated quadrant of the breast (6).

On the basis of the dosimetric study, it can be assumed that in carefully selected patients, IOERT can be part of the breast conserving approach during the first advanced trimester of pregnancy as well as the entire second trimester, even if It is no a standard procedure

In the event that, despite exceeding 1 mSv for the dose to the uterus estimated by the medical physicist, the specialist doctor recommends that it is necessary to expose to radiation a patient whose pregnancy cannot be excluded or is ascertained, particular attention must be paid to the optimization process concerning both the mother and the unborn child (Legislative Decree 101/2020, art.166 section 2).

2.9.2. IORT and Cardiac Implanted Electronic Devices (CIED)

The radiotherapy treatment of patients with implantable cardiac devices (Cardiac Implanted Electronic Device, CIED) requires a multidisciplinary approach (cardiologist, radiation oncologist, medical physicist, nurse, and anaesthesiologist for the intraprocedural management of complications in case of temporary deactivation of the device, etc.) for safe patient management. Radiotherapy can in fact induce malfunctions in devices that pose a risk to the patient (8-13). Several international guidelines have recently been published concerning the management of patients with pacemakers (PM) and cardiac defibrillators (Implantable Cardioverter Defibrillator, ICD) undergoing radiotherapy (14).

These guidelines (14-16) and the recent Italian intercompany consensus document (17) establish criteria for the stratification of risk to these patients and are a guide for their correct management. The parameters to be considered are multiple and complex and concern the type of radiation, the energy used, the type of device, the patient's PM-dependency, etc.

Existing documents agree that, as regards doses, it is prudently recommended not to exceed a dose of 2 Gy to patients with CIED.

An accurate dosimetric assessment cannot be separated from a global risk assessment as required by the guidelines. Due to its technical-dosimetric characteristics, partial irradiation of the breast could be an option in patients selected to comply with the CIED dose constraints (18).

Unlike other techniques, IORT is not usually based on a treatment planning through TPS. Therefore, for this type of procedure there are no data regarding the a-priori dose for patients with CIEDs.

A case report has been published regarding the execution of kV-IORT in a patient with PM. The dose measured at the PM by delivering the dose of 20 Gy to the surface of the applicator with thermoluminescent dosimeters (TLD) positioned in proximity to the X-ray source was on average 0.08 Gy (19). Luraschi et al. (20) report that thermoluminescent detectors (TLDs), positioned in the subcutaneous tissues of 24 patients without heart disease in the infraclavicular

area where the CIED would hypothetically have been housed, were used to directly measure the dose delivered during an IOERT procedure.

The TLDs, alternating with spacers, were inserted into two sterile catheters, one was positioned in the pocket created by the surgeon in the infraclavicular region, potential site of the CIED, with the protection disc (internal catheter), the other was positioned on the patient's skin close to the applicator (external catheter) and parallel to the internal catheter. The total uncertainty of the measurements was estimated to be about ± 15%.[1]

The study showed that the dose measured in the internal catheter decreases very rapidly as a function of the distance from the applicator and that at 2.5 cm from the edge of the applicator the measurements carried out show values less than 1.5 Gy, while in the external catheter the values were always less than 0.8 Gy. Regarding the internal catheter, no statistically significant correlations were observed, neither with the energy of the beam, nor with the quadrant involved, nor with the diameter of the applicator. In the external catheter a small statistical difference was found depending on the energy of the beam used. In fact, using 6 MeV beams, the average dose measured was 0.27 Gy (0.14-0.54 Gy), using 8 MeV the dose was 0.32 Gy (0.16-0.66 Gy), and finally with 10 MeV, the dose was 0.36 Gy (0.20-0.80 Gy). Although the dosimetric study has the limit of having measured the dose in the region of a virtual CIED, the data obtained support the clinical use of IORT in patients with CIED, taking care to maintain the minimum safety distance of 2.5 cm between the applicator edge and the cardiac device itself. It is recommended that each Center activates adequate Quality Assurance procedures specific to this type of patient.

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[1] The uncertainties reported in the text have a coverage factor of k=1, unless otherwise specified.

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Chapter 3
FOLLOW-UP

Therapeutic advances made possible by early diagnosis and innovative and personalized therapies have led to gradual improvements in survival for cancer patients. On the other hand, the number of new cases continues to rise year after year: in Italy, the number of oncological patients increased from 2 million and 244 thousand in 2006, to over 3 million in 2016, and is estimated to be 4 and a half million in 2020 (1).

Cancer-specific survival in Italy is in line with European data which testifies to the good quality of the Italian healthcare system. The increased chances of healing and in any case of controlling the disease over longer periods of time thus extending survival, make it ever more important to plan adequate patient follow-up.

As specified in a recent consensus document issued by Italy's leading scientific oncology societies, the clinical surveillance of patients with a previous diagnosis of cancer is not supported by adequate evidence-based knowledge, except in rare cases. A cultural shift is therefore necessary, which is well summarized in the document mentioned above, from providing follow-up to a culture of survivorship care (2). Cancer treatment needs to be a combination of diagnosis / therapy / surveillance that lasts over time also due to the chronic nature of the disease itself.

Cancer patients, compared to the general population:

- have an increased risk of recurrence for many years after therapy;
- often have a worse quality of life since the treatments received may cause long-term toxicity;
- have an increased risk of second malignancies;
- have greater psycho-physical fragility related to age, comorbidities, etc.

Therefore, it is important to define a multidisciplinary oncological follow-up process that combines the need to improve quality of life through early identification and treatment of side effects and recurrences, with the need for cost containment (reduction of unnecessary tests) (3).

However, since IORT is performed during surgery, it is often difficult to distinguish the adverse events caused by the radiation treatment from those induced by the surgical procedure, in order to establish their incidence. But there seems to be agreement in the literature that when IORT is associated with surgery there is an increase in side effects, especially acute side effects, at the site of the operation (4).

It is therefore advisable to adopt integrated follow-up procedures and validated score systems in order to spot and track the appearance of side effects and distinguish them from the recurrence of the disease.

In general, for the verification of acute side effects, the first clinical / instrumental control is carried out 6-8 weeks after treatment, while the frequency of subsequent follow-up is based on clinical and organizational variables such as:

- treated site;
- importance of the sequelae observed at the first follow-up;
- distinctive features of each Centre such as multidisciplinary programs, etc.

Today, the most commonly used grading scales, such as the RTOG / EORTC scale (European Organization for Research and Treatment of Cancer) (5) and the SOMA-LENT (6), tend to be replaced by the 2009 CTCAE version 4.0 grading scale (Common Terminology Criteria for Adverse Events) which does not break down adverse events into predefined time

periods and lends itself well to detecting the event and its severity whenever the examination is carried out (7).

In the follow-up of breast cancer where intraoperative radiotherapy is widely used, radiological control plays an important role in which the structural alterations of the affected quadrant correspond to parenchymal distortions that are to be correctly interpreted jointly with the breast radiologist (8).

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Chapter 4
INFORMED CONSENT

Informed consent is an essential aspect of medical activities: it is the process whereby a patient authorizes or agrees to undergo a specific medical intervention, freely and without mediation, after having been informed about the methods of execution, the benefits, the side effects, the reasonably foreseeable risks and the existence of any therapeutic alternatives.

Informed consent is an ethical-legal tool that allows the physician to share the responsibility of the diagnostic-therapeutic choice with their patient who has been made aware of their health conditions.

Article 32 of the Italian Constitution establishes that no individual can be subjected to medical treatment against their will, while Article 13 enshrines the inviolability of personal freedom; the physician, therefore, is not entitled to act except in the presence of an explicit or implicit (even in routine cases, although the presumed may not be implicit) manifestation of the patient's will.

The patient's consent is therefore essential specific, personal and cannot be delegated.

The information provided, which is independent of the purpose of obtaining consent, is an essential part of the therapeutic project and must be truthful, exhaustive and comprehensible.

Informed consent must include:

- a clear description of the method, so that the patient is able to understand the treatment they are to undergo;
- the therapeutic alternatives, so that the patient can actually choose;
- the chances of success;
- the risks involved (including those associated with the transfer of the patient from the operating room to the bunker for treatment, the increased risk of infections, the longer surgery and anaesthesia time);
- the side effects.

The obligation to provide thorough and adequate information cannot be fulfilled by merely giving the patient a brochure describing the proposed procedure. The information must be provided as part of a discussion, where the patient is given the opportunity to ask for clarification or for additional details. Written information is supplementary and never a substitute for the doctor-patient interview.

IORT is a procedure that involves several specialists who intervene in different phases with specific risks, therefore it is appropriate that, for an overall assessment, the information be referred to each of the individual steps, including anesthesia (not only general anaesthesia, but also other combined anaesthetic techniques that are shared with the surgeons according to predefined protocols).

It is good practice that the patient's consent be expressed to the physician who will perform the treatment. In case of treatment delivered by a team of an Operating Unit, the consent given to one physician is valid also for the other members of the team.

The following is a list of essential criteria for correctly documenting both the information provided by the doctor and the consent expressed by the patient:

- indicate the identification data and general information of the patient;
- acknowledge whether the patient is able (or not) to understand the technical language of the informed consent and to read the form;

- check whether the patient is an adult and has proper capacity, a minor, interdicted
- or incapable of self-determination, or subject to guardianship;
- specify the diagnosis made upon admittance and any subsequent diagnoses (if any);
- acknowledge whether or not the patient has already received other information at the facility and/or on previous occasions: check and acknowledge the level of the patient's understanding about their health conditions;
- give the patient in words (possibly with the aid of audio-visual media) all the information about their specific disorder and about the methods of intervention. All the information about the patient's disease should be provided also in writing in the consent form, indicating the therapeutic alternatives and possible complications, etc. Any additional information must also be documented. Patients must give their consent or dissent with regard to the proposed treatments;
- acknowledge any disease that is most likely to be discovered during the the intervention;
- acknowledge whether the patient has expressly refused to receive the information in whole or in part (specifying which part). Also, in this case the consent to the medical treatment is required;
- acknowledge whether the patient has refused treatment specifying if such refusal comes after the information received about the life-threatening aspects of the treatment;
- acknowledge whether the patient has expressed the will that all information be provided to a representative of the patient's choosing; in this case, specify whether the consent to treatment is to be expressed by this representative or by the patient themselves;
- have the patient specify whether or not their state of health is to be brought to the attention of any representatives, in which case they must specify their names;
- inform the patient that they can at any time revoke their consent to the treatment unless the treatment cannot be interrupted or in the event of a life-threatening situation;
- indicate the time and date of delivery of the information sheet (the date cannot immediately precede the treatment and in any case the patient must be given time to reflect on the information received and on consent);
- indicate the name of any witnesses: nursing staff and close relatives of the patient;
- attach the informed consent sheet to the patient's Medical Record.

Chapter 5
PHYSICAL ASPECTS OF IORT

5.1. Physical aspects of electron beam IORT

The physical and dosimetric aspects addressed in this section are related to intraoperative radiotherapy (IORT) performed with electron beams produced by conventional and non-conventional linear accelerators, at nominal energy values between 3 MeV and 12 MeV. In particular the focus will be on the criticalities of this treatment technique with regard to the characterization of the beams in both reference and non-reference conditions, on the periodic quality checks, on the system and its accessories, on the measurement instrumentation, on treatment set-up and on treatment verification by means of *in vivo* dosimetry.

Being a special technique, IORT requires specific dosimetric determinations that at times are different from those required in fractionated treatments with external beams (1-4). The rationale is that a single high dose is delivered to a target volume whose extent and depth are definitively determined in the operating room, often in the presence of internal shields to protect the structures downstream of the target.

Although specific commercial treatment planning systems (TPS) are used and other home-made solutions are being studied or in use (5-11), usually the MUs to be delivered are calculated in terms of dose at the point, and the selection of field size, energy and reference isodose is made on the basis of the geometric size of the target. This implies that all physical and geometric data, for each type of applicator and energy used, are to be available in a format that is quick to consult and easy to use. In particular, the dosimetric data must allow the calculation of the MUs necessary to deliver the prescribed dose to the target volume.

A further reason that differentiates IORT from transcutaneous radiotherapy is the use of specific applicators that contribute to determining the physical and dosimetric characteristics of the electron beam (quality, output, homogeneity and symmetry, etc.). These applicators are generally made of plastic material and may have a circular section (with diameters typically between 3 cm and 10 cm). For specific applications, square or rectangular applicators are available, with dimensions up to 20 cm (12-16). The distal part of the circular applicators may be oblique, i.e. tilted with respect to the geometric axis of the beam, with angles between 15° and 45° (base bevelled applicators). With this type of applicator, larger radiation fields can be obtained but they involve an asymmetry in dose distribution extending beyond the applicator edge and a less penetrating beam than is possible with a flat-ended applicator. The length of the applicator, which may depend on its size, determines the source-skin distance (SSD) in some cases. The SSD is generally between 50 cm and 120 cm.

Some authors (2,17-23) have shown that the presence of the applicator in IORT treatments determines an increase in electron scattering in the radiation field, compared to a collimated beam in standard mode, resulting in the widening of the energy spectrum and the angular distribution. The contribution to the dose by the scattering in the IORT configuration depends on the energy and the collimation system and may exceed 40% of the total dose at the depth of the maximum dose (z_{max}) for the lowest energies and the smallest fields. It should be noted that this contribution is about 10% in the case of conventional electron beams.

Figures 27 and 28 show a comparison of energy and angular distributions between the collimated beam in standard mode and in IORT mode for a non-dedicated accelerator (18).

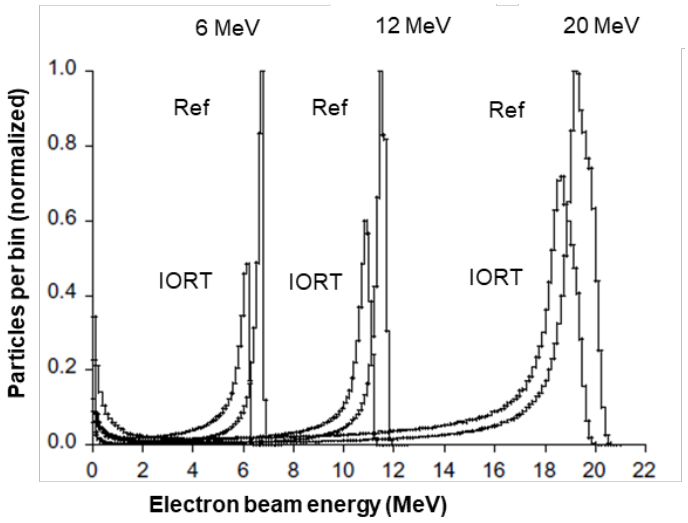

Figure 27. Comparison of electron energy distributions at the surface of the phantom for the 10x10 cm² reference radiation field (Ref) and the 9 cm diameter IORT radiation field for electron beams with nominal energy 6, 12 and 20 MeV. The sampling intervals are 0.100 MeV (for 6 and 12 MeV) and 0.125 MeV (for 20 MeV)

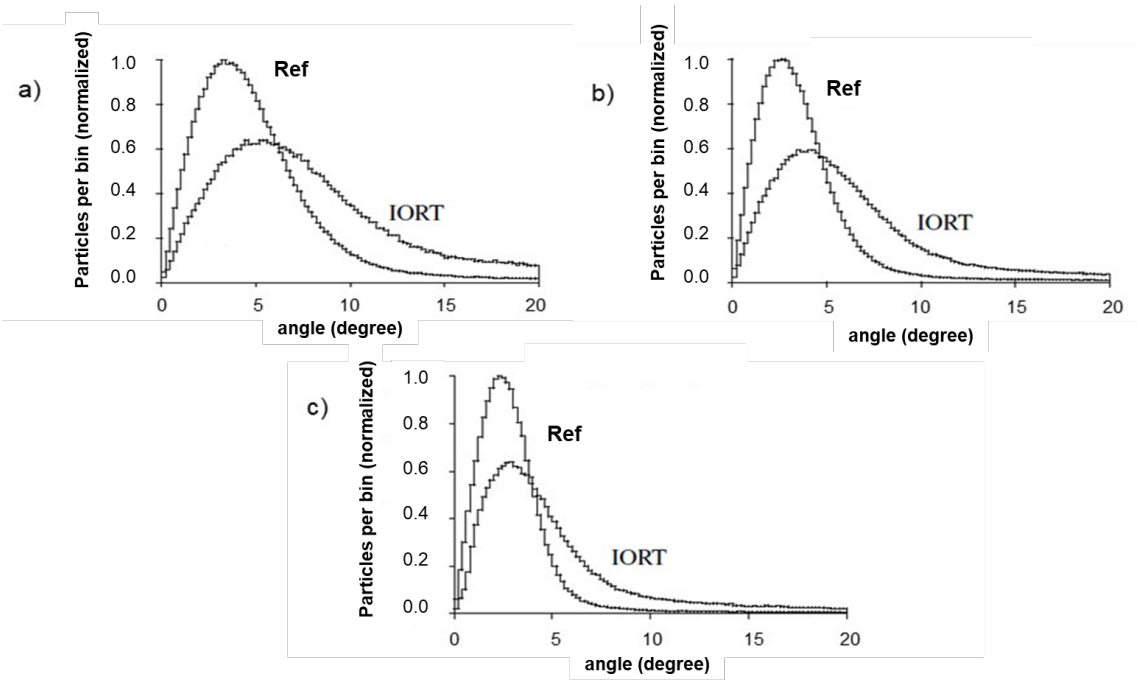

Figure 28. Comparison of the angular distributions of electrons at the surface of the phantom for the reference radiation field (Ref) 10x10 cm² and the IORT radiation field with diameter 9 cm for (a) 6 MeV, (b) 12 MeV, and (c) 20 MeV. The sampling interval is 0.2°

The broadening of energy spectrum and angular distribution due to the IORT applicator involves changes in the depth dose curves along the beam axis compared to those produced by standard collimation, with a significant increase in the surface dose and a decrease in the depth of the z_{max} position (Figure 29) (17).

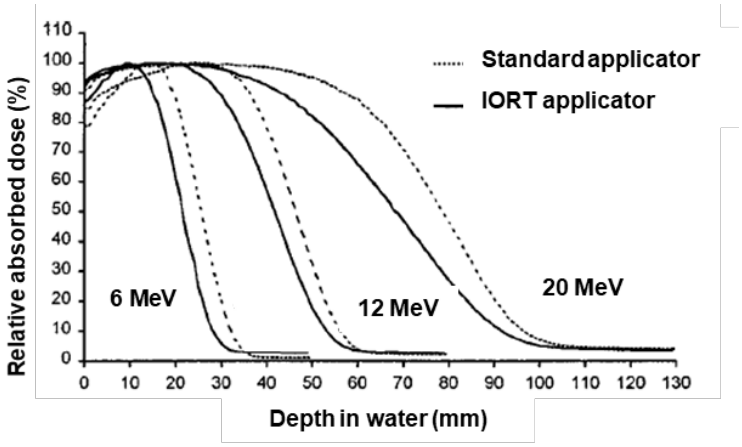

Figure 29. Comparison of depth dose curves on the beam axis related to IORT applicators with the curves obtained for the conventional beams (standard 10x10 cm2 applicator). The nominal energies of the electron beams are 6, 12, and 20 MeV

However, this effect is specific to IORT systems which, as in the case described by (24, 25), use a slab upstream of the IORT applicator to increase the surface dose. More generally, with the R_{50} parameter being equal, a comparison between depth dose curves for conventional and dedicated IORT accelerators is presented in Figure 30 (23).

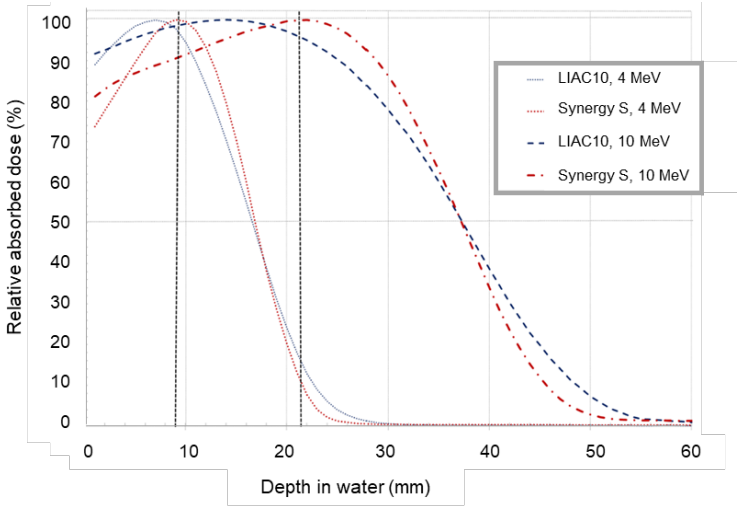

Figure 30. Comparison of PDDs related to a LIAC10 (Φ=10 cm, SSD=71.3 cm) and a conventional Linac (Elekta Synergy S, 6x10 cm^2 at SSD=100 cm, representing the maximum field for the energies considered), for electron beams with the same value of the R_{50} parameter. The dashed vertical lines indicate the z_{ref} depths (TRS IAEA 398) corresponding to the minimum and maximum value of R_{50}

In this case, the increase in the surface dose and the decrease in the depth of the maximum dose (z_{max}), already described in (17), are associated with a slight increase in dose at depths greater than R_{50}. The different characteristics in terms of energy and angular distributions of the IORT beams compared to conventional beams have an impact on the dosimetric parameters that cannot be easily determined. In the past, this aspect limited the choice of detectors to be used for IORT treatment dosimetry to those with dose response independent of energy and angle.

Thorough knowledge of the accelerator architecture and the availability of efficient computing systems have more recently made it possible to simulate, using the Monte Carlo methods, the characteristics of the electron beams produced in the different IORT configurations in terms of spatial, energy and angular distributions, to calculate the corresponding physical parameters and the correction factors required for dosimetric measurements and evaluations (8, 19, 20, 21, 26). As a result, today the recommendations on the properties of IORT dosimetry detectors are not as strict as they used to be.

Finally, a further difference between the IORT technique and transcutaneous radiotherapy is the high dose per pulse delivered by some types of dedicated accelerators. Indeed, these accelerators produce electron beams characterized by dose–per-pulse values greater than 10 mGy. This poses problems when using ionisation chambers for the dosimetry of these beams, linked to the effects of ion recombination in the cavity of the ionization chamber which, if not properly considered, may lead to errors that may be even higher than 40% in the determination of the absorbed dose (27). In the last two decades, various papers in the literature have addressed this issue, suggesting different solutions (27-36). In general, the papers suggest the use of semi-empirical functional relationships to express the correction factor for ion recombination, k_s, as a function of the dose per pulse, whose functional parameters must be determined specifically for the ionization chamber to be used.

For this purpose it is necessary to have, for the selected ionization chamber, a first set of k_s values *vs* the dose per pulse obtained experimentally by comparing the ionimetric dose measurements, without correction for the ion recombination effects, with dose measurements obtained using a dosimetry system with no dose-per-pulse dependence (essentially Fricke dosimeters, alanine dosimeters and radiochromic films).

From the initial set of k_s values, the parameters defining the functional relationship to be used next to calculate the correction factor k_s in dosimetry practice are determined by least squares curve fitting. The mentioned papers differ from each other mainly for the type of functional relationship they propose, with the exception of paper (27) which suggests a method to determine k_s that does not require a dosimeter whose response is dose-per-pulse independent. The method consists in adapting the standard two-voltage-analysis method to the Boag theory (37). The Boag theory indicates that as the dose per pulse increases, the contribution to the collected charge, due to the free electrons, becomes increasingly important and is no longer negligible at dose per pulse values of tens of mGy. Starting with three different models of charge distribution in the ionization chamber, three different expressions of collection efficiency are formulated which correspond to three variants of the two-voltage-analysis method (27). Based on the comparison between the absorbed dose measured with ionization chambers of different types, applying the three different variants of the two-voltage-analysis method, and the dose measured with an independent system (Fricke), Boag's third model is the one capable of providing sufficiently accurate k_s values (2%, 1SD) for all the types of ionization chambers considered (27).

The problems mentioned will be extensively explored in the following sections indicating possible solutions (see also Appendices A3 and A4).

5.1.1. Reference dosimetry conditions

Reference dosimetry must be performed for all the energies actually used in the IORT treatments.

In general, international dosimetry protocols can be used, with some precautions, for the dosimetry of dedicated and non-dedicated accelerators (even when they operate with specific IORT applicators) (2). In particular, the protocol of the American Association of Medical

Physicists (AAPM) (38) and the protocol of the International Atomic Energy Agency (IAEA) (39), allow the absorbed dose to water assessment with comparable accuracy. The IAEA protocol is recommended because, in addition to covering a larger number of ionizing radiation types and having greater international diffusion, it is easier to use. However, when using the dosimetry protocols in the IORT modality, reference dosimetry cannot be performed with the same accuracy typical of conventional non-IORT modalities (4). In fact, the presence of IORT applicators does not allow to be fully compliant with the reference conditions specified in the protocols, both for the field size, distance from the source and energy characteristics of the radiation beam. Furthermore, in the case of dedicated accelerators with high dose-per-pulse beams, methods other than those recommended in the dosimetry protocols for the evaluation of k_s are to be used for determining the absorbed dose with the ionization chamber. Specifically, k_s must be determined in accordance with the models proposed by Laitano et al. (27) which include the contribution of free electrons to the charge collection or, alternatively, semi-empirical methods based on dose-per-pulse independent measurement systems could be used (28, 29, 33, 35, 36). All this translates into increased uncertainty in the absorbed dose to water assessment, compared to the typical uncertainty of dosimetry performed with conventional applicators and in compliance with the reference conditions recommended by the protocol.

As regards the choice of the IORT applicator to be used for measurements made in reference conditions, it is recommended, for each energy, that a square section applicator of 10 x 10 cm^2 or a circular applicator of 10 cm in diameter with a flat end be used. If it is not possible to obtain the SSD indicated in the dosimetry protocol (100 cm) with the reference applicator, the nominal SSD of the reference applicator should be used.

5.1.1.1. Non-dedicated accelerators

Several papers (17-19,24) indicate that the electron fields collimated using the IORT applicators, due to the large amount of electrons scattered by the additional collimation system, have a more degraded energy spectrum at low energies and a broader angular distribution compared to electron beams collimated with conventional systems.

In the dosimetry protocols, the water-air stopping power ratios for the different energies is calculated for electron beams collimated with conventional systems. In the IORT modality it is not possible to obtain the same reference conditions generally required by the protocols for the non-IORT modalities, hence, an increase in dose uncertainty is to be accepted when, in dose determination by ionization chamber under IORT conditions, the values of the stopping power ratios and correlated quantities are used (e.g., the k_Q factors) as reported, for example, in the IAEA TRS 398 protocol (39). In fact, the energy spectra and the R_{50} values correlate differently to each other depending on whether you are working with a conventional applicator or with an IORT applicator and the values reported in the protocol refer to beams collimated with conventional applicators.

In (18), this additional uncertainty was estimated to be between 1% and 2%. These estimates represent an upper limit for the additional uncertainty since they concern a particular IORT system that uses an additional PMMA scattering foil placed upstream of the IORT applicator. In general, in the absence of specific data for your collimation system, 1% (1SD) figure can be assumed as a conservative estimate of the additional uncertainty.

In a non-dedicated accelerator, the aperture of the secondary applicators affects the dose per MU of the electron beam (as well as the dose distribution, see paragraph 5.1.2.1) (40-43). It is therefore recommended to check that, when the IORT applicator docking system is inserted, the aperture of these applicators is as established in advance by the manufacturer. If there is no indication from the manufacturer, it is recommended that the aperture of the secondary

applicators in the accelerator commissioning phase be set in accordance with the energy of the beam and the dimensions of the IORT applicator selected as reference applicator. In accordance with the indications of the dosimetry protocol, the type of ionization chamber must be chosen from among those with small angular dependence, since, as already mentioned, the angular distribution of the beams produced with the IORT applicators is significantly wider than the distribution generated by conventional electron applicators especially at the lower energies (18).

Finally, it is worth pointing out that it is equally possible to perform dosimetry under reference conditions using conventional applicators. By adopting this solution, all the dosimetry measurements carried out with the IORT applicators are classified as dosimetry under non-reference conditions.

5.1.1.2. Dedicated accelerators

As in the case of non-dedicated accelerators, the collimation system used in dedicated accelerators introduces a significant scattered radiation component into the radiation field which degrades the energy distribution of the electrons compared to conventional beams with the same R_{50} value. Therefore, with regard to the use of the water-air stopping power ratios reported in the dosimetry protocols, the indications given in paragraph 5.1.1.1 also apply to dedicated accelerators.

The dose rates produced by some dedicated accelerators are much higher than those of conventional accelerators and require specific dosimetric procedures. In particular, due to the high charge density produced in the volume of an ionization chamber for each radiation pulse, k_s may be largely overestimated if determined with the standard two-voltage method as recommended in international protocols. Therefore, in the case of dedicated accelerators with high dose per pulse beams (i.e. >10 mGy per pulse), the models proposed in (27), which include the contribution of free electrons to charge collection or, alternatively, the semi-empirical methods based on the use of measurement systems independent of the dose per pulse (28, 29, 33, 35, 36), are to be used to evaluate the absorbed dose with an ionization chamber.

It should be noted that corrections in the order of tens of per cent may be necessary for the dose per pulse values typical of IORT beams, especially when ionization chambers with electrode distances > 2 mm or when low polarization voltage values are used.

Therefore, for the absorbed dose to water measurements in reference conditions, plane-parallel ionization chambers can be used with the adoption of specific procedures as detailed below. However, an optimal choice is a dosimetry system with no dose-per-pulse dependence of the response such as the Fricke dosimeters (44, 45).

As regards the Fricke dosimetry system, it is recommended that it be managed by a Primary Metrological Institute or by a Calibration Centre accredited in the field of ionizing radiation. In fact, the use of such a system in non-metrological conditions may not guarantee the necessary dose measurement accuracy due to the high criticality of chemical dosimetry. An additional valid dosimetry system for reference measurements in IORT beams is the alanine dosimeter (45-47). Its dosimetric characteristics such as independence of the response from dose rate, beam energy and incidence angle of the electrons render this system suitable to that purpose.

Dose measurements obtained using Fricke dosimeters and alanine dosimeters were found to be in agreement with the respective uncertainties for flat applicators (45, 48). It is reiterated that for all dosimetry systems, including Fricke's system, traceability of the measurements to the primary standard of absorbed dose to water must always be guaranteed.

Where ionization chambers are used, among the methods proposed in the literature for the determination of k_s, it is believed that the two voltages analysis method, modified as proposed in (27), is the most suitable technique. The factor k_s is calculated with a numerical method from the values of the ionization signals obtained with two different polarization voltages, normalized

to the number of MUs and corrected for polarity effects. In particular, the correction for ion recombination is expressed as:

$$k_s = \frac{1}{\lambda + \frac{1}{u} ln\left[1 + \frac{e^{\lambda(1-\lambda)u} - 1}{\lambda}\right]} \tag{5.1}$$

where $\lambda = 1 - \sqrt{1-p}$

Parameter p, which represents the free electron fraction, is given by the following expression:

$$p = \frac{w\tau}{d}\left(1 - e^{-\frac{d}{w\tau}}\right) \tag{5.2}$$

where d is the nominal distance between the electrodes of the ionization chamber, and w and τ are parameters that depend on the polarization voltage of the chamber nd their values are obtained from data fitting processes (see expressions reported in (27).

The parameter u is obtained as a numerical solution of equation:

$$\frac{Q_1}{Q_2} = \frac{\lambda_1 u_1 + ln\left[1 + \frac{1}{\lambda_1}\left(e^{\lambda_1(1-\lambda_1)u_1} - 1\right)\right]}{\lambda_2 u_1 + \frac{V_2}{V_1} ln\left[1 + \frac{1}{\lambda_2}\left(e^{\lambda_2(1-\lambda_2)\left(\frac{V_1}{V_2}\right)u_1} - 1\right)\right]} \tag{5.3}$$

where Q_1 and Q_2 represent the value of the charge obtained with polarization voltage V_1 and V_2, normalized to the number of MUs and corrected for polarity effects.

The uncertainty of the k_s factor determined in this way is estimated to be 2% in Laitano's paper (27), as a value that can be used for all types of chambers and dose per pulse values typical of the IORT. The method has been tested over the years in numerous radiotherapy centres for the most widely used models of plane parallel ionization chamber. In (23) a retrospective analysis of the results obtained is presented which demonstrates the ability of the method to provide correct values of k_s for all types of chambers considered, with a 2% accuracy (1SD). Other studies have reported a tendency of the third Boag's model to underestimate the ion recombination correction for two types of ionization chambers with a 1 mm distance between the electrodes and indicated the first model as the most suitable for these types of chambers (32, 34). Considering that in these studies the results obtained with the third Boag model are in any case consistent, within the uncertainties, with the results obtained with independent methods it is not considered useful, on the basis of available data, to recommend different Boag's models for different types of ionization chambers. As regards the uncertainty of k_s, a recent study (49) shows that the 2% value mentioned above is an overestimation in the case of chambers where the distance between the electrodes is ≤ 1mm. For this type of chamber, 1% represents, in general, a more appropriate estimate. It should be noted that the uncertainty calculation method described in (49) provides an estimate of the specific uncertainty for type of chamber and dose per pulse.

Alternative methods based on the use of a dosimetric method independent of the dose per pulse can be used as long as the dose measurements carried out with the independent method are traceable to a primary standard of absorbed dose to water. In this case, the uncertainty regarding

the k_s values is of the order of 2% or greater depending on the dosimetric method used as a reference.

Correction values for ion recombination in beams with high dose per pulse often exceed the 5% limit recommended in the AAPM TG51 (38) and IAEA TRS 398 (39) protocols, and in some cases, they can reach values even higher than 20%. For chambers with a distance between the electrodes of 1 mm or less and a sufficiently extended guard electrode, corrections below the 5% limit can be obtained by appropriately choosing the polarization voltage (50). In general, it is recommended to use an ionization chamber and a working voltage that will not allow the aforementioned 5% limit in the IORT beams of interest to be exceeded. For this purpose, the polarization voltage can assume the maximum value allowed by the manufacturer, having verified that this value is in the linearity range of 1/Q *vs.* 1/V. If not, it is recommended to use the maximum voltage value in the linearity range.

In measurements using Fricke's dosimetry, or in general using dosimeters other than ionisation chambers, z_{max} is recommended as reference depth. The use of the reference depth recommended for example in the IAEA TRS 398 (39) protocol (other than z_{max}) is not necessary in this case since the dosimeter does not require the use of parameters and/or correction factors reported in the dosimetry protocols. On the other hand, when using Fricke's dosimetry, due to the suboptimal size of the dosimeters and the perturbation effect of the dosimeter walls, it is preferable to choose a measuring point in a low dose gradient area to reduce the number of corrections to be applied. For all types of detectors, the choice of z_{max} allows to reduce the uncertainty component associated with their positioning.

In measurements with an ionisation chamber, the reference depth recommended in the IAEA TRS 398 protocol is adopted (39). In this case, the Monte Carlo calculations showed that the use of the k_Q factors reported in the protocol for conventional beams entails an additional uncertainty of less than 0.5% (1SD) (20,21).

5.1.2. Dosimetry under non-reference conditions

Dosimetry under non-reference conditions, sometimes referred to as clinical dosimetry, is aimed at providing an experimental dosimetric characterization of electron beams (possibly supported by Monte Carlo calculation systems) (see for example: 15, 16, 40, 43, 51-53). This characterization must be performed for each applicator, energy and SSD in clinical use and it is recommended that it includes:

- PDDs measured in water along the clinical axis of the beam (different from the geometric axis, in the case of bevelled applicators), with an indication of the main parameters that characterize them: depth of the maximum dose (z_{max}) and depth at which it is reduced to 90%, 50% and 30% (R90, R50 and R30), surface dose and percentage of dose due to photon contamination of the beam (*bremsstrahlung* tail) (1);
- transverse dose profiles in water, measured along two directions orthogonal to each other at least at the depths of z_{max}, R_{90}, R_{80}, R_{50} and R_{30};
- isodose curves in water on the two main orthogonal planes (cross-plane and in-plane) containing the clinical axis of the beam, reconstructed from the PDDs and from the measured transverse dose profiles;
- OF values (for applicators for clinical use), measured in water at z_{max}, along the clinical beam axis;
- the correction factors identified by the MU calculation protocol adopted by the Centre.

The specificity of the IORT beams implies a higher surface dose (especially at lower nominal energies) and less steep dose gradients (more significant at higher nominal energies).

Furthermore, the use of the stopping power values and of the electron fluence perturbation factors reported in the IAEA TRS 398 protocol (39) could introduce an additional uncertainty in the dose determination by means of ionization chambers in non-reference conditions. Monte Carlo simulations have shown that this additional uncertainty depends on water depth, with negligible values around the reference depth and z_{max} but higher than 2% at depths larger than R_{50} (18, 20, 21).

IORT applicators are a critical element; if, after the commissioning phase, they are not properly managed (during clinical use and when washed and sterilized), even the slightest modification of their physical characteristics (cracks, distortions) could compromise the specifications of the treatment field (transverse dimension, homogeneity and symmetry, OF). The systematic verification, by the Sterilization Centre, of the overall integrity of the applicators at the end of the sterilization phase and the reporting of any anomalies is essential.

A thorough visual inspection and a check of the geometric characteristics of the applicators are recommended before the dosimetric commissioning assessments, before their use in clinical practice and before the periodic quality control evaluations.

In any case, reference must be made to the technical data sheet of the applicators, which provides washing and sterilization instructions and indicates the maximum number of sterilizations to which the applicators can be subjected without altering their nominal characteristics.

As an example, Figure 31 shows how even a small deformation of the main axis of the flat applicator can significantly change the transverse dose profiles. Consequently, a variation in the effective OF of the beam with respect to the tabulated value obtained for the same intact applicator can also be assumed (in this specific case, the 3 mm deformation of the axis along the longitudinal direction of the applicator has produced a 4% increase in the OF) (54).

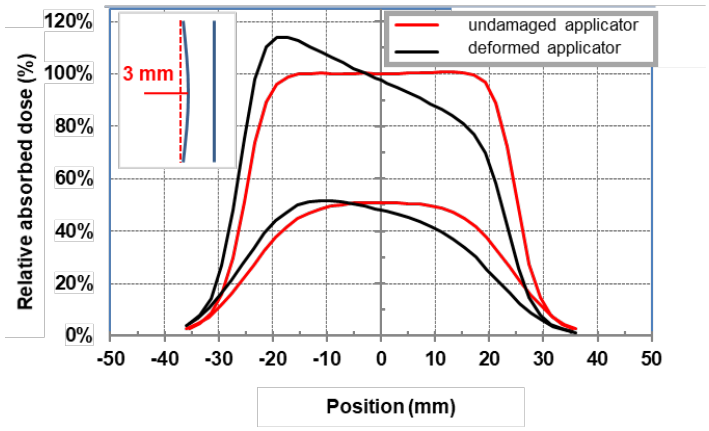

Figure 31. Comparison of transverse dose profiles at depth z_{max} and R_{50} of an intact flat applicator and a deformed flat applicator (profiles evaluated for a 5 cm diameter applicator for thehighest energy of a NOVAC7 accelerator)

The problems posed by dosimetry in non-reference conditions are discussed below broken down into three main groups: 1) determination of dose distributions, 2) determination of the OF and 3) determination of correction factors.

5.1.2.1. Determination of dose distributions

It is recommended that measurements of the PDDs, of the transverse dose profiles and of the isodose curves be carried out in water for each applicator, energy and SSD employed in clinical practice, at a dose rate equal to or as close as possible to the dose rate used for treatments.

For the evaluation of the PDDs, the detector reference point must be positioned along the clinical axis of the beam.

The specificity of the IORT beams puts a constraint on the dosimetry system to be used for dose distribution. In particular, it must have negligible energy and angular dependence of the response. In addition, for measurements in small fields and for the determination of transverse profiles, it is recommended to use high spatial resolution detectors like the solid-state detectors, such as diodes for electrons and microDiamond, or radiochromic films.

If solid state detectors are used, independence of the detector response from energy and dose rate must be guaranteed. A preliminary test on the suitability of the detector can be carried out by checking it against ionization chambers, in conventional electron beams with energy in the range of interest for IORT. For dose distribution measurements it is recommended to use an automatic system that ensures accuracy and reproducibility of the positioning of the detector of 0.1 mm; particular attention must be paid to the method used to synchronize the detector readout with the pulsed beam (especially if at high dose per pulse) and to the type and / or configuration of the electronics used. Normally the dedicated software that manages these dosimetry systems converts the measured data into relative dose values.

When using ionisation chambers, the depth-ionisation curve must be converted into a depth-dose curve and this raises the problem of selecting the appropriate water / air stopping power ratios for the IORT beams. It is worth recalling that, as in the case of conventional beams, the ionization signal must be corrected for polarity and ion recombination effects at the different measurement depths. It should be noted that in the case of dedicated high-dose-per-pulse accelerators, the corrections for ion recombination must be determined as described in paragraph 5.1.1.2.

If radiochromic films are used, the reading system must be calibrated in terms of the absorbed dose to water. Radiochromic films are specifically used mainly in periodic checks in which the use of plastic phantoms is allowed, due to the possible difficulties of placing the films in water, as indicated in the dosimetry protocols.

It is also recommended, for the reference applicator or for one of the most frequently used applicators in clinical practice and for all the energies used, that the backscattered radiation component in the target is adequately analysed and taken into account in treatment optimization (at least along the beam axis) if internal high atomic number shields are used. A significant contribution to its evaluation can be given by using the Monte Carlo codes, which must however be previously validated experimentally (21, 55-62).

5.1.2.1.1. Non-dedicated accelerators

Dose distribution determinations should be carried out in a water phantom, using an automatic system that guarantees a 0.1 mm accuracy and reproducibility of the detector positioning. Solid state detectors such as microDiamond or silicon diodes for electrons can be used. If ionization chambers are used, the same recommendations as reported in standard dosimetry protocols, such as IAEA TRS 398, apply (39). Normally the dedicated software that manages these dosimetry systems converts the measured data into relative dose values.

Radiochromic films are specifically applied mainly in periodic checks in which the use of plastic phantoms is allowed.

For the determination of dose distributions, the same aperture of the secondary applicators used in the determination of the OF is to be used. In fact, as already reported, the aperture of the secondary applicators affects not only the dose per MU but also the PDD, the transverse dose profiles, the surface dose and the *bremsstrahlung* component (40-42). In particular, in conventional accelerators, the transverse dose profiles are highly dependent on the field size defined by the secondary applicators and, as the size of the field increases, there is generally an increase in inhomogeneity at the field edges. With secondary collimation being the same, inhomogeneity of the field increases with increasing energy. Furthermore, as the aperture of the secondary applicators increases, the dose per MU increases, the *bremsstrahlung* component is reduced and the surface dose increases. To reduce field inhomogeneity, some IORT applicator models have an additional collimation consisting, for example, of suitable rings of high atomic weight material positioned along the collimation system.

5.1.2.1.2. Dedicated accelerators

It is recommended that the dose distribution determinations be carried out by means of an automatic system that guarantees a 0.1 mm accuracy and reproducibility of the detector positioning and with solid-state detectors, such as microDiamond or silicon diodes for electrons. If ionization chambers are used, the same recommendations as reported in standard dosimetry protocols, such as IAEA TRS 398, apply (39). Normally the dedicated software that manages these dosimetry systems converts the measured data into relative dose values.

Ionization chambers can be used for the determination of PDDs for high-dose per pulse beams (greater than 10 mGy per pulse), but this requires a careful evaluation of the corrections for ion recombination as the depth varies. In this regard, to improve measurement accuracy, it is recommended to use ionization chambers that require corrections for ion recombination that are weakly dependent on the depth of measurement. A comparison carried out on NOVAC11 and LIAC12 accelerators shows differences within 1 mm between the R_{90}, R_{50} and R_{30} indicators obtained with solid state detectors, ionization chambers and radiochromic films (63, 64).

Active detectors, such as silicon diodes and microdiamond, can be easily used in motorized water phantoms. The use of passive dosimetry systems, such as radiochromic films, in water is more complicated and are specifically used mainly in periodic checks where plastic phantoms are allowed.

5.1.2.2. Determination of the Output Factor

The OF of an applicator "x" is the ratio between the dose in water measured at z_{max} with applicator "x" and the dose in water measured at z_{max} with the reference applicator.

It is recommended that the assessment of the OF be performed for each applicator, energy and SSD used in clinical applications, at a dose rate equal to or as close as possible to that used for the treatments. The detector reference point must be positioned on the clinical beam axis.

Different types of detectors can be used to evaluate the OF: Fricke and alanine dosimeters, radiochromic films, solid state dosimeters, and ionization chambers. In recent years, numerous papers have been published on the subject, essentially for beams generated by dedicated accelerators. A detailed review of the main papers is provided in Table 17.

The choice of the dosimetry system depends on the type of accelerator (low or high dose per pulse) and on the type of applicators (dimensions, end angle). In this regard, it should be remembered that the IORT applicators contribute directly to the formation of the clinical radiation beam with the scattered radiation component. The scattered radiation component in the beam varies with the size (section and length) of the applicator and significantly affects both the energy distribution and the accelerator output. In general, the output increases as the section of

the IORT applicator decreases and in some accelerators the increase is reinforced by a reduction in the length of the clinical applicators compared to the length of the reference applicator. As a final result, the values of the OF for the IORT beams are generally greater than unity and increase as the applicator section decreases.

Table 17. Review of major studies on determining OFs for beams delivered by dedicated mobile accelerators

1st Author year (Ref)	Accelerator	Nominal Energy (MeV)	MC	Detectors	Notes
Mills 2001 (65)	Mobetron	4, 6, 9, 12		IBA: Diode EFD-3G	flat and beveled circular applicator
De Angelis, 2006 (45)	NOVAC7	9		Alanine; Fricke	flat and beveled circular applicator
Pimpinella, 2007 (20)	NOVAC 7	C, D	X	I.C. PTW: Markus	circular flat applicator
Janssen, 2008 (13)	Mobetron	4, 6, 9, 12	X	I.C. PTW: Markus	Rectangular applicator
Fiandra, 2008 (31)	NOVAC 7	A, B, C, D		Fricke; Ashland: Radiochromic EBT	flat and beveled circular applicator
Iaccarino, 2011 (26)	LIAC12	6, 8, 10, 12	X	I.C. PTW: Advanced Markus, Markus; I.C. IBA: PPC05	flat and beveled circular applicator
Soriani, 2012 (14)	LIAC 12	6, 8, 10, 12	X	I.C. PTW: PinPoint	rectangular collimation (hooked to the applicator)
Baghani, 2015 (22)	LIAC 12	6, 8, 10, 12		I.C. PTW: Advanced Markus, Pin Point	flat and beveled circular applicator
Di Venanzio, 2015 (63)	NOVAC 11	6, 8, 9		PTW: I.C. Advanced Markus, Diode 60017, microDiamond 60019	circular flat applicator
Marrale, 2015 (66)	NOVAC 7	10	X	Alanine; I.C. PTW: Markus	flat and beveled circular applicator
Hidarloo, 2017 (15)	LIAC12	6, 8, 10, 12	X	Ashland: Radiochromic EBT2; I.C. PTW: Advanced Markus	rectangular collimation (hooked to the applicator)
Wootton, 2017 (51)	Mobetron	6, 9, 12		IBA: Diode EFD-3G	flat and beveled circular applicator
Baghani, 2019 (16)	LIAC 12	6, 8, 10, 12	X	I.C. PTW: Advanced Markus	rectangular collimation (hooked to the applicator)
Gungor, 2019 (67)	LIAC 12	6, 8, 10, 12	X	I.C. PTW: Advanced Markus, Markus, Roos, PinPoint, Semiflex and Semiflex 3D; PTW: Diode 60017, Diode 60018, microDiamondf 60019; I.C. IBA: PPC40, PPC05, NACP02; SNC: Diode EDGE	circular flat applicator
Pimpinella, 2019 (50)	NOVAC 7	C, D		Alanine; I.C. PTW: Advanced Markus, Markus, Roos, PTW: Diodo 60017, microDiamond 60019; I.C. IBA: PPC40, PPC05; IBA: Diode EFD-3G	circular flat applicator
Winkler, 2020 (52)	LIAC-HWL SIT	6, 8, 10, 12	X	PTW: Diode 60017	flat and beveled circular applicator

MC : MonteCarlo simulations; **I.C.** :ionization chamber

In the case of dedicated high-dose-per-pulse accelerators, the output can increase by more than a factor of 2 between the reference applicator and the clinical applicator, therefore

knowledge of the detector response as a function of the dose per pulse is an essential requirement for the accuracy of OF measurements.

Fricke dosimeters ensure independence from beam energy and dose per pulse, and are particularly appropriate for dedicated high-dose-per-pulse accelerators. However, given their size (> 1 cm^3), in particular situations (e.g., for low energy electron beams or for bevelled or flat applicators with a diameter less than 5 cm), a correction factor for non-uniformity of dose distribution in the dosimeters is to be applied (68). For OF measurements, it is possible to use Fricke dosimeters produced by the user Centre itself or other detectors under study (e.g., Fricke's gel) for which reproducibility and accuracy of the response has to be assured by the Centre itself (69).

Alanine dosimeters and radiochromic films, in addition to having a response that is independent of beam energy and dose per pulse, can have reduced dimensions and have the advantage of being irradiated at dose values closer to those used in the clinic, even though handling radiochromic films in water could be problematic.

Solid state detectors, such as silicon diodes or diamond detectors, also demonstrate low energy and angular dependence, however the response of this type of detectors may depend on the dose rate. It is therefore recommended to use this type of detectors only after demonstrating the independence of the response from the dose rate in the range of interest for the IORT.

If ionization chambers are used it is recommended to determine the corrections for polarity and ion recombination for all the applicators whose OF is to be determined. In the case of high-dose-per-pulse beams, the correction for ion recombination must be determined as specified in paragraph 5.1.1.2. Finally, it should be remembered that if the depth z_{max} varies with the size of the applicator, the variation of the water-air stopping power ratio with depth must be taken into account when determining OF, as recommended for conventional electron beams. If the air $s_{w,air}$ values of the IAEA TRS 398 protocol are used for this purpose, an additional uncertainty of 0.5% is to be considered (1SD).

As indicated in the previous paragraph, it should be noted that a system that is adequate for the dosimetric characterization of the beams with non-bevelled applicators may not be equally adequate for bevelled applicators.

In particular, when using bevelled applicators, the small size of the dosimeter is an important feature to consider when selecting the detector.

In particular conditions and with the adoption of appropriate correction factors (see for example the IAEA TRS 398 protocol) (39), water-equivalent plastic phantoms can also be used (essentially with radiochromic films).

In the case of non-dedicated accelerators, an optimal aperture of the secondary applicators is to be used for each applicator, as described in paragraph 5.1.1.1.

5.1.2.3. Correction factors for dose calculation

For the calculation of the Monitor Units to be delivered, effects due to the non-correspondence between the geometry used for the beam characterization and the treatment geometry are to be evaluated. In particular, it is necessary to consider:

- the irregularities of the surface of the target volume which, in the case of contact applicators, may cause air gaps at the base of the applicator and herniation of the tissue inside the applicator and, in the case of non-contact applicators, they make it difficult to evaluate the treatment distance and the relevant correction factor;
- the internal shields (especially those with high atomic number).

Determining the correction factors for such irregularities is complex in the case of contact applicators. It is therefore preferable to provide operational indications so as to minimize the effect.

In practice, to reduce the air gap and herniation of the tissue inside the applicator and make the target volume and its surface uniform, a sterile film can be placed at the base of the applicator, or a plastic disk (having a larger diameter than that of the applicator with which it is coupled) can be interposed between the base of the applicator and the surface of the target (70-73). If the surface of the target volume is not uniform, dose distribution irregularities may be considerable. Some of these situations have been studied, evaluating surface morphology with scanning systems and calculating dose distribution with TPS (74).

For the presence of any internal shields, especially those with high atomic number, it is recommended to evaluate, for all the energies used and for the reference applicator or for one of the applicators most frequently used in clinical practice, at least the backscattered radiation component in the target on the beam axis. This contribution is a function of the atomic number of the shield, of the target thickness and of the beam energy and it should be taken into account when evaluating the maximum thickness that can be suitably treated and, in general, for treatment optimization (see, for example: 55-57, 60, 62).

5.1.3. Commissioning

Once the acceptance phase of the system and of its accessories according to the protocols defined by the manufacturer has been completed, the next step is the commissioning phase.

Commissioning involves the following aspects:

- dosimetric characterization of the accelerator (dosimetry in reference and non-reference conditions), possibly supported by Monte Carlo calculation systems for the evaluation of the PDD, profile and isodose curves, and the OFs;
- verification of the output reproducibility according to the typical timeframe of a treatment day);
- characterization of the equipment;
- implementation of the TPS, if any;
- implementation of the clinical treatment mode on the control console of the accelerator;
- verification of the calculation of the MU provided by the system, through an independent method (e.g., spreadsheet, tables);
- definition of the treatment technique and relevant dosimetric characterization (definition of the treatment set-up for which the dosimetric evaluations pertaining to the characterization phase are used; evaluation of the backscattered component from any internal shields, especially those with high atomic number);
- choice of the most appropriate measurement system for evaluating the thickness of the target (needle, ultrasound probe, X-ray imaging);
- definition of the methods for treatment set-up verification (visual-tactile, ultrasound, radiological, etc.);
- definition of any in vivo checks (dosimetric/geometric) during the treatment.

5.1.4. Quality control

In compliance with Legislative Decree 101/2020 (Article 163) (75) and taking into account the specificity of IORT (single high dose treatment), a strict quality control program should be established, both on a scheduled basis for the accelerator and its accessories and for the equipment, as well as after any significant maintenance intervention on the accelerator and after any replacement or repair of related accessories. The results of the checks must be compared with the evaluations and checks carried out in the commissioning phase or in the last status test.

Rapid procedures should be in place for periodic quality controls and they should be capable of providing suitable indicators. Ionization chambers in solid phantom can be used for output verification, provided that their equivalence to water and appropriate correction factors are evaluated (76-78), while radiochromic films in solid phantom can be used for relative dosimetry checks (21, 31, 59, 79).

A useful reference from the literature for defining the protocol for periodic quality controls are the documents published by the TG72 AAPM, specific for the accelerators used in IORT (2) and by the TG142 AAPM (80). Checks and schedules, as well as any additional testing, are dependent on the actual use made of the accelerators and related accessories. Each Centre must also define the corrective actions to be adopted whenever the corresponding stated tolerance level is exceeded.

In defining periodic quality control protocols, the minimum acceptability criteria regarding the performance of the radiological systems must also be taken into account, as defined in document RP-162 edited by the European Commission (81).

The checks include safety, mechanical, dosimetric controls and integrity verification of accessories (applicators and any internal shields, plastic disks).

Particular attention must be paid to the visual inspection of the plastic accessories that come into contact with the patient and which, if not properly washed and sterilized according to the specific indications of the manufacturer (possibly supplemented by requests by the users), could undermine the collimation, homogeneity and symmetry of the treatment beam.

Dosimetric controls are to be carried out at a dose rate and dose per pulse equal to or as close as possible to those used for the treatments.

The following sections describe the main aspects concerning the periodic checks to be carried out.

5.1.4.1. Dosimetry systems for periodic quality control

The dosimetry systems used to verify the stability of the dosimetric characteristics of radiotherapy beams, generally referred to as “routine dosimeters”, must be user friendly and ensure highly reproducible responses. These properties contribute to the reliability of the results of the checks and to a reduction in execution times.

Routine dosimeters can be both active (ionization chambers, solid state detectors, mosfet/micromosfet detectors) and passive (radiochromic films, TLDs). Some of these are best suited (if not exclusive) for the measurement of certain parameters, others may represent valid alternatives.

It is recommended that the dosimeters used for measuring the absorbed dose to water be calibrated with respect to the local reference dosimetry system whose calibration coefficient is traceable to a primary or secondary standard. The calibration procedures have the purpose of correlating the response of a routine dosimeter with the corresponding dose value obtained in the phase of dosimetric characterization of the beams.

Particular attention must be paid to measuring the absorbed dose to water with ionization chambers used for quality checks on dedicated accelerator beams characterized by high dose per pulse. In this case, indeed, it is necessary to determine k_s in accordance with the models proposed by (27), or with other alternative methods proposed in the literature (29, 31, 33, 35, 79).

It is recommended to check (according to the periodical schedule, or whenever deemed necessary) both the calibration and proper functioning of the dosimeters used for reference and non-reference dosimetry, as well as the dose evaluation techniques and methods.

If radiochromic films are used, the checks must be made for each lot of dosimeters.

5.1.4.2. Non-dedicated accelerators with relevant accessories

In addition to the quality controls carried out routinely for the clinical use of the equipment in transcutaneous radiotherapy, for a linear accelerator used also for IORT, specific periodic tests must be performed to verify the safety, the mechanical and dosimetric parameters that may prove to be critical in the intraoperative setting, and the integrity of the accessories used. For additional controls, refer to Table 18 which is specific for dedicated accelerators.

5.1.4.3. Dedicated accelerators with relevant accessories

The quality control program for dedicated equipment, while not substantially different from that of conventional accelerators, must take into account the specificities of both the equipment itself and the environment in which it operates. In particular, time limitations are to be taken into account and, above all, the radiation protection required by the fact of working inside an operating room, in an area that is generally unshielded, and in the presence of patients and operators. Periodic quality controls should therefore be performed with rapid procedures and low levels of exposure.

If there is no adequately shielded space in the operating room, checks requiring long irradiation times are to be carried out outside normal working hours, making sure that no one is present in the adjacent areas, above and below the operating room.

As already stated, systematic visual inspections of the applicators (and in general of all plastic accessories) are essential.

The schedule and frequency of quality checks to be performed on dedicated equipment are shown in Table 18.

If dedicated TPS are used to study the dose distribution and the calculation of the MUs, the periodic control schedule must be structured on the basis of the indications provided in the accompanying documentation.

Table 18. Program and frequency of checks and verifications to be carried out on dedicated LINAC and related accessories

Check/Verification	Assessment		Energy		Energy and applicators
	preventive (prior to the day of treatment) (*)	preliminary (on treatment day)	in use, with reference applicator	available (but not in use), with reference applicator	in use (including reference applicator)
Visual inspection of the accelerator, as a whole	X	X			
Visual inspection of the applicator hooking system to the accelerator head	X	X			
Visual inspection of the dosimetry monitoring system (camera-monitors), if possible	X	X			
Verification of environmental conditions in the operating room, for which accelerator operation is potentially warranted (temperature, temperature gradients), according to the manufacturer's instructions	X	X			
Verification of procedures for turning the accelerator on, warm-up, and off	X	X			
Verification of the alignment system for soft-docking accelerators	X	X			
Verification of acoustic warning devices, safety and emergency systems, and prescribed radiation protection systems	X	X			

Check/Verification	Assessment		Energy		Energy and applicators
	preventive (prior to the day of treatment) (*)	**preliminary (on treatment day)**	**in use, with reference applicator**	**available (but not in use), with reference applicator**	**in use (including reference applicator)**
Verification of mobile unit movements	X	X			
Verification of availability and visual inspection (integrity and sterility) of applicators and accessories required for treatment management	X (**)	X			
Reproducibility of the beam output (evaluation of the output and its reproducibility in the short and long term, in terms of dose per MU and dose per pulse)			G		
Linearity index of the beam monitoring system (camera-monitor)			G		
Reproducibility of beam output (in terms of dose per MU and dose per pulse), with accelerator management (power-up, warm-up, and irradiation) according to a typical treatment day			S		
Linearity of the beam monitoring system (camera-monitor)			S		
Reproducibility Indices of Quality, Homogeneity and Symmetry of the beam			S		
Reproducibility of beam output (in terms of dose per MU and dose per pulse), with accelerator management (power-up, warm-up, and irradiation) according to a typical treatment day				A	
Linearity of the beam monitoring system (camera-monitor)				A	
Evaluation of PDD curves and dose profiles (evaluated at least zmax, R_{90}, and R_{50})				A	A
Reproducibility index of beam quality (R_{50})				A	A
Beam homogeneity and symmetry				A	A
Verification of output factor, at z_{max}					A

G: on the treatment day; **S:** at semi-annual frequency; **A:** at annual frequency. **(*):Preventive Assessments means those inspections (or those checks) carried out prior to the treatment day (e.g., at the beginning of the week, in order to resolve any problems in good time);** (**): visual inspection of the condition of the applicators and accessories (and their bagging) should be carried out systematically upon return by the Sterilization Center.

If Fricke dosimeters or alanine dosimeters are used for dose measurement in reference conditions, it is recommended that beam calibration be checked every three years. Furthermore, it is recommended to keep an updated machine diary in which anomalies, adverse events, and maintenance interventions are recorded.

5.1.5. In vivo dosimetry

In radiotherapy, in vivo dosimetry is a useful tool as part of a global quality assurance program (3, 82).

This check is recommended for specific reasons in the case of IORT and it is desirable that resources be allocated locally to implement reliable and practicable dosimetric techniques.

Indeed, despite the definition of strategies to improve the treatment geometry and make it similar to the geometry used to characterize the beams, anomalous irradiation conditions could

occur (due to difficulties in preparing and maintaining the treatment set-up) which could result in absorbed doses that are significantly different from those prescribed.

It is essential to define in advance the aims to be pursued by introducing this dosimetric verification technique; each Centre that decides to implement an in vivo dosimetry program should first analyse, for an adequate number of patients and for each pathology treated, the variations found between the expected and measured doses, so as to optimize the measurement methods and possibly, in the next step, define appropriate intervention procedures.

The critical elements of the treatment technique for which it would be useful to activate an in vivo verification program of delivered doses are essentially (3,54):

- delivery of a high treatment dose in a single session;
- morphology of the target volume (surface irregularities and ensuing herniation in the applicator, or difficulty in evaluating the treatment distance, air gaps, possible accumulation of biological fluids);
- possible use of internal shields, especially those with high atomic number, which could involve significant backscattering of the dose at the interface with the target;
- possible presence of structures and organs at risk or presence of implanted electronic medical devices;
- how to use and manage the accelerator on a typical treatment day.

The literature reports numerous experiences on the use of active systems (essentially mosfets and micromosfets) (70, 72, 83-88) and passive systems (radiochromic films, TLD and alanine) (72, 87, 89-97) for checks and dosimetric/geometric evaluations of “in-field” and “out of field” treatment.

The use of active dosimeters allows online verification of the dose actually delivered, with the possibility of defining warning and intervention levels; the use of extended detectors can provide, in addition to absolute/relative dosimetric evaluations, also useful information regarding the alignment of applicator, target and internal shields.

For the measurement of the delivered dose (“in-field” measurements) the detector can be positioned at the entrance or exit of the target volume, while for the estimate of the dose to an organ/tissue at risk, to the fetus or to any implanted electronic medical device (“out of field” measurements), the detector can be placed on the skin or in adjacent cavities.

The manipulation of the dosimeters during positioning for the in vivo measurement must be carried out in sterile conditions and suitable safety procedures must be provided for their handling after irradiation, in order to reduce any biological risk for the operators (98).

In addition to the well-established use of micromosfet detectors, radiochromic films, TLDs and alanine, experiences of in vivo dosimetry with active fibre optic detectors (99) as well as research and development of active systems with plastic scintillators (100, 101) are reported in the literature.

5.1.5.1. Methods

The accurate characterization of the detector and of the in vivo dose measurement technique and the definition of an appropriate geometric treatment set-up, which can also guarantee the correct positioning of the detector, are necessary and essential conditions for reliable dosimetric results. In the case of active dosimeters, an intervention level could also be defined to modify the number of MUs to be delivered. In the implementation phase of the method, specific dosimetric evaluations must therefore be carried out and strategies are to be adopted to ensure these conditions.

For entrance dose measurements, a point detector is essentially used, positioned at the centre of the treatment field, on the surface of the target. The dosimetric characterization of the

measurement technique (detector calibration and determination of the correction factors) is carried out to provide the dose at z_{max}. The comparison is between the measured and the prescribed dose.

Alternatively, the exit measurements envisage that the detector (point-like or extended, depending on the purpose) be positioned at the centre of the treatment field, at the exit of the target. Usually, the dosimetric characterization carried out for the entrance dose measurements is used; in this case the aim is to evaluate the exit dose at the centre of the field and/or the planar distribution of the dose at the point or in the most distal plane of the target.

The use of extended detectors also allows for a geometric verification of alignment between applicator, target and internal shield.

Correct positioning of the detector is certainly facilitated by the presence of a rigid support. For the entrance measurements, the detector can be usefully bound to the plastic disk whose use, suggested to make the target surface uniform (avoiding air gaps and herniation inside the applicator), also usefully increases the dose to the surface. The detector is thus sandwiched between the disk and the target surface (70-72).

For exit measurements, the detector may be secured to the internal shield; in this case, direct contact between the detector and the high atomic number shield should be avoided, since the detector sensitivity could be affected by the low energy contributions originating from the backscattered radiation. The solution could be to interpose a plastic disk between the high atomic number shield and the detector.

For estimating the dose in out-of-field points or in organs/tissues at risk of being out-of-field, the detector, which is usually a point detector, is positioned on the patient's skin or inside the cavity. Since the calibration performed for the entrance dose measurements, is used, it is essential to carefully evaluate the uncertainties of the out-of-field results.

5.1.5.2. Dosimetry systems

The main properties of an ideal detector for in vivo dosimetry in IORT are:

– small size with negligible perturbation of the beam (especially for entrance dose measurements);
– linear response in the 5-25 Gy range;
– low directional, temperature, dose per pulse and dose rate dependence of the response;
– high reproducibility of the response;
– possibility of sterilization or, preferably, of insertion in a sealed sterile wrapping;
– easy to manage and easy to read;

In particular, the need for a negligible perturbation of the field is dictated by the fact that the dose is delivered in a single session and it is not feasible to remove the detector from the field itself after a first part of treatment.

The reliability of the dosimetric result (estimate of the absorbed dose and uncertainty evaluation) essentially depends on:

– adequate calibration of the detector for the energy, dose per pulse and dose rate of the IORT beam;
– intrinsic dosimetric characterization of the detector, in terms of:
  - linearity and reproducibility of the response;
  - dependence of the response on the dose per pulse and on the dose rate;
  - angular dependence of the response (angle factor);
  - dependence of the response as a function of the field size (field-factor);
  - dependence of the response as a function of the dose already accumulated by the detector (sensitivity factor) (especially for micromosfet/mosfet);

- dependence of detector sensitivity on the low energy contributions that could result from the presence of internal shields with high atomic number (this dependence could be significant if the detector is positioned in contact with the shields);

– algorithm used to calculate the dose, from in vivo measurements (details in the definition of the correction factors or in the evaluation of the measurement uncertainty);
– detector positioning for in vivo measurement (selected measurement point, ease with which the detector can be positioned, capability of maintaining the planned position during the measurement).

The overall uncertainty in the measurement of the dose delivered on the beam axis with the mentioned systems can be estimated between 3% and 5% for the doses of interest. The warning and intervention levels must be established consistently with the uncertainty estimated with one's own systems and measurement techniques.

5.2 Physical aspects of low energy photon IORT

This section deals with the dosimetric aspects of low energy photon IORT performed with Intrabeam Zeiss, the only kV-IORT system currently being used in Italy.

5.2.1. Dosimetry in reference conditions: general remarks

The Intrabeam source produces X-ray beams of unusual characteristics if compared to the beams produced by conventional equipments that generate photons at the same energies. The source is designed to be inserted inside the medium to be irradiated; this means that the dosimetry equipment normally available in a Medical Physics Unit, including water phantoms, is not suitable to perform acceptance, status and constancy tests and commissioning measurements that are normally performed on LINACs or on conventional low-energy X-ray machines.

The Intrabeam source provides an almost spherical beam geometry at distances of 0 ÷ 2 cm from the effective centre of the source (Figure 1, paragraph 1.2.2.1) therefore it does not allow measurements in "good geometry" conditions (i.e., collimated and "almost parallel" beams) and, again, it is designed to be inserted inside the medium to be irradiated; for these reasons, conventional dosimetry protocols cannot be easily and readily applied. From a dosimetric point of view, IORT with photons is considered to be similar to a brachytherapy source. The dose rate is known at different distances of interest in water and the delivery time required to obtain the prescribed dose at the distance of interest is calculated before the treatment. The system is calibrated by the manufacturer which provides the dose rate data as a function ofdistance from the source for all the available applicators.

For any radiotherapy technique, an independent measurement of the dose delivered by the system at the user Centre is recommended; however, Intrabeam presents some difficulties in measuring the absorbed dose - including the high dose gradient (about 10% dose per mm at 1 cm from the source) which makes the measurement very sensitive to the position of the detector -, and a lower dose rate with respect to a conventional X-ray source for superficial radiotherapy. Recently some methods have been described for measuring the absorbed dose (102) for soft photon beams by means of an ionization chamber (type 23342- PTW, Freiburg, Germany) calibrated in terms of air kerma. The chamber, which has the point-of-measurement on the inner side of the 0.03 mm thick entrance window, has a flat energy response for the energies of interest. This chamber has recently been replaced by the smaller PTW type 34013. To convert

the reading to the absorbed dose, the IPEMB method (103) for low (HVL 1-8 mm Al) or very low energy sources (<1 mm HVL) can be used, since the HVL of the Intrabeam source (0.85-1.30 mm Al) straddles the two IPEMB ranges (104).

In the first case, the dose is measured in air, using the backscatter coefficient Bw, which is dependent on the irradiation field and is not directly applicable to a point source such as the Intrabeam (102).

In the second case, the measurement is carried out at the surface of a phantom, and the correction factor k_{ch}, which takes into account the response variation of the chamber between the calibration conditions in air and the measurement in a water or plastic phantom, needs to be known. Eaton and Duck (102) compared the response of the PTW 23342 ionization chambers to the Intrabeam with applicators of 1.5 and 5.0 cm diameters (HVL 1.1 mm Al) and to a surface radiotherapy unit, the Therapak, finding them to be equivalent for the two units. It is therefore possible to calibrate a detector for the Intrabeam using similar X-ray sources, with the advantage of having a higher dose rate and less dependence on small variations in detector positioning.

A dosimetric inter-comparison (105) was performed using XR gafchromic films (International Specialty Products) in a PMMA fixed geometry in four Intrabeam units, resulting in differences of ± 3.9% among the four sources, with 4.7% being the estimated uncertainty.

A second audit was carried out at some UK hospitals using the PTW 23342 chamber inserted in a PMMA phantom. A spherical applicator among those with a larger diameter, 4.5 or 5.0 cm, was preferred to reduce dependence on positioning. The IPEMB method for very low energy was used, assuming a k_{ch} value equal to one (106). The ionization chamber was placed at a depth of 1 cm in a solid water phantom and the applicator was immersed in soft water-equivalent material to reach the full-scatter condition. In this configuration, the average difference between the calculated and measured doses in the Centres involved was -3.2% ± 2.7%.

With regard to flat and surface applicators, the HVL was measured in water for different applicators, using the special phantom provided by Zeiss and a PTW Roos 34001 ionization chamber (sensitive volume: 0.35 cm^3) (107).

For surface applicators, the HVL varies between 0.34 and 0.43 mm of aluminium depending on the applicator diameter. For flat applicators, the HVL is between 0.46 and 1.13 mm of aluminium. According to the IAEA TRS-398 protocol (39), the beam quality factors were then calculated by interpolation of the values given in the chamber calibration certificate, finding that, regardless of the type and size of the applicator, the k_Q values are always included between 0.996 and 1.008. Therefore, as a first approximation k_Q can be set equal to 1 in the expression used to calculate the absorbed dose to water (see equation 5.4, paragraph 5.2.3.6.).

5.2.1.1. Commissioning

The Intrabeam source is characterized by the Manufacturer, with a set of dosimetric data, part of which coincide with those tested during the quality controls, plus some additional controls described below.

In any case, each source and each set of applicators are provided with the full range of dosimetric data required to calculate the treatment time, as measured by the Supplier. The data set is updated at each ordinary and extraordinary maintenance.

The water phantom, which completes the items provided by the Manufacturer, may be used to perform some minimum checks which may constitute a solution to the problem of guaranteeing the accuracy required for commissioning.

5.2.2. Relative dosimetry

To calculate the treatment time of IORT with Intrabeam and estimate the dose delivered at the different depths, the 3D dose distribution needs to be known. The relative dosimetry of Intrabeam is made more difficult not only because of the high dose gradient, but also by variations in beam quality with distance due to the hardening of the spectrum, which may affect the response of the detectors. It is therefore advisable to use a detector with negligible energy dependence on the energy range of interest.

Since radiochromic films have a good energy response and high spatial resolution, they have been used to measure the relative dose distribution since the introduction of the IORT technique (108). MD-55 radiochromic films calibrated by means of a superficial radiotherapy source were used to characterize the dose distribution produced by the source without an applicator, both on the plane of the probe and on the plane orthogonal to it (109).

For the calibration of the radiochromic films, an irradiation method in air was used, where the film is placed on top of a PTW 23342 chamber. The dose at the film position is obtained from the ionization chamber reading according to the IPEMB method for very low energy (110). Alternatively, they can be calibrated using surface radiotherapy equipment and a solid water slab phantom (102).

5.2.2.1. Spherical applicators

Radiochromic films can be immersed in water: the PDDs of the Intrabeam with spherical applicator were obtained in water with EBT radiochromic films, cutting out the shape of the applicator from the film, so that the film would perfectly match the spherical applicator.

In a national audit carried out in the United Kingdom, the PDDs measured in different Centres were compared to the calibration PDD using the gamma index with a dose tolerance of 7% and 0.5 mm. The percentage of points within tolerance was on average 97%, and the mean difference was 4.9% ± 1.9% (106).

Thermoluminescence dosimeters (TLDs) were also used for measuring dose distribution. However, the TLDs have superlinearity and energy dependence for the radiation emitted by the Intrabeam. The isotropy was measured using sets of 3-4 thermoluminescence dosimeters (TLD-100 rods, LiF: Mg, Ti) positioned orthogonally to the surface of a large-diameter spherical applicator. The TLDs were randomly selected from a single lot, with sensitivity variation within 65% (102).

5.2.2.2. Flat and surface applicators

5.2.2.2.1. Dose distribution and uniformity

Studies (107, 111) using radiochromic films positioned at different depths in solid water , have shown that the dose distribution for surface applicators is more uniform at depths closer to the surface and that inhomogeneity increases with depth.

Near the water surface, in the first millimetres, flat applicators are characterized by a symmetrical but inhomogeneous profile, the off-axis dose being significantly higher than the dose on the beam axis; for greater depths the effect is reduced and the profile takes on the typical shape according to which the peripheral dose is reduced with respect to the dose on the beam axis. There is therefore a depth at which the homogeneity of the profile is highest.
For both types of applicators (surface and flat) the beam diverges at an angle that increases with depth (112).

5.2.2.3. Dose rate and PDD

All the studies (107,111) carried out with ionization chamber in water phantom show that the dose rate and the dose per pulse on the beam axis, for both types of applicators, are higher for the smaller diameters; for the same diameter, the surface applicators show a higher dose rate than the flat applicators.

5.2.2.4. Quality controls

The periodic checks envisaged for the Intrabeam are:
- integrity of the applicators;
- mechanical deflection of the probe;
- alignment of the electron beam inside the probe (Dynamic offset);
- emission isotropy;
- dose rate.

Among these, in particular, emission isotropy and dose rate checks are mandatory before each treatment session on each source to be used.

These controls are carried out using the tool set supplied with the equipment. Intrabeam includes two tube-shaped accessories in which the source is inserted during the control. One, called PDA (Photo-Diode Array), contains 5 diodes in the orthogonal position, four on the sides and one in front of the source and is used to check the spherical symmetry of the emission. The beam emission geometry can be adjusted.

The second accessory is called PAICH (Probe Adjuster Ion Chamber Holder) and contains a light source to verify that the needle-shaped source probe is not bent. In addition to the source, this accessory can house a parallel-plate ionization chamber specific for low-energy photons, the PTW 23342, with its entrance window in front of the source. The ionization chamber is calibrated in terms of air kerma by comparison with a secondary standard every two years. During the control of the dose rate, a radiation monitor inside the system is calibrated and will be used during treatment to control the emission.

The results of the checks are recorded in the Intrabeam software, installed in the computerized console of the equipment and are valid for 36 hours. The source is sent to the Manufacturer every two years for complete verification, and in case of extraordinary events.

5.2.2.5. Dose prescription

The choice of the dose prescribing point may significantly influence the dose delivered in IORT treatment with low-energy photons due to the steep dose gradient. Prescription at the applicator surface has the advantage of referring to the maximum dose, but it involves high variability in the minimum dose to the target tissue (113). It should also be noted that the dose at the applicator surface is not measured but is extrapolated through a function.

A prescription at 10 or 20 mm from the applicator surface guarantees greater control over the minimum dose at the expense of greater variability in the maximum dose as the applicator varies.

5.2.2.6. Evaluation of the dose

The curve of the dose rate versus the distance from the Intrabeam source is measured for each applicator used in a specifically designed water phantom where a PTW 23342 ionization chamber is inserted in a fixed position, while the source can be mounted and positioned with high accuracy at varying distances from the ionization chamber in water. Recently the PTW 23342 chamber has been replaced by the smaller PTW 34013, that has an active volume of

0.0053 cm^3, and energy dependence within 2% for energies close to 50 kVp. The dose rate curve (Gy / min) is calculated according to the following equation:

$$D_w(z) = M \times N_K \times k_Q \text{ x } k_{Kair\text{-}Dw} \quad (5.4)$$

where z is the distance in water in mm, $D_w(z)$ is the absorbed dose rate to water at distance z between the source and the ionization chamber (Gy / min); M is the current measured by the ionization chamber in the phantom at distance z, corrected for temperature and pressure (C/min), N_K is the calibration coefficient of the chamber in terms of air kerma (Gy/C) (reference quality TW30), k_Q is the correction factor that converts the calibration coefficient of the ionization chamber from the reference quality (TW30) to the beam quality of Intrabeam, and $k_{kair\text{-}Dw}$ is the conversion factor from air kerma to absorbed dose to water of the ionization chamber; both factors are provided by the ion chamber manufacturer together with the calibration certificate (114).

Since it is not possible to measure the PDD within 1 mm from the applicator surface with an ionization chamber, the data are interpolated with a mathematical function that is used to estimate the dose down to the applicator surface. The depth dose, corrected for the output of the machine measured during the quality control performed before the treatment, is used to calculate the treatment time.

5.2.2.7. Factors affecting dose distribution in the clinical use of applicators

The clinical use of the applicators may lead to variations in dose distribution and in the calculation of the dose itself with respect to the ideal case or to measurements made in homogeneous phantoms. Indeed, in clinical practice there may be an air gap between the target surface and the applicator, tissue inhomogeneity may occur and finally, with regard to flat and surface applicators, the position of the applicator may not be perfectly orthogonal to the treatment surface.

Flat and surface applicators have been extensively characterized for their use in non-standard conditions.

5.2.2.7.1. Presence of air gaps

When the applicator does not adhere perfectly to the skin, the PDDs in air do not follow the inverse square law but decrease more slowly because of the scattered radiation generated by the applicator. This behaviour is practically independent of the type of applicator (surface rather than flat) and depends almost exclusively on its size (107).

The authors emphasize that the measurements carried out show that even just 2 mm of air reduces the dose by more than 25% in the case of 1 cm applicators, and by about 15% for applicators with a diameter of 4 cm. It is therefore necessary to try to ensure the closest possible contact between the skin and the applicator in order not to lose accuracy in dose delivery.

From phantom measurements with radiochromic films it has been observed that at the prescription depth the dose rate is lower than in the ideal condition due to the air gap. In particular, by way of example, an air gap of 2 mm between the surface of the phantom and a flat applicator with a diameter of 4 cm results in a shift of about 1 mm of the isodoses towards the phantom surface (115).

This observation seems to be the result of the inverse square law and of tissue/air interface effects. The results of the measurements with a bevelled applicator also indicate that care must be taken in the alignment between applicator and surface to be treated. The presence of an air gap has produced an increase in the measured dose irrespective of the inhomogeneity. A 4 mm air gap can cause an increase in the dose of up to 35% at a prescription depth of 5 mm.

Conversely, a 2 mm cortical bone thickness causes a high (60%) decrease in the dose beyond the bone. There is a corresponding increase in the dose to the bone that was not investigated in this study. These results were validated with Monte Carlo dose calculation techniques. In the future, these findings will be fed into an image-based TPS (4).

5.2.2.7.2. Obliquity

The positioning of the applicator in a way that is not orthogonal to the treatment surface reduces the accuracy of the delivered dose. It has been determined that using a flat applicator having a 3 mm diameter at a 10° inclination with respect to the vertical, at a depth of 2 mm, entails a reduction of more than 20% in the dose on the central axis of the beam compared to its use in ideal conditions; for a surface applicator of the same size, under similar conditions (14° angle inclination) the dose reduction is almost 30% (115).

5.2.2.7.3. Inhomogeneity

The dose in IORT therapy with low energy photons is strongly influenced by the presence of inhomogeneities.

To simulate the presence of inhomogeneities in clinical treatments (presence of air or bone in the treatment field) and their influence on dose distribution with respect to the ideal situation in which the dose is calculated in water, gafchromic measurements were made using PMMA phantoms in water with and without a bone-equivalent insert.

It was found that, in the case in which the inhomogeneity is hypodense with respect to the surrounding material, the dose distribution is more evidently perturbed than in the case in which the inhomogeneity is hyperdense. Therefore, according to this study, treatments where the radiation passes through air are more critical for dose assessment (107).

This must be taken into account in the case of treatments in which air is present in the radiation field, such as for example the treatment of skin near the nostrils, beneath the tissue, such as when you want to treat the nasal ala (115).

Monte Carlo simulations have shown that there is a substantial increase in the absorbed dose for an equal fluence of photons in the bone material. It was concluded that IORT with low-energy photons does not pose a significant risk for radiation-induced fractures (113), however for correct dose prescription and for the calculation of the dose to the target tissue, for example for the treatment of bone metastases, the inhomogeneity of the tissue must be taken into account. For the intraoperative treatment of the breast, with spherical applicators, it has been calculated that, at a depth of 1 cm, the dose in the breast tissue is equivalent to the dose in water at a depth of 1.05 cm (113).

In 2007, a specific treatment planning system for photon IORT (TPS Radiance) was developed which uses a hybrid Monte Carlo algorithm for calculating the dose distribution on CT taking into account the presence of inhomogeneities (111).

5.3. Monte Carlo simulation of acceleration systems for IORT treatments

5.3.1. Monte Carlo Method

Monte Carlo simulations are now considered to be the most accurate and detailed calculation method in various fields of medical physics, such as in radiotherapy for the calculation of dose distributions and for the validation of the treatment planning system (TPS).

Monte Carlo applications make it possible to simulate the geometries of complex models and a wide variety of physical processes over an extended range of energies and to trace the path of each particle within different volumes. In addition, the experimental set-up is viewed through a graphic interface that can be managed by the user.

The codes that are mostly used for dosimetry studies are mainly GEANT4, EGS and FLUKA, thanks to which the radiation-matter interaction can be simulated.

EGS is a package that is used for the simulation of electrons and photons, while hadrons can be simulated with GEANT4 and FLUKA.

Depending on the energy of the particles and the cross-section, the following physical processes are simulated: production of electron/positron pairs, Compton and Rayleigh scattering, photoelectric effect, energy losses due to the ionization of matter, pair production and *bremsstrahlung* radiation, multiple scattering, nuclear scattering and fission.

The particles that are generated in accordance with the energy distribution that describes the source, travel for certain distances following a probability distribution that depends on the cross-sections for the type of process involved. On the path, secondary particles are produced, which in turn will also be tracked. The process is simulated until the particles are within the defined geometry and until they lose their energy; this is equivalent to considering a minimum threshold step below which the particle will stop and, therefore, will no longer be traced.

The generation of secondary particles involves hundreds of thousands of interactions with the surrounding matter. Due to this large number of interactions, every single event of the particle often cannot be simulated because of computing power limitations. In this regard, Berger (116) developed the so-called Condensed History (CH) technique for simulating the transport of charged particles. According to this method, a large number of subsequent transports and collision processes are “condensed” into a single step. The cumulative effect of the individual interactions is taken into account by sampling the energy variation of the particle, the direction of motion and the position at the end of the step itself.

For a finite number N of independent histories, the estimate of the quantities of interest is subject to statistical uncertainty, which decreases as $N^{-1/2}$. In this regard, a limitation that may be encountered when using the Monte Carlo method is related to the need to simulate a large number of histories which generally involves long calculation times. The particle tracks are processed sequentially, so simulation times can range from a few hours to a few weeks to several months on a single dedicated standard CPU.

To overcome this problem, distributed computing systems can be used or the possibility of using graphics processing units (GPUs) can be explored (117).

5.3.1.1. Monte Carlo Codes: GEANT4, EGS and FLUKA

5.3.1.1.1. GEANT4

GEANT4 (GEometry ANd Tracking 4) (118, 119) is a Monte Carlo toolkit for the simulation of the passage of particles through matter. Its areas of application include high energy physics, such as particle physics, nuclear physics, astrophysics, space engineering and, for medium-low energies also medical physics. It offers the user the possibility of creating a geometric model with a large number of components of different sizes and materials, and of defining the sensitive elements that record the information required to simulate detector responses (120).

With GEANT4 primary particles of different types and energies can be generated, simulating a default set of physical processes through the corresponding classes. Users can develop their application by modifying or adding further processes; thanks to its versatility, indeed, users can upload, use and modify only the components required by their calculation needs (118).

The validation studies carried out by the GEANT4 community have led to the comparison of a large number of physical observables between reference data and the corresponding simulated data. All electromagnetic models for electrons, photons, protons and α particles were compared against the database provided by the National Institute of Standards and Technology (NIST). A good agreement has been confirmed between all electromagnetic models simulated in GEANT4 and the NIST reference data (121).

In the field of medical physics, GEANT4 is a powerful simulation tool for various applications; The toolkit allows for the simulation of models of complex geometries such as particle accelerators, radioactive sources, as well as the anatomy of patients, and it is also possible to implement DICOM images (122-125).

The *iort_therapy* application was developed to meet the dosimetry needs of IORT treatments using a dedicated NOVAC7 accelerator (57).

5.3.1.1.2. EGS

The EGS (Electron - Gamma - Shower) system is a general purpose package for the Monte Carlo simulation of the transport of electrons and photons in an arbitrary geometry, developed in the 1980s at the Stanford Linear Accelerator Centre (126). Over the years the code has been continuously updated and the current version is called EGSnrc (http://nrc-cnrc.github.io/EGSnrc/). The code is written in the Fortran programming language (Mortran, an extended Fortran language) and the current version includes a C ++ package for dosimetry applications that require the simulation of complex geometries.

The EGSnrc system simulates the physical processes concerning the possible interactions of photons and electrons in various elements, compounds and materials; the energy range of charged particles (electrons and positrons) goes from 1 keV up to a few hundred GeV, while the energies of photons can vary from 1 keV up to several hundreds of GeV (126). The latest version of the code also includes the transport of radiation in the presence of electric and magnetic fields. EGSnrc is currently the most widely used Monte Carlo code for simulations of electron and photon beams produced by clinical accelerators and of the response of the detectors used for radiotherapy dosimetry. In particular, it has been shown that the code is able to reproduce the response of ionization chambers with an accuracy of 0.1% compared to the basic data used for the simulation of particle transport (127).

The EGSnrc simulation system was used to develop an application called BEAMnrc. The latter is an improved version of the BEAM package originally based on the EGS4 code (128). BEAMnrc can meet the specific needs related to the modelling of electron and photon beams travelling through consecutive components, which can range from simple slabs to complex

applicators; it also has a graphical user interface for setting the simulation parameters for the beam.

In addition, the EGSnrc system includes some application codes among which DOSXYZnrc and DOSRZnrc, for estimating the radiation dose within a volume respectively in Cartesian and cylindrical coordinates, thus obtaining the deposition of energy in each voxel. These applications also include data processing tools for analysing particle beam characteristics, depth dose distributions and profiles (129). Worthy of note is also the egs_chamber application for modelling in detail the different types of detectors and for simulating their response in clinical photon and electron beams (130).

5.3.1.1.3. FLUKA

FLUKA (FLUktuierende KAskade) is a Monte Carlo simulation package for the calculation of particle transport and interaction with matter. It has many applications in the fields of particle physics, experimental high-energy physics, engineering, radiation protection, cosmic ray studies, dosimetry, medical physics and radiobiology. This package was developed using the Fortran language, while the graphical user interface, called Flair, was developed using the Python language.

FLUKA offers simulations of the interaction and propagation in matter of about 60 different types of particles: photons and electrons from 1 keV to thousands of TeV, neutrinos, muons of any energy, hadrons of energies up to 20 TeV and all the corresponding antiparticles, neutrons and heavy ions. The code can also simulate the transport of polarized photons (for example, synchrotron radiation) and optical photons.

Like the other systems described above, also FLUKA can handle very complex geometries; in this case an improved version of the code is used, called FLUKA *Combinatorial Geometry* (CG). Furthermore, this package has been designed to track charged particles even in the presence of magnetic or electric fields (131, 132).

5.3.2. Dosimetry characterization

Through simulation of an accelerator head and the collimation system, the Monte Carlo method can contribute considerably to defining quantities of dosimetry interest (133).

In fact, it is possible to calculate the stopping powers and improve the accuracy of the reference dosimetry, calculate the photon contamination in the electron beam and evaluate the scattered radiation for radioprotection purposes, and perform dosimetry evaluations in non-standard irradiation conditions such as in inhomogeneous tissues (55, 134).

Several Monte Carlo applications have been developed using the previously described toolkits to simulate the acceleration system for IORT treatments with electrons. The models developed were validated by comparing the experimental and simulated PDDs and dose profiles (13, 18, 20, 21, 25, 26, 55, 57, 66). This comparison allows to establish the accuracy of the Monte Carlo simulations.

Simulations were used for studies on the energy spectrum of electron beams including the photon component, on the angular distributions at the phantom surface and on comparisons between measured and calculated PDDs for different applicators.

5.3.3. Calculation of Output Factors

The beam generated by a dedicated LINAC for IORT treatments is collimated using applicators that are fixed to the accelerator head. The applicators can be of different sizes and

can be both flat and bevelled at different angles. The use of different types of applicators requires the experimental measurements under reference conditions to be corrected with the OF (Output Factor) correction factors. Monte Carlo simulations have proven to be a valuable aid in determining these correction factors.

Some results in this regard have been published in the literature; in particular, using the BEAMnrc and DOSRZnrc application codes of EGSnrc, it was verified that the differences between the OFs for flat applicators, calculated through simulations and determined experimentally, are around (2-4)%. Results for applicators having different bevel angles are comparable; the maximum deviation (3.8%) was obtained with the smallest applicator, having a 30 mm diameter (26).

It should be emphasized that the reliability of the Monte Carlo results is determined by the accuracy of the Monte Carlo simulations that are to be validated through comparisons with experimental data for each accelerator. Even though the Monte Carlo calculation is useful in cases where the experimental measurements present some critical issues to overcome, the experimental determination of the OF for the applicators used for treatment is always recommended. On the other hand, OFs calculated with Monte Carlo method by type of accelerator may constitute the reference database in the commissioning phase of a new plant.

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Chapter 6
RADIOPROTECTION

The purpose of this chapter is to present the main instruments for the physical surveillance of radiation protection in compliance with the laws on the protection of workers and the public from ionizing radiation when intraoperative radiotherapy equipment is used.

It should be noted that, except when a traditional LINAC is used, intraoperative radiotherapy activity is often carried out in a conventional operating room without fixed shielding against ionizing radiation. The operating room and the adjacent rooms are frequented not only by personnel professionally exposed to ionizing radiation (radiation oncologist, medical physicists, radiation technologist) but also by personnel who are normally not exposed to ionizing radiation (nurses, surgeons, anaesthesiologists, operating room staff, etc.). Furthermore, since the radio protection aspects differ depending on whether the mobile equipment uses electrons or low-energy photons, the radiation protection aspects related to three types of equipment that may be used to perform IORT treatments will be discussed separately, namely:

- conventional LINAC;
- dedicated LINAC producing electron beams;
- kV-IORT system with low energy X-rays.

6.1. Treatment with conventional linear accelerators

In the case of IORT treatments performed with conventional accelerators in shielded bunkers, no additional specific radiation protection measures are necessary. If IORT treatment is introduced after the radiotherapy bunker has been designed and built, a preventive evaluation verifying the safety conditions in the rooms adjacent to the therapy room is advisable; in particular, the new environmental and personal dosimetry values, in view of likely increases in the workload, must remain within the regulatory limits.

6.2. Treatment with dedicated electron accelerators

6.2.1. Preliminary assessments

The implementation of IORT treatments require careful preliminary assessments regarding: choice of the type of equipment and of the treatment room (s), evaluation of the workload and its limitations, estimate of radiation shielding barriers that can be structural and/or movable and assessment of the load-bearing capacity of the floors.

Health Technology Assessment (HTA) methods can be used to select the type of IORT equipment to be purchased and consequently radiation protection considerations will differ depending on the selected equipment.

Also the choice of the treatment room must be dictated by radiation protection considerations, especially for mobile electron accelerators used in environments that are not endowed with specific structural barriers. In the absence of other requirements, which can only be assessed locally, large operating rooms should be preferred, adjacent to rooms with a low

occupancy factor and possibly located in peripheral areas of the building or in areas where one or more walls of the treatment room are exterior walls of areas not accessible to the public. The selection of the treatment room must be made by personnel regularly involved in health organization activities and who have thorough understanding of the structural aspects of the room, of organizational issues and of provision of protective devices, etc.

A preventive evaluation of the workload must include all the various components; by way of example but not limited there-to, it must include, where appropriate, equipment warm-up, quality control, expected IORT treatments to be delivered, radiation protection surveys, preventive and corrective maintenance, etc. In order to comply with the regulatory dose constraints for the protection of the public and the environment, workload limitation schedules (1) (weekly and annual) may be adopted or even, where possible, rotating operating rooms can be used. The workload related to equipment acceptance, commissioning and periodic quality control can be considered separately only if the healthcare facility provides a separate site (e.g., a radiotherapy bunker with conventional accelerator, etc.) suitable for carrying out the aforementioned activities. If it is impossible to relocate these operations to isolated areas, it is recommended to limit the access of personnel and the public to the adjacent rooms given the large number of radiation sessions involved. Radiation protection assessments must be carried out in all the rooms where the equipment can be used as well as in adjacent rooms and must consider the most unfavourable radiation conditions in terms of radiation protection (e.g., if applicable, select the highest electron energy, the largest applicator, the less advantageous irradiation direction). The determination of the maximum workload is subsequently carried out on the basis of data from direct measurements. If applicable and on an occasional basis, any further incompatibilities between the activities to be carried out and the maximum workload can be reduced by carrying out part of the work after hours and on non-working days with temporary checks of the areas adjacent to the irradiation room.

Radiation protection devices (structural or mobile shielding barriers) may include: shields to intercept the prolongation of the electron beam, shields for walls, ceilings and floors, doors and mobile vertical shields. Due to the weight of a mobile electron accelerator and of the shielding barriers, the load-bearing capacity of the floor should also be assessed (by a qualified technician) in all the operating rooms and in all the areas through which the devices transit and station.

6.2.2. Radiation protection issues

IORT treatment with a dedicated accelerator can be carried out in an operating room where ad hoc protection shields have been installed; in this case the structural shields (floor, ceiling, walls, doors) are installed in accordance with a preventive radiation protection plan and therefore no additional specific radiation protection actions are necessary.

IORT treatment with a dedicated accelerator can also be performed in a permanently unshielded operating room (2); in this case radiation protection strategies must be adopted because of the stray radiation consisting of four main components:

- leakage photons from the accelerator head;
- leakage electrons from the walls of the applicators;
- *bremsstrahlung* radiation;

neutrons if electron beam energies greater than 10 MeV are used.

The leakage radiation from the accelerator head is extremely contained for dedicated mobile accelerators thanks to the shielding present in the head itself and/or to specific design features, such as the absence of scattering foils.

A fraction of the electrons may pass through the walls of the applicator, especially if the applicator is made of plastic material, and be scattered in the environment. This fraction increases as the beam energy increases and as the size and length of the applicator increase (3).

The bremsstrahlung radiation produced by the deceleration of the electrons passing through the patient cannot be eliminated and, due to its energy, it represents the most important component in terms of radiation protection. In fact, the X-ray radiation in the direction of the electron beam (0° direction) is approximately 0.2-0.3% of the dose rate at $z_{max,}$ while the energy of the X-rays produced is equivalent to that of a monochromatic photon beam energy equal to $E_0/7$, where E_0 is the mean energy of the electron beam at the phantom surface (4). The energy and dose rate of the X radiation decrease as the angle between the initial direction of the electron beam and the direction of the emitted photon increases.

Each radiotherapy Centre will have to evaluate the need for either fixed or mobile shielding barriers, their composition, thickness and dimensions on the basis of the factors that are normally used in the calculation of mobile Pb shielding barriers (workload, intended use and occupancy factor of adjacent rooms, etc.). If the accelerator is not equipped with a beam stopper, a mobile Pb shield can be placed under the operating table of such dimensions as to intercept prolongation electron beams, while the stray radiation can be absorbed by mobile shieldings having an adequate Pb thickness and constructed in such a way as to be easily stored. Purely by way of example, mobile shieldings having a height of 150 cm, a width of 100 cm, a differentiated Pb thickness (1.5 cm from the floor up to a height of 50 cm, 1 cm from 50 to 100 cm, 0.5 cm from 100 to 150 cm) and a 15 cm Pb shield are adequate to achieve less than 0.02 mSv/week (1 mSv/year) at 3 m for high workloads (15 treatments/week, 20 Gy/treatment).

In order to attenuate the electronic component, a layer of light plastic material (e.g. PMMA or PVC) could be added to the side of the shielding facing the patient. With an electron beam having a nominal energy of 9 MeV, PMMA layers with a thickness of 0.5 cm and 1.5 cm respectively absorb approximately 50% and 99% of this component.

Electron and photon beams with an energy higher than the typical threshold for nuclear reactions of photodisintegration (γ, n) or electrodisintegration (e, e'n) cause, in addition to the activation of the materials involved, also the formation of a neutron field. With the exception of very light nuclei, such as lithium and beryllium, the threshold energies for the above reactions are equal to or greater than 10 MeV. In particular, they are of the order of 15 ÷ 30 MeV for reactions in some nuclei widely present in the human body (^{12}C e ^{16}O), and of about 11 MeV in the copper present in the accelerator heads. The same photon radiation generated by the deceleration of the electron beams in irradiated body tissues or in any other material that is in the beam, is able to produce, in turn, nuclear reactions of the (γ, n) type. The intensity of the neutron radiation field increases approximately linearly with energy: for electron energies of the order of 15 ÷ 20 MeV the neutron component at 1 m from the production site implies an equivalent dose rate of approximately 0.002% of the primary beam dose rate (5, 6).

Assuming a workload of 200 Gy of electrons per week and an equivalent dose of 0.12 mSv/week (6.24 mSv/year) for full occupancy at 3 m, the walls, and possibly the ceilings, must be shielded with 20 ÷ 30 cm of concrete, which is sufficient also for photon radiation. The access doors to the operating room must be shielded with a 5-6 cm thick lead plate plus a 4-8 cm layer of highly hydrogenated material, such as polyethylene rather than paraffin which has a low melting temperature and relatively high fire risk.

In the case of high workloads, the presence of a neutron component may limit the use of electron beams with energy greater than 10 MeV in operating rooms not specifically designed for carrying out IORT. A possible way to reduce the thickness of the barriers is to distribute the workload among the various available energies, limiting and planning in advance the treatments with beam energies greater than 10 MeV. For lower workloads, of the order of 30 Gy per week

(about 2-3 IORT per week), the activity may be carried out in a conventional room without additional shielding barriers, provided that a workload limit is set (dose per week), also taking into account the dosimetry and quality controls to be performed, so as to ensure compliance with the dose limits in adjacent rooms.

In conclusion, the neutron component in the case of dedicated accelerators operating in a conventional operating room is modest. Considering a workload of 250 Gy per week at 12 MeV, for Mobetron 2000 (IntraOp), the neutron dose was measured to be 14.3 microSv/week and 1.7 microSv/week on the floor below and in adjacent rooms, respectively. Furthermore, the neutron dose measured near the head was an order of magnitude lower than that of conventional LINACs (7, 8).

When making preliminary dose assessments, particular attention should also be paid to the rooms on the lower floor (9) because they may have a high occupancy factor (wards, doctors' offices).

Where conventional operating rooms are used for IORT, it is crucial to apply the radiation protection regulations for governing staff access to the treatment room and to the adjacent rooms. During IORT all the entrance doors to the IORT room should be locked, and, if available, an interlock should be used to block radiation beams when the door is opened. In addition, it is advisable to clear the antechamber of any staff that is not strictly necessary for the IORT treatment. Particular attention should be paid to the presence of windows in the operating room for the passage of instruments, in which case the staff should be prohibited from approaching those windows during the IORT treatment. The dose to the staff and the public must be kept under control by equipping adjacent rooms with environmental dosimeters, in particular at the doors and windows of the room and on the point of the ceiling of the lower floor underneath the LINAC. Environmental dosimeters sensitive to electrons/photons must be used at all measuring points, while at the points where the highest dose is expected (doors and windows and on the ceiling of the lower floor) environmental dosimeters sensitive to neutrons should also be installed.

In this context, Monte Carlo simulations can provide interesting information that is difficult to evaluate experimentally (10, 11).

6.3. Treatment with dedicated low energy X-ray sources

IORT with low-energy photons differs from other intraoperative radiotherapy techniques for the irradiation geometry and for the beam quality used; there are also less radiation protection problems.

The equipment currently available on the market uses applicators of various shapes and sizes and miniaturized X-ray sources with a maximum energy of 50 keV, which is extremely lower than other radiation therapy sources.

The most critical case for radiation protection purposes is the use of needle or spherical applicators due to the almost isotropic emission of the radiation, therefore with uniform radiation intensity on the solid angle, similar to a point source. This feature means that the whole environment can be hit by primary radiation, a major concern in terms of radiation protection. As for the use of surface or flat applicators, the dose distribution is flat and homogeneous respectively under the surface of the applicator and at a depth of 5 mm in water (12). In this case primary radiation is still the prevailing component from the radiation protection point of view, but it only strikes one wall.

However, it is worth recalling that since these are IORT treatments, the radiation is partially absorbed by the patient, and that the attenuation follows the inverse of the distance cubed law (13).

The dose rate emitted at 1 cm by the applicator in water varies from a few tenths of Gy/minute to a few Gy/minute, depending on the type and size of applicator used (12). In any case, it is much higher than the emissions of radiology equipment. It must also be considered that the delivery time of a single treatment may also be of the order of a few tens of minutes.

Due to the spectral hardening typical of the continuous low-energy spectrum, the half-equivalent thickness of the beam varies (approximately 0.1-3.8 mm Al) depending on the diameter of the applicators, the depth in water and the thickness of other attenuation materials (14).

Considering the low energy of the photons emitted by the equipment, radiations can be shielded with the standard mobile barriers used in radiology which are generally equipped with lead glass windows; this avoids the cost of structural interventions on the walls of the operating room. The shielding of the mobile barriers is a lead panel that is at least 0.5 mm thick. These barriers are more effective if located as close as possible to the patient, in order to shield as large an area as possible.

A second mobile shielding system may consist of rubber sheets impregnated with tungsten. The sheets may be positioned around the point of application of the source, so as to envelop the treated area, thus shielding the radiation emitted from inside. In the case of breast treatments, these shielding screens reduce the dose by 95% at 1 m from the irradiation point (15).

The ambient dose rate values for IORT treatment in a conventional room with tungsten impregnated sheets and mobile barriers are reported in a paper by Eaton et al. (15). The ambient dose in adjacent rooms, including the glass door of the operating room, is of the order of a few μSv per hour. Finally, the IORT can be carried out in an operating room with shielded walls and equipped with lead glass windows to allow the monitoring of the patient's vital parameters.

6.3.1. Safety devices

The systems available on the market are endowed with an interlock to prevent irradiation when doors are opened. Alternatively, the doors of the operating room can be locked to prevent accidental entry, with a sign indicating that ionizing radiation treatment is in progress.

6.3.2. Monitoring of the environment

For environmental monitoring it is advisable to periodically measure the radiation level in adjacent rooms, using thermoluminescent dosimeters positioned in the places most frequented by staff during irradiation such as, for example, the external side of the door to the operating room, or where the operator who monitors the patient's vital signs is stationed. If mobile shields are used in the room, the adequacy of these shields to protect the operators who remain in the room should be verified using environmental dosimetry. Particular attention should be paid to openings in the operating room such as windows for the passage of instruments. Radiation protection Standards and Local Prescriptions must also be drawn up and posted on notice boards in order to regulate access to the antechamber during IORT treatment.

6.4. Final remarks

Based on the above, it is clear that radiation protection where IORT treatment is delivered includes complex activities to be carried out both before the installation of the equipment and when delivering the treatment: it cannot be improvised and requires thorough knowledge of the sources and of the structure and organization of the health department and of the devices it is endowed with.

In summary, for IORT treatments with conventional accelerators:

– in shielded bunkers, no additional specific radiation protection actions are necessary;
– in unshielded operating rooms,
  - some radiation protection interventions are necessary due to the presence of a radiation field;
  - workload limitations may be necessary.

Each Radiotherapy Centre will have to evaluate the need for fixed or mobile radiation shields, their composition, thickness and dimensions on the basis of the factors that are normally used in calculating protective barriers (workload, intended use and occupancy factor of adjacent rooms, etc.).

In the presence of neutrons generated by electron beams with energies higher than 10 MeV and if high workloads are expected, the operating.

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Chapter 7
FMEA APPLIED TO IORT AS QUALITY SYSTEM TO PREVENT AND REDUCE RISK FOR PATIENTS

In any organization, whether public or private, it is essential to have management tools to effectively counteract the occurrence of adverse events that would undermine the organization's activities

In the health sector, where it is imperative for services provided to be effective and safe, adverse events can be counteracted by means of the Risk Management method. Risk management includes all the orchestrated and inter-related actions that are designed to ensure that the organization functions properly (1).

Since it is impossible to completely eliminate human error, the work needs to be organized in such a way as to make it difficult for the operator to make mistakes (preventive actions) and, in any case, corrective actions are to be readily implemented in order to limit the consequences of the damage once a mistake has been made. Usually when an adverse event occurs, it is due to a chain of uncontrolled activities, hence the most useful means of prevention seems to be that of designing step-by-step all the processes of the organization, identifying the possible risks at each step and defining measures to control them (1).

Risk analysis techniques may be retrospective or prospective. FMEA (Failure Mode and Effects Analysis: analysis of failure modes and their effects) is a proactive risk management tool; in fact, it involves the analysis of a predefined process and the identification, by a multidisciplinary team, of possible preventable defects or errors, in order to implement actions aimed at reducing the risk of such errors from occurring and to ensure greater safety of the treatments (2,3).

The proactive approach is considered particularly useful because it allows to identify potentially dangerous situations and, therefore, errors are spotted before they occur (4); it also studies the entire process (or one or more steps of the process), to implement corrective actions and evaluate the resulting benefits for patients and operators (5).

The FMEA was developed in the USA. The first document which mentions it is a military procedure (the Mil-P-1629 of 1949) developed in the aeronautical field (1). Subsequently, in the Sixties, it was applied to the Apollo space missions and since the Eighties it has been used in the automotive industry. The results obtained in these sectors have thoroughly validated the reliability of the method which was then applied to different fields including healthcare.

The FMEA was introduced in healthcare ten years ago to identify and treat the potential risks present in clinical-care processes, with the aim of preventing errors and accidents before they occur (6).

The application of this method to radiotherapy was adopted by the TG-100 AAPM for quality improvement in intensity-modulated radiation therapy (7).

Compared to the FMEA (which is a qualitative analysis), the FMECA (Failure Mode and Effect and Criticalities Analysis: analysis of the error modes, their effects and their criticalities) adds a semi-quantitative factor to estimate the level of criticality of the problems identified by assigning a risk priority number to them (Risk Priority Number, RPN) (Table 19) (2).

Table 19. Numerical scale for assigning severity, occurrence, and detectability during FMECA analysis for the assessment of RPN on the scale of 1 to 10, values on the scale of 1 to 5 in parentheses

Severity	Occurrence	Detectability
No damage 1-2 (1)	Extremely unlikely 1-2 (1)	Almost certainly detected 1-2 (1)
Minimal damages 3-4 (2)	Low probability 3-4 (2)	High chance to be detected 3-4 (2)
Early moderate damages 5-6 (3)	Moderate probability, occasionally occurs 5-6 (3)	Moderate chance to be detected 5-6 (3)
Significant late damages 7-8 (4)	High probability, repeatedly occurs 7-8 (4)	Low probability to be detected 7-8 (4)
Permanent damages 9-10 (5)	Very high probability almost inevitable 9-10 (5)	Remote chance to be detected 9-10 (5)

IORT is a very complex process which simultaneously involves the risks of a surgical procedure and the risks of radiotherapy (1,8). For this reason, the FMECA analysis may be a valid systematic method for identifying elements of vulnerability and for preventing the occurrence of errors. According to the FMECA, the IORT risk identification and analysis process can be divided into the following steps:

- establishment of a working group made up of all the professional figures involved in the process: risk management expert (coordinator), radiation oncologist, surgeon, medical physicist, nursing staff, therapeutic radiographer, anaesthesiologist, clinical engineer and Health Director (9);
- detailed analysis of the IORT process, and breakdown into its various steps (flow chart);
- identification of potential failure instances in each step;
- determination of possible causes and consequences;
- assignment of a score (RPN) to each step of the IORT process which takes into account 3 parameters: severity, occurrence and detectability of the potential adverse event;
- definition and implementation of corrective actions;
- evaluation of the effectiveness of the interventions over time by periodically calculating the RPN (1);

The RPN that is assigned to each step is defined as follows:

$$\text{RPN} = \textit{Severity x Occurrence x Detection} = \text{S } x \text{ O } x \text{ D}$$

where

S = SEVERITY: describes the extent of damage that the patient may suffer as a result of the real occurrence of a potential adverse event;

O = OCCURENCE: describes the possibility or frequency with which the problem actually occurs;

D = DETECTION: describes the possibility of detecting the occurrence of an adverse event.

By using a scale of 1 to 10, the RPN is between 1 and 1000; if, on the other hand, a scale from 1 to 5 is used, the RPN is between 1 and 125 (see Table 19)

Based on the calculated RPNs, 4 different classes of risk have been identified:
- low severity (RPN ≤ 30 scale from 1 to 5, RPN ≤ 50 scale from 1 to 10);
- moderate severity (RPN 31-40, RPN 51-70 scale from 1 to 10);
- intermediate severity (RPN 41-50, RPN 71-100 scale from 1 to 10);
- high severity (RPN ≥ 51, RPN ≥ 101 scale from 1 to 10).

The processing of the RPN is functional to the decisions to be adopted in respect of the improvements to be made. Indeed, the adverse events that are identified do not all have the same priority, so those characterized by a high RPN value are those with the highest priority for action (since they would cause serious consequences and/or have a high probability of occurrence and/or have little chance of being detected before reaching the patient/operator). Based on the priorities defined and the causes identified, actions are decided and taken to eliminate/reduce the likelihood of potential problems (preventive measures) and/or to reduce the severity of the consequences if they occur (measures of protection). To evaluate the effectiveness of the actions taken, the action plan must include accurate indicators for monitoring the results and a clear attribution of responsibility (1).

To date, very few studies have been carried out on the application of FMEA/FMECA in intraoperative radiotherapy focusing exclusively on treatments with Electrons (IOERT), with dedicated LINAC (10,11), or with conventional LINAC (12).

The IEO group of Milan (10) was the first to apply this methodology to intraoperative radiotherapy with dedicated LINAC in the treatment of early-stage breast tumors, showing that FMEA has proven to be a useful and simple tool for a multidisciplinary and prospective evaluation of patient safety. 24 sub-processes were identified highlighting the most risky events (failure mode), such as misalignment between the applicator and the protective disk, incorrect assessment of the size of the CTV, errors in communication between operators, and functional faults of the equipment. Additional security and control measures were introduced, such as the establishment of dedicated IORT staff, execution of double checks of the MUs and of data entry, and implementation of in vivo dosimetry.

The Spanish group (12) applied FMEA to intraoperative radiotherapy with conventional LINAC. In their analysis they included CT simulation and the pre-planning phases using the specific Radiance system for IORT with photons (13). 57 criticalities were highlighted whose effects were graded from inconvenient or sub-optimal treatment to total cancellation and treatment with a wrong dose. After the analysis, they introduced double checking of the MUs, some interlocks, automation of some processes, as well as structural changes all of which significantly reduced the initial risk ranking.

The Trieste group (11) has published the results of the FMECA analysis on dedicated LINAC in the treatment of early-stage breast cancer. 51 events (failure mode) were identified, 11 of which were assigned to the high-risk class (RPN ≥ 51). The steps found to be most critical were the incorrect definition of the tumor bed to be irradiated and its thickness, and the incorrect alignment of the protective disk on the chest wall with respect to the applicator (14). The introduction of corrective measures significantly reduced the RPN, which was recalculated 2 and 4 years after the introduction of the IORT procedure.

The application of the FMEA/FMECA quality system leads to multiple improvement actions such as training activities (audits, training courses, etc.), organizational changes (introduction of double checks and/or checklists), drafting/revision of procedures/protocols, acquisition/maintenance of equipment and technologies, and structural adjustments with ensuing improvements in the quality of care (15).

The adoption of a proactive quality system, such as the FMEA/FMECA, is of critical importance in preventing and reducing risks for patients and operators in the Centres that deliver IORT.

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Chapter 8
HEALTH TECHNOLOGY ASSESSMENT

The adoption of high-cost complex diagnostic/therapeutic technologies, such as IORT equipment, by healthcare establishments should be preceded and validated by an analytical process providing a general and synthetic assessment of the technical characteristics and possible clinical applications of the equipment, with a view to integrating such technologies into the clinical, organizational and social context.

Such an analytical process is justified not only by clinical and economic reasons, but also by welfare, organizational and ethical reasons, as well as by the need for the choices to be made on the basis of objective, proven and shared scientific criteria.

This need can be met by applying HTA principles which, in fact, have the purpose of guiding decision-makers in the healthcare sector through analyses aimed at assessing advanced health technologies or at making comparisons between two or more technologies, where Health Technology means any application of scientific knowledge to clinical practice or prevention.

The term Health Technology identifies a set of technical and procedural means made available by science and research to health professionals for prevention, diagnosis, treatment and rehabilitation activities.

The term Assessment in the field of medical technologies defines a multidisciplinary analysis process which must include:

- performance;
- clinical safety;
- efficacy;
- cost-effectiveness;
- social, legal, ethical, political impact.

An HTA analysis is therefore a process which, through well-defined steps, assesses the benefits, risks and costs associated with alternative options offered by different technologies, organizations, etc.

The assessment or comparison must consider not only the clinical advantages of the health technologies, both theoretical (efficacy) and practical (effectiveness), but also any direct or indirect economic, legal, ethical and social implications. The process must be in harmony with the social, environmental and political context of the healthcare establishment and must therefore take into account the overall impact of the health technologies on the organization as a whole.

The ultimate goal of HTA is to optimize health expenditure, using available economic resources in such a way as to maximize health outcomes for the community.

HTA represents a method for evaluating the health services provided, or otherwise available, to plan and manage care delivery in a more functional way, thus making it an essential tool of Clinical Governance, and it provides scientific support to the various decision-making tiers of the Health Service.

The decision-making elements may range from simple qualitative considerations to detailed and in-depth assessments of technologies which include an analysis of the related clinical, economic or safety risks. The discriminating factor for the type of approach to be adopted could be, in the first instance, simply the cost of the technology being assessed.

8.1. HTA analysis and report

8.1.1. Analysis method

The HTA report provides the answer to a query posed by Management or by the technical component of the health professionals (doctors, pharmacists, biologists, physicists, therapeutic radiographers, nurses). This query identifies a question which is a Policy question about whether one health technology should be chosen rather than another and which sets the stage for the entire process.

This phase is followed by a detailed analysis of the technology to be assessed, the target population, the dimensions considered (safety, effectiveness, organizational aspects, etc.), and of any alternative technologies and parameters (outcomes) that will constitute the baseline for the comparison: this analytical process is reflected in the acronym PICO which stands for Population, Intervention (the technology), Comparator (s) and Outcomes. These four elements are defined in the report.

The *outcomes* that constitute the basis for the comparison between different technologies must be sufficient and sufficiently diversified.

Once the parameters representing the variables and quantities associated with all the dimensions affected by the use of the technologies being examined (safety, effectiveness, costs, organizational structures, ethical-social aspects) are identified, they will be the basis for building a model of the query and its context, in order to elaborate a simplified representation of the query, in which the consequences of the use of the technologies in question are considered and weighed according to their actual importance and influence. Modeling is not always possible: some clinical situations may in fact be extremely complex (excessively large numbers of variables, presence of factors and parameters that are difficult to quantify, etc.).

After developing the predictive model, the evidence from which to extract the values of the parameters to be included in the model will have to be gathered.

This research preferably takes place through a systematic review of all the evidence that can be found in the literature, a process that attributes to the parameters a value that is as universal and as free from environmental bias as possible.

Subsequently, the evidence is pooled together, processed and synthesized in a single final datum, which represents the value of the parameter to be entered into the model. Only when all the values of the variables involved are available can an answer be given to the Policy question.

In addition to this modeling, research and calculation phase, if the suggested advice is accepted and implemented by the decision makers, the HTA report will have to be followed by a continuous monitoring of the effects it produces.

The content of HTA reports is not standardized, although the association that brings together most of the national and international HTA agencies (INAHTA) offers a template of the essential contents it should contain on its website. The assessment of a technology should therefore include the following components:

- gather evidence (or indication of the absence of evidence) of the benefits and costs of the intervention;
- summarize the evidence of research findings on the effectiveness of different health interventions;
- economic impact assessment and cost-effectiveness analysis;
- assess the social and ethical consequences of the dissemination and use of the technologies and their impact on the organization;
- identify best practices in healthcare to improve quality and contain costs.

8.1.2. Structure of the report

8.1.2.1. Identifying the policy question

The question to be analyzed and evaluated is asked by the decision makers following the spotting of a major problem. The evaluators must clearly understand the purpose of the evaluation and who are the recipients of the results of the evaluation. In fact, HTA can be applied at different levels of the health system: at the macro level, where planning, epidemiological and macroeconomic choices are made; at the meso level, which typically concerns the general management of health organizations; at the micro level, which involves the clinical and organizational management of Departments and Operational Units.

The different point of view of the user will affect both the results and the contents of the report, since health policies (macro level), institutional management (meso level) and guidelines (micro level) are underpinned by different rationales.

8.1.2.2. Size of the analyses (research questions)

The technology in question must be analysed in some or all of its aspects, in terms of needs, effectiveness, appropriateness, ethical aspects, patient satisfaction, equity, costs and safety, depending on the type of analysis being made.

8.1.2.2.1. PICO (Population, Intervention, Comparator and Outcomes)

The population (patients) to which the technology is addressed, the technology itself, the alternatives (controls) and the parameters on which to base the comparison must all be specified. The PICOs provide useful information on the criteria for including evidence from the literature.

Among the dimensions (outcome) on which to base the analysis, the issues concerning the following points are of crucial importance:

- *efficacy*, an index of the validity of a procedure or a service, expressed in terms of the health gain for a population, a subgroup, and an individual. In general, it measures compliance between objectives and results, and quantifies the ability of an action or program to fulfill the purposes. A distinction is made between theoretical efficacy, which is measured in experimental and selected contexts (efficacy), and practical efficacy obtained in real, operational contexts (effectiveness);
- *efficiency*, represented by the measure of the ratio between results obtained and resources employed. Efficiency can be allocative, i.e. the optimal distribution of resources among competing technical or operational uses, in other terms the best combination of production factors at the operational level;
- *appropriateness*, which concerns the use of a health service and measures the extent to which it complies with request or prescription in meeting a specific need/demand. The appropriateness criterion is met when its prescription/use can guarantee, with reasonable probability, when benefits will outdo damage for the patient, with a large enough margin, without being affected by economic considerations. It expresses the degree to which available knowledge and techniques are used well or misused in the treatment of diseases and in the achievement of health. It is useful to distinguish between clinical and organizational appropriateness. Clinical appropriateness refers to a treatment that is effective and appropriate: it mainly refers to the decision-making moment of medical care. Medical care is appropriate if it is of proven efficacy, if it is prescribed for

recognized clinical indications, and has acceptable adverse effects relative to the benefits it provides. Organizational appropriateness, on the other hand, concerns the pursuance and use of the best context to deliver the most effective, safest, most appreciated, least expensive intervention, delivered at the right time and in such conditions (care settings) as to use an appropriate number of resources.

Another dimension of the analysis concerns costs. This dimension of the analysis is fundamental in the final assessment report; in fact, the ultimate goal of the HTA is to optimize health expenditure by using the available economic resources in such a way as to maximize the health conditions of a population.

HTA is a method for evaluating the health services delivered, or otherwise available, for planning and managing care delivery in a more functional way, thus making it an essential tool of Clinical Governance, capable of providing scientific support to the various decision-making levels of the Regional/Provincial Health System

8.1.2.3. Analysis of the context

This is a crucial step in the HTA process: the assessment of a technology must combine scientific evidence with the local social and health contexts

8.1.2.4. Gathering evidence

The collection of scientific evidence for a particular research question must be summarized in a qualitative or quantitative way. Useful sources of data and evidence can be:

- databases in the literature;
- databases of clinical and administrative data;
- institutional and non-institutional reports and monographs;
- special inventories;
- specialized journals.

It may be appropriate to generate evidence for an evaluation process by collecting new data. This is possible, for example, through the analysis of epidemiological studies (randomized controlled clinical trials, non-randomized controlled clinical trials with contemporary controls, non-randomized controlled clinical trials with historical controls, cohort studies, case-control studies).

8.1.2.5. Summary and interpretation of evidence and data

The interpretation of the evidence consists in classifying the collected studies and attributing each a weight in order to include them or not in the summary. In HTA, conclusive results indicating that one technology is better than another do not exist. It is often necessary to combine the results of various studies and consider the wider social and economic context.

8.1.2.6. Results and recommendations

The conclusions summarized at the end of the analysis should be accompanied by recommendations addressed to the decision makers who will have the task of translating them from their standpoint (macro, meso or micro) respectively into public health strategies, clinical and organizational guidelines or practical guidelines.

8.1.2.6.1. Diffusion of the results obtained

It is important to disseminate the results and recommendations elaborated by the HTA report to all relevant stakeholders through publication in journals of international interest, conferences, specific courses or other.

8.1.2.6.2. Implementation of results in practice

When the recommendation emerging from the report is accepted by the decision makers and its implementation involves changes in practice at all institutional levels, implementation strategies designed to successfully bring about the required changes in the clinical, organizational, administrative and even cultural context will have to be adopted.

The impact produced by the evaluation and updating of the report is monitored to verify whether what has been implemented responds to the expectations created during the reporting phase. The typical effects induced by a technology assessment report are:

- acquisition of a new technology;
- change in the frequency of use (reduction or increase) of a technology;
- new allocation of resources in the regional or national health sector;
- changes in the marketing planning of a given technology.

These effects must be quantified and their compliance with the provisions of the HTA report verified so that the recommendations may be adjusted or even changed. Once the report is updated it is to be delivered to the decision makers.

8.1.3. Some HTA considerations for the introduction of IORT equipment

The introduction of this type of technology in a healthcare establishment involves a major economic and organizational investment. A well-structured HTA report based specifically on the healthcare reality in which the technology is to be introduced can therefore be a useful and effective tool.

The introduction of dedicated IORT equipment in the operating room also requires a high level of maturity and technical-professional experience of the surgical team that will use it and requires training for a thorough understanding of the guidelines, procedures and protocols to be adopted so as to ensure a high level of quality of the therapy.

With regard to the PICO analysis of the economic aspects, the considerations must take into account that there are three players in healthcare:

- the beneficiary, i.e. the Patient;
- the Provider, i.e. the health facility;
- the Payer, who may be the patients themselves or a third party which in Italy is the Regional / Provincial Health System or, more rarely, an insurance institution.

From the patient's point of view, without prejudice to the criteria of appropriateness set out above and assuming the IORT to be equivalent to transcutaneous radiotherapy, the advantage is expressed in terms of fewer outpatient visits, reduced travelling time, less absence from work and less fuel consumption for patients and accompanying persons.

The biological cost is zero only in the cases where at least equivalence between IORT and EBRT is demonstrated.

From the point of view of the Provider, the costs must include:

- outlay for the purchase of the equipment;
- depreciation of the equipment over the years;
- annual costs of technical assistance;
- cost of additional consumables compared to surgery alone;

– hourly cost of the operators involved in addition to those involved in surgery alone;
– non-reimbursement for outpatient treatment;
– cost of staff involved in any extraordinary follow-up;
– additional hourly cost of the operating room.

Revenues must include:
– any reimbursement by the third-party payer. At the time of writing this document in Italy there is no specific DRG (Diagnosis Related Group) that recognizes the intraoperative procedure;
– time slots freed for external beam radiotherapy equipment, which translate into reimbursements for outpatient treatments for other disorders which compensate for the non-reimbursement referred to in the previous point. In more practical terms, the waiting time for other cycles of transcutaneous radiotherapy is shortened;
– as regards the third-party Payer, the vision is reversed with respect to the Provider.

The costs must include:
– any reimbursement that could be negotiated with the Provider;
– the cost of the additional cycles of external beam radiotherapy that the Provider is able to perform thanks to the reduction of waiting times on the transcutaneous units in revenues;
– the difference in cost between external beam treatment and IORT treatment.

General references for Chapter 8

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Useful links

AGENAS The Italian National Agency for Regional Healthcare Services http://www.agenas.it/health_TA.html

(CCOHTA Canadian Coordinating Office for Health Technology Assessment). (2001). Guidelines for Authors of CCOHTA Health Technology Assessment Report http://www.ccohta.ca

EUNETHTA. European Network for Health Technology Assessment http://www.eunethta.net

INAHTA International Network of Agencies for Health Technology Assessment http://www.inahta.net

Italian Journal of Public Health World Quaderni: http://www.ijph.it

LEDHA. League for the rights of people with disabilities APS http://www.ledha.it

SITHA. Italian Society of Health Technology Assessment http://www.sihta.it

16.

APPENDIX A
Practical and technical-organizational aspects of IORT

A1. Treatment report

The first step in the execution of any radiotherapy treatment involves the prescription of the dose to the target volume and the definition of the dose constraints for the organs at risk. These data are generally reported in the patient's medical record together with other information ranging from the patient's personal details to the description of the disease and of treatment.

Prescribing is the responsibility of the radiation oncologist while the compilation and recording of the clinical data in its various formats (recording) and the drafting of the summary report of the treatment (reporting) are the responsibility of the radiation oncologist jointly with the medical physicist, each for their respective field of expertise.

The ICRU, in publications 50, 62 and 71 (1-3) on prescribing, recording and reporting, provides recommendations for reporting the radiation therapy doses and the volumes in which they are prescribed with the aim of promoting a common language that simplifies communication between different Centres. In particular, Report 71 (3) dedicates a chapter to intraoperative radiotherapy.

If the prescribing, recording and reporting activities are carried out properly, they will ensure full traceability of the treatments delivered, in accordance with common principles that are shared across the scientific community, and the comparison of treatment outcomes among different Centres.

The reports should therefore describe the patient's disease, the doses and volumes irradiated, the physical and technical parameters of the treatment, the fractionation scheme and any additional information that may have clinical implications.

ICRU 50 (1) identifies 3 reporting levels:

- level 1 (basic techniques): dose at the ICRU point and estimated maximum and minimum dose at the PTV determined from the PDD tables and from the isodose charts;
- level 2: dose distribution evaluated on planar-imaging of the treatment region (2D modality);
- level 3: dose distribution evaluated on volumetric imaging of the treatment region (3D modality).

As far as IORT is concerned, level 1 reporting prevails at this point in time, even though in recent years the market has been offering specific TPS.

A1.1. Reporting in clinical practice

IORT is a radiotherapy procedure that involves different professionals, each for their own field of competence. The preparation of an overall treatment report can therefore be an opportunity to clearly define tasks and responsibilities.

The report can be structured by each Centre according to its own needs and organizational structure; it therefore involves the surgeon specialist, the radiation oncologist, the medical physicist, and the Tr/RTT.

In general, the Centres include the following data in their reports:

1. personal data of the patient;
2. treatment site;
3. diameter and thickness of the PTV;
4. specifications of the treatment protocol adopted: the dose prescribed at the reference isodose, the use of any systems for homogenizing the target and for increasing the dose to its surface, systems used to protect organs at risk;
5. nominal energy of the beam and nominal specifications of the applicator used for the treatment;
6. specifications of any bolus/systems used to homogenize the surface of the target volume;
7. specifications of any systems used to protect organs at risk;
8. maximum and minimum dose assessed in the PTV;
9. MUs to be delivered (in the case of IOERT) or the delivery time of the beam (in the case of kV-IORT);
10. significant machine-data of the treatment carried out and the results of in vivo dosimetry, if any;

11. reference to the positive outcome of the results of the daily quality checks carried out on the equipment.

The information referred to in points 1 and 2 is already available before the procedure and is provided by the radiation oncologist.

The geometric specifications of the PTV, the prescribed dose at the reference isodose, the size of the applicator, choosing to use the bolus or not, target surface homogenization systems and systems for protecting the organs at risk are defined by the radiation oncologist during the preparation phases of the treatment set-up.

Based on these indications, the medical physicist identifies the most appropriate treatment energy, estimates the minimum and maximum doses at the PTV and calculates the MUs to be delivered (IORT) or the beam delivery time (kV-IORT). If necessary, the medical physicist - with the assistance of the Tr/RTT- prepares the measurement instrumentation for in vivo dosimetry on the patient and hands over the detector to the radiation oncologist, who positions it according to the instructions received.

The Tr/RTT is responsible for the operational procedure for managing the command console of the radiology equipment and for the execution of the treatment.

At the end of the treatment, after a final discussion involving the radiation oncologist, the medical physicist and the Tr/RTT the applicator can be removed and surgery can be completed.

The drafting of the treatment report is the joint responsibility of the radiation oncologist, the medical physicist and the Tr/RTT, each being responsible for their respective field of expertise.

According to Italian Legislative Decree 101/2020 (Article 163, paragraph 14) (4) particle accelerators with nominal energy greater than 1 MeV (the case of IOERT) and acquired after the date of entry into force of the Decree must be equipped with systems for recording and verifying the treatment parameters, while the equipment already in operation must be equipped with these systems within 2022.

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A2. INFORMED CONSENT

The following is an example of an informed consent form.

I, the undersigned _____ agree to undergo INTRAOPERATIVE RADIOTHERAPY (IORT), the nature and aims of which 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* Name and surname of physician

(signature) *(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.

A3 Critical issues and operational considerations on electron beam IORT

The optimization of an IOERT treatment plan, which is realized by personalizing the study, involves the consideration of geometric, dosimetric, clinical (definition and preparation of the target volume) and managerial issues, which are closely related to each other. Since treatment involves the irradiation of the tumour bed, the preparation of the set-up and the operational management of the treatment are of fundamental importance.

Geometric, dosimetric, clinical and managerial criticalities (which are all closely interrelated) may occur both in the initial phase and in the surgical phase during treatment.

The main geometric and dosimetric critical issues that may arise during the implementation and management of electron beam IORT are described in the following.

A3.1. Geometric critical issues

Non-correspondence between the geometric treatment set-up and the dosimetric characterization set-up (of the beams, the treatment technique and the in vivo dose measurement technique) is caused by target inhomogeneity and by the presence of air gaps, misalignment between applicator-target and internal shields, and incorrect evaluation of the target thickness.

A3.1.1. Positioning of the applicator

Critical issues:

- target inhomogeneity (irregularities in the target surface);
- air gaps at the surface and/or at the interface with internal shields, if any;
- possible accumulation of biological fluids at the surface.

Solution:

The target is the area at greatest risk of spread or local relapse of the disease. Generally, the surface of the volume to be irradiated is inhomogeneous and not smooth; its morphology and the way it is prepared may affect the accuracy of treatment, with significant dosimetric uncertainties in terms of absorption of the prescribed dose and relative dose distribution.

In order to use the dosimetric data of the beam obtained in the commissioning phase, it is essential that the treatment set-up matches the characterization set-up of the beam. It is therefore necessary to try to make the target volume and its surface homogeneous, avoiding herniation and air gaps. Operationally, where contact applicators are used, this can be achieved by wrapping a sterile film around the base of the applicator (Figure A3.1) or, preferably, by using a plastic disk (of suitable thickness and with a diameter of 2 cm larger than the applicator to which it is coupled) to be positioned between the base of the applicator and the target surface (Figure A3.2). The use of the disk also provides a good support for the applicator (which, when positioned, exerts a slight pressure on the target, compacting it) thus providing a useful support onto which the dosimeter can be fixed for in vivo dose verification, if any (the detector would be sandwiched between the disk and the target surface).

The use of plastic sterile wrap or of a disk is recommended also in the case of treatment using non-contact applicators.

For the typical energies used, plastic disks with a thickness of 2 mm and 5 mm are a good compromise, considering that the most distal point of the target cannot be underdosed.

From a dosimetric point of view, the disk also entails a useful increase in the dose at the surface of the target (build-up effect).

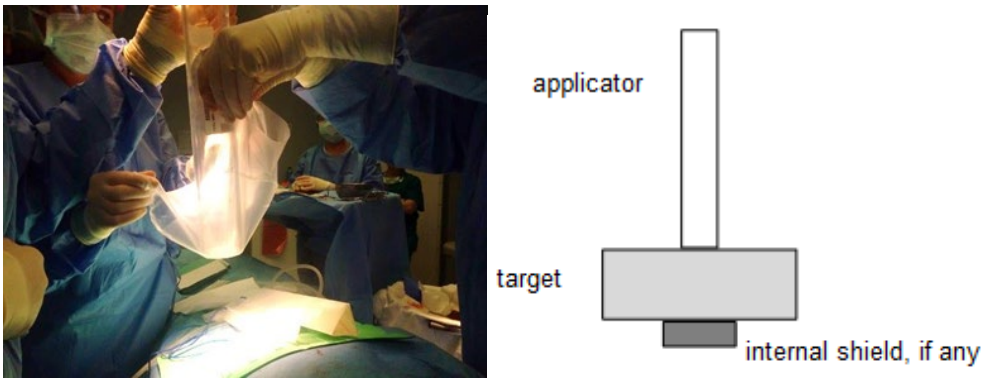

Figure A3.1. Positioning of a plastic sterile wrap at the end of the applicator to prevent, during treatment, herniation of the target in the applicator, also indicated is the corresponding treatment set-up (contact applicator treatment) (photo by S.Andreoli)

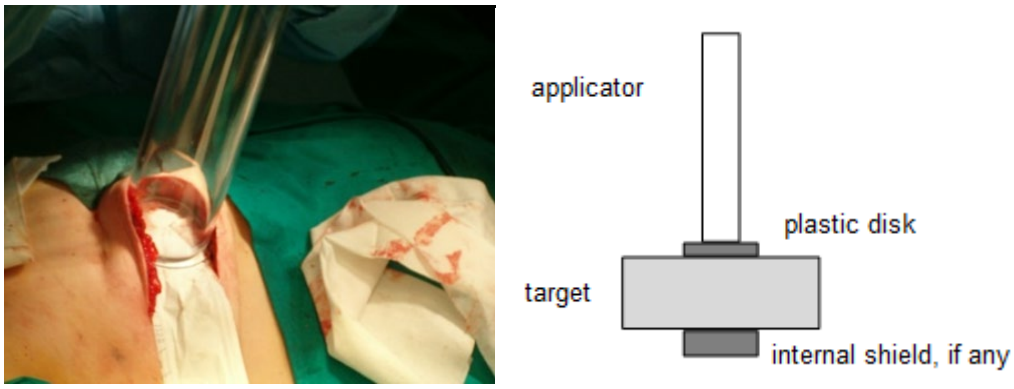

Figure A3.2. Typical treatment set-up for breast irradiation, using the disk between the applicator end and the target surface (contact applicator treatment) (photo by S. Andreoli)

The disk allows an ideal coupling between applicator and target surface. To ensure the stability of the geometric treatment set-up and a correct applicator-target-internal shield alignment - subject to limitations caused by the position of the target - it is suggested to use flat applicators - or applicators with small bevel angles - oriented in an almost vertical direction and, possibly, to stabilize the internal shields (for example, through temporary stitches). Operating tables with multiple degrees of freedom are instrumental for this purpose.

A3.1.2. Positioning of the internal shields and evaluation of target volume thickness

Critical issue:

- adequate and stable positioning of the internal shields (if envisaged);
- evaluation of target thickness (the most distal point of the target with respect to its surface at which the dose is usually prescribed).

Solution:

The correct positioning of the internal shields and their stabilization when preparing the treatment set-up is one of the essential requirements to ensure treatment optimization.
It is suggested, subject to limitations caused by the position of the target, to use flat applicators - or applicators with small bevel angles - oriented in an almost vertical direction and, possibly, to stabilize the internal shields (for example, through temporary sutures).
For treatments with electrons (essentially carried out with a single field - direct field) the target thickness (to be evaluated, transversely to the beam axis, in some significant points) determines the choice of the treatment energy.
Usually, a personalized treatment plan is not developed by assessing the dose distribution to the target; the calculation of the MUs to be delivered is calculated on the output evaluated in water, on the beam axis at the dose prescription point.
Since IORT involves the irradiation in the operating room of a freshly operated tissue, this depth must necessarily be assessed during the preparation of the treatment set-up, taking into account the strategy adopted to make the target surface smooth (to homogenize the target surface). Essentially, there are three ways to measure this parameter: by means of a needle, an ultrasound probe or through RX imaging.
The most frequently used technique for measuring treatment thickness involves the use of a simple needle which, inserted perpendicularly to the surface of the target, intercepts the internal screen (if envisaged) or an accessory temporarily positioned downstream of the target which is then removed before treatment.
As an example, the sequence of a typical breast treatment set-up is shown in the Figure below which involves the use of an internal protective disk (Figure A3.3-A3.6). To measure the thickness with a needle, the operator can place a perforated disk (typically 5 holes: at the centre of the field and at the cardinal points) on the surface of the target and apply a slight pressure to simulate the pressure exerted by the applicator-disk coupling during treatment.

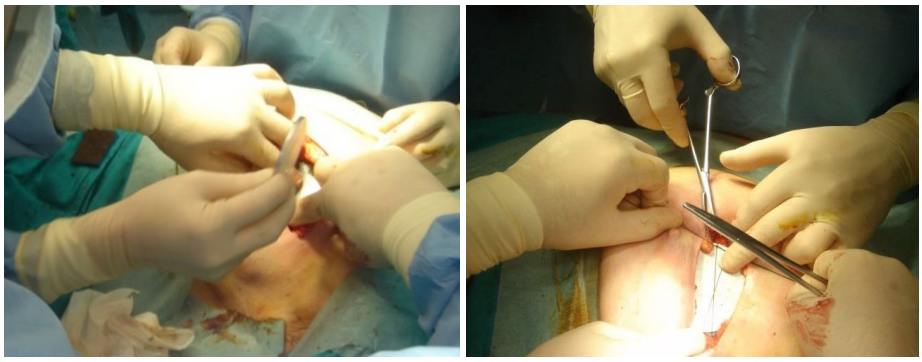

Figure A3.3. Positioning and stabilization of internal shields, if provided (for breast treatment) (photos by S. Andreoli)

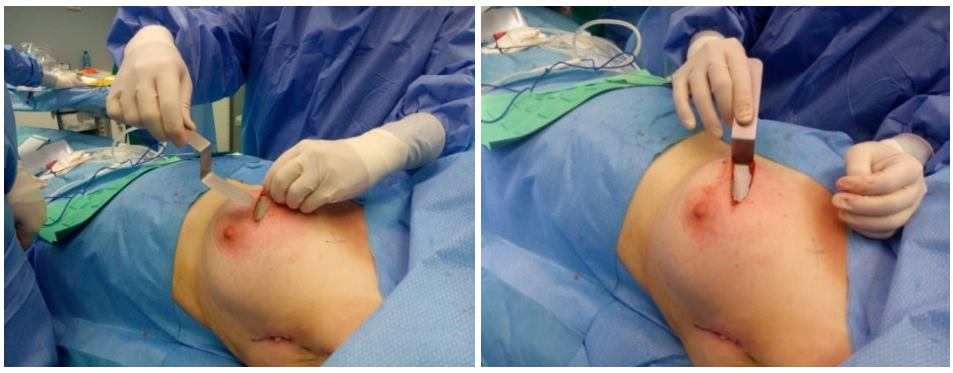

Figure A3.4. Temporary insertion of a "paddle" attachment only for the procedure of measuring target thickness through a needle, in case internal shields were not to be used (essentially when the chest wall is part of the target) (for breast treatment)
(photos by S. Andreoli)

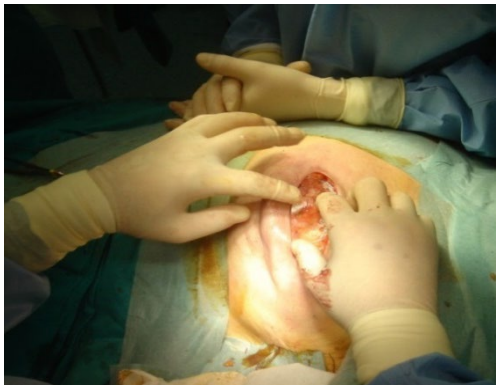

Figure A3.5. Positioning, at the target surface, of a perforated disk (e.g., at the center and cardinal points) for treatment thickness measurement through a needle (for breast treatment) (photo by S. Andreoli)

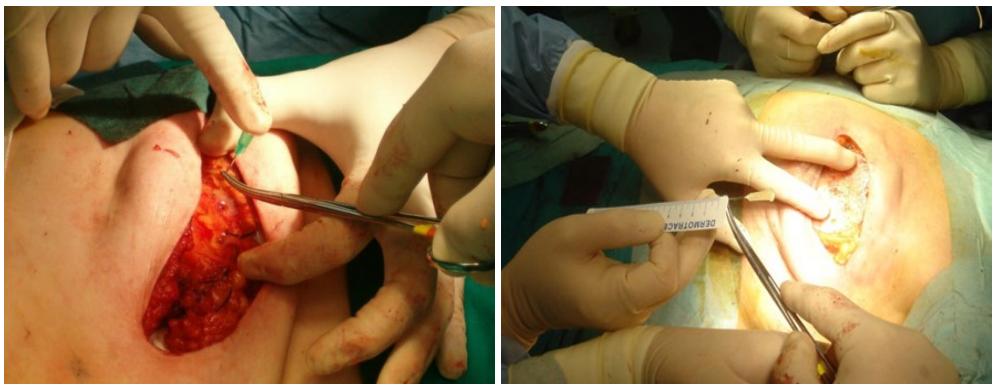

Figure A3.6. Insertion of a needle for treatment thickness measurement in the case of a breast treatment (to be inserted into the holes of the disk until intercepting the inner shields or the "paddle" accessory) (photos by S. Andreoli)

Valid alternative methods that are less frequently used consist in measuring the target thickness with an ultrasound probe (Fig. A3.7) or with RX imaging.
At times it may be difficult to verify the thickness; in this case an energy will be selected that ensures the dosimetric coverage of an *a priori* assessed thickness.

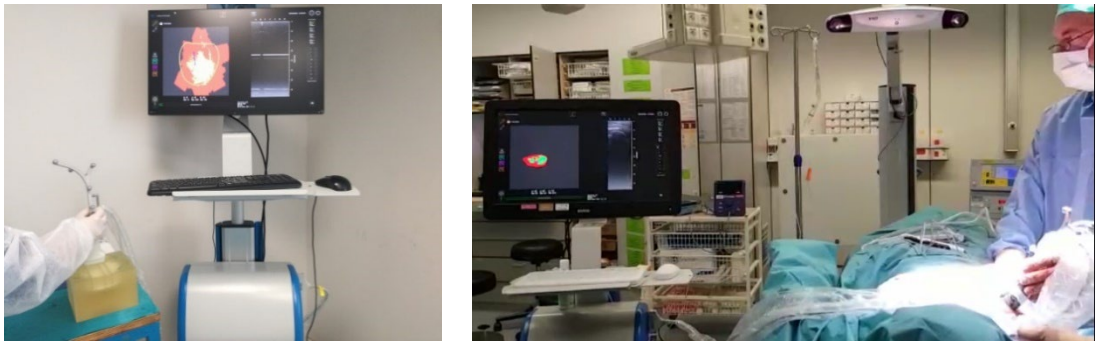

Figure A3.7.Simulating the use of an ultrasound probe to measure treatment thickness (left) and use of the probe during treatment set-up (right) (photos authorized by SIT)

A3.2. Dosimetric critical issues

A3.2.1. High doses delivered in a single session

Critical issue:

– calculation of the MUs necessarily carried out just before treatment, based on target size and thickness.

Solution:

Although the TPSs are currently available on the market and other non-commercial hand-made solutions are being studied or in use, usually the choice of the field size is made on the basis of geometric criteria of the transverse extension of the target and the calculation of the MUs in terms of dose at the reference point. This implies that all the physical and geometric data for the energy-applicator combinations need to be available in a format that is rapidly accessible and easy to use. In particular, the dosimetric data must allow the calculation of the MUs necessary to deliver the prescribed dose to the target.

A3.2.2. High dose per pulse, generated by some types of dedicated accelerators

Critical issue:

– problems with ionization chambers for dosimetry in reference (output) and non-reference conditions (output factor of clinical applicators), related to the effects of ion recombination in the chamber for beams characterized by doses per pulse greater than 10 mGy and which, if not properly considered, may entail significant errors in absorbed dose determination.

Solution:

Adequate dosimetric characterization of the ionization chambers, in particular in the evaluation of the ion recombination correction, k_s, which can be determined in accordance with appropriate methods reported in the literature.

The plane parallel chambers to be preferred are those with an electrode distance less than 2 mm. In any case, it is preferable to use high polarization voltages, within the limit of the linearity region of the charge-voltage response.

A3.2.3. Treatment-beam energy selection

Critical issue:

– dose coverage of target volume.

Solution:

By placing the disk between the end of the applicator and the target surface, from a geometric point of view, it is possible to make the target volume uniform and accurately estimate its thickness, while from the dosimetric point of view, the dose at the surface is usefully increased (build-up effect).
Usually, in electron beam radiotherapy, the dosimetric coverage of the target is obtained by choosing the treatment energy whose PDD in water at the identified prescription depth corresponds, at least to the reference isodose (typically, 90% isodose).
Specifically for IOERT, in order to improve the dosimetric coverage of the target, especially in the part most proximal to the applicator, the use of the plastic disk between the applicator and the target surface could allow one of the higher treatment energies to be selected by modulating the thickness of the disk so that the sum of its thickness and the identified prescription depth does not exceed the depth of the reference isodose.
As can be seen from the figure, by adopting such a strategy, the combination of a 10 MeV nominal energy beam (R50 = 36.2 mm) froma NOVAC11 accelerator with disks having thicknesses of 2 mm and 5 mm represents a good solution to cover a target of up to 23 mm, without considering any dose contributions due to the backscattering from internal shields (Figure A3.8). This approach does not affect the lateral coverage of dose profiles.

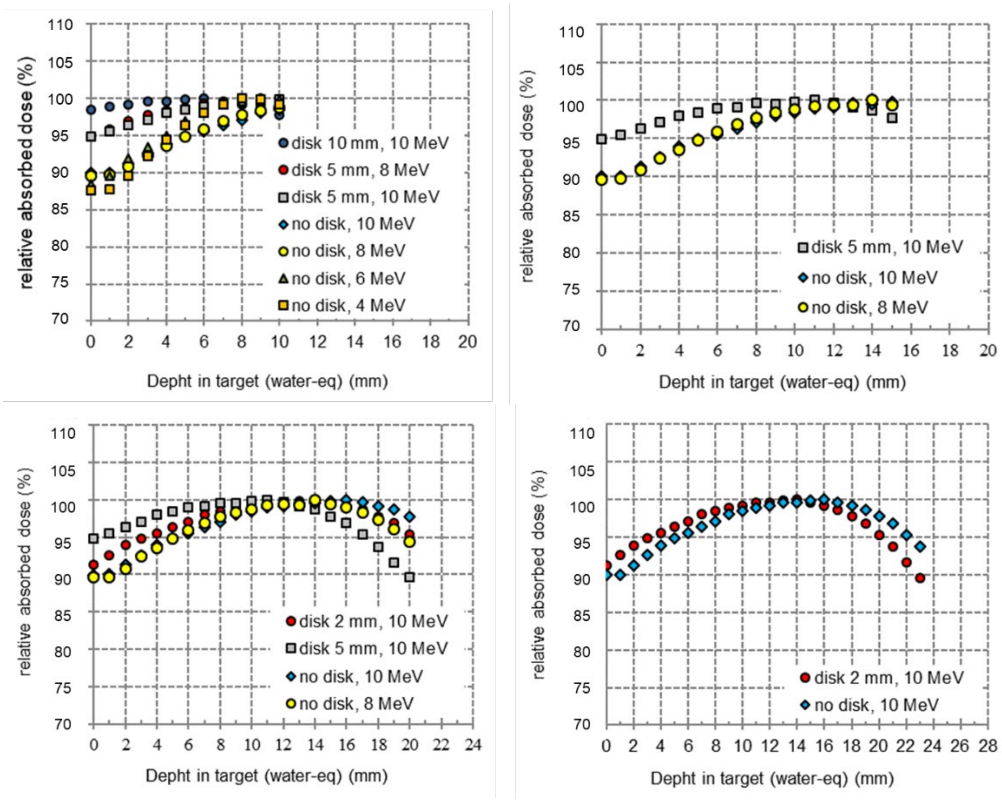

Figure A3.8. The PDDs in water for several target thicknesses using the reference applicator. The curves were obtained combining beam energy and thickness of the disk placed between the end of the applicator and the target surface. Note how the presence of the disk provides better dosimetric coverage of the target than the geometry without the disk. È ancora in ITALIANO

A3.2.4. Use of applicators, which must maintain the same physical characteristics (size/shape) over time to guarantee their dosimetric properties

Critical issue:

– inappropriate management of the applicators in routine use;

– inadequate application of the washing and sterilization procedure.

Solution:

The plastic applicators used to determine the physical and dosimetric characteristics of the beam are very delicate.

Careful management is absolutely necessary to ensure that the dosimetric properties evaluated during commissioning are maintained over time: thermal and mechanical stresses are to be avoided, housing in specific cabinets directly in the operating block must be ensured, the indications provided in the technical data sheet for washing and sterilization must be applied strictly and the maximum number of sterilizations to which the applicators can be subjected without altering their nominal characteristics must not be exceeded.

An integrity check (essentially, cracks and deformations) is useful when they are sent for sterilization and when the freshly sterilized material is returned.

As an example, Figure A3.9 shows how even a minor deformation of the main axis of the flat applicator can significantly modify the transverse dose profiles. Consequently, variations are also to be expected in the effective OF of the beam with respect to the tabulated value obtained for the same intact applicator (in this specific case, the 3 mm deformation of the axis along the longitudinal direction of the applicator produces a 4% increase of the OF value).

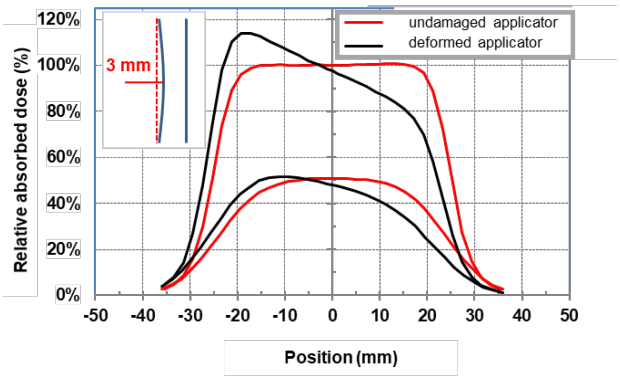

Figure A3.9. Comparison of dose profiles at depths z_{max} and R_{50} of an intact and a deformed flat applicator (profiles evaluated for a 5-cm diameter applicator for the highest energy of a NOVAC7 accelerator)

A3.2.5. Use of internal shields having a high atomic number

Critical issue:

– use of internal shields made of materials with high atomic number;
– hypothetical misalignment between the shields and the applicator-target unit.

Solution:

For treatment optimization it is essential to know the order of magnitude of the contribution from backscattered radiation and its coverage of the target, at least along the beam axis, through the evaluation of the backscatter factor. The backscattered radiation, especially in the case of materials with high atomic number, may contribute a significant additional dose to the target at its interface with the shield. The contribution is a function of the energy of the beam, the thickness of the target and the atomic number of the shield material that is in direct contact with the target. Knowledge of this contribution could, in principle, be exploited to cover higher treatment thicknesses.

Misalignment between the shields and the applicator-target coupling could result in an inhomogeneous backscatter dose contribution to the target-shield interface that is difficult to assess (essentially in the case of shields made of materials having a high atomic number). To minimize

unintentional displacements (slipping) of the internal shields with respect to the applicator-target unit, it is suggested, within the limits allowed by the position of the target, to use flat applicators - or applicators with small bevel angles - oriented almost vertically and, possibly, to stabilize the internal shields (for example, with temporary stitches).

A3.2.6. Reproducibility of the output on the day of the treatment

Critical issue:

- unusual timing and management modalities (switching on/off and warm-up, checking the output) of a mobile accelerator installed in the operating room where the treatments are carried out, which could affect the reproducibility of the output on the treatment day, compared to the initial daily assessment.

Solution:

It is essential to check the reproducibility of the output throughout the day, managing the accelerator as if it were a typical treatment day (in terms of switching on and initial warm-up, switching off, simulation of at least one treatment).

A3.2.7. In vivo dosimetric verification

Critical issues:

- possible abnormal irradiation conditions in terms of treatment set-up, for which the dose absorbed by the target could be significantly different from the prescribed dose;
- high dose delivered in a single fraction.

Solution:

Since IORT involves the irradiation in the operating room of a freshly operated tissue, even though strategies are adopted to make the treatment set-up similar to the set-up with which the beams and the treatment technique have been characterized, abnormal irradiation conditions may occur (due to difficulties in setting up or maintaining the treatment set-up). As a consequence, the dose absorbed by the target could be significantly different from the prescribed dose. In any case, in order for the evaluations to be considered reliable, in addition to an accurate dosimetric characterization of the system, it is essential that the set-up used to study the in vivo measurement technique be replicated during treatment.

To ascertain the dose actually absorbed by the target, it is desirable to perform an in vivo verification through an independent measurement system. For this purpose, point or extended dosimeters can be used, at the entrance or exit of the target, which may or may not provide a dosimetric evaluation in real time.

An in vivo online dosimetry system is however preferable, due to the immediacy of the dose assessment and the possibility of deciding the level of intervention. The use of an extended detector, although offline, would also allow a geometric verification of the alignment of the applicator, target and internal shield.

It is essential to define in advance the aims to be pursued by introducing this verification technique, the methods for positioning the detector and for calculating the dose. The Centres that decide to implement an in vivo dosimetry program should preliminarily analyse, even if only for an adequate number of patients and for each pathology treated, the variations found between expected dose and measured dose in order to optimize the methods of measurement and if any, at a later stage, identify appropriate intervention procedures.

The correct positioning of the detector is certainly facilitated in the presence of a rigid support. For entrance dose measurements, assuming that a disk is placed between the applicator and the target surface, the detector can be positioned on the beam axis, sandwiched between the disk and the target surface. For exit dose measurements, the detector can instead be fixed to the internal shield or to a plastic disk placed on top of it, to prevent the backscattered radiation component from affecting its sensitivity and leading to unreliable dosimetric evaluations.

Figure A3.10 shows the procedure whereby the treatment set-up is prepared with a disk on the target surface and a micromosfet detector positioned between the disk and the target surface. Figure A3.11 shows a detail of the positioning of a radiochromic film on the internal shield, to check the exit dose to the target and the applicator-target-internal shield alignment.

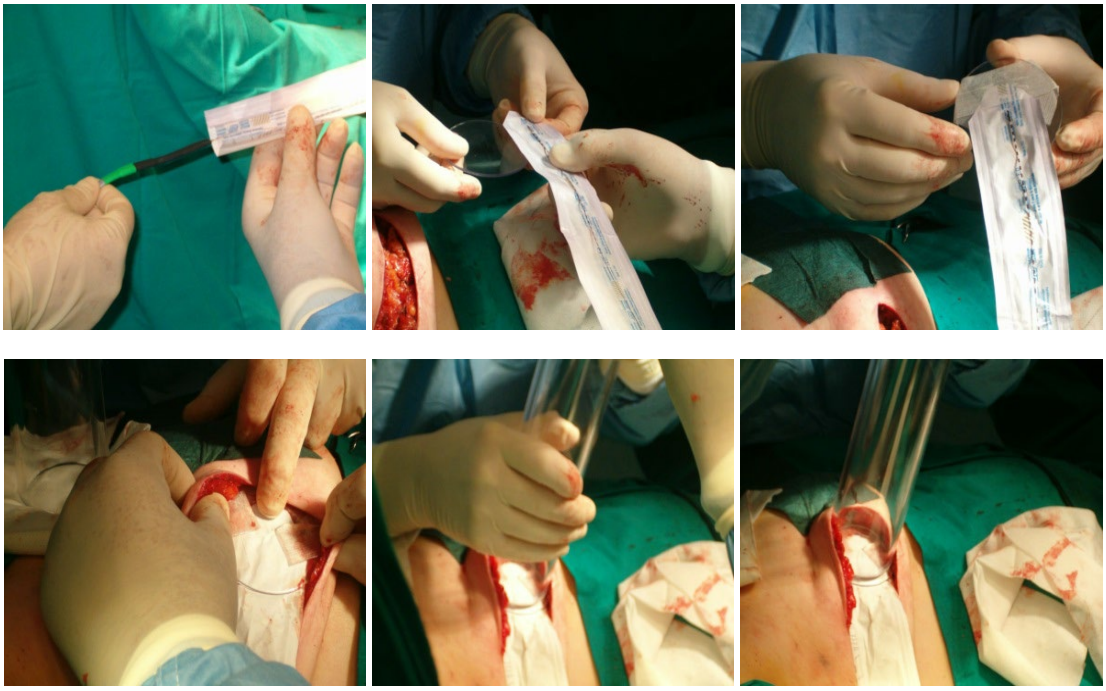

Figure A3.10. Procedure for treatment set-up and positioning of a micromosfet detector for entrance dose measurement in a breast treatment (note the disk between the applicator and the target surface and the micromosfet placed between the disk and the target surface) (photos by S.Andreoli)

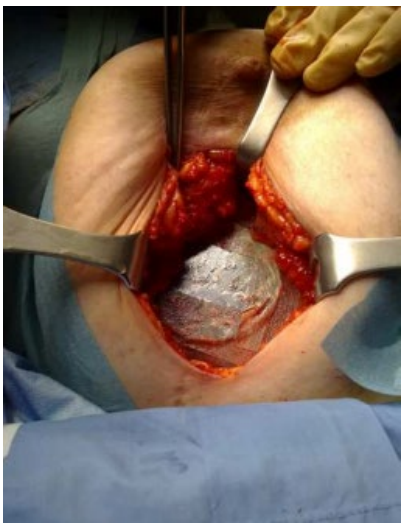

Figura A3.11. Positioning of a radiochromic film for exit dose measurement and applicator-target-disk alignment verification in the case of breast treatment (photo by M. Severgnini)

A4. Physical and dosimetric optimization of electron beam IORT

A4.1. Technical aspects

In advance, when defining the order:
- set up the Quality Group and the Operating Group;
- ask the manufacturers/retailers of the systems available on the market to provide the nominal technical specifications of the equipment they offer, the technical data sheets of applicators and internal shields, protective barriers and other accessories (including the TPS, if any), acceptance protocol and the periodic maintenance program they suggest.

After identifying the treatment protocols and estimating the workloads, the treatment set-up is defined through:
- an analysis to decide whether bevelled applicators, versatile radiotherapy treatment tables with multiple degrees of freedom, and internal shields to be used during clinical practice for the protection of OAR are needed;
- an analysis as to whether to have/implement a TPS or not;
- analysis of how to homogenize the surface of the target (for example, through plastic disks on which to place the end of the applicator or plastic film wrapping around the end of the applicator);
- analysis as to whether the specific measurement instruments/accessories necessary for the commissioning procedure and for periodic quality control should be purchased or not;
- planning of the commissioning protocol;
- identification of the operating mode (or operating modes) for evaluating target thickness;
- analysis of the use/creation of specific phantoms for daily quality control (attached to the reference applicator);
- analysis of the advisability of carrying out in vivo dose measurements (with active/passive dosimeters) and/or verifying of the applicator-target-internal shield alignment.

For the commissioning phase:
- characterization and preventive verification of the measurement instrumentation;
- typical characterization of the treatment beams;
- specific characterization of the treatment technique, definition of the set-up (e.g.: study of the backscattered component from the internal shields, study of the bolus, verification of the reproducibility of the output on a typical treatment day, etc.);
- implementation of the treatment beams on the TPS, if available;
- implementation of the technique (method) for evaluating the treatment thickness [needle that intercepts the internal shields or a support temporarily positioned for the purpose and then immediately removed before irradiation, ultrasound probe, X-ray imaging, etc.];
- definition of the methods to verify the treatment set-up (visual-tactile, ultrasound, radiological, etc.);
- implementation of the dosimetric techniques for treatment verification (in vivo dosimetry) with an active system (point dosimeter) or a passive system (point/extended) (passive system also for possible verification of applicator-target-internal shields alignment);
- definition of the procedures for evaluating outsourcing;
- definition of the protocol for periodic quality controls.

A4.2. Organizational and management aspects

Preliminarily:
- definition and sharing of the timeline for pre-treatment checks, periodic quality controls and maintenance checks;

– estimate workloads, for evaluating the set of applicators, internal shields and, in general, the various accessories needed to ensure clinical activity;
– sharing, with the Sterilization Centre, the washing and sterilization methods of the applicators, internal shields and various accessories (as indicated in the product data sheets);
– verification of the availability of cabinets, near the operating room, for storing the equipment needed for clinical practice (applicators, internal shields, various accessories, various instruments for quality controls, etc.);

In case of IORT outside the Operating Block:
– definition of the intra-hospital transport procedure of anesthetized patients;
– anaesthesia instrumentation for airway management;
– automatic respirator and multi-parameter monitor with channels for detecting invasive pressures and all the parameters needed to ensure clinical safety;
– trolley for emergencies, with defibrillator and drugs prepared according to the operating room schedule;
– algorithms for the management of critical events (intraoperative AMI, cardiac arrest, anaphylaxis, etc.);
– definition of the methods for supplying the equipment (applicators and various accessories) and consumables.

During clinical practice:
– periodic quality controls of the instrumentation, accelerator and related accessories;
– periodic verification of the procedures;
– critical analysis of anomalous events and malfunctions that have occurred (or that could occur);
– evaluation of outsourcing.

APPENDIX B
Synopsis on main indications for quality assurance in electron and photon IORT treatments

Fundamentals for quality assurance in electron and photon IORT treatments

B1. CLINICAL ASPECTS

ORGANIZATION

- **First stage**
  - Through their Quality Control Group, the Centres define:
    - the indications for treatment:
      - in accordance with the provisions set forth for the various districts;
    - the procedure for requesting treatment.
  - The Operative Group:
    - assesses the appropriateness of the entire therapeutic program;
    - forwards to the Quality Control Group the therapeutic programs approved by the various bodies in charge according to the rules of good clinical practice;
    - fills in the forms drawn up by the Quality Control Group for requesting treatment;
    - keeps a logbook of treatments performed.
  - The Centre keeps records of the:
    - treatment steps and operators involved;
    - procedures adopted to inform the operators involved about the IORT planning (FLOW CHART)
  - The radiation oncologist prescribes the dose, taking into account:
    - the meaning of 'single dose' according to the most accredited radiobiological models;
    - the radicality of surgery and size of the residual tumour, if any;
    - pre-or post-operative radiotherapy treatments combined or not by chemotherapy;
    - the position, accessibility and size of the target;
    - the presence or absence of critical organs in the irradiation field, their size and measures to protect them;
    - the international systems for providing guidance on dose prescription in treatments with electrons (ICRU).

- **Preparation of the rooms and setting up the instruments for treatment**
  - The procedures for the various operative aspects are to be implemented, among which:
    - preparation of the radiotherapy bunker or of the operating room and execution of treatment;
    - transfer of the patient from the operating room to the radiotherapy bunker, where treatment is delivered;
    - procedure for delivery, washing and sterilization of applicators and accessories in general and for returning them to the Sterilization Unit.

All these steps are to be carefully evaluated, tracked and managed through appropriate check-lists and it is advisable to appoint a person specifically responsible for each step.

TREATMENT PLANNING

Refer to the specific paragraph in Appendix A for the reporting of IORT treatments.

RADIOTHERAPY TREATMENT PROCEDURE

- The different steps in the preparation of the geometric treatment set-up must be carried out with the intention of replicating the ideal set-up so that the dosimetric evaluations made in the commissioning phase can be used.

  In particular, these steps include:

  - positioning and stabilization of internal shields, if any;
  - preparation of the target, homogenization of its surface and evaluation of the its thickness;
  - choice of the applicator (in terms of size and bevel angle) and its positioning.
- The use of a shielding disk (having a larger diameter than that of the applicator with which it is coupled), positioned between the end of the applicator and the surface of the target, guarantees a good correspondence between the geometric treatment set-up and the set-up for the dosimetric characterization of the technique;
- The use of flat applicators - or applicators with small bevel angles - oriented in an almost vertical direction can guarantee, within the limits posed by the position of the target, the stability of the geometric treatment set-up and the correct applicator-target-internal shields alignment. Operating tables with multiple degrees of freedom;
- A thorough visual inspection must be carried out of all sterile materials (in particular, applicators and internal shields); in particular the integrity of the sterilization pouches must be checked.
- If the calculation of the MUs to be delivered is carried out in terms of point dose, all the physical and geometric data for each type of applicator and for the energies used should be in a readily available and easy to use format, for each prescription dose defined in the treatment protocols (e.g., through spread-sheets, tables);
- In case of in vivo dosimetry, the positioning of the detector must be easy and its presence must not affect the quality of the treatment.

In addition, it is recommended:

- to continuously monitor the patients and their vital parameters throughout treatment;
- if necessary, it must be possible to temporarily interrupt the treatment and have immediate access to the room;
- to record:
  - the irradiated region,
  - size of the irradiated region,
  - the procedure for positioning the applicator (possibly indicating the position and angle relative to the patient/operating table)
  - the procedures put in place to protect the organs at risk, if any;
  - the dose delivery method and the delivered MUs;
- to verify the correct sequence of the planned actions (e.g., through a check-list);
- to draw up a treatment report to be attached to the clinical report.

ANAESTHESIA

- It is required that:
  - the cardiovascular, respiratory and metabolic conditions be stable in order to proceed with position change and transfer of the patient;
  - adequate analgesia be guaranteed and appropriate multi-parameter monitoring be possible throughout the entire procedure and during transport;
  - the patient be curarized and then automatically ventilated in order to avoid any movement that might affect the correct irradiation of the tumour/tumour bed; and that normothermia and warming of the patient, during and at the end of the procedure, be maintained;
  - the anaesthesiologist be in a position to be able to promptly reach the patient in a matter of seconds to intervene in case of need, upon suspension of the radiotherapy procedure.
- The head of the anaesthesia department or the delegate must:
  - participate in the initial definition of the IORT planning;
  - agree on the procedures and resources that are to be available during the execution of the IORT for transporting the patient, if necessary, and for managing emergencies;
  - appoint the person who will be a member of the Quality Control Group.

- The anaesthesiologist must:
  - define the patient's care plan, prior to hospitalization, on the basis of the information previously received from the surgical team, and inform the patient about the procedure itself and about the periprocedural risks according to their evaluation;
  - describe the anaesthesia procedures used in the clinical diary in accordance with the policy of the Centre;
  - participate in drawing up the information sheets or check-lists as agreed when planning the IORT.

SURGICAL PROCEDURE

- The Surgeon:
  - may modify the surgical incision to improve the view of the operating field, or to improve exposure and centring of the target;
  - provides accurate haemostasis so as to allow adequate vision of the organs at risk (OAR) and of the target and to avoid accumulation of fluids in the treatment area;
  - reports the surgical procedures used;
  - participates in drawing up information sheets or check-lists, if any.
- The Surgeon and the Radiation Oncologist:
  - make an accurate intraoperative assessment of the extent of the disease in relation to the feasibility and appropriateness of performing an IORT treatment;
  - cooperate in defining the target (tumour or tumour bed) and any structure involved or adjacent to the target that might be inside the treatment field.
- The persons responsible for the surgery units involved in the IORT program or their delegate, shall:
  - participate in the initial planning of the IORT;
  - agree on the procedures and resources that are to be available during the performance of the IORT;
  - appoint the members of the Quality Control Group.

MANAGEMENT OF EMERGENCIES

- Each Centre shall draw up:
  - a list of the main surgical and anaesthesiology emergencies that might occur when transporting the patient and the procedures to be adopted where such emergencies were to occur;
  - the procedures for verifying who is available and the resources deemed necessary for prevention and first intervention in case of an emergency (one or more check-lists);
  - a periodical program for updating the staff and checking the reliability of resources.

FOLLOW-UP: GATHERING AND CLASSIFYING SIDE EFFECTS / ADVERSE EVENTS

- It is recommended to:
  - carry out integrated follow-ups, to identify signs of toxicity due to recurrence of the disease.

INFORMED CONSENT

- It is good practice for the person delivering the treatment to administer the informed consent form to the patient.
- Regarding the Informed Consent procedure for IORT treatment, please refer to the paragraph on Informed Consent above.

INDICATIONS FOR TREATMENT WITH ELECTRONS AND PHOTONS

◆ **Clinical, histological, biomolecular and radiological criteria for the main pathologies**

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.

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.

ONE 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.

B2. PHYSICAL AND DOSIMETRIC ASPECTS IN ELECTRON IORT

PHYSICAL AND DOSIMETRIC ASPECTS

The physical and dosimetric commissioning should include:

- **Characterization of accelerator beams and of measurement instrumentation which includes:**
  - dosimetry in reference conditions;
  - dosimetry in non-reference conditions, possibly supported by Monte Carlo simulations for the evaluation of the PDD, profile and isodose curves, and of the OFs;
  - reproducibility of the output of the beam used (or of the beams that can be used) on the day of treatment, according to the typical timing of the switching on/off, irradiation and shutdown phases of the accelerator.
- **Definition of the treatment technique which requires:**
  - the definition of the treatment set-up, for which the dosimetric evaluations made during the beam characterization are applied;
  - the dosimetric characterization (or the estimate, also on the basis of references from the literature) of the backscattered radiation component from any internal shields, especially those having a high atomic number.
- **Definition of the method for verifying the treatment set-up (visual-tactile, ultra-sound, radiological, ...);**
- **Definition of the technique for assessing the target thickness which implies:**
  - identifying the most appropriate measurement system and defining the operating methods (needle, ultrasound probe, RX imaging);
- **Implementation of the clinical treatment modality on the accelerator consolle;**
- **A method for calculating the MUs, in terms of point dose, to independently verify the number of MUs provided by the system;**
- **The implementation of the TPS, if any;**
- **The implementation of in vivo checks (dosimetric/geometric) during treatment which requires:**
  - definition of the purpose of in vivo measurements;
  - definition of the dosimetry system and method for positioning the dosimeter, on the basis of the selected treatment set-up;
  - Dosimetric characterization and absorbed dose calibration of the dosimeter ;
  - method for dose calculation and, where active dosimeters are used, definition of the levels of attention/intervention.

DOSIMETRY IN REFERENCE CONDITIONS

- Dosimetry in reference conditions should be carried out for all the energies used for the treatments, using a reference applicator having a square section of 10 cm x 10 cm or a circular section with a diameter of 10 cm, with a flat end and with an SSD of 100 cm (if not available, use the nominal SSD);
- Traceability of dose measurements to a national primary standard of absorbed dose to water should always be assured by using dosimeters calibrated by a Primary laboratory or by an accredited dosimetry calibration laboratory;
- For beams with low dose per pulse (i.e., less than 10 mGy):

  - application of the IAEA TRS-398 protocol is recommended for the choice of the ionization chamber type to be used, the definition of the reference measurement depth and the determination of correction factors;

- For beams with high dose per pulse (i.e., greater than 10 mGy):
  - plane parallel ionisation chambers can be used, provided that the effects of ion recombination are adequately evaluated. For the reference measurement depth and the correction factors other than the correction factor for ion recombination, the application of the IAEA-TRS 398 protocol is recommended;
  - the use of a dosimetry system with response independent of the dose per pulse such as Fricke dosimetry or alanine is an optimal choice as long as traceability to a primary standard of absorbed dose to water is established. The depth of the maximum dose is recommended as reference depth.

DOSIMETRY IN NON-REFERENCE CONDITIONS

- Dosimetry in non-reference conditions should be performed for each applicator, energy and SSD in clinical use and at a dose rate equal or as similar as possible to the treatment dose rate; it should include the PDD curves, dose profiles at fixed depth, OFs and various correction factors identified by the MU calculation protocol adopted by the Centre;
- The detector reference point must be positioned on the clinical axis of the beam for PDD and OF determinations;
- The ionization chambers can be used for measuring the PDDs and the OFs following the recommendations of the IAEA TRS-398 protocol;
- Solid state detectors (silicon diodes and microDiamond) and radiochromic films can be used for PDD, profile and OF determinations;
- Fricke dosimeters and alanine dosimeters can be used for OF determination;
- For the selection of the dosimetry system, consider that:
  - in the case of ionization chambers, the depth-ionization curves must be converted into depth dose curves;
  - in the case of beams with high dose per pulse, to improve measurement accuracy, it is recommended to use ionization chambers that require corrections for ion recombination that have a weak dependence on the measurement depth;
  - in the case of solid state detectors (diodes and microDiamond), it is necessary to ascertain that the detector response is almost independent of energy and angle and to assess dose rate and dose per pulse dependence in the range of interest;
  - radiochromic films can be specifically used in periodic controls for which, due to the possible difficulties of placing the films in water, the use of plastic phantoms is allowed, in accordance with the indications provided in the dosimetry protocols;
  - Fricke and alanine dosimeters are independent of energy and dose per pulse and therefore are particularly suitable for high-dose-per-pulse-beams. However, given the size of Fricke dosimeters, in particular situations (e.g. for low energy electron beams or for bevel or flat applicators with a diameter of less than 5 cm) it may be necessary to apply a correction factor that takes into account the non-uniformity of the dose distribution in the dosimeter sensitive volume.

IN VIVO DOSIMETRY

- The implementation of in-vivo dosimetry techniques is recommended, through dosimeters placed at the entrance or exit of the treatment volume;
- the resolution of geometric criticalities (identifying an adequate and stable treatment set-up) and assurance that the detector has and can maintain the correct position during irradiation are absolute prerequisites;
- under the above specified conditions, and being confident in the reproducibility of the daily output of the IORT system, the in-vivo in-field dosimetry in clinical practice should be understood as an independent tool to verify the delivered dose and to intercept abnormal irradiation conditions that could result in absorbed doses being significantly different from the prescribed doses;
- the use of active dosimeters allows online verification of the delivered dose, with the possibility of defining, for in-field measurements, appropriate levels of attention and intervention for changes in the MUs to be delivered;
- in addition to dosimetric evaluations the applicator-target-shield alignment can be verified by using extended passive dosimeters;
- the use of dosimeters in contact with internal shields, especially if with high atomic number, should be carefully considered, given the possible variations in dosimeter sensitivity with the energy spectrum of the backscattered radiation;
- operationally, once the position of the dosimeter for in-vivo measurements has been defined, it is recommended, for each energy used:
  - to characterize the dosimetry system;
  - to define and verify the algorithm for calculating the absorbed dose, assessing the different coefficients and correction factors;
  - to define levels of attention/intervention, if any (if active dosimeters are used).

QUALITY CONTROL

- The definition of a strict quality control program for the accelerator and its accessories, for the measurement instrumentation, and for the TPS used, if any, helps to maintain high quality performance standards;
- quality controls must be planned according to a precise schedule (periodic), after each major maintenance intervention and, in any case, whenever there are signs of inadequate operation of the accelerator and/or its related accessories, and of the measurement instrumentation;
- the protocol for quality controls must be tailored to the specificities of the accelerator and its accessories, also by discussing them with the manufacturer, who has full knowledge of their physical and dosimetric characteristics;
- among the quality controls on accessories, particular attention must be paid to the visual inspection of the applicators which, if not properly managed in the washing and sterilization phase, could undermine the collimation, homogeneity and symmetry of the treatment beam;
- for each control, each Center must also define the corrective actions to be adopted when tolerance values established in the protocol for quality controls are exceeded;
- checks and their frequency, must be planned according to the actual modes of use of the accelerators and related accessories.
- Operationally, it is recommended:
  - to carry out the measurements at dose rates that are equal or as close as possible to the treatment dose rates;
  - to assess the appropriateness of carrying out measurements in a water-equivalent solid phantom, determining in advance any correction factors that may be required.

B3. PHYSICAL AND DOSIMETRIC ASPECTS IN IORT WITH RX (INTRABEAM, Zeiss)

PHYSICAL ASPECTS

- In IORT with low-energy photons, the source is inserted inside the surgical bed and irradiates the target volume from the inside;
- the source produces 40-70 kVp X-ray beams with an almost spherical geometry;
- the source is fixed to a flexible, precision arm which allows the applicator to be easily set in any position;
- the equipment is easy to transport and suitable for being used in any operating room;
- spherical, flat kV-IORT applicators are available with a flat emission geometry for surface therapy; they can be sterilized and reused;
- the prescription at the applicator surface entails a high variability in the minimum dose to the target tissue and requires extrapolation. It is recommended to prescribe the dose at a given distance (e.g. 1 cm) from the applicator surface;
- the depth dose, corrected for the output of the machine measured during the quality controls performed before treatment, is used to calculate the irradiation time;
- tungsten-impregnated rubber sheets can be positioned around the point of application of the source, wrapping the treated area, thus providing a shield against the radiation emitted from inside;
- the additional anaesthesia time during IORT varies from 20 to 50 minutes, and depends mainly on the diameter of the applicator used.

COMMISSIONING

- Even though the dosimetric calibration of Intrabeam systems is carried out by the manufacturer, it is recommended that each Centre performs independent measurements of delivered doses;
- the source does not allow measurements in conditions of “good geometry”, that is why traditional dosimetry protocols are not easily and readily applicable;
- dosimetry measurements can be carried out using an ionization chamber for low energy X-rays (plane parallel chamber with a thin entrance window (< 4 mg/cm2) calibrated in terms of air kerma), converting the reading into dose using the IPEMB method for low energy sources (HVL 1-8 mm Al) or very low energy sources (<1mm HVL). The HVL of the Intrabeam source (0.85–1.30 mm Al) straddles the two IPEMB ranges.

◆ **Dosimetric measurements in points other than the point chosen as reference**

- Use of a plane parallel ionization chamber for low energy X-ray beams in a water phantom or radiochromic films.

◆ **Measurements for each applicator**

– dose rate curves as a function of the distance from the source for each available voltage-current combination;

– dose distribution at a constant distance from the spherical applicator (e.g. d = 5 mm and d = 20 mm).

◆ **Use of radiocromic films**

In positions where the space occupied by the ionization chamber (“backward” directions) prevents measurements from being made.

◆ **Temperature measurements**
In contact with the applicator surface.

QUALITY CONTROLS

- The following controls are performed on each source before treatment:
  - integrity of the applicators;
  - mechanical deflection of the probe;
  - alignment of the electron beam inside the probe (Dynamic offset);
  - emission isotropy; dose rate.
- Controls of the emission isotropy and of the dose rate are mandatory before each treatment session on each source to be used.

IN VIVO DOSIMETRY

- In vivo dosimetry is an independent verification of the dose delivered to the patient in the absence of a personalized treatment plan;
- the use of dosimeters with high spatial resolution and good energy response such as MOSFETs, TLDs or radiochromic films, positioned on the skin, is recommended.
- the dosimeters can be calibrated using the same source or a similar source (e.g. for superficial radiotherapy) in terms of peak voltage and HVL.

GLOSSARY

Accredited calibration laboratory. A suitable laboratory in technical and organizational terms that ensures the best accuracy in determining the accelerator output.

Active dosimetric systems. Dosimeters whose response allows immediate determination of the dose.

Acute side effects. These are side effects that occur in healthy tissues relatively quickly, usually within 90 days after IORT or combined treatment; they are mainly oedema, exudation, erythema.

Alanine. Amino acid whose chemical composition, electronic density, effective atomic number and physical density are very similar to those of biological tissues and to water. It can be used as a reference and transfer dosimeter, and for in vivo dosimetry.

Applicator for IEORT. Plastic tube which usually has a circular cross section. Hooked to the accelerator head, it confines the electron beam and defines the size of the treatment field. Usually bi-sectioned, it can have a flat or angled tip. It can be of the "contact" or "non contact" type with regard to the surface of the irradiated volume.

Applicator for kV-IORT. Made of various materials, usually of different shapes (spherical, cylindrical, needle-like, flat, ellipsoidal). Hooked to the X-ray source, these applicators define the target treatment distance.

Check-list. Tool to facilitate the correct and complete sequence of activities that make up a procedure. Operators are invited to review the various steps shown in the checklist, ticking them off as they are performed. The use of a checklist presupposes the definition of the various steps of a procedure indicating who is responsible for the execution of each step.

Clinical axis. Axis perpendicular to the surface of the phantom (or of the irradiated volume) which intersects the geometrical beam axis at the surface of the phantom (or of the irradiated volume). For flat applicators the clinical axis coincides with the geometrical beam axis.

CTV (Clinical Tumor Volume). Probable or certain anatomical region (if documented with extemporaneous histological examination) where the microscopic tumor residue is located; in the case of radical surgery, it is generally represented by the tumor bed, by the regional lymph nodes or by the areas contiguous to the macroscopic tumour lesion.

Dedicated accelerator. Accelerator specially designed to perform IEORT in common operating rooms. Dedicated accelerators are mobile and, compared to conventional accelerators, they have greater degrees of freedom of the head and the stand (to facilitate treatment set-up).

Documentation. Analytical description of the anatomical areas, of the doses delivered to the irradiated volume and to the organs at risk, according to the reference points. It must include a description of the surgical specimen, of the surgical procedure (radical surgery, debulking, exposure, etc.), and of the technical and dosimetric modalities of the IORT.

Dose at the surface. Dose absorbed by the tissue, at the surface. It can be measured with a suitably calibrated dosimeter, having adequate characteristics, positioned on the surface of the tissue.

Dose due to photon contamination of the beam (bremsstrahlung tail). In electron beams there is always a photon field produced by the braking processes (bremsstrahlung) of the electrons themselves; it consists of two components: the main one, is generated by the electrons along the path in the accelerator head, the other is due to the absorption of electrons by the patient. The dose due to photon contamination is determined from the depth dose curves by extending the measurements beyond the practical range of the electrons (bremsstrahlung tail).

Dosimetry in non-reference conditions. Dosimetric characterization of radiation beams (depth dose curve, dose profiles, Output Factor).

Dosimetry in reference conditions. Measure of the absorbed dose to water applying the conditions of reference defined in the dosimetric protocol.

Emergency. Any event of a medical, physical or dosimetric nature, not foreseen nor foreseeable, which occurs during the intraoperative radiotherapy procedure and implies its immediate interruption.

Entrance dose. Dose absorbed by the tissue at maximum dose depth. It can be defined through a measurement using a suitably calibrated dosimeter, positioned on the surface of the tissue.

Fricke dosimeter. Chemical dosimeter with a ferrous sulphate solution, contained in a sealed glass ampoule, for measuring the dose absorbed in water under reference conditions.

GTV (Gross Tumor Volume). Macroscopic tumor lesion; it is represented by the tumour as a whole in case of inoperability and tumor exposure only, or by any macroscopic residue in case of non-radical surgery (debulking). It is not present in the case of microscopically radical surgery.

Hard-docking. For IOERT with a contact applicator, hard-docking is the coupling procedure between the upper part of the applicator (already positioned on the accelerator head) and the lower part of the applicator (already positioned on the surface of the anatomical area to be irradiated of the accelerator).

Information sheet / form. Tool for identifying the information required to carry out a specific process and for providing support for storage of the information. The signature on the document, or on its specific parts, identifies the person responsible for the compilation.

Informed consent. A tool for providing patients with clear and exhaustive information describing the proposed medical intervention. Informed consent must be obtained before carrying out any medical-surgical procedure; indeed, Article 32, section 2 of the Italian Constitution states that “no one can be obliged to undergo any specific health treatment except under the provisions of the law” and that “the law cannot, under any circumstances, violate the limits imposed by respect for the human person”. The patient’s consent is therefore indispensable, specific, personal and cannot be delegated. According to the rules of Good Clinical Practice, the conditions that qualify the soundness of consent are at least 3: quality of the information and how it is presented, its comprehensibility and the patient’s decision-making ability and freedom. Obviously, informed consent on intraoperative radiotherapy, like all invasive medical treatments, requires that the patient be provided with details describing the method, including technical notes and possibly study protocols, a description of possible benefits and side effects, name of contact staff, and information about how the patient’s

details will be processed (privacy regulations); information must be provided also about therapeutic alternatives. It is good practice that the informed consent form be administered by the specialist performing the treatment. The informed consent form is to be attached to the Medical Record.

Late side effects. These are side effects that occur in healthy tissues some time after IORT, generally after 90 days; the most typical are fibrosis, neuropathy, vasculopathy, and loss of sensory-motor functions.

Non reference conditions Conditions of measure for the dosimetric characterisation of the electron beams.

Non-dedicated accelerator. Conventional accelerator for transcutaneous photon and electron beam radiotherapy, located in a bunker with a tertiary collumation system which houses the electron beam collimators for IOERT.

Organs at risk (OAR). Tissue or organ, which due to radiosensitivity and contiguity/coincidence with the treatment field could be the site of acute or late complications, therefore, such as to influence the dose prescription and/or the manner in which the treatment is executed.

Output. The output is the dose delivered per Monitor Unit (for the IOERT) and per unit of time (for the kV-IORT) assessed at the point of maximum dose. It is a function of the energy of the beam and of the size of the applicator.

Passive dosimetric systems. Dosimeters whose response is analyzed after irradiation.

Perioperative complications. These are complications that occur in the immediate postoperative period and may be related to the anaesthetic or surgical procedures and, more specifically, to the manoeuvers required to carry out the IORT treatment; examples are surgical site infections, suture dehiscence, bleeding, and/or delays in surgical healing.

Prescribed dose. Dose deemed necessary by the radiation oncologist to achieve the purpose of IORT treatment (eradication or palliation), compatibly with predictable and acceptable complications.

PTV (Planning Target Volume). This is a geometric rather than an anatomical concept and is represented by the volume on which treatment is planned; it must take into account the possible sources of uncertainty related both to the identification of the CTV and to geometric causes.

Reference conditions. The definitions for every energy of electrons beams, of the material and dimensions of the phantom, type of dosimeter, SSD, dimensions of the field, depth and methodology of measurement of the absorbed dose to water. They are defined in detail in every dosimetric protocol. The absorbed dose to water under reference conditions is simply the product of the response of the dosimeter by the calibration factor, without the need of introducing corrective factors. For IOERT, the set-up established by the dosimetry protocol of reference.

Report. Tool for providing a clear description of the procedures carried out in accordance with the recommendations of the reference documents. This document must be signed by the person in charge of the procedure as agreed in the planning of the IORT treatment.

Reproducibility of the beam output (in the short term). Beam efficiency stability, determined as the coefficient of variation of a consecutive series of measurements.

Reproducibility of the beam output (long-term). Stability of the beam yield. The regularity check is performed before each treatment and on a scheduled basis as part of the periodic quality control program.

Secondary collimators (photon jaws). If present in the accelerator head, these are diaphragms that delimit the irradiation field. The opening of the diaphragms may be established by the manufacturer.

Soft-docking. For IOERT with a non-contact applicator, soft-docking is the alignment procedure between the applicator (already positioned on the accelerator head) and the anatomical area to be irradiated.

Target volume. Volume of tissue that must receive the dose planned by the radiation oncologist according to the purpose of the IORT treatment (eradication or palliation), with limits for acceptable complications.

Tumour or operative table. Tissue adjacent to the excised gross tumor disease (GTV) where the probability of finding tumour cells is higher and which is therefore at greater risk of local recurrence.