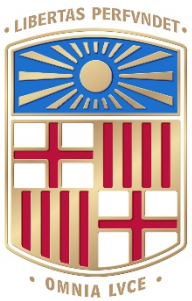

UNIVERSITAT DE BARCELONA

Final Degree Project

Biomedical Engineering Degree

"Analysis of the existing technologies in intraoperative radiotherapy"

Barcelona, June 7, 2023

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ABSTRACT

Intraoperative radiation therapy (IORT) involves the application of a high radiation dose to the tumor bed during surgery, after removing the tumor through conventional surgery techniques. IORT technique allows a direct application of the radiation to the tumor site, increasing the dose received and allowing the retraction of the normal tissues from the radiation field. The use of intraoperative radiotherapy has gained popularity in the last years due to the development mobile, self-shielded IORT systems that allow the delivery of radiation in the operating room.

The different IORT modalities that are currently used in clinical practice are intraoperative electron radiotherapy (IOERT), low-kV X-ray IORT and high-dose-rate intraoperative radiation therapy (HDR-IORT). Each modality has distinct characteristics pertaining to the equipment used, radiation beams employed, associated costs, and optimal clinical scenarios in which they can perform.

This work aims to provide a comprehensive analysis of the characteristics of the different IORT modalities. The findings of these research may provide useful insights and guidance for clinicians and healthcare providers in choosing the most appropriate intraoperative radiation modality for their clinical practice.

Keywords: intraoperative radiotherapy, mobile electron accelerators, low-kV IORT, HDR-IORT

ACKNOWLEDGMENTS

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GLOSSARY OF ABREVIATIONS

IORT	Intraoperative radiotherapy
IOERT	Intraoperative electron radiotherapy
HDR-IORT	High-dose-rate intraoperative radiotherapy
OR	Operating room
ISIORT	International Society of Intraoperative Radiation Therapy
SSD	Source–surface distance.
PMMA	Polymethyl methacrylate
PTFE	Polytetrafluoroethylene
IRM	Internal radiation monitor
H.A.M	Harrinson-Anderson-Mick
DICOM	Digital imaging and communications in medicine
LINAC	Linear accelerator
QA	Quality assurance
mR/h	milliRoentgen per hour
PDD	Percentage depth dose curve
R_{100}	100% depth in water used as the beam quality index for electron beams
R_{90}	90% depth in water used as the beam quality index for electron beams
R_{50}	Half-value depth in water used as the beam quality index for electron beams
R_{10}	10% depth in water used as the beam quality index for electron beams
ELIOT	Electron intraoperative radiotherapy
TARGIT	Targeted intraoperative radiotherapy
EBRT	External beam radiation therapy
WBS	Work Breakdown Structure
PERT	Program Evaluation and Review Technique

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1. INTRODUCTION

1.1 Context and justification

Nowadays, millions of individuals worldwide are affected by cancer, and its treatment can be challenging and complex. The use of radiotherapy is crucial in cancer treatment, as 50% of cancer patients will undergo radiation therapy over their cancer course. In the last decades, a modality named intraoperative radiation therapy has appeared allowing the delivery of a high and single dose of radiation during surgery to tumor cells, minimizing potential damage to surrounding healthy tissues. IORT has been postulated as an innovative and promising technique in cancer treatment that seeks to optimize the interaction between surgery and radiation. Firstly, it acts on the minimum residual tumor, thus reducing the chances of recurrence. Secondly, it avoids the interval of time between surgery and postoperative external radiotherapy, because IORT directly administers the radiation in the operating room (OR) avoiding the transport of the patient to the shielded bunker.

This work evaluates the different IORT technologies available, which are intraoperative electron radiotherapy, low-kV IORT, and HDR-IORT. Electron IORT uses a linear accelerator that directs the electron beam using a collimator to the target tumor. In the case of low-kV IORT, it uses a miniature X-ray source that is placed directly to the surgical cavity to deliver radiation. Finally, HDR-IORT is based on placing a flexible catheter to the tumor bed delivering a high dose of radiation, typically using iridium-192 which is controlled remotely. So, the characteristics of each IORT modality will be evaluated, capturing all the information needed for making decisions on selecting the most suitable option for use in operating rooms.

1.2 Objectives and scope

Ultimately, the goal of the project is to evaluate the different intraoperative radiotherapy technologies considering several factors. The study aims to determine which option is the most effective, efficient, and feasible for use in clinical practice, with the aim to guide healthcare professionals and decision-makers in making informed choices about intraoperative radiotherapy technologies.

1.3 Structure and methodology

The body of the present paper presents several sections, each one with a specific focus. The first part aims to introduce the different IORT technologies and analyze various technical aspects about

them. To achieve this, a previous theoretical study of the three main modalities used in IORT has been conducted and a market analysis has been performed. Then, the technical specifications of different equipment are explained as well the room environment in which they work. The next section of the project is focused on the radiation beams used in the different IORT modalities. A thorough examination of the main concepts related to their energies and dose distributions of the different modalities is conducted. Additionally, the succeeding part of the paper involves a detailed study of the different clinical situations in which IORT is used, with the aim to evaluate the effectiveness of the different modalities in treating patients. This analysis will provide valuable insights into the clinical utility and benefits of each modality, as well as their limitations.

The next phase of the project focuses on the proposed advancements in various IORT technologies, alongside the development of a comparative table to assess the most suitable option for IORT. Subsequently, the following section delves into the implementation of IORT, examining the key stakeholders involved and their expectations. Lastly, an economic analysis of the different modalities is conducted, accompanied by a comprehensive evaluation of the legislative and regulatory aspects surrounding the implementation of IORT.

The project has been conducted between January 2023 and June 2023 with the collaboration of the Hospital Clínic de Barcelona. Throughout the research and development of the process, guidance from Dr. Albert Biete was provided, providing valuable insights for the correct development of the whole study.

2. BACKGROUND

2.1 General concepts

Intraoperative radiotherapy is a modality of radiation therapy that involves delivering a high and focused dose to the surgical site or to an unresectable tumor during surgical procedure, while protecting and moving sensitive structures away from radiation. The radiation delivered in IORT is administered in a single fraction during a surgical procedure while the patient is under anesthesia, using the surgical incision to direct radiation directly to the tumor bed and having visual control of the treatment volume and the healthy tissues to be excluded [1].

The use of IORT has several benefits, including the delivery of an elevated dose, a reduction of the total administration treatment time, a meticulous targeting of the affected region, and the preservation of healthy tissues [2]. IORT has the capacity to reduce tumor regeneration by delivering high radiation doses, and apart from apoptosis and mitochondrial detention in cancer cells, it provides an instantaneous necrotic impact. It is estimated that when IORT is applied, the biological effect of the effective dose is maximized, estimating that it has two to three times more efficacy than fractionated external radiotherapy. Moreover, it has been noted that IORT mitigates the secretion of cytokines that encourage cellular repair and proliferation, reducing the risk of the proliferation of tumoral cells that are residual [3]. Finally, IORT is used to treat unresectable tumors, resectable tumors with residual disease that is difficult to eliminate after surgery, and high-risk tumors for local recurrence (combined with radiochemotherapy and chemotherapy), describing its use as a boost to the conventional external radiation treatment [4].

2.2 State of the art

The feasibility of IORT in cancer was reported as early as 1905 by Comas and Prió [5], with the main goal to spare healthy tissues from radiation and treat deep tumor lesions that couldn't be reached with external therapy due to limited penetration of X-rays. In the 1960s, Abe et al. [6] from University of Kyoto started to use electrons to administer IORT in various intra-abdominal tumors, with the main advantage that electrons reduced the exposure time required and offered the possibility of collimating them to the desired shape. Nonetheless, a primary challenge faced by IORT was its implementation within conventional radiotherapy treatment rooms, which were located separate from operating rooms. Consequently, the patient needed to be transported to the radiotherapy bunker after surgical intervention, exposing the patient to potential surgical risks.

Then, in the mid 1990s, the availability of high-dose-rate equipment and mobile linear accelerators that could be used directly in the operating room facilitated the diffusion of IORT. Nowadays, IORT is widely used and its benefits in certain types of cancers have been achieved. In Spain, the "Clínica Universitaria de Navarra" where the first patient was treated in 1984 and the "Hospital General Universitario Gregorio Marañón" are the notable centers of activity and serve as a reference for IORT technique [7].

In addition, an International Society of Intraoperative Radiation Therapy (ISIORT) Europe program has been created, where data from centers active in intraoperative radiation therapy is collected in a database, allowing to know the treatment modalities for the main tumor types effectively treated in international centers that use IORT.

Overall, in the context of IORT there are three different modalities available, each one referring to different approaches and techniques used to deliver radiation therapy during surgery. These modalities include electron IORT, low-kV X-rays, and HDR-IORT.

2.2.1 Electron IORT

In the context of intraoperative radiation therapy, mobile accelerators can operate directly within the operating room. These accelerators are designed to be mobile and flexible, allowing a precise positioning for optimal treatment delivery. The designs of the mobile accelerators are specialized for producing low stray radiation by avoiding materials with high atomic number, which can contribute to increased bremsstrahlung. Mobile electron accelerators also incorporate special techniques for beam focusing, which help to reduce interactions between defocused electrons and the beam line and accelerator structures. As a result, they produce significantly lower stray X-ray radiation compared to conventional radiotherapy accelerators. Then, to create different field sizes, electron beam is collimated with the use of cylindrical applicators of different diameters, which play a crucial role on tailor the requirements of each case [8].

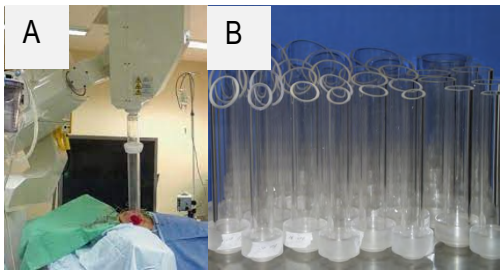

Figure 1. A) Mobile electron accelerator in an operating room B) Cylindrical applicators used in electron IORT

These sterilized applicators are inserted into the surgical opening by the surgeon and the radiation oncologist. The applicator is positioned in a way that directs the beam through the underlying target tissues and its alignment is adjusted by moving the accelerator to the correct position and angle

[9]. Additionally, in a IORT procedure it is necessary to bring together the lateral walls of the excision cavity to create a compact target volume that can be covered by the applicator. Treatment volume is generally several centimeters thick, and the selection of the electron energy is based on achieving a deposition of 90% of the maximum dose at the deeper side of the target area. A big limitation of IOERT is that it can only be used in areas accessible for the applicator. Narrow cavities or areas where treatment delivery requires a turning corner may not be accessible for the applicator. Consequently, IOERT may be less feasible in sites such skull base, deep pelvis, and retropubic areas which are frequent sites of residual disease after maximal surgical resection of cancers in those locations [10].

Currently, there are three commercially available linear accelerators on the market. One of the linear accelerators is manufactured by the American company Intraop Medical Corp, called Mobetron. The others include Novac 7 (no longer commercialized), developed by the Italian company Hitesys, which has transitioned to another company called Sordina IORT technologies, which is currently developing Novac 11 and LIAC in various versions.

2.2.1.1 Mobetron

Mobetron is an equipment mounted on a C-arm gantry, which is attached to a stand that has the accelerator cooling system and a transportation system. Mobetron weights 1400 kg approximately, which includes an absorber shield to block the radiation if it is not aligned. The mobile unit has a length of 224 cm, width of 109 cm and a minimum height of 198 cm. Gantry is flexible and movable, allowing rotation and movement. Mobetron includes a modulator rack, a lightweight control console, and connecting cables, and its transportation is accomplished using a pallet jack at the rear of the gantry stand, allowing it to fit in many elevators. Additionally, the control system features dosimetry readout, accelerator controls, interlock status, and treatment viewing video. Mobetron produces electron beam energies of 4,6,9 and 12 MeV. Dose rate ranges from 2.5 to 10 Gy/min at Source-surface distance (SSD) of 50 cm with applicator of 10 cm diameter. Mobetron applicators range from 3 to 10 cm (flat) and 3-6 cm (beveled), offering angles of 0º, 15º, 30º and 45º for optimal targeting. Plastic bolus (5-10 mm) can reduce surface irregularities. IntraOp radiotranslucent accessories enable 3D treatment planning and dose calculation [11].

Figure 2.The Mobetron electron accelerator used in IORT

2.2.1.2 Novac 11

The first model named Novac 7 (Hitesys SpA, Italy 1997) is an accelerator with 3, 5, 7, 9 MeV energies. The Novac 11 is the evolution of Novac 7 and has a range of energies available from 4 to 10 MeV and a stand structure with a form of an articulated arm with four rotational joints. The mobile unit weights 630 kg approximately, with a length of 235 cm, a width of 95 cm, and a minimum height of 235 cm. The dose rate for the reference applicator is in range of 4-30 Gy/min. Beam collimation is performed by PMMA (methyl methacrylate) applicators. Applicators are hard docked, and they consist of cylindrical tubes of 5 mm thickness, with diameters ranging from 3 to 10 cm and angles go from 0 to 45º to allow their correct positioning on the target surface. The length of its reference applicator is from 80 cm. A mobile radiation protection barrier and a horizontal beam absorbed are provided. To protect organs and tissues, the manufacturer provides with polytetrafluoroethylene (PTFE) and steel discs [12].

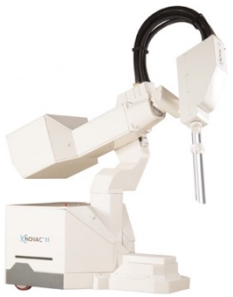

Figure 3. The Novac electron accelerator used in IORT

2.2.1.3 LIAC HWL

The LIAC HWL is the latest version of LIAC with a weight of 570 kg. Its mobile unit has a length of 210 cm and a width of 76 cm, with a minimum height of 180 cm. The LIAC HWL offers 5 degrees of freedom: 3 for the treatment head (elevation, rotation, and pitch) and 2 for the mobile unit, enabling movement in the operating room. It also has four clinical energy points, which are 6, 8, 10 and 12 MeV, and a dose rate between 10 and 30 Gy/min. LIAC HWL uses PMMA applicators with diameters from 3 to 12 cm and angles 0º, 15º, 30º and 45º to allow the applicator positioning on the surgical gap. These applicators allow the visualization of the surgical gap because they are transparent. LIAC HWL applicators are also compatible with RX images. The applicator length is 40 cm and have an SSD of 64.5 cm. To protect the organs and tissues near the target, some PTFE disks are used, which are biocompatible and sterilized and have diameters of 6, 7, 8, 9, 10 and 11 cm. Additionally, a Monte Carlo simulation software facilitates the LIAC commissioning and the dosimetry characterization of the accelerator beams, like the dose profiles or isodose curves [13].

Figure 4.The LIAC HWL electron accelerator used in IORT

2.2.2 Low-kV IORT

In the last years, there has been an increase of the use of mobile IORT devices that use low-kV X-rays. The X-rays are produced at a maximum operating voltage of 50 kV, which has the advantage

of having a dose gradient pronounced. Consequently, no special shielding is needed and the interaction between the patient and the medical team can take place during the treatment. As this modality is commonly used with spherical applicators, one disadvantage is that it requires the bed to have the more spherical shape as possible, reaching a maximum irradiation depth in the tissues of 1 to 2 cm. Some examples of low-KV mobile IORT devices are Intrabeam (Carl Zeiss) and Axxent Electronic Brachytherapy system (Xoft Inc).

2.2.2.1 Intrabeam

The Intrabeam radiotherapy system (Zeiss Surgical, Oberkochen Germany) is in direct contact with tumor bed, through the surgical incision to deliver radiation. The Zeiss Intrabeam workplace doesn't exceed the 155 kg and the floor stand weights 285 kg, allowing it to be easily moved within the operating room and from one room to another thanks to a platform with rollers. The floor stand also has a six-axis mechanical arm and electromagnetic brakes for precise positioning during irradiation. The Intrabeam system uses a miniaturized accelerator, where the electrons emitted by the cathode are accelerated through the drift tube with a maximum difference of potential of 50 kV. It features a 10 cm probe and 3,2 mm in diameter, whereby accelerating electrons onto a gold target, low energy photons are distributed isotropically. The effective emitted X-ray radiation energy rapidly reduces dose deposition due to its low energy (~$1/r^3$) allowing effective shielding of healthy tissue while targeting the treated lesion. The Intrabeam is also composed by a control unit, a dosimeter, and other components necessary. Real-time dose monitoring is provided by the internal radiation monitor (IRM), displayed on the software graphical user interface for treatment monitoring [14].

In Intrabeam spherical applicators are the mostly used to treat breast cancer, varying from 1.5 to 5 cm diameter. These applicators are biocompatible, and are made of polyetherimide or stainless steel, enabling them to be reused. Other types of applicators like flat and surface ones are also available. Full digital imaging and communications in medicine (DICOM) offers customizable integration of Intrabeam into hospital infrastructure ensuring secure data exchange. Intrabeam integrates 3D treatment planning simulation software for IORT operations, with the possibility of dose computation near critical organs with Monte Carlo algorithm to correct tissue heterogeneity [15].

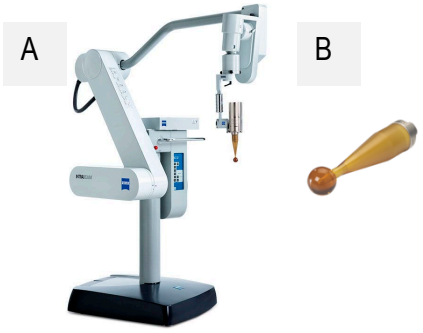

Figure 5. A) The Zeiss Intrabeam system used in IORT. B) Spherical applicator used by Zeiss Intrabeam system

2.2.2.2 Axxent Xoft

Axxent Xoft is an electronic brachytherapy device operating at energy between 20 and 50 kV. The system is designed to deliver doses of X-ray radiation directly to the excised tumor bed when the physicians desire to deliver intracavitary or interstitial radiation to surgical margins. Radiation is delivered by a disposable, microminiature X-ray source located at the end of a flexible cable. The X-ray source at the distal tip of the cable is inserted into the central lumen of the appropriately sized applicator. It does not utilize a radioactive isotope, or require an HDR isotope afterloader, and thus does not require the heavily shielded treatment rooms necessary for the delivery of isotope based HDR brachytherapy. When treatment is intended, a trocar is used to create a pathway for the applicator via a centimeter-sized skin incision. A stiff metal is placed in the balloon applicator to help guide it into cavity. The applicator is positioned, for example in breast cavity and inflated with sterile saline. Ultrasound, plain film, or computed tomography is used to verify the position of the applicator and ensure the cavity is filled. Prior to each treatment, the probe with the electronic activated source is advanced to the central lumen of the applicator. A typical plan requires the source to be stepped through 5-10 dwell positions. Water is pumped continuously during the treatment in the cooling sheath to provide cooling. The controller has a display showing the elapsed time, the time planned, time remaining at the current dwell position and a visual display of source position [16].

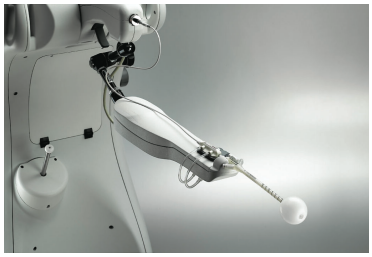

Figure 6. The Axxent Xoft system used in IORT

2.2.3 HDR-IORT

Intraoperative radiotherapy using high-dose-rate brachytherapy was introduced in the late 1980s to deliver a high dose of radiation during surgery while minimizing damage to surrounding healthy tissues. The procedure involves the use of a remote-controlled after-loading device containing the radioisotope. Specialized applicators and catheters are used to guide the radioactive source to the target area. A treatment planning must be done to calculate precisely how long the source needs to remain in different positions on the treatment volume. HDR brachytherapy requires specific equipment, facilities, and software for treatment planning and delivery [17]. Different applicators are developed like the Harrinson-Anderson-Mick (H.A.M). As being the vehicle through which the source travels, applicators must provide maximum adaptability to the surface of the bed to be treated at the time of irradiation, which is often curved body surfaces. Consequently, they need to be flexible and transparent. This applicator has the capacity to house several catheters through which the radiation source is positioned, generating uniform dose distributions at certain depths.

Different applicators, such as the H.A.M, have been developed to adapt to curved body surfaces and deliver uniform dose distributions at specific depths. The H.A.M applicator is made of liquid silicone rubber and contains multiple hollow tubes for positioning the radioactive sources [18].

HDR-IORT offers advantages like better adaptation to curved surfaces, irradiation of small volumes, and the possibility of treating the skin. The treatment duration typically ranges from 20 to 30 minutes, and the maximum irradiation depth is 0.5 cm.

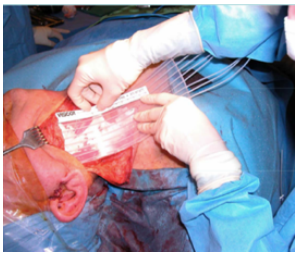

Figure 7. HDR-IORT applicator in a IORT clinical procedure

2.3 State of the situation

In the IORT field there are different technologies and equipment used, each one with different characteristics. As we have seen, one technology commonly used is the electron accelerators, which have distinct features such as heavy weight and large dimensions. Additionally, electron accelerators have greater depth of penetration and dose homogeneity relative to HDR-IORT and low-kV IORT. Although they have the advantage of deliver high radiation doses in short time, their size and cost can pose challenges in terms of mobility and accessibility. Moreover, low-kV X-ray machines are also frequently used in IORT, which are more maneuverable and have steep dose gradients. This modality does not need special shielding requirements. The spherical applicators used in low-kV IORT have a limited depth penetration and are well suited for spherically target volumes like in breast cancer. Another important technology is the HDR-IORT, which involves the use of a remote afterload system and a small radioactive source to deliver a precise dose. HDR-IORT machines provide a steep dose fall-off, allowing the delivery of high doses specifically to the tumor bed while minimizing doses to nearby structures.

All the three methods have a set of advantages and disadvantages, and each of them is best suited for one situation or another. However, there are few studies that compare the different technologies available for IORT. This lack of direct comparison makes it difficult to determine which technique is most effective and efficient when treating cancer patients. Therefore, there is a need for further research on comparing the different technologies and their effectiveness in different clinical situations.

3. MARKET ANALYSIS

The field of IORT has undergone continuous development over the past few decades. Although still considered a relatively new and evolving technology, IORT holds tremendous potential to revolutionize cancer treatment in the near future. Over the years, new technologies have been developed including advancements in equipment, imaging, and dosimetry to improve the delivery of radiation during surgery. An increase of cancer incidence is projected to drive the intraoperative radiation therapy, as it will increase its demand. Additionally, the implementation of IORT in hospitals reduce the number of radiation treatments required per patient and allows a decreased need for conventional equipment, which is viewed as a positive factor in the market of this devices. However, the lack of skilled personnel to operate with IORT equipment and some preferences for conventional radiotherapy may hinder the market growth.

Based on geography, the market is segmented in North America, Europe, Asia, and the rest of the world. North America is expected to have the largest share of the market followed by Europe in the following years.

3.1 Main manufacturers of IORT equipment

There are different companies, hospitals, and universities that are currently working on IORT. The major companies in the market are implementing various strategies, such as launching new products and focusing on new acquisitions. Some key players in the market are:

- Ariane Medical Systems Ltd
- Eckert & Ziegler
- Elekta AB
- Intraop Medical Corporation
- Sensus Healthcare Inc.
- Sordina IORT Technologies
- Varian Medical Systems Inc
- Carl Zeiss Meditec AG.

4. CONCEPTION ENGINEERING

As stated before, this project aims to identify the most suitable option for IORT by analyzing the key characteristics of each modality. The operational features, radiation beams, and clinical situations associated with each modality are important characteristics that will be discussed in the following parts.

4.1 Equipment and operational room characteristics

First, it is crucial to analyze the equipment and operational room characteristics associated with each option. This analysis allows us to assess the characteristics of the equipment, its compatibility with existing infrastructure, and the operational requirements needed to ensure the successful delivery of IORT.

4.1.1 Equipment and operational room characteristics in electron IORT

Electron IORT devices allow to treat patients in the operating room. Although they have certain mobility and can move within the surgical area, some accelerator positions for surgical set-ups are not possible due to interference with treatment table. The ceiling and entrance room height and the OR dimensions must be sufficient for the use of intraoperative accelerators, and the floor capacity must have at least 500 kg/m^2 [19]. The room where accelerator is located may be lined with materials such as lead or concrete, which can absorb radiation. These accelerators can be equipped with an integrated, gantry mounted beam stopper, that follows the movements of the accelerator head, ensuring the precise alignment with gantry position, including when underneath with the surgical table. This beam stopper also blocks the machine if the beam shield is misaligned, and horizontal protection barriers should be included to contain scattered radiation. The scattered radiation at 3 m from the patient plane should be less than 0.3 μSv/Gy [11].

Electron accelerators can work in an operating room respecting its specific characteristics in terms of cleaning possibility, noise, and heat dissipation. The mobile unit of electron accelerators is the one placed in the OR near the patient with a remote-control device. The control unit remains outside the operating theatre and controls the equipment and is connected to mobile unit through several cables. Mobile structure is sterilized with adequate disinfecting vapors, and control console only requires regular cleaning. Electron accelerators are equipment of plug and use. Only by connecting the mobile and control unit with a cable the system can be connected.

The electron accelerators like LIAC need to connect directly to the hospital power supply, and their installation requires approximately 200-240 VAC with a frequency of 50-60 Hz and a separate safety ground connection. Additionally, the maximum electrical current that equipment draws in treatment is about 10 - 11 Amperes. For the case of the Mobetron, it requires a three-phase electrical power which costs about 7,000 € for an operating room. The wiring of Mobetron consists of two-line wires and a separate safety ground. Mobetron power cord connects using an AC power plug and receptacle. Additionally, the power consumption of electron accelerators is approximately 2-3 KVA, which refers to the power that the devices consume during operation [20]. Then, in the following table the technical specification of one equipment LIAC HWL are specified [21].

Table 1. Technical specifications of a mobile electron accelerator

LIAC HWL TECHNICAL SPECIFICATIONS	
Manufacturer	S.I.T – SORDINA IORT TECHNOLOGIES SPA
Device Classification	Type II
Design structure	Irradiating unit, control unit and applicators
Emission	Electron beam
Type of structure	Linear accelerator (LINAC)
Remote Control	Yes
Nominal energies	6, 8, 10 and 12 MeV
Working Environment Conditions	
Maximum operating temperature	25ºC
Temperature operational room	+18ºC to +25ºC
Relative humidity operational room	30% - 75% non-condensing
Temperature storage room	+10ºC to 50ºC
Relative humidity storage room	30 – 90%
Device design – Technical features	
Tension	230 V

LIAC HWL TECHNICAL SPECIFICATIONS	
Nominal frequency	50 Hz
Power consumption	3 kVA
Power environment dissipation	0.8 kW
Current intensity	11 A
Isolation resistance	>100 MΩ
Protective ground	<0.2 Ω
Dispersion current	<2.5 mA
Surface dose	>90% (12 MeV)
Field symmetry	<3%
Pulse repetition frequency	5 – 50 Hz (depend on selected energy)
Beam current	<1.5 mA
Long term stability	<3%
Short term stability	<1%
Dosimetry symmetry linearity	<1%
Dose rate (applicator 10 cm diameter)	10-30 Gy/min
Stray X-ray radiation (PDD Bremsstrahlung tail)	<0.4%
Source-surface distance (SSD)	64.5 cm
Uniformity of field flatness (value at maximum energy bevel angle 0º for applicator 10 cm diameter)	<7%
Translation mobile unit	2 freedom degree
Rotation mobile unit	3 freedom degree
Mobile unit dimensions	76 x 210 x 180 cm (width, depth, height)

LIAC HWL TECHNICAL SPECIFICATIONS	
Weight mobile unit	570 kg + (< 230 kg of shield)
Control unit dimensions	80 x 60 x 120 cm (width, depth, height)
Control unit weight	120 kg
Applicator length	40 cm
Applicator size	3, 4, 5, 6, 7, 8, 9, 10, 12 cm with each bevel angles 0º, 15º, 30º, 45º
Applicator material	PMMA

Additionally, the quality assurance (QA) is very important for accelerators used in radiation therapy. It involves checking the readiness of the equipment, proper connection and remote controls, verification of the equipment movements, verification of the emergency devices, or ensure the integrity of the applicators. Moreover, the quality and accuracy of the radiation beam should be assessed, by performing symmetry and flatness tests to assess the uniformity of the radiation field in water phantoms. Also, the stability of the electron beam through the percentage depth dose curves is assessed. In Table 2, a summary of the assurance recommendations for mobile electron accelerators is provided, with their frequency and tolerance [22].

Table 2. Quality assurance protocol for mobile electron accelerators

PARAMETER	FREQUENCY	TOLERANCE
Verification of accelerator startup, warm up and shutdown procedures	Before each treatment	Functional
Verification of audible warning devices, safety, and emergency systems	Before each treatment	Functional
Output constancy	At least every week and before each treatment	3%

Energy constancy	At least every week and before each treatment	Range of energy ratios of 2 mm shift in depth dose
Mechanical motions and stopping operators of motors	At least every week and before each treatment	Functional
Integrity of applicators	At least every week and before each treatment	Integer
Reproducibility of beam output. Long-term stability of the dosimetry monitoring system	At least every week and before every treatment	±3%
Flatness and symmetry constancy	Monthly	3%
Docking system	Monthly	Functional
Beam Quality (R_{50})	Monthly	±1 mm or ±5% (reference applicator =100 mm)
Output calibration for reference conditions	Annually	2%
Percent depth dose for standard and selected applicators dose profiles	Annually	2 mm in depth over the range of clinical interest
Monitor chamber linearity	Annually	1%
Applicator output factors	Annually	2-3%

Finally, to ensure that the electron accelerators have proper utilization, conservation, and longevity of the equipment, a strict maintenance service should be done, consisting of both preventive and corrective measures. For preventive maintenance, it is recommended to have at least three maintenance visits per year, with intervals not exceeding four months. For corrective maintenance in equipment malfunctions, a prompt response is crucial and there should be a technician's

response of less than 24 hours. To ensure that patients can receive their treatments without interruptions or delays, the electron accelerators should be available for 96% of the time equipment can work. Finally, maintenance service should also handle management and storage of necessary materials required for repairs. A sufficient stock of spare parts is needed to ensure timely responses.

4.1.2 Equipment and operational room characteristics in low-kV IORT

The use of low-kV X-ray equipment offers significant advantages in radiation protection and facility costs. The low-energy radiation makes conventional walls sufficient to stop the scattering of radiation produced in the OR. Then, personnel present in room can wear lead aprons, allowing to interact with the patient. Measurements indicate a radiation exposure of 12-15 mR/hour at about 2 meters from source. The electrical requirements of the Intrabeam includes a power supply of 100-240 V, 50/60 Hz. The system should be proper connected on the grounding system. The power consumption is approximately 400 VA. The mobile, miniature X-ray is provided by a 12-V supply and the maximum beam current is 40 μA [14]. The next table collects all the technical characteristics of the Intrabeam equipment.

Table 3. Technical specifications for a low-kV X-ray equipment

INTRABEAM 600	
Manufacturer	Carl Zeiss Meditec AG
Device Classification	Type II
Design structure	Intrabeam Stand Floor and Intrabeam Workplace. It has fully enclosed cart that provides: Control Console 600, Computer, Touchscreen Monitor, Keyboard, Mouse, UNIDOS E (Dosimeter), Ionization Chamber, V-guide.
Type of structure	X-ray radiation therapy system
Emission	Radiation source XRS4. Electrons are emitted by cathode, accelerated by an electrical field along a drift tube inside the X-Ray source and hit a gold target resulting in the generation of X-rays.
Method of treatment	Intraoperative, intracavitary, interstitial, post-operative

INTRABEAM 600	
Working Environment Conditions	
Maximum operating temperature	25ºC
Temperature operational room	+15ºC to +40ºC
Relative humidity operational room	30% - 75%
Temperature storage room	-20ºC to 70ºC
Relative humidity storage room	10% – 90%
Device design – Technical features	
Tension	(100 V): 100 V (115 V): 110 V - 125 V (230 V): 220 V - 240 V
Nominal frequency	50 - 60 Hz
Power consumption	400 VA max
Maximum Power Range	2W (50 kV x 40 µA)
Maximum radiation output	0.6 Gy/min (at 2cm from isocenter)
Maximum photon energy	50 keV
Geometry of dose emitted (without applicator)	Mostly spherical
Dose fall-off (in water)	~$1/r^3$
Maximum Beam Current	40 µA
Weight floor stand	285 kg
Workplace unit dimensions	90 × 60 x 169 cm (width, depth, height)
Control unit weight	max. 155 kg
System Quality Assurance (SQA) Tools	Probe adjuster ionization chamber holder (PAICH), photo diode array (PDA), ionization chamber (IC)

INTRABEAM 600	
Radiation Treatment Planning Software	Radiance
Compatible Applicators	INTRABEAM spherical applicators, flat applicator set, surface applicator set, needle applicator

Intrabeam system incorporates different QA tools proper functioning of the equipment. The system is calibrated with the specific depth dose curves and reference measurements with the ion chamber integral to the system. Before each treatment, two-step quality control check is done to ensure all parameters are well defined. A shielded water phantom verifies dose distribution, and an internal radiation monitor detects the X-ray photons emitted and records dose output in real-time. So, in an operating room, the doctor examines the cavity and inserts the applicator on it. An ultrasound image is employed to verify the positioning of the applicator. Subsequently, the physicist enters the applicator size and prescription dose into the computer system, with the dose at the surface being prescribed. A comparison is then made between the computed calculated time and a ready-made look-up table before proceeding to treat the patient. In the following table, a summary of the assurance recommendations for low-kV equipment is provided [23].

Table 4. Quality assurance protocol for a low-kV X-ray equipment

TEST/PROCEDURE	FREQUENCY	TOLERANCE
Optic and acoustic warning devices of the radiation	At least every week and before each treatment	Functional
Stability of the reference dose and the internal radiation monitor	Before each treatment	±3%
Mechanical checks on probe straightness	Before each treatment	Functional
Verification of the dose symmetry and isotropy	Before each treatment	±5%
Temperature and Pressure check	Monthly	± 1ºC and ± 2mbar
Alignment (Probe adjuster)	Monthly	0.1mm
Steering (Dynamic offsets)	Monthly	0.1mm

Environmental dose survey	Six monthly	According to local legislation
Chamber constancy check	Six monthly	±1%
Internal radiation monitors linearity with dose	Annually	±3%
XRS4 calibration. Distance dose curve should be measured for every voltage and current settings and compared with those taken at the time of the commissioning using the water phantom	Annual check	±5%
User chamber and electrometer returned to standards laboratory to update calibration factors	Every 2 years	-

There are also some characteristics regarding the general conditions and maintenance of these type of equipment. First, the maintenance company should perform software and hardware updates of the equipment. A minimum of three annual visits should be conducted. The continuous downtime of the equipment should not exceed three days. In one month, there should not be more than two downtimes that exceed 24 hours from notification time. The service company should also provide a training program for personnel to learn how to use the equipment.

4.1.3 Equipment and operational room characteristics in HDR-IORT

A shielded operating room is required for HDR-IORT facility. Doors will always carry lead inside, and it is advisable that at the entrance there is a labyrinth or a corridor that makes it difficult for the direct beam to reach the door. The room will also have security systems that prevents the access to it during the treatment by placing a “closed door” microswitch and a radiation monitor with an alarm. In a radioisotope based HDR brachytherapy treatment room, no one except the patient himself can remain inside during the irradiation moment. When the HDR-IORT must be developed, the remote after loading machine is transported by the physicist and brachytherapy technologist and cleaned with antiseptic before entering the operating room. So, applicator is in contact with

area at risk using sutures or packing to hold the applicator in place. Packing is used to displace normal tissues like large bowel, bladder, and small intestines. Lead shields are also located to reduce dose to normal structures in contact with applicator. Applicators are then connected to the HDR machine, staff leaves the room, and patient is prepared to treatment using remote after loader control. In HDR-IORT is very important the automatic retraction of the source when all the dwell positions in each channel have been treated or when potentially dangerous situations arise. Some of these dangerous situations can be an obstructed source-guide tube, the open of the treatment room door, operation of the interrupt switch on the console and operation of one of the emergency switches [24]. Afterloaders used in IORT commonly have a power supply of 110 – 220V, with a power consumption of 500 VA, approximately. The following table represents information from an afterloader commonly used in HDR-IORT, which is the Varisource.

Table 5. Technical specifications for an HDR-IORT afterloader

Varisource afterloader	
Manufacturer	Varian
Intended Use	High Dose Rate Brachytherapy
Maximum source strength	407GBq
Maximum Surface Dose	<0.5 μGy/h at 1 m
Working environment conditions	
Ambient Temperature	15 - 35°C
Relative Humidity	30% - 75%
Atmospheric Pressure	70 kPa - 110 kPa
Device design – Technical features	
Power Requirements	110 - 220 V
Power Consumption	550 VA
UPS	Yes
Rotation of head	No (rotate unit)
Variable Height head	No
Dimensions	61 x 56 x 107 cm (length, width, and height)

Varisource afterloader	
Weight	142 kg
Treatment Length in Catheter	70 to 150 cm
Source material	Enriched iridium
Source position verification	Internal, allows daily QA of source positioning accuracy
Number of channels	20
Step increment	2 - 99 mm
Source travel	150 cm
Storage safe	Tungsten

Quality assurance in HDR-IORT involves several aspects to ensure treatment accuracy. It includes daily hardware functionality checks, treatment planning system, applicator position, and imaging system. Treatment planning verifies applicator digitization, channel lengths, dose reference points, and dwell-time calculation. Prior to sterilization, it is important to check the catheter length and intensity, as well as the labels on the equipment. After the treatment, it is also very important to inspect applicator integrity to ensure it has not been damaged. Completion of quality control tests should be documented and signed by responsible personnel [25].

Table 6. Quality assurance protocol for an HDR-IORT equipment

TEST/PROCEDURE	FREQUENCY
Emergency systems to withdraw source	Daily test
Door interlocks on the treatment room	Daily test
Interrupt button on control console	Daily test
Emergency stop button	Daily test
Interruption of the power supply	Daily test
Source positioning	Daily test

Room radiation monitors	Daily test
Check applicators integrity, internal shields, welds, and joints.	Monthly
Iridium-192 in IORT requires replacement every 3-4 months due to radioactive decay. Other sources with different half-lives need adjusted exchange intervals, and regular quality assurance tests should be conducted at least 3 times per year.	Quarterly tests

4.2 Investigation of radiation beam characteristics in IORT modalities

In this section, the radiation beams of the different modalities will be examined, focusing on the characterization of the beams used, their energy, penetration depth, and spatial distribution.

4.2.1 Energy and dose distribution analysis in electron IORT

For the case of electron IORT treatment, a single radiation field is delivered at a fixed distance between the radiation source and the target. This approach requires careful treatment planning and the calculation of monitor units, considering the choose of an appropriate energy and applicator to achieve the desired dose distribution. As commented before, currently available accelerators offer electron beams with energies that range from 4 to 12 MeV, with increments of 2 MeV or 3 MeV, resulting in a penetration increase of approximately 7-10 mm per step. When intermediate penetration is required, a water equivalent bolus can be inserted between the applicator and the patient to achieve the desired result [26].

The dosimetry of the LIAC equipment has been studied, as it is the mobile electron accelerator present in Hospital Clínic. In Figure 8 the representation of dose deposition with depth is represented, illustrating the percentage depth dose (PDD) at various energies. Notably, we can observe an initial raise reaching 100% at certain depth, followed by a decrease of PDD as depth increases. LIAC uses cylindrical applicators for beam collimation, which causes greater decrease in the average of beam energy at the end of applicator due to multiple scattering of electrons from applicator wall. We can also determine that in any case, the surface dose is not lower than 85% of the maximum dose measured on the axis for all energies.

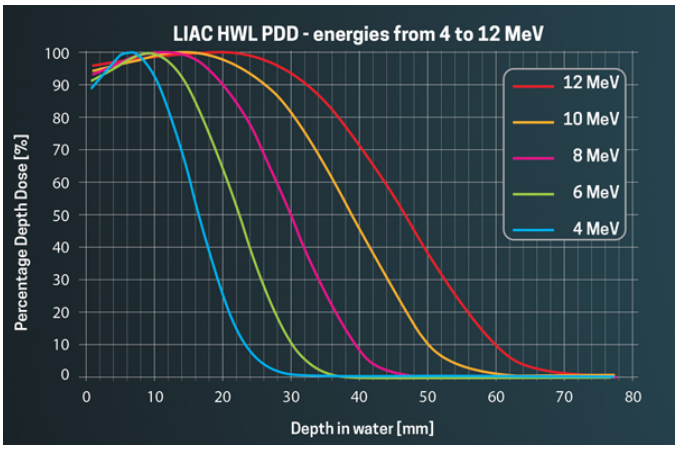

Figure 8. LIAC HWL Percentage depth dose comparison across various energies [22]

A study made by Baghani et Al. [27] shows the PDD profiles along the clinical axis for 10 cm beveled applicators at different energies. Results indicate that PDDs of beveled applicators exhibit a more rapid decrease compared to flat applicators. The decrease in penetration depth is more evident as bevel angle increases, resulting in a narrower penetration range along the clinical axis. Moreover, the use of beveled applicators leads to an increase in surface dose due to the oblique incidence of the electron beam. These findings highlight the importance of considering the impact of beveled applicators during treatment planning for electron IORT.

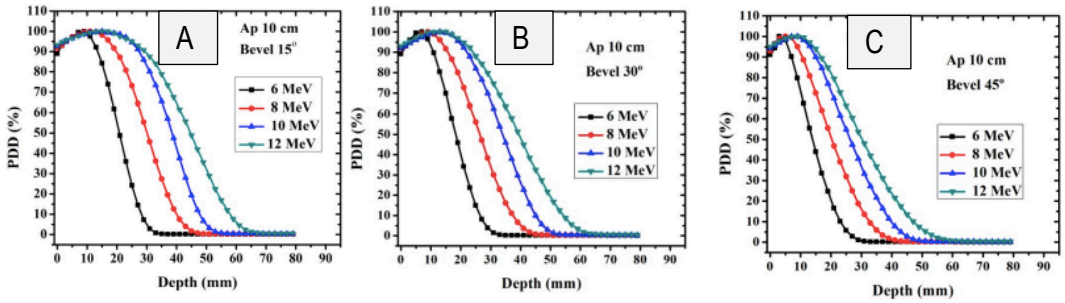

Figure 9. Percentage depth dose (PDD) variation with depth for different beveled applicators and energies. A) PDD for a 15º beveled applicator. B) PDD for a 30º beveled applicator. C) PDD for a 45º beveled applicator [27]

Table 7 represents key beam parameters extracted from the PDD analysis of LIAC using 10 cm circular applicator [22]. The parameters include R_{90} and R_{50}, which indicate the penetration distances where the dose reaches 90% and 50% of the maximum dose, respectively. Moreover, the table displays the corresponding dose rates for LIAC in the range 4-10 MeV, ranging from 2 to 20 Gy/min. The last row of the table represents the data obtained from LIAC HWL (12 MeV), which has dose rates ranging from 10 to 30 Gy/min, depending on the selected energy and installed applicator. Moreover, the dose per pulse reaches the 45 mGy for the 12 MeV configuration. In conclusion, these beam parameters provide insights into dosimetric characteristics of mobile electron accelerators, aiding in treatment planning and optimization for effective intraoperative radiotherapy.

Table 7. Percentage depth dose parameters for LIAC [22]

Nominal Energy (MeV)	R_{100}(mm)	R_{90} (mm)	R_{50}(mm)	R_{10}(mm)	Dose rate (Gy/min)
4	8	11	16	23	3
6	10	15	22	30	4
8	14	20	30	38.5	8
10	16.5	25.5	39	49	16

12	25	38	46	59,5	27

In Figure 10 we observe that the congruence between the theoretical parameters from Table 7 and the obtained values at Hospital Clínic is evident [22].

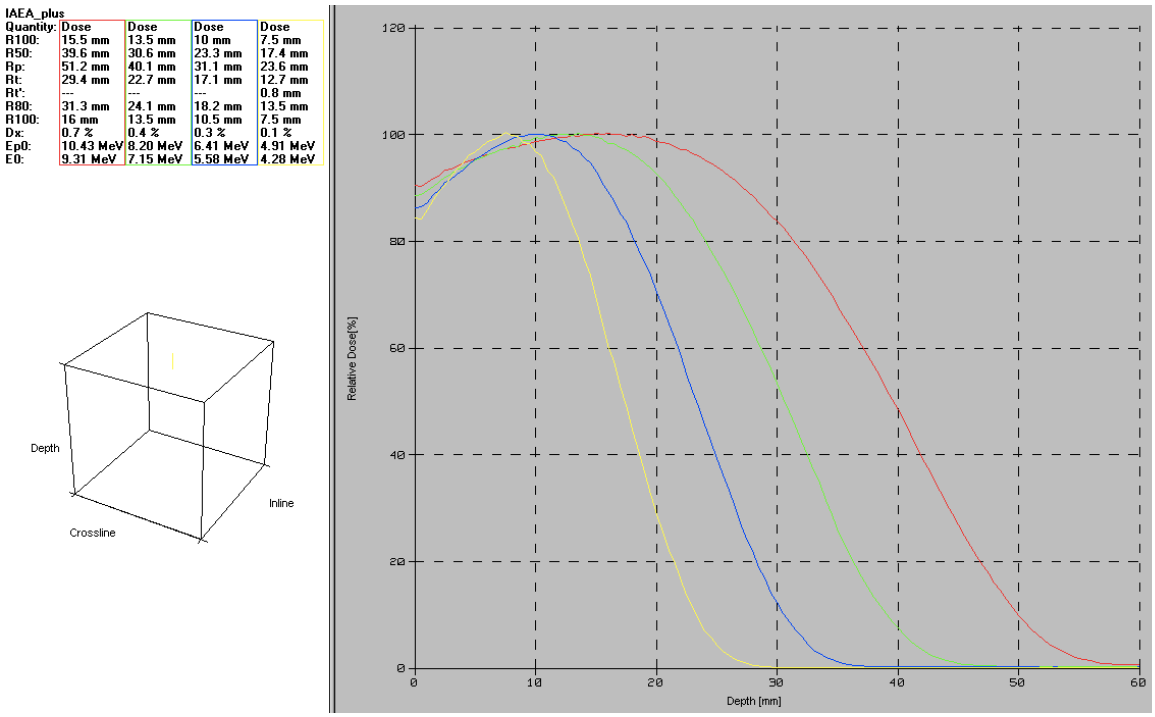

Figure 10. Calibration of LIAC at Hospital Clínic [22]

Finally, since the dose profiles of electron beams are only flat in the central region, applicator must be selected approximately 2 cm larger than target diameter to cover all the volume with the reference dose [28].

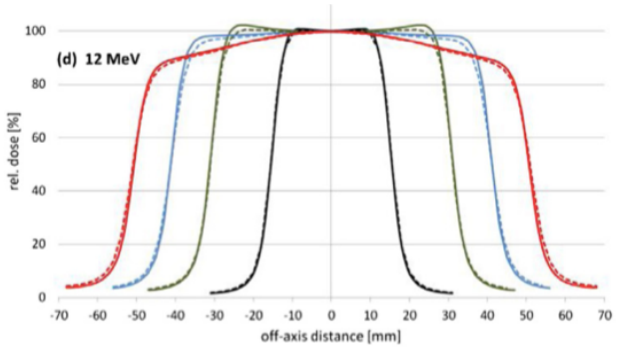

Figure 11. Transverse dose profiles for applicators of varying diameters [28]

4.2.2 Energy and dose distribution analysis in low-kV IORT

In this section, the dosimetry characteristics of the low-kV equipment are discussed, focusing specifically on the Intrabeam system. The devices of this modality generate low energy X-rays, resulting in a rapid dose fall-off from the radiation source. In the spherical applicators used in Intrabeam, dose is prescribed at the applicator surface, and it drops to 28-37% of the surface dose at a distance of 10 mm from the applicator, and to 11-20% of the surface dose at 20 mm distance. In comparison to electron IORT doses, the dose levels achieved at 1 cm in low-kV IORT result in around 46-80% of the electron doses. Similarly, at 2 cm, the dose levels achieved range from 22% to 40% of the electron doses. To deliver a treatment, the required delivery time needs to be calculated to achieve the desired dose at the distance of interest. Consequently, dose-rate distance curves are calculated for these applicators.

A work made by Zhenhua Xiao et al. [29], shows the dose rate measured as a function of the distance from the surface for spherical applicators with diameters ranging from 1.5 to 5 cm. It can be observed how the dose rate is the highest at the surface of the applicators, which falls as the distance increases. Also, the dose rate varies significantly with the size of the applicator, because for small diameter applicators, dose rate is high reducing treatment times. Consequently, as applicator diameter increases, the falling gradient in dose rate slows down.

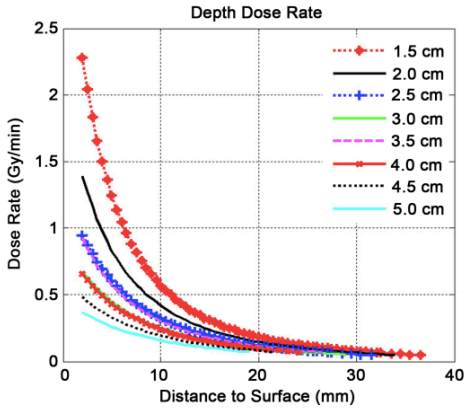

Figure 12. Depth dose rate curve for Intrabeam spherical applicator [29]

In the following figure the dose distribution for a 4.5 cm diameter spherical applicator is presented, with a 20 Gy dose prescribed at applicator surface. We can see how at 10 mm the 20 Gy dose would result in 6.4 Gy, and at 20 mm it would result in 2.7 Gy. Consequently, the limited region and depth of treatment may restrain these applicators from its potential in clinical application [29].

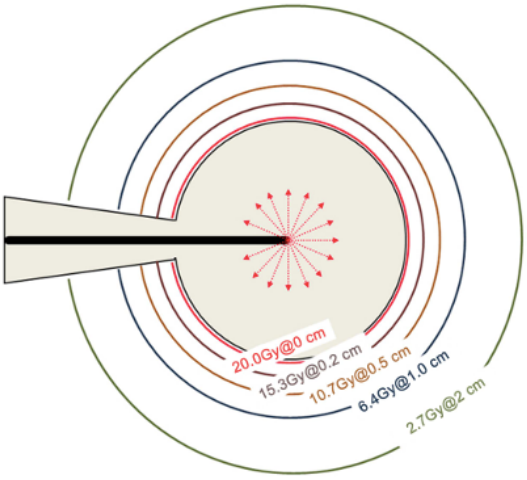

Figure 13. Dose distribution for a 4.5 cm diameter spherical applicator with 20 Gy prescription at the surface [29]

Moreover, the Northwestern Memorial Hospital Department of Radiation Oncology conducted a study using the Zeiss Intrabeam system with a prescription dose of 20 Gy [30]. The output achieved was about 2.3 Gy/min, and they obtained the following times to deliver the dose prescribed at certain distances. The table results suggest that larger applicator sizes in low-kV IORT result in increased delivery time for the specified dose, both at the surface and at deeper distances. The time difference between applicator sizes becomes more pronounced as the depth increases. Therefore, careful consideration of applicator size is essential in optimizing treatment efficiency and ensuring accurate dose delivery in these procedures [31].

Table 8. Influence of applicator size on time required to administer specified dose at various distances [30]

Applicator size (mm)	Time to deliver dose at surface (min)	Time to deliver dose at 5 mm (min)	Time to deliver dose at 10 mm (min)
30	29.76	56.32	95.83
35	21.3	44.08	79.22
40	29.43	57.32	97.53
45	39.65	72.59	118.91
50	52.47	92.12	145.26

An important consideration in the application of the device is the effect of tissue inhomogeneities and the dose absorption in such inhomogeneities. When applicator is not adhered perfectly to the skin, air gap between applicator and skin causes a decrease in the dose due to scattered radiation. For measurements in a 4 cm diameter applicator, a 2 mm air gap reduces the dose 15%.

Additionally, the presence of bone may also be a dose-limiting factor because a dose increase to bone can be produced, leading to significant decrease in the dose beyond the bond structure [32].

Intrabeam also employs flat applicators where the dose uniformity perpendicular to the beam direction is at 5 mm, as it can be seen in Figure 14. In addition, with a prescription of 10 Gy at 5 mm, 19.4 Gy would be delivered in skin-surface. Larger applicators are characterized by superior dose homogeneity, low surface dose, smaller output factor and larger treatment times. Flat and surface applicators provide a uniform planar dose which is useful in abdomen regions, for example [33].

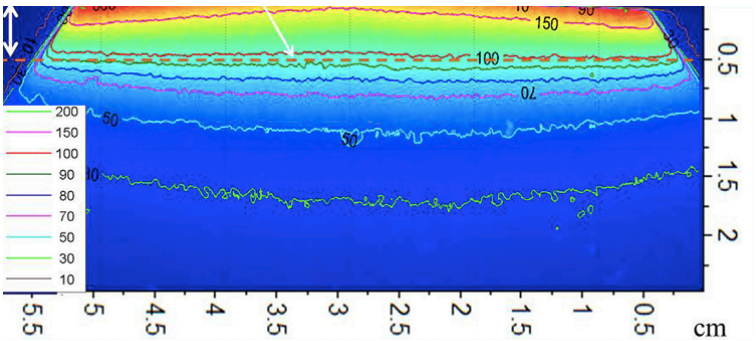

Figure 14. Dose distribution for a flat applicator [33]

4.2.3 Energy and dose distribution analysis in HDR-IORT

In HDR-IORT the typical treatment depths involve the surface of the applicator as well as depths of 0.3 cm, 0.5 cm, and 1 cm from the applicator surface. Moreover, the pre- scribed dose at 1 cm, 2 cm and 3 cm is reduced to approximately 70%, 50%, and 35%, respectively [34]. The flexible intraoperative template is a 0.5 cm thick flexible silicon template that contains the parallel catheters spaced 1 cm apart (Figure 15). The shape of it can be rectangular or corners can be cut to conform target area. Treatment planning is performed considering the flexible template, and active dwell positions are chosen according to the size and shape of it. Dose is specified normally at 1 cm from the surface of the template [35].

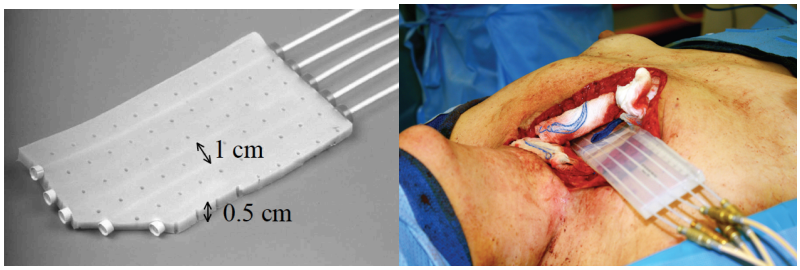

Figure 15. A) Flexible intraoperative template used in HDR-IORT [35]. B) Flexible applicator located to deliver treatment. [36]

Then, in the following graph the dose vs distance along an axis perpendicular to the applicator at its center is represented for different thickness. We clearly see how dose decreases rapidly with distance, and that how doses are higher with the more thickness applicator. However, if we want to achieve improved flexibility, the applicator thickness needs to be reduced [24].

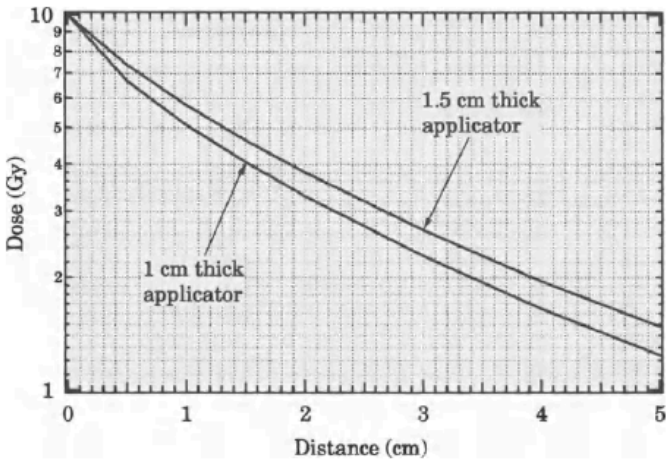

Figure 16. Dose variation with distance for different applicator thicknesses [24]

Additionally, in the following table, some delivery times for various applicator sizes and depths is displayed [37]. We can observe how in HDR-IORT, the time needed to deliver 10 Gy to various treatment depths increases with larger target sizes due to the increased volume that needs to be irradiated. As the treatment depth increases within a given target size, more tissue needs to be traversed by the radiation, resulting in longer delivery times. The larger target sizes require significantly more time for dose deposition, emphasizing the importance of considering target size when planning HDR-IORT treatments.

Table 9. Time required in HDR-IORT to administer 10 Gy at different treatment depths based on target size [37]

	Time to deliver 10 Gy to various treatment depths (min)		
Target size (cm x cm)	**0 cm depth**	**0.5 cm depth**	**1 cm depth**
3 x 3	2.6	5.2	6.9
5 x 5	5	8.3	11.3
10 x 10	12.8	19.9	22.3
20 x 20	37.5	53.3	66.6

4.3 Analysis and comparison of clinical situations for IORT

In this section an analysis and comparison of how each modality works in different clinical situations has been developed. First, some clinical indications are explained, referring to various cancer types where IORT is applied. Moreover, an analysis and comparison of how the three modalities perform in frequent treatment locations is explained. Finally, this section assesses the benefits and utility of IORT in clinical practice. The analysis helps healthcare professionals in evaluating the effectiveness of IORT and make informed treatment decisions depending on the cancer type they need to perform.

4.3.1 Exploring clinical indications for IORT

To promote a scientific approach to the IORT activity, the International Society of Intraoperative Radiation Therapy (ISIORT) has been found. It records information of IORT treatments using its database registry, focusing on clinical and technical aspects, tumor characteristics, or treatment data. In a pooled analysis done by Pr. Krengli et al. [38], until 2013 a total number of 7,196 IORT procedures were recorded, with more than 80% of the cases being females, and around the 95% of the treatments being applied with electron linear accelerators. The analysis revealed that the highest number of cases treated with IORT belonged to breast cancer, accounting for 5,659 cases (78.7%), followed by rectal cancer with 643 cases (8.9%) and soft tissue sarcoma with 262 cases (3.6%). The objective of the ISIORT analysis is to offer a comprehensive understanding of patient selection practices, and the invaluable data it provides serves as an asset for developing forthcoming clinical trials with the purpose of determining the impact of IORT in a personalized multimodal treatment approach.

4.3.1.1 Breast cancer

As stated before, the percentage of patients treated for breast cancer is about 80% of all the IORT, and this percentage has been quite stable over the last few years. In the 2013 ISIORT study, data from 5,659 women with breast cancer were collected, showing that in more than the 94% of the cases IORT was identified as a component of radical treatment for primary newly diagnosed disease. In a smaller proportion of cases (5.8%), IORT was employed as an approach to manage localized recurrent breast cancer. Moreover, the 2014 pooled study [39] revealed that the most used applicator had a diameter of 6 cm, accounting for 38% of the cases. In the majority of instances (77%), this applicator was employed with a beveled angle of 0º. Subsequently, the

predominant energy utilized was 9 MeV, accounting for 25% of the cases, followed closely by 6 MeV at 24%. Only a small fraction of cases (8%) utilized the low kV modality of 50 kV. Finally, the study specified that in 52.2% of all indications, IORT was used as a single radiation treatment (with doses from 16 to 21 Gy), and in 47.8% of the cases IORT was used as a boost before or after external beam radiation therapy (EBRT).

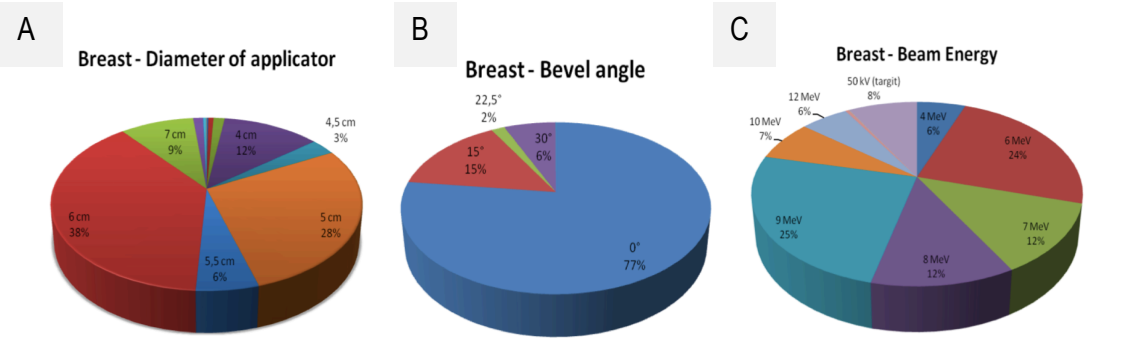

Figure 17.A) Distribution of applicator diameters in breast cancer (%) B) Beveled angles utilized in breast cancer (%) C) Distribution of beam energies employed in breast cancer (%) [39]

4.3.1.2 Rectal cancer

In the ISIORT analysis performed in 2013, around 643 patients with rectal cancer were treated with the main purpose to enhance local control in cases of locally advanced high-risk disease and in recurrent tumors where therapeutic failure is primarily attributed to pelvic relapse. In rectal cancer, the achievement of R0 resection is the most important prognostic factor for local control. According to the study, in rectal cancer IORT was employed in 86% of the cases as a treatment for primary disease. Additionally, a non-negligible percentage (16.3%) of cases involved the use of IORT for managing locally recurrent disease. Moreover, in more than 80% of the cases IORT was given with curative intent as boost intensification dose, and as a part of multidisciplinary approach including surgery, EBRT, and chemotherapy.

The 2014 pooled analysis conducted in Europe showed a local recurrence rate of just 14%. In addition, the study discusses some technical aspects for rectal cancer, defining that the most used applicator was 6 cm diameter, and that in most cases had a beveled angle of 45º. Furthermore, the analysis indicated that among the cases, 59% of patients received a radiation dose of 12.5 Gy, while 28% received 10 Gy. In terms of beam energies, the most frequently utilized were 12 MeV, accounting for 32%, followed by 15 MeV, which constituted 29% of the cases.

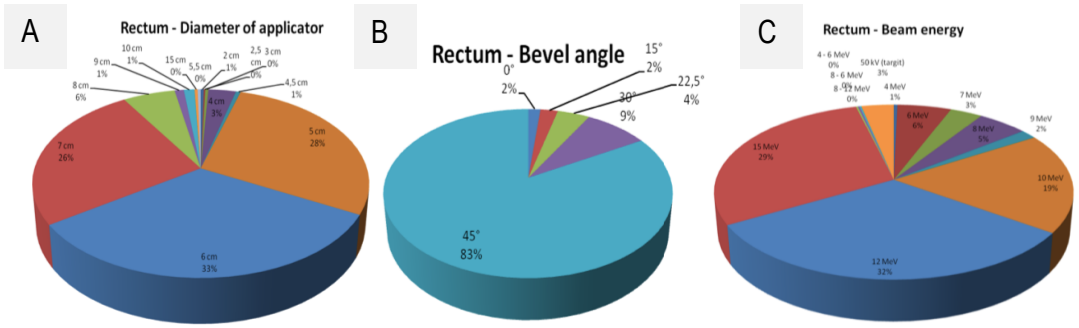

Figure 18. A) Distribution of applicator diameters in rectal cancer (%) B) Beveled angles utilized in rectal cancer (%) C) Distribution of beam energies employed in rectal cancer (%) [39]

4.3.1.3 Sarcoma

Finally, in the pooled analysis of 2014 data from 345 cases of sarcoma were available. In 57.8% of cases IORT was used for primary tumor and in 42.2% for local recurrence. IORT was delivered after surgical resection in 99% of cases. For electron IORT, in the 46% large collimators were used with diameters of 10, 12 and 15 cm and 30º beveled angle was mostly used. The most frequently administered doses were 10 Gy in 40% of the cases and 12.5 Gy in 32 % of the cases. Radiation beam energies ranged from 4 to 18 MeV. Consequently, in terms of technical aspects, soft tissue sarcoma required a wide range of applicator diameters, most likely in relation with the frequently large tumor extension and the post-resection tumor bed in soft tissues.

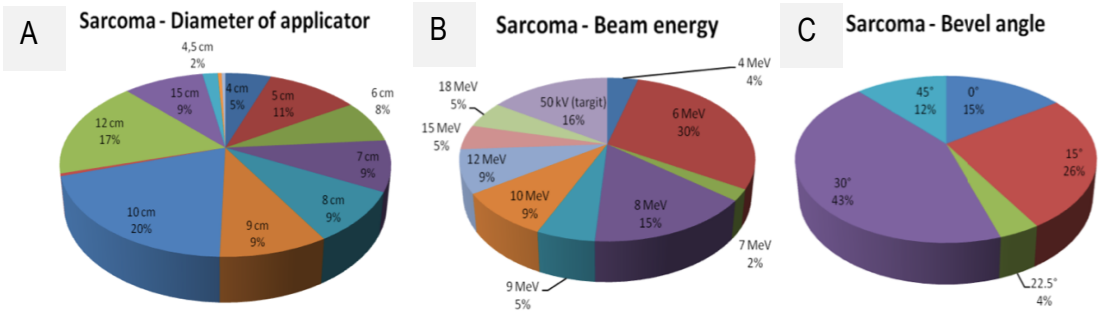

Figure 19. A) Distribution of applicator diameters in soft tissue sarcoma (%) B) Beveled angles utilized in soft tissue sarcoma (%) C) Distribution of beam energies employed in soft tissue sarcoma (%) [39]

4.3.2 Illustrative IORT cases in common treatment sites

The technique of intraoperative radiotherapy has been extensively utilized in several common localizations. These frequent localizations are described to provide a comprehensive comparative analysis of the three IORT modalities in each clinical situation.

4.3.2.1 Intraoperative radiotherapy in breast cancer

Electron IORT treatment has been widely used for breast cancer treatment. A study conducted by Oses et al. [40] at Hospital Clínic between 2013 and 2017 examined the use of IOERT for breast cancer treatment. A total of 103 patients were selected, with 59.6% receiving the treatment as partial breast irradiation and 40.3% receiving it as a boost based on histopathological characteristics. Exclusive IOERT was administered at a mean dose of 15.5 Gy, while the boost was given at a mean dose of 10.9 Gy, in addition to EBRT ranging from 39 - 50 Gy. The median IOERT energy used was 6 MeV, and applicators with a diameter of 5 cm were employed. The study revealed that 7 patients experienced grade I-II skin toxicity. One patient had local and distant recurrence (0.9%), while 4 patients (3.8%) experienced distant recurrence but maintained proper local control. As of 2019, from these five patients two patients were alive, and three had passed away. Based on the experience at Hospital Clínic, IOERT appeared to be feasible, efficient, and beneficial for selected patients.

So, talking about the radiation beam employed with mobile electron accelerators, it is more penetrating than low-kV X-rays and require shields to be inserted in the posterior lumpectomy to provide healthy tissue protection. The shield is positioned between the gland tissue and the pectoral muscle, implying a reduction of local pains, and eliminates the arm articulation difficulties during IORT.

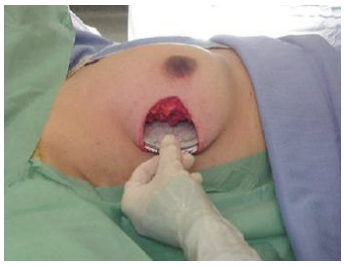

Figure 20. Shield inserted in the posterior lumpectomy [41]

Considering the diameter of the tumor and the location, a specific applicator is selected, preferably with a diameter greater than 5 cm. In ELIOT trial they used 4 cm applicator, and they found that larger applicators would have reduced recurrence rates, which later was demonstrated by Leonardo et al. [42]. Consequently, to ensure uniform coverage of all the microscopic disease, applicator diameter is chosen according to cover the entire tumor bed plus a safety margin from 1.5 to 2 cm. Additionally, the electron energy employed in the procedure is selected considering the target thickness, in such a way that 90% isodose level covers the distant end of tumor bed. Moreover, in electron IORT flat applicators are the best suited in breast cancer, especially in vertical position, with the objective to locate the electron beam perpendicular to the incident surface. When locating applicator, it is important to avoid herniation of glandular tissue. The area needs to be flat and homogeneous to locate the applicator angled according to the anatomical plane, avoiding

making a lot of pressure. In some situations, a sterile film or plastic discs are employed on the terminal part of the applicator, placing them between the terminal part and the gland.

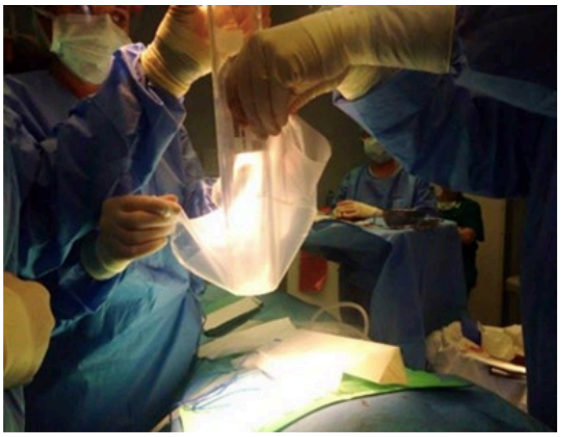

Figure 21. Positioning of the applicator using a sterile film to avoid herniation in breast cancer IORT [43]

The discrepancies observed between actual treatment and dosimetry characterization can be attributed to various factors such as irregularities on the tumor surface, presence of air gaps, misalignment between the applicator and target, and inaccurate assessment of target thickness. Additionally, challenges arise when attempting to achieve suitable and stable positioning of internal shields, if applicable. Finally, the time of radiation is less than 2 minutes and the duration of all the procedure is 15-20 min. After irradiation, shielding disk is removed and the incision is closed.

IORT with low energy X-rays has also been widely used to treat breast cancer. In a 2014 study by Evelin Martinez et al. [44], 85 women with early-stage breast cancer who underwent lumpectomy were treated with a single session of Intrabeam irradiation. The study found low acute toxicity levels, with 30% of patients receiving exclusive Intrabeam radiotherapy and the remaining 70% receiving it as a boost. The average applicator size used was 3.5 cm, and the irradiation time averaged approximately 21 minutes. Intrabeam demonstrated notable advantages over conventional radiotherapy, maintaining tumor control while minimizing toxicity.

So, Intrabeam device is mostly used in this modality, and it is inserted in the tumor cavity. Its spherical applicators are ideally shaped for breast lumpectomy cavity. The problem of using low energy X-rays is that there is a steep gradient in dose with distance to the source, being easily perturbed by local heterogeneities like air, tissue, and bone. The rapid fall-off in dose results in a minimized dose to the distal breast region, necessitating the avoidance of any liquid within the surgical cavity. The presence of liquid would significantly reduce the thickness of the tissue receiving the planned dose. So, it's important to note that low-kV X-rays used in IORT may introduce three potential sources of error: steep depth-dose variation, tissue/air interface effects,

and dose perturbation caused by heterogeneities. With the Intrabeam system, it's important to note that the applicator should not be too tight, because adequate tissue oxygenated is required for radiotherapy to be effective. However, the applicator should not be too loose because breast tissue must be in contact with the applicator, as any space will cause an inadequate radiation dose delivered to the tumor. Hemostasis is very important, because poor hemostasis causes changes on cavity geometry due to blood collection, leading to a delivery of suboptimal radiation doses. During the application process, caution must be exercised to avoid touching the delicate electron drift tube. Firm pressure should be applied to ensure a secure attachment of the applicator to the Intrabeam device, allowing the optical interlock system to register the correct application and enable radiation delivery

To measure the diameter of the lumpectomy cavity, a disposable tape is used to determine the size of the applicator. The dose administration depends on diameter applicator, and it needs to fit perfectly to the cavity to optimize radiation treatment. The spherical applicators can have diameters that range from 1.5 to 5 cm with 0.5 cm increments. Diameters of 4 to 5 cm are normally used, and they are chosen to be adhered tightly to the tumor bed. The prescribed dose is 20 Gy at the surface, and 10 Gy at 5 mm distance from the applicator surface. The dose rate is about 0.5 - 2 Gy/min at applicator surface. The skin is closed around applicator with a suture, to make tissue adhere to the applicator. As there is a rapid drop of radiation, shielding is not required to protect heart and lung. When irradiation is completed, applicator is removed, and wound is closed. The system delivers the prescribed dose over 20-45 min, and larger the diameter of the applicator, the longer irradiation time will be [45].

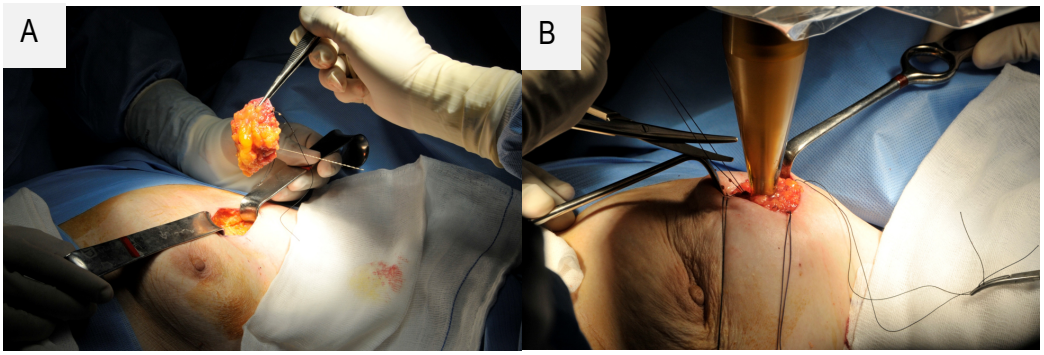

Figure 22. Steps involved in a IORT procedure for breast cancer using Intrabeam. A. Surgical specimen extraction. B. Spherical applicator inserted into the cavity of the breast tumorectomy [46]

Finally, HDR-IORT in breast cancer has been delivered with a H.A.M applicator, which is bulky and may not conform to the lumpectomy cavity. The procedure is performed in a dedicated, shielded, image-guided brachytherapy suite with full anesthesia capabilities and in-room imaging with

computer tomography on-rails. A treatment plan is created and optimized to a dose of 12.5 Gy in a single fraction delivered to a depth of 1 cm from the balloon surface. Then the catheter is removed, and incision closed by the breast surgeon [47]. This technique still needs further investigation, as there is limited evidence for outcomes.

Table 10. Comparison of the IORT modalities in breast cancer

Comparison of the characteristics of intraoperative radiation therapy techniques: electron beam, low-kV X-rays and HDR-IORT in breast cancer				
Technique	**Dose to 1 cm from lumpectomy cavity**	**Dose homogeneity**	**Strengths**	**Weaknesses**
Electron IORT	21 Gy	Major	Linear accelerator based and wide range of available energies	Higher energy requires greater shielding
Low-kV X-ray IORT	5 - 7 Gy	Not at all	Rapid attenuation, low shielding requirements	Poor depth penetration, high surface dose necessary to achieve adequate dose at 1 cm
HDR-IORT	12.5 Gy	Minimal	Customizable treatment planning	Expensive, limited evidence for outcomes

4.3.2.2 Intraoperative radiotherapy in rectal cancer

Rectal cancer has been one of leading causes for cancer morbidity and mortality, with one million of new cases every year. Improvements in surgical techniques have significantly reduced the incidences of local recurrences below 10%, but the risk of distant metastasis is still a challenge, with a 5-year survival rate of 70%. In a pooled analysis of Kusters et al. [48], the IORT in rectal cancer has been evaluated in 605 patients that had locally advanced rectal cancer. The treatment

program consisted of preoperative chemoradiotherapy, and then surgery followed by IORT between 10 - 12.5 Gy. At 5 years, the rates of local recurrence obtained were from 12%, the overall survival was 67% and cancer-specific survival was 74%, which was data more favorable compared to studies made without IORT.

In the context of local rectal cancer, IORT has predominantly been developed using electron linear accelerators. The electron beam energy and dose are determined based on the resection status and target geometry. Ensuring complete coverage of the target area, typically located on the presacral or pelvic sidewall, is crucial when selecting the applicator. However, due to anatomical constraints within the pelvis, achieving optimal placement of the electron beam in the treatment site can be challenging [49]. Nonetheless, applicators with beveled angles can facilitate positioning on sloping surfaces in the pelvis (see Figure 23). Therefore, applicators with diameters ranging from 4 to 10 cm and beveled ends tailored to the anatomical configuration of the presacral region are recommended for small pelvis sites to adequately encompass the surgical bed.

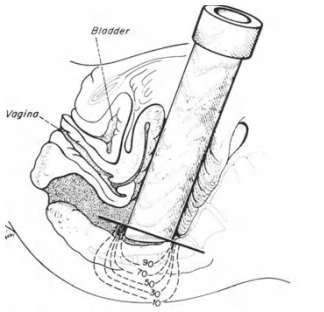

Figure 23. Beveled applicators used in rectal cancer

For pelvic tumors, cylindrical applicators with beveled angles of 15º or 30º are commonly employed to conform to the anatomical structures of the presacral area, pelvic sidewall, or anterior pelvis. It is important to note that the use of a 30º bevel angle results in a shallower depth of the isodose, which should be taken into consideration. In cases involving extrapelvic lesions, rectangular and elliptical applicators with either a flat or 20º angle are utilized in addition to circular applicators, depending on the specific requirements. Typical radiation doses administered during IORT for rectal cancer range from 10 to 20 Gy. Lower doses are typically used for cases with minimal residual disease, while higher doses are employed for cases with gross residual disease following maximal resection.

The accumulation of fluid could influence radiation penetration in an unpredictable way and should be avoided, so suction catheters should be collocated to minimize fluid build-up within applicator. The applicator serves in electron IORT to retract sensitive normal tissues, like small bowel and

ureter. Additionally, surgical retractors are used to displace the uninvolved structures such as rectal stump, bladder, prostate, uterus, vagina, descending colon, and ureters. The risk areas include presacral space (common site for pelvic recurrence), the parietal mesorectum, lateral spaces with frequent microscopic disease spread, and sites of tumor fixation to non-resectable adjacent structures.

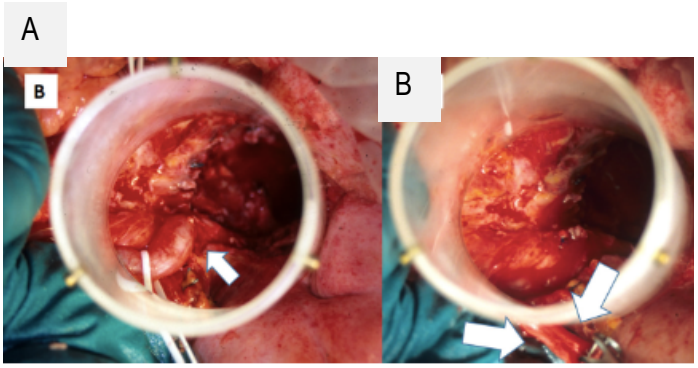

Figure 24. Electron IORT procedure for a recurrent rectal cancer A) IOERT applicator positioned to treat tumor bed B) Area ready to be treated by IOERT after the mobilization of the ureter out of the field [49]

For the case of using Intrabeam in rectal cancer, some limitations have been reported. The largest applicator, being 5 cm, restricts the area to be treated. So, in some scenario low-kV IORT has been aborted because the target could not be adequately covered with the largest applicator. However, in a study done Guo et al. at the Cleveland Clinic [50], IORT was delivered using the Intrabeam device after tumor resection. The study included 42 patients, which were treated with a 5 Gy dose to the tumor bed, calculated for depth of 1 cm. Spherical applicators from 2 to 5 cm were used, and the overall 3-year survival rate was 43% for recurrent rectal cancer and 65% for primary rectal cancer. The one-year local recurrence rate obtained was from 16%.

In the case of high-dose-rate intraoperative radiation therapy, the tumor bed is carefully delineated following resection. Specialized retraction devices are employed to displace normal tissues and create a clear path for the procedure. To target the intended area, typically the presacral region and one or both pelvic side walls, an appropriately sized H.A.M applicator is either placed or sutured in position. Packing materials are utilized to secure the applicator in place, ensuring stability during the treatment. The applicator is then connected to the HDR remote afterloader system. Depending on the geometry of the target and the extent of the disease, the delivered dose ranges from 10 to 20 Gy. The prescribed dose is determined at a tissue depth of 5 mm from the surface of the applicator and 1 cm from the HDR source. In situations where treatment is required near organs such as the ureter or bladder neck, lead shields are utilized to displace and protect these structures, ensuring their safety during the procedure [51].

4.3.2.3 Intraoperative radiotherapy in gynecologic cancer

Electron IORT offers potential applications in gynecological pathologies, including cervix, endometrium, and ovary, both in recurrent cases and as part of curative treatment. For the case of locally advanced cervical cancer, it is based on radiochemotherapy followed by brachytherapy, which is sometimes not feasible, and stereotactic radiotherapy may be used instead, with tumor control being inadequate in certain instances. Martinez-Monge et al. [52] evaluated the efficacy of IORT after surgery in patients with surgically removable cervical cancer. The employed technique to pelvic sidewalls with electron accelerators delivering doses of 12 Gy using 9 or 12 MeV showed a 10-year control rate of 92,8% and pelvic control rate of 78,6%, concluding that IORT can be a valuable technique for enhancing treatment in advanced resectable cervical tumors. In recurrent cervical cancer, IORT has various applications in locations as central pelvis, pelvic walls, parametria and nodal areas. After surgical resection or in cases where unresectable recurrence remains due to infiltration or adherence to anatomical structures, treatment is administered. In a study conducted by Albert Biete et al. [53], at Hospital Clínic since 2013, they reported 16 patients including tumors of uterine cervix (11 patients), uterine corpus (4 patients), and ovarian cancer (1 patient). IORT was delivered using LIAC equipment with electron beams ranging from 4 to 12MeV with a mean diameter of 5 cm, and a median dose prescribed of 11 Gy. All irradiated patients presented with pelvic recurrences. Follow-up revealed five cancer-deaths, two lost patients, and eight patients that achieved incomplete remission without recurrence in the irradiated area, except for one marginal relapse. The study concluded that there are limitations to obtain definitive conclusions due to variations in relapse characteristics, IORT doses, surgical procedures, but incorporating IORT in surgery may offer additional benefits in terms of local control. However, the impact on overall survival appears to be limited due to the high probability of pelvic carcinomatosis or distant metastasis development.

Similarly, for recurrent endometrial cancer with positive margins, combining surgery with IORT may be considered to enhance treatment outcomes. In the case of vulva-vaginal cancer, IORT can be contemplated when the disease extends to the pubic symphysis, which presents challenges for radical surgery. Additionally, in endometrial cancer, recurrence patterns differ with isolated relapses in the vaginal fundus. Standard treatment of endometrial cancer involves external radiotherapy and brachytherapy, producing satisfactory results. Adding IORT to surgical cases may offer benefits, as it yields better outcomes for endometrium-isolated relapses compared to cervical cancer, with manageable toxicity at doses below 15 Gy. However, it is crucial to acknowledge that technical

limitations may affect the feasibility of IORT in such cases. Careful evaluation and individualized decision-making are essential to determine the appropriateness of IORT in each specific scenario [54]. For the case of ovarian cancer, a few IORT cases have been done, so it is difficult to extract conclusions. Yap et al. [55] presented 24 patients undergoing cytoreductive surgery with IORT delivered to areas at high risk of residual disease. In that case, IORT was delivered using a 2000 kV X-ray beam, with an average dose of 12 Gy. At a 2-year follow-up, 5 of the patients demonstrated relapse in the irradiated surgical site, and other 5 achieved complete remission. The remaining patients presented relapses occurred in other regions. Consequently, authors concluded that IORT has a limited impact on prognosis, exhibiting some level of activity.

Overall, if we look at the surgical process conducted in gynecological cancers using electron accelerators, surgeons need to pay attention to nervous and vascular structures before making a pre-treatment verification of the applicator position in the pelvic cavity in relation to the abdominal surgical incision and the anatomical patient conformation. The main limitation of IOERT in these types of cancer is the size of the abdominal surgical incision and the anatomical conformation of the patient, which may not allow sufficient angulation for the position of the applicator which will be connected to accelerator. For pelvic wall lesions, applicators with diameters from 4 to 7 cm are usually used. The applicators utilized have beveled angles up to 30º. In cases of microscopically infiltrated resection margins, the use of wet gauze as a bolus to increase surface dose is advisable. Some limiting factors for the dose include proximity of vessels and nerves. Vessels are resistant to high doses and can be easily moved away from irradiation field, but nerves are more sensitive to high doses and are located at greater depth and require special attention to minimize risk of neurological damage, so the recommended maximum dose is 12 Gy.

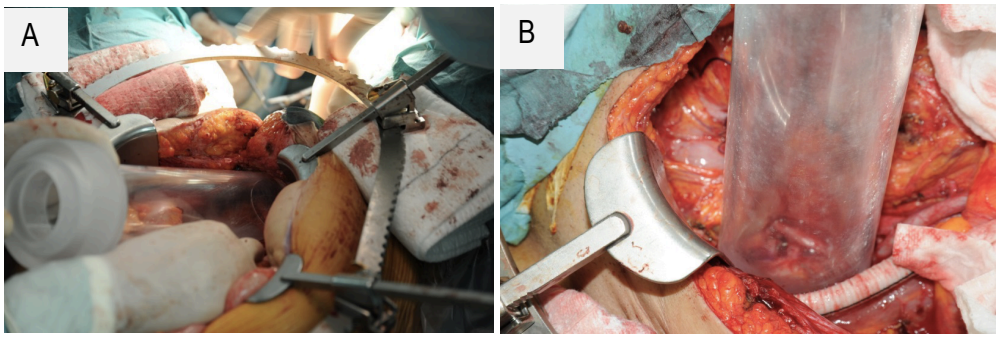

Figure 25. Electron applicator positioned in an abdominal surgical incision. A. Pre-treatment verification positioning of the applicator in pelvic cavity, considering width of the incision and anatomical conformation of the patient. B. Applicator positioned in the pelvic cavity prepared for the radiation treatment with blood vessels visible, moved away from radiation field. [43]

For the case of low-kV modality, it is a treatment option for gynecological cancer in the field of IORT. Devices such as the Axxent Xoft system have been used, coming with applicators of various sizes, shapes, and materials, specifically designed for vaginal and cervical applications. This technique has demonstrated the potential to spare organs at risk better than traditional techniques. However, it is important to note that higher doses near the applicator and within the treated volume have been observed with electron brachytherapy. Unlike traditional brachytherapy techniques using radioactive isotopes, with electron brachytherapy the need for a shielded room and the storage and handling of isotopes is eliminated, eliminating the risks associated with radionuclides.

4.3.2.4 Other localizations in intraoperative radiotherapy

Intraoperative radiation therapy has been used less frequently with inconclusive results in other locations like for brain tumors, pancreas, bladder, prostate, stomach, and lung. The limited application of IORT in these areas suggests further research and clinical studies are needed to understand its potential efficacy and outcomes in this specific cases. The actual results of the efficacy and safety of IORT in these types of cancers are inconclusive, due to the heterogeneity of study populations and treatment protocols, and the presence of confounding factors. Larger studies are needed to establish the role and potential benefits of IORT in these types of cancers, identifying the most effective treatment strategies for patients with tumors in these locations.

4.3.3 Benefits and utility of IORT

IORT approach offers several benefits, such as an increased precision to only the necessary tissues, with a positive impact on the late toxicity and cosmesis. IORT results in a better quality of life for the patient, because it's a technique that reduces risk of local recurrences. In earlier cancer, after the surgery, the intraoperative radiotherapy has had a significant advantage, as its high dose delivered has avoided the need for external radiotherapy and offers a good tumor control.

The clinical efficacy of IORT is highlighted by two large, randomized trials, the ELIOT, and TARGIT-A. ELIOT study [56] has demonstrated that local recurrences in early breast cancer can be as low as 1,5% when treated with electron accelerators in low-risk patients, where 21 Gy were delivered to the tumor bed. For the case of TARGIT-A study [57], the use of low-kV X-rays offering a 20 Gy at the surface reported a 5-year risk local recurrence of 3,3%.

Additionally, some studies have used IORT alone or in combination with EBRT [58, 59]. It has been found that IORT as a standalone treatment is effective in cases of small tumors that are less

aggressive in terms of their histological characteristics. For cases with larger or more aggressive tumors, IORT may be applied in combination with EBRT to achieve optimal results. Consequently, the combination of EBRT with IORT has shown better results compared with IORT alone, particularly for more advanced tumors. However, the benefits for IORT are based on improved local control, a reduced time of overall radiotherapy, low complication rates, a decrease exposure to medical environments, and lower costs if recurrences are avoided.

To conclude, the integration of intraoperative radiotherapy has shown promising results in terms of cancer control and improved quality of life, as it effectively reduces the risk of recurrence in different cancer types. However, certain types of cancer present still challenges regarding the high incidence of metastasis, like esophageal and stomach ones, because although there is an improved local control, it does not translate into increased survival rates.

5. DETAILED ENGINEERING

In the following section, the improvements that can be done for each modality are described. As technologies continue evolving, there are constant opportunities to optimize the existing technologies, and by identifying areas where enhances can be implemented, the performance, efficiency and effectiveness of each modality can be improved. Moreover, a comparative table has been prepared to assess the various modalities to determine the most suitable option for implement IORT in clinical practice.

5.1 Proposed advancements in IORT

5.1.1 Proposed advancements in mobile electron accelerators

When considering mobile electron accelerators, there are several aspects that could benefit from improvement:

- **Reduction of weight and size**: the overall equipment weight and dimensions must be minimized because the machines would be easier to use and perform in the operating room. The miniaturization of the components of the electron accelerator can be explored, like reducing the size of cooling systems, electronic controls, or dosimetry systems. Additionally, as technology continues to advance, it would be great to design smaller magnetron, reducing the overall dimension of the machine. The size of the accelerator itself is challenging to reduce due to the essential need for sufficient length, providing the necessary space for effective electron acceleration to a specific velocity.

Figure 26. Proposed evolution for mobile electron accelerators in intraoperative radiotherapy

- **Improve the gantry:** the gantry contains the accelerator, cooling system, and beam stop. It permits the beam delivery from different angles, and it could incorporate additional

rotational mechanisms providing smoother and faster movements. Additionally, it would be great that gantry could be reduced in size and weight.

- **Improve electron accelerators energy efficiency**: the efforts could be guided to reduce the energy consumption of these equipment as they have a high consume, using high-efficiency electronic components.
- **Create a beam forming system simple and light:** beam forming system needs to be compact and short to allow system maneuverability and flexibility with still delivering beams of excellent therapeutic quality. Nevertheless, to minimize energy losses, it is possible to reduce the thickness of the foils. However, this approach comes with a trade-off, as it would compromise the compactness of the system. To maintain the desired flatness of the therapeutic beams, the distance from the accelerator's exit to the patient plane would need to be increased, resulting in a loss of system compactness. A dual-foil setup could be a possible solution, to first make the fluence distribution wider, and then with a second foil make distribution flat, and finally collimators and applicators could absorb electrons scattered outside the field such that dose is limited to the field area only.

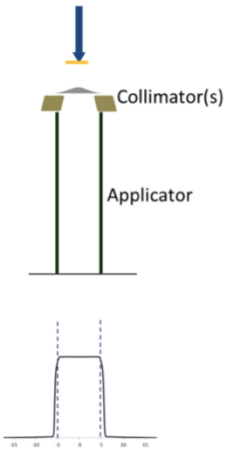

Figure 27. Beam forming system performing with a dual-foil setup

- **Design of new applicators:** nowadays, only flat applicators for electron beams are available, generating flat dose distributions. For some areas, spherical dose distribution would be more desirable, like in brain or breast cancer. It would be great to design spherical applicator for electron accelerators, for example, a cylindrical collimator can be employed to focus and guide the beam, while a middle scatter foiling can disperse the beam and shape its energy. Additionally, a lower hollow sphere can be utilized to contour the beam and achieve a spherical dose distribution. Applicators also need to be made by lightweight materials and being compatible with imaging and steam sterilization.
- **Modify the control unit:** control unit is connected to the mobile unit through a group of cables and controls the equipment, and it could be useful to reduce the dimensions and its weight.

5.1.2 Proposed advancements in low-kV IORT equipment

When considering low-kV IORT equipment, there are several aspects that could benefit from improvement:

- **Expand the energy options:** this equipment could provide a wider range of energies to have a better customization of the radiation dose and their penetration respect the specific requirements of the tumor. X-ray source could be improved to increase energy output, because the low-kV X-ray equipment requires long treatment times due to low dose rate they deliver.
- **Improve the mounting of the X-ray source:** Mounting the X-ray source onto suspension system is one of crucial steps in Intrabeam. A guide for the XRS4 could be designed to improve the speed on mounting the XRS for IORT procedures
- **Advances in applicator designs**: there could be more versatile and specialized applicators for different tumor types and anatomical sites, to optimize dose distribution. Although there are a range of IORT applicators for sizes and types, the existing applicators in use are typically designed to align the X-ray generator and the affected area in a vertical orientation. However, there are situations where the tumor and X-ray generator are not positioned vertically, making it challenging to achieve optimal alignment. In such cases, it becomes necessary to consider the scenario where the tumor and X-ray generator are at an angle other than vertical, and this requires the use of an applicator capable of irradiating the beam at an oblique angle, rather than the standard 0° angle, ensuring accurate and effective delivery of radiation to the desired target area.

5.1.3 Proposed advancements in HDR-IORT equipment

When considering HDR-IORT equipment, there are several aspects that could benefit from improvement:

- **Integration of 3D imaging:** Currently the use of 2D imaging guides HDR-IORT therapy, but the integration of 3D anatomical information could improve the treatment. Magnetic resonance image with its excellent soft tissue contrast holds great potential. However, will not be easy to have afterloader and imaging equipment in the same room to ensure optimal utilization.
- **Reduce treatment times**: shortening HDR-IORT time needs to be achieved, at it can be done by implementing multichannel afterloaders that allow concurrent irradiation using multiple sources. Future afterloaders should offer flexibility and applicability, accommodating increased channels for reduce treatment times.
- **Explore the use of new low-energy isotopes:** Ytterbium-169 or Thulium-170 are examples that could minimize the shielding requirements of treatment rooms.

- **Develop customized 3D-printed HDR-IORT applicators**: this could facilitate the delivery of high doses to irregularly shaped tumor cavities, offering an attractive option for high-risk patients and those undergoing complex reconstructions.

5.2 Comparative summary of IORT modalities

Understanding the distinct characteristics and performance of each modality is essential for making informed decisions in clinical practice. To facilitate the analysis of the three modalities, a comparative table has been created to evaluate the relevant parameters in IORT equipment. By evaluating these parameters, healthcare professionals can gain insights into the strengths and limitations of each modality.

Table 11. Comparison table of the different IORT modalities

	IOERT	LOW-KV IORT	HDR-IORT
Energy source	LINAC electrons 4-12 MeV	Low-kV X-rays (50 kV)	Radioisotopes (Iridium-192)
Equipment weight	570 kg + (< 230 kg of shield)	285 kg	140 kg
Equipment dimensions (width, depth, height)	76 x 210 x 180 cm	90 × 60 x 169 cm	61 x 56 x 107 cm
Voltage input	230 V	100 - 240 V	110 - 220 V
Power consumption	3 kVA	400 VA	550 VA
Cost	1,200,000€	400,000€	Afterloader: 200,000€ Applicators: 25,000€
Capital expense: installation	25.000€ per O. R	None	HDR shielded room expense
Superficial dose	The lowest one (75-93%)	Very high (300%)	High (150- 200%)
Dose at 2 cm	The highest (70-100%)	Very low (20%)	Low (30%)

Dosimetry homogeneity (from surface to deep areas)	Variation < 10%	Variation > 150%	Variation > 100%
Dose prescription (breast)	10 - 20 Gy	20 Gy	30 Gy
Time of irradiation	2 - 4 min	30 – 45 min	5 – 30 min
Time procedure	30 - 45 min	45- 120 min	45 -120 min
Treatment areas	Accessible areas	Areas with less than 0.5 – 1 cm of risk depth. Only small volumes.	Areas with less than 0.5 – 1 cm of risk depth
Personnel shielding	Must leave room	Lead aprons – screen leads	Must leave room
Applicators	Cylindrical. Diameters range from 3 to 12 cm with beveled angles 0º, 15º, 30º, 45º	Spherical (commonly used), flat, and needle	Flexible and personalized applicators
Treatment sites	Breast, gynecological tumors, skin, colorectal, vaginal wall, spine, abdominal, pelvis, stomach, pancreas, neck, head, renal, sarcoma	Brain, breast, colorectal, vaginal wall, spine, prostate	Pelvis, colorectal, gynecological tumors, retroperitoneal sarcoma, head, neck
Applicator or catheter displacement	None	None	Yes

5.3 Evaluating the best approach for IORT

Based on the results obtained, we can determine the modality that offers best advantages and extract some relevant insights.

First, electron IORT modality equipment tends to have larger dimension and weights, suggesting the need for improved mobility features to facilitate movement in the OR. Additionally, electron IORT equipment consumes a significant amount of power, typically around 3 kVA on average, and necessitates the implementation of adequate shielding in the OR to ensure radioprotection. One big advantage of this modality is the high dose rates and increased penetration capability that electron accelerators have comparing them with other technologies. It should be noted that in the other modalities, a higher percentage of the dose is typically delivered at the surface. However, at the depth of 2 cm, IOERT shows a greater dose percentage. Moreover, the electron dose distribution offers several advantages in specific clinical scenarios because its homogeneous distribution with an abrupt stop at a specific depth allows for targeted radiation delivery to the desired area, while minimizing radiation dose to surrounding healthy tissues. More advantages of this modality are based on its relatively short treatment time associated, typically requiring an irradiation time of 2-4 minutes. However, it is important to consider that electron IORT requires longer operational room setup time compared to other modalities such as low-kV IORT, due to complex calibrations and equipment warm-up procedures. Consequently, the total procedure time for electron IORT usually ranges from 30 to 45 minutes. Electron IORT is also limited by the type of applicators used, making it unsuitable for narrow cavities or areas with steep surfaces. Regions such as paranasal sinuses, diaphragm, skull base, deep pelvis and retropubic areas can pose challenges for electron IORT. Finally, it is worth noting that both the acquisition and maintenance costs of electron accelerators are high, as it will be discussed in section 7. The initial investment can exceed 1 million euros, while the annual maintenance expenses can amount to approximately 100,000€. These financial considerations should be carefully evaluated when considering the implementation of a mobile electron accelerator in a clinical setting.

Secondly, in the case of low-kV IORT modality the equipment offers advantages such as smaller dimensions and lighter weight compared to electron accelerators. With a weight of approximately 300 kg, the low-kV IORT provides a highest maneuverability and flexibility of the placement arm, allowing precise positioning and being particularly beneficial for accessing small cavities. In addition, low-kV IORT equipment has lower power consumption with a maximum of 400 VA,

compared to electron accelerators. Another advantage of this modality is the reduced shielding requirements, as personnel can be present in the operating room, which doesn't need to be remodeled and shielded. However, it should be noted that low-kV modality offers a limited penetration, so dose decreases rapidly in distance, posing challenges in cases where prescribed doses at different depths may not be sufficient. Additionally, the spherical applicators that are widely used with this modality in breast cancer, require spherical cavity and that may not be the case in most situations. Moreover, in approximately 40% of the cases there is the presence of liquid, blood, or air, which can limit more the penetration. Despite these limitations, the equipment that works with low-kV IORT has less complex calibration and maintenance compared to mobile electron accelerators. The operational room setup is fast, lasting only 10 minutes. The entire process, including the treatment, typically lasts between 25 and 45 minutes. The Intrabeam device, which is commonly utilized in low-kV IORT, proves to be valuable and effective for breast cancer malignancies. Thus, hospitals conducting numerous procedures for these types of cancer may find it beneficial to invest in this equipment. However, for operations focused on pelvic regions or gynecological cancers, low-kV IORT equipment may not be the optimal choice due to its limited penetration and specific applicator requirements. Additionally, this equipment offers cost advantages, with a price that is approximately half of an electron accelerator. The cost is around 400,000€, and annual maintenance cost approximately 40,000€.

Finally, HDR-IORT is proposed as an advantageous technique for treating small tumor beds, but it requires specific considerations. Current afterloaders are less heavy and consume less than other modalities, but the use of radioisotopes necessitates of strict protection measures, including shielding of the treatment operating room with lead to protect personnel involved. Compliance with legal requirements for transportation and handling of radiation sources is also important. HDR-IORT is effective for tumors up to 0.5 cm thick and can be applied in various anatomical locations, even in challenging cases such as colorectal malignancies that can be sometimes inaccessible for electron accelerators. HDR-IORT also ensures the risk of inadequate coverage due to beam angle or field matching issues. Similar to low-kV IORT, HDR-IORT exhibits a rapid dose fall-off with distance, allowing for precise radiation delivery. However, it's important to consider that the treatment process for HDR-IORT is relatively long, typically lasting 45-120 minutes. Additionally, a challenge in implementing HDR-IORT is the need for a shielded building, which increases equipment costs. The afterloaders are priced around 200,000€ and constructing a dedicated shielded operational room can present a significant obstacle to adopting this technique.

As an engineer, if I had an unlimited budget and were faced with the decision of choosing a modality for intraoperative radiation therapy, I would choose electron IORT, as it offers several advantages over other modalities:

- Deep tissue penetration
- High dose conformity
- Rapid dose fall-off beyond target area
- Versatile applicators, with cylindrical applicators with beveled angles.
- Treatment flexibility, as it can be used in a wide range of cancer types.
- Efficient treatment time, as time required for irradiation is relatively short.
- Real-time imaging capabilities

The second option would be a low-kV X-ray machine, but it lacks the energy range that electron accelerators have to treat cancer, and they are more focused on treating breast cancers. Limitations in treatment times, dose distributions, field sizes of low-kV X-ray equipment pose a significant limitation compared to electron accelerators.

In summary, electron IORT presents unique advantages compared to low-kV and HDR-IORT modalities. Nonetheless, the selection of the appropriate technology should consider the specific clinical situation, treatment needs, and available resources within the hospital setting.

6. PROJECT IMPLEMENTATION AND STAKEHOLDER ENGAGEMENT IN INTRAOPERATIVE RADIOTHERAPY

In this section we delve into the critical aspects when implementing IORT and the importance of stakeholder engagement in ensuring its implementation success. IORT is defined as a multimodality approach, so there is the need to focus on implementation process defining the expectations of the different key players, the interactions among them, and the challenges that may arise when implementing IORT in clinical practice.

6.1 Expectations for intraoperative radiotherapy

First, the process of constructing and implementing IORT in the clinical practice needs to explore the expectations associated. Several key players should be considered, which are physicians, engineers, and healthcare institutions.

6.1.1 Expectations of physicians regarding intraoperative radiotherapy

The physicians have several expectations about the IORT technology. First, they expect to have the IORT equipment in a fast way, avoiding waiting for years to get access to the technology, as this equipment is fabricated based on demand and there is no equipment stock available. Portability is a key factor they consider because they require equipment easy to move and set up in the operating room, enhancing the ability to provide timely treatments. Versality is another important factor, as physicians prefer equipment able to treat different clinical indications, allowing their use in different cancer types and reducing the overall need for multiple specialized devices.

Cost-effectiveness is crucial, with physicians expecting affordable equipment that can be easily maintained. Additionally, they want the technology to be reliable, being able to deliver the treatment accurately and precisely with minimal exposure to healthy tissues. Quick treatment time, adjustable penetration depth, user-friendly interface, and safety features are additional expectations that physicians have.

6.1.2 Expectations of engineers regarding intraoperative radiotherapy

Engineers that design IORT equipment aim to develop the most advanced medical devices, using advanced technology to ensure a precise and accurate delivery of radiation during surgical

procedures, minimizing the stray radiation. The equipment designed needs to be easy to maneuver, searching for equipment with reduced size and weight to enhance the mobility within the operating room. Moreover, the equipment designed needs to be reliable and minimize problems during surgery, using high-quality components with rigorous testing.

6.1.3 Expectations of companies and healthcare institutions regarding intraoperative radiotherapy

By implementing advanced IORT equipment, facilities want to achieve a return on investment as well as a competitive advantage in the healthcare market with the acquisition of advanced technology. This not only attracts patients seeking for latest technology, but it also provides confidence to physicians and healthcare personnel. The equipment needs to be clinically proved, supporting its effectiveness, and enhancing their productivity by optimizing treatment time, treating more patients, and reducing waiting times. In addition, healthcare centers aim to receive a good training and technical assistance, with the knowledge of ongoing updates and maintenance to ensure a smooth operation of the equipment and an uninterrupted patient care.

Moreover, these facilities do not only search financial interests, but they also have the objective to make a meaningful contribution to society. The improvement of patient outcomes and their contribution to enhance the capabilities of medical professionals in delivering high-quality care are some of their objectives. Facilities, understand the importance of creating a positive image for their equipment, building reputation for reliability, efficiency, and effectiveness. To achieve all these objectives, they need to constantly research about the technological innovation on the market.

6.2 Interactions among key stakeholders in intraoperative radiotherapy

Physicians, engineers, and healthcare companies are the key stakeholders in IORT. The continuously interaction between these three main players creates a dynamic feedback loop with the main objective to improve and innovate the intraoperative radiotherapy technology. Each key stakeholder brings unique expertise, perspectives, and responsibilities, contributing to the overall success of IORT integration in clinical practice.

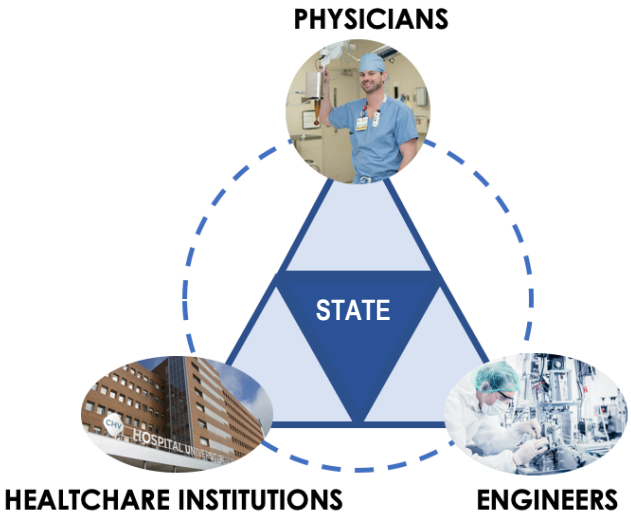

Figure 28. Key stakeholders present in Intraoperative radiotherapy

Physician expectations influence how **engineers** develop and design IORT equipment. Challenges, observations, and experiences from physicians are important factors engineers use to acquire a better understanding of the features and functionalities IORT equipment needs.

Additionally, **physicians** also share their expectations, preference, and equipment requirements when **healthcare institutions** need to acquire a IORT equipment. Physicians may evaluate and compare the different equipment options available to purchase, considering factors like clinical efficacy or ease of use. Consequently, facilities consider physicians feedback ensuring that the equipment acquired aligns with their specific needs.

When we focus on interactions between **engineers** and **facilities**, they work together to share different design concepts, safety requirements, and regulatory standards. Engineers provide information about product developments, manufacturing, quality control, and ongoing improvements. Facilities provide guidance and support to them, with a shared vision of the market insights, users feedback, and future requirements, allowing engineers to understand the business objectives and the technological advances they must perform.

Above the three players mentioned (physicians, engineers, and healthcare institutions) the **state** plays important role in the establishment of regulations and guidelines for using IORT equipment. Government entities and regulatory bodies develop decrees, laws, and regulations that affect the operation, maintenance, and safety of the IORT facilities. They also establish certification

requirements for IORT equipment, radiation protection for personnel, licensing, and authorization processes.

In addition, the successful implementation of IORT relies on the coordinated efforts of a diverse team, based on **surgeon, oncologist radiotherapist**, **sanitary physician**, **anesthetist, nurse,** and **radiation technologist**. These professionals need to bring their specialized knowledge in oncology, surgical procedures, and radiation technology to ensure a successful implementation the treatment.

Surgeons play a crucial role in IORT procedures, as surgeon is responsible for identifying the appropriate intervention and devising a surgical plan. In IORT, the incision size is typically bigger than the one used in conventional surgery, or surgical approach may need to be modified to accommodate the insertion of IORT devices, sometimes requiring the use of retractors. Surgeon must explain to the radiotherapy staff the surgical procedure that intends to use before the start of the surgical procedure. The **oncologist radiotherapist** plays a crucial role in making the patient selection, collaborating with the surgeon in pre-operative evaluations, and planning any pre or post operation radiotherapies if necessary.

Together, surgeon and oncologist radiotherapist determine whether irradiation is needed based on the surgical situation of the patient. If IORT is determined as appropriate, the oncologist radiotherapist, surgeon and **sanitary physician** determine the size of the irradiation field, beam energy, dose percentage, administered dose, and physical setup of the machine. During the procedure, the radiotherapist prepares the irradiation field and locates the applicator together with sanitary physician and surgical staff. Sanitary physician is the one responsible for acquiring dosimetric data and ensuring the correct positioning of mobile shields, if required. Additionally, **anesthetist** oversees patient stability during all surgical procedure.

The **nurses** prepare the operating theatre and assist surgical team, handling with the sterilization of IORT applicators, and the preparation of surgical instrumentation, assisting surgeon and radiation oncologist during treatment. Finally, **radiation technologist** performs the operations to control the mechanical operation of the equipment used for IORT, moving the equipment to the surgical site, and recording the data of the treatment.

In Table 12 a comprehensive training program has been developed for these professionals to ensure their proficiency in IORT. The table outlines the subjects to be covered and the designated hours allocated for each topic. The educational initiative has the main objective to provide the healthcare team with a plan to develop the necessary knowledge and skills to have a successful implementation of IORT in the clinical practice.

Table 12. Training program designed to implement IORT in clinical practice

SUBJECT	HOURS	Surgeons	RT oncologists	Radiotherapy technologists	Medical Physicists	Nurses
Equipment and IORT technique	2	x	x	x	x	x
Technical description of the equipment	2		x	x	x	
Dosimetry characterization of the equipment	5				x	
Equipment software	4		x	x	x	
Equipment quality assurance	2			x	x	
Operational training of the equipment	4	x	x	x	x	x
Treatment simulation	3	x	x	x	x	x
Maintenance	2		x	x		

6.3 Challenges in implementing intraoperative radiotherapy

Finally, the implementation of IORT may present various challenges that need to be acknowledged and effectively addressed. The transition from theory to practice brings forth unique considerations, making it crucial to thoroughly understand and anticipate the potential obstacles that may arise during the implementation process of IORT. By identifying and proactively addressing these challenges, we can minimize their impact and ensure a smooth and successful integration of IORT into clinical practice.

One challenge is the technological complexity of the equipment, requiring for staff trained and a deep understand of radiation physics, treatment planning, and dosimetry. In addition, the cost of the equipment is high, making it difficult for smaller facilities to adopt and maintain this technology. Acquire a IORT equipment is a significant investment in terms of equipment purchase, maintenance, and staff training, so it's important to evaluate financial feasibility of the project. It also requires logistical challenges, as there are specific infrastructure modifications required from the operating room to deliver IORT in some modalities.

For the case of developing countries, the access to new technology is limited, and they have lack of technical expertise and maintenance capabilities that are a significant challenge when implementing IORT equipment in these regions. Without appropriate infrastructure with specialized shielding and treatment planning, it is difficult to implement IORT. Consistent power supply may also be a challenge, as these hospitals experience frequent power outages and unstable electricity grids, having a negative impact on equipment operation. Finally, the adherence of a strict regulation and radiation safety standards also hinder the implementation of IORT technology, especially in these countries.

7. ECONOMIC VIABILITY

As with many advanced medical technologies, the successful integration of them into clinical practice needs a thorough assessment of its economic impact. Intraoperative radiotherapy is no exception, and to have an idea of the economic considerations associated, a study of the equipment price and its maintenance has been performed for each modality. By examining the initial investment and the maintenance cost, this section provides a clear understanding of the financial considerations involved in IORT. In Table 13 a breakdown approximation of the prices from the different modalities is shown.

Table 13. Economic evaluation of the different IORT modalities

	Purchase price	Maintenance cost
Mobile electron accelerators	1,200,000 €	100,000 €/year
Low-kV X-rays equipment	490,000 €	60,000 €/year
HDR equipment	200,000 € (afterloader) 25,000 € (applicators)	48,000 €/year

When comparing all the prices, we can observe that the mobile electron accelerators are the most expensive IORT equipment options, with prices of more than one million euros. This high cost can be due to the complexity of electron accelerators, as they have electron guns, waveguides and other components designed for a precise delivery of radiation. Additionally, sophisticated monitoring systems and beam verification tools are required, adding to the overall expenses. Then, maintenance costs for electron accelerators can be around 100,000 € every year.

In comparison, low-kV IORT equipment has a lower price around 490,000€. The maintenance costs for this equipment are also lower than electron accelerators, around 60,000 € every year. This equipment uses an X-ray source that operates at a single level, focusing on low-kV X-rays and simplifying the overall equipment design and costs. Electron IORT accelerators require multiple energy levels, which produce beams to treat at different depths, requiring more powerful and sophisticated accelerator components contributing to expand the cost.

Finally, HDR-IORT equipment include afterloaders and applicators. The initial acquisition cost of the equipment is 200,000€ and 25,000€, respectively. The additionally running costs for HDR-IORT include source changes and preventive maintenance inspections, which costs around 48,000€ every year. It's important to note that implementing HDR-IORT also comes with the construction of a shielded operating room to ensure radiation safety, which involves additional expenses.

Overall, electron accelerators are the most expensive ones, both in terms of initial acquisition and maintenance costs, while low-kV IORT and HDR-IORT equipment offer relatively more affordable alternatives.

Additionally, focusing on the economic costs regarding the creation of this comparison paper, the acquisition of data and relevant information for the realization of this work has not involved any costs associated, as all the necessary documents were accessible online and through the University of Barcelona, granting me free access. Moreover, hospitals and individuals contacted provided the information without any charges, and there were no additional expenses for phone calls and emails. Considering that I personally conducted all the project, only the cost of human resources could be taken into consideration, accounting for the time dedicated to project development, which amounted to a total of 600 hours. Assuming a theoretical salary of 15€/hour, the total theoretical cost for human resources to develop this paper would be 9,000€. It is important to note that the term "theoretical" is used because no actual monetary compensation was involved, as this project was part of a degree program.

8. EXECUTION CHRONOGRAM

The following section is focused into the various techniques that have been employed to organize the overall project. These management strategies have facilitated the organization and planning of diverse tasks, enabling a correct development of all the thesis. Work Breakdown Structure (WBS), Program Evaluation and Review Technique (PERT) and a Gantt diagram are the three techniques employed to ensure a clear understand of the project objectives and have a clear view on what is to be done.

8.1 Work Breakdown Structure (WBS)

The WBS technique has been used to divide the project into different packages that are composed by smaller tasks, providing a comprehensive understanding of the work that needs to be done in each package. This decomposition offers a visual representation of the different tasks to be done, becoming easier to handle each approach and improving the effectiveness in project management. In this project, the WBS has been structured in four levels of work, which are project definition and preparation, data collection, data analysis and finalization.

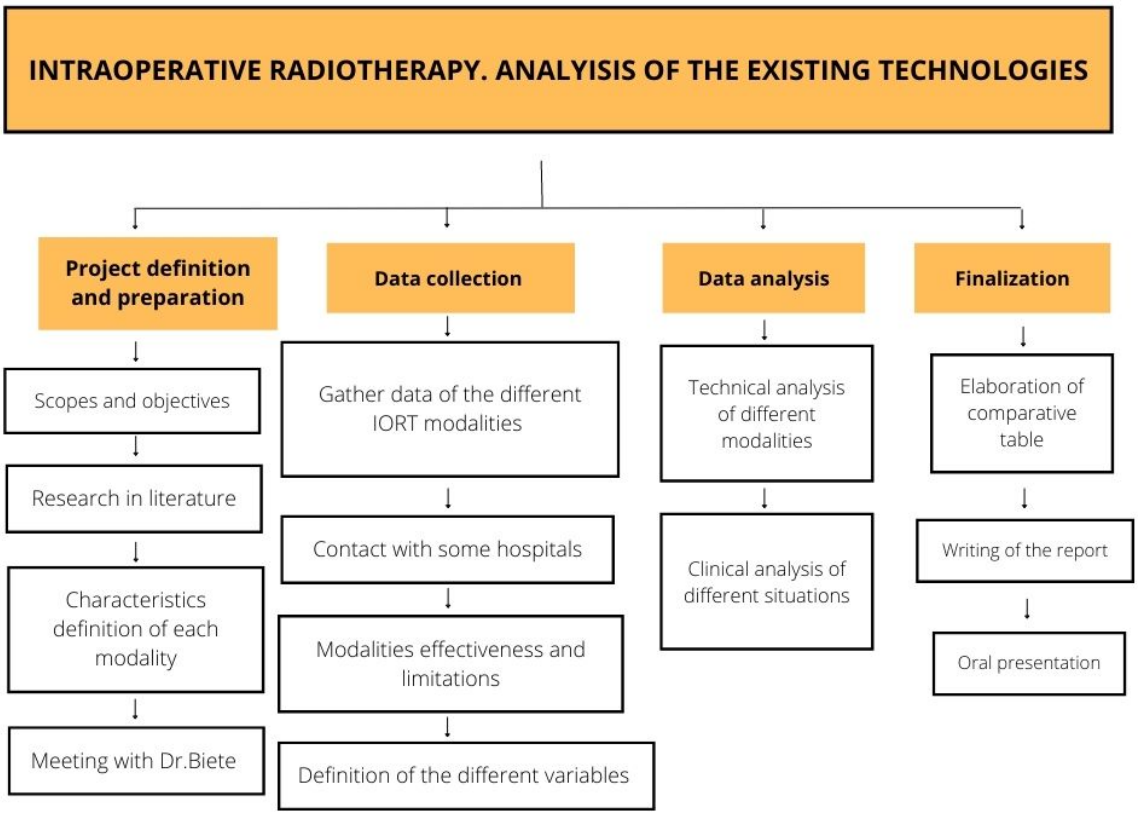

Figure 29. Work Breakdown Structure of the project

In Table 14, a comprehensive enumeration and description of the different project tasks is provided.

Table 14. Enumeration and description of the different project tasks

Nº	TASK	DESCRIPTION
	Project definition and preparation	
1.1.	**Scope and objectives**	Definition of the project scopes and objectives, determining the aim and what will be covered in the overall work.
1.2.	**Research in literature**	Research and identify relevant literature to gather information and insights on the different IORT modalities existent.
1.3.	**Characteristics definition of each IORT modality**	Define the characteristics of each IORT modality, identifying the applications and features of each one.
1.4.	**Meeting with Dr. Biete**	Conduct a meeting with Doctor Biete to define the different characteristics of the project, and all the methodology and approach that will be implemented.
	Data collection	
2.1.	**Gather data of the different IORT technologies**	Obtain relevant information about the different intraoperative radiation modalities (electron IORT, low-kV X-ray IORT, and HDR-IORT).
2.2.	**Contact with some hospitals**	Contact with some hospitals to get relevant information about the equipment they employ. Specially, contact with Antonio Herreros to gather relevant documentation about the equipment used in Hospital Clínic of Barcelona.
2.3.	**Modalities effectiveness and limitations**	Assess the efficacy and constrains of each IORT modality, analyzing data about performance, outcomes, and drawbacks for each IORT modality.
2.4.	**Definition of the different variables**	Determination of the different variables that will be considered during the comparison process.
	Data analysis	
3.1.	**Technical analysis of the different modalities**	Technical analysis of the environment needs, equipment cost, maintenance, radiation beams and dosimetry for each IORT modality.
3.2.	**Clinical analysis of the different situations**	Clinical analysis of the different clinical situations and patient outcomes for each IORT modality.

Nº	TASK	DESCRIPTION
	Finalization	
4.1.	**Elaboration of a comparative table**	Elaboration of comparative tables to summarize information and facilitate data analysis.
4.2.	**Writing of the report**	Write the final report summarizing the findings of the project.
4.3.	**Oral presentation**	Oral presentation of the project with an explanation of all that has been done during the project.

8.2 PERT diagram

To ensure timely completion of the project tasks, a PERT diagram is created. This diagram represents the different project tasks and their corresponding timeframes, defining the total duration of the project and the identification of what tasks must be completed before others begin. In Table 15 the time required to complete the specific tasks has been determined.

Table 15. Table of the task dependencies and durations

ID WBS	ID PERT	PREVIOUS ACTIVITY	Estimated time (days)
1.1	A	-	7
1.2	B	A	15
1.3	C	B	10
1.4	D	C	1
2.1	E	D	5
2.2.	F	D	3
2.3.	G	E, F	5
2.4.	H	G	5
3.1	I	H	20
3.2	J	H	20
4.1	K	I, J	10
4.2	L	-	86
4.3	M	L, K	1

This table provides valuable insights into the independencies among tasks. It determines the tasks that can be done simultaneously and the ones that are dependent on the completion of preceding

tasks. The early and last time are calculated for each task. Early time represents the minimum duration required to complete the task and the last time represents maximum time for task completion. With the PERT diagram, the critical path has also been determined, outlining the tasks that must be executed without delay, because any delay could modify the final project timing.

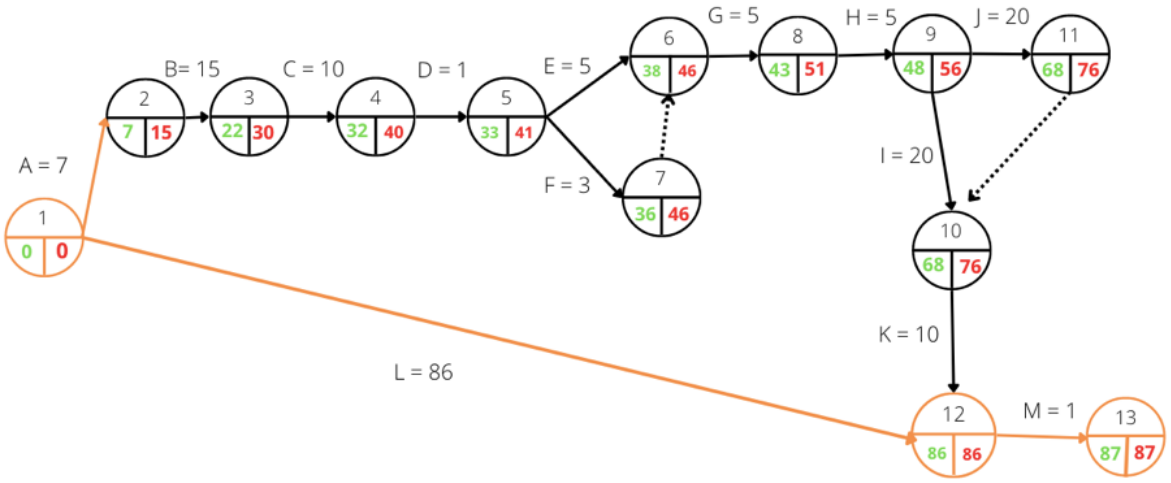

Figure 30. PERT diagram of the project

The critical path depicted by the orange line is composed by the activities L and M. This critical path represents the overall completion of the report, which is very important as it contains all the technical characteristics and comparisons of the IORT modalities studied. Consequently, the project cannot be finished until the writing part is over.

8.3 Gantt diagram

Finally, the duration of each task in days is represented in a Gantt diagram. On the left site of the diagram the different list of tasks is represented with their respective days needed to be performed. All the tasks that were original planned have been strictly followed, so a well-planned organization of the project has enabled a good development of all the activities and timings without missing deadlines.

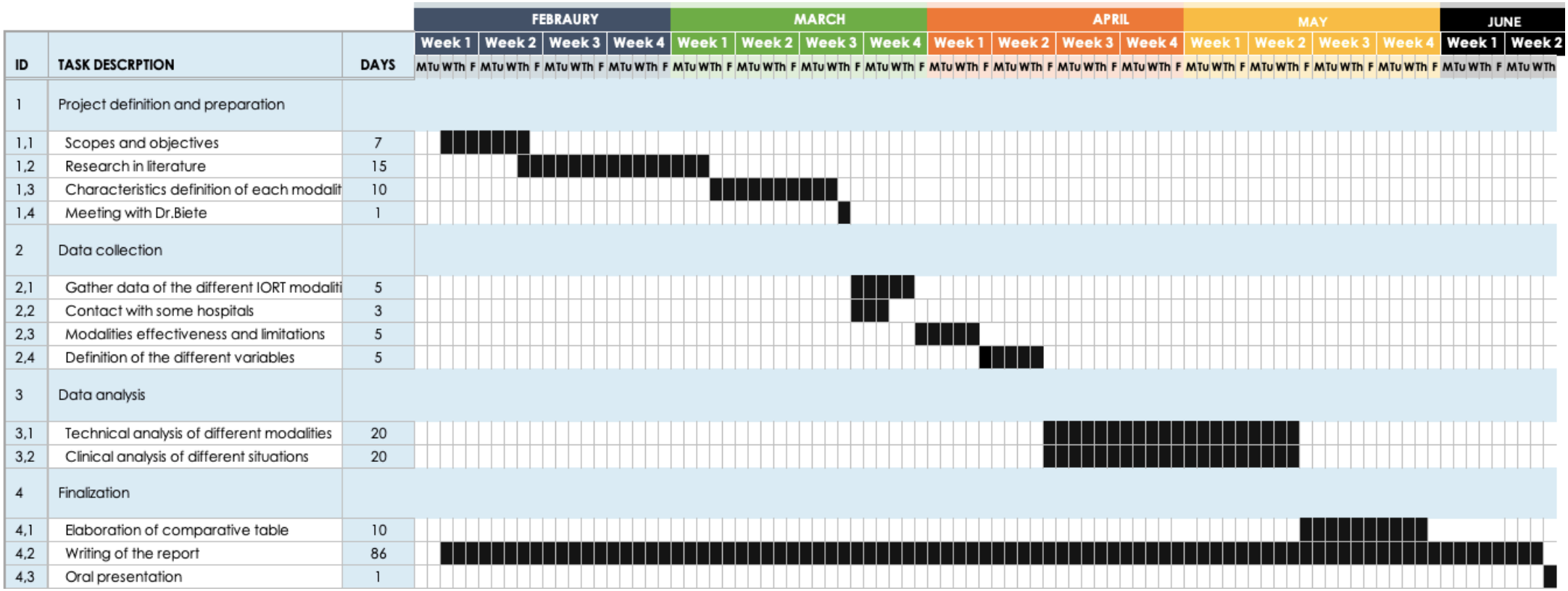

Figure 31. GANTT diagram of the project

9. REGULATIONS AND LEGAL ASPECTS

The implementation of intraoperative radiotherapy in Spain is regulated by Spanish guidelines and regulations related to radiological protection and the use of the equipment. These regulations are established and governed by several decrees, and compliance with them is essential to maintain the highest standards of quality and safety in the use of IORT equipment.

First, Royal Decree 1029/2022 [60], which approves the regulation on health protection against the risks derived from exposure to ionizing radiation, establishes some rules and protective measures to ensure the safety and health of individuals exposed to ionizing radiation. For IORT equipment, the main responsibility lies with the practice holder to ensure compliance with all the regulations about radiological protection. This involves on the maintenance of an optimal level of environmental protection, a proper maintenance of protection devices, the implementation of necessary equipment and measurement procedures for radiological protection, the conduction of calibration procedures, and the equipment verification with periodic checks, among other measures.

Additionally, Royal Decree 601/2019 [61], on justification and optimization of the use of ionizing radiation for the radiological protection of people on the occasion of medical exposures, outlines various considerations and general guidelines applicable to medical procedures involving ionizing radiation, including those used in IORT. The medical exposures must be justified based on patient characteristics, considering potential risks and benefits associated with radiation exposure. It also states that the radiation physicist is the responsible for the physical and clinical dosimetry to assess the dose delivered to the patient. This specialist also needs to provide its expertise and advice in the participation of the technical specifications needed for the equipment, the installation design, and the acceptance testing of the equipment. Finally, the decree states that there should also be a surveillance of medical radiation facilities, including monitoring of radiation levels to ensure compliance with safety regulations.

Finally, Royal Decree 1836/1999 [62], which approves the regulation on nuclear and radioactive facilities, includes the requirements for obtaining operating authorization, and the need to have documentation such as a descriptive report of the installation, safety studies, verification of the installation, and internal emergency plans, among others.

10. CONCLUSIONS

In conclusion, when healthcare institutions need to purchase an equipment for intraoperative radiotherapy, it is crucial for them to evaluate and analyze the different modalities available, as they offer distinct technological characteristics and considerations. The comparative analysis of the three available modalities (electron IORT, low-kV X-rays, and HDR-IORT) reveal that each has distinct technological considerations, operational room requirements, radiation beam characteristics, clinical indications, and financial implications. By conducting a comprehensive comparative analysis, healthcare institutions can gain a deeper understanding of the advantages and limitations of each modality, enabling them to make informed decisions based on their requirements and treatment objectives.

10.1 Future directions

It is convenient to consider several future aspects that can further advance the IORT field, because the need for continued research to improve the equipment and technology available is necessary to enhance the actual precision and effectiveness. Additionally, a deeper analysis on the clinical outcomes associated with each modality could provide valuable insights into having more information of how each modality performs in different cancer types. Furthermore, promoting ongoing collaboration between healthcare institutions, researchers, and manufacturers is crucial because by collaborating diligently, these stakeholders can improve the actual techniques, introduce new technological components, and create new innovative solutions. Overall, the continuous pursuit of advancements in IORT technology can significantly improve the delivery of IORT, aiming to enhance quality of care provided to patients undergoing intraoperative radiotherapy.

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