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Intra-Operative Radiotherapy with Electron Beam

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1. Introduction

Surgery is in many cases the most effective therapy to eradicate tumors in the human body. It is applied effectively in cases of tumors with low production of metastasis. However since the early decades of the last century a large fraction of recurrence after the operation have been observed. The number of cases with the onset of recurrence greatly decreases when the region which underwent surgical resection is treated with radiotherapy. External beam radiation therapy with photons is currently the most widely used. The conformal techniques and the intensity modulated radiotherapy reduce but do not completely eliminate damage to healthy tissues traversed by the radiation. In cases where the tumor is located very close to radiosensitive normal tissues or in cases of cancer for which fractioned treatments are ineffective, external beam radiation becomes difficult to apply. The technique of intra-operative radiotherapy (IORT) is effective in such cases as it allows direct visualization of the region to be irradiated after the removal of the lesion and it allows healthy tissue to be protected. The IORT technique consists in the delivering of a single high dose of radiation to the target volume, by shielding the healthy tissue, during the operation.

In the early years of application of IORT, beams of low energy photons (Comas & Prio, 1907; Beck, 1909) were used. The penetrating ability, however, produced damage to underlying tissues traversed by the radiation. This approach was then abandoned until beams of electrons instead of photons were used in Japan (Abe & Takahashi, 1981; Abe, 1989).

Fig. 1 shows the trends of the absorbed dose in water as a function of depth normalized to the value of maximum dose. Two beams generated by a Varian Clinac 2100 DH were used: A 6-MV photon beam and an electron beam of energy 6 MeV. It can be observed that the release of the maximum dose occurs at depths very similar for both electrons and photons. However, while the dose of electrons is released in a few cm from the entry point, the dose of photons is released at greater depths. The electrons are the most suitable particles to give the required dose of radiation directly to the tissues displayed during surgery, thus protecting the underlying healthy tissues.

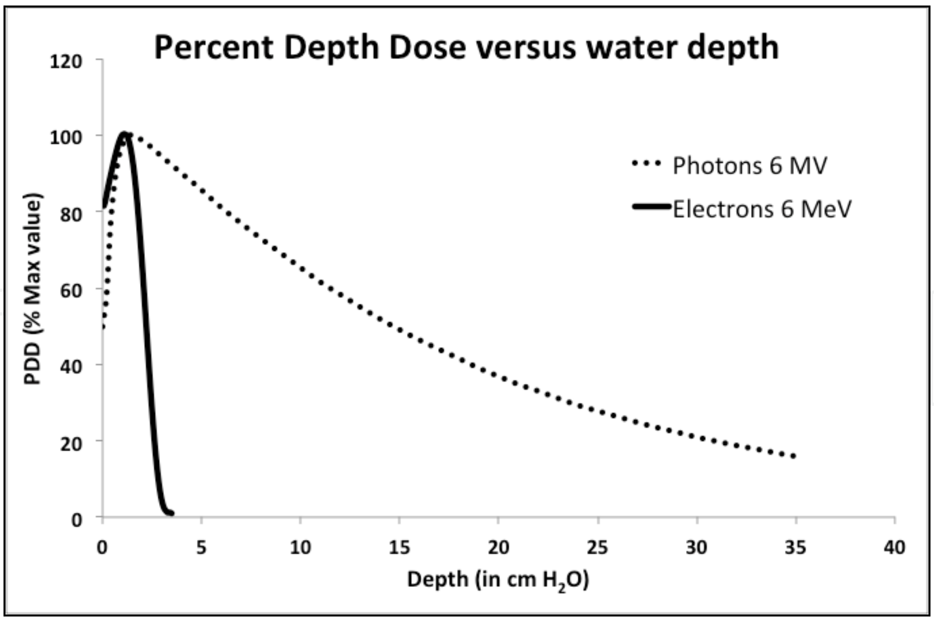

Fig. 1. Per cent Depth Dose (PDD) as a function of depth in water. The photon behaviour is compared to the electron delivered dose. In a few cm the electron dose is absorbed while a greater depth is needed to absorb the photon dose.

The results obtained with electrons have contributed to the diffusion of IORT in the world and to the development of dedicated mobile accelerators to be used in operating rooms. The three compact Linac (linear accelerator), Mobetron (IntraOp Medical Inc., 2011), NOVAC7 (Ronsivalle et al., 2001), LIAC (Soriani et al., 2010), were the most used in the first decade of 2000. These machines generate electron beams of variable energy range 3-12 MeV. The ability of high dose rate (up to 20 Gy/min) allows the delivering of the required dose in a few minutes. The experience accumulated over the past ten years for the research of more versatile systems has produced new proposals on the market (NRT, 2011).

In the next section we will describe such systems. Two were completely designed and built in Italy.

A detailed description of the technique and a presentation of results according to disease-site may be found in the recent textbook "Intraoperative Irradiation" (Gunderson et al., 2011).

However, two aspects of IORT technique with dedicated accelerators have not yet been fully defined. The first is the difficulty of making a treatment plan similar to that prepared for treatment with external beam. The second is the difficulty of using dosimeters recommended by the standard protocols for radiotherapy, due to the high dose per pulse (3-12 cGy/pulse).

In the following paragraphs we present some results and methods intended to overcome these difficulties and provide a good basis for future developments.

2. Dedicated LINAC

Until some years ago, it was not possible to perform intraoperative radiotherapy with electrons in a conventional operating theatre. In fact, the accelerators were located within a bunker of radiotherapy departments and patients had to be transferred under anesthesia from the operating theatre to the accelerator room for treatment. In some cases, the entire surgical procedure was performed in a modified accelerator treatment room.

In the last ten years there has been an increasing interest in the IORT technique due to the development of mobile accelerators which produce only electron beams. This type of machine can be introduced directly into the operating room without any other special fixed shielding systems. Several types of mobile accelerator are now available on the market (Mobetron, Novac7, Liac®). These mobile machines have solved logistical and radioprotection problems which are related to their use in conventional operating theatres. These machines have allowed a widespread use of this approach. In the following paragraphs, we will describe the most important features of the three mobile accelerators mentioned previously.

2.1 Mobetron

The Mobetron® (Mobetron is a registered trademark of IntraOp Medical, Inc.), has been designed and configured for intraoperative radiotherapy.

The Mobetron is a lightweight X-band linear accelerator mounted on a C-arm gantry. The gantry is attached to a stand that contains the accelerator cooling system and a transportation system. A mobile modulator rack, a lightweight operator control console, and connecting cables complete the Mobetron system. The Mobetron may be adjusted for two configurations: accelerator horizontal with a low center of gravity for transportation and storage; and accelerator vertical for treatment. In transport configuration, the Mobetron is compact; its dimensions are such that it may fit on to many elevators. The unit can be removed from the operating theatre for maintenance and annual calibrations. The control system contains the dosimetry readout parameters, accelerator controls, machine interlock status, and a color video output of the treatment viewing system.

The Mobetron produces electron beams of nominal energies 4, 6, 9, and 12 MeV.

At 12 MeV, R_{50} value (i.e. the value of the depth in water at which the dose is 50% of its maximal value) is 47.7 mm.

While conventional medical linear accelerators operate in the S band (10 cm wavelength, 3 GHz frequency), the Mobetron operates in the X band (3 cm wavelength, 10 GHz frequency) and this allows transportability and positioning flexibility. In fact, the diameter of the accelerator structures is therefore reduced by a factor of three.

The gantry is in the configuration of a C-arm, but with some additional flexibility of movement. The gantry may be rotated ±45° downward in the transverse plane. In addition, the gantry may be tilted ±30° in the radial plane. Also, the gantry may be moved in and out, and from side to side in the horizontal plane, ±5 cm. The gantry tilt and horizontal movements are unique features not found in conventional accelerators used for intraoperative radiotherapy. The axis of rotation is 99 cm above the floor and the nominal electron source to treatment surface distance (SSD) is 50 cm (i.e to the end of the treatment applicators). Gantry rotation and tilt movements are controlled by the hand held pendant and are variable from 0 to 1° per second. Horizontal movements are controlled in a similar manner and vary from 0 to 2 mm per second. The gantry design includes an integral beamstop to intercept photon contamination generated in the accelerator, collimation system, and the patient. The gantry with accelerator, cooling system, beamstop, and transportation system has a mass of 1250 Kg. Mobetron transportation is accomplished by using a modified pallet jack, located at the rear of the gantry stand. Wheels attached to the front of the gantry support legs and wheels integral to the pallet jack provide a stable support for transportation.

The Mobetron uses two X-band linear accelerators in tandem. One-third of the radio frequency power is injected into the first accelerator, producing electron energy of 4 MeV. The remaining two-thirds of the power may be absorbed in a water load and/or injected into the second accelerator guide. Adjusting the phase to change the amount of power that enters the second guide, as opposed to the water load, varies the energy. As the power in the second guide is changed, the phase of the microwaves in the second guide is simultaneously adjusted to maintain optimal resonance in the accelerator structure. This allows energy control between 4 and 12 MeV without using a bending magnet, which corresponds to a therapeutic range of 4 cm. The injector system, together with a prebuncher and beam alignment system, control the electrons to occupy a very narrow energy spectrum, reducing radiation leakage. Since the bending magnet is a major source of radiation leakage in conventional accelerator designs, this design feature also contributes to a significant reduction of photon leakage.

Applicator sizes ranged from 3 to 10 cm diameter for flat applicators, and 3 to 6 cm diameter for 30° beveled applicators. The Mobetron uses a soft-docking system in which the treatment applicator is connected to a special rigid clamp system attached to the surgical bed and the gantry is optically guided to the docking position above the applicator. During irradiation, the docking is interlocked for both alignments of the treatment head with the applicator and for treatment distance.

The dose-rate ranges from 2.5 to 10 Gy/min at SSD of 50 cm with an applicator of 10 cm diameter.

As the unit is designed to operate only in the electron mode, beam currents are low, producing less inherent radiation leakage. Together with the compact beamstop opposite the electron beam, the overall design allows the system to be used in rooms with no additional shielding.

2.2 Novac

The first model, named Novac7 (Hitesys SpA (LT) Italy 1997), is a dedicated accelerator with four nominal electron energy levels: 3,5,7,9 MeV. At 9 MeV, R_{50} value is 31 mm. This value is related to the mean energy of electrons, about 7.2 MeV, on the surface of the water equivalent phantom.

The most important Novac7 dosimetric characteristic is the very high dose-per-pulse, ranging from 2.5 to 12 cGy/pulse, values up to 100 times greater than the doses per pulse produced by a conventional accelerator.

Novac7 has both a mobile and a fixed unit. The mobile unit is a stand structure on a motorized base, which supports the accelerator and modulator. The stand structure has the form of an articulated arm with four rotational joints, allowing movements similar to those of human arms. The base permits the entire structure to move without modifying the head orientation.

The beam collimation is performed through poly methyl methacrylate applicators consisting of two separated sections: the upper is fastened to the accelerator's head, with the lower in contact with the patient. These sections are aligned and finally hard-docked together before dose delivery. The applicators set consists of cylindrical tubes with a wall thickness of 5 mm, diameter ranging from 4 to 10 cm, and face angles of 0–45°. The length of the applicators varies according to the diameter: 80 cm for diameters up to 8 cm and 100 cm for those up to 10 cm. Using an applicator of 10 cm diameter and the maximum energy, the depth corresponding to 85% of maximum dose, measured in water, is about 18 mm on the geometrical central axis. When beveled applications are used the dose distribution is asymmetric and with high gradients of dose.

The Novac7 does not employ scattering filters which in conventional machines are the main source of stray radiation, but for this reason it is complicated to modulate accelerator dose rate, which is high compared to conventional accelerators. The total bremmstrahlung photon dose for conventional accelerators is at least 2-3% of the dose at the depth of R_{max}, mainly due to head scatter. For Novac7 9MeV nominal energy this value is 0.2% of the dose value at R_{max}.

The novelty of the Novac7 system (NRT, 2011) concerns the accelerating structure. The accelerating structure consists of a β graded SW 2998 MHz on-axis coupled linac operating in π/2 mode with 11 accelerating cavities and is 50 cm long, powered by a 2.6 MW magnetron: it is a compact accelerating structure in which the beam focusing is automatically achieved without using external magnetic lenses and the losses are kept at low energy so getting a negligible diffused X radiation.

Model	Old Novac7 (Hitesys)	New Novac7 (NRT)
Nominal Energy	3 – 5 – 7 – 9 MeV	4 – 6 – 8 – 10 MeV
Beam current	1.5 mA	1.5 mA
Frequency of emission	5 Hz	9 Hz
Scattering foil	No	No
Dose rate	9 > e < 21 Gy/min	>6 e < 39 Gy/min
Field Diameter	4,5,6,7,8,10	3,4,5,6,7,8,10
X-ray contamination	< 0.2 %	< 0.2 %
Power dissipation	<1kW	<1kW

Table 1. Novac system evolution

The single cavity shapes were optimized in order to maximize the efficiency and to reduce the dark currents, which could be a serious problem for the operation of the system at very low currents. In particular the beam hole diameter was reduced from 8 to 6 mm and the cavity nose shape was modified. The shunt impedance was increased of 15%: in this way adding only four cavities to the Novac7 structure it is possible to increase the maximum energy with the same power.

The main characteristics are reported in Table 1.

2.3 Liac

Liac® 10 MeV (SORDINA SpA Italy) is an intraoperative radiotherapy system, which produces electrons with energies of 4, 6, 8 and 10 MeV with a dose rate between 5 and 20Gy/min and a pulse frequency between 5 and 20 Hz.

At 10 MeV, R_{50} value (i.e. the value of the depth in water at which the dose is 50% of its maximal value) is 38 mm.

The Liac® system consists of a mobile radiant unit and a operator control rack, connected by a 10 meter cable, which during the irradiation supplies the radiant unit with electrical power and transmits the treatment parameters. During the IORT session the Liac® is not connected to the local electrical system but is fed by the UPS (Uninterruptable Power Supply) hosted in the control rack. The weight of the Liac® radiant unit is less than 400Kg, so that there are no installation problems in any surgical suite; a battery system lets this unit move independently in the operative block. An innovative robotic system allows the LIAC to be extremely mobile and strongly simplifies hard-docking procedures. The LIAC head has three degrees of freedom: it can be moved up and down for a maximum excursion of 100 cm, it has a roll angle of ± 60° and a pitch angle between + 30° and – 15°.

The standing wave S-band linear accelerating structure, specifically designed for Liac , is 850 mm long and consists of 17 autofocusing cavities; it is supplied with a 3.1MW Magnetron, with 2.5 µs pulse length and produces an electron beam of 12 MeV maximum energy. The pulse repetition can vary from 1 up to 20 p.p.s (pulse per second).

The output beam has a 3 mm diameter and is collimated by a sterilizable cylindrical perspex applicator 60 cm long, different diameters and terminal beveled angles. The dose homogeneity on the surface to be treated is generally guaranteed by a 100 µm brass foil scattering filter inserted in front of the titanium window. This technique allows the optimization of the accelerator performances keeping the level of stray radiation below the required limits. A new type of dosimetric system has been implemented to monitor the beam. It is based on a properly designed resonant cavity. The signal, proportional to the absorbed dose, is picked up from the cavity, acquired and displayed in real time on the control rack, with a good signal-noise ratio. This dosimeter is not affected by saturation phenomena and temperature, pressure and humidity are independent.

Due to the need to minimize the length of the Perspex applicator, a scattering foil, made of brass (50- 150 µm thickness), was introduced in the beam to produce a homogenous profile. This technique allows the optimization of the accelerator performances, keeping the level of stray radiation below the required limits.

Sordina's 10 MeV model has been on the market since 2001 and, to meet customer demands, a new Liac® model able to accelerate electrons up to 12 MeV was developed in the last few years.

The Liac® 12 MeV accelerating system is a newly designed linac operating in the $\pi/2$ mode at 2998 MHz. The electron energy is set by varying the radiofrequency power from 1.2 up to 3 MW. The new machine setup provides four clinical energy points: 6, 8, 10 and 12 MeV. At 12 MeV, R_{50} value (i.e. the value of the depth in water at which the dose is 50% of its maximal value) is 48 mm.

The 12 MeV LINAC is 92.5 cm long (19 accelerating cavities) and its total weight, including electron gun and ionic vacuum pumps, is less than 30 kg. Radiofrequency power is supplied by an E2V magnetron MG6090.

The particular design of the LIAC 12 MeV accelerator head guarantees a minimal head leakage radiation, much lower than target scatter radiation. The accelerating waveguide has no external solenoid for electron beam radial focusing, but electrostatic focusing is used instead. This radial focusing system decreases the tail of electron beam distribution hitting the copper waveguide, reducing bremsstrahlung radiation, and focalizes the electrons along the beam line. It was manufactured in accordance with Italian regulations of radioprotection.

Furthermore there is no bending magnet and the metallic elements which the electron beam crosses along its path are a titanium window, 55 μm thick, an aluminum scattering foil, 820 μm thick and four ionization chamber electrodes, in total 20 μm thick. The total head leakage is less than the scatter radiation by a factor 10. The choice of using an aluminum scattering foil (820 μm) for the 12 MeV instead of a brass one (75 μm), as in the previous model (10 MeV), was made after an experimental study where the optimization parameters had the following characteristics: limited applicator length (for manageability reasons), beam flatness (within ± 5% evaluated at 80% of the dose profile), a controlled environmental x-ray radiation and a low neutron contamination.

It is worth noting that by reducing the applicator diameter (from 100 mm to 40 mm) the dose per pulse increases correspondingly. This type of collimation together with the absence of a bending magnet and the planning choice of light material make this equipment workable in operating rooms, keeping the stray radiation at a low level. Pulse Repetition Frequency (PRF) can be varied from 1 to 60 Hz. The PRF is set by the manufacturer according to the various e-beam energies to keep the dose rate around 10 Gy/min with an applicator diameter of 100 mm. However, up to 30 Gy/min higher or lower dose rates are readily obtained. A newly designed system has been used to guarantee the LIAC output reliability. The current injected by the electron gun can be adjusted (± 5% maximum) by an automatic dose control board (ADCB) to keep constant the read-out of the two monitor chambers so that the ratio cGy/MU is kept reliably constant. Radiofrequency power is supplied by E2V magnetron MG6090. Electron energy is set by varying the radiofrequency power from 1.2 up to 3 MW. The new machine setup provides four clinical energy points: 6; 8; 10 and 12 MeV.

The PMMA applicators are 60 cm long and 0.5 cm thick and fully gas sterilizable; various diameters (from 30 to 100 mm typically) and bevel angles are available. The distance from the scattering foil to the end of the applicator or SSD is 713 mm.

This passive beam shaping technique allows good uniformity and flatness of the radiation field and a very low x-ray contamination. Furthermore, the electron beam interaction with the PMMA applicator generates low energy electrons which deposit the dose in the region very close to the surface: this fact explains the higher value of the skin dose with respect to (External Beam Radiation Therapy) EBRT linac. Surface dose is greater than 85% with 4 MeV e-beam and reaches about 94% with 12 MeV e-beam. The main characteristics are reported in Table 2.

Model	LIAC 10 MeV	LIAC 12 MeV
Nominal Energy	**4 – 6 – 8 – 10**	**6 – 8 – 10 – 12**
Beam current	1.5 mA	1.5 mA
Frequency of emission	1 – 60 Hz (variabile)	1 – 60 Hz (variabile)
Scattering foil	75 micron brass	850 micron aluminum
Dose rate	2-30 Gy/min	3-40 Gy/min
Field Diameter	3,4,5,6,7,8,10 & 12 opz	3,4,5,6,7,8,10 & 12 opz
X-ray contamination	< 0.5 %	< 0.5 %
Power dissipation	2 kW	2 kW

Table 2. Liac® system characteristics

3. Dosimetry of the beam

The IORT technique using the dedicated Linac machines requires special dosimetrical determinations, which are sometimes different in comparison to conventional external-beam radiotherapy. The main reason stems from the fact that a single high dose of radiation is delivered to a selectively defined volume of tissue, whose extension and depth are directly determined in the operating theatre. Particularly, the dosimetric data must allow the calculation of the Monitor Unit (MU) necessary to deliver the dose prescribed to the target volume. A further difference between IORT and external radiotherapy is related to the use of specific applicators that contribute to the determination of the physical-geometrical characteristics of the electron beams (quality, topology, homogeneity, etc.). All definitions are reported in the main international guideline (Istituto Superiore di Sanità [ISS], 2003; Palta et al. 1995; AAPM, 2006; Beddar et al., 2006).

A square applicator 10×10 cm^2 or a circular applicator of diameter 10 cm with a plane basis is recommended for measurements in reference conditions and for each energy. This choice should allow, in most cases, to have a SSD = 100 cm or a nominal SSD when the length of the applicator does not allow it. The depth of R_{max} (i.e. the depth at which the maximum dose is obtained) is recommended as reference depth for the dosimetry, both in reference and in no reference conditions.

The use of ionization chambers for the calibration of the beam in terms of dose per MU may be ineffective with dedicated machines because of the high density of electric charge produced in the chamber volume per radiation pulse. In particular the correction factor for ion recombination (K_{sat}) can be largely overestimated if the correction methods recommended by the international protocols are used. (AAPM, 1999; IAEA, 2001)

Italian guidelines (ISS, 2003) recommend the use of the absolute dosimetric system of Fricke for the measurement of the absorbed dose in water in reference conditions.

If other dosimetry systems are used, it is in any case required that all measurements can be traceable to national and international standards of the quantity “absorbed dose to water”. This goal can be achieved through the calibration of the dosimeters at a Primary Metrological Institute or by a recognized Calibration Centre.

The Fricke dosimeter is a chemical dosimeter based on a solution of iron sulphate (Olszanski A. et al., 2002) and it consists of a glass-sealed ampoule (8.7 mm in diameter and 28 mm in length, thickness of glass 0.5 mm) filled with a ferrous sulphate acqueous solution. Dose assessment is performed through optical absorption measurements with a spectrophotometer at a wavelength of 304 nm. The perturbation introduced by the glass walls of the vial should be taken into account. The calibration in terms of dose to water is made using a 60Co gamma ray field in a Primary Standard Laboratory. The stated uncertainty in dose measurement has been evaluated to be 1.5% (1s).

An alternative dosimetric system with sensitivity independent from the dose-rate, from the beam energy and from the angle of incidence of the electron beam is the alanine dosimetry.

This type of dosimeter consists of a blend of alanine (95% by weight) and polyethylene (5% by weight) pressed into pellets of 4.9 mm in diameter and 2 mm in length (1.2 g/cm^3 mass density) (De Angelis et al., 2006). The sample is measured with a spectrometer using the Electron Paramagnetic Resonance (EPR). Typically a set of five alanine pellets is used for each point of dose measurement. Each set is inserted into a quartz tube that is positioned in the microwave cavity for measurement. The alanine dosimeters should be calibrated in terms of dose to water in a 60Co gamma ray field against a Primary Standard Laboratory. The combined uncertainty in the measure is 1% (1s) for a test dose of 10 Gy.

Dose measurements performed using Fricke and alanine dosimeters have shown a good agreement, generally within 1% for plane-base applicators (De Angelis et al., 2006).

However, since the ionization chamber is the online absolute dose measurement device accepted as a reference dosimeter in clinical dosimetry, several authors have proposed corrections to take into account the free-electron fraction component which causes the overestimated value. The correction is introduced through the estimation of a saturation factor K_{sat}.

All the approaches are based on three improved theoretical models proposed by Boag (Boag et al., 1996). These authors did not provide particular criteria for choosing any of their three different expressions of k_{sat}.

Italian researches propose two different experimental approaches. Di Martino (Di Martino et al., 2005) suggested a new equation for k_{sat} in high dose-per-pulse beams based on the first Boag's formulas and experimentally derived the free-electron fraction p. The evaluation of some chamber-specific parameters is needed for calculation of ion recombination correction factor. The intercalibration with a second dose-per-pulse independent dosimeter is needed. Laitano (Laitano et al., 2006) proposed the evaluation of k_{sat} starting from Boag's two voltages analysis (TVA), suggesting that the third of three Boag's models is more adequate. The latter approach has the advantage of being able to avoid any chamber calibration using, however, the calculated value of p as a function of chamber characteristics and experimental conditions.

In the general dosimetric characterization of the electron beams produced by an accelerator dedicated to IORT, the absolute dose in the point of the clinical prescription (buildup depth in water on the clinical axis) for the beveled applicators must also be determined. We refer to this type of dosimetry as "in non reference conditions".

Dosimetric characteristics of the electron beams requires the knowledge of:

- PDD (Percentage Depth Dose) measured along the clinical axis of the beam (which is different from the geometrical axis in the case of base-beveled applicators, with the indication of the values of the main parameters: R_{max}, practical range (R_p), depth in water at which the dose is reduced to 90% and 50% of maximum dose (R_{90}, R_{50}), surface dose and per cent dose due to the photon contamination of the beam (tail of bremsstrahlung radiation);
- Beam profiles measured in two orthogonal directions at the depths of R_{max}, of R90, of R80 and of R_{50};

Values of the output expressed as dose per Monitor Units (MU) (cGy/MU), measured in a point at the reference depth on the clinical axis of the beam;

Such characteristics must be measured for every applicator, energy and SSD of clinical interest.

For low energy electron beams (4-10 MeV), as suggested by international protocol, a parallel-plate ionization chamber should be used. Ross, Markus and advanced Markus types (PTW Freiburg Germany) are the most utilized (PTW, 2011). But the response of these types of chamber is angle dependent so their use with a beveled applicator is not possible.

Because of its high spatial resolution and independence on beam direction, a small cylindrical chamber, such as CC01 (Wellhofer, 2011) or Pin point (PTW), seems to be particularly suitable to perform absolute dose measurements for electron beams collimated with inclined applicators (Karaj et al 2007, Iaccarino et al. 2011).

Due to the presence of electrons scattered by the applicator, the electron fields obtained with IORT-dedicated applicators are characterized by a wider energy spectrum and a wider angular distribution than electron beams collimated with conventional systems. This implies a higher surface dose (especially for the lower nominal energies) and less steep dose gradients (especially for the higher nominal energies).

For this reason, a dosimetry system must be selected characterized by a minimum dependence of the response from the beam energy and from the angle of incidence of electrons. It is recommended that, when measuring the dose distribution, the same dose-rate (MU/min) should be used during the determination of the output and during the treatment of the patients. It is also recommended to investigate and determine the percentage of the radiation scattered through the applicator's walls, as a function of the beam energy and of the distance from the walls and from the base of the applicator.

For PDDs and Profiles diodes or diamond detectors should be used in water phantom. Relative absorbed dose measurements, i.e. percentage depth doses (PDDs) and off-axis profiles (OAPs) could be performed using a p-type diode in the water phantom. The signal from the diode detector is stated to be approximately proportional to the absorbed dose to water. The uncertainty in the diode position is typically less than 0.2 mm and PDDs and OAPs are acquired with a spatial resolution of 1.0 mm.

For the Output measurements, in no reference conditions and in particular in the case of small and or beveled applicators, a solid phantom and radiographic or radiochromic films (Fiandra et al., 2008), or TLD (Palta et al., 1995) may be employed.

Because of its high spatial resolution, weak energy dependence, and near tissue equivalence, Gafchromic films have been selected as the reference detector for relative measurements of the output factor, for applicators of various dimensions length, diameter and angle of incidence.

4. Decision parameters during surgery

The final goal of IORT is an enhanced control in loco-regional tumor. IORT is feasible for intra-abdominal, retroperitoneal, pelvic and other malignancies. More recently, clinical experiences have shown that IORT may improve local control and disease-free survival, especially when used in adjuvant setting, combined with external beam irradiation in the stomach, pancreas, colon-rectum cancer and soft tissue sarcoma.

The rationale for the use of this segmental radiation therapy in place of whole-breast irradiation (WBI) is based on the results of some long-term studies reporting that local relapses after conservative surgery and External Beam Radio Therapy (EBRT) occur at the original tumor site at a rate of 80% or more, with few exceptions. This has been also confirmed by the results of the Milan III trial, which compared quadrantectomy alone with the same conservative surgery plus EBRT on the whole breast, have confirmed that 85% of local relapses were in, or close to, the previous index quadrant (Ivaldi et al., 2008). Another important advantage of the IORT is the avoidance of interaction with systemic therapy that may determine delays in the initiation or in performing conventional EBRT when CT, and particularly anthracyclin-based cycles, are given.

Widespread applications of IORT at various disease sites are feasible due to improvements in technology. By increasing the maximum energy of the linear accelerators of IORT and the total radiation dose it is possible to improve the therapeutic ratio and the tumor local control without increasing morbidity. Moreover, IORT is used as an adjuvant therapy, i.e., given as a boost after conventional fractionated radiotherapy.

IORT is generally given as a single fraction of 10 to 20 Gray (Gy). The single fraction is considered biologically equivalent from two to three times that of conventional fractionation for tumors while it is radiobiologically inferior due to impaired cellular repair of surrounding normal tissues, thus the protection of these tissues is mandatory. In fact the benefit in local recurrence needs to be carefully considered against the complications arising from the addition of IORT. This means that the appropriate entrance of the beam should be selected as well as the appropriate applicator diameter/kind and beam energy. This determines the Output factors (OFs) to be used and the monitor units evaluated using on an appropriate formula. In order to determine a dose-response effect a dosimeter could be placed within the field to be representative of the tumor bed or close to an Organ at Risk (OAR) near the applicator or under an additional shield.

The dose to be prescribed to target depends on the kind of disease, as well as on the microscopic spread expected in the tumor bed. This is particularly important when the resection margins are positive and depends on tumor stage and on radio-resistance of cells.

5. Simulation of treatment plans

Treatment planning is the process in which a team of radiation oncologists, surgeons and physicists plan the most appropriate radiation treatment for the patient using an external beam or by means of an internal beam such as IORT.

Currently, it is very complicated to plan the radiotherapy process beforehand, this is because the team of specialists must choose at the very moment of operation the cone dimension, its positioning, the bevel angle and the electron beam energy according to its medical and surgical experience and the information gathered during surgery. One of the main limitations of IORT is due to the removal of diseased tissue from the patient during surgery which will change the geometric shape. In this way it is difficult to carry out a feasible dosimetry calculation using pre-operative images.

This aspect highlights two main problems for the planning of the intervention:

- Before the operation: it is difficult to estimate the dose to be received;
- After the operation: since such images are not available, the results cannot be assessed.

Today, treatment planning is entirely focused on the use of specific software. This software uses algorithms that exploit the patient's images, by means of the computed tomography (CT), for extremely realistic simulations.

Systems like Novac11 and Radiance are now a single integrated platform, which include not only the dedicated mobile accelerator, but also simulation software (NRT, 2011).

Radiance (Radiance, 2011) is the only available Radiotherapy Treatment Planning System (RTPS) that has been specifically designed for Intraoperative Radiotherapy (IORT) and the only one that works in such a field of radiotherapy. Radiance allows the specialists to simulate the whole IORT workflow. The operator can simulate the full delivery of the dose loading and visualizing CT images of the patient. The best choice of the parameters needed may be taken (applicator geometry, accelerator energy, number of MU …) to maximize the dose on the tumor or tumor bed and to minimize the contribution to the healthy tissues.

A new step in the IORT procedure has been introduced, the preplanning phase. In this pre-simulation, it is possible to modify the different parameters of the procedure to evaluate the outcome without stress in the real treatment decision-making process. Thus, it improves the safety of the global procedure. Radiance is a state-of-the-art development unrivalled today worldwide. It uses advanced visualization, simulation and dosimetry algorithms that are far ahead, concerning performance, of any current software. DICOM images are loaded and their volumetric representation built online. The computation of both graphics and dosimetry computation algorithms is almost in real time. The capability of simulation of different tissue densities opens a new era in the planning of IORT. At the same time the measurements required for commissioning a linear accelerator have been reduced considerably.

The dose calculation is carried out by means of two dosimetry computation engines which are available in radiance:

- An adapted and validated fast implementation of the Pencil Beam algorithm used in external radiotherapy.
- A parallel implementation of Monte Carlo algorithm.

In the future built-in tools that make use of advanced simulation software, as described, will be increasingly used. This software will be able to improve not only the quality of the radiosurgery procedure, and therefore the results on patients, but also the interaction of the various specialists involved (radiation oncologists, surgeons and Physicists) through simulations of different scenarios.

6. Use of scintillating fibers for dosimetry

Several types of dosimeters have been developed to measure the precise dose and the percentage depth dose (PDD) using detectors such as ion chambers, silicon-diode detectors, diamond detectors, liquid ion chambers and radiographic films. They are partially ineffective, considering requests for new approaches to therapy such as: small sensitive volume, dose rate independence, measurements in real-time, use of high doses, no dependence on environmental conditions, such as temperature, humidity and pressure. For this reason new dosimetric systems have been studied and proposed in recent years (Aoyama et al., 1997; Staub et al., 2004; Archambault et al., 2005; Consorti et al. 2005).

These include dosimeters based on scintillating fibers. Difficulties arising in the conventional techniques have been overcome by providing features such as: small sensitive volume, high spatial resolution, water or tissue equivalent material, linear response, independence from energy and from dose rate, independence from environmental conditions such as temperature, pressure and humidity, high resistance to radiation exposure, real-time response.

One of the first works that showed the potential of scintillating fibers to measure the depth-dose for electron beams was published in 1997 (Takahiko et al., 1997). Over the past 10 years several proposals have appeared in literature with the use of scintillating fibers. Some of these have used small volumes of scintillating fibers coupled to light guides for reading the response to light (Archambault & Arsenault, 2005 ; Frelin & Fontbonne, 2006 ; Bongsoo et al., 2008 ; Staub, 2004). In others, detector elements have been incorporated in a water phantom equivalent in order to have a 3D representation (Fontbonne et al., 2002; Guillot et al., 2010; Lacroix et al., 2008). In all these approaches, the technique of elimination of Cerenkov light was needed. This contribution is very small and negligible compared to the scintillation light in the scintillating fibers. However the Cerenkov light becomes dominant, in the light guides, connecting the scintillating fibers to the electronic readout, when the guides are subject to radiation (Archambault et al., 2006).

The approach described in this paragraph is different because it is very similar to that adopted in X-ray diagnostics (Bartesaghi et al., 2007a, 2007b). The dose absorbed along the beam is read by scintillating fibers assembled in homogeneous planes orthogonal to the beam axis. The light produced is integrated and collected for the read out at the end of each fiber, giving the projection of the signal in one dimension. The fibers assembled in each homogeneous plane are ready at one end. The approach is similar to the reading of one-dimensional Radon transformation of the dose absorbed. In a previous work (Lamanna et al., 2009) we studied the basic elements constituting the device. In this chapter we present the results of the study of the therapeutic beam of electrons (the system can be used for other particles, photons, protons etc.) with a homogeneous layer of plastic scintillating fibers.

6.1 Dosimeter characteristics

According to the clinical dosimetry, the absorbed dose is calculated in the biological tissue. For this reason, dosimeters built with equivalent tissue are more suitable. Water is the source material for phantoms taken as equivalent tissue in all electron beam dosimetry protocols. This choice comes from the fact that approximately 2/3 of the human body is made up water. The dose distribution curves in water and in tissues are very similar, because water is an excellent image of diffusion and absorption properties of the human body. However, in many cases the employment of water as a test phantom is not very useful. Thus it can be replaced by solid materials with similar physical properties like polystyrene and perspex (PMMA). In theory, water tissue-equivalent materials should have effective atomic number Z_{eff} (electron number per gram), and a density equal to water. In clinical applications, however, a material with electron density as close as possible to water is fairly suitable (McLaughlin & Chalkey, 1965).

For these reasons the system DOSIORT (IORT Dosimeter) is conceived as a box made of a tissue-equivalent material (polystyrene) with a density ρ = 1.05 g/cm^3. Inside the box there are six sensitive layers spaced 4 mm apart and set perpendicularly to the Z direction of the incident beam, as shown in Fig 2.

Each layer is composed of a grid consisting of two bundles of 190 scintillating optical fibers having a square cross section of 0.5×0.5 mm^2 and crossing one over another so as to define a XY layer with an area of approximately 10×10 cm^2. We use 380 BCF-60 scintillating optical fibers produced by Saint Gobain Crystals.

The light emitted in the fibers is read-out by two photodiode (Phd) arrays Hamamatsu S8865-128 for each bundle. The Phd are read sequentially using the Hamamatsu driver C9118 and the signal is digitized and processed by a computer with dedicated software.

The read-out system is therefore composed of 24 arrays. A dedicated electronic system is able to acquire, process and display the reconstructed electron beam image in real time (within a few seconds).

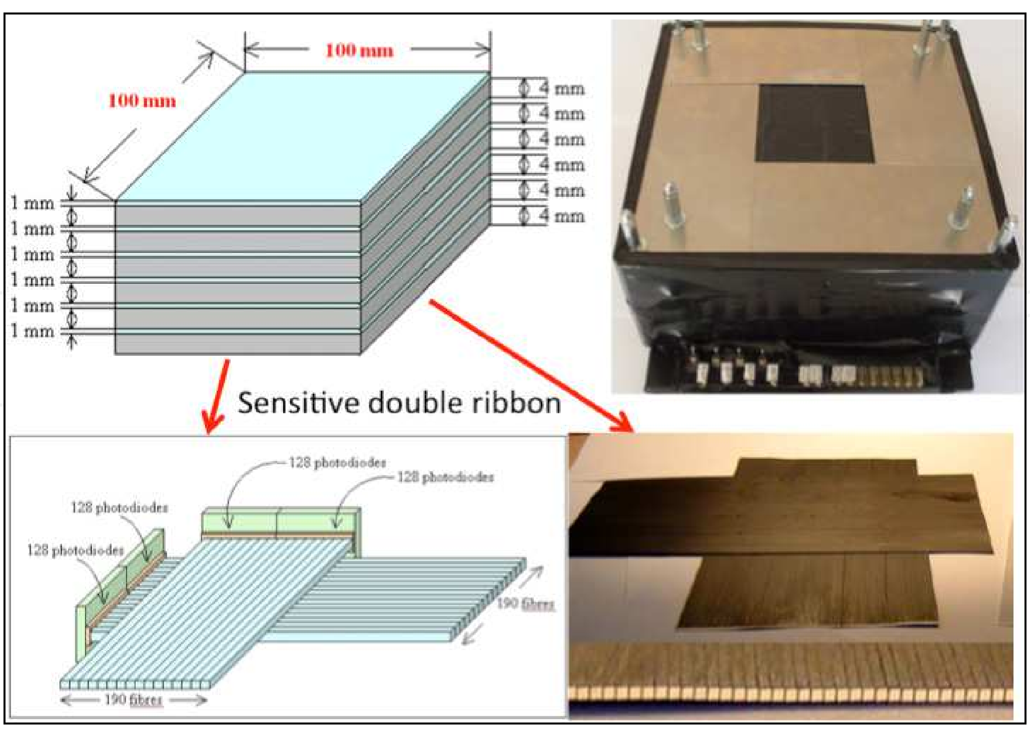

Fig. 2. Scintillating fiber dosimeter. On the left the characteristics of the layers are shown. On the right the photo of the dosimeter and of one double ribbon are shown.

The system is thus a solid phantom having a density approaching 1 g/cm^3, with sensitive layers of scintillating fibers set at fixed positions in a calorimetric configuration for the containment of electrons of energy 4-12 MeV. The prototype is able to define the physical and geometrical characteristics of the electron beam (energy, isotropy, homogeneity, etc) and to measure the parameters needed to select the energy, the intensity and the Monitor Units (MU) for the exposure: the Percentage Depth Dose (PDD); the Beam profiles; the Isodose curves; the values of dose per MU (cGy/MU).

Another important thing that must be considered is spatial resolution. The spatial resolution is a key feature for next-generation dosimeters. This feature will become more important in the next few years, in fact next-generation accelerators have a beam size up to 3 mm. DOSIORT responds fully to the demands of new approaches to radiotherapy. Its innovative detection system, made up of optical fibers which provide high spatial resolution and photodiodes with a sensitive area of 0.3×0.6 mm^2 with pitch of 0.4 mm, gives a high spatial resolution approximately 0.5 mm.

The materials used to make the detector and the operations needed before the data taking have been studied and described in details in previous papers (Lamanna et al., 2009a, 2009b). The sequence of the most relevant steps before beginning are: electronic noise measurement to be subtracted; choice of the integration time to ensure a dynamic range large enough to have a linear response from the detector electronic; evaluation of calibration factor for each Phd response by exposing the fibers homogeneously to the same beam.

In this paragraph we include the results obtained from testing the system with a photon beam of 6 MV and an electron beam of energy 9 MeV generated through a Varian Clinac 2100 DHX. The data are compared to the measurements obtained using the PTW Freiburg TM31010 ionization chamber and the PTW MP3 water phantom, when they are available.

The data taken through DOSIORT may be selected and elaborated considering the full detector or only part of the system. There are three different configurations for applying the dosimeter: using one layer (1D) at fixed depth and rotating it around the beam axis , using one double layers (2D) at different depths and using all six double layers (3D) at different depths. All the configurations are able to get the results in real time but the first system gives a more accurate measurement of the dose at fixed depth and it provides a series of measurements at different angles, the second one gives the results in depth more quickly but is less accurate in the reconstruction of the dose outside the FOV (field of view) region, the third is able to give a 3D estimation of the beam in depth into a single measure. However, all configurations require the acquisition of a number of measurements in a time that is in any case about a tenth of that needed to obtain the results with the ionization chambers or other traditional dosimeters. The choice is connected to the level of accuracy needed in the measurements.

6.2 Results using one layer of DOSIORT

The response of the detector was tested through exposure to a beam orthogonal to the layer surface using only one layer. The photon beam of 6 MV was selected with a FOV of 8x8 cm^2. The system was rotated manually around the beam axis and the projected data were collected every 5 degrees for a total of 37 positions from -87.5 to 92.5 degrees.

The projection of the dose in arbitrary units at different angles and positions along the rotating axes is shown in Fig. 3,a.

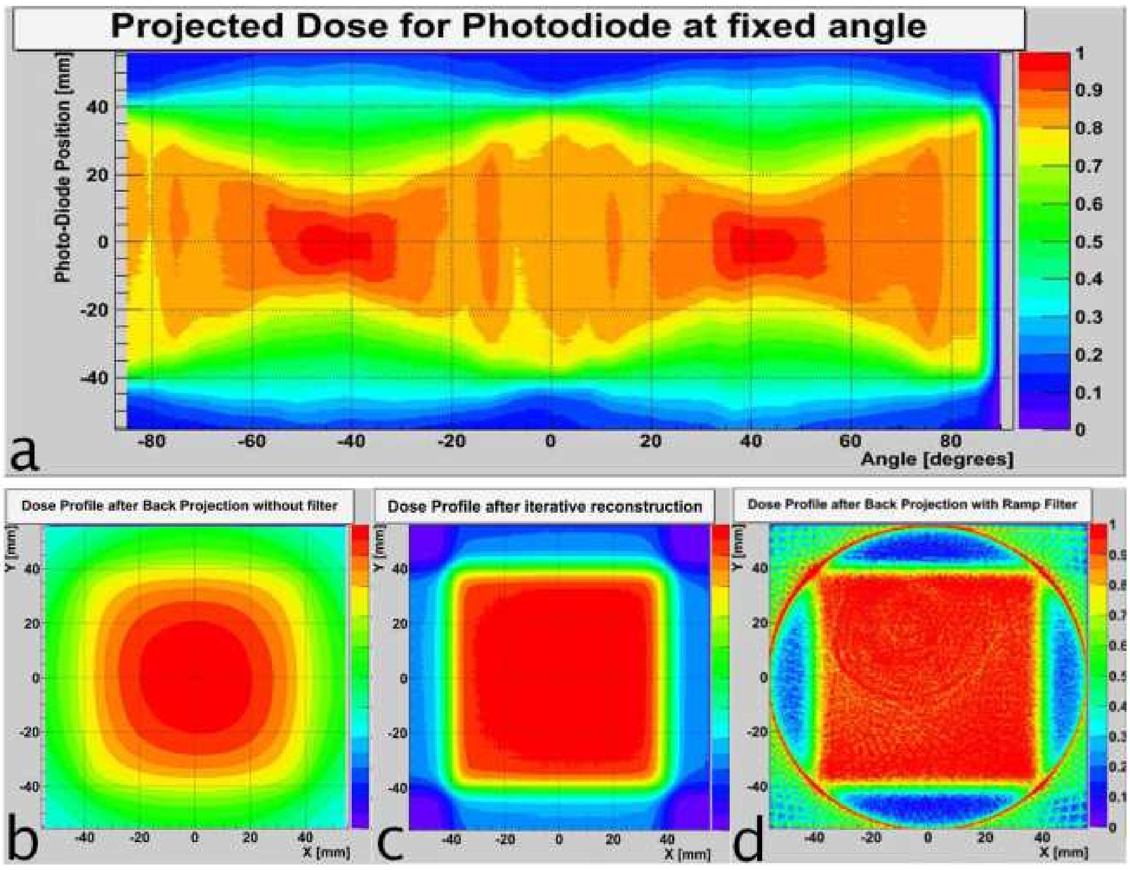

Fig. 3. a) Projected dose at 37 rotating angles around the beam axis; b) Back Projection without filter; c) Iterative reconstruction; d) Filtered Back Projection with ramp filter.

The plot shows the typical behaviour of a square FOV with maximum values around the diagonal at -45 and 45 degrees.

The 37 projections were used to reconstruct the transverse profile of the dose. The fibers collect the light generated along their axis, thus each acquired profile corresponds to the projection of the beam delivered along an axis. This system is not dissimilar to image reconstruction problems in tomography, where several projections have to be composed to trace them back to the original image. For this reason the first reconstruction method chosen was the back-projection algorithm widely used in tomography. Nevertheless using a back-projection approach without a filter we obtained a poor profile (Fig.3,b) while with the introduction of a ramp filter (Fig. 3,d) a better reconstructed image can be obtained. We additionally developed a dedicated algorithm based on the principle of the tomographic iterative methods.

The iterative method uses only two orthogonal projections. The choice of the two projections is very important to determine a good result in the reconstruction. We have selected the projections at 0 and 90 degrees. The idea is to sum the data collected by each fiber along an axis with the corresponding fiber for each of the two different angles, weighing the projection contribution on the basis of its concordance with the other projections results.

The image obtained in this way is a weighted sum of the contributions of two projections. Then the difference between the sum along an axis of the reconstructed image and the acquired values is calculated. This parameter is taken as the error to minimize iterating the method. Each value difference is projected back on the reconstructed image to correct the values along the fiber and then a new difference between reconstructed and acquired data is calculated. This method, described in (Brancaccio et al., 2004), is able to converge into seven/eight steps and in less than a second. The reconstructed image seems to be more precise (Fig. 3,c). A more accurate comparison is shown in Fig. 4 where the reconstructed dose profiles are superimposed on the profile obtained using the ionization chamber around the centre of the beam.

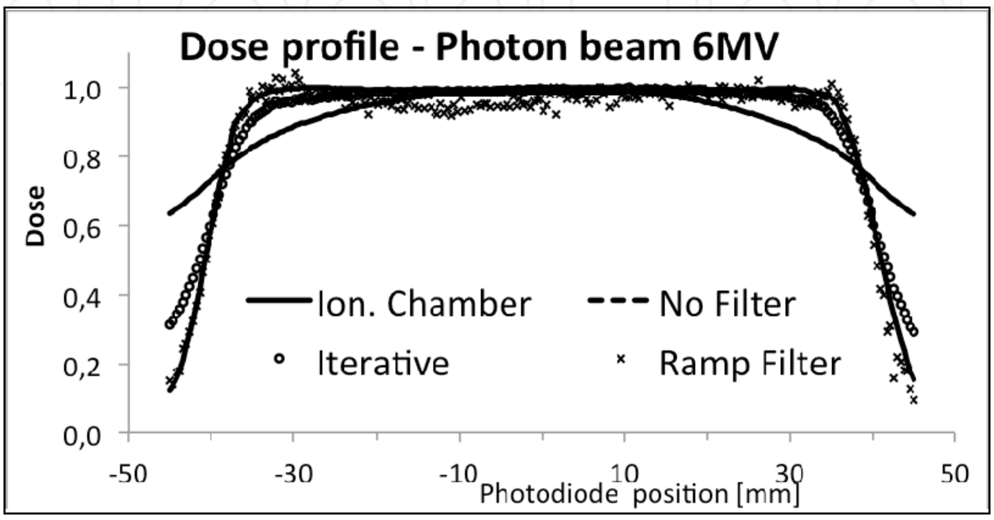

Fig. 4. Dose profile measured using Ionizing chamber superimposed on the reconstructed dose profiles using the iterative and the back projection with and without filters.

The reconstruction using the back projection with ramp filter reproduces quite accurately the dose profile from the maximum to about 10%. Some fluctuations are visible in the flat region. The iterative approach describes quite well the profile in the FOV used [-40 to +40 mm] where the dose varies from 100% to 50%.

6.3 2D Results using one double layer of DOSIORT

The energy 9 MeV was selected for the test of 1 double layer (XY) of DOSIORT. The FOV was set at 4×4 cm^2 in order to study the energy response containing the doses absorbed.

The data were taken in different acquisition tests. In each test we changed the geometry of the setup superimposing over the previous configuration a sheet of polystyrene of 4.2 mm in water equivalent thickness. In this way we simulated a homogeneous phantom with measurements at different depths.

The double layer 2D was used for the reconstruction of the XY map of dose absorption at different depths. The XY projections collected for each acquisition, after correction for noise and calibration, were used to reconstruct the dose through the iterative method used for 1D detector and explained in (Brancaccio, 2004).

In Fig. 5 isodose curves at four fixed depths are shown for electrons of 9 MeV. The performance is similar to the reconstructions obtained in medical imaging using only two projections. The results are acceptable in a region coinciding with the FOV, [-20 to +20 mm] in the pictures. Outside this region the reproduction is poor.

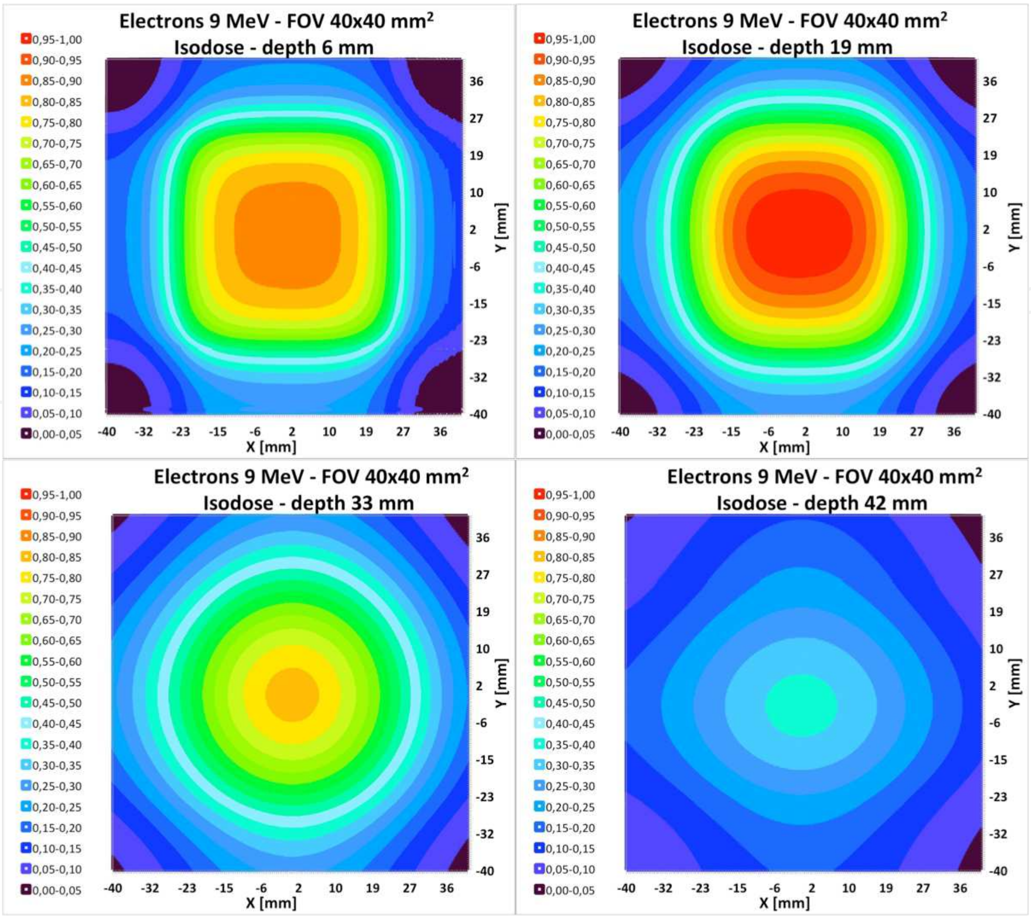

Fig. 5. Isodose at four fixed depths for electrons of energy 9 MeV. A FOV 40×40 mm² was selected.

The reconstructed doses may be used to visualize the depth dose profiles, selecting one central slice for each fixed step. The performance obtained is shown in Fig. 6.

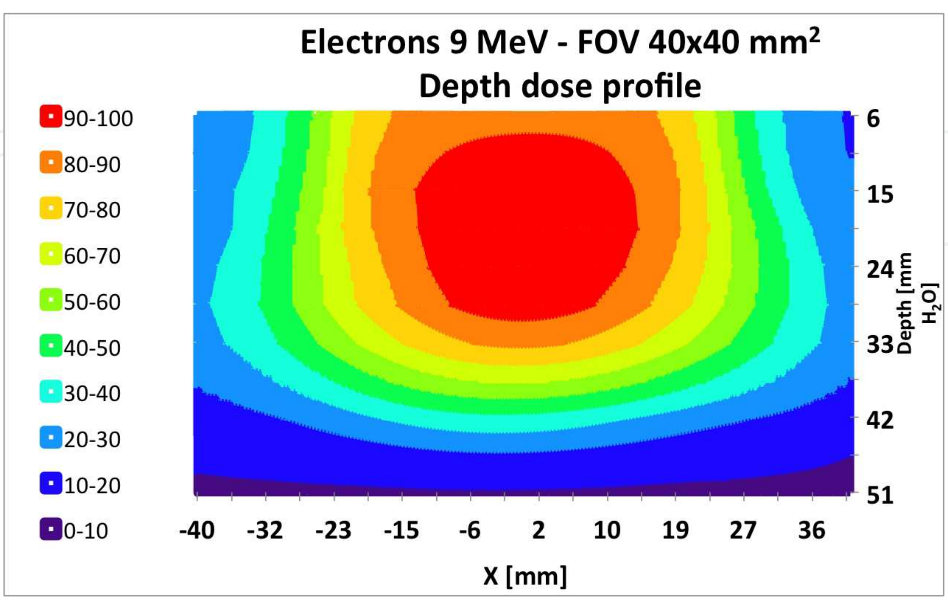

Fig. 6. Depth dose profile for electrons of energy 9 MeV. A (FOV) 40×40 mm² was selected.

Also in this picture the region inside the FOV is well represented.

6.4 3D Results using DOSIORT

The full detector DOSIORT may be used to measure the dose in three dimensions.

The system, optimized through Monte Carlo simulation as explained in (Lamanna et al., 2009a), is able to contain the full shower produced with electrons of energy 6 to 9 MeV. Greater energies may be measured using the same technique as in the previous paragraph: by superimposing sheets of polystyrene over the detector. The thickness of the sheets must be selected to position the build-up inside the detector. The isodose curves measured in each double layer for a beam of electrons of energy 9 MeV, using a FOV of 40×40 mm² without external sheets are shown in Fig. 7. The dose is reconstructed using the iterative method described previously. The curves are well described in the FOV region. Outside some artefacts connected to the reconstruction method are visible.

The central X slice of the isodoses shown in Fig. 7 are represented on the left side of Fig. 8. The dose profile in depth is well reconstructed. The comparison with the ionization chamber results is done in the right part of the same figure, using the average of the dose in a central surface of area 2×2 mm², corresponding to 4×4 scintillating fibers. The measurement through DOSIORT reproduces the PDD curve obtained through the ionization chamber.

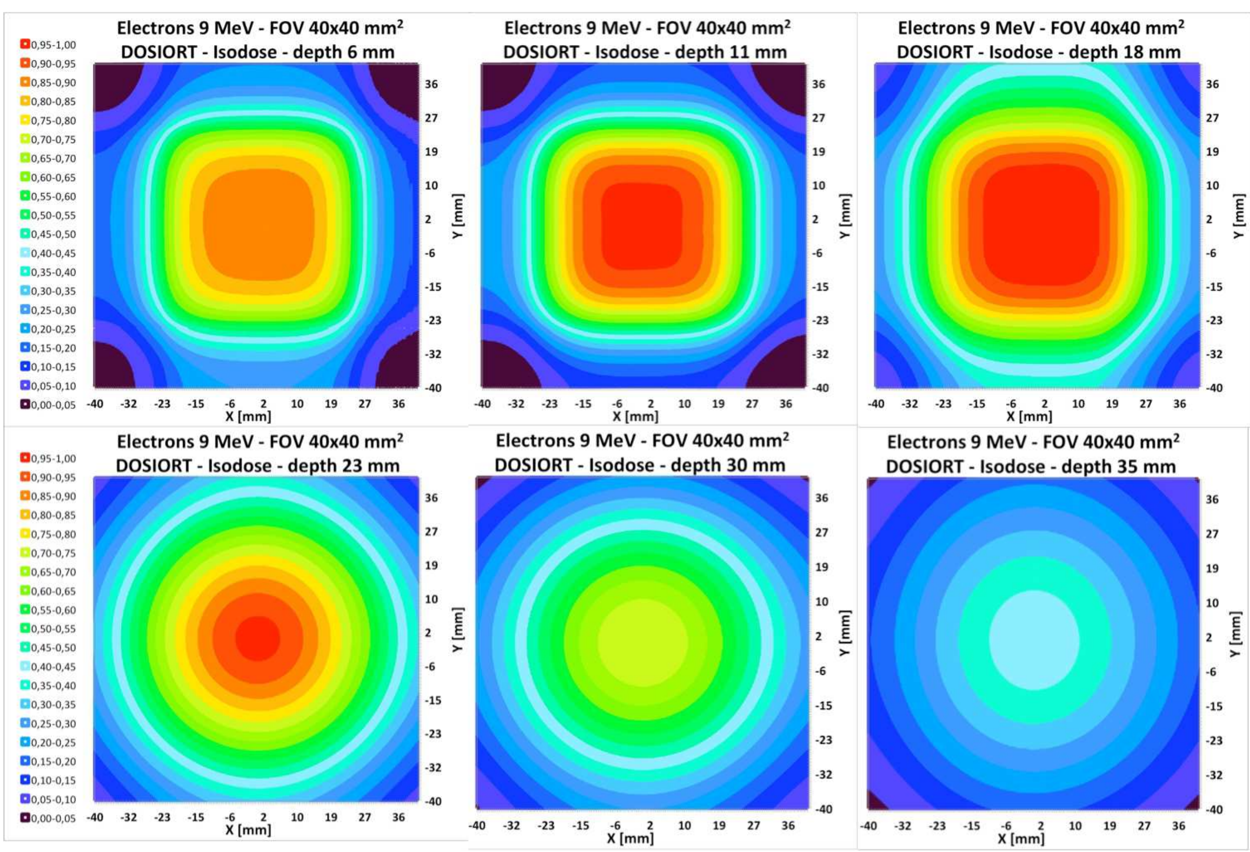

Fig. 7. Isodose curves reconstructed through the iterative method described in the test using data taken with 6 double layers of DOSIORT.

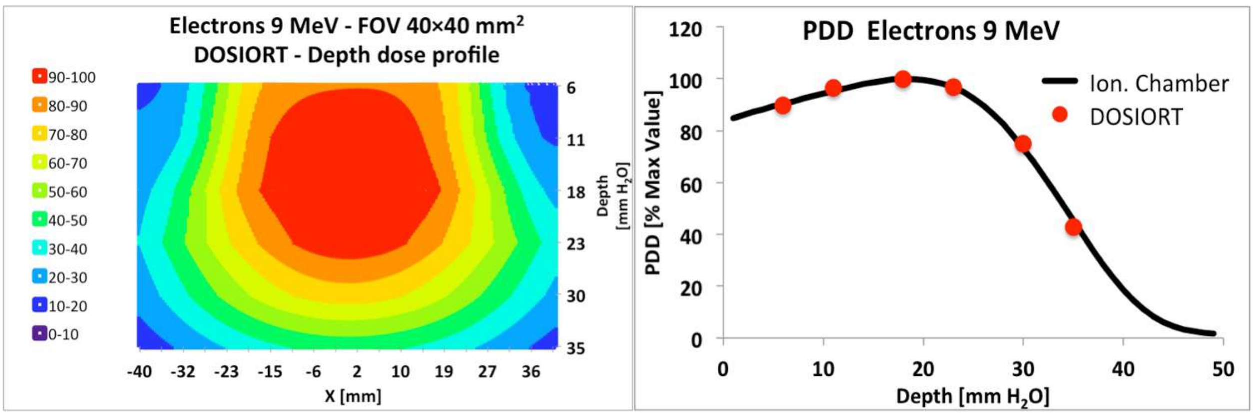

Fig. 8. Depth dose X profile on the left and PDD curve on the right: DOSIORT compared to the results of the Ionization Chamber.

7. Current activities and future clinical perspectives

Many efforts have been made by physicists and physicians in order to improve this therapeutic approach. In the main, medical physicists have conducted many studies to determine the dosimetric characteristics of the beams produced by these dedicated devices, in order to overcome the limits of the dosimetric systems, such as ionization chambers. In particular, dosimetric data and the OFs of flat and bevelled applicators for all available applicator/angle combinations have been investigated using Monte Carlo simulation. The aim was to predict with higher accuracy the dose distributions delivered to the target and Organs at Risks, and to use this information in modern treatment planning systems, which are mandatory to improve the knowledge of dose-effect relationships.

In fact, even if the Monte Carlo method requires longer computing time, it is capable of accurately calculating the dose distribution under almost all circumstances and can be employed as a benchmark of conventional treatment planning systems.

Another future clinical perspective is based on the deep investigation of radiobiology of IORT. In fact, the current radiobiological models should be applied up to 16-18 Gy, i.e. for higher doses the validity of Linear Quadratic model should be proven. Because IORT is used as an adjuvant therapy, i.e. given as a boost after conventional fractionated radiotherapy, the modality to combine the expected effects of fractionated and single dose fraction should be tested and verified in a clinical setting.

Moreover, the development of on-line systems to monitor the three dimensional dose distributions should be encouraged in order to reduce the time of verification and quality assurance before treatment delivery; as well as during the acceptance tests in order to reduce the time of the physical characterization of these machines for each combination of energy and applicator diameter or collimator systems.

Finally, the availability of large field sizes (larger than 10 cm), as well as of beam modifiers should prove to be more efficacious for larger targets such as sarcomas, while sparing normal tissues.

8. Conclusion

The implementation of the new Linac for the production of electron beams dedicated to IORT in the last 10 years has allowed a diffusion of the therapeutic approach in a large number of health facilities by making the approach easier to use. Its use has facilitated the possibility to carry out clinical trials in international contexts for different types of tumor. Accelerators available on the market are today excellent for use in operating rooms. The improvements of the IORT technique pass through the proposal of means that include devices and methods to cover completely the therapeutic intervention. In particular through introduction of tools that help operators to select parameters required for this radio-surgical technique. Among these the most important are: a specific treatment planning system, and an efficient distribution map of the beam dosimetry. Today effort is devoted to introducing improvements in these two fields.

GMV-RADIANCE (GMV, 2011) has recently introduced on the market a Proposal for IORT treatment planning. This package is included in the method ELIOT (Electron Beam Intraoperative Radiotherapy) of the NRT (NRT, 2011) and it is really promising.

The Dosimetry of the beam is assessed using conventional systems with some difficulties to provide all the necessary measurements. In this chapter a method based on scintillating fibers is described. The results of the tests performed using a Varian electron beam are promising. The system allows, quickly and in detail, the measurements of the dosimetric distributions of the beam. The evolution of the system will be the engineering of the prototype to improve the electronic read-out and its stability.

9. Acknowledgment

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10. Abbreviations used in this chapter

AAPM: American Association of Physicists in Medicine;
ADCB: Automatic Dose Control Board;
DICOM: Digital Imaging and COmmunications in Medicine;
EBRT: External Beam Radiation Therapy;
FOV: Field Of View;
IORT: Intra-Operative RadioTherapy;
IAEA: International Atomic Energy Agency;
INFN: National Institute of Nuclear Physics;
ISS: Istituto Superiore di Sanità;
K_{sat}: Correction factor for ion recombination in ionization chamber;
Linac: Linear Accelerator;
MU: Monitor Unit;
NRT: New Radiant Technology;
OFs: Output factors;
PDD: Per cent Depth Dose;
Phd: Photodiode;

PMMA: Poly(Methyl Methacrylate);
PRF: Pulse Repetition Frequency;
R_{max}: Depth in water at which the dose has the maximal value;
R_p: Practical Range;
R_{50}: Depth in water at which the dose is 50% of its maximal value;
R_{90}: Depth in water at which the dose is reduced to 90% of its maximal value;
SSD: Source to treatment Surface Distance;
TLD: Thermo Luminescent Dosimeter;
TVA: Two Voltages Analysis;
UPS: Uninterruptable Power Supply;
Z_{eff}: Electron number per gram;

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