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**Guidelines for quality assurance
in intra-operative radiation therapy**
English version

Edited by Antonella Rosi and Vincenza Viti
Laboratorio di Fisica

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Guidelines for quality assurance in intra-operative radiation therapy. English version.

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2003, vi, 68 p. Rapporti ISTISAN 03/1 EN

Intraoperative Radiation Therapy (IORT) facilities, especially accelerators specifically designed for unshielded operating theatres, have proliferated in the last few years in Italy. In the framework of a national project on quality assurance in radiotherapy, the Istituto Superiore di Sanità (the Italian National Institute of Health) established a multidisciplinary working group in order to develop guidelines on quality assurance for IORT technique. All involved staff (radiation oncologists, medical physicists, surgeons and anaesthetists) has experience in IORT clinical practice. The document presents these Italian guidelines, therefore addressing both clinical and physical-dosimetric aspects. The document has received the consensus of the Italian Radiotherapy Centres and Medical Physics Services operating in this field.

Key words: Intra-Operative Radiation Therapy (IORT), Quality assurance

Istituto Superiore di Sanità

Linee guida per la garanzia di qualità nella radioterapia intraoperatoria. Versione inglese.

A cura di Antonella Rosi e Vincenza Viti

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Il crescente numero di Centri italiani che effettuano trattamenti di radioterapia intraoperatoria (*Intra-Operative Radiation Therapy*, IORT), soprattutto con acceleratori dedicati, ha posto l'esigenza di stabilire linee guida sulla garanzia di qualità in relazione alla IORT. In questo documento sono presentate le linee guida italiane elaborate con il coordinamento attivo dell'Istituto Superiore di Sanità, da medici oncologi radioterapisti, fisici medici, chirurghi e anestesisti italiani con larga esperienza nella IORT e condivise da tutti i Centri di radioterapia e Servizi di fisica sanitaria italiani che effettuano questo tipo di trattamento. Il documento illustra la filosofia globale della garanzia di qualità nella IORT, considerando quindi sia gli aspetti clinici sia quelli fisico-dosimetrici.

Parole chiave: Radioterapia Intraoperatoria, Garanzia di Qualità

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PREFACE

The drafting of new laws and directives in national and European circles on the subject of protection against the dangers of the ionising radiation connected to medical exposures (1-3) and the consequential demands from rapid technological developments, have directed particular attention to the subject of quality assurance in radiotherapy. The present legislation (1) underlines that in all organisational-functional contexts the use of guidelines, prepared by scientific associations or groups of experts, are recommended for ensuring good clinical practice in various medical branches.

For several years the Laboratory of Physics of the *Istituto Superiore di Sanità* (ISS) has been proposing initiatives related to quality assurance in radiotherapy, organising courses/debate and elaborating guidelines on this subject. The role of the ISS in this regard has also been confirmed in its new regulation (4) where it is highlighted that, among its institutional assignments, ISS is designated as a Consultant body for public Health protection in relation to the production and application of energy for diagnostic and therapeutic purposes.

Within this context the ISS has established an Interdisciplinary Study Group on quality assurance in radiotherapy, which, on the basis of inputs from Italian Centres working in this sector, has felt it necessary to begin elaborating guidelines for special techniques. A document has already been produced on the Brachithery (5) and, more recently, it has been decided to start the development of guidelines for the Intra-Operative Radiation Therapy (IORT), and for the Total Body Irradiation (TBI), which are techniques frequently used in Italian Centres.

With regard to IORT, which is the focus of the guidelines presented here, there are at present seventeen Italian Centres, located in different geographical areas, that have started therapeutic programmes that foresee the employment of this technique of radiotherapy.

It has been considered fundamental that such guidelines be jointly elaborated by radiation oncologists and by experts in medical physics with long experience in this sector, in accord with their respective Scientific Associations: AIRO (*Associazione Italiana di Radioterapia Oncologica*, Italian Association of Oncology Radiotherapy) and AIFM (*Associazione Italiana di Fisica Medica*, Italian Association of Physics in Medicine), with the collaboration of the surgeons and the anaesthetists from the SIC (*Società Italiana di Chirurgia*, Italian Society of Surgery), the SICO (*Società Italiana di Chirurgia Oncologica*, Italian Society of Oncological Surgery) and the SIAARTI (Italian Society of Anaesthesia Analgesia Reanimation and Intensive Therapy). Also radiation technologists (radiographer) in accord with the AITRO (*Società Italiana di Anestesia Analgesia Rianimazione e Terapia Intensiva*, Italian Association of Technicians on Oncological Radiotherapy) have been consulted in their areas of expertise.

A working group, including experts experienced in the use of the IORT technique, has been constituted for the design of the guidelines and a consensus group from the Centres already employing the technique has been formed to provide additional input. This activity is co-ordinated with that of specialist professional groups, creating a synergy leading to the improved application of the IORT technique. The guidelines have been organised in a modular structure in order to facilitate their future revision and updating.

Finally, we highlight some fundamental points on the philosophy within which the guidelines have been developed and elaborated.

The continuous improvement of quality is a main component of the operational objectives, which are considered more and more a priority in health structures. Such a concept, together with that of quality assurance, does not insure *per se* the optimal implementation of health standards, but allows the Institution to demonstrate that it works according to rules of good

behaviour and practice, reducing the potential risks connected to the implementation of complex clinic procedures.

The guidelines must be regarded as systematically elaborated recommendations of behaviour, with the purpose of assisting operators to decide on the most appropriate lines of action in specific clinical situations.

They must be seen, therefore, as a tool for decision-making but not be taken as having binding force. The variability of conditions and situations is so great and the progress of knowledge so rapid that it would be necessary or even recommended in some instances to draw away from what is suggested in the professional guidelines. In such cases it would be useful to point out the possible reasons and motivations for divergence, in order to facilitate the revision and up dating of guidelines.

Guidelines should not act as a brake on the promotion of, or participation in, research that verifies the validity of alternative approaches to those suggested by the guidelines.

While guidelines, if rigidly imposed, can threaten innovative research, they can also serve to promote such research in the following ways:

- in the elaboration or in the discussion of the guidelines can emerge areas in which the scientific knowledge is still insufficient and in which it is necessary to implement further research;
- in the application the operators can identify problems at first not seen or seen in an unclear manner.

INTRODUCTION TO INTRA-OPERATIVE RADIO THERAPY

The term Intra-Operative Radiotherapy (IORT) refers to the application of radiation during a surgical intervention, after the removal of a neoplastic mass. IORT uses the incision to direct radiation to the tumour bed, to the possible localisation of sub clinic illness or to macroscopic residue in the case of non- radical resection.

Intra-operative Radiotherapy foresees a single session only, generally preceded or followed by radiotherapy with external beam. It allows the achievement of a selective radiation boost on the tumour volume. In some cases, it can also be used as a one- time/stand alone treatment in initial cancers of small volume, or in unresectable malignancies for palliative purpose.

Modern intra-operative radiotherapy is carried out with electron beams produced by a linear accelerator generally used for radiotherapy with external beam, transporting the patient, in the course of the surgical intervention, to the shielded radiotherapy facility and re-transporting him to the operating theatre after the irradiation. Recently dedicated accelerators producing only electron beams of a maximum energy of 9-12 MeV have been designed, that can be introduced directly into an operating theatre without particular needs for special fixed shielding barriers. The use of this type of equipment avoids the transport of patients outside the operating theatre, but presents more complex problems in terms of dosimetry.

The possibility also exists to use equipment producing low energy X-ray beams or other equipment containing a high activity radioactive source for intracavitary irradiation. Both types of equipment allow to deliver the prescribed dose to the tumour bed during the surgical intervention under the same technical conditions of IORT with electron beams. It does not seem correct, however, to include in the procedures of IORT the intra-operative positioning of radioactive sources since the radiation dose is delivered after the removal of the tumour and the closing of the surgical wound. In these cases one of the main property of IORT that is its ability to deliver the dose after separating the structures between the tumour and the skin surface, which could be potentially damaged, is missing.

To maintain the homogeneity of the text it was decided to target the issues related to IORT carried out with electron beams (e⁻-IORT), leaving a final chapter to IORT using low energy X-ray beams produced by dedicated miniature sources.

Instead, it was felt to be more opportune to include the treatment with high dose-rate radioactive sources (High Dose Radiation–Intra-Operative Radiation Therapy, HDR-IORT), based on a completely different technology, in a future guideline related to the general theme of “brachithrapy.”

The aim of IORT is to improve the local control of the illness. Many aspects related to this objective can benefit from a programme of quality assurance.

The prescription has to clearly identify the dosimetric reference point, keeping in mind that the dose of radiation is delivered in a single application. The clinical significance of an elevated single dose is controversial. In the attempt to establish a dose value biologically equivalent to the dose administered with traditional external beam radiotherapy, models such as the α/β (6) are used. It is important however to outline that extrapolations going beyond the theoretical limits of the reference model are always unadvisable.

The technical advantages of IORT consist in the direct visual control of the target volume, and in the possibility to protect the healthy tissues by moving them away from the path of the radiation beam. The use of electron beams allows the administration of a homogeneous dose to a selected layer of tissues surrounding the tumour.

The toxicity of IORT is correlated to the dose and the type and extent of anatomical structures involved in the treated volume. The toxicity is mainly of the late type (7-9). In fact the procedures to guarantee the sterility of the operating field are clearly planned and easily observed. The increase of intraoperative risk related to the extended duration of the operation is, in general, easily controllable by the anaesthetist. The late toxicity effects of IORT more frequently described in the literature refer to the peripheral nerves and to the ureter. Collapse of the vertebral bodies, bleeding from rupture of big vessels and brain demyelination (10, 11) has been rarely reported. In all these situations the late toxicity has not been associated to IORT as only cause, but also to the surgical manipulation and to the neoplastic infiltration (12). It is, however, common observations that single doses $> 20\text{-}25\text{ Gy}$ are significantly correlated with a higher incidence of late toxicity (13). In order to evaluate its incidence it is useful to use international coding systems for recording toxicity.

IORT has been used in the treatment of various malignancies. Local control has always been very high and the toxicity related to the methodology very low. The cancers of the stomach, pancreas, colon rectum and the sarcomas, in which the local recurrence is the main cause of failure, have been the objects of numerous clinical studies. The long-term results confirm a positive impact on local control that is generally associated with increased survival. New fields of application are the cancers of the breast, lung, bladder and uterine cervix. Reported experiences, however, are almost always limited to one institution, which represents the principal constraint to the statistical significance of the results. There is, therefore, a need for multiple Phase III randomised studies to confirm the relative contribution of IORT in combined therapies. The prospect of involving more Centres, made possible by the diffusion of the mobile accelerators, represents an interesting possibility for overcoming these limitations. In prescribing IORT indications, for which consolidated experience exists in the literature, should be taken into account and distinguished from those of a more innovative character, with the purpose of performing the treatment in line with good clinical practice.

IORT is a technique in which the radiation oncologist has the full clinical responsibility (prescription and execution of the treatment), but which requires, necessarily, a multidisciplinary collaboration with the surgeon, anaesthetist, medical physics experts, radiation technologists and nursing personnel. The surgeon not only removes the tumour, but also gives useful indications for the identification of the tumour bed and for the treatment procedure acting always in collaboration with and in the presence of the radiation oncologist. It is recommended that the radiation oncologist work in a health structure belonging to an Operating Unit (OU) of Oncological Radiotherapy (excluding the treatments used in neurosurgery for which different local situations can be foreseen). Likewise, the medical physics expert, with the title required by the Italian legislation (3) should work in a Medical Physics Department.

Defining the physical characteristics of the electron beams used for IORT requires an accurate initial dosimetric study (14), particularly with the new mobile accelerator (15); moreover, an accurate protocol for a regular quality control of the equipment based on international recommendations has to be prepared (16).

The definition of the procedures to be followed during the execution of IORT and its documentation is essential for the optimisation of the programme of quality assurance in this radiotherapy treatment.

IORT with electron beams is performed in two different ways, depending on the type of equipment used for the irradiation, which, in turn, is associated with differential management of the patient during the surgical intervention:

– *Irradiation with transport of the patient*

- In the bunker of the radiotherapy OU:
after the surgeon has exposed the area to be irradiated, the patient is transported to the radiotherapy OU. The preparation for the IORT requires 1-2 hours: during this time, outpatient therapy is discontinued. After the IORT treatment is finished, the patient is reported to the operating theatre where the intervention is completed.
- In the dedicated bunker:
an operating theatre is prepared in the bunker; during IORT the patient is moved the few necessary meters to the accelerator for radiation treatment. The accelerator is exclusively used for IORT.

– *Irradiation without transport of the patient*

The treatment is performed directly in a normal operating theatre, with a mobile linear accelerator that is moved to the operating table for the execution of IORT. Since problems related to radiation safety could be relatively easily solved, these therapy units can be used in several adjacent operating theatres.

It is important to keep the above differences in mind, because they directly affect the organisational aspects and therefore the characteristics of the procedures used for the execution of IORT. For this reason, we consider it necessary to introduce the clinical and physical/technological aspects of IORT using an X-ray source in a separate chapter.

We believe that for IORT with electron beams, which is the technique with wider diffusion both at the national and international levels, it was relevant to include in the document an analysis of the principal cost considerations associated with the method. This will facilitate the evaluation of demand for this therapeutic approach by operators in the sector (17).

IORT with electron beams

1. PROFESSIONAL FIGURES (ROLES AND RESPONSIBILITIES) AND EQUIPMENTS

The definition of the roles and the corresponding responsibilities of the different professional figures is formulated on the base of available national and international documents on quality assurance in radiotherapy (18, 19) and adapted to the IORT procedure according to the indications reported in different publications (16, 20). We would like to underline that, besides the operational group for the IORT treatment, it is essential the institution of a group for the quality assurance, formed by physician-physical-technical-nursing personnel identified inside every department involved in the programme IORT (Surgery, Radiotherapy, Medical Physics and Anaesthesia), in order to favour the multidisciplinary integration that characterises this procedure and to define and to supervise the programme of quality assurance for the different strategies of treatment. These should be preferably promoted in the framework of clinical research studies or guidelines of the Centre.

1.1. Quality group

The following professional-operational staff forms the group: radiation oncologist, surgeon, medical physics expert, anaesthetist, radiation technologist, nurse, health direction, clinical engineering. Coordination of the group is delegated to the radiation oncologist.

The assignments of the group are:

- to write and to periodically up-date the description of the IORT procedures;
- to write and to periodically up-date the documentation that must be gathered during the carrying out of the IORT;
- to verify the congruity with the programme of quality assurance of research programmes and treatment protocols according to the clinical evidences;
- to ensure that the planned procedures of quality assurance are constantly practised;
- to prepare a programme of continuous training of the personnel involved in the execution of the IORT;
- to maintain a file of the programmes of treatment in progress and of the possible publications.

1.2. Operational group

The operational group is the team that implements the treatment.

1.2.1. Radiation oncologist

IORT is a radiotherapy technique, in which the radiation oncologist has the full clinical responsibility (prescription and execution of the treatment) according to what is mentioned in the Italian legislation (3). The assignments and the responsibilities have been largely detailed in

the document: *Garanzia di qualità in radioterapia. Linee guida in relazione agli aspetti clinici e tecnologici* (Rapporti ISTISAN 02/20) (19) on quality assurance in radiotherapy.

According to the Italian legislation (3), radiation oncologist is defined as the physician who, subsequently to the MD degree, has achieved the post-graduate degree as Specialist in Oncological Radiotherapy and is therefore authorised to employ ionising radiation for therapeutic purposes; or the surgeon without specialisation that has 5 years of service in the corresponding discipline on the date in which the aforesaid decree has gone into effect.

In IORT, the radiation oncologist:

- proposes clinical research protocols and is responsible for the selection of potential patients for treatment and the necessary clinical planning;
- is responsible for the management of the equipment of treatment;
- in the evaluation of the eligibility of the patient for IORT, discusses with the surgeon the intended surgical procedure and together they agree on the definition of the area to be treated;
- participates in the evaluation of the extension of the malignancy and of its relationships with the adjacent structures and evaluates the technical feasibility of the treatment for which he has the full responsibility;
- is responsible for the definition of the volume to be irradiated: Clinical Target Volume (CTV) and Planning Target Volume (PTV). This evaluation in collaboration with surgeon takes into account the suspicious areas of infiltration, the assessment of the margins of resection, mobilisation and removal of the healthy structures;
- is responsible for the prescription of the dose, of the choice of the applicators to be employed and of the energy of the electron beams. For this evaluation he is supported by the medical physics expert. The formal execution of the treatment must be discussed and communicated to the technical staff of radiotherapy (e.g. position of the applicator, position of the patient on the table, etc.);
- is responsible for the procedure that foresees the position of the applicator on the region to be irradiated and the hard/soft-docking of it to the radiating head of the LINAC (LINear ACcelerator). In this phase he collaborates with the technical staff of radiotherapy;
- is responsible for the description of the procedure that will be reported in a special form at the end of the treatment;
- is responsible together with surgeon for the organization and the execution of the follow-up of the treated patients.

1.2.2. Surgeon

The surgeon discusses with the radiation oncologist the protocols of clinical research and the treatment details in individual patients. Specifically, he is responsible for the identification of the intervention, for the surgical procedure and for the management of the patient in the post-surgery period. Before the intervention, he discusses with the radiation oncologist the planned surgical procedure, deciding the definition of the region to be irradiated, with the aim of planning possible variations in the intervention to enhance the feasibility of IORT:

- performs the surgical procedure of resection or exposure of the tumour based on what was agreed with the radiation oncologist and on technical feasibility;
- appraises during surgery the extension of the tumour and the presence of a macroscopic residue after the surgical resection, specifying localization, relationships and dimensions of it, using samplings, if necessary, for extemporaneous histological examinations;

- helps the radiation oncologist to define the area to be irradiated and is jointly responsible for its optimal exposure and, particularly, for the mobilisation and removal of the surrounding healthy structures;
- is responsible for the temporary closing of the surgical wound, safeguarding the sterility of it (IORT with non-dedicated LINAC);
- follows the patient during the eventual transport to the radiotherapy unit and is present during the radiation treatment, to act in the case of possible surgical emergencies;
- in case of IORT with the intrahospital transport in the bunker, the surgeon is responsible of the surgical re-opening of the area to be irradiated;
- verifies the absence of related procedure lesions at the end of the treatment;
- is jointly responsible together with the radiation oncologist of the organisation and the implementation of the follow-up of the patients submitted to IORT.

1.2.3. Anaesthetist

The medical anaesthetist is responsible for the anaesthesiological procedure and for monitoring the patient during the surgical intervention, during the transfer to the radiotherapy treatment room and the return in the operating theatre (non-dedicated LINAC) and during the irradiation. In all these phases he collaborates with the nursing staff of the Department of Anaesthesia (not all the institutions have dedicated nurses) and is responsible for:

- the preparation of the anaesthesiological instrumentation in the bunker of the Radiotherapy Department (IORT with non-dedicated LINAC) and for the procedures of verification for its operation;
- the preparation of the necessary portable instrumentation to assure a patient's suitable ventilation and monitoring of the vital parameters during the possible transport;
- the preparation of the instrumentation and the necessary medicines in the bunker of the Radiotherapy Department and has to guarantee an immediate access to the patient in any phase of the procedure for the management of possible emergencies;
- the monitoring of the vital parameters of the patient during the IORT treatment visualised with a closed television circuit or through a monitor connected to a central line. In case of need, means must be provided to stop immediately the irradiation;
- the prevention and management of possible anaesthesiological emergencies for which the availability of necessary instrumentation and pharmacological support must be foreseen. (see § 1.3.3).

1.2.4. Medical physics expert

The activities in radiotherapy and in the IORT process of the medical physics expert are primarily those related to preventive evaluation, optimisation and verification of the doses delivered to the patients in the medical exposures, as well as to the quality control of the radiological equipment used, according to the Italian legislation (3). The medical physics expert contributes to: the process of optimisation, the choice of equipment, the programmes of quality assurance and the radiation protection of the patient, according to the Italian legislation (3). The assignments and the responsibilities have been largely detailed in the above-mentioned guideline (19).

In particular, in IORT the medical physics expert:

- is responsible of the dosimetry of the radiation beams produced by the used equipment (see chapter 2);
- is responsible of the procedures of acceptance of the equipment used for IORT and of the periodic tests of operation, to pre-determined intervals, and after every relevant intervention of maintenance;
- collaborates with the responsible for the equipment used for IORT and on the layout of programmes of quality assurance through specific protocols;
- is responsible of the execution of the quality control before and during the delivery of the dose IORT foreseen by the protocols of quality assurance of the equipment (see § 2.3);
- collaborates with the radiation oncologist in the choice of the applicators and the energy of the beams for a suitable coverage of the target volume;
- is responsible of the preventive evaluation, optimisation and the verification of the dose delivered to the patient, which is reported on an appropriate form.

1.2.5. Radiation technologist (radiographer)

The assignments and the responsibilities of the medical radiology technician have been broadly detailed in the above-mentioned report (19).

The radiation technologist particularly in IORT:

- manages the organisation of the regular activity of the Department of Radiotherapy when the IORT procedure is planned (non-dedicated LINAC) according to the criteria pre-stated by the Responsible Person of the Operative Unit;
- performs the operations of control to verify the mechanical operation of the equipment used for IORT;
- prepares the equipment (adapter for the applicators) and the room of radiotherapeutical treatment for the IORT procedure (availability of the sterile applicators, scialitic lamp, additional television cameras, movement of the table, etc.);
- performs the quality control on the equipment based on available protocols (see § 2.3);
- organises the route, in the Department of Radiotherapy, for the patient's transport in collaboration with the nursing staff of the Department, according to the preestablished formalities (non-dedicated LINAC);
- performs the operations of intrahospital transport of the patient (from the operating theatre to the Department of Radiotherapy);
- collaborates with the radiation oncologist in the execution of the IORT procedure (patient's positioning), moving of the table and the equipment in relation to the position of the applicator;
- implements the irradiation according to the instructions of the radiation oncologist and of the medical physics expert and is responsible of their correct execution;
- is responsible of the recording of the data of the treatment.

1.2.6. Nursing staff

Two main professional operators are necessary:

a) Professional operating theatre nurse

- prepares the operating theatre and assists, depending of his/her duty, the surgical team during the intervention;
- is jointly responsible for the sterilisation and handles the preparation of the operating theatre for the IORT procedure with non-dedicated LINAC that foresees the employment of the operating theatre of the radiotherapy;
- could organise the route for the transport of the patient from the operating theatre to the radiotherapy in the IORT procedure and facilitates the intervention in the conventional operating theatre, according to the established procedures;
- handles the sterilisation of the IORT applicators and is responsible of their availability for the execution of the procedure;
- handles the preparation of the surgical instrumentation and the consumable materials (white uniforms, gloves, sterile cloths, etc.) in the IORT treatment room;
- assists the surgeon and the radiation oncologist during the treatment phase of IORT.

b) Professional radiotherapy nurse

- collaborates with the radiation technologist in the planning and the management of the routine activity of the department of radiotherapy when an IORT procedure is foreseen (non-dedicated LINAC) according to the criteria pre-established with the person responsible of the OU;
- is responsible for the sterilisation of the bunker where IORT is performed and collaborates with the radiation technologist in the preparation for the procedure;
- handles the sterilisation of the IORT applicators and their availability for the execution of the procedure, (when an OU performs IORT with different surgical groups, it is important that the equipment resides in radiotherapy and that the radiotherapy nurses takes care of the sterilisation of the applicators);
- collaborates with the radiation technologist to organise the route in the department of radiotherapy for the transport of the patient from the operating theatre;

Where other nursing specialists exist, it will be the responsibility of the physicians and involved experts to determine the assignments and the responsibilities of the additional nursing personnel.

1.2.7. Health direction

The health direction has to:

- authorise and locate the places used for the execution of the treatment;
- authorise and secures the route for the transport of the patient;
- identify the personnel necessary for the transport of the patient.

1.2.8. Clinical engineering

The clinical engineering has to:

- take care of the necessary changes to the equipment in the operating theatre for the use of the dedicated accelerator and the required security according to existing standards;
- define the necessary changes to the equipment in the bunker for the execution of IORT and the required security according to existing standards;
- define the optimal technical aspects of the route to use for the transport of the patient (elevators with continuity, isolation of the route, etc.) and guarantees their operation;
- collaborate on the definition of the procedures to adopt in case of emergency.

1.3. Equipment for the execution of the treatment

1.3.1. Non-dedicated accelerators

1.3.1.1. Characteristics of the accelerator

The non-dedicated LINAC can be used for IORT without requiring any structural or functional modification (e.g. no change in system of production of the electron beams, interval of energy or dose-rate).

Nevertheless, the IORT procedure requires the use of accessories for the beam collimator, which are different from the applicators of electrons used for conventional external radiotherapy. The type of collimation system, with the possible docking of the distal part of the applicator, characterises these accessories.

1.3.1.2. Accessories

Accessories for the IORT procedure are:

- principal adapter to be fixed to the main collimator of the LINAC;
- adapter for the docking connected to the principal adapter that can be fixed or telescopic;
- set of applicators of different sections and angulation of the terminal part;
- set of applicators for the simulation of the treatment, to be performed in the operating theatre, equal to those used for the treatment;
- system of visualisation and verification of the volume to be irradiated after the completion of the docking, with periscope provided of mobile mirror or with fiber optics periscope, generally inseribile in the adapter and possible system of recording of images;
- TV camera in the LINAC Control Group, to visualise the monitoring system of the patient's vital parameters (see § 1.4.1).

1.3.1.3. Radiation treatment couch

In the IORT procedure either the radiation treatment couch of the LINAC or a dedicated couch can be used.

In the first case, is necessary to employ a mobilizer that allows the transfer of the patient from the table of the operating theatre to the couch of the LINAC.

In the second case a system of transport of the table of the operating theatre can be employed with a dedicated stretcher that facilitates the transfer of the patient and the execution of the

docking with movements along the three Cartesian axes and in Trendelenburg. In this case it is also necessary, before the patient's arrival, to move or to remove the LINAC couch.

1.3.2. Dedicated accelerators

1.3.2.1. Characteristics of the accelerator

"Dedicated accelerators" are accelerators that can be used in the operating theatre without particular modifications of the room itself. They have been designed to facilitate the emission of a lower power of braking radiation.

There are two types of dedicated accelerators currently present on the market. Their weight is 600 kg and 1250 kg, respectively.

They are both movable and can be moved into the operating theatre and from one operating theatre to another.

They can be articulated to provide the required positions to perform the intra-operative radiotherapy.

They produce electron beams with energies of 3-5-7-9 MeV in one type of machine and of 4-6-9-12 MeV in the other.

The typical dose-rate is 15 Gy/min in one type of machine and varies in the range of 2.5-10 Gy/min in the other; allowing an opportune reduction in treatment times.

They are endowed with articulated movements for the implementation of the IORT: macromotions to move the couch and micromotions to facilitate the alignment and the docking with the applicator.

1.3.2.2. Accessories

The dedicated accelerators are equipped with applicators in Perspex or in plastic of a diameter varying between 30 and 100 mm. The distal end of these applicators may be plane or may be cut at angles from 0° to 45°. In one type of linear accelerator the length of the applicators determines the Surface Source Distance (SSD) which may be equal to 80 or 100 cm; in the other type the distance is fixed at 50 cm. The connection of the applicators with the accelerator can be done in two ways: hard-dock or soft-dock; in the case of soft docking, the applicator must be secured through an appropriate surgical device.

The applicators must be sterilised after use and accurately kept in a particular easily accessible closet during the IORT procedure. It is necessary to have at least two sets of applicators of all diameters and angles and at least three sets of applicators with the diameters and angles most used. In the clinical practice, it could be necessary to protect the skin and organs placed under the radiation field. To shape the radiation field light plastic material (type PVC) or lead can be used; both materials can be cut in any required shape during the IORT procedure; the thickness of the material must be related to the used energy: generally 2.5 cm of PVC or 5 mm of lead are enough to absorb the electron beams of the maximum available energy.

To protect the underlying tissue is advisable to use some hard disks of Perspex or lead of a diameter slightly greater than that of the applicator. Small bags of saline solution, or other equivalent material, can also be used. All these accessories should be sterilised and kept in a special closet.

1.3.2.3. Radiation treatment couch

The radiation treatment couch should be driven mechanically and not electronically, and endowed with micrometric movements in all directions, measurable and reportable. The couch is kept generally hidden in the operating theatre.

1.3.3. Anaesthesia

The anaesthesia, the surgical procedure and the intraoperative irradiation should be carried out in an IORT-dedicated operating theatre. (21). As an alternative, the induction of the anaesthesia, the surgical incision and the isolation of the tumour can be effected in an operating theatre prepared in the radiotherapy area (22). This last solution facilitates the continuous use of the room with the linear accelerator for the treatment of other patients while the patient is prepared for IORT.

In both cases it is necessary to have suitable anaesthesiological equipment with appropriate monitoring of vital functions, as well as of the pharmacological support for any emergency, in order to increase the safety of the anaesthesia and optimise the assistance of the patient (23).

Essential equipment and monitoring system for the execution of IORT are:

– *Anaesthesia*

- high precision safety flow-meters;
- evaporators with a system of loading the anaesthetic halogenated pin-safety type
- manual ventilation system;
- automatic ventilator provided with analyser for the inhaled concentration of oxygen;
- acoustic alarm system of the pressure of insufflations and spirometer with sensor set on the expiratory line of the ventilator endowed with alarms;
- system of gas evacuation, preferably active;
- 1 cylinder of oxygen for emergencies;
- ECG monitor;
- arterial blood pressure measuring device;
- body temperature measurement system;
- wrist saturimeter;
- capnometer;
- trolley with material for anaesthesia (laryngoscope, cannule, endotracheal tubes, autoexpansion ball, material for difficult airways) and medicines.

– *Monitoring system*

- arterial blood pressure instrument;
- heating and cooling systems.

In addition it would be useful to employ a simple device for monitoring neuromuscular transmission to evaluate the mioresolution and a system for monitoring the anaesthetic level.

In order not to interfere with the movements of the LINAC and in the eventuality that a modification of the position of the patient on the couch is needed, the anaesthesia instrument, with a complete monitoring system of vital parameters, must be easily detachable from the operating table. It therefore, would be desirable to avoid using a suspended monitoring instrument.

During the patient's irradiation, when the personnel leaves the operating theatre to avoid an undue exposure to the radiation, the patient, the instrument of anaesthesia and the monitors should be kept under visual control through a closed circuit television. Additionally, a telemetry

system should be employed for the direct monitoring of the patient located outside the dedicated operating theatre or in the bunker of the Radiotherapy Department.

In the case in which the bunker of the Radiotherapy Department is placed far from the operating theatre (in some cases on different levels of the same hospital) it is essential to be able to have a stretcher equipped for transport endowed with a defibrillator, ECG monitor, wrist saturimeter and transportable ventilator.

1.4. Facilities

1.4.1. Bunker for non-dedicated accelerator

The bunker must always be specially structured and adequately equipped with all those safety and hygienic facilities normally associated with an operating theatre and with everything that guarantees complete assistance to a patient under general anaesthesia (additional monitor inside and outside the room for monitoring vital parameters, suitable illumination, suitable space for the anaesthetic equipment, etc.). The preparation of the bunker must be jointly carried out by personnel of the operating theatre and the UO and this must be verified with all members of the team (anaesthetist, surgeon and radiation oncologist) according to codified operational procedures and instructions.

1.4.2. Operating theatre for dedicated accelerator

The position of the accelerator in an operating theatre must be selected according to norms for dedicated and non-dedicated operating theatres.

a. *Dedicated*

shielded floors, walls, and doors. An appropriate placement of the operating tables, of the lamps and of the television cameras of control (to avoid possible interference with the movements of the LINAC).

b. *Non-dedicated*

mobile shields for the ground and the areas surrounding the operating table. In this case the position of the shields and the television cameras must be predetermined.

Provision should be made for television cameras to control the operating field and the patient, monitors for the anaesthesiology equipment and the movement of cables inside and outside of the operating theatre including the control panel of the LINAC and the cables for the dosimeters.

Outside of the operating theatre provision should be made for:

1. acoustic and light signal indicating radiation emission;
2. space for the LINAC control panel;
3. space for the monitors connected to TV cameras;
4. space for the allocation of the sterilised applicators;
5. space for the telemetry system monitoring vital parameters.

The best way to exploit the potential of the dedicated mobile accelerator is to plan the organisation of the room keeping in mind the innovative characteristics of IORT .

The issues to check when judging the adequacy of the room are the following:

- loading capacity of the floor (at least 500 kg/m²);
- position inside the operating block;

- surface, that should be at least of 25-30 m;
- width and height of the door entry (better if at least 2,50 m) and of the ceiling of the room;
- suitability for introducing mobile/portable monitoring instruments for the patient.

The local in front of the operating theatre needs to be sufficiently large to contain the control panel, the monitors connected to control TV cameras, a closet in which to preserve the collimators and other accessories for the IORT procedure, and to provide sufficient space for the operations of the staff (radiation oncologist, medical physics expert, radiation technologist), without interfering with the surgical staff waiting to reinitiate the surgical intervention. The availability of further space would be advisable to park the accelerator and the shielding barriers during the non-operational phases, in order to avoid congesting corridors or transit areas with this equipment.

2. PHYSICAL ASPECTS OF IORT

The physical and dosimetric aspects that will be dealt with in this chapter are related to the IORT performed with electron beams produced by conventional and non-conventional linear accelerators and with energy's values between 4 MeV and 20 MeV. The specific issues that will be treated are dosimetry (under reference and non-reference conditions), quality control of the equipment, verification of the treatment through *in vivo* dosimetry and, finally, some aspects of radiation protection.

The IORT requires special dosimetric determinations, which are sometimes different in comparison to those, associated with conventional external-beam radiotherapy (20, 24-27). 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. It is also in the operating theatre that the IORT team selects the shape and the diameter of the applicator, the energy and the isodose of reference more suitable for assuring the therapeutic prescription. Since there is no possibility of using a Treatment Planning System (TPS) and there is little time to make the dosimetric calculations, it is necessary that all the physical data for every type of applicator and energy employed, are available in a format of fast consultation and easy use.

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 contributes to the determination of the physical-geometrical characteristics of the electron beams (quality, output, homogeneity, etc.). Such applicators are generally made of plastic (PMMA) and can be of circular section, with diameters between 4 and 12 cm, or of rectangular section, with dimensions up to 13 by 17 cm. The circular- applicators can have an oblique distal part that is tilted with respect to the geometric axis of the beam, with angles ranging from 15° to 45° (base bevelled applicator). The use of an applicator of more complex form called "bevelled squircle applicator" has been reported in the literature (28). The length of the applicator can depend on its diameter and in some cases determines the source-skin distance (SSD). The SSD is generally between 80 cm and 120 cm. Finally, a further difference with external radiotherapy derives from the high dose/pulse delivered by some types of dedicated accelerators. These characteristics rise specific problems for the determination of the dose that will be discussed in the following paragraphs.

2.1. Dosimetry in reference conditions

In general, international dosimetric protocols can be used, with some precautions for the dosimetry of non-dedicated accelerators, operating with specific applicator for IORT. In particular, at least two protocols: that of the AAPM (29) and that of the IAEA (30), allow the determination of the absorbed dose to water with comparable accuracy. We consider it important to recommend the IAEA protocol because, besides concerning a larger number of radiation types and having a greater international diffusion, it can be easily implemented. Nevertheless, using the dosimetric protocols in the IORT, the reference dosimetry cannot be effected with the same accuracy typical of the conventional non IORT treatments. In fact, the presence of specific applicators does not allow a total conformity with the reference conditions specified in the dosimetric protocols, giving rise to an increased uncertainty in the determination

of the absorbed dose to water, in comparison with the dosimetry effected with a conventional applicator and in conformity with the conditions of reference of the protocol.

In the case of dedicated accelerators, characterised by a high dose/pulse, it is impossible to follow the recommendations of the protocols of measuring the dose with an ionisation chamber, due to the problems of ion recombination inside the gas of the chamber. We therefore recommend those solutions which, at the present level of knowledge, appear most suitable and are most often applied in the Centres of radiotherapy that use this type of accelerators.

The dosimetry in reference conditions should be performed for all the energies effectively used in the IORT treatment.

2.1.1. Non-dedicated accelerators

With regard to the choice of the IORT applicator to be used in the measurements carried out in reference conditions, a square section applicator of 10 cm × 10 cm or a circular applicator of 10 cm in diameter with a plane base is recommended. Whenever it is not possible to get the SSD recommended by the dosimetric protocol with the reference applicator, it is recommended to use the nominal SSD of the reference applicator.

Different references (31-36) point out that the fields of electrons coming from the IORT applicators (due to the great quantity of scattered electrons, whose contribution to the dose could be of up to 40% of the total dose to the depth of maximum absorption, R_{max}) present an energetic spectrum downgraded towards low energies and a wider angular distribution in comparison to the electron beams collimated with the conventional systems.

The ratio of the stopping power water-air for the different energies is calculated, in the dosimetric protocols, per beams collimated with the conventional systems. Using IORT dedicated applicators it is not possible to obtain the reference conditions required by the dosimetric protocols for non IORT modalities. Since the energy spectrum and the values of R_{50} are correlated in different way depending on whether operating with conventional applicator or with IORT dedicated applicators, it is necessary to accept an increase of the uncertainty on the dose when measured by means of ionisation chambers, using the values of the stopping-power ratios and the related quantities (i.e. k_Q factors) reported, for instance, in the IAEA TRS 398 (30) protocol. It has been estimated that such additional uncertainty should be between 1% and 2% (31).

In the non-dedicated accelerators the aperture of the secondary collimators photon jaws has an influence on the dose per MU and on the dose distribution of the electron beams (s. 3.3.2.1) (20, 37, 38). It is therefore recommended to check that the aperture of the docking system of the IORT-dedicated applicators be that stated from the manufacturer. In the case of lack of indications from the manufacturer it is recommended of optimising the aperture of the secondary collimators as a function of the beam energy and of the IORT-dedicated applicator chosen as reference applicator. The type of the ionisation chamber must be selected, in agreement with the indication of the dosimetric protocol, among those presenting the less angular dependence: as already mentioned, in fact, the angular distribution of the electron beams produced by IORT-dedicated applicators, is significantly wider especially at the lower energies, than that produced by conventional electron applicators (31). The need is anyhow confirmed of calibrating the ionisation chamber at a Primary Metrological Institute, or at a recognised Calibration Centre.

As a conclusion, it is worthy to underline that it is equally possible to perform the dosimetry in reference conditions using the conventional applicators. If this choice is made, the dosimetrical measurements performed with IORT-dedicated applicators fall again in non-reference conditions dosimetry.

2.1.2. Dedicated accelerators

As for non-dedicated accelerators, for the measurements in reference conditions and for each energy, a square applicator $10 \times 10 \text{ cm}^2$ or a circular applicator of 10 cm in diameter with a plane bases is recommended. This choice should allow, in most of the cases, to have a SSD = 100 cm. Would it not be possible, using the reference applicator, to have a SSD = 100 cm, the nominal SSD of the reference applicator is recommended.

The dose-rates produced by some dedicated accelerators are much higher than the dose-rates of conventional accelerators. This fact sets a limit to the employ of ionisation chambers for the beams calibration in terms of dose per MU. In particular, due to the high density of electric charge produced in the chamber's volume per radiation pulse, the correction factor for ion recombination can be largely overestimated if the correction methods recommended by the international protocols are used (15, 39, 40). For this reason, for the measure of dose to water in reference conditions, ionisation chambers cannot be employed and no published dosimetry protocol can be used. In these guidelines, for the measurement of the absorbed dose to water in reference conditions the use of the absolute dosimetric system of Fricke (chemical dosimeter based on a solution of iron sulphate) is recommended (41). It is also recommended that such system be managed by a Primary Metrological Institute or by a recognised Calibration Centre. The use of such system in non-Metrological conditions, in fact, due to high criticality typical of chemical dosimetry, cannot always guarantee the required accuracy in the dose measurement. As an alternative, dosimetric systems can be employed whose sensitivity is independent from the dose-rate, from the beam energy and from the angle of incidence of the electron beam. A good solution is represented by alanine dosimetry (42, 43). Dose measurements performed using Fricke and alanine dosimeters have shown a good agreement, generally within 1% for plane-base applicators.

For the Fricke dosimetry, as reference depth, the depth of R_{max} is recommended. The use of the reference depth (different from the depth of R_{max}) recommended, for instance, in the protocol IAEA TRS 398 (30) is not, in this case, necessary, because the employed dosimeter is not an ionisation chamber. Moreover, when using Fricke dosimetry, due to the large size of the dosimeter and to the perturbation introduced in the radiation beam by its walls, it is better to perform the measurement at a depth where the dose gradient is low.

If dosimetry systems other than Fricke are used, it is anyway indispensable to guarantee that all measurement 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 recognised Calibration Centre.

2.2. Dosimetry in non reference conditions

Dosimetry in non reference conditions, sometimes referred to as clinical dosimetry, has the aim of the dosimetric characterisation of the electron beams. Such characterisation must be performed for every applicator, energy and SSD of clinical interest. It is recommended that the dosimetric characterization of the electron beams include:

- *PDD (Percentage Depth Dose)*
measured along the clinical axis of the beam (which is different from the geometrical axis in the case of base-bevelled 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 (25) e per cent dose due to the photon contamination of the beam (tail of *bremssstrahlung* radiation);

- *Beam profiles*
measured in two orthogonal directions at the depths of R_{\max} , of R_{90} , of R_{80} and of R_{50} ;
- *Isodose curves*
measured in the two principal orthogonal planes (cross-plane and in-plane) containing the clinical axis of the beam;
- *Values of the output*
expressed as dose per Monitor Units (MU) (cGy/UM), measured in a point at the reference depth on the clinical axis of the beam;
- *Correction factors*
such as the factor for taking into account the presence of an air-gap between the applicator and the patient's surface, as stated in the protocol adopted by the Centre for the calculation of the MU.

The problems connected with dosimetry in non reference conditions are treated in the following in three main chapters: 1) determination of the dose per MU, 2) determination of dose distributions, 3) determination of correction factors.

As discussed for the dosimetry in reference conditions, electron beams generated by IORT-dedicated applicators, due to the presence of electrons scattered by the additional collimation system, show a larger energy spectrum and a wider angular distribution than the electron beams produced with conventional collimation systems. This implies a higher surface dose (especially for the lower nominal energies) and less steep dose gradients (especially for the higher nominal energies). Moreover, the use of the stopping power ratios and of the perturbation factor of the electron fluency reported in the Protocol IAEA TRS 398 (30) could introduce an additional uncertainty, in the range between 1% and 2%, to the dose determination in non reference conditions obtained through measurements performed with a ionisation chamber.

2.2.1. Determination of the dose per Monitor Unit (output)

The dose per MU, D^* , depends on the energy of the beam and on the dimensions of the applicator; for this reason the calibration of the electron beams (that is the determination of D^* in terms of cGy/MU), must be performed for each applicator, energy and SSD of clinical use.

It is recommended that the determination of D^* be performed in a water phantom, with a dose-rate similar to that employed during the treatments. In particular conditions, and with the adoption of suitable correction factors, (s. for instance the protocol IAEA TRS 398), also solid phantoms can be used.

2.2.1.1. Non-dedicated accelerators

For the determination of the dose per MU it is necessary, for each applicator, to use the optimal aperture of the secondary collimators, according to what is written in 2.1.2. The reference point of the chamber must be positioned on the clinical axis of the beam; the measurement depth is that indicated in the protocol for the determination of the dose per MU in non reference conditions (R_{\max}).

The choice of the ionisation chamber must be done among those that present the less angular dependence (30).

In the case of base bevelled applicators, due to the asymmetry of the beam, the use of small size detectors is recommended. Moreover, the use of dosimeters whose response is independent

from the beam's incidence angle is recommended, such as alanine dosimeters, radiochromic films, TLD or even small size ionisation chambers (with the exception of plane-parallel ionisation chambers). Independently from the dosimetric system used, it is recommended also to previously compare its response with the response of a plane-parallel ionisation chamber, using a plane-base applicator.

2.2.1.2. Dedicated accelerators

As reference depth, the depth of R_{\max} is recommended.

As in the case of dosimetry in reference conditions, the high dose-rate produced by some dedicated accelerators represents, at present, a limit to the use of ionisation chambers for the determination of the dose per MU. The use of the absolute Fricke dosimetric system is therefore recommended, with the modalities described in 3.2.2, or of relative dosimetric systems with a response independent from the dose-rate, such as alanine dosimeters or radiochromic films (41-50). It is also possible to use Fricke dosimeters produced by the same Centre (51), provided that declared reproducibility and accuracy are guaranteed.

It is also recommended to check the energy dependence of the dosimetric system for all the energies of clinical employ, for comparison with Fricke dosimeters calibrated at a Metrological Centre. For this check, the reference applicator can be used.

It is indispensable that all the measurement are referred to national or international standards of the quantity "absorbed dose to water".

As already outlined in the previous paragraph, it must be noted that a dosimetric system suitable for plane-base may not be suited for bevelled applicators. For this situation, an important characteristic is the small size of the detectors. When using Fricke dosimeters, whose size is rather large, it may be necessary (especially for low energy electron beams and for bevelled applicators) to apply a correction factor taking into account the non uniformity of the dose distribution inside the Fricke dosimeter (41).

Alanine dosimeters and radiochromic films have the advantage of a small thickness and a small size, but also of a low sensitivity, allowing to be irradiated with a dose next to the clinically employed one (approximately 10 Gy).

2.2.2. Determination of dose distributions

The measurements of PDD, of beam profiles and of isodose curve must be performed for each applicator and energy employed in the clinical practice.

As previously reported, due to the presence of electrons scattered by the additional collimation system, the electron fields obtained with IORT-dedicated applicators are characterised by a wider energy spectrum and a wider angular distribution than electron beams collimated with conventional systems. For this reason, a dosimetry system must be selected characterised 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) is used as 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 these measurements, a solid phantom and radiographic or radiochromic films (49), or TLD (20) may be employed.

2.2.2.1. Non-dedicated accelerators

In the case of a conventional linear accelerator, it is recommended to measure the dose distribution of electron beams with an ionisation chamber in a water phantom, using an automatic system able to guarantee accuracy and a reproducibility of the detector position of 0.1 mm. As an alternative, solid state detectors, such as silicon diodes or diamond detectors may be employed. Normally, such type of detectors produce electrical signals which are converted into relative dose values by the software of the system.

For the evaluation of dose distributions, the same aperture of the secondary jaws used for the determination of D^* must be selected. As already mentioned, in fact, the aperture of the secondary jaws not only influences the dose per MU, but also the PDD, the dose profiles, the surface dose and the amount of *bremsstrahlung* radiation. In particular, in conventional linear accelerators the dose profiles strongly depend from the field size, as defined by the secondary jaws; an increase of the field size is usually accompanied by an increase of the non homogeneity towards the periphery of the field. Moreover, with a fixed secondary collimation, the field non homogeneities increase with increasing energy. When the aperture of the secondary jaws is increased, an increase of the dose per MU, a reduction of the amount of *bremsstrahlung* radiation and an increase of surface dose are observed. In order to reduce the field non homogeneities, some models of IORT-dedicated applicators are provided with an additional collimation, made for instance by rings of a high Z material placed along the collimation system.

2.2.2.2. Dedicated accelerators

As far as the determination of the dose distributions generated by high dose-rate electron beams is concerned, particular attention must be devoted to the dosimetry system to be used.

Ionisation chambers, as previously reported, are advised against: due to the high density of electric charges produced in the volume of the chamber for each radiation pulse, in fact, the correction factor for the ion recombination (11, 15, 39, 40) can be largely overestimated when the correction methods recommended in the international dosimetry protocols are applied. The recombination factor, moreover, may vary depending on the depth in the phantom of the point of measurement. The recommendation of not employing ionisation chambers is therefore due to the facts that, at present, the dependence of the ion recombination effects on the depth is not known with sufficient accuracy, and that it is uncertain how such dependence may influence the measurement of the PDD.

Among the active-type detectors (characterised by the real-time indication of the dose), silicon diodes can be easily used in a computer controlled water phantom. In any case, particular attention must be given both to the synchronisation of the detector's signal with the pulsed beam and to the type and to the characteristics of the used electronics. It is therefore suggested to check the accuracy of the response of such diodes at some point representative of the PDD and of the beam's profiles by using detectors which are not influenced by the ion recombination effect and whose response is independent from the beam's energy in the range of interest.

Other "active" dosimeters, such as diamond detectors and MOSFET (Metal-Oxide Semiconductor Field-Effect Transistor), though interesting for their reduced size, have not yet been adequately investigated in the literature regarding their possible employ in high dose-rate beams.

Another possible solution is represented by the use in a water phantom of "passive" dosimeters (whose reading is made after the irradiation), characterised by the independence of the response by the dose-rate and by a reduced size such as radiographic and radiochromic films. These detectors are usually employed in the periodical quality controls.

Taking into account the problems set by the use of such films in water, it is allowed, in agreement with the dosimetry protocols, the use of water-equivalent solid phantoms.

2.2.3. Determination of correction factors

To evaluate the correct number of MU necessary to deliver the prescribed dose, it is also necessary to experimentally determine the correction factors to the output taking into account the possible presence of an air gap between the entrance surface of the patient and the base of the applicator. In order to increase the accuracy in the calculation of the number of MU in presence of partial shielding inside the irradiation field, it is also recommended to introduce the corresponding appropriate correction for the output factors (dose/MU).

2.3. Quality control

In compliance to the Italian Decree 187/2000 (art. 8) (3) and taking into account the particular nature of IORT (single treatment at high dose), it is necessary to submit the radiation equipment used to a strict programme of quality control which includes: acceptance test before the utilisation of the equipment and, subsequently, tests of operation in the frame of a quality control programme and status tests after every relevant maintenance intervention. For every control it is necessary that each Centre also defines the corrective actions to adopt when the values of some parameter exceed the corresponding pre-arranged tolerance range. The main aspects regarding periodic quality control are described in the following paragraphs.

2.3.1. Dosimetric systems for periodical quality control

The systems used for verifying the stability of the dosimetric characteristic of the radiotherapy beams, generally referred to as the current use dosimeters must be characterised by high reproducibility of response as well as practicality of use. Such properties contribute to the reduction of the control time.

The current use dosimeters can be passive, as the radiographic and radiochromic films and the TLD, or active, as the ionisation chambers and the silicon diodes. The first ones are generally used for the control of homogeneity, symmetry, centring of the beam alignment and sometimes also for the verification of the quality or the energy of the radiation, while the second are typically employed for the control of the dosimetric monitoring system and the energy of the radiation beams.

It is recommended that the dosimeters used for quality control are calibrated in comparison to the local reference dosimetric system. The procedures of calibration have the purpose of correlating the response of the dosimetry currently used with the corresponding value of the dose obtained in the phase of dosimetric characterisation of the beams (see § 2.2).

Particular attention must be given to the calibration of the dosimeters employed for the quality control of high dose rate electron beams. In such cases, if active dosimeters are used, it is in fact necessary to determine the corrective factors for the ion collection efficiency of the dose/pulse (15). This can be effected by comparing the depth dose distributions, measured with active detectors, with those determined by means of dosimeters whose response is independent from the dose rate.

It is recommended that the calibration of both the dosimeters used for dosimetric measurements (in reference and non-reference conditions) and the dosimeters used for quality control be verified periodically. It is recommended, nevertheless, to effect such verification every time a new batch of dosimeters is used.

2.3.2. Non-dedicated accelerators

In addition to routine quality control applied to the equipment used in conventional external radiotherapy, specific periodic tests have to be performed for LINACs used for IORT, in order to verify the stability of all the parameters that can become critical in an intra-operative context. (25-28). For the additional controls to be effected, reference can be made to the chart (Table 1) that indicates the main controls to carry out for the dedicated accelerators.

2.3.3. Dedicated accelerators

The programme of quality control for dedicated equipment does not differ substantially from that of the conventional accelerators; however, regarding the dedicated equipment, special attention must be given to both the specificity of the equipment and of the environment in which it operates. In particular, it is necessary to bear in mind the time limitations and, above all, the need for radiation protection imposed by working inside the operating block, in an area not generally shielded, around which other patients and personnel might be present who are not classified as exposed people. It is therefore important that periodic quality control is performed with rapid procedures resulting in low levels of exposure. From this point of view, for instance, for the verification of homogeneity, symmetry and beam energy it is generally preferable to expose films set in solid phantoms rather than to use an automatic water phantom. Not having a place adequately shielded in the operating block, it is also necessary to evaluate the possibility that the controls requiring long time of “beam on” are performed outside normal working hours, verifying that nobody is present in the adjacent areas of the operating theatre.

As an example, the principal controls to be carried out, with the corresponding indicative value of tolerance and the frequency are reported in Table 1.

Table 1. Principal periodic quality controls (electron beams produced by a dedicated accelerator)

Parameter	Tolerance	Frequency
Movements and stopping operation of motors	functional	before every treatment
Emergency devices	functional	before every treatment
Integrity of the applicators	integer	before every treatment
Optic and acoustic warning devices	functional	before every treatment
Long-term stability of the dosimetric monitoring system	$\pm 3\%^*$	before every treatment
Laser equipment for alignment (soft-docking system)	± 1 mm	weekly
Short-term stability of the dosimetric monitoring system (repeatability)	$\pm 1\%$	monthly
Linearity of the dosimetric monitoring system	2%	monthly
Symmetry and flatness of the field	$\pm 3\%$ (simm.); $\pm 5\%$ (flat.)	monthly
Radiation energy	± 2 mm or $\pm 4\%$	monthly
Long-term stability of the dosimetric monitoring system		
<i>dosimetry in non reference conditions</i>	$\pm 2\%^{**}$	yearly
<i>dosimetry in reference conditions</i>	$\pm 2\%^{**}$	biennial

* Performed with dosimetry of current use

** Performed with the recommended dosimetry under reference and non reference conditions

The reported frequencies are to be considered indicative, susceptible to changes depending on the specific technical characteristics of the equipment employed and on the degree of reliability shown by the equipment when in operation. For example, for accelerators that do not have a system of deflection of the electron beam nor coils for centring the same beam, the controls of stability of the energy, of homogeneity and of symmetry can be effected with quarterly or six-monthly, rather than monthly, frequency.

The suggested value of tolerance is also indicative, since could be affected by the adopted procedure (type of instruments, reference parameter, and experimental geometry).

With the indication “before every treatment” we refer to the 24 hours preceding the surgical intervention. Although not displayed in the Table, it is recommended to perform, at least yearly, eventually in the context of an intervention of periodic maintenance, also a more detailed verification of the correct operation of all the movements of the accelerator following the indications and the procedures recommended by the manufacturer.

The charge ratio Q_1/Q_2 measured at a depth equal to R_{\max} by means of an ionisation chamber can be considered as a parameter useful in that it is related to the constancy of the dose per pulse delivered by the dedicated accelerators (at dose per pulse values of about 30 mGy/pulse). Q_1 is the charge measured by the ionisation chamber at the polarizing voltage V_1 and Q_2 is the charge measured at the polarizing voltage V_2 (with, for instance, $V_1 = 3 \cdot V_2$). A significant variation in the value of the charge ratio Q_1/Q_2 (e.g. more than 10% at $V_1=300$ V, $V_2=100$ V, using the most diffused types of commercially available plane-parallel chambers (Laitano RF, 2001 – personal communication) possibly indicates an operation of the accelerator anomalous when compared with the conditions of the acceptance test. In such case it is recommendable to call for technical assistance

2.4. *In vivo* dosimetry

In radiotherapy, the *in vivo* dosimetry represents an important tool in the context of a global programme of quality assurance (52). The shortage of available bibliographical references underlines that, unlike in external radiotherapy, the employment of the *in vivo* dosimetry in the IORT treatment has been very limited. Nevertheless, there are specific reasons for performing such verification (24). During IORT, some specific irradiation conditions could be present as a consequence, for example, of the irregularity of the surface being treated or of the accumulation of biological fluids, significantly different from the standard conditions of the beam characterisation in a phantom. This can result in uncertainties -which are hardly quantifiable, in both the delivered dose and the homogeneity of its distribution. The *in vivo* dosimetry could allow to effectively verify both the accuracy and the uniformity of the dose delivered to the target volume, and to determine the dose to tissues and critical organs, provided that the points of measurement are carefully selected and the dosimeters are firmly positioned on the surface to be treated. It was therefore considered useful to introduce and to discuss in these guidelines the principal problems of the *in vivo* dosimetry in IORT. Due to the limited experiences reported in the literature, however, it is not held opportune to provide recommendations on the procedures to adopt. In the absence of a well tested *in vivo* dosimetry method, it is recommended that local resources be identified, in order to develop reliable and feasible dosimetric procedures.

2.4.1. Methodology

As in the case of conventional external radiotherapy with electron beams, the *in vivo* dosimetry of IORT with electron beams consists in the determination of the entrance dose defined as the dose at the depth of R_{\max} (25, 53). The entrance dose can be evaluated on the base of the surface dose, which is measured by placing the dosimeters on the surface to be treated (25). To calculate the entrance dose from the *in vivo* measurement, it is so necessary to apply appropriate corrective factors, determined in a phantom, comparing the results obtained by locating the detector on the surface of the same phantom and at the depth of R_{\max} (53).

For *in vivo* dosimetry, Usually different detectors are used that are calibrated in terms of dose to water. According to the type of dosimeter selected, and with the purpose of increasing the accuracy of the measure, it may be necessary to apply further correction factors, determined in a phantom, to the parameters (energy, angle of incidence of the beam, temperature, SSD, etc.) that can influence the detector response when the conditions of the *in vivo* measure are different from those of the calibration. In order to reduce the level of experimental uncertainty it is also recommended to periodically verify the calibration of the dosimetric system used.

It is essential that the positioning and the removal of the dosimeters for *in vivo* dosimetry are performed under conditions of sterility and that safety procedures for their manipulation after the irradiation are established, in order to reduce any possible biological risk for both the patient and the operators (55).

The choice of the number of measurement points should be based on the analysis of a series of considerations: physical, geometrical, clinical, organisational and economical. The need for a consistent number of measurement points is based on: a) the irregularity of the surface in relation to the dimension of the field, b) the presence of organs at risk in the treated field and/or in the proximal areas, c) the possible junctions among adjacent fields and/or the possible presence of shields in the field. On the other hand, factors which favour the reduction of the number of points of measurement are: a) the need to limit as much as possible the time employed on the preparatory phase to the irradiation, b) the reduction of the perturbation introduced by the dosimeters in relation to both the dimensions of the treated field and the dimensions of the same dosimeter, c) the reduction of the cost and of the workload. It seems therefore, that the choice of the number of measurement points should be done at every Centre, taking in each case into account the advantages and disadvantages.

2.4.2. Dosimetric systems

The main characteristics of an ideal dosimetric system for the IORT are: reduced dimensions, negligible perturbation of the beam, response (possibly linear) in the interval 10-25 Gy, independence from the direction of incidence of the beam, from the temperature, from the dose-rate and from the energy of the beam, high reproducibility, possibility of sterilisation or insertion in a sealed sterile wrap and facility and immediacy of reading. In particular, the need for perturbing the field as little as possible is based on the fact that the dose is delivered in a single session and it is often not practicable to remove the detectors from the same field during the treatment. Thus far, no one of the available systems has all the above-mentioned characteristics; the detectors reported in the literature for employment in *in-vivo* measures, and for applications characterised by a high dose-rate, are of the passive type, such as radiochromic films, the alanine dosimeters and the TLD (27, 37, 45, 56-61).

The active dosimetric systems such as, for example, small ionisation chambers, diodes, diamonds, plastic scintillators and MOSFET (34, 53, 62-68), could offer the significant advantage of allowing the immediate determination of the dose and, therefore, the definition of

opportune intervention levels on the specific IORT treatment in progress (for example correction of the UM or control/modification of the set-up). Currently their employment appears conditioned, besides the limited experience on their use, by the perturbation introduced in the radiation field, due to the presence of the cables of connection with the reading system and from the difficulties of sterilisation (69).

The overall uncertainty in the measure of the dose under reference conditions with the above quoted systems can be assumed between 3% and 5% for the doses of interest. It is expected that these values can increase, also considerably, in *in-vivo* measures, even if enough information to provide valid estimations does not exist.

Every Centre that decides to activate a programme of *in-vivo* dosimetry should initially analyse, for a sufficient number of patients and for every treated pathology, the variations found between the expected and the measured dose, with the purpose of optimising the method of measure and eventually, in a following phase, to define appropriated procedures of intervention.

2.5. Radiation protection issues

The use of a linear accelerator for radiotherapy always requires that particular attention is devoted to radiation protection issues. In the case of IORT treatments performed with conventional accelerators in a shielded bunker, additional specific radiation protection measures are not necessary.

However, in the case of IORT treatments performed in a unshielded operating theatre, some interventions are necessary due to the presence of a field of radiation stemming from four main sources:

- leakage radiation from the accelerator head;
- leakage electrons from the walls of the applicators;
- radiation produced in the patient by the braking of the electron beam (*bremsstrahlung* radiation);
- neutron radiation if electron beams of energy superior above 10 MeVs are used.

Leakage radiation from the accelerator head is very low in the dedicated mobile accelerators thanks to the presence of shields in the head itself and/or to specific constructive measures such as the absence of scattering foils. The situation is different in the case of conventional accelerators used in the operating theatre, for which the leakage radiation is not negligible and requires an adequate shielding on the accelerator head (if feasible) and of the walls and the ceiling of the same room.

A fraction of electrons can cross the walls of the applicator, especially if this is made in plastic material (PMMA), and be scattered in the environment. Such fractions increase with the increase in the energy of the beam, and with the dimensions and length of the applicator (70).

The *bremsstrahlung* radiation produced in the interaction of the electrons with the patient's body is unavoidable and, due to its energy, represents the most important component in terms of radiation protection. In fact, the amount of X-radiation produced in the direction of the beam of electrons (direction 0°) is around $0,2 \pm 0,3\%$ of the dose of the electron beam at the depth of R_{\max} and its mean energy is equivalent to that of a monochromatic beam of energy equal to $E_0/7$, where E_0 is the mean energy of the electron beam at the entrance of the phantom (71). The energy and the amount of the X-rays decrease with the increase in the angle with respect to the direction of the beam.

In every Centre, therefore, adequate shielding barriers, fixed or mobile, must be available; their composition, thickness and dimensions must be calculated on the basis of the factors that,

as a rule, are employed in the calculation of the “normal” shielding barriers (work-load, destination of use and occupation factor of the adjacent places, etc.). If the accelerator is not endowed with a beam stopper, a mobile protective shield in Pb, of such surface as to intercept the prolongation of the electronic beam, can be positioned under the operating table; sideways, the stray radiation can be absorbed by lead mobile shielding barriers of suitable thickness. For example, mobile barriers of 150 cm height, 100 cm width and variable thickness of Pb (1.5 cm from the floor to up to 50 cm, 1 cm from 50 to 100 cm, 0.5 cm from 100 to 150 cm) can be adequate. Together with a beam stopper of lead 15 cm thick, they allow to reduce the dose to the operators to less than 0.02 mSv/week (1 mSv/year) at a distance of 3 meters, even in the presence of a high working-load (15 treatments/week, 20 Gy/treatment).

In order to attenuate the electronic component of the stray radiation it is useful to add a layer of light plastic material (for instance PMMA or PVC) to the side of the barrier turned towards the patient. With a beam of electrons of nominal energy equal to 9 MeV, 0.5 cm and 1.5 cm of PMMA absorb respectively around 50% and 99% of the scattered electrons. The weight of such barriers can be remarkable (200 kg or more) and it is necessary therefore to evaluate the maximum load that the floor of the operating theatre is able to sustain.

Electron and photon beams and of energy higher than the typical threshold for nuclear reactions of photodisintegration (γ , n) or of electrodesintegration ($e, e' n$) cause, besides the activation of the interested materials, also the formation of a neutronic field. With the exception of very light nucleus, like lithium and beryllium, the threshold of energy for the aforesaid reactions is equal or superior to 10 MeV. Such energy thresholds are in the range between 15 and 30 MeV for reactions in some largely present nucleus in the human body, (^{12}C and ^{16}O) and of approximately 11 MeV for the activation of the copper present in the head of the accelerators. The same photonic radiation produced by the braking of the electron beams in the body tissues radiated or in any other material crossed by the beam, is able to produce, in turn, nuclear (n, γ) reactions type. The intensity of the neutron field increases in an approximately linear way with the energy: for energies of the electrons in the range 15 ± 20 MeV the neutronic component at 1 m from the site of production involves a dose equivalent rate approximately equal to 0.002% of the dose-rate of the primary beam (20, 72). Assuming a workload of 200 Gy of electron/week and a dose equivalent of 0.12 mSv/week (6 mSv/year) for a full occupation at 3 m, the walls, and if necessary the ceilings, should be shielded with 20 ± 30 cm of concrete, enough also for the photonic radiation. The doors of access in the operating theatre should be shielded with some centimetres of Pb (5 ± 6) plus a few centimetre (4 ± 8) of a highly hydrogenated material (as, for example, the polyethylene, in preference to paraffin that has low temperature of fusion and relatively elevated risk of fire).

In conclusion, the presence of a neutronic component limits the employment of electron beams of energy >10 MeV in operating theatres not designed for IORT treatments. A possible methodology to reduce the thickness of the barriers is to share the workload among the various available energies, limiting and preventively defining the treatments with beams of energy above 10 MeV.

3. GENERAL ORGANISATION AND EXECUTION OF THE TREATMENT

This chapter takes into consideration the various phases of the IORT treatment with electron beam, giving special attention to the quality assurance procedures to follow in each phase. In particular, it describes the roles of the Group that will define, implement and verify the programme of quality assurance of the operational group and the minimum requirements of such a programme in the various phases of the IORT treatment. For each phase the principal objectives to pursue will be described, as well as some operational procedures for the implementation of the quality assurance programme.

3.1. Quality group

All Centres with an active IORT programme are advised to constitute a quality group. This Group should be composed by the person Responsible for the programme of Quality Assurance (RQA) and from representatives of all the sanitary operators involved in the IORT treatment, each of them nominated by the Director of the Department or affiliated service.

The components of the quality group therefore reflect the composition of all the categories of sanitary personnel involved in the IORT-procedure. Personnel with secretarial assignments can also be included in the quality group, as well as representatives of the Sanitary Direction and of the clinical engineering Services of the Hospital, upon invitation of the RQA.

Every Centre should define the duration of the assignment of every member of the quality group, the procedures for their substitution, the frequency of the meetings and their management.

The assignments of the quality group are:

- to define the programme of quality assurance to follow during the various phases of the IORT treatment;
- to define the responsibilities in the various procedures for guaranteeing the required level of quality;
- to write up the specific forms for quality assurance to be adopted in the various phases of the IORT treatment;
- to define the emergency procedures;
- to ensure that the planned procedures of quality assurance are constantly practised, possibly through periodic controls;
- to record and to communicate to the responsible persons involved, the results of the verifications, eventually drawing the attention to the necessary corrective actions to be taken and to the adjustments to be made;
- to take care that the documentation related to the programmes of quality assurance is preserved for at least 5 years, as pointed out by the Italian Decree 187/2000 (3), article 9, comma 9);
- to verify that any new procedures, including those connected with research programmes, are in agreement with the programme of QA;

- to file the protocols of on-going research and of the publications on the clinical data produced in the Centre;
- to manage the collection of information regarding the documentation of the training activities carried on in the Centre for the personnel involved in the procedure;
- to compile an annual report on the activities carried out and to discuss it with all the participants to the IORT treatment.

3.2. Operational group

The operational group includes all the operators (health personal, technical and administrative personnel) involved in the execution of the IORT treatment, who have been trained to follow the indications of the quality assurance programme prepared in each Centre.

The responsible persons of the department or service involved in the execution of the IORT treatment nominate the participants to the operational group and assign their responsibilities, as required by the programme of quality assurance. Members of the Operational group can also belong to the quality group.

The assignments of the operational group are:

- to confirm indications of the IORT treatment;
- to perform, in their respective competencies, the various phases of the IORT treatment;
- to participate in the planning of the various phases of the IORT treatment;
- to write up the specific forms for quality assurance to be adopted in the various phases of the IORT treatment;
- to define the emergency procedures;
- to perform the follow-up of treated patients;
- to participate in the training activities implemented in the Centre.

3.3. Indications for applying the method

A IORT treatment is effected following a request regarding a particular clinical problem of a single patient or as part of a therapeutic programme, formalised and designed for a specific type of illness.

The Centres are expected to define indications for requesting and delivering the treatment. It is advisable that the description of these aspects is reported

In the case of a request for application to a particular illness, the adequacy of the whole therapeutic programme is evaluated by the operational group, according to the norms of good clinical practice, and in line with previously defined guidelines. The various prospective therapeutic programmes, defined by the operational group, should be communicated to the quality group, and approved by the various competent organisms according to rules of good clinical practice.

The operational group should compile the forms used for the treatment request defined by the Quality group, and maintain a register of the performed treatments.

3.4. Criteria for the choice of the indication

Within the context of modern multidisciplinary strategies in oncology, IORT represents an interesting model of therapeutic integration. In particular, it can increase the effectiveness of the traditional association between surgery and radiotherapy by strengthening:

- *surgery*, with the elimination of the possible microscopic tumour residue;
- *radiotherapy*, with the attainment of dose levels non achievable with only external pre- or post-operative irradiation, strengthening the therapeutic combination, through the inhibition of the neoplastic regrowth in the interval between surgery and the following post-operative radiotherapy.

IORT could therefore be indicated in a context in which:

- there is a non-negligible possibility of local relapse with the conventional approach;
- the systemic risk is not too high or at least there is no demonstrated metastasis.

The consequent increase in the control of the early illness is very important to assure the definitive recovery; furthermore its employment does not jeopardise in any way a subsequent therapeutic intervention with external radiotherapy and with chemotherapy.

3.5. Criteria for the prescription of the dose

The prescription of the dose is the exclusive competence of the radiation oncologist.

When prescribing the dose the radiation oncologist has to keep in mind:

- clinical meaning of the single dose, taking into account the most accredited radiobiological models. Instead, the RBE should not be taken into account, due to the scarce available data;
- radicality of the surgical intervention and the possible entity of the residual neoplasm;
- possible intensification due to chemotherapy of pre- or post-operative radiotherapy treatments;
- Code systems for the prescription of the dose in the treatments with electrons proposed at international level (*International Commission on Radiation Units and Measurements* (ICRU) 29 (54), Task force 48 *American Association of Physical Medical* (AAPM) (29), etc.);
- position, the accessibility and the extension of the target volume;
- presence of critical organs in the field of irradiation, of their extension and the possibility of protection.

For the realisation of an appropriate programme of quality assurance each Centre is invited to define the forms to use, that must be signed by the responsible person.

3.6. Procedures for the planning of the treatment

The procedures for planning the treatment are designed to facilitate:

- evaluation of the completeness of the necessary documentation for the execution of the treatment (informed consent, anaesthesiological evaluation, etc.);

- definition of the sequence and the timing of the various phases of the treatment;
- procedure for communication of the treatment planning to all the involved personnel.

For the development of an appropriate programme of quality assurance each Centre is invited to prepare a document regarding:

- various phases of the treatment and the involved operators;
- modalities of information to the various operators for the planning of IORT (check list).

3.7. Preparation of the environment

3.7.1. Non-dedicated accelerator

3.7.1.1. Bunker

The procedures for preparation of the environment for the IORT treatment performed in the radiotherapy bunker are intended to support:

- suitable cleaning of the bunker before and after the execution of IORT (the activity of conventional radiotherapy can normally be performed in the bunker on the same day as the IORT treatment; it is interrupted only for allowing the cleaning procedures. Other interventions of special sterilisation can be performed within a procedure arranged with the Sanitary Direction of each Centre);
- preparation of the bunker through the removal or covering of the accessories or objects that can make the correct carrying out of the IORT treatment difficult or unsafe;
- positioning in the bunker and, after the treatment, the quick removal, of the equipment necessary to the various involved specialists to guarantee the correct and sure execution of the treatment.

For the development of an appropriate programme of quality each Centre is invited to prepare a document regarding:

- list of tasks to be followed for the execution of IORT in the radiotherapy bunker, approved by the persons responsible and by the Sanitary Direction;
- correct sequence of arranged activities, signed by the responsible person (one or more check lists).

The time employed for the whole procedure depends on the logistics of each Centre (e.g. distance from operating theatre to bunker) and can be of about 40-60 minutes:

- preparation of the bunker: 10 minutes;
- positioning of the patient and centring of the target: 10-20 minutes;
- execution of IORT: 5-10 minutes;
- removal of the applicator and transport of the patient out of the bunker: 5-10 minutes;
- rearrangement of the bunker: 10 minutes;

This estimated time does not necessarily include preventive changes of schedule in the sequence of the normal treatments, particularly if the possibility exists to perform the daily treatments on more than one LINAC.

3.7.1.2. Route from operating theatre to bunker

The possible problems related to the preparation of the route between the operating theatre and the radiotherapy bunker can be specific and depend on the type and length of the way itself.

When the surgery and radiotherapy areas are distant, it is necessary to transport the patient under general anaesthesia with the surgical wound temporally closed. This transport involves an accurate and rigorous organisation. The selected way must be isolated from the rest of the hospital and the transport of the patient has to involve different sanitary operators.

It is advisable that the sequence of the plan of operations is described and approved by the chief of the involved personnel and by the Sanitary Direction, and that a check list is prepared for the verification and for the appropriate identification of the person responsible of the plan of operations.

3.7.2. Dedicated accelerator

3.7.2.1. Operating theatre

The procedure for the preparation of the operating theatre for the IORT treatment with a dedicated accelerator is directed to:

- prevent the contamination of the operating theatre during the execution of IORT;
- reduce the radiation exposure of the operators involved in the IORT treatment within the limits pointed out by the norms in force.

For the development of an appropriate programme of quality assurance each Centre is invited to prepare a document regarding:

- succession of the tasks to be followed for the execution of IORT in the operating theatre, approved by the responsible persons and by the Sanitary Direction;
- correct sequence of the planned activities, signed by the responsible person (one or more checks list).

The general duration of this phase is of 30-60 minutes. At the end of the treatment procedure the accelerator and the shielding barriers are brought in the place of standstill. This phase is of competence of the radiation technologist and the necessary time is usually of 15 to 20 minutes.

3.8. Planning of the treatment

Contrary to conventional radiotherapy, in IORT it does not appear feasible at the moment the elaboration of a custom designed plan of treatment, based on manually acquired profiles or TC images acquired immediately before the execution of the treatment. Then, the planning of the treatment is necessarily limited to the consultation of graphs and charts containing the isodose curves measured under standard conditions (water phantom, normal incidence of the beam on a plain surface), taking into account the extension, position and accessibility of the target.

The planning procedures of the IORT treatment are directed to:

- facilitating the positioning of the applicators in the patient, taking into account:
 - presence of possible conflicts between the accelerator and the operating breach (interference with anaesthesiology and/or surgical equipment, patient's position, movements of the couch);

- adaptability of the collimators to the target region and the possibility of temporary displacement of the healthy organs (in some cases, the execution of an intra-operative Ultra Sounds (US) examination can confirm the indication to the treatment and verify the diameter of the applicator and the programmed energy);
- employment of the bevelled-base applicator, in order to reduce or to completely eliminate a possible air gap between the surface to be treated and the base of the same applicator.
- define:
 - extension of the margins around the target region, keeping in mind the course of the isodose curves in the region of penumbra of the beam; in most cases, 1 cm of margin appears suitable;
 - energy of the beam, based on the thickness of the target volume, determined with manual methods or, preferably, through a US-equipment, and on the possible presence of organs at risk below. In this phase it is useful to measure the possible presence of an air gap and to evaluate the opportunity to employ shields, in surface or internal, to protect healthy tissues. If the extension of the area to be treated makes necessary the junction of adjacent fields, it is necessary to carefully evaluate the geometry in function of the selected energy, in order to get the better possible uniformity of dose in the region of junction.

For the development of an appropriate programme of quality each Centre is invited to prepare forms signed by the responsible person and indicating:

- definition of the extension and the location of the target;
- possible macroscopic presence of neoplasm;
- selected energy;
- dimensions of the applicator;
- used surgical access;
- possible presence of air gap or shields;
- realisation of juxtaposition of the fields.

3.9. Treatment procedures

The procedures to be followed during the IORT treatment are intended to:

- guarantee that the dose prescribed on the target is administered with the maximum safety for the patient and the operators through:
 - the continuous visualisation of the patient and of the applicator, possibly with the employment of one or more TV-cameras;
 - the continuous visualisation of the vital parameters by the anaesthesia monitor;
 - the possibility of temporary interruption of the treatment and the immediate access in the room whenever necessary;
 - a careful definition of the irradiated region for the compilation of the report of the treatment.

For the development of an appropriate programme of quality assurance each Centre is invited to prepare a document regarding:

- steps in the plan of operations to be followed for the delivery of the dose, the calculation of the MU, the definition of the region to be irradiated and the reporting of the whole procedure;
- verification of the correct sequence of the planned activities, signed by the responsible person (one or more checks list). For the calculation of the MU is recommended an independent control from a second operator;
- preparation of a form to report the extension of the irradiated region and if it is the case, of the procedures adopted for the protection of the organs at risk,
- report of the treatment to be delivered to the patient, that must be attached to the clinical documentation.

3.10. Calculation of the Monitor Unit

3.10.1. Dedicated and non-dedicated linear accelerator

Once the energy of the beam and the applicator have been selected and the dose prescribed, it is necessary to calculate the number of MU to pre-set. To be able to quickly effect this operation and to avoid casual errors, the use of a form reporting the fundamental parameters and factors for the calculation of the MU is recommended.

The expression for the calculation of the MU is of the type:

$$UM = (D_p \times 100 \times GF \times SF) / (IR \times D^*)$$

where D_p is the prescribed dose (expressed in Gy) in a point of reference along the clinical axis of the beam, GF is the correction factor for the possible presence of an air-gap, SF is the correction factor for the possible presence of shields, IR is the value of the Percentage Dose (PDD) along the clinical axis of the beam in the point of reference and D^* (expressed in Gy/MU) is the dose per MU related to the applicator, to the energy and the used SSD, as defined in 2.2.1.1 and 2.2.1.2.

Before the execution of the treatment, it is recommended that the calculation of the MU be submitted to double independent control of which at least one is effected by a medical physics expert.

The employment of a computational automatic system of the MU can be useful to further reduce the probability of error.

It should be remembered that the medical physics expert is responsible for the calculation of the MU.

3.11. Anaesthesia procedure

By and large, the anaesthesia procedure (pre-operative evaluation, informed consent, general anaesthesia, combined anaesthesia or loco-regional anaesthesia) adopted for IORT, does not introduce particular differences in comparison to that used for traditional surgical interventions of the same kind. Nevertheless, it is necessary to consider some peculiarities connected to the IORT procedure (73), namely:

- longer duration of the surgical intervention;
- possibility of changing the decubitus of the patient on the operating table;
- possibility of having to transfer the anaesthetised patient into a different room, sometimes distant from the operating theatre;
- need to remove medical and paramedical personnel during the irradiation process.

The patients generally receive a conventional general anaesthesia with tracheal intubation. The change of position of the patient during the procedure, as well as the transport, is a moment of potential precariousness (74,75). Stable cardiovascular, respiratory and metabolic conditions are prerequisites to proceed to the variation of the decubitus and for the transfer of the patient (75). It is important to guarantee a suitable analgesia and to establish an adequate monitoring during the transport.

During IORT, the patient has to be curarised and therefore automatically ventilated in order to avoid any movement that can alter the correct irradiation of the target volume. During the radiation treatment, it is essential to monitor the patient and the instruments of anaesthesia with a closed circuit TV-system. Nevertheless, the anaesthetist has to be able to speedily reach the patient in order to intervene in case of need, after immediate interruption of the irradiation procedure. In some particular situations the patient can be submitted to procedures of local anaesthesia.

The responsible person of the Anaesthesiology Department or one delegate, should participate in the initial definition of the planning of IORT to define the procedures, arrange the resources that must be available during the execution of IORT, and select the participants in the quality group. The anaesthetist involved in each individual IORT treatment records the anaesthesiology procedures adopted in the clinic diary, according to the usual formalities adopted in the Centre, and participates in the compilations of any forms or check list, as agreed to during the planning phase of IORT.

3.12. Surgical procedure

The surgical procedure has specific demands during the IORT treatment:

- the surgical incision can be modified for facilitating good vision, exposure and centring of the target;
- an accurate intra-operative estimation of the extension of the illness is crucial to be able to select corrected therapeutic choices and for the appropriate execution of IORT; if the operating risk is acceptable and the illness is not disseminated, radical surgery should always be carried out
- an accurate haemostasis is essential, both to allow a suitable vision of the Organs At Risk (OAR) and of the target and to avoid the formation of an haematic collection;
- an important surgical procedure is represented by the mobilisation of the possible OAR which have to be separated from the field of irradiation within the limits of technical feasibility;
- surgeon and radiation oncologist collaborate in the definition of the target (tumour or tumour bed) and of the possible interested or adjacent structures that will be included in the field of treatment. It could be useful to preventively simulate in the operating theatre the mobilisation of the OAR and the centring of the target.

The responsible person of the Surgery Department or one delegate involved in the IORT programme, should participate in the initial definition of the planning of IORT, define the

procedures, arrange the resources that have to be available during the execution of IORT and select the participants in the Quality Group. The surgeon involved in each IORT treatment records the surgical procedures adopted in the clinic diary according to the usual formalities adopted in the Centre and participates in the compilations of any forms or check lists, as agreed to during the planning phase of IORT.

3.13. Management of emergencies

The management (and prevention) of emergencies includes specific aspects related to the logistic peculiarities of IORT, particularly if performed with non-dedicated accelerators, and the consequent need to transport the patient from the operating theatre to the bunker. The emergencies can be classified in three types:

- surgical (related to the transport of the patient);
- anaesthesiologic (related to the transport of the patient);
- radiotherapeutic.

The identification of possible emergencies and the procedures to be adopted must be included in the initial planning of the IORT treatment and in the activities of the quality group.

The procedures for the prevention and management of emergencies to be followed during the treatment IORT are:

- verifying that all the involved operators are informed on the useful resources available during the execution of IORT;
- monitoring that the training of the involved operators and the reliability of the resources to be used are up-to-date on the base of a default programme.

For the development of an appropriate programme of quality assurance the individuals Centres are invited to prepare a document regarding:

- the list of the principal possible emergencies and the procedures to be adopted in the case that one of them occurs;
- the verification of the availability of the operators and of the resources held necessary for the prevention and first intervention in case of emergency, duly signed by the person responsible (one or more check list);
- a periodic programme for the updating of the personnel and for the verification of reliability of the resources.

3.14. Follow-up: report and classification of side effects

A suitable programme of follow-up is necessary to be able to define the control of the evolution of the neoplasm and the possible medium- and long term side effects of the multimodal treatments that include IORT as one element of the therapeutic strategy.

Taking into account that the aim of IORT is the local control of the tumour, in case of local recurrence, it is indispensable to specify its spatial relationship with the IORT field:

- *central*: in the IORT field;
- *peripheral*: loco-regional, but outside or marginal to the IORT field.

It is useful that the late side-effects on healthy tissues and/or organs at risk are reported and classified according to the international systems (LENT: Late Effects Normal Tissues; SOMA: Subjective, Objective, Management, Analytical; RTOG EORTC: RadioTherapy Oncology Group of European Organization Research Therapy of Cancer) (76) pointing out, if possible, the spatial and time relationship between these and the treatment.

Finally, the possible onset of new tumours, with particular information of the localisation of the tumour in relation to the irradiated volume, should be reported.

For the development of an appropriate programme of quality assurance each Centre should prepare a document regarding:

- periodicity and the typology of the examinations to be performed during the follow-up;
- systems of reference to be used for reporting and grading of the side effects;
- forms to be used for recording the controls.

4. INFORMED CONSENT

The informed consent for IORT should take into account the norms in force related to the rules of good clinical practice.

It is recommended that the informed consent, duly signed, includes an informative note to be given to the patient, in which is clearly indicated:

- description of the procedure;
- purpose of the treatment;
- advantages in terms of duration of the total treatment, control of illness, possible minor side effects if compared to the alternative treatments;
- possible side effects related to IORT;
- faculty of the patient to refuse at any moment the treatment before its execution.

5. COST ANALYSIS

Procedures for defining the costs of IORT with electron beams should foresee homogeneous evaluation criteria for the two available modalities: i) conventional, with non-dedicated LINAC, that foresees the transport of the patient and ii) that with a dedicated LINAC in the operating theatre. The criteria of evaluation have to consider the different operational phases that characterise the IORT programme:

– *Pre-clinic phase*

It involves:

- activation and orientation of the multidisciplinary collaboration among oncology, radiotherapy, surgery, anaesthesiology and medicine on the programme IORT with the involvement of the departments of intensive anaesthesia-therapy and medical physics (interdisciplinary meetings);
- identification of a physician-physical-technical-nursing staff inside every department involved in the IORT procedure (operational group) and activation of a programme of formative training-stage of the operational group IORT;
- acquisition of the equipment (dedicated LINAC) or of the necessary tools for the execution of the treatment with not dedicated LINAC (applicators for IORT, dedicated couch, procedures for transport/treatment, possible instruments and furniture of operating theatre);
- dosimetric characterisation of the equipment and of the IORT applicators.

In this phase it is necessary to evaluate the cost of the acquisition of the equipment (for dedicated LINAC), of the accessories, of the stretcher for the transport of the patient (for non-dedicated LINAC) and of the possible tools for the dosimetric controls, the costs for their maintenance and the costs for the involved personnel (radiation oncologist, surgeon, anaesthetist, medical physics expert, technical-nurse).

– *Clinical phase*

It includes the organisational aspects, the planning and the execution of the treatment as described in chapter 3. Particularly:

- multidisciplinary visits;
- IORT procedure (the personnel's cost/hour);
- ordinary and extraordinary sterilisation of the places (non-dedicated LINAC);
- recovery of the clinical activity/treatments (non-dedicated LINAC);
- cost of the use of LINAC (dedicated and non-dedicated) for IORT application (amortisation cost LINAC + maintenance);
- number of treatments in 10 years of use of the equipment;
- consumption for procedure (sterilisation, medical gas, uniforms and sterile cloths, etc.).

In this phase the costs related to the personnel directly involved in the procedure must be considered, together with those of consumable materials and, in the case of non-dedicated LINAC, the lack of utilisation for the conventional treatments.

According to these criteria of evaluation, the costs of the IORT procedures are conditioned by the modality with which the treatment is performed. In the traditional procedure (non-dedicated LINAC) organisational costs predominate, while in the procedure with dedicated LINAC investment amortisation and maintenance costs of equipment predominate (77, 78).

IORT with an X-ray source

Introduction

Specific miniaturised sources of X-rays can be used for IORT, that emit X-rays of low energy ($V_{\max} = 50$ kV for the sources currently in commerce) from the point of a probe inserted in a spherical applicator, resulting in a uniform dose distribution to the surface of the applicator (79, 80). The dose-rate is of around 0.5 - 2 Gy/min at the surface of the applicator, with a strong gradient of dose (typically equal to 10-20% per mm from the surface, in function of the diameter of the applicator). Applicators are available with diameters from 1.5 to 5 cm. They are made of plastic material characterised by high resistance to the radiation damages and can lodge a filter in aluminium to absorb the low energy spectral components.

In view of the limited experience acquired thus far, this part of the guidelines on IORT are not intended to give prescriptions but rather to underline some problems and to describe possible solutions.

Indications and criteria of treatment

In Italy the employment of sources of rays for intra-operative irradiation is limited till now to the brain tumours. In European, North American and Australian Centres the method is also employed in the treatment of some forms of breast and colon-rectal cancers. With regard to brain tumours the principal criteria to follow are:

- *Histological criteria*
 - malignant glioma,
 - brain metastasis (single),
 - local recurrence of operated and irradiated glioma with fractionated technique,
 - recurrence of primary or secondary lesions with character of cerebral infiltration;
- *Clinical-radiological criteria*
 - a roughly spherical shape
(so that, after the removal of the tumour, the residual cavity can be conformed to the applicators of various diameter (up to 5 cm),
 - the diameter of the tumour
(can be also superior to 5 cm, because after the surgical resection a collapse of the walls of the cavity takes place),
 - big or diffusely infiltrant tumours
(as, for example the so-called “butterfly glioma” of the corpus callosum or the forms of gliomatosis) must not be included,
 - the localisation of the tumour
(it conditions the treatment and the prescription of dose);
- *Prescription of the dose*

The dose prescription must be based on some characteristics both of the x-ray source and of the parameters of the patient to be treated, such as:

 - the RBE of the X- radiation of low energy, as it results from experimental studies, can be greater than 1 (81, 82);
 - the persistence and the thickness of residual tumour;
 - the previous and the successive external radiotherapy.

Dosimetry

It is not possible to use the existing protocols for the determination of the dose from low energy X-ray sources, since they foresee the measure under conditions of “good geometry” (collimated and *quasi*-parallel beam) and they imply an external source: both these conditions are not verified with the type of source under consideration. The solutions that will be described below, although not rigorous, have been adopted by all Centres where this type of source is used.

The high gradient of dose sets dosimetric problems, which are not easy to solve (83). One of these is the fact that the distance of the point of prescription from the point source is typically in the interval 1-3 cm; in this situation the uniformity of dose-rate may not to be guaranteed on the whole active volume of the used dosimeter.

Another problem is the determination of the radiation quality and the consequent choice of a calibration factor for the dosimetric system used: in fact the Half Value Layer (HVL) measured in air may not be, in principle, a good index of the quality of the radiation at some centimetres of distance from the source in water, since the energy spectrum is significantly modified in depth.

Finally, the measure of the dose in certain areas close to the probe is not easy (back-emitted radiation with respect to the direction of the probe), due to the size of the detector.

With regard to the dosimetry in a reference position (generally 5 or 10 mm from the surface of the applicator), a possible solution is the employment of a plane-parallel electrodes ionisation chamber in a water phantom. For instance, chambers PTW N23342 and PTW TN34013, covered by a thin plastic material (Gammex Solid Water 0.5 mms or other water-equivalent plastic) to be able to be used in a water phantom can be used. The Quality Factor (k_Q) of these chambers presents a limited variation (maximum 2%) in the range of the HVL of the radiation emitted by the source. For this reason, the possible errors due to the difficult determination of the radiation quality are negligible. Besides, the dimensions of the active volume are significantly less than the distance of the chamber from the source (particularly for the second chamber), at least for a point of measure placed at a distance of 10 mm from the applicator.

Ionisation Chambers of the type specified above, are generally used also for dosimetric measurements in a water phantom in different points from that selected as the reference.

For every applicator, the following parameters are determined:

- curves of dose-rate in function of the distance from the source for every available combination voltage-current;
- dose distribution at a constant distance, d , from the spherical applicator (for instance for $d = 5$ mm and $d = 20$ mm).

In positions where the size of the camera (backward direction) prevents the measurement unreliable, it is possible to use radiochromic films (45).

The source dissipates a maximum power of around 2 watt during the irradiation; it is therefore suggested to perform measurements of contact temperature on the surface of the applicator. The gained experience has shown that the overheating constitutes a limit in the case of employment of the naked source (interstitial radio-surgery) while, in presence of the IORT applicator, the heat is absorbed by the applicator itself in sufficient measure. Nevertheless, in case of employment of radiochromic films, considered the dependence of their sensibility from the temperature, a suitable system of cooling is usually used during the exposure of the film.

Quality control

A complete series of controls are usually performed in a shielded room where a dosimetric system can be easily used and under conditions of non-sterility. In the initial phase of clinical employ the tests are generally carried out before every treatment; subsequently, on the base of the acquired experience, it is possible to plan a programme with monthly frequency. Besides the already mentioned dosimetric measurements, the following minimum controls are usually carried out:

- integrity of the applicators (visual control);
- mechanical deflection of the probe;
- emission isotropy;
- short and long-term reproducibility;
- independence of the dose-rate from the position and orientation of the source;
- linearity of the dose in function of the counts.

Control of the linearity of the dose in function of the counts is performed up to a value higher than the predictable maximum count in a treatment.

Since the process of sterilisation to which the source is submitted could alter its characteristics, before every treatment the followings controls are carried out and the following parameters are measured directly in the operating theatre and under conditions of sterility:

- integrity of the applicators;
- mechanical deflection of the probe;
- isotropy of emission;
- functionality of the external backup monitor;
- dose-rate in a point of reference;
- independence of the dose-rate from the position and orientation of the source;
- count per minute at the voltage and current employed.

In vivo dosimetry

Thus far there are no available clinical experiences on the *in vivo* dosimetry with this type of source. The principal problems are related to the energy dependence of the dosimeter and to the control of its position. Pre-clinical studies are now directed to the employment of MOSFET or radiochromic films (45, 84-86).

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ANNEX

IIORT centres (beams and kind of accelerator) in Italy

Region	IIORT Centre	Beam	Accelerator	Status
Abruzzo	Azienda Ospedaliera ASL 3 Lanciano-Vasto, Lanciano (CH)	electrons	dedicated	operative
Calabria	Azienda Ospedaliera Bianchi Melacrino Morelli, Reggio Calabria	electrons	dedicated	operative
Emilia Romagna	Azienda Ospedaliera di Parma, Parma	electrons	dedicated	Installation in progress
Friuli-Venezia Giulia	Centro di Riferimento Oncologico Aviano (PN)	electrons	non-dedicated	operative
		X rays	sorgente miniaturizzata	non operative
Latium	Policlinico Gemelli, Roma	electrons	non-dedicated	operative
	Ospedale San Pietro Fatebenefratelli, Roma	electrons	non-dedicated	operative
	Ospedale S.Filippo Neri, Roma	electrons	dedicated	operative
	Istituto Regina Elena, Roma	electrons	dedicated	operative
Lombardy	Istituto Europeo di Oncologia (IEO), Milano	electrons	dedicated	operative
	Ospedale San Raffaele, Milano	electrons	non-dedicated	operative
Puglia	Ospedale Oncologico, Bari	electrons	dedicated	Imminent beginning of the clinical activity
Tuscany	Azienda USL 9, Grosseto	electrons	dedicated	operative
	Azienda Ospedaliera Pisana, Pisa	electrons	dedicated	operative
Trentino-Alto Adige	Ospedale S. Chiara di Trento, Trento	electrons	non-dedicated	operative
Veneto	Ospedale Ca' Foncello, Treviso	electrons	dedicated	operative
	Ospedale Maggiore, Verona	electrons	dedicated	installation in progress
	Ospedale S. Bortolo, Vicenza	X rays	sorgente miniaturizzata	operative

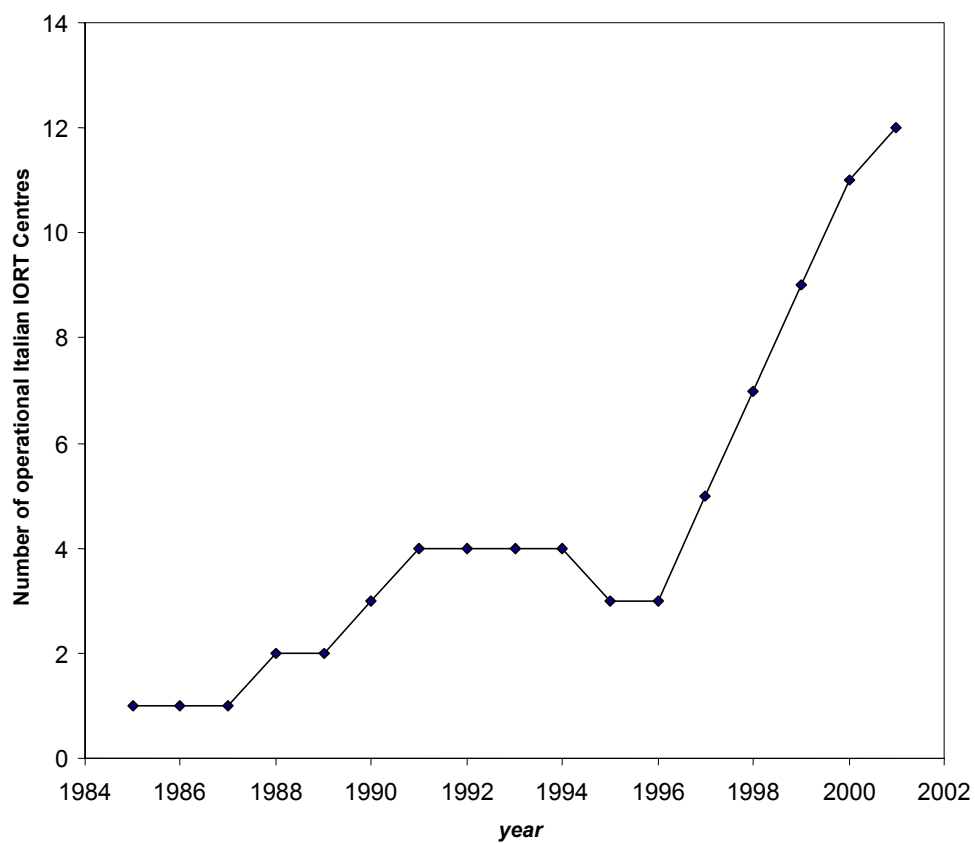


Figure 1: Operational Italian IORT Centres (1980-2001)

MAIN RECOMMENDATIONS FOR QUALITY ASSURANCE IN IORT WITH ELECTRON BEAMS

Tables

CLINICAL ASPECTS

ORGANIZATION

◆ Initial phase

- The Centre defines:
 - the indications of the treatment in a context in which:
 - there is a relevant possibility of recurrence with the conventional therapeutic approach,
 - the systemic risk is not too high;
 - the procedures for requesting the treatment.
- The operational group has:
 - to confirm indications of the IORT treatment;
 - to perform, in their respective competencies, the various phases of the IORT treatment;
 - to participate in the planning of the various phases of the IORT treatment;
 - to write up the specific forms for quality assurance to be adopted in the various phases of the IORT treatment.

◆ Pre-treatment

- The Centre prepares a document defining:
 - the various phases of the treatment and the involved operators;
 - the modalities of information to the various operators for the planning of the IORT (check list);
- The radiation oncologist prescribes the dose on the basis of:
 - the meaning of the single dose according to the more accredited radiobiological models;
 - the extension of the surgical intervention and the possible entity of the neoplastic residual;
 - possible pre- or post-operative radiotherapy treatments with or without chemotherapy;
 - the position, accessibility and extension of the target;
 - the presence and extension of critical organs in the field of irradiation and the possibility for their protection;
 - the systems of coding of the dose prescription in the treatments with electrons as proposed at international level (ICRU 35, Task force 48 AAPMs, etc.).

◆ Preparation of the environment

■ *Non-dedicated accelerator*

The procedures of preparation of the environment involve:

– *Bunker*

The following points should be specified:

- the succession of the activities to be followed for the execution of the IORT in the bunker of radiotherapy with approval of the responsible person and of the Sanitary Direction;
- the correct sequence of the planned activities, signed by the responsible person (one or more checks list).

- *Transfer operating theatre-bunker*

It involves:

- an accurate and rigorous organisation of the transfer;
- the description of the sequence of the activities;
- the approval by the responsible of the involved personnel and of the Sanitary Direction;
- the preparation of a check list for monitoring and evaluation and for the appropriate identification of the responsibilities on the implementation.

■ **Dedicated accelerator**

The procedures of preparation of the environment involve:

- operating “room”.

It is recommended that the Centre:

- prepares a document defining the succession of the activities to be carried out during the execution of the IORT in the operating theatre;
- requires approval from the responsible persons and from the Sanitary Direction for the correct sequence of the planned activities.

PLANNING OF THE TREATMENT

- It is recommended that:

- the position of the applicator in the patient is facilitated

taking into account:

- the possible incompatibility between the accelerator position and the surgical breach;
- the adaptability of the collimators to the target and the possibility of displacing the healthy organs
- the employment of bevelled base applicators, in order to reduce or to completely eliminate possible air gaps between the surface to be treated and the base of the same applicator

- define:

- the width of the margins around the target taking into account the course of the curves of isodose in the region of penumbra of the beam;
- the energy of the beam.

- The forms signed by the responsible person should contain:

- the definition of the extension and of the position of the target;
- the possible macroscopic presence of cancer
- the selected energy;
- the dimensions of the applicator;
- the access used;
- the possible presence of air-gap or shielding;
- in the case of two or more adjacent fields, the juxtaposition of the fields.

IMPLEMENTATION OF RADIOTHERAPY TREATMENT

- It is recommended:

- to continuously control the patient and the applicator;
- to continuously control the vital parameters displayed by the monitor for the anaesthesia;
- to make the necessary provisions to temporary interrupt the treatment and have immediate access to the room whenever is held necessary;
- to prepare a document containing the indications of:
 - the region irradiated;
 - the extension of the irradiated region,
 - the possible procedures adopted for the protection of the organs at risk,
 - the dose-rate;
 - the calculation of the Monitor Unit.

- to verify the correct sequence of the planned activities (one or more check lists).
- to compile the report of the treatment to be given to the patient, attaching the clinical documentation.

It is recommended that the calculation of the MU is submitted to independent double control from some of the qualified personnel, among which a medical physics expert should be obligatorily included.

ANESTHESIOLOGY PROCEDURE

- It is necessary that:
 - for changing the decubitus and for transferring the patient, cardiovascular, respiratory and metabolic conditions are stable;
 - a suitable analgesia is guaranteed and an opportune monitoring is ensured during the transfer of the patient;
 - the patient is curarised and thereafter automatically ventilated, with the purpose of avoiding any movement that can alter the correct irradiation of the tumour volume;
 - the anaesthetist is in condition, in case of need, of quickly reaching the patient, after having stopped the irradiation.
- The Person responsible of Anaesthesiology or one delegate:
 - participates in the initial definition of the planning of the IORT;
 - plans the procedures and the resources that must be available during the execution of the IORT;
 - designates the person that will participate in the quality group.
- The anaesthetist:
 - reports in the clinical diary the anaesthesiology procedures adopted, according to the usual procedures of the Centre;
 - participates in the compilation of check lists, according to the IORT programme.

SURGICAL PROCEDURE

- The surgeon:
 - can modify the surgical incision to facilitate a good vision, exposure and centring of the target;
 - can perform an accurate intra-operative diagnosis of the extension of the illness;
 - has to pursue a radical surgery if the operating risk is acceptable and the illness is not disseminated;
 - provides an accurate homeostasis, both to allow a suitable vision of the organs at risk (OAR) and of the target, and to avoid the formation of sero-haematic collections;
 - reports the surgical procedures adopted;
 - participates in the compilation of report forms or check lists.
- The surgeon and the radiation oncologist:
 - collaborate to define the target (tumour or tumour bed) and the possible adjacent or interested structures that will be included in the treatment field;
- The responsible person of the Complex Structure of Surgery involved in the programme IORT or one delegate:
 - participates in the initial definition of the planning of the IORT;
 - defines the procedures and allocates the resources that have to be available during the execution of the IORT;
 - appoints the participants to the quality group.

MANAGEMENT OF THE EMERGENCIES

- Each Centre will prepare a document defining:
 - the list of the principal possible surgical and anaesthesiology emergencies related with the transfer of the patient and the procedures to be adopted in the case that one of them occurs;
 - the verification of the availability of people and resources held necessary for the prevention and first intervention in case of emergency (one or more checks list),
 - a periodic programme for the updating of the personnel and the verification of reliability of the resources.

FOLLOW-UP-COLLECTION AND CLASSIFICATION OF SIDE EFFECTS

- It is recommended:
 - to specify, in case of local recurrence, the spatial relationship with the IORT field:
 - *central*: in the IORT field;
 - *peripheral*: loco-regional, but outside or marginal in relation to the IORT field;
 - to report and to classify, according to the international systems, the late side-effects on healthy tissues and/or organs at risk pointing out if possible the spatial and time relationship between them and the treatment;
 - to report the possible onset of new tumours, with particular attention to the relationship between the point of onset and the irradiated volume.
- The Centres will define in writing:
 - the periodicity and the typology of the examinations to be performed during the follow-up;
 - the systems of reference to be used for the report and the gradation of the side effects;
 - the modules forms to be used for recording the controls.

INFORMED CONSENT

- It is recommended that the informed consent for the IORT:
 - is signed by the patient;
 - respect the rules of good clinical practice;
 - includes an informative note for the patient with the clear indication of:
 - the description of the procedure;
 - the purpose of the treatment;
 - the advantages in terms of control of illness, duration of the general treatment and of possible reduction of side effects compared to the alternative treatments;
 - the possible side effects to the IORT;
 - the faculty of the patient to refuse in any moment the treatment before its execution.

PHYSICAL ASPECTS

All the dose measures must be performed with dosimeters calibrated at a Primary Metrological Institute or at an accredited Centre for the calibration in the sector of ionising radiation.

DOSIMETRY IN REFERENCE CONDITIONS

◆ Non-dedicated accelerators

It must be performed for all the energies used in the IORT treatments with an ionisation chamber, chosen among those characterised by the less angular dependence of the response.

It is recommended:

- the use of the protocol IAEA TRS 398
- for every energy, the use of a square applicator of $10 \times 10 \text{ cm}^2$ or of a circular applicator with a diameter of 10 cm with plane base
- SSD=100 cm (where not available, the nominal SSD).

◆ **Dedicated accelerators**

It is not possible the use of protocols:

It is recommended:

- for every energy, an square applicator of 10 x 10 cm² or of a circular applicator with a diameter of 10 cm with plane base
- SSD=100 cm (where not available, the nominal SSD)
- R_{max} as reference depth
- the use of a Fricke dosimetric system managed by a Primary Metrological Institute or by accredited Centre for the calibration in the sector of ionising radiation (in alternative, relative dosimetric systems can be used with independent sensibility from the dose rate, from the beam energy and from the angle of incidence of the electrons, such as alanine dosimeters)

DOSIMETRY IN NON REFERENCE CONDITIONS

◆ **Determination of the dose per Monitor Unit (D^* , cGy/UM)**

■ **Non-dedicated accelerators**

It must be performed for each applicator, energy and SSD employed in the clinical practise.

It is recommended:

- to position the ionisation chamber at the reference depth of R_{max} , along the beam axis;
- to use a dose-rate similar to that used for the treatments;
- in the case of plane base applicators, to use an ionisation chamber with a reduced angular dependence;
- in the case of bevelled base applicators, to use dosimeters of small dimensions, with independent response from the beam's angle of incidence, such as alanine, radiochromic films, TLD or, in alternative, small size ionisation chambers , excluding plane-parallel electrodes ones.

■ **Dedicated accelerators**

It must be performed for each applicator, energy and SSD employed in the clinical practise.

It is recommended:

- to perform the measurement on the beam's clinical axis, at the depth of the R_{max} ;
- to use the absolute Fricke dosimetric system or relative systems with independent sensibility from the dose-rate, such as alanine or radiochromic films;
- to verify the energy dependence of the dosimetric system used to all the energies of the beams of clinical use, managed by a Metrological Centre.
-

For both types of accelerators, it is recommended to determine the correction factors for the possible presence of an air gap between the surface to irradiate and the base of the applicator. In the case of employment of additional shielding inside the irradiation field it is also recommended to introduce the appropriate correction for the output factors.

◆ **Determination of dose distributions**

It must be performed for all the geometric configurations and for every energy of the beams employed in the clinical practise with a dosimetric system characterised by a negligible energy and angular dependence:

It is recommended that includes:

- the PDD measured along the beam's clinical axis with the indication of the principal parameters: R_{max} , R_p , R_{90} , R_{50} , surface dose and percentage of dose due to the photon contamination of the beam;
- the transversal profiles of dose, measured along two orthogonal directions at least at the depths where the dose has the 100% (R_{max}), 90% (R_{90}), 80% (R_{80}) and 50% (R_{50}) values;
- the isodose curves on the two principal orthogonal planes containing the beam's clinical axis.

It is also recommended to determine the percentage of radiation scattered through the walls of the applicator, in function of the beam energy and of the distance both from the wall itself and from the base of the applicator.

■ **Non-dedicated accelerators**

It is recommended:

- to use an automatic system that guarantees an accuracy and a reproducibility of positioning of the detector of 0,1 mm with ionisation chambers or solid state detectors, such as silicon diodes or diamond detectors;
- to use the same aperture of the secondary collimator used in the determination of D^* ;
- to employ a dose-rate similar to that used during the treatment of the patients and for the determination of the dose per MU.

■ **Dedicated accelerators**

It is not recommended the use of ionisation chambers. Small size dosimeters are recommended with independent response from the dose-rate. It is a common practice the utilisation of silicon diodes. Radiochromic and radiographic films constitute a possible alternative.

QUALITY CONTROL

- It is necessary to plan a strict programme of quality control that includes:
 - acceptance tests before the entrance in service of the equipment;
 - tests of operation, as a programmed periodical activity and after every remarkable intervention of maintenance.
- It is recommended:
 - that the systems used for verifying the stability of the dosimetric characteristic of the radiotherapy beams offer high reproducibility of response besides the practicality of employment;
 - that the dosimeters used for the controls of quality are calibrated on the local reference dosimetric system;
 - to periodically verify the calibration of the dosimeters used both in reference and non-reference conditions, as well as of the dosimeters for quality control. Such verification must be performed every time that is used a new batch of dosimeters.
- For each control it is necessary that every Centre defines the corrective actions to adopt whenever from Quality Controls demonstrate a discordance with the corresponding pre-stated tolerance.
- The followings minimum controls are recommended:
 - movements and end raced of the motors;
 - emergency devices;
 - integrity of the applicators;
 - sterility of the applicators;
 - optic and acoustic warning devices;
 - long term stability of the dosimetric monitoring system;
 - alignment laser (soft-docking systems);
 - short term stability of the dosimetric monitoring system (repeatability);
 - proportionality of the dosimetric monitoring system (linearity);
 - symmetry and homogeneity of the fields;
 - energy of the radiation beams.

IN VIVO DOSIMETRY

- It is desirable that the Centres allocate resources with the purpose to arrange reliable and practicable dosimetric procedures.
- Before making operational a programme of *in vivo* dosimetry, it is recommended to optimise the methodology of measure for every treated pathology and eventually, in a following phase, to define in an appropriate way, levels of intervention and corrective actions.

RADIATION PROTECTION ISSUES

- IORT treatments
 - *With conventional accelerators in a shielded bunker*
 - additional specific radiation protection measures are not necessary.
 - *In a unshielded operating theatre*
 - some interventions are necessary due to the presence of a field of radiation.
- Every Centre will have to evaluate the need for shields, fixed or mobile, choosing their composition, thickness and dimensions on the base of factors normally employed in the calculation of the protective barriers (work-load, destination of use and factor of occupation of the adjacent rooms, etc.).
- The presence of a neutronic component in electron beams of energy above 10 MeV implies the use of specifically projected operating theatres for the carrying out of IORT.

DETERMINATION OF THE MONITOR UNIT (MU)

- It is opportune that a form is prepared to report the fundamental parameters for the calculation of the MU and that one or more charts are available to clearly report the different factors to be applied.
- It is recommended that the calculation of the MU is submitted to double independent control from qualified personnel among which a medical physics expert should be obligatorily included.

MAIN RECOMMENDATIONS FOR QUALITY ASSURANCE IN IORT WITH X-RAYS SOURCES

Tables

POSSIBLE SOLUTIONS

CLINICAL PROBLEMS

◆ Clinical radiological criteria

- *Histological criteria:*
 - malignant glioma;
 - brain metastasis (single);
 - local recurrence of operated and irradiated glioma with fractionated technique;
 - recurrences of primitive or secondary lesions with character of cerebral infiltration.
- *Clinical radiological criteria:*
 - relatively spherical conformation, of the residual cavity after the removal to be conformed to the applicators of various diameter (up to 5 cm),
 - the dimensions of the tumour can be also superior to the 5 cm of diameter since, after the surgical resection, there is generally a collapsing of the cavity's walls,
 - extended cancers or diffusely invasive (as the so-called "butterfly glioma" of the callous body or the gliomatosis) should not be included,
 - the localisation of the tumour conditions the treatment and the prescription of the dose.
- *Prescription of the dose*

The prescription of the dose must be based on some characteristics of the source employed and of the parameters related to the patient to be treated:

 - the relative biological effectiveness (RBE) of the X radiations of low energy, as it has been demonstrated in experimental studies, can be larger than 1,
 - the persistence and the thickness of residual cancer,
 - the previous or successive external radiotherapy.

POSSIBLE SOLUTIONS FOR DOSIMETRIC PROBLEMS

- *Dosimetry in the reference point*
 - employment of a plane-parallel electrodes ionisation chamber in a water phantom.
- *Dosimetric measurements in different points from that selected as reference*
 - employment of a plane-parallel electrodes ionisation chamber in a water phantom.
- *Determinations for each applicator*
 - of curves of dose-rate in function of the distance from the source for every available combination of voltage-current;
 - of distribution of dose at a constant distance, d, from the spherical applicator (for instance for d = 5 mm and d = 20 mm).
- *Radiochromic films*
 - in the positions in which the size of the chamber (back direction) prevents the measurement.
- *Temperature measurements*
 - on the surface of the applicator.

QUALITY CONTROL

- At least the followings controls should be performed:
 - integrity of the applicators (visual control);
 - mechanical deflection of the probe;
 - isotropy of emission;
 - reproducibility at short-and long-time term;
 - independence of the dose-rate from the position and orientation of the source;
 - linearity of dose in function of the counts.

- In the operating theatre and under conditions of sterility, should be performed at least the followings controls or measured the following parameters:
 - integrity of the applicators;
 - mechanical deflection of the probe;
 - isotropy of emission;
 - functionality of the external monitor of backup;
 - dose-rate in a reference point;
 - independence of the dose-rate from the position and orientation of the source;
 - number of counts per minute at the voltage and current of employment.

***IN VIVO* DOSIMETRY**

Pre-clinical studies suggest, up to now, the employment of MOSFET or radiochromic films.

GLOSSARY

Accredited calibration laboratory

Laboratory designated by the appropriate national governmental authority as that having the measurement capability to perform calibrations of measuring instruments by comparison with a secondary, periodically compared with the national primary standard of the same quantity

Acute side effects

Effects which occur in the healthy tissues at a relatively short time after IORT or the combined treatment, generally from zero to three months. They are in prevalence oedema, exudation, erythema.

Alanine

Amino acid with chemical composition, electronic density, atomic number and physical density very similar to those of the biological tissues and of water. Usable both as reference and transfer dosimeter and for *in vivo* dosimetry.

Check list

Tool to facilitate the correct and complete sequence of various activities that compose a procedure. The operators should check the various steps of the check list by documenting their execution. The use of a check list implies the definition of various phases of a procedure and the responsibilities in their execution by all the involved operators.

Clinical axis

Perpendicular axis to the surface of entry of the beam long which, to one defined depth, the dose is prescribed. In the case of the plane base applicators the clinical axis coincides with the geometric axis of the beam. In the case of the base bevelled applicators the clinical axis intersects the geometric axle of the beam at the surface of entry forming with it an angle $\Phi > 0^\circ$.

CTV (Clinical Target Volume)

Probable or certain anatomical region (if documented with extemporaneous histological examination) site of microscopic tumour residue; in case of radical surgery it is generally represented by the tumour bed, by the regional lymph nodes or by contiguous areas to the macroscopic tumour lesion.

Dedicated accelerator

Mobile accelerator designated specifically to perform IORT in the common operating theatres (not shielded) In comparison to conventional accelerators it allows greater freedom of movement of the gantry and/or of the whole structure (to facilitate the positioning of the applicators on the patient).

Documentation

Analytical description of the anatomical areas, of the doses to the radiated volume and the organs at risk, according to the points of reference. It has to include the description of the operating findings, of the surgical procedure (radical surgery, debulking, exposure, etc.), of the technical formalities and dosimetry of IORT.

Dose on the surface

Dose measured positioning the dosimeters on the irradiation surface.

Dosimeter of current use

Dosimeter set by the Centre of Radiotherapy by comparison with the reference dosimeter.

Dosimetric system (active type)

Dosimeters whose responses allow the immediate determination of the dose (ionisation chambers, diamond detectors, diodes, MOSFET, plastic scintillators).

Dosimetric system (passive type)

Dosimeters whose responses are analysed in delayed times after the irradiation. (TLD, alanine, radiographic and radiochromic films).

Dosimetry in reference conditions

Measure of the absorbed dose to water applying the conditions of reference defined in the dosimetric protocol.

Emergency

Every event of medical, physical or dosimetric nature, not anticipated or predictable, that takes place during the procedure of IORT and implies its immediate interruption.

Entrance dose

Absorbed dose at the depth R_{max} where it reaches its maximum value. Can be derived from measures of dose positioning the dosimeters on the irradiation surface (see dose on the surface).

Form

Instrument to identify the necessary information for the execution of a specific procedure. Constitutes support for the reporting of activities. The signature allows the identification of the person responsible for the reporting.

Fricke dosimeter

Chemical dosimeter based on a solution of ferrous sulphate, contained in a sealed phial of glass, for the measure of the absorbed dose to water under reference conditions.

GTV (Gross Tumour Volume)

Macroscopic tumour lesion. It is represented by the tumour *in toto* in case of inoperability, isolated exposure, or by the possible macroscopic residue in case of debulking. It is not present in case of microscopically radical surgery.

Hard-docking

Procedure of hooking up to the gantry of the accelerator the applicator already positioned in the anatomical area to irradiate.

Independent check

Procedure to document the verification by a second operator of an activity that, because of its delicacy or importance, is considered necessary to carefully check before its execution. The independent check can be confined to a control or the parallel execution from a second operator of the phase of formulation of the same activity that will be performed, only if the result of the two operators coincides. The form for the independent check should underline the activities performed by the various operators, duly signed.

Informed consent

Instrument of clear and complete information for the patient regarding the medical procedures applied on him. It is an essential condition for the beginning and the carrying out of every medical-surgical procedure. In fact the article 32 of the Italian Constitution (2° paragraph) affirms that “nobody can be forced to a determined medical treatment if not provided for by the law” and that “the law can not in any case violate the limits imposed by the respect of the human person.” According to the norms of Good Clinical Practice the conditions that qualify the goodness of the consent are at least 3: *i.* the quality of the information and communication, *ii.* the comprehensibility and *iii.* the ability and decisional freedom of the patient. Obviously the informed consent on IORT has to cover every clarifying element on the method, including the technical notes, the possible insertion in research protocols, the possible benefits and side effects, the referent personnel, the data treatment and the rules on privacy.

IORT applicator

Tube of light plastic or metal material, with circular, angular or other complex geometry section. This tube collimates the electron beam and delimits the surface of. As a rule bi-sectioned, it is attached to the

gantry of the accelerator directly or through adapters. The terminal part can be plane or bevelled with respect to the geometric axis of the beam.

Late side effects

Effects which occur in healthy tissues after a long period of time following IORT, generally later than three months; the most typical are: fibrosis, neuropathy, vasculopathy, loss of sensorial-motor functions.

Local control

Therapeutic goal that proposes to reduce or to reset with the ionising radiation (or with the combined treatment) the number of cloned neoplastic cells able to be reproduced in the primitive site of the tumour and to cause therefore the local recurrence of illness.

Long-term stability of the system of dosimetric monitoring

Reproducibility of the output. The check of the output stability is performed before each treatment and with a frequency planned in the contest of periodic quality control.

MOSFET

Metal Oxide Silicon Field Effect Transistor, solid state detector mainly employed for *in vivo* dosimetry.

Non-dedicated accelerator

Conventional accelerator for external radiotherapy with photon and electron beams. As a rule, installed in a bunker, can be modified for producing only electron beams and for being used in a non shielded operating theatre.

Non reference conditions

Conditions of measure for the dosimetric characterisation of the electron beams.

Organs At Risk (OAR)

Normal tissues or organs, that for radiosensibility or proximity with the IORT field can be target of acute or late complications and therefore influence the dose prescription and /or the modalities of treatment and their execution.

Output

Dose per Monitor Unit delivered by a linear accelerator. It is measured in phantom at the depth of maximum dose R_{max} . It varies with the type of radiation, the energy of the beam, the dimensions of the field of irradiation and with the SSD.

Peri-operative complications

Complications occurring in the immediate post-operative period that can be correlated to the anaesthesiological or surgical procedures and, in more specific way, to the manoeuvres of IORT. Examples are represented by the infection complications, suture dehiscence, bleeding, delayed surgical recovery.

Prescribed dose

Dose held to be necessary by the radiation oncologist to complete the treatment with IORT (eradication or palliation), in line with predictable and acceptable complications.

PTV (Planning Target Volume)

It is a geometric rather than an anatomical concept and is represented by the volume on which the treatment is planned. It must consider the possible sources of uncertainty related to the identification of the CTV and to geometric causes.

Radiochromic film

Radiosensitive emulsion, contained in covering of polyester, without colour and transparent before the irradiation, which develops an intense blue colour after the exposure without the need of chemical treatments. It could be used both for relative dosimetry and as dosimeter of current use.

Reference conditions

The definitions for every energy of electrons beams, of the material and dimensions of the phantom, type of dosimeter, SSD, dimensions of the field, depth and methodology of measurement of the absorbed dose to water. They are defined in detail in every dosimetric protocol. The absorbed dose to water under reference conditions is simply the product of the response of the dosimeter by the calibration factor, without the need of introducing corrective factors.

Reference dosimeter

Dosimeter calibrated in terms of absorbed dose to water by a Primary Laboratory or an accredited Centre of calibration.

Report

Instrument to report with clarity and following the recommendations of the documents of reference, the procedures carried out. Such a document must be signed by the responsible person of the procedure as stated in the planning of the IORT treatment.

Secondary collimators (photon jaws)

The collimators that, in a non-dedicated accelerator, delimit the field of irradiation of the photon beams. In the case of electron beams, the opening of the secondary collimators is pre-arranged by the manufacturer in function of the dimensions of the IORT applicator and/or of the collimators used for transcutaneous radiotherapy.

Short-term stability of the system of dosimetric monitoring

Repeatability of the output, determined as coefficient of variation of a consecutive series of measures.

Soft-docking

Procedure of fastening to the radiating head of the accelerator the applicator already positioned in the anatomical area to irradiate.

Surface dose

Absorbed dose at a depth of 0.05 cm from the entrance surface of the beam.

Tail of *bremsstrahlung*

In the electron beams it is always present a field of photons owed to processes of braking of the electrons and composed by two components: *i.* the principal one, is produced by the interaction of the electron beam with any object (like scattering foils) crossed from the exit window of the accelerator to the entrance surface of the patient, *ii.* the other is due to the interaction of the beam with the patient's tissues. The dose caused by the photon contamination is determined by the PDD-curves extending the measurements beyond the practical range of the electrons ("tail of *bremsstrahlung*").

Target volume

Volume of tissue that has to receive the dose planned by the radiation oncologist according to the complete IORT treatment (eradication or palliation), with the limits of acceptable complications.

Tumour bed

Tissue close to the gross tumour volume (GTV) in which there is a higher probability to retrieve neoplastic cells and that is, therefore, subject to greater risk of local recurrence.

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