ISTITUTO SUPERIORE DI SANITÀ

Indications for quality assurance in intensity modulated radiation therapy

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Intensity-Modulated Radiation Therapy (IMRT) is an advanced and promising technique of external beam irradiation. IMRT is able to conform the dose distribution to the 3D tumour shape also for complex geometries, preserving surrounding normal tissues and reducing the probability of side effects. IMRT is a time consuming and complex technique and its use demands high level quality assurance. It is, therefore, very important to defineconditions for its utilization. Professionals of Radiotherapy Centres, with experience in the IMRT use, have constituted a multidisciplinary working group with the aim of developing indications in this field. Purpose of the present document is to highlight relevant aspects of the technique, but also to underline the high complexity of the technique, whose implementation requires extreme attention of the staff of Radiotherapy Centres involved.
Key words: Intensity Modulated Radiation Therapy, Quality Assurance

Istituto Superiore di Sanità
Indicazioni per l'assicurazione di qualità nella radioterapia ad intensità modulata.
A cura di Fabrizio Banci Buonamici, Cinzia De Angelis, Cinzia Iotti, Marta Paiusco, Patrizia Olmi, Antonella Rosi e Maria Antonella Tabocchini
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La radioterapia ad intensità modulata (*Intensity Modulated Radiation Therapy*, IMRT) rappresenta una delle più avanzate e promettenti tecniche di radioterapia oncologica. La possibilità di adattare la distribuzione della dose terapeutica alla geometria, anche molto complessa, di una massa tumorale consente di salvaguardare in modo ottimale i tessuti sani adiacenti riducendo quindi la probabilità di complicanze. L'IMRT è una tecnica di difficile esecuzione, dispendiosa per tempo impiegato e richiede particolare precisione. È quindi fondamentale cercare di definire in quali situazioni può essere appropriato il suo impiego. Per questo si è costituito un gruppo di lavoro che ha visto coinvolti, con un approccio multidisciplinare, i Centri Italiani di Radioterapia con maggior esperienza nell'uso di questa tecnica. Questo documento si è posto come obiettivo quello di delineare le peculiarità della tecnica e di evidenziare come la sua elevata complessità esiga il massimo rigore nella sua implementazione.
Parole chiave: Radioterapia ad Intensità Modulata, Assicurazione di Qualità

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PREFACE

With respect to patient's radioprotection, the Quality Assurance (QA) in radiologic sciences represents an outstanding issue of the Department of Technologies and Health within Istituto Superiore di Sanità (ISS, the National Institute of Health in Italy). Since the 70s the Laboratory of Physics of the ISS has been standing out for its activities aimed at promoting and spreading such issues, in particular by elaborating a specific set of guidelines. Within this context, the ISS Working Group for Quality Assurance in Radiotherapy (QAR) was established, which has issued a number of documents concerning general topics, in accordance with the goals of its mandate. In particular, the ISS Working Group for QAR has promoted different initiatives in order to issue documents and guidelines for QA in non conventional radiation techniques, by constituting working groups *ad hoc*, including all those expert professionals involved in the radiotherapy process.

In this context, the present document was elaborated to provide indications on QA in the employment of Intensity Modulated Radiation Therapy (IMRT). Given the complexity of this technique and the lack of a national complete assessment, the Working Group agreed on arranging a document to provide essential indications for QA in the employment of IMRT, as a supporting instrument for all operators in this phase of implementation, rather than producing guidelines.

IMRT represents one of the most advanced and promising techniques in radiation oncology. The possibility to conform the therapeutic radiation dose to the 3-dimensional shape of the tumour, which is very often a complex one, with a fast dose fall-off to the tumour boundary, allows to best save the adjacent normal tissues. By reducing the probability of side effects to the normal tissues, a higher radiation dose can be delivered to the target volume, compared with 3-Dimensional Conformal Radiotherapy (3DCRT). This translates into a better local control for some tumours, such as prostate neoplasms.

The enthusiasm towards IMRT is counterbalanced by its complexity concerning technical-dosimetric aspects and, to a still further extent, patient education and clinical therapy evaluation, which implies a specific expertise and a deep knowledge of all the advantages and disadvantages of this procedure.

At the time being, 3DCRT is still the most employed therapeutic technique for cancer patients in radiation therapy Centres and it represents a prerequisite for the next employment of IMRT for radiation therapy operators. The choice of IMRT should be properly weighed against the clinical features of the tumour, and the radiation oncologist is required to select the most appropriate patient-tailored technique, by carefully evaluating the goals to be achieved with the available resources.

Within this general approach, particular attention was focused on multidisciplinarity and the coordinators of the IMRT Group of AIRO (*Associazione Italiana Radioterapia Oncologica*: Italian association of radiotherapy oncology) and AIFM (*Associazione Italiana di Fisica in Medicina*: Italian association of physics in medicine) were put in charge of the accomplishment and coordination of the present document. A contribute was also asked to AITRO (*Associazione Italiana Tecnici sanitari Radioterapia Oncologica e fisica sanitaria*: Italian association of medical technician in radiotherapy, oncology and medical physics). Other working groups were also established, involving radiation oncologists with an expertise in medical physics and TSRM (Tecnici Sanitari di Radiologia Medica: medical technicians in medical radiology) with a particular experience in the employment of IMRT.

The document deals with all the clinical and technical aspects of IMRT. These include:

1. different IMRT delivery systems, with chapters dedicated to thermotherapy and Cyberknife;
2. criteria and indications for clinical decision making, advantages and expectations relating to the employment of IMRT;
3. major physics and technological aspects relating to the employment of IMRT, including equipment quality controls;
4. aspects related to human and technological resources;
5. acute and late toxicity monitoring.

The Italian Centres presently employing IMRT are listed in the Appendix, along with those currently in the phase of implementation. Nonetheless, this list is not meant as a comprehensive one, as although all the Italian Radiation Therapy Centres have been contacted, some responses were still lacking at the publication time this document was published.

INTRODUCTION

IMRT represents one of the most advanced and promising techniques in radiation oncology. The possibility to conform the therapeutic radiation dose to the 3-dimentional shape of the tumour, which is very often a complex one, allows to best save the adjacent normal tissues, thus also reducing the probability of side effects. Besides, the conformity to tumour shape and the quick dose fall-off to its boundary also allow to deliver a higher radiation dose to the target volume, compared with 3DCRT. This translates into a better local control for some tumours, such as prostate neoplasms.The enthusiasm towards IMRT is counterbalanced by its complexity and all the advantages and disadvantages of its employment should be fully understood.

IMRT can be defined as dose delivery modality with intensity modulated radiation beams through multileaf collimators (binary or conventional), passive modulators (used in very few Centres, none in Italy) or dedicated accelerators (i.e. Cyberknife, see below). Dose modulation is optimised by means of specific planning techniques, both inverse and forward (the latter being less performed).

One of the goals of IMRT is to conform the delivered dose as much as possible to the target volume, according to the constraints relating to the Organs At Risk (OARs). Nonetheless, IMRT can hardly be defined as a more developed 3DCRT modality, as the main aim of IMRT may be other than just an elevated conformity. The peculiar feature of IMRT, then, may be better defined as the use of radiation beams at a non uniform intensity (fluence profile) delivered to patient, so as to model dose distribution into the Volumes of Interest (VOI). In most cases IMRT is strictly correlated to an inverse planning, a technique through which the prescribed dose distribution is specified according to the VOI.

The agreement between dose to tumour and dose to normal tissue is the characteristic aspect of IMRT prescription and optimization. The software used to calculate the intensity profile of the radiation beams will try and comply with the clinical requirements but it will also take into due account the constraints related to the treatment equipment, as well as those concerning technological aspects.

In order to best understand IMRT, the following points should be carefully considered:

- Beam orientation, open field and dose distribution may be unconventional and hardly comprehensible to radiation oncologists, medical physicists and TSRM.
- Dose distribution is often heterogeneous within targets and its prescription to a single organ may not be applicable.
- Both macroscopic disease areas and those areas at risk of sub-clinical disease may be simultaneously irradiated, though at different doses. In this case a non conventional fractionation should be adopted, as the standard fractionation can not be maintained to both volumes.
- The dose distributions generated by IMRT are particularly sensitive to organ motion and to set-up errors. For this reason, tracking the motion of the involved organs, along with a careful choice of patient positioning and immobilization systems are all crucial issues.
- IMRT, more than 3DCRT, requires a very deep knowledge of the radiological anatomy of the VOI.
- Expensive equipment quality controls and a specific patient education are necessary.
- With an equal prescribed dose, in IMRT a larger quantity of Monitor Unit (MU) needs to be delivered compared to 3DCRT. From a radioprotection point of view this translates into a higher total body dose for the patient because of the radiation delivery and leakage, which leads to a potential increase of radio-induced risk of carcinogenesis.

- An IMRT session might be by far much longer than usual, which might affect the maintenance of patient's position during treatment and the biological efficacy of treatment.

IMRT is a very complex technique, it is time consuming and it requires a very high precision. For this reason it is very important to define those selected cases when it should be properly employed. According to the currently available data, IMRT is clinically indicated when one or more of the following conditions are present:

- The target volume has an irregular shape and it is close to critical structures to be spared
- The critical structures are in concavities of the target surface
- The margins between target and critical organs are very narrow
- The optimal dose distribution can not be obtained by any other technique
- A higher dose escalation than the one allowed by conventional therapy is planned.
- A simultaneous boost delivery technique is to be employed, either SIB (Simultaneous Integrated Boost) or SMART (Simultaneous Modulated Accelerated Radiation Therapy)-
- A previous radiation treatment requires incident beams and dose distributions minimizing the tissue volume exposed to re-irradiation and hot spots.

At the time being, 3DCRT is still the most employed therapeutic technique for cancer patients in radiation therapy Centre and it represents a prerequisite for the next employment of IMRT for radiation therapy operators. The choice of IMRT should be properly weighed against the clinical connotations of the tumour, and the radiation oncologist is required to select the most appropriate patient-tailored technique, by carefully evaluating the goals to be achieved with the available resources.

The so far published comparative studies between 3DCRT and IMRT are often limited to a single Institution and they refer to very small heterogeneous series. On the other hand, randomized studies comparing different techniques can hardly be expected, both because IMRT has already won a favourable acknowledgement within the radiotherapy Community and because each patient should be given the best possible radiation therapy mode.

Comparisons among centres would be, instead, advisable, concerning the possible ways to treat a given clinical case.

The main objective of a document on IMRT is to describe all the peculiar features of this technique and to underline how its complexity requires the highest possible assurance in its employment.

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1. IMRT DELIVERY TECHNIQUES

The present chapter briefly describes different delivery techniques using beam intensity modulation. These are listed into the following three categories:

- *Fixed gantry technique*
  The gantry does not move during irradiation and the beam direction is constant during the whole fluence modulation.
- *Rotating gantry technique*
  The gantry moves during irradiation while beam intensity modulation
- *Pencil beam technique*
  Each beam is broken into many small beamlets and the intensity of each beamlet is determined.

A further distinction can be made between delivery techniques using conventional linear accelerators and those using dedicated equipment (tomotherapy and Cyberknife), which require a beam intensity modulation (see chapter 7 and 8).

1.1. IMRT delivery techniques

Figure 1 describes a diagram of the herein described IMRT techniques. Three different categories are distinguished: fixed gantry, rotating gantry and pencil beam techniques. A further distinction is made according to the employed equipment (dedicated equipment, i.e. those equipments which can only be employed for IMRT).

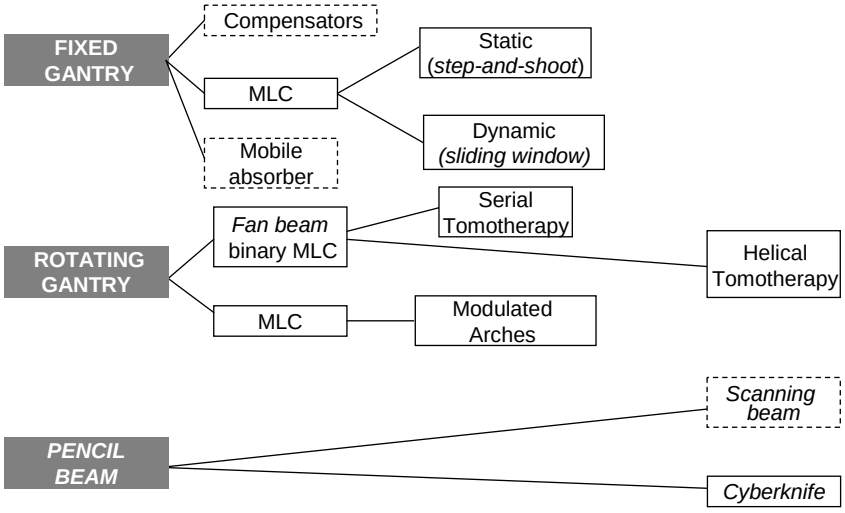

Figure 1. Scheme of IMRT delivery modalities
(hatched boxes refer to fallen into disuse or sporadically utilized techniques)

The fixed gantry techniques include all those irradiation delivery modes which employ conventional Multi-Leaf Collimators (MLC). This category also includes compensators (Jiang & Ayangar, 1998) and mobile abosorbers (Fiorino *et al*., 1995; Webb, 1997; Webb, 2000), which are not dealt with in the present chapter, because they are no longer in use. The static technique makes use of multiple-shaped static field segments, each one with a uniform fluence; radiation is turned on only when the MLC leaves are stopped at each prescribed segment position. This technique is also called *step-and-shoot* or segmental IMRT (Kallman *et al*., 1988, Galvin *et al*., 1993; Bortfield *et al*., 1994; IMRT-CWG, 2001; Ezzel *et al*., 2003). In the dynamic technique (sliding window technique) the beam is always on during leaf motion (Convery & Rosenbloom, 1992; Spirou & Chiu, 1994; IMRT-CWG 2001). By varying the distance among each leaf pair and their sliding speed, dose intensity to each point in the treatment field is also varied. For a more detailed description of the delivery techniques, see the published AIFM document.

The second category, with rotating gantry, includes all the techniques of dose delivery during the gantry rotation. Serial tomotherapy (Sternick *et al*., 1998) was the first IMRT arc therapy to be clinically developed and employed. It makes use of a binary multi-leaf collimator, which can be mounted on a conventional collimator. During serial tomotherapy the gantry rotates once or twice around the patient, thus irradiating a narrow slice of the same, while the treatment couch is maintained fixed during the whole irradiation. Once the irradiation of one slice is completed, the couch is moved longitudinally and the treatment is completed by serial delivery to all the patient's adjoining axial slices. In helical tomotherapy (Mackie *et al*., 1993) the couch is continuously moved during the irradiation of a fan beam, which is thus delivered through a helical movement. This technique is performed by means of a compact 6 MV accelerator, whose head rotates within a gantry similar to that used for a CT (Computed Tomography) study. A primary collimator defines the width of the fan beam in the cranio-caudal direction, while the modulation is accomplished by a binary MLC.

The Intensity Modulated Arc Therapy (IMAT) is a rotational technique which makes use of a linear accelerator equipped with a dynamic MLC (Yu, 1995). The shape of the radiation field, as defined by the MLC, varies continuously during the gantry rotation and, as opposed to conventional Conformal Dynamic-Arc therapy (CD-ARC), it is not defined by means of a Beam's Eye View (BEV), so as to conform to the whole Planned Target Volume (PTV), but it changes in order to optimize the dose distribution. The intensity modulation is accomplished with multiple arcs, each one having its own weighed and leaf configuration.

The third category, pencil beam, includes all those IMRT techniques, in which the intensity modulation is not accomplished with mechanical systems, but directly by superimposing small beams, called pencil beams (Webb, 1997; Webb, 2000). A pencil beam technique currently used in the clinical practice is Cyberknife, made of a light and compact 6MV photon beam accelerator, mounted on a 6 degree-of-freedom robot arm. The couch can be moved in all the three shifting and rotating directions.

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2. CRITERIA FOR IMRT IMPLEMENTATION

2.1. Clinical-dosimetric advantages and disadvantages

In each Centre, where IMRT is to be implemented, careful consideration should be given to all the available resources and the disease dealt with. IMRT may well be employed for a number of radiation treatments, but given the complex implications required, its use should strictly be reserved to those cases when other therapies are unfeasible, in particular 3DCRT and stereotassic radiotherapy. As mentioned above, IMRT is typically employed for curative purposes, or when the target to be irradiated has a concave or convex shape, in presence of dose-limiting critical organs.

The advantages of IMRT may be summarised as follows:
- high dose conformità;
- critical organ preservation;
- possibility of dose escalation;
- possibility of SIB;
- possibility of hypofractionation;
- possibility of re-irradiation.

A first advantage offered by IMRT, compared to 3DCRT, relies on the possibility to achieve a higher dose conformity to PTV, particularly for concave tumour volumes. This peculiar goal may be obtained by exploiting IMRT ability to create non uniform fluence profiles, thus producing, whenever needed, a marked dose fall-off. High conformity, along with steep dose gradients, reduces the exposure of normal tissues to elevated radiation doses, thus it allows, on the one hand, to reduce radio-induced toxicity risks and, on the other hand, to safely proceed, if needed, to dose escalation. It should be noted, though, that conformity and steep gradients may also translate into markedly dishomogenous dose distribution to target volume and into hot spot. Besides, the conformity level may be deteriorated in case of constraints to critical organs, which force dose accumulation into other regions. For this reason, IMRT planning should always take into account all quantitative and qualitative issues, as mentioned so far.

In some cases, IMRT is also employed in order to make dose distribution more uniform to the target, besides reducing toxicity to normal tissues around the tumour.

SIB is an IMRT technique that allows to deliver different doses to different volumes with a single treatment plan and during the same treatment session. The delivery of the integrated boost is typically accomplished by increasing the dose fractionation to the Gross Tumour Volume (GTV) (e.g., 2.2 - 2.3 - 2.4 Gy), while those volumes prophylactically irradiated receive a conventional daily dose. The total number of fractionations is reduced according to the increase of dose/fraction. This means that the fractionation is an accelerated one, also called SMART.

The radiobiological advantage of SMART relies on the improved efficacy of the high dose-fraction and the shortening of treatment time, which prevents the typical cell proliferation of fast growing tumours.

Although SIB is often identified with treatment acceleration and dose/fraction escalation, it may also be employed with a conventional fractionation to the GTV, which requires that the daily dose to phophylactic volumes be reduced (1.6-1.7 Gy).

SIB has radiological advantages, as well as other advantages relating to sequential treatment: planning and verification of a single treatment plan, instead of different plans, for the whole

radiation treatment, which results into a reduction of the risk of those errors which may be generated and transmitted with each single treatment plan; an improved conformity of high doses to target volumes (with a subsequent better preservation of normal adjacent tissues) and, as far as head and neck is concerned, the possibility to deliver radiation treatment without employing electrons allows to skip these problems related to the junction of fields.

Of course, the delivery of different doses for each target volume requires non conventional fractionations and, consequently, total dose and dose per fraction may need to be modified according to the number of fractions. This procedure brings about, on the one hand, the question concerning the biological effect of dose per altered fraction and, on the other hand, the issue concerning the volumes of normal tissues irradiated with dose gradients.

This requires that, besides physical dose distribution, the equivalent "biological dose" be calculated, according to the Linear-Quadratic pattern and its values (relation α/β, tumour double time, etc.) specific for each tumour and the normal tissues involved in the radiation field. Generally speaking, the most critical aspects relating to integrated boost are, in case of accelerated techniques, the potentially detrimental effect of the high dose fraction to the normal issues included in the boost volume and, in the opposite case, the potentially poor tumouricide efficacy of low doses per fraction (about 1.6 Gy) delivered with a prophylactic purpose. The higher dose conformity and the possibility of a wider preservation of critical organs allow more safely to employ hyperfractionation techniques with much higher doses per fraction than standard ones and with a dramatic reduction of the number of fractions and total dose, as in stereotassic radiotherapy.

IMRT cannot be employed as the sole solution to all the dosimetric problems or as the only technique to preserve all the critical organs within a treatment plan.

In some cases it is not possible to both protect OARs and duly cover the target. In this case, it might be necessary to give up the expansion to PTV (as also indicated in the ICRU Report 62) (ICRU, 1999), and to accept areas of underdosing, as it is in other radiotherapy techniques. IMRT cannot be expected to generate, a priori, the best possible treatment plan. The result of the treatment planning is, in fact, influenced by the appropriateness of those inputs supplied by the system (in terms of VOI delineation, and definition of the dose restraints and the related weights). Inappropriate planning requirements result into sub-optimal treatment outcome, though sophisticated the system might be.

One of the most important aspects of IMRT is the risk of "tumour missing" related to the peculiar produced dose distribution, which requires the most possible accurateness in the target definition, along with a correct management of the geometric irregularities. Therefore, the employment of IMRT should be carefully evaluated in case of lesions of moving organs (e.g., lung) or organs whose movement is induced by adjacent organs (e.g., prostate). The presence of strong dose gradients, as well as the employment of non uniform incident beams, especially those generated by dynamic techniques (see paragraph 1.1), make this treatment particularly sensitive to variations of intra-fraction positions. In these cases any devise should be employed to either limit or eliminate the negative effect of movement. Without such devises IMRT might be even detrimental.

The comparison between IMRT and 3DCRT shows how different the dose distribution profile may be within the irradiated volume. In general (taking into due account the variations according to the irradiated site and the irradiation technique), IMRT implies a reduction of the normal tissues receiving high doses, which leads, nonetheless, to an increase of the volume exposed to lower doses. The so called "dose scattering" effect is particularly to be avoided when, for instance, liver, kidneys or any other extremely radio-sensitive organ is involved (e.g. the crystalline). The radiobiological effect of the exposure to low doses of a greater tissue

volume is still unknown but in young and long-living patients this might increase radio-induced neoplasms incidence rates.

Moreover, it is important to stress once again that an IMRT session may even take a remarkably long time, sometimes up to 30 minutes, which may affect patient's compliance and comfort during treatment, thus requiring immobilization procedures for the patient to maintain the position for a long time; additional complications concern organ motions and the reduction of the biologic effect related to dose "dilution" throughout a prolonged time.

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2.2. Clinical-technical indications to IMRT employment

2.2.1. IMRT in head and neck neoplasms

Head and neck neoplasms represent one of the sites for which IMRT is most frequently employed. IMRT is particularly effective because it is capable of conforming high dose to complex volumes, by sparing those several adjacent OARs which are present in this region. Moreover, the relative hypomobility of these anatomic structures, along with the possibility to obtain a good immobilization, improve those geometric complications experienced in other regions. The clinical rationale for IMRT in head and neck cancers can be summarised in the following three points, which can be superimposed and integrated to one another:

1) The first goal, which is the most studied as well, is the reduction of radio-induced toxicity, in particular to parotid glands. Compared to other treatment techniques, IMRT improves the residual salivary function, as well as the Quality of Life (QoL). This result is not accompanied by higher rates of disease relapse, despite the sharp dose fall-off within critical regions. Although IMRT is particularly indicated in head and neck cancers for salivary function preservation purposes, it has important potential advantages also as it limits dose to other normal tissues, such as nervous structures, optic canals, internal ear, temporal-mandibular articulation, swallowing and masticatory muscles, aero-digestive mucosae. In this area, the ability of IMRT to minimize high dose exposure to normal tissues is particularly important both in the light of the potentially considerable toxicity from radiation, and because these tumours are usually treated with integrated therapies with chemotherapy and/or other specific target drugs, associated themselves with toxicity and potentially increasing the toxicity from radiotherapy.
2) In general, for head and neck neoplasms dose is directly correlated to local control rates. Compared to conventional radiotherapy techniques, IMRT allows higher dose delivery

without increasing toxicity risk. Nonetheless, the available trials on dose escalation with IMRT are still scanty and still on going. Dose increase may translate into an increase in the single fraction dose, the total dose being almost the same as the standard one administered to head and neck cancer patients (70 Gy). Conversely, the dose increase of each single setting translates into the increase of the total dose. In a trial on dose escalation, carried out by Lauve in 20 patients, the fraction dose to primary tumour was increased from 2.27 to 2.36 and 2.46 Gy, with a total of 30 fractions. The maximum tolerated dose was 2.36 Gy (total dose 70.8 Gy), wth 2-year actuarial control rate of 76.3%. A dose escalation protocol for SIB-IMRT (mostly associated with concomitant chemotherapy – CHT) was tested in 50 T3-T4 nasopharyngeal cancer patients. A dose of 76 Gy in 35 fractions was delivered to primary GTV (Kwong, 2006). Preliminary results are very encouraging: 2-year locoregional control was 95.7% (historical data: 76% at 4 years), the association with CHT resulted feasible and toxicity rates were acceptable. A proper follow-up is, nonetheless, needed to confirm these data.

3) IMRT allows the simultaneous irradiation, within a single treatment plan, to multiple target volumes with different doses per fraction (SIB). In this way, higher daily doses can be delivered to GTV (or parts of it) and progressively lower doses can be delivered to those regions estimated as at high or low risk for microscopic disease. The dose/fraction differentiation implies, in turn, treatment acceleration and, consequently, an increase of the dose/fraction (>2 Gy) to GTV or, conversely, the dose/fraction decrease (<1.8 Gy) to elective CTV (Clinical Target Volume). In both cases, if the same efficient dose as the one conventionally delivered should be maintained, an adjustment to the nominal total dose is required. SIB has been employed for different anatomic sites (e.g., prostate and breast) but it is in the head and neck cancers that it is mostly used. The major reason lies in the frequent necessity, in this district, for prophylactic irradiation of areas at risk for occult disease, which conventionally requires multiple plans and junctions by different beams. From a dosimetric point of view, SIB offers the advantage of a higher dose conformity to GTV, which allows a better OAR sparing, as long as the possibility to increase the dose. In the accelerated technique, the most employed, the reduced treatment time and the dose/fraction increase to the tumour give further radiobiological efficacy. Treatment acceleration is also practically convenient, as the reduced number of treatment sessions contributes to the equipment maintenance. It is important to underline that the effects of altered fractionations adopted in SIB, in particular the dose/fraction increase, are only partially known and published results are still preliminary. This technique, therefore, requires particular caution and its employment should be limited within controlled clinical studies.

Many studies are available within medical literature, confirming the dosimetric superiority of IMRT over standard techniques; nonetheless, more and more clinical studies have lately been carried out. Although published results are very encouraging, these studies are limited to retrospective, monoinstitutional and heterogeneous series (as for anatomic sites, employed techniques, fractionation schemes and associated medical therapies). Besides, mean follow-up time is not yet long enough for a definitive assessment of long term sequelae.

The largest set of data available refers to IMRT in nasopharyngeal cancer. Lee *et al*. (Lee et al, 2007) evaluated a series of 67 patients with a mean follow-up of 31 months, reporting a loco-regional control of 98%, which is higher than any historical data; at 24 months after treatment completion, 66% of patients presented no xerostomia and only 2.4 had a grade 2 xerostomia. An update of this series on 118 patients confirmed these excellent results. Kam et al (Kam *et al*., 2004) published superimposible results: within a series of 63 patients with a mean follow-up of 29 months, actuarial local control, actuarial lymphnode control and actuarial survival at 3 years

were 92%, 98% and 90%, respectively. An experience from Memorial Sloan-Kettering (Wolden *et al.,* 2006) on 74 patients also confirmed the trend toward better loco-regional control of IMRT over 3DCRT, as long as a reduced incidence of grade 3 and 4 toxicity to internal ear and parotid glands.

Another head and neck anatomic site typically treated with IMRT, which is also object of some ongoing clinical studies, is oropharynx. In the study carried out by Garden et al on 51 patients, IMRT was associated with 2-year actuarial control of 94%, which is superimposible to the results obtained with conventional radiotherapy, but with a larger salivary tissue sparing. No advantage was, instead, reported concerning acute mucosal toxicity. The experience from Memorial Sloan-Kettering Cancer Center on 50 patients with stage I-IV oropharyngeal cancer (de Arruda *et al*., 2006), with a mean follow-up of 18 months, reported 2-year local and regional control of 98% and 88%, respectively, which is superimposible to published figures, but with a clear decrease of salivary toxicity. In a series of 74 patients with oropharyngeal cancer, mostly stage III-IV disease, treated both post-operatively and with a curative intent, 4-year loco-regional control rate was 87% and grade 2 xerostomia incidence was 12% (grade 0=45%, grade 1=43%) (Chao *et al*., 2004). Another anatomic site typically treated with IMRT is represented by nasal sinuses, due to their complex extension to a number of sensitive structures. Claus et al (Claus et al, 2002) published the preliminary results obtained in 47 patients. The follow-up being too short, no analysis could be carried out on optic nerve and retina, but the results showed the absence of a very common acute side effect, such as the dry eye syndrome. In this specific anatomic site, rival plans should be compared to 3DCRT, which would guarantee a lower percentage of low doses and a smaller "scattering" of these latter, thus allowing lower doses to be delivered to those critical organs surrounding this anatomic site. Many other anatomic sites are currently under investigation but, in general, the evidence currently supporting the employment of IMRT in head and neck neoplasms is limited to those structures of the skull base and parotid glands.

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2.2.2. IMRT in prostatic cancer

Prostatic cancer currently represents a complex problem for cancer care clinicians. In some cases, in fact, this neoplasm can only be approached with an active surveillance (after the first therapeutic approach patients will be submitted to a different treatment at a different time from that first one). Conversely, this disease may require a radiation treatment with doses up to 80-90 Gy. Prostatic cancer presents very different risk levels, which are ranked according to the values of *Prostate Antigen Antigen* (PSA), Gleason Score (GPS), T classes and life expectancy (over versus under 10 years).

Low-risk patients are those with PSA≤10ng/mL, GPS≤3+3, cT1-T2a; intermediate risk patients are those whose PSA values range between 10.01-20ng/mL, GPS≤3+4, cT2b-c; high/very high risk patients are those with PSA>20ng/mL, GPS≥4+3/4, cT3-T4 N1-3.

As widely demonstrated in clinical studies on 3DCRT, the local control probability increases with increasing the delivered dose. Doses up to 72-76 Gy, usually considered appropriate for low-risk tumours, may be successfully delivered by means of 3DCRT, which allows an optimal normal-tissue sparing, while intermediate and high risk tumours benefit from an additional dose increase (78-80 Gy), which can not be delivered by means of conformal technique due to the associated unacceptable toxicity. The rationale for IMRT in prostate cancer may be explained as follows:

1) IMRT allows a dose escalation without a simultaneous increase of side effects and toxicity risks. This remains the major reason for introducing IMRT into prostate cancer treatment. The studies on dose escalation, carried out at Memorial Sloan Kettering Cancer Center, demonstrated that a dose of 86.4 Gy may safely be achieved with a low risk of mortality and an expected b *Relapse Free Survival* (bRFS) of 90%. Although there is no clear evidence supporting the need to exceed 80 Gy, some feasibility studies showed intensity modulation allows to overdose the dominant intraprostatic lesion, identified at functional RM, up to 90 Gy. Delivered doses being equal, rectal and bladder toxicity rates with IMRT are 2-3 fold lower than they are with 3DCRT. Besides, thanks to a rapid dose fall-off at the level of bulbus penis, the intensity modulation favours a better preservation of sexual power. Encouraging results were also retrieved by analysis on quality of life. A prospective study on quality of life, carried out in Utrecht (Lips *et al.*, 2007) on 78 patients treated with 3DCRT at 70 Gy versus 96 patients treated with IMRT at 76 Gy, reported superimposible results in both groups and, to some extent, even better results were associated to patients treated with high dose IMRT.
2) IMRT in prostate cancer allows to safely perform a prophylactic irradiation to pelvic lymph nodes, which is considered suitable in case of intermediate and high risk localised prostate cancers, but can be associated to higher rates of morbidity if performed by means of conventional techniques. In this case, an alternative to sequential plans is represented by the integrated boost technique (SIM IMRT), through which the dose can be differentiated to lymphnode stations and prostate. SIM IMRT usually requires dose/fractions to the prostate higher than 2 Gy. An example of dose fractionation is that illustrated in the Study AIRC n. 2764, in which simultaneous doses of 65 Gy to the prostate, 56, 25 Gy to the seminal vesicles and 50 gy to pelvic lymph nodes in 25 fractions were delivered.
3) IMRT is the most suitable technique for hypofractionation schemes, validated by recent radiobiology studies, which assigned a low α/β relationship. Thanks to the optimization of the dose distribution within the treated volume, the dose fraction to the prostate can be increased (≥2.5 Gy) while the risk of rectal complications can be maintained at a very low level. Hypofractionation requires a particular caution, as the actual α/β value of prostate cancer is still object of debate, and should be validated within clinical trials. It should be stressed that IMRT, especially when dose hypofractionation schemes are employed, requires a particular caution in the management of geometric uncertainties (both associated to set up and organ movement) and devises for Image Guided RadioTheraphy (IGRT) should be adopted. Despite a large medical literature, a real superiority of IMRT over 3DCRT in the treatment of prostate cancer has not yet been supported by any evidence from phase III randomized studies. Nonetheless, IMRT is widely employed, as it is considered as the best treatment option for patients, both for local control and for side effects. The most important studies on IMRT are those carried out at Memorial Sloan Kettering Cancer Center (Zelefsky *et al*., 2002), where it has been routinely employed since 1996. In 2002 a study from Memorial Sloan Kettering Cancer Center on 772 patients treated at 81 Gy in 45 fractions was published, which reported an incidence of grade 2 rectal acute toxicity of 4.5% and the absense of grade 3 toxicity. In a later study Zelefsky reports long term results showing an association between high dose IMRT and a very low late toxicity rate, as long as an excellent disease control (8 year actuarial percentage of biological control in low, intermediate and high risk equal to 85%, 76% and 72%, respectively). Similar results were published by the Ghent Group (De Meerleer *et al.*, 2007), relating to a cohort of 133 patients treated at a dose of 74-76 Gy. Based on the

results obtained by Zelefsky and those on 3DCRT, Konsky et al assessed the cost-effectiveness relation of IMRT in a patient with intermediate grade prostate cancer, by applying a decisional analysis pattern (the Markov pattern). Although hardly significant, IMRT resulted superior in terms of cost-effectiveness, due to its potential to prevent disease relapse, thus avoiding salvage therapy and reducing side effects. Feasibility and dosimetric studies are mostly available on the employment of IMRT in pelvic irradiation, demonstrating a reduction up to 20-50% of the volume of small intestine, bladder and rectum exposed to high doses, as long as a better pelvic lymphnode coverage. The published clinical results, though preliminary they may be, confirm the reduced toxicity obtained with IMRT compared to 3DCRT. Pollack et al reported results on 100 patients treated with 70.2 Gy/26 fr image guided-IMRT, showing toxicity rates superimposable to those following 3DCRT treatment up to 76 Gy in conventional fractionation. The follow-up being too short, no conclusion can be drawn on disease control.

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2.2.3. IMRT in breast cancer

The rationale for IMRT in breast neoplasms is correlated to:

1) first of all, the need to minimize morbidity, especially pulmonary and cardiac morbidity;
2) then, the need to improve post-treatment cosmetic outcomes, strictly correlated to dose dishomogeneity within the treated volume. In fact, as survival for women with breast cancer has improved, quality of life for these patients has become a more and more

important factor and, consequently, post-treatment outcome now represents a crucial aspect;

3) the need for a loco-regional radiation therapy (concurrent irradiation to both breast and tributary lymph nodes), especially when the internal mammary lymphatic chain is planned. In this case, standard irradiation requires junction plans which, as it is well known, introduce problems relating to planning, target coverage, dose distribution and treatment precision.

Different theoretical studies, both comparative and prospective ones, validated the employment of complex techniques for breast irradiation, showing a reduced dose to heart, lung and contralateral breast, as well as a reduction of the hot spots within treatment volume. However, there is no evidence yet of a correlation between dosimetric advantage and clinical result, which requires a long follow-up.

A randomized trial (IMRT *vs* conventional radiotherapy) on 305 breast cancer patients evaluated the late sequelae, in terms of breast consistency and shape modifications, reporting a significant advantage for patients treated with IMRT (36% *vs* 52%) (Donovan *et al*., 2002). The limit of this study, nonetheless, lies on the fact that IMRT was compared with a 2D technique and in most cases very simple technical devices, as well as the correction factor for lung, would significantly improve treatment quality.

As most published studies only involve small series, without much detailing patient's characteristics, it is difficult to identify the categories that might significantly benefit from a complex treatment. In general, patients with voluminous breasts, whose central lung distance and maximal heart distance exceed safety values are considered as best candidates for IMRT.

IMRT, therefore, may play an important therapeutic role in some specific anatomic cases, such as Pectus Excavatum and in all those conditions – severe cardiopathies, Obstructive Chronic Bronchopneumopathy (OCBP) bullous emphysema–, which require the maximum reduction of the dose to be delivered to heart and omolateral lung. IMRT may also be employed for the treatment of very voluminous breasts, when dose dishomogeneity, as well as acute toxicity, must be reduced. Even in breast cancer IMRT can be employed by simultaneously delivering surgical bed boost. As illustrated above for head and neck and prostate tumours, IMRT has the advantage of better high dose conformity and an improved preservation of critical structures. Besides, treatment time reduction may improve patients' treatment compliance (5 weeks *vs* 6/7 weeks). According to a feasibility study (Guerrero, 2004), patients who mostly benefit from SIB-IMRT dosimetric advantage are those with local deep breast cancer, which would require boost to be delivered by means of photons instead of electrons.

SIB-IMRT, however, is still associated to not completely satisfying parameters (larger dose heterogeneity to breast, increased average dose to heart) which, along with high dose/fraction effect on the surgical bed, require further clinical studies to evaluate advantages vs disadvantages. Another potential advantage of IMRT is the continuous irradiation of the thoracic wall and the breast internal lymph node chain, thus avoiding dose distribution heterogeneity determined by the junction of adjacent fields and significantly reducing the exposure of pulmonary normal tissues. When IMRT is to be employed to irradiate organs subject to respiratory movement, respiratory control systems are required, in particular when an important target shifting (1-2 cm) is determined by respiratory movement. A study carried out on patients receiving loco-regional radiation therapy (including internal breast lymph node station), showed a significant advantage in terms of dose reduction to heart and lung by using a deep inspiration breath hold system during IMRT.

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2.2.4. IMRT in paraspinal tumours and in other diseases

Paraspinal tumours generally comprise those lesions including vertebral bodies or those lesions, independent from these latter, next to the spinal marrow. The dose distribution performed with IMRT favours spinal marrow sparing and, if IMRT is associated with a lesion tridimentional (stereotassic) localization, critical organ preservation is further improved. Sterotactic Body RadioTherapy (SBRT) with IMRT may represent the optimal option for metastatic or primary lesions, both as esclusive radiotherapy and post-operative radiation therapy. The employment of complex radiotherapy modalities is justified by the nature of paraspinal lesions, which are often referred to as histotypes requiring very high curative doses, such as chordomas, chondrosarcomas or high-grade glial tumours. In chordomas, doses of 66-79 Gy allowed 5 year disease control in 44-59% of cases. It can be easily understood how better results may be obtained by using higher doses in radiosensitive tumours and how these doses may only be delivered by means of sophisticated modalities, such as IMRT, in order to avoid any high risk of severe damage to healthy surrounding structures. Generally speaking, IMRT may be employed to treat almost any neoplastic site, as any other radiotherapy modality. The experience so far, as well as the data retrieved from medical literature in the field of IMRT now enable to single out clinical cases in which this technique is most efficient. On the other hand, there are cases where tumour extention may justify the employment of IMRT even if no evidence can be derived from clinical practice. These cases include limb and intraperitoneal sarcomas, cervical carcinomas, cervical or sacral chordomas, laryngeal carcinomas, thyroid carcinomas, esophageal carcinomas and small cell lung cancer (NSCLC). When considering whether to use IMRT radiation oncologists should perform rival plans and make a comparative analysis among these.

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3. PHYSICS ASPECTS

3.1. Introduction

IMRT is a highly complex and sophisticated technique, as far as both planning and treatment delivery are concerned. Its activation implies the implementation of an important Quality Assurance (QA) program to guarantee treatment accuracy. The QA program should be addressed to the whole IMRT process, particularly to the Treatment Planning System (TPS), delivery system, to the connection among different elements and the final patient dose verification.

The system complexity, as well as the strict interconnection among its elements, and the different architectures available on the market make it difficult to define a general QA programme. Although many papers (Kutcher *et al*., 1994; Ezzel *et al*., 2003) have been so far published on the importance of an extensive program of mechanic and dosimetric tests, there is no general consensus, yet, on general needed procedures or acceptability criteria. If considering only those aspects relating to the intensity-modulated obtained through MLC, it is important to underline that 3DCRT quality protocols are not adequate for a system in which the position accuracy of leaflets, position reproducibility, as well as shifting speed, are all critical topics. Unlike 3DCRT, in fact, not only does MLC define the field shape, but it also modulates the dose within PTV; for this reason, tolerance for specific parameters should be more stringent.

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3.2. Accelerator Commissioning and Quality Assurance

The modelling of high dose-gradients, which are peculiar in IMRT, requires that the dose distribution be very precise and accurate. In particular, it is necessary that the functioning of MLC and accelerator be guaranteed in compliance with the planned dosimetric goals to be achieved, during the typical processes of intensity-modulated radiation therapy. This requires the implementation of dedicated QA procedures, in particular those relating to MLC.

Regardless of the type of modulation, delivered dose accuracy is very sensitive to leaf position errors (LoSasso *et al*., 1998; Low *et al*., 2001; Sharpe *et al*., 2000; Budgell *et al*., 2000). In SMLC (Segmental MultiLeaf Collimator) modality an incorrect calibration may cause hot or cold spots in the junction between adjacent segments, according to how these add up to generate the total treatment plan. Moreover, in presence of small segments, even slight differences in field size may cause severe errors of the order of 10% (Sharpe *et al*., 2000). Likewise, in the dynamic modality, a difference of 0.2 mm in a gap of 1 cm determines a dosimetric difference of the order of 3% (LoSasso *et al*., 1998). The same criticities are

indicated for IMAT technique (Ramsey *et al*., 2001; Grebe *et al*., 2001), in which, as in DMLC (Dynamic MultiLeaf Collimator) modality, the position reproducibility error is also correlated to leaf speed. It is, therefore, necessary that, whenever feasible, each Centre adapt the minimum accepted segment size or the minimum acceptable leaf gap to the precision of their MLC.

Medical literature suggests, for each modality of radiation delivery, accurate MLC calibration procedures (Graves *et al*., 2001, Sastre-Padro *et al*., 2007, Zygmanski & Kung, 2001). In this respect, particolar care should be taken for single-focus MLC (rounded end) (Boyer & Li, 1997). In spite of the rounded shape, it is generally not possible to make both the light and radiation field edges agree along the whole useful interval dimensions. The correct calibration suggests the employment of the radiation field, while the light field may be utilized in case the planning system should require a correction parameter (Graves *et al*., 2001). In some systems a DLS (Dosimetric Leaf Separation) is available to define the disagreement between the light and radiation field.

With regard to the selection of a QA testing techniques for MLC (Graves *et al*., 2001; Sastre-Padro *et al*., 2007; Zygmanski & Kung, 2001; Boyer & Li, 1997; Bayouth *et al*., 2003; LoSasso *et al*., 2001), in the case of step-and-shoot modality, particular care must be taken to verify MLC alignment along the leaf motion direction, position precision and reproducibility, and gap consistency between adjacent leaves; in the case of dynamic modality, the correct value of leaf speed, its stability and the effect of possible accelerations and decelerations, are all issues to be added. Many of the above tests must be repeated as the ganrty position varies, in order to evaluate the effect of gravity onto position. Of course, this is particularly important, when rotation techniques (IMAT) are employed. Tests available in literature offer a list of consistency checks, in which, whenever possible, it is recommended that film-dosimetry be replaced by Electronic Portal Imaging Device (EPID).

In the step-and-shoot technique, moreover, it is fundamental to evaluate, for small MU (<5), output linearity, field homogeneity and symmetry, in order to avoid, at planning, the use of segments, whose MU do not guarantee dosimetry to comply with the established acceptability criteria (Aspradakis *et al*., 2005). Table 1 supplies a quick consultation guide to one of the most important references, as published to date, concerning verification tests. One of the aims of a QA Program is to guarantee the output stability, as well as to identify possible error sources. Once the system reliability level has been established, then, referring and intervention criteria must be defined.

Table 1. Verification test references

Test	SMLC	DMLC	IMAT
Transmission		Arnfield 2005	
Penumbra	Arnfield 2005	Arnfield 2005	
Leaf position offset	Boyer 1997	Graves 2001, Sastre-Padro 2007, Zygmanski 2001	
Position accuracy	Sastre-Padro 2007, Zygmanski 2001, Boyer 1997	Zygmanski 2001, Boyer 1997	Ramsey 2001, Grebe 2001
Gap reproducibility		LoSasso 1998, 2001	
Speed constancy		LoSasso 1998, 2001	
Acceleration and deceleration effect		LoSasso 1998, 2001	
Beam stability for small MU	Aspradakis 2005		

In their recent paper Palta *et al*. (Palta *et al*., 2003) summarised, as shown in Table 2, the most important parameters of a constancy programme, by suggesting the tolerance values required to guarantee delivered dose accuracy within 3%. The same table was herein re-elaborated by suggesting minimal criteria in compliance with the most common clinical realities, delivery and check systems Centres are supplied with, and proper dosimetric accuracy. Each Centre is, therefore, invited to establish verification timetable and tolerance and intervention values according to treatment criticities and their own experience.

Table 2. Major parameters and tolerance values for delivery stability verification

Parameters	Step-and-shoot		Dynamic	
	ISS working group	***Palta***	***ISS working group***	***Palta***
MLC				
Position accuracy	1 mm	1 mm	0.5 mm	0.5 mm
Position reproducibility	0.5 mm	0.2 mm	0.5 mm	0.2 mm
Gap reproducibility	0.5 mm	0.2 mm	0.5 mm	0.2 mm
Speed constancy	–	–	+2% (*)	1 mm/s
Isocentre	radius 0.75 mm	radius 0.75 mm	radius 0.75 mm	radius 0.75 mm
Beam				
Output constancy for small MU (<5)	2% compared to value at regimen	(<2) 2%	3%	3%
Uniformity and symmetry for small MU	2% compared to value at regimen	2%	2%	2%

(*) Speed constancy is established according to dynamic field profile uniformity (Bayouth, 2003)

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3.3. TPS Commissioning

The commissioning phase refers to the verification of the correct functioning of the delivery system, as dealt with in the section above, as well as the configuration and validation of the dosimetric and geometric parameters of the planning system (Aspradakis *et al*., 2005; Van Esch *et al*., 2002; Saw *et al*., 2001).

From a procedural point of view, TPS commissioning can be subdivided into the following three phases:

- dosimetric data measurement needed for configuration;
- verification of the configuration parameters and possible adjustment;
- calculation limit evaluation and system optimization.

The accuracy for dosimetric data acquisition of a specific delivery system, such as dose profiles, is of the uttermost importance for accurate calculation in IMRT, so that TPS commissioning requires a measurement which is methodologically similar to that indicated for a stereotassic system (Wang *et al*., 2005).

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3.3.1. Dosimetric parameters

Dose calculation accuracy is strictly correlated to TPS configuration parameters, as well as, of course, to intrinsic accuracy of the calculation algorithm. Anyway, the appropriateness of the configuration data is strictly correlated to the optimization algorithm.

One of the most important parameters is MLC transmission (LoSasso *et al*., 1998; Sharpe *et al*., 2000; Budgell *et al*., 2000; Ramsey *et al*., 2001; Graves *et al*., 2001; Sastre-Padro *et al*., 2007; Zygmanski & Kung, 2001; Boyer & Li, 1997; Bayouth *et al*., 2003; LoSasso *et al*., 2001; Grebe *et al*., 2001; Aspradakis *et al*., 2005; Palta *et al*., 2003; Kutcher *et al*., 1994; Arnfield *et al*., 2005; Ezzel *et al*., 2003; MacKenzie *et al*., 2002; Mohan *et al*., 2000; Van Esch *et al*., 2002; Saw *et al*., 2001; Wang *et al*., 2005; Arnfield *et al*., 2000, Low *et al*., 2001). Since TPSs currently in use do not take into consideration different inter-leaf and intra-leaf components, an average value should be acquired by means of a sensitive wide-volume detector (LoSasso *et al*., 1998).

Radiation field fragmentation into many small fields makes penumbra an extremely critical parameter. Dosimetric accuracy of treatment strongly depends on how much faithfully it is represented. For this reason, it is recommended that configuration profiles be acquired, in particular for small fields, by means of high-resolution detectors, such as diode films or micro-chambers (Arnfield *et al*., 2005). Tongue and groove architecture, too, may be responsible for underdose up to 30% (LoSasso *et al*., 1998). Its dosimetric characterization is not so far necessary, since, although some sequences are trying to reduce the effect thanks to leaf synchronization, most optimization algorithms are not able to model this aspect.

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3.3.2. Dosimetric tests

Configuration parameter verification implies the comparison between calculated and measured dose distribution. During the phase of commissioning verification is usually performed by means of increasingly complex modulation; subsequently, during the phase of patient QA, it is useful, within the adopted protocol, to continue the planning system set-up and verification, by taking into account that each IMRT plan is patient-tailored. Tests should be studied according to the following aims:

- configuration parameter assessment, as described in the previous paragraph;
- planning system performance assessment, at optimization and calculation parameters variation.

With regard to the latter aim, it is important to take into consideration that, as a modulation effect, the relationship between dose and MU is not as immediate as in 3DCRT. The test being performed with increasing frequency and gradient modulation, a higher confidence in the dose-MU relationship (Mohan *et al*., 2000) can be achieved and optimization limits of the system can be better understood.

In the phase of commissioning the comparison between calculated and measured doses implies that the employment of film dosimetry be accompanied by Ionization Chamber (IC) dosimetry or, even better, by micro ionization chamber dosimetry. Film dosimetry in phantom allows multi-aspect high resolution verification. Portal dosimetry can be adopted by Centres with sufficient experience.

Methodology relating to multi-field treatment verification is described in the section dedicated to patient QA.

Acceptability criteria represent a critical aspect, both in the phase of system commissioning and in phase of treatment plan acceptance for each single patient. In the documents TG53 (Fraass *et al*., 1998) and ESTRO Booklet No7 (Mijnheer *et al*., 2004), some combinations of Dose Difference (DD) and Distance to Agreement (DTA) are recommended, relating to the different dosimetric regions of a radiation field (high dose, penumbra, dose outside the treatment field). These reported criteria, although largely employed in the dosimetric assessment of conventional treatment plans, are not particularly suitable in IMRT, because of the presence of intermediate gradient regions, in which none of the two criteria can be duly employed. In order to obviate this problem, the γ index has been introduced and it is currently implemented in all film-dosimetry systems. The γ index is a parameter combining "dose adjustment" and DTA (Depuydt *et al.,* 2002; Low *et al.,* 1998). This parameter has the advantage to summarise in a single number the agreement between calculated and measured dose distributions.

There is no consensus regarding the values to be assigned to the two parameters "dose agreement" and DTA to be used in γ index calculation. However, 3÷5% is considered a valid value for "dose agreement" and 2÷3 mm can be considered a valid value for "distance to agreement" (Nelms & Simon 2007; Both *et al.,* 2007). Similarily, there are ambiguous indications also concerning treatment plan acceptability criteria, in terms of percentage satisfying $\gamma \leq 1$ condition; It is very important to take into account that acceptability criteria should be determined and justified also according to the complexity of the clinical goals and the employed modality. The documentation phase plays an important role, as all the chosen criteria must be clearly reported (commercial softwares, in general, do not specify whether the accepted error percentage on dose difference is relating to either punctual or normalized dose. Due to its synthesizing character, the γ index can not be considered as a comprehensive parameter in the dosimetric accuracy analysis. A treatment plan can present an excellent value in the γ distribution, although the few points in which the acceptability condition is not fully respected may, for instance, correspond to an OAR. A treatment plan acceptance requires, therefore, a comprehensive evaluation, taking into account all the possible forms of analysis, such as isodose map comparisons, dose profiles, as well as the clinical aim of treatment.

QA procedures on treatment plan system may include the selection of representative clinical tests performed in the commissioning phase. In these sample tests the treatment plan is re-calculated by including the optimizing phase and the periodical dosimetric verification; this guarantees data integrity and is particularly important in case a release software is employed, which implies substantial differences. Test timetable should always be scheduled, in order to guarantee system integrity and treatment safety.

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3.4. Patient quality assurance

3.4.1. Patient QA procedures

Clinical implementation of IMRT requires the application of precise pre-treatment patient QA protocols. The goal is to verify the whole treatment process and delivered dose accuracy. Such procedure is justified by the typical IMRT related criticities (high space gradients in treatment field, closeness of critical organs) the fact that the relationship between MU and modulation is not intuitive, together with the consideration that each IMRT treatment is "patient tailored". The standard approach is described in Figure 2 and requires CT scan phantom, generally water-equivalent, on which treatment plan dose is calculated.

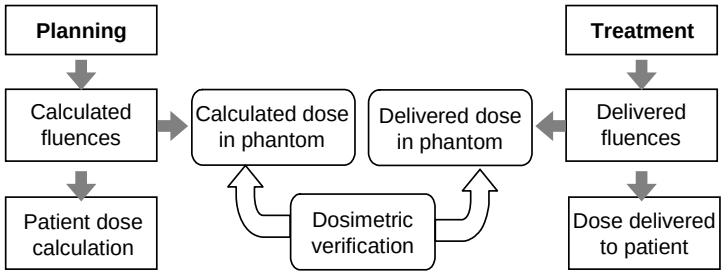

Figure 2. Verification diagram of calculated dose and delivered dose in phantom

The plan, as transferred to the accelerator, is delivered to the same phantom and the dosimetric comparison is finally performed between calculated and measured data inside the phantom. No particular dosimetric phantom is required; altough cylindric phantoms are preferred for rotation techniques, while a list of dosimetric values is described in paragraph 3.5. Dosimetric comparison can be made in 2 possible ways: dosimetry can either be performed on the whole treatment plan configuration or a field by field verification can be carried out, in which dosimetry and verification are performed for each single field. Both strategies present advantages and disadvantages. AIFM (AIFM, 2006) Report can be read for further details.

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3.4.2 Acceptability criteria

What has been described above for commissioning can also be applied to acceptability criteria. Interestingly, the indicated criteria have a general validity and, therefore, can be modified against justified clinical reasons.

It may be useful to introduce evaluation criteria based on γ (gamma histogram) value series, derived from patient QA analysis concerning homogeneous patient populations treated with similar optimization criteria (Nelms & Simon, 2007; Both *et al*., 2007).

A typical example is represented by the measurement point fractionation value $\gamma<1$. Such criteria can not prescind from the specific Centre experience, including delivery modality, measurement instruments, the anatomic district, the "stress" degree of delivered fluences, etc. Nonetheless, it is important to underline that in a patient QA procedure, the dosimetric accordance acceptability implies a discussion, involving radiation oncologists, concerning the meaning of measured deviations in terms of γ index, as well as spatial position of possible "small" areas/volumes with γ values <1. Statistical analyses of γ histograms enable to compare the accordance degree between fluences as measured and calculated in different Centres or, even more usefully, to compare the "concordance degree" of a certain Centre to those Centres using, for instance, the same delivery and/or planning system.

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3.4.3. Patient QA protocol development

If QA procedures recommend that each treatment plan be submitted to a pre-treatment verification, each Centre is expected to introduce more rapid procedures, after a reasonable training period and after a sufficient monitoring of system accuracy and stability.

Thus, systemic film dosimetry can gradually be replaced by one or more, or by a combination of, the following options:

a) utilize a more rapid dosimetric system (e.g., matrix chambers/diode or EPID);
b) reduce the number of patient-specific checks, by performing, for instance, a sample patient-QA, selecting the sample number according to the modulation complexity;
c) introduce methods alternative to the direct dosimetric accordance measurement, such as calculation systems independent from MU (Georg *et al*., 2007), Monte Carlo based commercial dose calculation modules (Sanchez-Doblado *et al*., 2007), verifications of delivery files of MLC position during delivery (Stell *et al*., 2004).

It is important to underline that, in this case, a QA procedure within IMRT process should be integrated with a robust program of accelerator/MLC performance in IMRT modality. Constancy measures can be planned, such as the delivery of a daily field test and/or, if feasible, verifications of delivery files of MLC position during delivery.

Data on timing and modes to pass from a systematic patient-QA procedure to alternative procedure cannot be supplied, because this depends on the degree of system reliability and on the confidence level acquired in each single Centre. The common experience of the most experienced Centres, reports the application of systematic QA for a number of patients, approximately 100, as to acquire a deep knowledge of both limits and potentialities of their own delivery systems.

It is also important to stress that a systematic patient QA should be maintained for some particularly complex treatment modalities or in case of fluences dissimilar to the consolidated practice experience.

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3.5. Dosimeters for IMRT

3.5.1. Punctual dose measurement

IC represents the reference dosimeter for determining the absolute dose. This kind of dosimeter is particularly indicated for a good isotrope response, for linearity even at low doses and dosimetric accuracy. In IMRT dosimetry chambers with small sensitive volume (<0.1 cm^3)

are to be preferred, in order to avoid averaging effects on the sensible volume (Laub & Wong, 2003; Low *et al*., 2003). Different micro-chambers, specially studied for radiosurgery, are nowadays available and applicable to IMRT as well (Leybovich *et al*., 2003; Francescon *et al*., 1998). Measurement conditions in IMRT are significantly different from those relating to chamber calibration, due to beam modulation and the presence of small field segments. Measurement uncertainty generally exceeds 2%, as reported in standard conditions (IAEA TSR 398) (International Atomic Energy Agency; 2000). The uncertainty associated to dose values at sampling points for PTV and OAR points, as estimated by means of the Monte Carlo method, is equal to 3%, when the whole treatment is performed (Sanchez-Doblado *et al*., 2005a, Sanchez-Doblado *et al*., 2005b). As the sensitive volume decreases, the measurement point positions become more and more critical and, therefore, it should be chosen, whenever possible, within a homogeneous dose region. When micro-chambers are employed, it is important to verify whether the response might be dependant on polarity effect and leakage.

Punctual measurements of dose in phantom can even be obtained by employment of silicon diode or natural diamond (Bucciolini *et al*., 2003; Fidanzio *et al*., 2000). Diode has a high spatial resolution and a high sensitivity. Due to the high atomic number of silicon, diode has a higher response rate for low energy photons and, due to the SI high density, output factors of small fields tend to be overestimated (Bucciolini *et al*., 2003). Overestimation is reduced by employing mini-diodes.

Diamond has a high spatial resolution, a response independent of Energy and, in particular, it can be considered tissue-equivalent; when available, it represents a valid alternative to ionization chamber. The only negative aspect, specific for each single diamond, is its possible dependence on dose rate (Fidanzio *et al*., 2000).

MOSFET, characterized by a high resolution, can be employed for IMRT dosimetry with high doses, its major limit being the lack of linearity for doses <30 cGy (Marcié *et al*., 2005).

The major limit making dosimeters, in particular IC, accurate but not much efficient instruments, is the need to deliver the single field or, even the whole treatment plan, to acquire a single measurement point. In order to solve this problem, new phantoms are currently being developed to simultaneously house different dosimeters, thus allowing dose map acquisition.

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3.5.2. Dose measurement

3.5.2.1. Radiographic films

Radiographic films play a key role in IMRT dosimetry, especially for their ability to obtain a 2D dosimetry with a high spatial resolution (Martens *et al*., 2002; Bucciolini *et al*., 2004). Film dosimetry procedures are very complex and depend on a number of parameters, such as the selection of the scanner to be utilized (Bos *et al*., 2002; Messerman *et al*., 1998). Films can be employed both for relative dosimetry and for absolute dosimetry. In this case, an accurate calibration must be performed, for which even very rapid methods have been suggested (Childress *et al*., 2002). XV2 and EDR2 are the most widely used films (Dogan *et al*., 2002). EDR2 films are preferred for the verification of the whole treatment, since they are characterized by a lower sensitivity and can, therefore, be irradiated at doses < 2Gy without saturation. Films are a very accurate dosimeter, when positioned perpendicular to the incident beam while, when differently orientated, the response is dependent on measure depth (AIFM, 2006). In general, when radiographic films are utilized as dosimeters in IMRT, it is important to take into consideration the effect of the modified incident radiation spectrum on film response. Moreover, the development and fixing process is also a particularly critic aspect.

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3.5.2.2. Gafchromic films

Gafchromic films (External Beam Therapy – EBT for radiation therapy) present many advantages compared to traditional radiographic films and, of course, they also have some disadvantages (Meigooni *et al*., 1998; Butson *et al*., 2006). Among advantages, the following ones can be mentioned: an energy-independent response (from 20 kV to 20 MV), the possibility to avoid development processes, the high spatial resolution, the ability to be manipulated in the presence of light and the possibility to obtain phantom-tailored scans. The major disadvantage is that the response, besides not being immediate (advised minimum reading time 4 hours after exposure, 6 hours) is dependent on digitizer light (Devic *et al*., 2005; Fiandra *et al*., 2006; Paelinck *et al*., 2007; Wilcox *et al*., 2007) (in particular, reading proved not uniform towards scanner periphery).

In a complex condition, in which the radiation field strongly differs from the one defined under reference standard conditions, the energy-dependence makes an optimal method for quality checks of the whole treatment plan out of gafchromic films (Menegotti *et al*., 2008). For the employment of IMRT a correct absolute dose calibration is necessary.

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3.5.2.3. Matrix detectors

The complexity of the film-dosimetric approach is turning matrix detectors into widely employed devices. Matrix detectors are diode arrays or ionization chambers, geometrically arranged – either regularly or irregularly – employed for 2D dosimetry of radiation fields, both in conventional radiation therapy and in IMRT. Major advantages of this kind of detectors are the real time reading, the dose linearity, the dose-rate independence, as well as the independence on the energetic spectrum of the radiation field. For all these reasons, QA procedures by means of matrix detectors are more simple and faster than those based on film-dosimetry.

However, matrix detectors also present some disadvantages. They generally can exclusively measure one beam perpendicular to their surface, thus avoiding the evaluation of composite axial dose distributions. Matrix detectors can be employed in rotational techniques only when they are mounted on the accelerator gantry, or when they are inserted into appropriate phantoms (Van Esch *et al*., 2007).

The most relevant disadvantage is represented by a spatial resolution limited by the detector spacing and size. For this reason matrix detectors do not represent a valid device in the commissioning phase but they are still recommended as efficient instruments in patient QA programs. Besides, even within a QA program, the accuracy of measurement sampling, related to the distance between detectors, must be carefully evaluated (Poppe *et al*., 2007; Banci Buonamici *et al*., 2007).

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3.5.2.4. EPID

Although EPID is currently mainly utilized for the verification of patient positioning, many other applications as portal dosimetry are reported in the literature. Due to its high resolution and acquisition quickness, it is the ideal instrument for routinary quality checks on MLC (position accuracy, reproducibility, speed constancy). In fact, given the rapidity with which a field can be acquired, planned and delivered fluences can be compared with one another. Due to its complex structure, it can not be employed for a dose measument through a simple intercalibration with an ionization chamber. The process of energy deposition is different from the one in a homogeneous phantom, besides, the presence of high Z material determines an over-response at low doses.

Thus it is necessary, to characterize the detector in terms of signal reproducibility and dependence on dose rate, dose per impulse and temperature. Dosimetry can be performed either in forward or backward modality. The former measures “dose” on the EPID plan which will be compared to what has been calculated by TPS on the same plan (Van Esch *et al*., 2004; Nicolini *et al*., 2006); the latter determines, starting from the portal image, the dose in a plan inside patient. Many papers in which an amorphous silicon flat panel, a-SI, is employed as dosimeter in forward modality, showed the high accuracy and efficacy of this instrument (McDermott *et al*., 2006).

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3.6. Intra-fraction movements

Intra-fraction movement is significant for radiation treatment of thoracic, hepathic, pancreatic, breast and, to a minor extension, prostatic neoplasms. Systematic errors caused by respiratory-induced organ movement may be introduced in CT execution phase, if this is performed with no control on respiratory movements or with a small acquisition time (1 s). Tumour movement due to respiration might introduce artefacts, in theoretic or calculated dose distribution (dose blurring), that can be reduced by using a wider margin. This effect depends on both width and characteristics of tumour movement and not on the employed IMRT technique (Bortfeld *et al.*, 2002).

If a dynamic IMRT modality is employed, the interplay effect is added to the blurring effect, caused by the possible asynchrony between respiration-related tumour movement and that related to multileaf leaflets. Such effect may cause cold spots inside the treatment field, resulting into significant variations compared to the planned dose (Yu *et al*., 1998). Simulations on phantom reproducing the respiratory movement, demonstrated that the interplay effect is reduced if multiple fields and a conventional fractionation are employed. Nonetheless, in hypofractionation treatments this effect can not be neglected. The maximum measured dose variation amounts to 30% for one field and 18% for five fields, for a single fraction IMRT treatment. Such variation is reduced to 1-2% after 30 fractions thanks to the effect of dose superimposition (Yu *et al*., 1998). Some Authors showed that the intreplay effect depends on the relative speed of movement of both tumour and MLC leaflets, and it is maximum when the two speeds are similar. Therefore, in order to limit this effect, the leaflets should move at a slower speed than the tumour speed that, in the proximity of diaphragm, is about 1 cm/s. The interplay effect depends on the leaflets gap width in correlation to the tumour movement width (Yu *et al*., 1998).

For a comprehensive employment of all the IMRT potentialities in those cases with an important organ movement, respiratory control techniques are necessary, such as respiratory gating, breath-hold o tumour tracking.

The respiratory gating technique requires that the patient breathes freely and that irradiation is synchronized to a pre-concerted respiratory phase (Kubo & Hill, 1996; Hugo *et al*., 2002). The breath-hold techninque implies that the patient performs forced-respiration maneuvers, either in inhalation or exhalation, and that radiation is only delivered concomitantly with such manouver (Wong *et al*., 1999; Remouchamps *et al*., 2003).

The tumour tracking technique consists of the synchonization of the radiation beam opening obtained by means of a dynamic multileaf with the tumour movement induced by respiration (Neicu *et al*., 2003; Shirato *et al*., 2000).

Although respiration control techniques are employed, a residual tumour movement persists and, therefore, the effect of such residual movement on the dose to the target volume must be studied. For instance, in case of respiratory gating, the beam is always turned on in the same patient respiratory phase and, subsequently, the interplay effect between the MLC leaflets movement and the residual tumour movement may cause a systematic error in dose delivery and such error does not decrease according to the increase of the number of fractions. If not accurately evaluated, the interplay effect may potentially affect more treatments fragmented with respiratory gating, rather than those treatments performed at current respiration rate (Jiang *et al*., 2003).

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4. IMRT PROCESS

The present chapter describes all those elements needed to establish the criteria relating to patient immobilization and re-positioning during centering procedures and of different treatment fractions, the imaging necessary for an optimal definition of VOI and their contouring, in order to reach an approved IMRT treatment plan.

4.1. Patient positioning and immobilization

IMRT presents some peculiarities that make a good treatment reproducibility a critical issue that may influence the choice of patient positioning and immobilization; in fact:

- due to the elevated conformation and rapid dose gradients, positioning variations, even minimum ones, may cause significant geographic omissions, and/or higher irradiation than the scheduled one to OARs;
- treatment times are generally longer than in non IMRT techniques, in part due to the need to acquire frequent portal images.

Most utilized systems are individualized, although for some anatomic districts they are considered as unnecessary. The choice among individualized, semi-individualized and standard systems may also be based on the data retrieved from the literature, but it is recommended that the actual efficacy of the employed system be quantitatively evaluated within each single Centre through an error analysis, by means of portal imaging techniques, either analog or digital. For IMRT treatments each Centre should standardize its own procedures by distinguishing according to either disease or irradiated site, in order to limit errors in the subsequent phases of execution: position definition, selection or arrangement of the immobilization system, verification, use of anatomic data during acquisition and therapy.

In order to reach the maximum possible precision in the phases of treatment planning and execution, the following factors relating to patient positioning should also be taken into consideration:

- the need to acquire the anatomic data necessary for the definition of volumes by means of the same modalities that will be employed in treatment sessions;
- an accurate positioning and its reproducibility are very important for critical organ preservation, when the distances between these and GTV/CTV is minimal, as it generally is in those cases submitted to an IMRT treatment.

When a single patient must be submitted to a non standard positioning, compared to conventional written procedures, the proper reason should be given. The peculiar issues concerning patient positioning and immobilization in IMRT procedures vary according to the specific anatomic district and to the kind of treatment. For instance, in head and neck cancer, when IMRT is delivered to the whole volume (T plus N, low neck included), a long mask or another device should be used, for a proper shoulder immobilization. In fact, if for the irradiation of smaller volumes with a direct field or AP-PA field technique accurate shoulder positioning may be irrelevant, in case of oblique incident beams at non uniform high intensity, the impact on dose distribution may, conversely, be relevant. In this district a radiotransparent couch extension may be considered, which offers a wider choice for beam orientation, by avoiding the problem of interception with metallic parts of the couch.

4.2. Imaging

The identification of the target volume (GTV, CTV) or of OAR represents a crucial issue in IMRT, not only for dose distribution characteristics, but also for the optimization modalities of the inverse planning system, which works rigidly on the outlines contours. A CT scan with contrast medium must be performed whenever it is considered necessary. In order to improve volume definition, other imaging devices should be employed, such as MR (Magnetic Resonance), SPECT (Single Photon Emission Computed Tomography), PET (Positron Emission Tomography), CT/PET and it is necessary to have access to proper instruments to record images and algorithms for their segmentation. Due to the procedure complexity and the elevated costs, the employment of multi-modal imaging techniques should be justified at least by a hypothetical expected benefit, subject to a clinical evaluation, in order to determine the potential impact on treatment outcome.

For each single neoplasm and for each single imaging technique, a technical protocol on image acquisition should be accomplished, including a clear definition of the volumes to be acquired, the pace, the possible use of contrast medium. In any case, it is recommended that the acquired volume comprise the whole anatomical district and all the involved OARs and that the distance between the axial sections be such as to allow a proper reading of the DRR (Digital Reconstructed Radiograph) images employed as reference images in positioning verification. The recommended inter-scan interval is <5 mm for the anatomical district including the target volume and <7 mm for the adjacent body sections. Some anatomic districts, such as head and neck, requires smaller paces, ≤3 mm for GTV and CTV, and ≤5 mm for the adjacent structures. In case of image acquisition of moving targets, such as in thoracic neoplasms, if the Center is not equipped with respiratory movement control systems, images must be acquired by means of a technique which allows the target movement evaluation (e.g., low speed scan and/or scans during the phase of maximum inhalation and maximum exhalation). In case of post-operative treatments, pre-operative imaging should be available.

4.3. Volume contouring

Univocal identification and a precise contouring of the target volumes and OARs, create the necessary conditions not only for the correct execution of IMRT, but also for an efficient clinical application of the treatment modality. The phase of contouring represents a critical step in the whole radiation therapy and it is a crucial moment for the clinician's decision making. In compliance with ICRU Reports n. 50, n. 62 e n.71, GTV, CTV and OAR contour is not dependent on treatment modality, thus representing a major issue in the treatment planning procedure. As for contouring procedure, a QA program is recommended, which includes a written protocol to guarantee a uniform behaviour among clinicians. The protocol should be based on the volume definition, as mentioned in ICRU Report n. 62 and should include the following points:

1. OARs to be contoured should be defined for each single anatomical district. Given the elevated dose gradients that can be present right in correspondence with OARs to be spared, possible set-up errors for OARs should be considered, by outlining the Planning organ at Risk Volume (PRV) at least for serial organs. This requirement should be fulfilled in particular as far as spinal marrow is concerned.

2. All the areas of interest should be contoured on every scan where they are recognizable, by taking into account that parallel organs require a whole outlining for a correct evaluation of dose-volume histograms.
3. For VOI (GTV/CTV/OAR) of each anatomical district univocal instructions for contouring procedures should be available.
4. In the PTV definition margins should be consistently determined in a standardized way. 3D expansion of GTV/CTV may in most cases be automatic or manual, if this represents a safer element for the OARs close to the target (e.g., head and neck). Margin definition should be performed after a preliminary assessment of the impact on internal moving organs during treatment and a set-up error evaluation within the single Centre. In those more complex cases Internal Margin (IM) and Set-up Margin (SM) should be separately identified.

In more recent times, there has been a growing research interest on functional characteristics of tumour, in which areas exhibiting different levels of radiosensitivity are to be found. The actual goal, as opposed to the common dose uniformity assessment, is a dishomogeneous dose delivery, higher in those regions that are considered as more radioresistent, Novel functional imaging techniques show the ability to recognize, within the neoplastic volume, areas that can be defined as actual biological targets or, even better, radiological targets, to which either absolute doses can be delivered and/or dose can be delivered at a different dose per fraction. Therefore, the concept of Biologic Target Volume (BTV) is introduced, although caution is needed, as no evidence on its clinical validity is yet available. According to the specific imaging technique that is employed, BTV expresses different functional characteristics of tumour, such as proliferative activity or hypoxia. This volume is not to be intended as a replacement for the common CT-based volumes the radiotherapist is so acquainted with, but it is rather integrated to them, supplying additional information, which can differently be considered within therapeutic strategy.

For speculative purposes, these concepts may be adopted in VOI contouring, when an IMRT treatment is performed, although it is important to underline that this issue needs further investigation and evidence and it is to be considered, therefore, as only investigational.

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4.4. Initial dose prescription

Initial treatment dose prescription consists of VOI definition, indicating for each one:

- total prescribed dose;
- dose fractionation;
- critical organs and relating dose constraints;
- possible therapeutic associations (particularly important in order to evaluate additional toxicities).

At prescription, particular caution must be exercised to dose distribution to specific VOI, rather than to dose prescription to specific points as mentioned in ICRU 50 and 62.

Dose prescription requires the definition of dose-volume constraints for both healthy organs and tumour, even though it must be taken into account that in the clinical practice the proposed goal might be out of reach in a single patient and, therefore, in some regions some compromises must be accepted, in terms of disagreement between dose limits and dose distribution.

The dose prescribed for a specific volume might be irrelevant, either physically impossible to be achieved, or in contrast with that of other VOIs. Part of the PTV obtained from CTV expansion might exceed patient's body contour and, although it is important to define the correct collimator opening, it might be irrelevant for dose prescription because it is in air. In case of PTV and PRV very close to one another, prescription may require dose gradients that can not be achieved. A prescription conflict may also be present if PTV and PRV overlap, even partially. In this case dose should be defined and prescribed to overlap volume. For such reasons, IMRT dose prescription may be modified compared to the initial indications.

In case more target volumes are defined to receive different doses, for each one of these the total prescribed dose and dose fractionation must be indicated.

Due to the nature of IMRT, the concept of ICRU point of dose definition and the possibility to respect homogeneity constraints (-5%, +7%) have a relative importance; the presence of multiple PTVs and isocentres outside PTV make the definition of geometric points of specific interest a difficult one.

For this reason, the dose is rather prescribed as central trend index (mean dose) or, better still, according to a reference isodose surface, such as PTV-D95 (the isodose surface covering 95% of VOI). Dose prescription rates, too, require volumetric evaluations: D_{98} and D_2 may be used, respectively, as minimum and maximum reference dose, D_{98} and D_2 representing, on the histogram, the dose volume levels below and over which 2% of VOI stays.

Some biological motivations exist suggesting the use of D_{98}-D_{95} as reference dose to be prescribed to PTV in case of macroscopic disease, and D_{mean} for subclinical disease.

From an operating point of view, plan acceptability criteria should be defined, that may be specific by plan typology. As far as critical organs are concerned, dose constraints must be identified and defined for each single irradiated volume. Those agreements, proposed and adopted in many clinical protocols, still need further study and validation, both in terms of cost-effectiveness and in terms of comparison with conventional modalities of dose irradiation and prescription; no conclusive evidence on their appropriateness is yet available.

The use of margins surrounding OAR to define PRVs may influence operative choices and dose prescription to critical organs. Serial OAR toxicity is correlated with maximal dose and in these cases it is convenient, as a precautionary measure, to express maximal dose constraints to PRV, rather than to unexpanded OAR; the need of expansion for organs with parallel functional structures is still under investigation. For this reason, it is recommended to suggest positive expansion margins only in case of remarkably critical serial OAR.

Prescriptions of dose-volume constraints to serial functional unit refer to Dmax or, more commonly, to D_2. Much more arbitrary is dose prescription to those organs constituted by parallel functional units, for which the choice of dose-volume threshold is less critical; however, in these cases multiple dose indexes should preferably be expressed (e.g., rectus in prostate RTT: up to 50% of the volume should receive a dose exceeding 65% Gy; up to 30% should receive a dose exceeding 70 Gy and up to 5% should receive a dose exceeding 75 Gy), which should allow treatments with more homogeneous intra- and inter-Centre goals.

4.5. Planning criteria

For the definition of body volumes the terminology of ICRU 50, 62 and 71 is recommended, as it is here following described:

- GTV: macroscopic tumour volume;
- CTV: Clinical Target Volume;
- PTV: Planned Target Volume, obtained, according to ICRU 62, starting from CTV, taking MI and MS into account;
- TV: Treated Volume;
- IR: Irradiated Volume;
- OAR: critical organs;
- PRV: Planned Risk Organ Volume, similarly to PTV.

In IMRT planning with automatic plan elaboration systems, particular caution should be exercise to some issues mentioned above that, due to the automatic optimization process, may make the difference against non automatic planning:

- PTV extension beyond body margin;
- PTV extension to margins of build-up regions not infiltrated by tumour:
- TV portions in which no OAR have been defined:
- treatment duration.

During the planning phase it is important to prescribe goals that are either clinically irrelevant or impossible to be achieved. Dose prescriptions that are incompatible with VOI partially superimposed to one another should be avoided, as well as inadequate dose contributions outside targets. Such conditions require specific devices, during planning; however, each device presents advantages as well as criticities and, therefore, compromise solutions are often necessary.

Some proposed suggestions to solve the above-mentioned problems, are summarised as follows:

- *Build-up and PTV in air*
  - PTV segmentation into sub-volumes.
  - Increased extension of fields without modulation for those parts of PTV outside profiles or extension of the modulated field outside body contour.

- *Superimposing areas between PTV, PTV e PRV, PRV*
  - Definition of priority criteria for dose-volume constraints.
  - Segmentation of VOI with different dose prescriptions.

- *Distribution of not adequate doses outside PTV or PRV/OAR*
  - Prescriptions to fictitious volumes, creation of virtual critical structures outside the contour of PTV and pseudo OAR, outlining of protection areas, even segmented, for modulated dose prescriptions, definition of differentiated dose constraints at different distances from PTV.
  - Creation of virtual structures for hot spot control

4.6. Optimization

IMRT plays an important role in improving radiation treatment outcome, as it allows to strictly modulate dose distributions to the target volume geometry, thus sparing sensitive organs and tissues much more than it happens with 3DCRT modalities. However, IMRT does not guarantee an ideal dose distribution that is totally adherent to what initially prescribed by the physician. The employment of IMRT, therefore, aims at accomplishing the best possible plan within physical limitations of the employed machine and of the utilized modality itself: this represents an optimization problem to be faced. The optimization mechanism may either be direct or inverse. In the latter, constraints are typically defined in terms of dose to specific volumes and a relative weight can be assigned to each one. According to the employed system, a different cost function is used, which represents these goals. The optimization process consists of minimizing, by means of an algorithm, the cost function, in order to obtain a dose distribution as close as possible to the optimal initial one. The beam ballistics being initially designed, at the end of the optimizing process the system calculates the fluence matrices that will, in turn, be converted by a proper algorithm (leaf sequencer) in terms of MLC jaw or leaf movement.

The quality of the dose distribution optimized by TPS is mainly determined by the goal function, which is usually not selected by the user but it is defined within TPS, and by dose constraints. A very important step in the optimizing process is, in fact, the accurate definition of such constraints according to the following two criteria categories:

- physics criteria (dose, dose/volume);
- biological criteria.

IMRT "forward planning" process is conceptually different from the above described inverse planning system. In fact, forward planning does not need any calculation of the ideal fluence or the subsequent employment of an algorithm (leaf sequencer) to create segments. The initial input rather directly consists of the segments (aperture-based), created in a semi-automatic modality, starting from BEV of those structures defined on CT-based sections. For instance, a typical sequence used to create segments may be derived from the BEV of the following structure: PTV, PTV -cord, PTV -parotid, PTV -cord-parotid, etc. The resulting segments have, therefore, an intuitive shape and they are basically similar to those created with 3D conformal modality. Segment weight optimization is similar to the process in the inverse planning technique, since an algorithm is used (Cimmino), which minimizes a cost function based on dosimetric constraints (Dose Volume Histogram, DVH) and priorities assigned to the structures (target and critical ones). If at the end of the optimizing process a plan does not meet the specified requirements, the initially defined weights, as well as the shape of the segments, can manually be modified.

Such an IMRT plan has the advantage to use a reduced number of segments and MU compared to inverse planning modality, without affecting the plan quality. Moreover,

dosimetric checks may also be reduced and simplified compared to the method of inverse planning, as reported by Bedford and Webb.

However, it is important to point out that each Centre should define its own constrains based both on the literature and on its own experience and that each Centre should report such constrains in written procedures and, possibly, modify them according to the logical rules contained in the Quality Manual.

4.6.1. Physics criteria

Optimization systems currently in use for IMRT treatment are mainly based on physics criteria. Such criteria remarkably characterize dose distribution and can be expressed in terms of quality measurable as dose and dose/volume. The adopted criterion for the formulation of constraints usually consists of the requirement that these be maintained within given limits or, if included in the formulation of the goal function, the goal is to either maximize or minimize the different quantities. A very important criterion consists of delivering to the target volume (PTV) a dose that matches as much as possible the prescribed one, i.e. with a limited standard deviation of the dose distribution within PTV. The sum of squared deviations from the prescribed dose considered on each single element of the target volume (*voxel*), i.e. the minimum square goal function, is the most utilized cost function. Since underdosing and overdosing are not, usually, given the same importance within the target volume, cold spots being considered as more critical, some weight factors must be introduced into the goal function to be associated to dose constrains.

Dose constraints for PTV, used in the optimizing process are generally expressed in terms of minimum and maximum dose (D_{min}, D_{max}). It should be pointed out that such restrains do not represent the real minimum and maximum dose distribution but, rather, they simply represent those values to be used in the goal function.

As far as OARs are concerned, maximum dose constraint or, rather, maximum dose constraint to a minimum volume (e.g., V46<1%, that is up to 1% of the volume can receive a dose exceeding 46 Gy) is the criterion to be fulfilled for serial structures, such as spinal marrow, in which the complication probability is strictly correlated to maximum dose. No minimum dose restraints is recommended to OARs.

Another useful element for the formulation of the goals to be achieved in the treatment plan is mean dose (D_{mean}), which is an efficient clinical parameter for the evaluation of the possible effects on critical organs and structures. This criterion is an efficient clinical parameter for the evaluation of the possible effects on those organs and structures with a parallel arrangement, such as lungs. It should be pointed out that within such organs there might be areas with different radiosensitivities, so that only mean dose represents a gross parameter to predict the possible side effects. This implies that in the optimization process for some organs and structures, more criteria and constraints might be useful to obtain a better and more effective solution. For this reason, on those structures with either a parallel or mixed arrangement, such as rectum, dose/volume constraints are defined to the DVH, thus controlling also the effects that might be present at lower doses, when, however, important volumes of single organs are involved. In fact, complication probability increases according to the damaged volume fraction. Constraints on DVH may be formulated as follows: “up to a certain organ volume percentage (V%) may receive a dose higher than D” (see Figure 3). This is outlined on the DVH as a “barrier” corresponding to the point (D, V%). Some systems allow to define more points for each single organ on the DVH, thus providing a useful approach in the definition of the constraints to be fulfilled by the goal function, as there is a proper representation of the ideal DVH trend for the single structure.

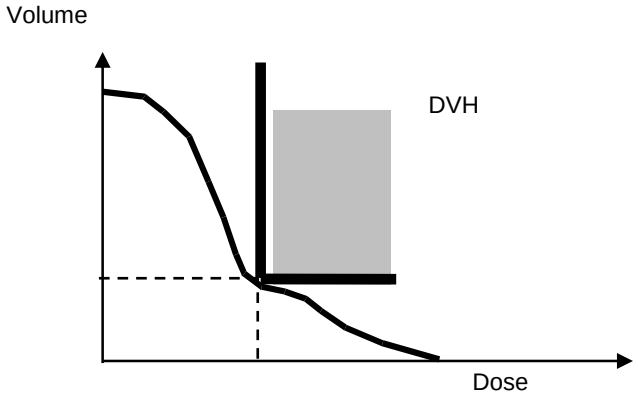

Figure 3 Dose/Volume Histogram

It might easily be understood that the employment of physics criteria in the formulation of treatment goals also offers the advantage to design clinical protocols, in which the established constraints for target volumes and OARs in the optimization process form integrating part of the protocol itself.

By way of example, the constraints indicated in the RTOG H022 protocol of the Radiation Therapy Oncology Group (RTOG) are reported for IMRT treatments of oropharyngeal neoplasms:

- *Target volume prescriptions*
  - Up to 1% of PTV may receive less than 93% of the prescribed dose
  - Up to 20% of PTV may receive only one dose exceeding 110% of the prescribed dose
  - Up to 1% or 1 cm^3 of the tissue outside PTV must receive a dose exceeding 110% of the dose prescribed to PTV

- *OAR Dose constraints*
  - Encephalic trunk: 54 Gy
  - Spinal marrow (+ 5 mm): 45 Gy
  - Mandible: 70 Gy
  - Parotides:
    - Mean dose to parotides lower than 26% (D_{mean} 26 Gy), or
    - Up tp 50% of the volume summing both parotides must receive a dose ≥30 Gy(V30<50 %) or
    - Up to 20 cm^3 of the volume summing both parotides must receive a dose ≥20 Gy

As pointed out above, it is far more significant to identify a volume percentage that should not receive a certain maximum dose, e.g. for encephalic trunk 54 Gy as maximum dose should be interpreted as dose at 1% of the volume, i.e. V54 <1%. For other anatomic sites the existing bibliography should be made reference to.

4.6.2. Biological criteria

An acceptable mathematical optimization of a goal function may be unacceptable from a clinical point of view, if using a minimum square goal function. In the cost function minimization, for instance, small PTV percentages may be remarkably underdosed, in order to maintain the rest at full dose, rather than, "distributing" an underdosage to the whole PTV, which may not affect treatment outcome. One percent of PTV may contain millions of clonogenic cells that, if not irradiated, may cause a complete treatment failure. On the other hand, a 10% underdosing may still result into an acceptable probability of tumour control. For this reason, goal functions have been introduced, that use biological patterns of tissue response. It is possible to include the calculation of Tumour Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) as a supplement to dose/volume constraints. Further developments of biological goal functions include the combination of TCP and NTCP to directly optimize the so called probability of complication-free tumour control P+. One should always take into consideration the probabilistic nature of these and other functions, which are still under investigation and should further be validated.

Another indicator, which takes into account the radiobiologic aspects of the IMRT plan optimization, is g Effective Uniform Dose (gEUD). By definition, EUD is the uniform dose that in a given organ would produce the same biological effect given by the dose distribution (not uniform); such definition is based on the linear-quadratic model of cell survival and it is extremely complex to be used in the clinical practice.

The introduction of gEUD as:

$$\mathrm{g}\,EUD = \left(\sum_i v_i * d_i^a \right)^{1/a}$$

has, instead, provided a simplified function, already currently implemented on some TPS. In the above expression there is the voxel volume fraction divided by the total organ volume, "d" is the dose to a fraction of the voxels, while "a" is a specific parameter of the single organ.

As "a" varies, different parts on the dose/volume histogram are weighed in a different way; When a=1 gEUD conicides with the mean dose, while when a= ∞ the dose is maximum and it is minimum when a<0. The parameter is negative for those target volumes, for which cold spots must be avoided. When "a" has a value comprised between 1 and ∞ all scenarios are possible, both for organs with a parallel and serial arrangement. The main advantage offered by gEUD is that, theoretically, all organs and structures may be characterized by one single numerical parameter.

It should be pointed out that gEUD is a phenomenological expression of EUD, as it is not really based on the linear-quadratic model; it, then, represents an optimization instrument and not a proper radiobiological indicator, since the correlation between "a" parameter values and the behaviour in terms of tissue clinical response, has not yet been established (Djajaputra, 2006).

4.7. Plan acceptability evaluation, final prescription and dose registration

Technological developments of the treatment delivery systems, along with the advances in 3D dose distribution, made new radiotherapy techniques available, which have the ability to conform dose distributions even to volumes with an extremely irregular geometry, such as, for instance, concave shaped volumes. These advances, however, did not coincide with a proper

ability to evaluate and compare dose distributions according to the expected clinical outcomes. For prescription, specification and reporting, new irradiation techniques require new instruments able to identify the best possible treatment plan within the chosen modality, to compare different techniques and to develop optimal clinical solutions.

ICRU Reports 50 and 62 certainly contributed to a language consistency and a common methodology in volumetric imaging-based treatment planning, even in view of a subsequent comparison and sharing of treatment clinical data. However, the introduction of intensity-modulated techniques emphasized some weak sides of the standardization proposed by ICRU, which become more end more critical when the introduction of SIB and the more and more frequent margin reduction is added to increasing steepness of dose gradients between PTV and PRV.

4.7.1. Plan acceptability evaluation and final prescription

3D dose distribution maps and differential and cumulative dose/volume histograms are proper instruments to comprehensively describe treatment from a dosimetric point of view. Quantitative parameters are represented by numerical indexes, either obtained from dose/volume histograms or directly, or by means of simple elaborations.

Some of these parameters are listed as follows:

- minimum, maximum and mean dose to PTV;
- maximum permitted dose to a critical or serial organ;
- the volume of a critical organ, either parallel or semi-parallel, that receives a given dose (e.g., V50, V60 and V70 for rectum);
- Target Coverage, that represents the PTV volume percentage within the established isodose (e.g., isodose 95% of prescribed dose) or, alternatively, the index used in some RTOG Studies, which expresses the same figure and is derived from the relationship between the minimum dose to PTV and the prescription dose (a value comprised between 0.9 and 1 is considered as acceptable);
- Conformity index according to different definitions (e.g., ICRU, RTOG);
- Homogeneity index, which expresses dose distribution homogeneity within PTV, according to different definitions.

Dosimetric evaluations based on DVH are not conclusive, especially if one considers that intensity-modulated techniques are often characterized by the presence of hot and cold spots even in unexpected areas, not directly detectable by analysing DVH. By way of example, a cold spot in the middle of the target would have the same effect in DVH as an analogous cold spot in the PTV periphery, against a remarkably different clinical impact. As reported in paragraph 4.6.2, EUD represents the biological equivalent dose that, if uniformly delivered to a tissue, produces the same cell death amount as the current non uniform dose distribution. Such concept is particularly useful in IMRT study, in consideration of its peculiar dose distribution dishomogeneity within the target volume. EUD application into the clinical practice is still under investigation. A modified EUD (mEUD) model, taking into account also the dose fractionation using Biological Effective Dose (BED), has recently been proposed. An additional critical element of intensity-modulated treatments is represented by the different dose prescription modalities used.

ICRU 50 and 62 has given complete freedom to both oncologists and radiotherapists concerning prescription, even though this latter should always be performed in compliance with the best possible current practice, in order to produce, with radiation therapy, the expected clinical result. In the treatment planning phase, when inverse planning modules are used, dose or dose-volume constraints are introduced to PTV and PRV/OAR, which may differ, even significantly, from what obtained at the optimization process completion.

In the light of the above, one can infer that in case of IMRT treatments, the final result is very often dependent on the type of algorith implemented in the inverse planning, of the score function guiding the optimization of the technology available to deliver dose and the last analysis of the global result may lead to a redefinition of the initial prescription.

4.7.2. Dose reporting

As far as treatment Reporting is concerned, ICRU recommendations proposing, for 3DCRT, to specify minimum, mean and maximum dose to PTV and the dose to the ICRU point, can hardly be applied to intensity-modulated radiotherapy, particularly when dose distributions are far from uniformity and no indicator seems to be reliable enough to represent them. In fact, it is sometimes impossible to identify the geometric and dosimetric parameters of the fields used for dose planning and delivery

In order to provide a comprehensive set of documents and to allow a future correlation with clinical results, the following instructions should be followed to:

- attach complete DVH, including all VOI (CTV, PTV, PRV), to each single IMRT treatment plan;
- indicate with uttermost precision the dose prescription criterion;
- report, if possible:
  - doses covering 95% and 100% of PTV and CTV;
  - maximum dose (as D_2) and mean dose to PTV;
  - percentage volume of CTV and PTV receiving 100% of the prescribed dose (V100).
- report data relating to critical organs.

In any case, all the documents concerning treatment should report treatment acceptability criteria adopted in the planning phase.

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4.8. Verification of treatment reproducibility

4.8.1. Patient positioning

As far as patient positioning verification is concerned, it is important to periodically verify the isocentre position relative to bony landmarks or to other possible internal or external landmarks. For this reason, it may be useful to report contours of anatomical structures, as designed on CT images, to DRR, to be utilized for a comparison. The test timetable is to be established according to the accuracy rate of the immobilizations systems a single Centre is equipped with, as well as the closeness of critical structures to the target and the gradient entity

generated by treatment plan. However, at least a weekly check is recommended. Furthermore, proper protocols should be arranged, according to the treated anatomic district, in order to evaluate the levels above which patient shifting should be performed.

4.8.2. Image-guided radiation therapy techniques

The accuracy of an IMRT dose distribution is correlated to the correct patient positioning, as well as to organ movement. In fact, any deviation from the planned position may expose critical structures to high doses, thus creating hot and cold spots in the target volume. Volume movement-related errors may be reduced by means of image-guided (Image-Guided Radiation Therapy, IGRT) techniques, which allow a daily visualization of either the target volume – ultrasound systems, Cone Beam Computed Tomography (CBCT), CT in room – or of radio-opaque bony landmarks inserted into the tumour (portal imaging systems, x-ray systems). These techniques also allow to reduce margins between CTV and PTV.

2D ultrasound systems, based on the acquisition of axial, transversal or 3D images, by means of the acquisition of multi-axial images, enable to visualize CT-based volume projections derived from treatment plan in all three directions, and to make all the online needed modifications, including both set-up and organ motion errors. The ultrasound-guided localization procedure, which is not invasive and does not expose patients to ionizing radiations, only needs a short training for operators and is very quick, as it takes only 5 minutes for each patient (Lattanzi, 2000).

The IGRT technique, based on CBCT, utilizes a CT-based image of the patient in treatment position, acquired by means of an x-ray device (kV-CBCT), mounted on the accelerator, or by means of the accelerator high-energy source (MV-CBCT). Both devices are positioned opposed to an amorfous silicon flat panel detector mounted on the accelerator.

CBCT registration to planning CT scan (and thanks to the superimposition of treatment plan designed volumes on the cone-beam image) enables error detection (set-up and organ movement errors) and its correction by means of calculated couch movements. CBCT can be exported to TPS for a re-evaluation of the original plan, along with the related DVH and a possible new planning (adaptive radiotherapy).

Doses per scan typically range between 1cGy (head and neck) and 4-5 cGy (pelvis) (McBain *et al.,* 2006; Islam *et al.,* 2006; Sykes *et al.,* 2005) for kV-CBCT, while they are higher for MV-CBCT. The extra time taken by the accelerator for IGRT treatment with CBCT, varies from 3-4 min (effective acquisition time for off-line corrections) to a maximum of 10-12 min (reconstruction, registration and clinical evaluation for online corrections). An alternative technique is the visualization, by means of an electronic portal image device (EPID) or a stereoscopic x-ray imaging technique, of radio-opaque markers inserted into the target volume. Al least three markers are needed, in order to obtain information on the position of 3D target volume. Algorithms for the automatic detection of landmarks and the fusion between DRR and the images acquired in the treatment position, allow both set-up and organ movement related errors.

4.8.3. Organ volume variations

IGRT techniques allow to highlight possible potential target volume variations during treatment. In case no device should be available to visualize the target volume during treatment (ultrasound-guided systems, CBCT, CT in room), a possible alternative is CT repetition, whenever initial anatomic data are expected to change during treatment.

In this case, if feasible, a new optimized treatment plan should be performed to the new target volume. Some studies on this issue are reported in the literature, as indicated in the reference list below.

4.8.4. Respiratory control techniques

Target volume shifting that occurs within each single treatment fraction, are mainly related to respiratory cycle. Such shifting is more relevant in some anatomic districts, such as thorax and abdomen, and may represent a remarkably critical issue in IMRT treatments. The techniques employed to minimize such movements are described in paragragh 3.6.

4.9. Treatment parameter verification

In view of the verification of treatment parameter constancy, the TSRM staff, in charge of treatment delivery, should have acquired specific expertise for a correct data interpretation and the detection of potential abnormalities.

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5. TOXICITY MONITORING

The major indications to the clinical employment of IMRT are the possibility to improve local control through dose escalation, without a concomitant increase of radio-induced damages and the decrease, regardless of total dose increase, of tissue toxicity. As a consequence, the clinical efficacy of this technique is confirmed by the accurate detection of treatment related acute and, above all, chronic toxicity, as well as by disease control evaluation. Integrated boost techniques, which introduce altered dose fractionations, besides allowing, as IMRT does, to investigate hypofractionation techniques, emphasize the need to have a punctual registration of treatment side effects and complications. In fact, the radiobiological effect, especially the long-term effect, related to non conventional fractionation schemes and to their association with drug therapies, is still largely unknown.

The comparison between clinical data and dosimetric data of the treatment plan, may provide useful information for a better optimization during the planning phase.

It is important to point out that the typical IMRT dose distribution, extensively illustrated in the above paragraphs, may affect toxicity profiles significantly different from those commonly observed in the same anatomic areas treated with non IMRT modalities. Differences may concern both the amount of radiations and the type of involved organs and tissues. Radiations oncologists should, therefore, be able to promptly evaluate those signs and/or symptoms unusual in conventional radiotherapy.

The most used score systems, such as RTOG/EORTC (European Organisation for Research and Treatment of Cancer) and SOMA-LENT (Subjective, Objective, Management and Analytic - Late Effects on Normal Tissues), are going to be replaced with CTCAE vers. 3 (Common Terminology Criteria for Adverse Events), which does not subdivide adverse events into predefined temporal periods and is suitable to detect the adverse event and its severity at any time the detection is performed.

During treatment, in the following month, a weekly adverse event detection should be planned. Thereafter, a detection every 2-3 months can be sufficient during the first year, every 3-4 months during the second year and once every six months for the following years. Detection timing may vary, depending on the irradiated tumour site, as well as on reported adverse event type and severity.

Besides toxicity detection, quality of life (QoL) questionnaires, based on patient's subjective opinion, are recommended.

A continuous clinical observation longer than the usual 5-10 years is strongly recommended, even with long intervals, to evaluate not only possible late sequelae but also the potential cancerogenous effect of IMRT. In fact, the literature reports the agreed opinion that the increase in irradiated tissue volume and, still more, the increase in the whole body dose as a consequence of the elevated number of MU in IMRT, may increase cancerogenesis risk by a factor of 1.5, especially in paediatric patients and in young long-term survivors.

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6. RESOURCES

When analysing the needed resources for an IMRT treatment, the following issues must be taken into consideration:

- essential technological requirements;
- needed staff;
- organizational measures aimed to optimize both.

This analysis will allow an assessment, although it might be a rough one, as it depends on the wide range of possible choices, on the necessary resources to start the chosen modality and the subsequent ones enabling its employment in the clinical practice.

6.1. Technological requirements

The guarantee of a correct IMRT technique delivery requires the presence of:

- dedicated patient immobilization and containing systems, as much individualized as possible, depending on the anatomic district to be irradiated.
- a contouring station for VOI definition and multimodal image fusion (CT +/- RM +/- PET, etc.);
- a TPS elaboration system, preferably including an inverse planning module, used for the optimization of the modulated field fluences, and a sequencer, dedicated to the conversion of fluences into MLC leaflet motion files of the MLC leaflets;
- a multi-leaf collimator (MLC, mMLC, μMLC) equipped with a software for the execution of the movimentation files calculated by the sequencer, in step-and-shoot, sliding window o IMAT modality; such devices are included in the standard accelerator supply, even though they obviously have a different impact on the total LINAC (LINear ACcelerator) cost, depending on the specific characteristics of each single device.;
- a system for the execution of physical checks and tests on treatment geometric reproducibility, to be used in the delivered fluence verification, generally consisting of a film-dosimetry module (scanner with analysis software), a micro ionization chamber with an electrometer, a water-equivalent layer phantom with a micro-chamber support and, possibly, a matrix detector. In this case, too, costs may vary depending on the specific characteristics of the different systems currently available on the market;
- a Record and Verify (R&V) system for control and registration of the correct radiation treatment execution, both relating to accelerator and MLC parameters;
- an electronic device for portal image (EPID) acquisition and for the verification of the correct patient alignment during treatment;
- a computerized system for image registration, assessment and archiving.

If the IMRT treatment is delivered to anatomic areas, whose position is strongly dependent on patient's respiration, it is recommended to employ specific techniques for respiration control and/or treatment gating (synchronization with respiration) techniques. Accuracy during treatment delivery may be improved by means of IGRT devices and techniques and/or with adaptive radiotherapy.

6.2. Organizational requirements and human resources

The workload for the execution of IMRT treatments is markedly higher than it is for other modalities and it requires that the involved human resources (radiation oncologists, medical physicists, TSRM) be strengthened, in particular because of the ever increase of extra working times due to volume *contouring* procedures, commissioning, planning procedures, dosimetric characterization and Quality Assurance programs.

The workload for IMRT treatment completion, based on the current technological experience, is on the whole markedly higher than it is required for conformal treatment modalities, although it is different with respect to the complexity of the planning problems, to the previous experience, to the availability of organizational solutions to optimize the operators' work. Preliminary indications on workload related to IMRT treatments, have been proposed in the Guidelines for the Provision of a Physics Service to Radiotherapy (IPEM, 2002), while more precise data are becoming available in the medical literature.

In the changeover from 3D conformal techniques to IMRT, training programs for all the involved operators are necessary. Of course, the experience gained by each single Centre allows to arrange, in a subsequent phase, original protocols to optimize times for the different treatment performances. One should consider that for given malignancies and for specific groups of patients, candidate to non standard modalities, rival plans should be compared, which requires an additional expenditure of time and resources.

The points that should be taken into consideration in the planning phase are the following ones:

- presence of medical, physicist and technical staff expert already in 3DCRT radiation techniques, trained in IMRT procedures, numerically adequate for the amount and quality of the delivered services;
- implementation of a training and periodical continuing education programs for the whole staff involved;
- arrangement of protocols and procedures, written in collaboration with the Medical Physics Unit, for the treatment of the primary anatomic sites and for image acquiring and registration;
- settlement of collaboration procedures with the Diagnostic Imaging Unit and, possibly, also with organ specialists for the correct VOI definition;
- guarantee of access and/or direct acquisition of the modern multimodal imaging systems;
- evaluation of the potential reduction of the number of treated patients of the potential additional resources needed to maintain productivity unchanged, since an IMRT treatment setting duration is usually longer than in other treatment modalities.

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7. HELICAL TOMOTHERAPY

Helical tomotherapy is a treatment unit dedicated to intensity modulated beam irradiation, in which radiation treatment is delivered by means of a helical modality, through a completely integrated Image Guided system, which is able to acquire MVCT scans before treatment. This treatment unit may be described as a combination between a helical CT scanner and a conventional linear accelerator.

The radiation source, constituted by a 6 MV linear accelerator mounted on a circular gantry similar to a CT scanner, rotates in synchrony with the continuous longitudinal couch movement, thus creating a helical trajectory. Unlike LINEAC, the isocentre is placed at a source to axis (SAD) distance of 85 cm and the system has no homogenizing filter, which allows to obtain higher nominal dose rates (800-900 UM/min) and, subsequently, shorter treatment times. The system is equipped with a collimator 64. Beam modulation is obtained by varying time fraction, so that leaflets result either open or closed.

The same radiation source, with a lower nominal dose of 3.5 MV, is used for megavoltage (MVCT) image acquisition: an array detector of 738 xenon ionizing chambers, mounted at the opposite end of the radiation source, allows the 3D volume reconstruction of the body structures in order to verify, when necessary, patient position. Volume image acquisition may be obtained at dose values comparable with those obtained by with EPID images of conventional accelerators (of the order of 1-3 cGy

7.1. Accelerator quality commissioning and assurance

The accuracy of the irradiation delivered with helical Tomotherapy depends on the correct geometric and dosimetric performances of all the different components: irradiation source, collimators, MLC, gantry and couch.

The mechanic and geometric characterization of the TomoTherapy unit, similarly to conventional accelerators, requires the alignment verification of all the system components: laser, radiation source, moveable collimators, MLC and array detectors.

The major difference from LINAC is the conic shape in the transverse profile, due to the absence of the flattening filter: symmetry and flatness measures lose their relevance with this system and it is then important that the shape of the profile measured during commissioning and modelled by treatment planning system be maintained constant. Given the helical nature of irradiation, the periodical acquisition and monitoring of longitudinal profile results crucial, so as to avoid undesired overdosing or underdosing effects. Due to the reduced source-isocentre distance (85 cm), dose fall-off in Percentage Depth Dose (PDD) results faster compared to PDD of conventional LINAC.

Particular attention should be paid to characterization and synchronization of all the components present in the system: couch movement uniformity and accuracy, leaflet effective opening time, synchronization among leaflet opening, couch movement, gantry rotation and LINAC impulses. Leaflet effective opening time differs from the scheduled time, because of the leaflet latency effect, due both to the finished leaflet opening and closing times (about 15 sec) and the slight delays of electronic check. Latency corrections (progression from leaflet real opening time and scheduled time) will obviously depend on projection time, while they may be considered as approximately independent from the considered leaflet. Similarly to the output

factors of latency times, once they have been measured, they are inserted into the treatment planning system and they are taken into account in dose distribution calculation.

Finally, a characterization of the MVCT image acquisition system should at least include an image and contrast resolution verification, along with a verification of the dose delivered during the scan.

7.2. Planning system commissioning

Helical tomotherapy is a unit dedicated to intensity-modulated treatments, so that planning is essentially based on an iterative process of inverse optimization, charatcterized by quadratic minimization function. Dose distribution calculation is, instead, supported by a convolution/superposition algorith. Helical tomotherapy treatment planning and delivery basically depend on three parameters able to inversely influence conformation of dose distribution and treatment time:

- *Field width*
  It is the beam direction in the direction of the longitudinal couch movement. This parameter tends to influence more dose conformation in the cranio-caudal direction.

- *Pitch*
  It is defined as couch rotating shifting in field width unit.
  This parameter, too, mainly influences conformation of dose distribution in the longitudinal direction. Typical pitch values range between 0.25 and 0.5, thus determining a superimposition of adjacent rotations during helical irradiation.

- *Modulation Factor (MF)*
  It is defined as the relationship between maximum leaflet opening time against average opening time of all the leaflets. Higher values mean more conformed dose distributions to the axial plan, as well as longer treatment times. MF values range between 1 and 6.

The choice of the above-mentioned three parameters determines the required rotating period to deliver prescription dose to target volume. These three parameters, together with target volume length, also determine total treatment time.

Helical tomotherapy planning system is a model based system, in which irradiation beam is modelled and predefined by means of Monte Carlo methods and it is not based on directly measured dosimetric data.

During commissioning is, therefore, necessary to verify that the dosimetric characteristics of the pre-modelled beam and those of the used machine be superimposible: it is important to verify the agreement between PDD, transverse and longitudinal profiles, as calculated by the treatment planning system, with the corresponding curves measured in the water phantom. In case the agreement should not be satisfactory, the model parameters are adapted directly by tomotherapy physicists, until they adequately fit the experimental measures.

Besides beam modelling, specific parameters relating to MLC must be measured and inserted into the treatment plan: output factors for different leaf opening and closing combinations, so as to take into account the tongue-groove effect and the latency curves of the leaflets.

The verification of the configuration parameters concerns, of course, the comparison between calculated and measured dose distribution. To date, no specific dosimetric tests are

available in the literature for the dosimetric accuracy verification of the modulated fields. The only proposed test implies the verification of the agreement between measured and calculated dose distributions in homogeneous phantom for simple IMRT plans, with target on-axis and off-axis OAR and, conversely, with target off-axis and on-axis OAR, for the different opening of commissioned collimators.

7.3. Patient quality assurance

The aim is to verify the whole process and delivered dose accuracy.

The approach is similar to that reported for IMRT techniques with linear accelerators, which implies the calculation of the treatment plan dose as planned in a phantom, and the dosimetric comparison between measured and calculated dose distributions in phantom. Given the helical nature of irradiation, cylindrical phantoms are preferable. Unlike LINAC techniques, a single dosimetric comparison modality can be applied, that is the treatment plan verification in its overall configuration.

A homogeneous cylindrical phantom has been specifically assigned to helical tomotherapy (Cheese Phantom), allowing the simultaneous verification of punctual doses with chambers (A1SL, 0.056 CC chambers) and the verification on a plan with film. With such a specific phantom the simultaneous measurement with chambers and films can be performed on two different plans.

7.4. Impact of intrafraction movements

Nowadays there are no conclusive studies on the impact of respiratory movements during helical tomotherapy dose delivery. However, the elevated number of segments, which are typically employed in tomotherapy, together with the helical geometry minimizing under- and over-dosing due to synchrony between respiratory cycle and couch movement, demonstrates that this IMRT delivery modality is associated to lower rates of criticity compared with the other techniques, thus suggesting that in most clinical cases no gating techniques might be necessary in order to minimize the interplay effect.

On the other hand, the same helical modality does not favour any gating and/or tracking technique implementation. Some feasibility studies on different gating techniques have recently been published. Particularly promising is the approach using the detector systems utilized for MVCT image acquisition.

7.5. Resources

As for current practice, work method and inactivity times among different techniques (diagnostic CT, verification, treatment, control, etc.) allow to treat 20 patients per working day, which is about 1/2 or 2/3 of average number of patients treated with 3DCRT or IMRT, respectively.

Tomotherapy treatment-related management costs (organizational and human resources) are comparable with those relating to IMRT treatments, while they are almost twice as much compared to 3DCRT treatment-related costs.

None of the Italian regions has so far arranged any specific computer-based model for reimbursement relating to tomotherapy treatments and, for this reason, the treatment is computed under the item "IMRT" and it is summed up to simulation CT.

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8. CYBERKNIFE

8.1. Physics-technical characteristics

Cyberknife has been conceived for radiosurgery and stereotassic radiotherapy. It is constituted by:

- a 6 MV collimator, mounted on a 6 degree-of-freedom robot, with static 5-60 mm circular collimators, characterized by non-isocentricity and non-complanarity;
- an image-guided system (IGRT), both useful for the correct patient positioning and for the target movement monitoring.

The image-guided system consists of two radiogenic tubes placed on the ceiling at 90° from each other and inclined by 45° to patient axis, correlated to a couple of silicon detectors (flat panel) placed on the floor, beside treatment couch.

Position verification system varies according to target localization. Intracranial targets are "tracked" by means of a skull-tracking algorithm based on a intensity pattern, without any fiducial markers (either external or internal). The more recent tracking system is represented by spine-tracking, a method similar to the skull-tracking method, but exclusively dedicated to spinal lesions, by using a so-called fiducial tracking method. It consists of identifying position and orientation of a set of fiducial markers before the irradiation of each single beam. The spatial information is utilized to correct robot position before each irradiation. Moving targets are, instead, "tracked" by a system based on the use of internal fiducials inserted into the lesion and it allows to correlate lesion position together with fiducial, with external-marker position, of optical sensors placed on patient's thorax and CCD (Charge Coupled Device) couches, which determines the real time position of the latter.

Since the system has an intrinsic response delay of about 200 ms, which the system takes into account by performing a tumour position estimation based on the position of the external markers and by using an adapting filter to estimate position, starting from noise assessment.

All the above-mentioned techniques are based on a 2D-3D registration method, consisting of comparing DRR images with x-ray-obtained real images, in order to calculate the six translation and rotation parameters used to correct robot position.

Set-up errors are initially corrected by means of the automatic couch movement. Subsequent corrections are directly performed by the robot, up to 10 mm for transactions (25 mm in case of Syncrony system) and up to 1° for right left and cranio-caudal rotations and 3° for clockwise and anticlockwise rotations.

Treatment is performed along a predefined path in the space and is subdivide into points, called "knots", where the robot can stop for delivery. These points are approximately 100 and in each of them the accelerator can take up to twelve different directions, thus being able to reach a total of 1200 different beam entry directions.

This system allows to obtain dose distributions with a high gradient, an elevated conformation isodoses to the target and an extremely elevated precision with maximum errors of the order of one millimeter.

Cyberknife does not use stereotassic frames and offers the opportunity for a smooth dose functioning, allowing continuative treatment, thus making this technique more similar to the traditional radiation modalities. Treatment setting duration usually ranges between 30 and 60 minutes.

Some peculiar aspects of Cyberknife equipment, in particular its non isocentric targeting system, require a specific quality assurance control program. Whenever feasible, individual checks indicated for other techniques are recommended. Quality checks related to Cyberknife system concern the dosimetric and mechanic part of the accelerator, the robotic component and its relating safety devices, as well as the imaging component, which is essential for an accurate treatment.

Cyberknife LINAC does not utilize any homogenizing filter and, therefore, beam homogeneity if different from that of the traditional accelerators.

Among usual checks on beam, machine and relating devices, the output check is particularly important, since the monitor chambers utilized for Cyberknife are non-sealed chambers and are affected, therefore, by sudden ambient changes. Because of the system complexity, a fundamental test for the accuracy verification of the whole process is the so-called end-to-end test. It starts from the CT acquisition of an anthropomorphic phantom (which simulates a skull in case of "Skull Tracking", and a thorax, abdomen in case of fiducial tracking or motion tracking through Synchrony™). Images are then transferred to the treatment planning system (TPS), where the target is outlined, a treatment plan is calculated and DRR are generated. The phantom is irradiated by placing radiochromic films in correspondence to the target and the dose delivered to the film is analysed and compared with the dose distribution obtained with TPS.

8.2. Clinical indications

The size of those lesions that can be treated tehoretically have no limit, but treatment times are longer in case of irregular shapes and, for lesions exceeding 5-6 cm, the advantages offered by Cyberknife are less effective, compared to the conformation obtained with traditional accelerators or modern radiation techniques.

Cyberknife has been implemented in order to improve radiosurgical treatment, or stereotassic radiotherapy, not only for cranial but for total body irradiation. This machine can, therefore, be used in all those cases in which over the past years treatments were performed with conventional machines, either equipped or dedicated, as Gamma Knife. The major advantage is represented by the possibility to have a fractionation, which facilitates patient positioning, avoiding coercive immobilization procedures.

This experience has been consolidated in cranial irradiation, both in case of vascular disorders, benign and malignant tumours and it has also been extended to motor and functional disorders (trigeminal neuralgia), as well as other non invasive diseases. The employment of a fractioned boost following conventional chemo-radiation has been successfully validated for nasopharyngeal lesions.

As for extracranial radiosurgery, lesions have been divided into: a) spinal, close or in the proximity of vertebral bodies, b) body, far from bony landmarks and often moving in correlation with respiratory movement. The experiences started at Standford in 2000, and carried on in many different Centres, have been growing in ever greater numbers and have become more and more diversified, specifically orientated to spinal, lung and abdominal sites (pancreas, liver and retroperitoneal lymph nodes), as well as pelvic sites (prostate).

Peri-rachial lesions can be treated without any fiducial implant, since the system can recognize vertebral bodies as reference. With such bloodless modality, benign and malignant lesions have successfully been treated in all the Centres, thanks to both the system precision and the particular radiosensitivity of the treated lesions. In particular, meningiomas, arteriovenous defects, hemangioblastomas, metastatic lesions, etc.

For body lesions, i.e. distant from bony landmarks or with a movement correlated to respiratory movement, it is necessary to implant a fiducial into the tumour site or very close to it. This modality allows motion tracking during radiosurgery, by both tracking and anticipating respiration-related target motions (as illustrated below). Experiences have been addressed to early-stage lung tumours, not clinically operable, or as an alternative to surgery, in the light of the excellent results reported in the literature, and to solitary secondary lesions, still as an alternative to a surgical metastasectomy. The dosimetric conformation of Cyberknife should guarantee reduced long-term toxicity compared to non-tracking modalities.

A phase I-II study on the treatment of pancreatic lesions, carried out by the Standford School, established both tolerance dose of duodenum to radiosurgery in a single setting, and the limits of the indication to radiosurgery in pancreatic tumours. For all these reasons, a gold marker should be implanted into the pancreatic site and the extension to duodenum must be better defined, once the critical organ tolerance has been taken into consideration.

There are also initial experiences on accelerated treatments for early-stage prostate cancers. In this case, too, the implantation of fiducials, usually four, into the prostatic cavity, is necessary. Treatment is usually compared with high dose rate brachytherapy. Five treatment settings are usually performed on a daily basis.

In conclusion: Cyberknife offers the advantage of smooth fractioned cranial and body radiosurgery. For lesions that are close to vertebral bodies, this technique does not require any invasive marker placement. For moving lesions that are far from rachis, gold markers must, instead, be used. Although such approach may be very unfavourable to patients, this system also represents a very refined kind of radiosurgery, with its unique "motion tracking" detecting process, in which after creating a target movement model, the robot predicts its movement, by anticipating it by 4 seconds, and is right on target.

Among disadvantages, structure relating costs, staff training (physicians, physicists, TSRM and nurses), as well as clinical case selection, which are still in an initial phase, are to be mentioned.

8.3. Resources

In terms of human resources, Cyberknife implies, besides the staff usually employed for radiation treatments, also the involvement of other professionals, according to the specific treatment to be performed.

In case of cranial lesions, the team includes personnel coming from the Departments of Radiotherapy, Neurosurgery and Neuroradiology. Radiation oncologists and neurosurgeons account for 50%, radiologists for 2%, medical physicists for 19%, TSRM for 22% and operating theater nurses for 7% of the whole treatment process.

The treatment of body lesions involves a staff from the Departments of Radiotherapy, Surgery and Radiology. Oncologists and radiation therapists account for 35%, radiologists for 5%, medical physicists for 25%, TSRM for 2o% and operating theater nurses for 10% of the whole treatment process.

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APPENDIX

List of operative and implementing Centres in the use of IMRT updated to 2008

List has been updated taking into account only Centres answering to the request of partecipating to the elaboration of "Indications for Quality Assurance in IMRT" and that had been partecipated to the meeting of January 2006.

OPERATIVE CENTRES

Calabria
- Azienda Ospedaliera "Pugliese Ciaccio", Catanzaro

Campania
- Istituto polidiagnostico "D'Agostino e Marino", Salerno

Emilia Romagna
- Arcispedale di Santa Maria Nuova, Reggio Emilia
- Policlinico di Modena
- Ospedale Bellaria, Bologna
- Azienda Ospedaliera Bologna - Policlinico Sant'Orsola Malpighi ed Università degli Studi, Bologna

Friuli-Venezia Giulia
- Centro di Riferimento Oncologico, Aviano e Ospedale di Pordenone

Latium
- Istituti Fisioterapici Ospitalieri – Istituto Regina Elena (IFO-IRE), Roma
- Università Cattolica del Sacro Cuore - Policlinico Universitario "A. Gemelli", Roma
- Ospedale "S. Giovanni Calibita" - Fatebenefratelli, Roma
- Azienda Ospedaliera S. Camillo-Forlanini, Roma
- Ospedale S. Andrea - Università "La Sapienza", Roma
- Azienda Ospedaliera S. Camillo, Roma

Liguria
- Istituto Nazionale per la Ricerca sul Cancro, Genova
- Ospedali Galliera, Genova

Lombardy
- Spedali Civili - Università di Brescia, Brescia
- Azienda Ospedaliera S. Anna, Como
- Istituto Nazionale Tumori, Milano
- Istituti Ospitalieri, Cremona
- Ospedale S. Raffaele, Milano
- Istituto Europeo di Oncologia, Milano
- Azienda Ospedaliera S. Gerardo ed Università "La Bicocca", Monza
- Istituto Clinico Humanitas, Rozzano (MI)
- Azienda Ospedaliera Niguarda Ca' Granda, Milano

Molise
- Università Cattolica del S. Cuore - Centro di Ricerca e Formazione ad Alta Tecnologia nelle Scienze Biomediche "Giovanni Paolo II", Campobasso

Piedmont
- Ospedale San Giovanni Battista - Università degli Studi, Torino
- Ospedale Mauriziano "Umberto I", Torino
- Istituto per la Ricerca e la Cura del Cancro, Candiolo (TO)
- Ospedale Civile – ASL TO4, Ivrea (TO)
- Azienda Sanitaria Ospedaliera OIRM S. Anna, Torino

Apulia
- ASL TA - Presidio Ospedaliero "S. G. Moscati", Taranto

Sicily
- Presidio Ospedaliero "San Vincenzo", ASL5 Messina, Taormina
- Ospedale Oncologico "M. Ascoli", Palermo

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- Azienda Ospedaliera Universitaria Pisana – Presidio Santa Chiara, Pisa

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- Ospedale Clinicizzato SS. Annunziata, Chieti
- Ospedale S. Spirito, Pescara

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- Azienda Ospedaliera S. Giovanni di Dio e Ruggi D'Aragona, Salerno
- Università Federico II, Napoli
- Istituto Nazionale per lo studio e la cura dei Tumori - Fondazione "G. Pascale", Napoli

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