

## Radiation Oncology

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**Published Date:** November 06, 2016

## GENERAL ASPECTS OF RADIOTHERAPY

### Introduction

Radiation Therapy (**RT**) is a commonly used localized treatment for tumors. The earliest experiences of RT are from the late 19th century, soon after the discovery of X-rays. The intent of the RT may be curative or palliative while preserving organ function. In the first case the aim is for definitive patient cure while the latter is the relief of symptoms produced by an advanced stage cancer. In many centers palliative RT represents an important percentage of treatments. Unlike curative/radical RT, palliative RT is typically performed with low doses of radiation (generally sufficient to treat the symptoms) and with fewer treatment sessions. For example, in the case of bone metastasis, it is frequent the use of one single fraction of 8 Gy.

The effectiveness of RT depends on: 1) delivery to a properly defined target of an appropriate total prescribed dose of radiation, 2) treatment fractionation, 3) total duration of treatment, 4) individual radiosensitivity and oxygenation of different cells, 5) damage repair of irradiated cells [1].

Like any other therapy, RT can produce side effects that may occur earlier or later. The risk of side effects depends on the delivered dose and on the chronological treatment characteristics. Moreover, toxicity can increase depending on the volume of the irradiated healthy tissues.

Currently it is estimated that about 60% of cancer patients need RT in the course of their medical history. A significant proportion of patients achieving healing as a result is often credited to RT. Although RT can be used independently in patients management, in most cases, RT is often integrated with other types of treatments such as surgery or chemotherapy.

The integration with the surgery takes place in various ways:

1. preoperative RT: which typically has the purpose to reduce the size of the tumor to facilitate the subsequent surgery;
2. intraoperative RT (**IORT**): in which radiations are administered during surgery;
3. postoperative RT: with the aim to eliminate any microscopic residual tumor that could have remained from insufficient surgical margins elimination or seeding during the intervention.

There are basically two main technical modalities of RT administration irrespective of the treatment aim. These modalities are known as external beam RT and brachytherapy (**BRT**). The external beam RT is based on the administration of radiation to the patient from an external source at a distance, while in BRT radioactive sources are placed directly into or near the tumor.

## Mechanisms of Action of Radiation Therapy and Therapeutic Window

### Mechanisms and phases of RT effect

RT uses ionizing types of radiation, which release energy in the tumor tissue either directly (from charged particles: electrons, protons, alpha particles, heavy ions) or indirectly (neutral particles: x-ray, gamma, neutrons). The unit used for measurement of the dose of RT is the Gray (**Gy**), which is defined as the dose corresponding to the energy of 1 Joule released to a mass of 1 kilogram.

The release of energy by RT produces both physical and biological effects that occur in different phases:

1. Physical phase: radiation interacts with the atoms (in particular with orbital electrons) causing excitation and ionization that yields to the atomic instability.
2. Chemical phase: as a result of ionization of the atoms since the major part of the body is made of water, chemical reactions develop mainly affecting intracellular water and determining hydrolysis with formation of free radicals. These latter interact with biological molecules and in particular with the DNA; this mechanism mediated by water, is called “indirect”. The resulting DNA alterations are usually reversible but in the presence of oxygen they can become permanent (oxygen effect); these mechanisms are partially offset by antioxidant mechanisms in the cell.

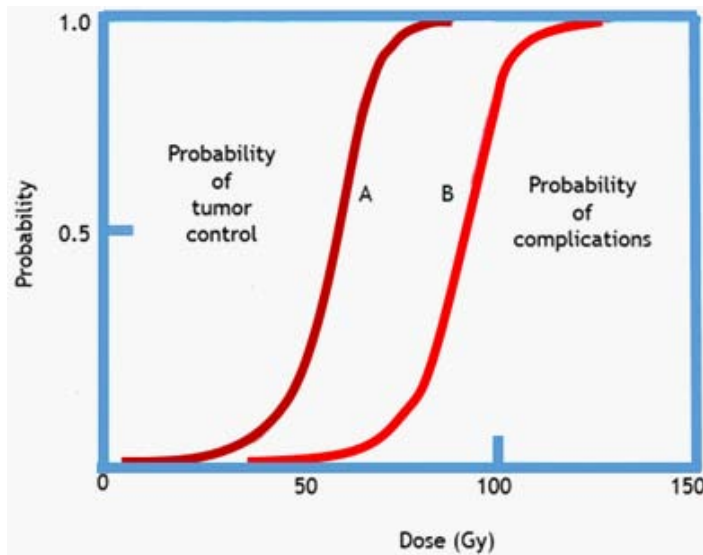
3. Biological phase: the molecular damage is usually repaired by enzyme systems controlled by genetic mechanisms. In case of no repair the damage can produce either the cell necrosis or apoptosis (resulting in biological damage in tissues) or mutations (with the risk of radiation-induced cancers).

Generally most of the effects of RT are dependent on the indirect damage mediated by hydrolysis reactions. However it is also possible to have cell kill from direct damage where radiation acts directly on the DNA double strand. Both damages may have several consequences on the DNA molecule: 1) damage to the single-base; 2) Single Strand Break (**SSB**); 3) Double Strand Break (**DSB**); 4) cross-link DNA-DNA or DNA-proteins. Of all these different modes, the DSB is the most important in terms of biological consequences.

### **Therapeutic interval and window**

The aim of RT is to eradicate cancerous cells by accurately delivering high radiation dose to the tumor site with “no delivery” of dose to surrounding normal tissue. As previously mentioned, the probability of tumor control (Tumor Control Probability: **TCP**) depends on the total dose administered to the neoplasm. The relationship between dose and TCP can be represented in a graph, in which the curve generally has a sinusoidal shape (Figure 1). A similar relationship also exists between total dose and probability of effects on healthy organs, and therefore of radio-induced toxicity (Normal Tissues Complication Probability: **NTCP**) [2].

Thus, the possibility of curing cancer with RT is easily derived by placing the two curves on the same graph (Figure 1). If the distance between the curves (therapeutic ratio) is small, it is impossible to control cancer without a high incidence of toxicity from the normal tissues.<sup>3</sup> On the contrary, if the distance is larger, it is possible to identify a dose for which the TCP is very high and the NTCP is very low, meaning with a very “large” therapeutic window. It follows that tumors presenting with a close TCP and NTCP curves are hardly curable with RT. In contrast, in tumors with a wide therapeutic window, tumor cure is easily achieved without side effects on healthy tissues.



**Figure 1:** Therapeutic window: curve A represents the tumor control probability and curve B represents the normal tissue complication probability.

In clinical practice it is possible in various ways to expand the therapeutic window, For example the TCP curve can be moved to the left by increasing the sensitivity of the tumor to RT. This increase in sensitivity can be obtained with the use of other treatments concomitant to RT (hyperbaric oxygen, drugs for sensitizing hypoxic cells, chemotherapeutic “radiosensitizers”) or with non-conventional temporal distribution of the dose (accelerated fractionations). Alternatively, NTCP curves can be moved to the right using radioprotective drugs, with treatment techniques aimed to reduce the irradiation of healthy tissues (conformal or intensity modulated RT) and, also in this case, by changing the chronology of RT (hyperfractionated treatments) [3].

## Concurrent Chemoradiation

The administration of chemotherapeutic drugs during RT, as anticipated, has the aim to broaden the therapeutic interval by improving the TCP. The theoretical advantages of this combination therapy are many:

1. there is a spatial cooperation, where RT cures cancer locally while chemotherapy prevents its metastatic spread;
2. there is an enhancement of the local RT efficacy due to the radiosensitizing effect of several chemotherapy drugs;
3. often the toxicity of these two treatments is different and therefore there is no significant deterioration of individual side effects.

In particular, the improvement of local RT effects occurs through different bio-molecular mechanisms: inhibition of sublethal damage repair, cell cycle arrest in the most radiosensitive phases, and improved tumor oxygenation.

Furthermore, *in vitro*, *in vivo* studies and later even clinical trials have documented the radiosensitizing effect of different chemotherapy drugs (fluoropyrimidine, mitomycin C, cisplatin and derivatives, gemcitabine) both in exclusive treatments (esophageal cancer, NSCLC, H&N cancer, anal canal carcinoma, cervical carcinoma) and in adjuvant therapies (carcinoma of the rectum, stomach, pancreas, tumors of the brain).

More recently the effect of combining RT with targeted drugs as anti EGFR (cetuximab), tyrosine kinase inhibitors (gefitinib, erlotinib) and antiangiogenic drugs (bevacizumab, sunitinib) has been assessed.

## EXTERNAL BEAM RT

### Equipment and Radiation Beams

The treatment machine most commonly used in modern external beam RT is the linear accelerator (**LINAC**). Since the beginning of its invention, there has been an increasingly sophisticated evolution of LINACs. However in developing countries, cobalt-60 therapy machines are still the backbone in most RT departments since the technology is easier to support and maintain than LINAC with the available human resource. The LINACs eclipsed the cobalt units because they are capable of producing two different beams of radiation which are:

#### Photon beams

The photon beams are characterized by the ability to penetrate deep into tissues (depending on their energy) and therefore they are used in RT for “deep” neoplasms.

#### Electron beams

The electron beams are absorbed much more on the surface (also in this case based on their energy); for this characteristic they are used for the treatment of more superficial tumors (e.g. skin carcinoma).

Modified LINACs can be used where stereotactic RT (**SRT**), stereotactic radiosurgery (**SRS**) and standard RT are done. The LINAC should be equipped with special cylindrical collimators or micro-multileaf collimator and specialized treatment planning software is needed. The system is often composed of a micro-multileaf collimator system with leaf thickness ranging from 3 to 5.5 mm. Two kVp orthogonal X-ray cameras are mounted on the system to track bony landmarks or implanted fiducials in relation to the digitally reconstructed radiograph generated from computed tomography (**CT**) simulations. The patient is then aligned in the treatment position in accordance with identified positions of markers.

As the evolution of technology still continues in the era of advanced computing power and microprocessors, more complex accelerators (synchrotrons and cyclotrons) are able to produce hadron beams meaning particles beams. These ion beams (protons and ions) can simply be considered to be the next logical step in the advancement of RT. However, light ions are not necessarily competitive to conventional RT but they could simply provide an additional treatment modality for particular cases. These radiation beams, depending on their specific characteristics, have a very high biological effect and/or by the ability to hit the target with great precision and therefore to obtain the maximum saving of healthy tissues. Dose conformation of the light ion beams allows to achieve reduced entrance dose with a low dose behind the tumor as a result of the Bragg peak effect and differential biological effects in tumor/ normal cells tissue. Protons and ions are used for the following reasons:

1. Scattering is minimal compared with x - rays and cobalt - 60
2. Most of their energy is deposited near the end of the range where the dose increases at high value and then drops off rapidly to zero.
3. The proton beam has a sharp dose fall-off near to zero shortly after the spike in dose distribution.

Irradiation with protons is generally realized with pencil beams. A spinning circular modulator is positioned in the beam to spread out the width of the high dose distribution. The modulators can be adjusted to obtain the required spread out Bragg peak (**SOBP**).

## Evolution of Techniques of External Beam RT

In recent decades there has been a radical evolution of RT techniques. This development, in particular focused on the methods of targeting with emphasis on identification and definition of the RT target.

In the past, RT was not guided by images but only by the view of the radiation oncologist. Irradiated tumors were mainly superficial (both benign and malignant) and either treated with BRT or simple external beam RT equipments (superficial x-ray machines, orthovoltage x-ray machines, or roentgen therapy) (Figure 2). Currently we define such techniques as one dimension (**1D-RT**), since targeting was based on estimation of the single extension (size) of the tumor.



**Figure 2:** Orthovoltage RT machine

With the introduction of external beam RT devices with higher energy beams (telecobalt and telecesium therapy) it was possible to irradiate also “deep” tumors (Figure 3).



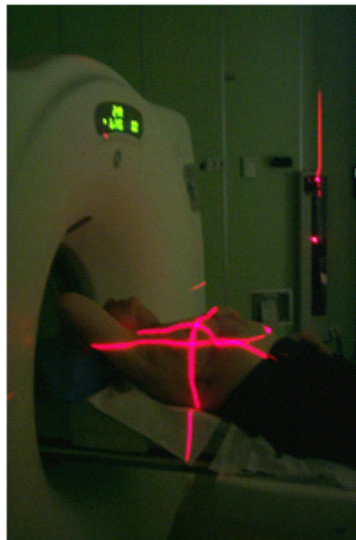
**Figure 3:** 60-Cobalt machine for external beam RT

For this reason it was necessary to use radiography equipment (conventional simulator) (Figure 4) to identify or at least to estimate the site and size of the tumor, with a technique later defined as two dimensional (**2D-RT**).



**Figure 4:** Conventional simulator

Subsequently, the introduction of CT allowed a better definition of the site and extent of the tumors, although not entirely detectable with conventional radiology methods (e.g. prostate cancer, tumors of the pancreas). The CT scans have the additional advantage of allowing dose calculation based on tissue density. Therefore, the introduction of CT-simulators in RT allowed the use of this method for more precise targeting of all cancers (Figure 5).



**Figure 5:** CT-simulator; on patient skin are clearly visible the laser projections for patient alignment.



In parallel, the introduction of LINACs equipped with advanced systems of collimation of the beam (multileaf collimators: MLC) has allowed to shape the profile of the radiation beam to adapt it to the shape of the tumor (target) (Figure 6). These newer three dimensional (**3D-RT**) techniques (or conformal RT) allowed a better sparing of healthy tissues and consequently the escalation of the dose delivered to the tumor. Furthermore, the possibility to use in a dynamic way the MLCs, together with the introduction of new algorithms for the calculation of the dose distribution, allowed to optimize conformal-RT with the introduction of the intensity modulated RT (**IMRT**), enhancing further sparing of the healthy tissue.



**Figure 6:** linear accelerator

The availability of more advanced imaging systems has also allowed to evaluate how the target may undergo changes of position and morphology during RT. This awareness produced further evolution of the techniques that took into account the “time factor”. These techniques, generally defined as four dimensional (**4D-RT**), have exploited the possibilities of new imaging methods (Image Guided RT: IGRT) also from the point of view of the progressive adaptation of irradiation to the progressively reduced dimensions of the target (adaptive RT).

Finally, a further frontier for the development of RT is represented by the growing awareness of the biological heterogeneity of the tumor. Within the tumor, in fact, there are areas characterized by different radio sensitivity (for example in relation to different genetic characteristics or different oxygenation levels). From this knowledge came the five dimensional (**5D-RT**), aimed at the delivery of differentiated RT doses according to the biological characteristics of the different sub volumes of the target.

# BRACHYTHERAPY

BRT is based on the placement of sealed radioactive sources close or directly into or near the tumor, to deliver radiation at a short distance by interstitial, intracavitary, or surface application. The theoretical advantage is the rapid dose fall off with increasing distance from the radiation sources following the inverse square law. This rapid dose fall off favors the administration of a high dose to the tumor with a low dose to surrounding organs. There are several techniques that differ depending on the treatment modality. From the point of view of treatment time, we define:

1. temporary implants (with removal of the sources at the end of therapy)
2. permanent implants.

Depending on the site of the source implant, we define:

1. interstitial BRT: sources implanted within the tumor tissue,
2. intracavitary BRT: placement of sources within natural cavities (e.g. uterine cavity),
3. intraluminal BRT: placement of sources within the lumen of an organ (e.g. cancer of the esophagus),
4. contact BRT: placement of sources on the surface of the tumor (e.g. carcinomas of the skin).

Furthermore, according to the timing of the source positioning into the applicators (containers that facilitate the positioning of the source close to the tumor), we define:

1. preloading technique: sources are prior placed inside the applicator, which subsequently is placed at the site of treatment; a disadvantage of this older technique is represented by prolonged exposure of health personnel to radiation;
2. afterloading technique: source is positioned in the applicator after it had been placed at the site of treatment; afterloading treatments can be based on manual afterloading (in which the operator manually positions the source in the applicator);
3. remote-afterloading: the source is placed in the applicator by automated systems while operators are at a safe distance from the sources.

Finally, depending on the rapidity with which the source releases radiation, we define:

1. Treatment with low dose-rate, in which the irradiation has a duration of a few days; these kind of treatments require overnight accommodation of the patient in special wards, with appropriate shielding of radiation from other personnel and the public.
2. Treatment with high dose-rate, in which patients are subjected to multiple and brief applications of radiation. Usually this kind of treatment can be fractionated hence patients are able to stay in the hospital only for the duration of single treatment.

# TREATMENT PLANNING

## Rationale of Treatment Planning

The goal of radiation therapy is to irradiate tumor bearing tissues while sparing normal structures. According to Williams & Thwaites [4], the aims of treatment planning can be summarized as follows:

1. Definition and localization of the target volume for treatment;
2. Definition and outline of the target volume and other anatomical structures position, which may affect the dose distribution or for which dose constraints should be evaluated;
3. Calculation of the resultant dose distribution in the patient;
4. Preparation of an unambiguous set of treatment instructions for the radiographers;
5. Accurate and homogeneous delivery of the prescribed tumor dose to achieve the highest tumor control rate;
6. Delivery of the lowest possible dose to the organs at risk (**OAR**) with acceptable morbidity.

## Virtual Simulation

Virtual simulation is a process by which treatment fields are defined using patient CT image data and treatment unit geometric information. Specialized software is used to contour patient anatomy, set up the treatment beam arrangement, identify the location of patient markings and design blockings for the treatment fields. Most of the simulation process is completed without the presence of the patient. Because the virtual simulation software contains treatment machine parameters, the limitation of conventional simulators such as the presence of image intensifiers and possible difference between simulators and treatment unit geometry, do not interfere with the field arrangement [5].

Virtual simulation is a computer-based simulation that was introduced by Sherouse and colleagues in the mid 1980s. Virtual simulation uses computer software that allows the user to carry out simulation at a computer monitor instead of a real simulator. This software simulates the therapy machine and operates on a digital representation of the patient derived from the CT scans being this process is known as virtual simulation [6].

The images are obtained from the CT scanner with the patient lying on a flat CT couch in the required treatment position. The data is then exported to the virtual simulation software which has the capability of 3D reconstruction usually required for treatment planning. The radiation oncologists and radiation therapists will draw the external contour of the patient, the target volumes and organs at risk. After the anatomy modeling has been done on the patient model, all the data is transferred to the planning computer software. Once the physicist has placed the radiation beams and isodose distribution is produced, the data is then passed back to the virtual

simulation software where the digital reconstructed radiographs (**DRR**) can be produced. DRR are used as reference images for subsequent verification on the treatment machine.

## 3D-CONFORMAL RT

### Introduction

Conformal RT is defined by Kutcher and colleagues [7] as, “an attempt to shape the high dose volume of the radiation treatment to the tumor while minimizing the dose to surrounding normal tissue.” Clinically this means that the aim for conformal therapy is to maximize tumor control while giving as low as reasonable achievable radiation to normal tissue to reduce normal tissue toxicity [7]. The main features of 3D-CRT (conformal RT) have been previously anticipated. Conformal RT conforms or shapes the prescription dose volume as closely as possible to the PTV in terms of adequate dose to the tumor while at the same time keeping the dose to specified organs or normal tissues at risk below their tolerance dose. Several number of beams are often used as compared to standard RT techniques in order to reduce the high dose region. The conformal RT chain is based on 3-D target localization, 3-D treatment planning and 3-D dose delivery technique [8]. Furthermore the concept of conformal dose distribution has also been extended to include clinical objectives such as maximizing tumor control probability (**TCP**) and minimizing normal tissue complication probability (**NTCP**) [9].

The use of conformal therapy was initially restricted to radical treatments. It is particularly useful in the following situations:

1. where the microscopic/macrosopic tumor remains in situ (e.g. pre-operative treatment for carcinoma of the rectum);
2. where increasing the total tumor dose is expected to be advantageous (e.g. in prostate, head and neck tumors, or lung cancer);
3. where the treatment volume include sensitive normal tissues (e.g. brain and lung);
4. for pediatric tumors and other special sites such as the breast where limiting the volume of normal tissue irradiated (e.g. growing muscle, heart, etc.) is especially important;

Conformal RT comprises a series of elements, all of which are essential to making it work successfully:

1. localization of the disease and normal organs,
2. immobilization of the patient,
3. computed tomography (**CT**) scan,
4. outlining of the target and other organs [7].

When patients come to planning for the first time, they should be positioned in a way that will be reproducible. Immobilization devices are used and recorded down so that the position can be reproduced during RT delivery. A simulator may be used to determine the best positioning of the patient before the patient goes for the CT scan. Appropriate reference lines /or marks are placed on the patients skin or cast. The patient is then scanned in the treatment position in the immobilization devices on a flattop couch to mimic the treatment unit table. Alignment lasers in the CT scanner are used to setup the patient exactly the same way as at the simulator couch using the marks drawn on cast or on the patient's skin.

After the scan has been done the radiation oncologist, will draw the target volumes: the gross tumor volume (**GTV**), the clinical target volume (**CTV**) and the planning target volume (**PTV**). Barret and colleagues [10], defined the GTV as “the demonstrable macroscopic extent of tumor that is palpable, visible or detectable by conventional radiography, ultrasound, radioisotope, CT or MRI (magnetic resonance imaging).” The CTV is, “the margin around GTV which represents the region of not palpable undetected microscopic tumor or primary tumor infiltration.” Finally the “PTV is the margin of error beyond CTV which compensate for CTV tissue movement out of the treatment volume due to setup errors or internal patient movement.” According to ICRU Report 50, in 3D-RT treatments, the minimum dose to PTV should not be less than 95% of the prescribed dose and the maximum dose to the PTV should not be greater than 107% of the prescribed dose. Conceptually, PTV is composed by the integration of two different margins to be added to the CTV: 1) the innermost is the so-called Internal Margin (**IM**), which is the margin to be added to the CTV to take account of the possible movements of the CTV (organ motion) in the patient; 2) the outermost is the so-called Set-up Margin, which takes into account the possible deviations of the set-up of the patient, generally represented by the positioning inaccuracies. Treated Volume (**TV**) is the volume of tissue receiving the prescribed dose, usually larger than PTV, given the impossibility of perfectly fitting the shape of prescription isodose to the PTV shape.

Three dimensional treatment planning is based on: 1) Beam's eye view perspective; 2) Non-coplanar beams; 3) 3D dose calculation; 4) dose display in all planes (transverse, sagittal and coronal); 5) dose volume histograms [7].

The radiation beams are positioned in three dimensional spaces to match optimally the beams to the planning target volume shape, to minimize the treated volume (all the area that is receiving radiation) and keep the doses to critical organs within acceptable limits. After the beams have been positioned the contoured structures are displayed on a computer monitor in different colors and they can be displayed from the beams eye view perspective. The shielding blocks and non-coplanar beams can be used where necessary [4]. Based on CT image data and beams characteristics, radiation doses deposited at all points within the patient are computed. Each beam is assigned an optimum weight and the sum of the dose distribution of all beams to all points is also computed. These data, which constitutes a 3D dose distribution, are used to create

displays in which the dose distribution, overlaid on the patient's image or anatomical display is shown. Based on an iterative process (forward planning) the dose distribution is progressively optimized. Plan evaluation, optimization and comparison are facilitated by the elaboration of the Dose Volume Histograms.

## Use of Multileaf Collimators (MLCs) in Conformal RT

Multi-leaf collimators are used in 3D CRT (three dimensional conformal radiation therapy) for shaping the beams so that the radiation beam match the contour of the PTV and customizing radiation dose delivery. The leaves of the MLCs are made of tungsten to minimize undesired radiation transmission. They also have the ability to adjust beam intensity rather than just changing the shape. Conformal RT is based on:

1) CT-simulators: a prerequisite for 3D target localization is a CT equipment dedicated to RT, possibly equipped with a gantry with a diameter larger than the standard CT-machines (to allow the definition of the patient body profile even with immobilization systems) and equipped with laser systems to define the position of the patient (necessarily the same position during CT-simulation and treatment);

2) Treatment Planning Systems (**TPS**), able to allow the 3D-reconstruction of target and healthy organs through the process of contouring (delineation or segmentation) by the operator. According to this process, the TPS reconstructs the three-dimensional anatomy of the patient. These systems allow calculating the dose distribution within the patient thus allowing to establish the better treatment modality based on the clinical-anatomical patient characteristics. The adequacy of the planned treatment, compared to therapeutic targets, is based on both qualitative methods (evaluation of the "coverage" of the target by the prescribed dose) and quantitative parameters (dose-volume histograms, meaning a graph summarizing the distribution of dose in the tumor volume and in the volume of the different healthy organs).

3) Linear accelerators equipped with MLC, to allow the use of beams shaped in a manner corresponding to the profile of the target from the different possible directions of the RT beams; accelerators must also be equipped with verification systems in order to evaluate the correctness of the irradiation geometry (**EPID, cone-beam**) and must be connected with suitable and secure computer networks with the TPS. In order to ensure treatment reproducibility, with high accuracy and precision thus immobilization systems for the patient (thermoplastic masks, support systems for body and limbs) should be in place.

## Inverse Planning

Inverse planning is a procedure based on a treatment planning software which is designed to allow the user to program optimal isodose distribution around the tumor volume, while at the same time prescribing maximum doses to be delivered to the tumor volume. Target volumes and critical structures are defined and beams are arranged in an attempt to maximize the dose to

targets while minimizing the dose to critical structures [5]. The clinical objectives are specified mathematically and a computer optimization algorithm automatically determines the beam parameters (fluence and weights) that will lead to the desired dose distribution. Limits to the specified critical organs are identified at the same time. Only the beam arrangements are set up by the planner.

The treatment planning program will then generate the dose distribution to accommodate the goals of the patient. IMRT inverse planning systems calculate dose distributions and create MLC patterns based on initial dose delivery and avoidance parameters. The intensity of the beams is then altered, by opening and closing the MLC, to achieve the requested doses. In most cases, thousands of plans are generated and then evaluated using parameters and constraints set by the radiation oncologist and the physicist. The plans are then evaluated to see if they meet the objectives established for the patient. The dose distribution can be shaped so that high-dose volumes are produced conforming to planning target volumes that are concave in shape. The planning system then computes alternative intensity patterns until the best possible solution is achieved [5].

## 4-Dimensional CT Scan (4DCT)

The ability to account for motion during all stages of the RT process is the underlying basis for 4D RT. Respiratory motion is one of the important problems in the management of radiation therapy for “thoracic and abdominal tumors”. CT scans acquired synchronously with the respiratory signal can be used to reconstruct a set of (3-D) CT scans, representing the 3-D anatomy at different times (or respiratory phases). This collection of 3-D CT data sets is called 4-D CT, which describes the snap shots of patient’s 3-D anatomy over a periodic respiratory signal. 4-D CT scans can be used for 4-D treatment planning to explicitly account for respiratory motion [9]. Traditionally, target definition is based on a single planning CT scan acquired during quiet breathing. When tumors in the thorax and abdomen are imaged using fast multi-slice CT scans, these ‘random’ scans may generate artifacts of the patient’s anatomy, and give an inappropriate representation of the shape, volume and position of normal organs and tumors [11]. During 4DCT scanning, which is also known as respiration-correlated CT scanning, spatial and temporal information on organ mobility are generated by scanning while synchronously recording respiration waveforms. A common approach involves co-recording respiratory signals using infrared-reflecting markers on the upper abdomen of the patient during quiet breathing.

## INTENSITY MODULATED RT (IMRT)

In the traditional external beam photon radiation therapy, most treatments are delivered with radiation beams that are of uniform intensity across the field (within the flatness specification limits). Occasionally, wedges or compensators are used to modify the intensity profile to offset contour irregularities and/or produce more uniform composite dose distributions such as in

techniques using wedges. However IMRT refers to a radiation therapy technique based on inverse planning in which nonuniform fluence is delivered to the patient with different beams to optimize dose distribution.

The planner specifies the treatment criteria for plan optimization and the optimal fluence profiles for a given set of beam directions are determined through “inverse planning”. Therefore, IMRT is a treatment technique using beams with varying intensities to conform the high dose region to the target volume while sparing normal tissue structures, enabling dose escalation and improved local tumor control. In fact, IMRT is widely used in head and neck tumors in order to limit doses to normal structures such as the parotid glands, oral mucosa and spinal cord, and single-institution studies show high rates of loco regional control.

The fluence files thus generated are electronically transmitted to the linear accelerator, which is computer-controlled, that is, equipped with the required software and hardware to deliver the intensity modulated beams (**IMBS**) as calculated. A simplified version of IMRT is represented by ‘forward planning’ IMRT, an extension of 3D conformal treatment planning although an increased number of fields / segments are required. Beam intensities are modulated using physical, virtual or dynamic wedges, tissue compensators, full or partial transmission blocks, asymmetric jaws and MLC. In this case, designing the modulated fields is an interactive trial and error process based on human intelligence that begins after a conventional 3D dose distribution has been computed and evaluated [9].

The superiority of IMRT compared to 3D-RT has been proven both in planning studies. Among the advantages of IMRT is the possibility to deliver a simultaneous integrated boost (**SIB**) to the macroscopic tumor, with clear dosimetric advantages with respect to a sequential or concomitant boost delivered with 3D-RT. A theoretical disadvantage of IMRT is that this technique allows a better conformation of “high doses” but is associated with irradiation of larger volumes with “low doses”. This low-dose irradiation of large volume is generally not associated with worse short and medium term toxicity, but could theoretically be associated with a higher incidence of radio-induced tumors.

As a profound characteristic of IMRT being the use of beams with variable fluence. This fluence modulation can be achieved in several ways. The easiest way is represented by the “step and shoot” technique. This is based on the irradiation for each predetermined direction of the beam, of a series of “segments” in sequential steps. By summation of these segments the fluence modulation of any single beam is carried out. Furthermore, from the summation of the different modulated beams the dose distribution required by the operator can be achieved.

The same result, in shorter times, can be achieved using the “sliding windows” technique, where the fluence modulation is dynamically produced through the continuous movement (opening and closure of successive areas of the beam) of the MLC leaves.



IMRT treatments can be performed with “hybrid” treatment machines like “Tomotherapy”. This accelerator is structurally similar to a spiral-CT; it allows a modulated irradiation with a rotational technique with the dose delivered during a translational movement of the patient bed. Tomotherapy even allows to obtain axial tomography images through the use of detectors using the same radiation (of megavoltage energy) used for the treatment.

Further evolution of IMRT techniques still continues to take place as are represented by:

- 1) Intensity Modulated Arc Therapy (**IMAT**): in which the continuous movement of the leaves for the beam modulation is combined with the continuous movement of the gantry; with this rotational technique it is possible to obtain further optimization of the dose distribution, especially for small targets;
- 2) Volumetric Modulated Arc Therapy (**VMAT**): in which the prior technique is further optimized thanks to the possibility to vary during the irradiation, the speed of rotation of the gantry and the dose-rate of the accelerator.

## IMAGE GUIDED RT (IGRT)

IGRT has been defined as the use of frequent imaging in the treatment room so that treatment decisions can be made on the basis of these images. With optimal IGRT approaches, knowledge of the target location is instantly available and uncertainties associated with daily positioning variation of the patient and tumors can be reduced, thereby permitting reduced CTV to PTV margin. Consequently, reduction in doses to normal tissues and/or radiation dose-escalation with improvement in tumor control rates is possible.

The way to check the geometric correctness of treatment is based on Electronic Portal Imaging Devices (**EPID**), with images produced by the same radiation beams used for treatment.

Many manufacturers have developed new linear accelerators with volumetric imaging devices that are physically attached to the treatment delivery system and permit MV and kV CT scans (Figure 7). For example, the kV cone beam CT images offer sufficient direct soft tissue visualization to localize many target volumes or critical structures.

These advanced techniques are used to assess the “organ motion”, i.e. the movement of the target due to physiological phenomena (e.g. respiratory movements, filling of bladder or rectum). They also allow evaluation and correction of set-up deviations. Cone-beam-CT uses an orthovoltage radiation beam to realize axial tomographic images during the gantry rotation. In this case, unlike what happens with the EPID and Tomotherapy, the radiation beams used for image production are not those used for the treatment but those produced by a traditional X-ray system, mounted on the same gantry of the linear accelerator. The use of these orthovoltage (and not megavoltage) radiation beams significantly improves the image quality.



**Figure 7:** linear accelerator with kilo-voltage radiologic system (cone-beam CT).

Furthermore, IGRT regards to the use of advanced morphological or functional imaging techniques to define the target or sub-volumes of the target. In some cases, for example, it is well known that imaging techniques different from the traditional CT (and therefore from the CT-simulator used for planning) allowing a better definition of the macroscopic tumor. This is the case of lung and esophageal cancers, where  $^{18}\text{F}$ FDG-PET allows a better tumor definition, while for H&N or cervical tumors MRI allows to achieve the same improvement.

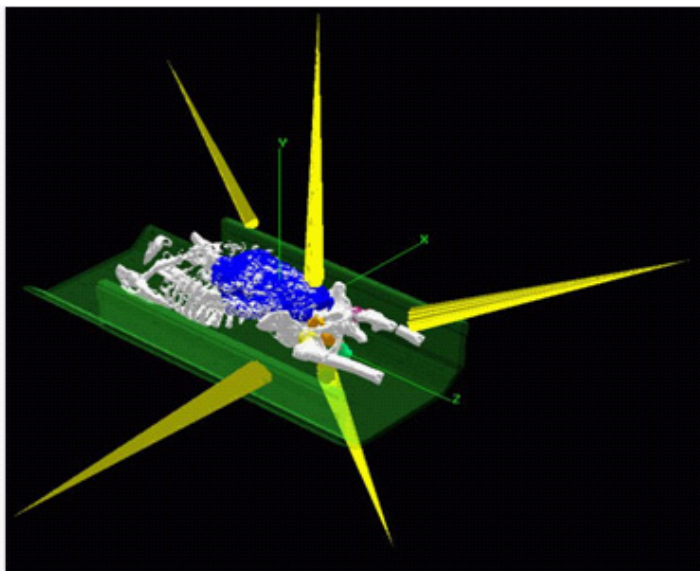
Methods of IGRT even more advanced are those in which the use of PET tracers different from  $^{18}\text{F}$ FDG, or the use of MRI with spectroscopic or perfusion techniques, allow to obtain more specific information on the biology of different tumor areas, in terms of metabolism, cell proliferation or oxygenation. Since these factors are related to radioresistance, these methods theoretically allow modulating the dose distribution in order to adapt it to tumor biology.

IGRT frequently requires the use of image fusion technique, able to transfer the information obtained from the different imaging techniques on the images of the CT-simulator used for treatment planning.

## **STEREOTACTIC RT (SRT)**

The term SRT refers to precise positioning of the target volume within three dimensional (**3D**) spaces. SRS is a specialized form of radiation whereby a high dose of radiation is delivered to a very specific area in the body. SRT is a technique that was originally devised for functional neurosurgery to accurately perform intracranial biopsies, but has been adapted into a precision

RT technique for the treatment of small inoperable lesions, most commonly located in the brain. In fact, the first use of SRT took place in malignant or benign intracranial diseases. It is based on the localization of a target within an independent three-dimensional co-ordinate system defined by a SRT frame (Figure 8). SRS was introduced by Lars Leksell in 1949 when he reported on the treatment of the brain tumour using many small stationary treatment beams and SRT frame. More recently, also extracranial SRT has been introduced.



**Figure 8:** irradiation of a pelvic tumor using non-coplanar fields.

SRT is a treatment in which a high RT dose is administered in few fractions and generally on a relatively small target. An extreme variant of SRT is SRS in which the treatment is performed in a single fraction, delivered to the tumor using multiple non - coplanar beams. The target volume is usually localized in space using an external frame of reference that can be related to the treatment machine.

Furthermore it uses sophisticated patient immobilization systems with SRT coordinates to reproduce the placement of the isocentre with an accuracy of less than 1 mm. Non-coplanar arcs are directed at the tumor by changing the treatment table rotation between treatment arcs. By distributing the dose delivered to normal tissue over an even greater area, the high dose is increasingly focused on the target volume. This has in recent times promoted several methods of hypofractionated RT.

The purpose of SRT treatments is completely different compared to traditional RT. In fact, in standard RT the treatment is divided into many fractions in order to promote the cells redistribution in the different phases of the cell cycle and to promote the progressive tumor re-oxygenation. Furthermore, the use of small doses per fraction reduces the risk of late toxicity. On

the contrary, SRT has an “ablative” purpose, i.e. the aim is to produce the necrosis of the tumor cells by using high intensity hypofractionated and accelerated treatments. The theoretically high risk of late side effects (due to hypofractionation) is concentration of the dose only within the target.

SRS and SRT requires treatment planning. Large amount of data is needed for complex dose calculations, treatment setup parameters, monitoring of dose delivery and quality assurance procedures. CT scans are required for tumor localization and to acquire patient geometric information. In centers which have access to MRI and PET scans, these scans are taken and fused with the CT images to provide even more detail and better evaluation of the extent of the disease.

SRT treatments are characterized by a rapid dose fall-off at the target borders. This result is generally obtained with the use of several beams, often even by using non-coplanar beams and even more frequently with the use of arc therapies. The use of these rotational treatments, in fact, favors the concentration of the dose in small volumes and the reduction of the dose to healthy organs by “diluting” the same dose in very large volumes. The same dose prescription process is based on this purpose to obtain a rapid dose fall-off outside the target.

In SRT treatments the aim to concentrate the dose in a small volume may take priority over the traditional tendency, of “classic” RT, to achieve a homogeneous target irradiation. To obtain this result, in fact, the dose is generally “prescribed” not to a point within the PTV (as indicated by the ICRU reports) but to an isodose placed at the target periphery, so that the target is entirely “covered” by the prescription isodose. This type of prescription has the consequence of often delivering much higher doses compared to the prescribed dose, at least in some target sub-volumes.

The rapid dose fall-off at target periphery makes the treatment accuracy of absolute importance, in some way similar to what happens for BRT treatments. Indeed, small deviations between planned treatment and delivered treatment are likely to produce severe PTV under dosing and/or dangerous healthy organs overdosing. The critical issue of SRT is thus represented by management of organ motion and set-up accuracy problems. Therefore, it is not a coincidence that the first SRT treatments were performed on intracranial lesions, a site with minimum organ motion problems and with anatomical characteristics (rigidity of the skull) able to ensure a perfect immobilization of the patient at the irradiated site.

However, over the years, SRT was even applied to extracranial tumors, thanks to: 1) the introduction of more efficient immobilization systems, in some cases with SRT localization methods; 2) the evolution of organ motion (IGRT, gating, tracking) and set-up accuracy (IGRT) management techniques.

Currently SRT is used in almost all body sites, representing in some cases an alternative to surgical treatment (e.g. inoperable lung cancer due to comorbidities or advanced age), or even

as standard radiation therapy protocol (e.g. prostate cancer, reducing the duration of treatment from 7-8 weeks to 5 days). SRT is also used in the treatment of oligometastatic patients (i.e. patients affected by widespread disease but with only few metastatic lesions). The combination of chemotherapy and SRT can often allow one to plan treatments for curative purposes in patients who, only a few years ago, were palliative treatment candidates only for palliative treatments.

The growing interest in SRT fostered the technological evolution with development and marketing of treatment machines specifically designed for this technique. Sophisticated image guidance is a feature common to these treatment systems. Systems equipped with image guidance minimize the uncertainty associated with tumor localization. Most delivery systems allow integration of immobilization devices. Examples are:

1. Gammaknife: a therapy machine dedicated to intracranial lesions, equipped with multiple  $^{60}\text{Co}$  sources. Leksell gamma knife models C is the latest model of gamma knives which was introduced in the United States in 1999. This gamma knife contains 201 cobalt sources that generate gamma rays beams, ranging in energy from 1.17 to 1.33 MeV, all focused on the same isocenter, realizing a treatment based on multiple fixed non coplanar beams. There are four helmets that vary in diameter in which the beam of the cobalt - 60 sources are collimated. Four different collimator sizes are available (4 mm, 8 mm, 12 mm, and 18 mm). The collimator size used depends on the area and volume of tissue to be treated.

2. Cyberknife: a linear accelerator mounted on a robotic arm enabling target irradiation by a very large number of different beam directions. The robotic arm, along with systems tracking fiducial markers implanted into the tumor, is able to allow the irradiation of movable target.

3. Flattening-Filter-Free (**FFF**) accelerators: linear accelerators modified to significantly increase the dose-rate and thus to significantly reduce treatment duration; this feature allows a quick administration of very high doses to minimize the problems related to intra-fraction changes.

## ADAPTIVE RADIATION THERAPY

Although the term “adaptive RT” has different meanings, the simplest meaning regards the adaptation of the treatment technique to set-up or organ motion changes. A widespread way of “adaptive RT” in this sense is represented by the production and registration of several portal images (or cone-beam CT) during the first RT fractions. Based on the analysis of these images the planned treatment can be changed (for example by changing the width of the RT field) to “adapt” it to the variations (in terms of organ-motion or set-up deviation) actually measured on the patient.

A more complex meaning of “adaptive-RT” is the adaptation of the treatment to target variations and patient anatomy occurring during the treatment. In fact, it is well known that during RT, especially for most radiosensitive tumors, an early tumor response can take place with

a marked reduction of the neoplastic mass. Therefore, the initially planned dose distribution can get inappropriate after some week of RT, e.g. due to a tumor reduction able to change radiation absorption and therefore with irradiated volume exceedingly large compared to the size of the residual tumor.

In addition, during RT relevant anatomical variations can take place, able to substantially modify the dose distribution. An example of these changes are weight reductions occurring in patients suffering from radiation-induced nausea and anorexia (e.g. irradiation of the upper abdomen) or weight gain occurring in patients receiving supportive therapy with steroids (e.g. irradiation of brain tumors).

Other forms of adaptive-RT include IGRT the procedures we mentioned earlier, in which the prescribed dose of RT is adapted to the biological characteristics of the different tumor subvolumes. More sophisticated adaptive-RT modalities are those using imaging systems able to evaluate tumor response during RT. These modalities can theoretically allow a further RT adaptation, in the course of RT itself, with intensified therapy delivered to the subvolumes showing a less favorable response.

Adaptive RT aimed at a modulated dose within the target according to the biological tumor characteristics, is often integrated with the Simultaneous Integrated Boost (**SIB**) IMRT techniques. In other words, the IMRT-SIB technique is useful to prescribe and administer different doses to different tumor subvolumes (the so-called “dose-painting”). An ultra-sophisticated modality of this technique is represented by “painting by numbers”, in which a different dose is prescribed to any single tumor voxels, based on imaging data (for example, according to the metabolism measured in that voxel by <sup>18</sup>FDG-PET).

## INTRA-OPERATIVE TECHNIQUES (IORT)

IORT is a special radiotherapeutic technique that delivers in a single session a radiation dose the order of 10-20 Gy to a surgically exposed internal organ, tumor or tumor bed. IORT attempts to achieve higher effective doses of radiation while dose-limiting structures are surgically displaced. Thus IORT combines two conventional modalities of cancer treatment, surgery and RT with the potential to improve the therapeutic ratio of local control versus complications.<sup>8</sup>

For an IORT program to be successful, several health professionals are required. These professionals include surgeons, radiation oncologists, medical physicist, anesthesiologist, nurse, pathologist and radiation therapist. IORT requires an operating room (**OR**) for surgical procedure and a treatment room for delivery of the radiation dose to the patient. Another option is to merge the OR and the treatment room in one room, to avoid patient transfer. In this way the operating room will have to be shielded for a dedicated radiation treatment unit permanently installed. A third option is based on the use of small, mobile LINAC (electron beam only) that can be moved in the same day from one operative room to another.

A transparent cone connected with the accelerator is placed on the tumor or tumor bed (after surgical removal) to deliver a RT dose in the areas with higher risk of local recurrence.

Traditionally, the following points were considered advantages of this technique: 1) the exposure of the tumor or of the tumor bed allowing an accurate “visual” definition of the target; 2) the ability to mechanically displace, during the surgical procedure, at least some of the surrounding healthy organs in order to limit their irradiation.

On the contrary, the following issues are considered as disadvantages of IORT: 1) irradiation with a single fraction increases the risk of late toxicity; 2) irradiation during surgery with a prolongation of anesthesia times and theoretical risk of infections.

Different technical solutions have been proposed to realize IORT treatments: a) by moving the patient from the operating room to the RT bunker during the surgical procedure; b) by realizing IORT-dedicated surgical areas (e.g. operating rooms built inside bunkers containing the accelerator); c) use of mobile accelerators able to be transported within operating rooms.

There are three different modalities that can be used to deliver IORT, they include; orthovoltage x-rays, electron beams and high dose rate iridium-192 BRT sources. Van Dyk [12] stated that, “the choice of treatment modality for IORT will have a definite effect on the overall dose homogeneity, with an electron beam of carefully selected energy producing the most homogenous distribution. Normal tissue sparing is as important in IORT as it is with standard radiation therapy. Normal tissue sparing can be done by selecting a radiation modality with a rapid dose fall-off beyond the treatment volume or by shielding or displacing the sensitive structures from the primary radiation beam.

An applicator system must be chosen once the radiation modality and location of treatment unit is selected. The applicators serve three purposes: (1) they define the target area; (2) shield tissues outside the target area from radiation and (3) keep sensitive tissues from falling into the target area during irradiation. For the treatment verification in IORT, fiber-optic imaging devices and periscope system are used to visually identify any critical structures adjacent to the treatment field.

IORT is used to treat tumor sites which can be exposed surgically and isolated from nearby sensitive tissues. Tumors including pancreatic, gastric and rectal carcinomas have been commonly treated with IORT. Other sites such as the bladder, breast and gynecological malignancies have also been treated with IORT [12].

## **MOTION MITIGATION TECHNIQUES**

Some aspects about this issue were already anticipated in the previous paragraphs and here some more concepts are added. The obvious prerequisite for the therapeutic success of a RT treatment is the correspondence between the planned and the delivered treatment, during the

entire duration of any single fraction. Unfortunately, in the clinical setting the treatment actually given may be different from the planned one due to different problems. These can arise:

1. from the presence of physiological movements of the organs that can affect both the target position and the position of the healthy organs (organ motion),
2. from the presence of patient displacements due to positioning and/or immobilization errors (set-up errors).

These variations may have different timing and therefore they can be classified as:

a) Inter-fraction changes: meaning that variation in patient position occurring between different fractions, such as those related to some error in the positioning of the patient or those related to organs position, due to filling or emptying of hollow organs (rectum, bladder).

b) Intra-fraction changes: meaning geometric variations occurring during the single fraction, as for example changes due to unintentional patient movement or to organs displacements occurring in a short time in the same single fraction. These latter are typically represented as movements induced by breathing. However, it was shown that even bladder filling can significantly change during a single fraction, especially if the duration is prolonged.

Obviously, in order to control these variations, systems aimed at planning verification are needed. A first level, as we have previously pointed out, is represented by EPID tests. From the organizational point of view, this is a simple type of verification because it is performed with the same machine and radiation beams used for tumor irradiation.

A limitation of this method is represented by the poor image quality (megavoltage beams, scarcely efficient for images production compared to kilovoltage radiation). Furthermore, independently from the energy, X-ray beams do not allow to visualize soft tissues. EPID systems, therefore, are mainly used to check the patient position based on bony landmarks. However, the position of radiotransparent organs can be checked thanks to the placement of fiducial markers.

Other systems are based on the use of different imaging methods. Indeed, in several centers the organ motion is checked using ultrasound devices, especially for RT of prostatic tumors. Another solution is represented by the cone-beam systems previously described. These are based on hybrid machines combining an accelerator with a kilovoltage CT. The advantage of these systems is the possibility of using CT images to evaluate organ motion also in organs with worse soft tissue contrast (prostate, uterus, pancreas, etc.). Nowadays also hybrids cobalt-MRI or MRI-accelerator machines are available. These newer machines would be useful to improve the visibility of the target in those tumors in which MRI have a better definition compared to CT.

One of the most common causes of organ motion is represented by breathing, mainly due to diaphragm movements. Different strategies have been used to reduce these shifts. One of the simplest is the use of abdominal compression, as used in SRT treatments. It has been shown that in most patients this method is able to significantly reduce the respiratory movement. Furthermore,



a relatively simple system is represented by the breath hold techniques: both CT-simulation and treatment are performed by asking the patient to temporarily stop breathing (typically during inspiration). Obviously it is a technique requiring a strong collaboration from the patient. A more precise system is the Active Breathing Control (**ABC**), in which a non-invasive system assists the patient in interrupting the breathing for about 10 seconds. A further benefit of this device is in breast cancer RT, where inspiratory phase the chest is moved anteriorly, strongly reducing heart irradiation.

More complex systems are those based on tumor tracking. An example is given by the Cyberknife machine: the robotic arm supporting the accelerator is able to change the beam direction instantly, adapting it to the target movements. This possibility requires the use of X-ray systems able to detect the position of fiducial markers placed into the tumor, or to follow the movements of bony structures close to the target. The tumor tracking can also be realized with conventional accelerators through the continuous movement of the MLCs, adapting the beams shape to the target movement.

Another complex solution is represented by gating systems. In this case the irradiation of a moving target occurs only when it is in a position useful to be “hit” by the radiation beam. In other words the delivery of the radiation beam is interrupted each time the target is outside the radiation beam. Obviously, this system requires continuous monitoring of the organ motion. This can be accomplished either by placing fiducial markers within the patient, or positioning landmarks on the skin surface. In this case the treatment planning requires to define the correlation between the movements of the body surface with the movement of the target.

More advanced solutions are represented, for example, by the Calypso system. This method requires the placement of some transducers into the target (e.g. prostate) whose position is exactly detected through a GPS communication system allowing an instant detection of the target position. This can allow to consequently adapt the beams direction.

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