RADIATION THERAPY

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Summary

During the last 30 years radiation therapy has developed from classical rectangular beams via conformation therapy with largely uniform dose delivery but irregular field shapes to fully intensity modulated dose delivery where the total dose distribution in the tumor can be fully controlled in three dimensions. This last step has been developed during the last 15 – 20 years and has opened up the possibilities for truly optimized radiation therapy.

Today it is not only possible to produce almost any desired dose distribution in the tumor volume. It is also possible to deliver the dose distribution, which has the highest probability to cure the patient without inducing severe complications in normal tissues. In order to fully exploit the advantages of intensity-modulated radiation therapy, quality of life or radiobiological objectives have to be used, preferably combined with predictive assay of radiation sensitivity.

The present review of the radiotherapy process starts by explaining the radiobiological bases of radiation therapy and briefly discusses the biological objective functions and the associated advantages in the treatment outcome using new treatment approaches such as intensity-modulated beams. Finally, different possibilities for realizing general three-dimensional intensity-modulated dose delivery are described. Once accurate genetically and/or cell survival based predictive assays become available, radiation therapy will become an exact science allowing a truly individual optimization considering also the panorama of side-effects that the patient is willing to accept.

1. Introduction

Today surgery and radiation therapy are the major treatment modalities for curing of cancer patients. About 20 - 25 per cent of the diagnosed cancers can be cured by each of these treatment modalities either alone as sole modalities or together in adjuvant treatments. In addition, some 5 per cent can be cured by cytostatic drugs and other chemo-therapeutic agents. Thus, over one half of all cancer patients may be cured and this is also true for that half of the patients who are receiving radiation therapy.

During the last three decades radiation therapy has gone through a very dramatic development: During the 1970s Computed Tomography (CT) also known as Computer Aided Tomography (CAT) and during the 1980s Magnetic Resonance Imaging (MRI) have revolutionized the diagnostic phase of radiation therapy by providing truly three dimensional (3D) diagnostic tools of sub mm accuracy. This phase has matured further during the nineties and has been amplified by an equally important development of radiation therapy equipment allowing truly 3D dose delivery to the tumor. The time between the first introduction of new advanced medical tools and the full realization of the potential benefits in the clinic is often quite long specially considering the long follow up periods (5 - 10 years) required for many cancer sites. Hopefully, during the first decade of the new millennium we will start to see the benefits of these developments in improved local cure and survival as new 3D intensity modulated treatment modalities are taken into clinical use.

After a brief review of the whole radiotherapy process, the main goals of radiation therapy will be formulated in radiobiological terms. Furthermore, the treatment results of classical and advanced intensity modulated radiation therapy will be discussed. Finally, the different treatment modalities employed today for radiation therapy as well as the characteristics of the different treatment units will be discussed and the future development of radiation therapy will be indicated.

2. Overview of the Radiation Therapy Process

2.1. Diagnostic Work-up

Dependent on the patient history an increasing arsenal of diagnostic procedures will be used starting from visual inspection and palpation often complemented with different forms of endoscopy, ultrasound and fine needle aspiration biopsy of suspected nodules. In addition, tumor related host factors such as Prostate Specific Antigen (PSA) etc are evaluated.

All modern diagnostic imaging tools may also be useful in the work-up of the patient for diagnostic and treatment planning purposes. Both as a first step in the evaluation of the stage of the disease and for the delineation of the clinical tissues that will be target and organs at risk during the treatment, as shown in Figure 1. Most commonly CT and MRI are used as the base for treatment planning but also Diagnostic X-ray, Mammography, PET, SPECT, Ultrasound (US) may generate useful data for defining the clinical target volume (CTV). The CTV is often the same for the two major treatment modalities: radiation therapy and surgery. Depending on the uncertainty in the diagnostic information gained by all diagnostic modalities and the motions of the tissues inside the body a margin has to be added to the CTV to ensure a curative treatment. For radiation therapy this so called "internal margin" has to be added to the CTV to get the internal target volume (ITV) accurately defined inside the body in relation to superficial anatomic landmarks as indicated in Figure 2. The ITV has to be irradiated to a curative dose of radiation to ensure a beneficial treatment but at the same time the dose to surrounding normal tissues should be low enough to avoid severe normal tissue damage.

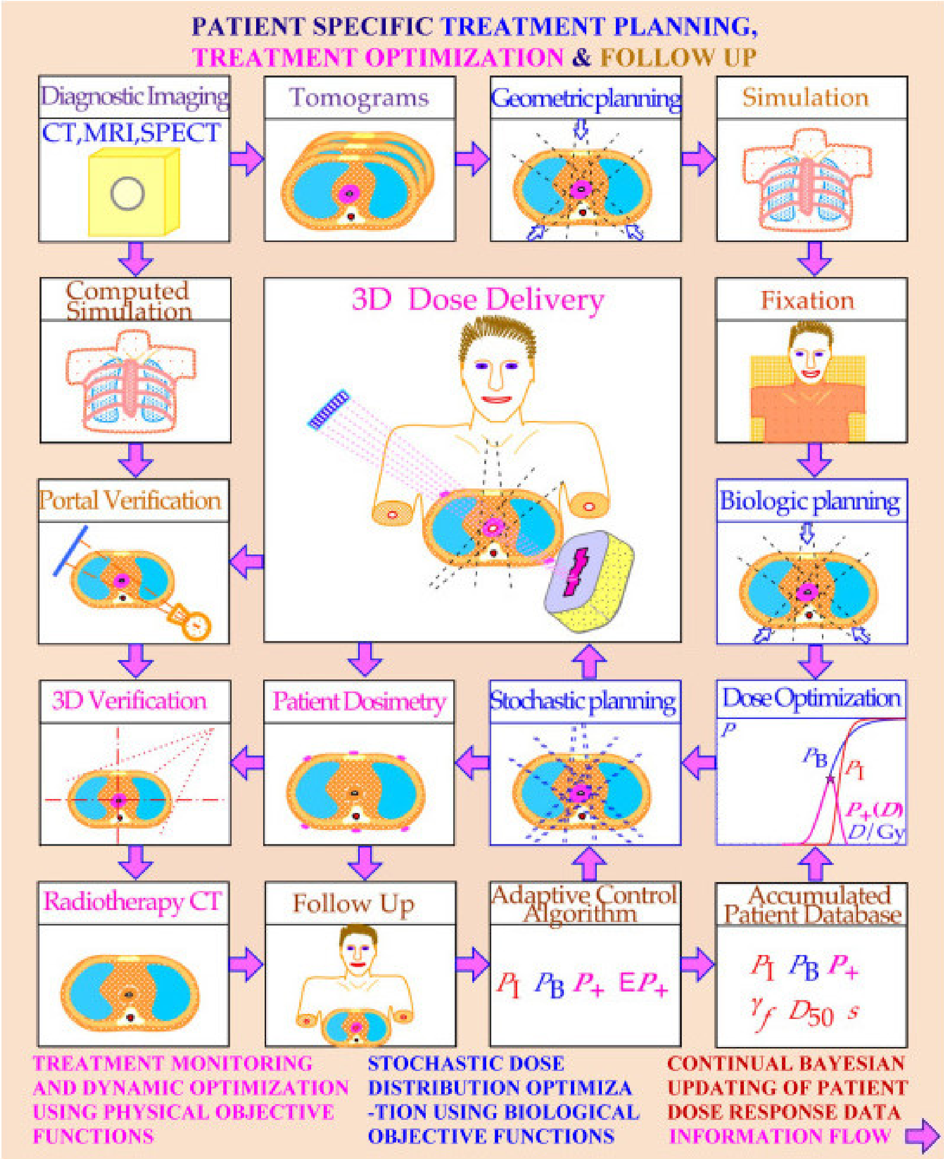

Figure 1. Schematic overview of the radiation therapy process describing some of the main activities and their interaction. Two types of imaging are involved projected 2D and true 3D images. To the former simulator, portal imaging and digitally reconstructed radiographs belong. Most modern diagnostic methods produce 3D images including CT, MR, PET and SPECT. In addition to diagnostic CT images the therapeutic beam itself can be used to make truly 3-dimensional radiotherapeutic CT images of the patient in treatment position. The information flow during radiation therapy including the interaction between the different imaging modalities and the adaptive control and correction of the treatment set-up are illustrated. The possibility of continued sequential updating of dose response relations during treatment follow-up are indicated in the lower part of the figure.

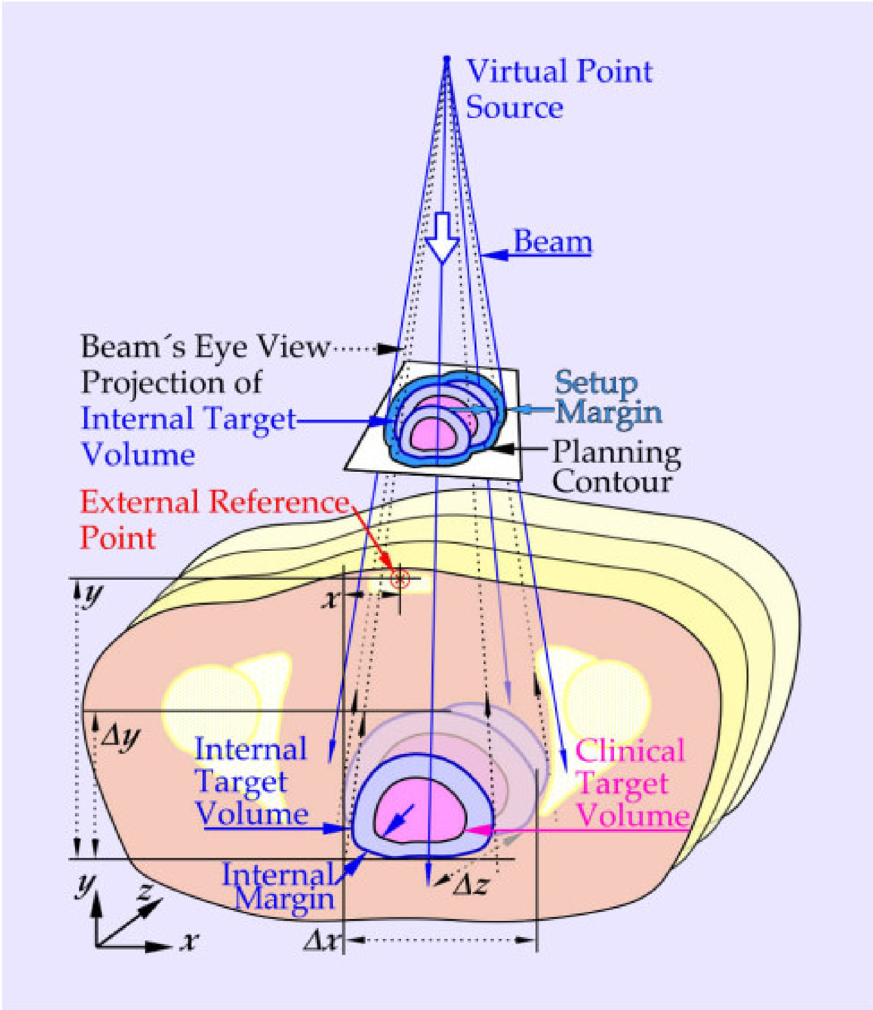

Figure 2. Illustration of how the internal margin due to organ motion and tumor spread uncertainties is added to the *Clinical Target Volume* to get the *Internal Target Volume* accurately defined in relation to extended reference points. The *Setup Margin* is added to the beam's eye view projection of the *Internal Target Volume* (here drawn on a stack of CT or MR slices) to get the cross section of the therapeutic beam since the *Internal Target Volume* is accurately defined in relation to superficial external reference points on the patient surface a very accurate beam alignment is possible even if the tumor is not visualized during set-up.

2.2. Aim of Treatment

2.2.1. General

Radiation therapy is the modality of choice for about half of the cancer patients at some stage during their treatment. However, the aim and intent of the treatment can differ significantly from case to case. For a radical treatment with curative intent, radiation therapy may be used alone or in combination with other adjuvant modalities such as surgery or chemotherapy. In the former case all clonogenic tumor cells should be eradicated by radiation alone, and in the latter case in combination with other modalities. Radiation therapy may also be used with a non-radical or palliative intent in very advanced tumors. In such cases the target for the irradiation may not necessarily be all the clonogenic tumor cells but those tissues that are giving an immediate clinical problem or are responsible for the symptoms at hand.

In all forms of radiation therapy a balance has to be found between the radiation effects in the target tissues and surrounding normal tissues. Maximum probability of tumor eradication without serious side effects calls for optimal fractionation and precision of the dose to the target volume as well as minimal irradiation of the organs at risk. If the probability of cure is very small or negligible the treatment will often be considered palliative. Since all these aspects will have a considerable influence on the selection of volume and dose concepts in radiation therapy, clear definitions of the therapeutic intent have to be formulated.

2.2.2. Treatment Aims

The aim of radiotherapy could be either curative or palliative. In *Curative Radiation Therapy* the aim is to decrease the number of clonogenic tumor cells to a level that results in permanent tumor control. In *Curative Radiation Therapy* it is commonly understood that 1) radiation therapy is used as the main local treatment modality, 2) it has a significant probability of tumor eradication, and 3) all tumor cells have a high probability of being included in the defined target volumes. Due to the random nature of cell kill, the clinical uncertainty in microscopic tumor spread and the individual differences and variations in radiosensitivity, all patients may not be cured. For a curative treatment the irradiated volumes have to include all macroscopic tumor tissues (the gross tumor) and volumes with risk for subclinical spread. To minimize the adverse effects of the irradiation, the gross tumor and subclinical malignant disease should preferably be irradiated to individually selected dose levels (cf. NACP, ICRU 50).

Palliative Radiation Therapy is given to maintain local tumor control, to relieve a symptom, to prevent or delay an impending symptom, and generally to improve the quality of life but not primarily to increase the probability to eradicate the tumor or improve survival. The target volume(s) for symptom relief does not necessarily need to encompass all tumor tissues in the patient. The doses are generally lower than those used for curative treatments, but they should be sufficient to relieve the symptoms and/or reduce the tumor cell burden in the target volume(s) such that the life span or quality of life is increased.

2.2.3. Treatment Types

In *Radical Radiation Therapy* the delivered dose should be high enough to decrease the *local* tumor cell burden to a level that results in permanent local tumor control.

In *Adjuvant Radiation Therapy* radiation therapy is combined with surgery such that the combined modalities have a high probability to eradicate all clonogenic tumor cells to a level that results in permanent local tumor control. To be more specific the terms pre-, post- or intraoperative radiotherapy are used, as described below.

Preoperative Radiation Therapy is the situation where radiation therapy is given before planned surgery and the combined procedure has a high probability to eradicate all clonogenic tumor cells.
Postoperative Radiation Therapy is the situation where planned radiation therapy has a high probability of eradicating all clonogenic tumor cells left after earlier surgery, and therefore all tumor tissues should be included in the target volume(s).

Intraoperative Radiation Therapy is the situation where at least one high dose fraction is delivered as the tumor bed is opened for treatment related surgery.

In *Radiotherapy of Benign Diseases* such as arteriovenous malformations, eczemas, keloids, and inflammatory processes all of the affected tissues are not necessarily included in the treatment.

2.3. Patient Data for Treatment Planning

The first part of the treatment preparation consists of the acquisition of patient data for the delineation of target volume(s) and organ(s) at risk and a selection of the suitable treatment modality and patient fixation technique. The patient fixation is of importance early in the treatment planning particularly for the large number of advanced tumors where it is important to ensure that the same patient position will be used, both during the anatomic work up, simulation and treatment execution. In modern radiation therapy other types of clinically relevant information are also of interest, such as the radiation sensitivity of the patient and the tumor as determined by predictive assays or genetic markers, the tumor growth rate as measured by the tumor doubling time and the oxygenation status as determined by electrodes, MRI or nuclear medicine techniques. These latter factors are of great importance particularly when advanced treatment optimization procedures are employed.

In general it is important that the images are generated in a geometry which is as similar as possible to that during treatment execution. Otherwise the anatomy can be severely distorted between imaging and dose delivery. Contrast agents may be used to identify the affected tissues. However, contrast-filled organs such as the urinary bladder and rectum may be distended more during the diagnostic procedure than during radiation treatment. This will alter the pixel information in CT images and may complicate density corrections in dose planning. Short image detection times will give sharp images without motion artifacts, while long image detection times may give information about the mean target tissue movements during treatment. Several image processing methods can be used to get more information out of the images, such as regional histogram equalization to improve the contrast range and image matching and fusion to identify different aspects of the target volume in different imaging modalities. This will also make it possible to generate new images such as beam's-eye-views or digitally reconstructed radiographs and to apply 3D surface rendering to improve visualization (cf. Figure 1). For this purpose it is important to use a local patient coordinate system describing as accurately as possible the location of organs in relation to the target volume.

An efficient image handling system is necessary in defining target volumes and critical organs. Diagnostic systems, dedicated to radiation therapy, are often integrated with the treatment planning system. Especially when 3D information is needed, such systems are mandatory. The system should be able to combine information from all different imaging modalities available in the clinic such that volumes identified by one modality can be transferred to the others. MR images are often distorted, and nuclear medicine images are affected by attenuation and scatter and this has to be taken into account when they are combined with other imaging modalities.

2.4. Treatment Planning

The treatment planning process consists of several methods for treatment preparation and simulation to achieve a reproducible and optimal treatment plan for the patient. Irrespective of the temporal order, these events include:

- Patient fixation, immobilization and reference point selection
- Dose prescriptions for target volumes and the tolerance level of organ at risk volumes
- Selection and optimization of
  - radiation modality and treatment technique
  - the number of beam portals
  - the directions of incidence of the beams
  - beam collimation
  - beam intensity profiles
  - fractionation schedule
- Dose distribution calculation considering geometric, stochastic and biological factors
- Treatment simulation

The position of the patient must be very reproducible throughout the entire treatment course, making adequate and reproducible fixation a necessity (cf. Figure 1). There exist several systems which can be used, such as shells, masks, bite-blocks etc. Two setup techniques are in common use: the isocentric and the fixed source to surface distance methods. Both techniques have advantages and disadvantages, and one must be aware of these.

For both techniques laser alignment of the patient will enhance the precision and reproducibility of the patient position. Such equipment should be positioned identically when preparing fixation aids, doing CT or MR imaging, and performing simulations and treatments. Reference points and reference lines for patient and beam positioning are essential for correct setup.

To find the best dose plan several parameters of the list above have to be optimized. Filters are often used for shaping the lateral dose distribution across the beam. Both compensation filters and wedge filters are used. The collimation system and/or scanning beam on some accelerators can be used to vary the dose distribution dynamically instead of using static filters or wedge filters. The dose calculation algorithms should be able to handle 3D anatomical information and allow accurate dose calculation in strongly heterogeneous situations. One should be aware of the limitations and inaccuracies of the algorithms employed, since improper use can give rise to unacceptable errors in the delivered dose distribution. The dose calculation system should also be able to utilize all the technical capabilities of existing treatment units, and have reliable routines for optimization of most important treatment parameters. For brachytherapy the optimization should include parameters like: number and shape of applicators and sources, positions of applicators, retractors and sources, treatment time for each source position, and shielding.

The conventional simulator is used both as a localizer like other imaging techniques and as simulator of the treatment setup. A major part of the simulator procedure is to identify suitable anatomical reference points and markings for the beam portals. For these procedures both CT scanners and ordinary simulators can be used, and equipment has been developed that combines the benefits from both. Digitally reconstructed radiographs similar to simulator Setup images can be generated by several treatment planning systems and CT scanners, and this will enhance the precision of beam setup and treatment verification.

The performance of each of the methods used should be known, since inaccuracies and variations can alter delivered dose distribution severely. These inaccuracies and variations have to be taken into account when defining beam portals. The estimation of the uncertainties of the different steps in the preparation process can also give rise to mistakes and inaccurate transfer of treatment parameters. A complete information system for radiation therapy, where treatment parameters can be transferred automatically from planning computer to the treatment unit, will reduce this problem, but does not replace the need for a well trained and educated staff. Also one must be aware that automatic transfer of treatment parameters to the treatment unit, while reducing the risk of data transfer errors in individual fractions, carries the risk of introducing systematic errors which could affect the complete course of treatment.

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Biographical Sketch

Anders Brahme is Professor of Medical Radiation Physics at the Department of Oncology-Pathology, Karolinska Institutet and Department of Medical Radiation Physics, Stockholm University, and Manager of the Research Center for Radiation Therapy, Karolinska Institutet. He got his Master of Science degree in electrical engineering at the Royal Institute of Technology in 1969 and his Ph.D. thesis on the application of the Microtron accelerator for radiation therapy was presented 1975 at Stockholm University. Since then he has been active in the development of radiation dosimetry, quality assurance and radiation therapy equipment and techniques for most types of radiation from electrons and photons to neutrons, protons and heavy ions. He initiated the development of inverse radiation therapy planning and intensity modulated radiotherapy using scanning beams and dynamic multileaf collimator systems. During the last two decades he has been mainly active in the field of radiotherapy optimization using accurate radiobiological models describing the response of tumors and normal tissues. By such techniques he has been able to maximize the expectation value of the complication free tumor cure under consideration of intensity modulation, dose fractionation, radiation modality, the number of beam portals and their angles of incidence as well as uncertainties in geometrical and biological parameters.