ISSN 1100-1704

ACTA ONCOLOGICA

SUPPLEMENTUM 10

SPECIFICATION OF DOSE DELIVERY IN RADIATION THERAPY

Recommendations by the Nordic Association of Clinical Physics (NACP)

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1. INTRODUCTION

1.1 Background

During the past two decades we have seen considerable development in radiation therapy procedures. The performance of external beam radiation therapy accelerators, brachytherapy and other specialized radiation therapy equipment has improved rapidly. Developments taking place in the quality and adaptability of radiation beams have included new targets and filters, improved accelerators, increased flexibility in beam-shaping through new applicators, collimation and scanning systems and beam compensation techniques, and improved dosimetric and geometric treatment verification methods have been introduced. Furthermore, accurate dosimetry protocols have been developed allowing precision in dose calibration of about 1–2% for most radiation modalities. A number of new powerful three-dimensional (3D) diagnostic techniques have been developed, ranging from computed tomography (CT), positron and single photon emission computed tomography (PET and SPECT) to ultrasound and magnetic resonance imaging and spectroscopy (MRI and MRS). Equally important is our increased knowledge of the biological effect of fractionated uniform and non-uniform dose delivery to tumours and normal tissues and new assay techniques, including the determination of effective cell doubling times and individual tissue sensitivities, allowing us to optimize the dose delivery to tumours of complex shape and advanced stages. Finally, during the last decade, advanced 3D computed treatment planning and not least biologically based treatment optimization methods have been developed capable of taking the improved diagnostic and therapeutic information fully into account.

One of the weakest links in this development in recent years has been the way we define our target volumes and specify and prescribe the dose delivery (1, 2). This is partly due to the uncertainty of the diagnostic methods but more importantly to the inaccuracies in basic definitions. The aim of the present report is to bring these volume and dose definitions up to date with the other developments in advanced radiation therapy. This goal is accomplished through accurate and consistent principles and definitions and methods that apply throughout the whole radiation therapy procedure. The report is also written in such a general way that the principles are valid for most radiation modalities, from external beams of photons, electrons, protons and neutrons to brachytherapy, even though the clinical emphasis is on external beam therapy.

The present proposal has evolved from discussions among radiotherapists and physicists in the Nordic countries during the past five years, and has been influenced by numerous discussions with international colleagues, not least on uncertainties and radiobiological factors and recent publications on the subject (3–16). The present report is therefore more detailed in its consideration of organ motions and setup uncertainties and the handling of dosimetric and biological parameters.

This emphasis was particularly clear after a consensus meeting with representatives from almost all Nordic radiation therapy centers in Umeå 1995, when it was decided to try to harmonize the terminology and specifications as far as possible with the existing ICRU 50 recommendations. At the same time, to avoid contradictions and to clarify the needs for accurate radiation therapy, it was acknowledged that the *Planning Target Volume* of ICRU (see Sect. 3.3.7) was insufficient for accurate dose specifications. The representatives of the ICRU working group therefore promised to try to integrate the more clinically relevant *Internal Target Volume* (see Sect. 3.3.4) concept in their dose specifications.

The terminology in the present report is therefore practically identical with that in the upcoming ICRU recommendations (17), whereas the dose specifications have been modernized relative to the older ICRU 50 report (4), not least to take account of advanced conformal treatments. However, there are no contradictions between the present recommendations and those of ICRU 50, and dose specifications according to the present report are more accurate and self-sufficient.

1.2 Aim of the report

To maintain high quality in radiation therapy it is necessary to have a precise system for patient fixation and dosimetric and portal verification, as well as a standardized code of practice for dosimetry and treatment follow-up, including registration of tumour response and acute and late normal tissue reactions. These steps are therefore

an essential part of accurate quality assurance systems (5). They are also particularly important when more advanced treatment optimization methods are introduced and employed, and the quality of each treatment must be assured (15). One of the principal functions of the follow-up of acute and late normal tissue reactions is continuous monitoring and improving of the accuracy of existing dose-response relations in order to improve future radiation therapy (cf. Fig. 1). This is only possible if volume concepts and definitions of the dose delivery are accurately defined and uniformly applied.

The principal aim of this report is the proposition of basic principles and methodologies for the accurate and unambiguous delineation of the target volume and potential dose-limiting normal tissues for high precision radiation therapy. Special attention is also given to the dosimetric concepts, so that radiation responses and dose delivery can be related precisely. Also the direction and magnitude of possible organ motions within the patient, and of the patient relative to the coordinates of the treatment unit, need to be specified so that they can be incorporated within the treatment planning process. Well-documented procedures are necessary for prescribing the desired dose distribution and for reporting how the dose is delivered over the course of treatment, especially if the results are to be used in prospective multicentric trials. This report attempts to provide guidelines for each of these steps, in the hope that a more uniform approach to dose prescription and treatment reporting in radiation therapy will be encouraged.

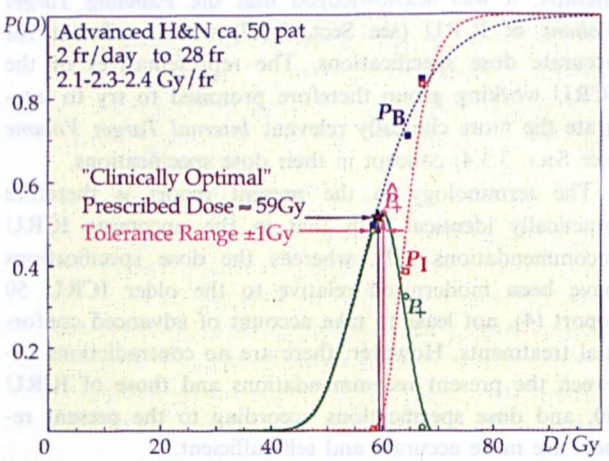

Fig. 1. Clinically established dose-response relations for advanced head and neck tumours. The dashed curves labelled P_B and P_I correspond to the probabilities of tumour control (Benefit) and severe normal tissue damage (Injury), respectively. The solid curve labelled P_+ represents the probability that patients are cured without severe complications in normal tissues. The symbols are from clinical data and the curves from the Poisson model (18). It can be seen that the absorbed dose should be within 1 Gy of the clinically optimal dose in order not to lose more than 5% of the patients that potentially can be cured without severe complications (see Sects. 4.4, 4.6 and Appendix IV for further details).

The aim of this report is therefore to address and deal with the situation at clinics with state of the art equipment and procedures. For obvious reasons, this NACP report is also written primarily with the fairly uniform equipment situation in the Nordic countries in mind. However, it is our firm belief that once general high quality procedures have been developed for advanced equipment they can also be transferred and adapted to more traditional equipment once the basic underlying principles have been developed and established. Many of the definitions introduced here have obvious counterparts in classical radiation therapy procedures, and they are usually in close agreement with established methods even though some new proposals have had to be made here to improve the accuracy of advanced irradiation techniques. It is impossible to give strict guidelines for every existing and future treatment technique. The aim is therefore to suggest principles that are generally applicable and can be adopted to new situations. For example, it may be desirable to combine brachytherapy, radionuclide or boron capture treatments with external beam treatments and use commensurable quantities for the different modalities. Obviously this will require different corrections, such as for radiation quality, dose rate and heterogeneous organ irradiation. However, the detailed consideration of these topics is beyond the scope of this report. Similarly, it may be desirable to use the present basically 3D definitions for 1D or 2D cases. This could be done simply by assuming constancy of known variations in the missing directions, as briefly discussed in Section 3.4.

2. RADIOTHERAPY PROCEDURE

2.1 General

Accurate volume and dose specifications are important concepts in all phases of the radiotherapy procedure. A multitude of methods have been used for target definition and specification of the delivered dose distribution to the patient (2), and it is essential that all those involved in the treatment process are aware and familiar with the methods and concepts used in the clinic. After the diagnostic work-up, the radiotherapy procedure starts to describe the aim of the treatment, relevant target volumes and doses to the patient and the associated radiation effects. For operational reasons the radiation therapy procedure can thus be divided into five major groups: (i) Aim of the treatment, (ii) patient data for treatment planning, (iii) treatment planning, (iv) treatment execution, and (v) follow-up. These main procedures are briefly described below.

2.2 Aim of treatment

2.2.1 General. Radiation therapy may be the modality of choice for about half the cancer patients at some stage during their treatment. However, the aim and intent of the treatment can differ markedly from case to case. For

radical treatment with curative intent, radiation therapy may be used alone or in combination with modalities such as surgery or chemotherapy. In the former case all clonogenic tumour 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 advanced cases. In such cases the target for the irradiation may not necessarily be all the clonogenic tumour 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 those in surrounding normal tissues. Maximum probability of tumour 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 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 tumour cells to a level that results in permanent tumour control. In *Curative Radiation Therapy* it is commonly understood that (i) radiation therapy is used as the main local treatment modality, (ii) it has a significant probability of tumour eradication, and (iii) all tumour cells have a high probability of being included in the target volume(s). Because of the random nature of cell kill, the clinical uncertainty in microscopic tumour spread and the individual differences and variations in radiosensitivity, not all patients may be cured. For a curative treatment the irradiated volumes have to include all macroscopic tumour tissues (the gross tumour) and volumes at risk for subclinical spread. To minimize the adverse effects of the irradiation, the gross tumour and subclinical malignant disease should preferably be irradiated to individually selected dose levels (cf. Sects. 3.3.12, 4.6 and (4)).

Palliative Radiation Therapy is given to maintain local tumour control, to relieve a symptom, to prevent or delay an impending symptom, and generally to improve quality of life, but not primarily to increase the probability to eradicate the tumour or improve survival. The target volume(s) for symptom relief does not necessarily need to encompass all tumour 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 tumour cell burden in the target volume(s) such that 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* tumour cell burden to a level that results in permanent local tumour control.

In *Adjuvant Radiation Therapy* radiation therapy is combined with surgery, such that the combination has a high probability of eradicating all clonogenic tumour cells to a level that results in permanent local tumour 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 where the combined procedure has a high probability of resulting in the eradication of all clonogenic tumour cells.

Postoperative Radiation Therapy is the situation where planned radiation therapy has a high probability of resulting in eradication of all clonogenic tumour cells left after earlier surgery, and therefore all tumour tissues should be included in the target volume(s).

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

In *Radiotherapy of Benign Diseases*, such as arteriovenous malformations, eczemas, keloids, and inflammatory processes, not all of the affected tissues are necessarily included in the treatment. Most of the present dose and volume definitions are primarily intended for malignant processes, but they are also generally applicable for benign diseases.

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 techniques. Patient fixation is of importance early in the treatment planning, particularly for the large number of advanced tumours, where it is important to ensure that the same patient position is used during 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 tumour as determined by predictive assays or genetic markers, the tumour growth rate as measured by the tumour doubling time and the oxygenation status as determined by electrodes, MRI and nuclear medicine techniques. These factors are of great importance, particularly when advanced treatment optimization procedures are employed, but will not be considered here as they are still of an experimental nature (cf. also Sects. 3.5 and 4.6).

The anatomic work-up methods fall within two main groups: imaging methods and methods without the use of images. Normally one would use different imaging methods for direct delineation of gross tumour and target volumes, while methods without the use of images would be of indirect help in this process.

The imaging methods comprise one or a combination of several techniques, such as:

- CT and MRI
- conventional radiographs (including angiographs/DSA)
- nuclear medicine images (including SPECT and PET)
- ultrasound images
- contouring devices
- general image handling and manipulation systems (image registration and fusion, etc.)

Strictly speaking, the last two are not imaging methods, but combined with other methods internal structures too can be localized to give an adequate set of contours. CT and MRI are the best methods for delineating important volumes geometrically, and are increasingly being used. CT is superior for getting density information, and MRI for anatomical information about soft tissues near bony structures such as the central nervous system. Conventional radiographs are normally used together with contouring devices to localize internal organs, bony structures and reference points. Nuclear medicine is a good diagnostic method when functional aspects are important and can be very valuable for delineating the extension of the target volume.

In general, it is important that the images are generated in a patient geometry as nearly identical to that during treatment execution as possible. 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 then 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. The images should preferably be digital for direct use in image handling and treatment planning systems. 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. For this purpose, it is important to have 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 when defining target volumes and critical organs. Diagnostic systems dedicated to radiation therapy are often integrated with the treatment planning system. Such a system is mandatory, especially when 3D information is needed. It should be capable of combining information from all different imaging modalities available in the clinic so 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, a fact that has to be taken into account when other imaging modalities are combined with them.

Methods *without* the use of images are based on prior knowledge or diagnostic information, such as clinical and pathological staging oxygenation status or predictive assay. These form part of the general information about the patient and the disease. Hence, information from such methods may be a vital part of the target volume delineation and treatment prescription.

2.4 Treatment planning

The treatment planning process comprises several methods for treatment preparation and simulation towards achieving 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
- Treatment simulation

The position of the patient must be very reproducible throughout the entire treatment course, making adequate and reproducible fixation a necessity. There are several systems that can be used, e.g. 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 their advantages and disadvantages, and one must be aware of them.

In both techniques laser alignment of the patient will enhance precision and reproducibility of the patient position. Such equipment should be positioned identically when fixation aids are being prepared, CT or MR imaging is being carried out, or simulations and treatments are being performed. Reference points and reference lines for patient and beam positioning are essential for correct setup, as described extensively below (Sects. 3.2, 4.1, 4.5 and Appendixes I and II).

To find the best dose plan, several of the parameters on the above list 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 rather than 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 has to 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 capable of utilizing all the technical capabilities of existing treatment units, and have reliable routines for optimizing the most important treatment parameters. For brachytherapy, the optimization should include parameters such as 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 a simulator of the treatment setup. A major part of the simulation procedure is to identify suitable anatomical reference points (see Fig. 2 and Sect. 3.2) and facilitate the placement of markings for the beam portals. Both CT scanners and ordinary simulators can be used for these procedures, 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 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 the delivered dose distribution radically. These inaccuracies and variations have to be taken into account when defining beam portals. 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 the planning computer to the treatment unit, will reduce this problem, but does not take the place of a well-trained and educated staff. One must also 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 (19).

2.5 Treatment execution

During the treatment course, measures have to be taken to ensure that dose delivery corresponds to the established plans. Any deviations have to be recorded and dosimetric consequences have to be evaluated. Equally important are the different methods for treatment verification:

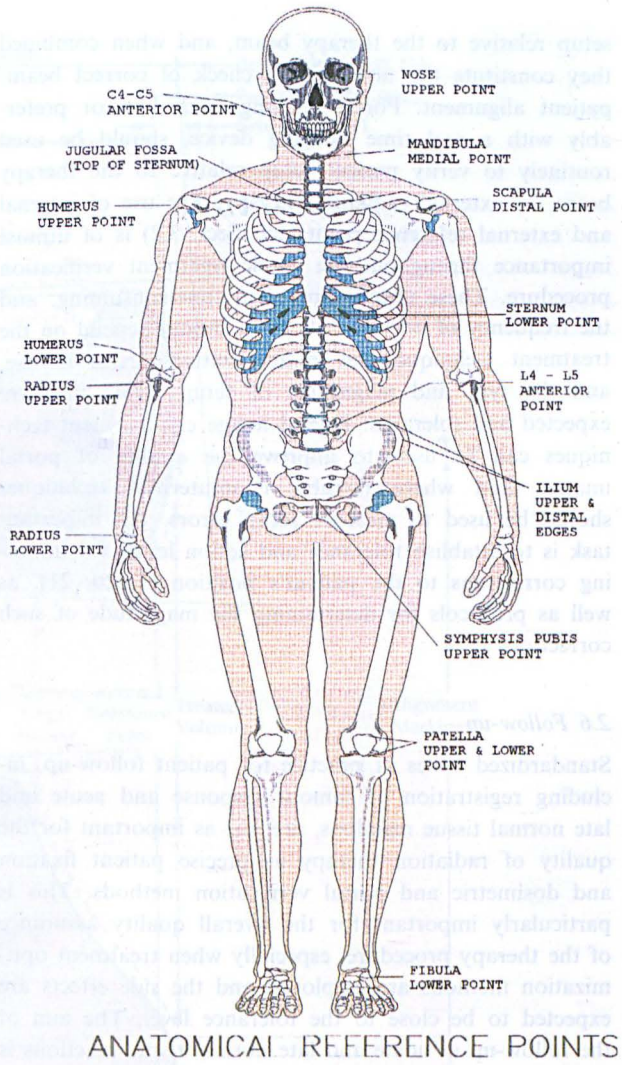

Fig. 2. Overview of different external anatomic reference points of interest for target volume definition and patient alignment and setup (cf. Sect. 3.2).

Patient dose measurements (in vivo dose verification)
Portal imaging
Isocentre verification by orthogonal X-ray projections ($0° \pm 90°$)
Verification systems for dose monitor, gantry, treatment couch, light and radiation beam setup
Repeated imaging during the course of therapy to verify treatment setup and target volumes

Verification systems for all treatment parameters are valuable and should be mandatory for checking the beam patient setup and for verifying monitor settings. However, it is important to use as direct a transfer of treatment parameters as possible, preferably directly from the planning computer to the simulator and treatment unit to minimize errors. Portal imaging and radiotherapeutic computed tomography, if available, will verify the patient

setup relative to the therapy beam, and when combined they constitute the ultimate 3D check of correct beam/patient alignment. Portal imaging, with film or preferably with a real time imaging device, should be used routinely to verify patient setup relative to the therapy beam for external radiation therapy. The use of internal and external reference points (cf. Sect. 3.2) is of utmost importance throughout the whole treatment verification procedure. These checks are often time-consuming, and the frequency of portal verification should depend on the treatment technique, the immobilization device in use, and the type and magnitude of setup errors that are expected and tolerated. Digital image enhancement techniques can be used to improve the quality of portal images, and where possible computerized techniques should be used to measure setup errors. An important task is to establish tolerance and action levels for initiating corrections to the patient's position (5, 20, 21), as well as protocols for determining the magnitude of such corrections (15).

2.6 Follow-up

Standardized codes of practice for patient follow-up, including registration of tumour response and acute and late normal tissue reactions, are just as important for the quality of radiation therapy as precise patient fixation and dosimetric and portal verification methods. This is particularly important for the overall quality assurance of the therapy procedure, especially when treatment optimization methods are employed and the side effects are expected to be close to the tolerance level. The aim of the follow-up of acute and late normal tissue reactions is therefore to continuously improve the accuracy of established dose–response relations and, hopefully, generate a beneficial impact on future radiation therapy. In the case of cancer cure, the follow-up is thus not restricted to recording of possible recurrences, but also for meticulously scoring normal tissue damage several years after the treatment. It is extremely important that, in studies of tumour control and adverse reactions in normal tissues, the correlation between benefit (tumour control) and injury (severe normal tissue damage) is reported, since they seem to be statistically dependent endpoints (22), even though this is not generally assumed to be the case. If well planned, the frequency of follow-up may still be quite low in most cases.

3. DEFINITIONS AND BASIC RECOMMENDATIONS

3.1 Rationale

Specification of the dose delivery and documentation of radiation therapy procedures and results should always be as complete as possible to facilitate prescribing and performing of the treatment and to allow accurate reporting of treatment results for retrospective investigations. Accurate and complete documentation is even more essential for prospective clinical trials. If sufficient background information is included in the treatment records there is a possibility that the development of new techniques and evaluation methods in the future will increase the accuracy and significance of earlier treatment results. Improvements in dose calculation algorithms may for example increase the accuracy of delivered doses, provided that the incident beams and the patient anatomy have been accurately documented. This section therefore mainly covers such treatment parameters as may become of interest in prospective and retrospective investigations. The same parameters are generally used for prescribing and performing the treatment and for reporting the treatment results with regard to tumour and normal tissue effects or the general quality of life of the patient after radiation therapy.

3.2 Reference points and coordinate systems

There is no rigid connection between different tissues and organs of the patient and the radiation beams. This is so since the volumes inside which the organs and tissues are moving are defined in a local patient coordinate system, whereas the beams are generally defined in the system of the treatment unit. Often, anatomic reference points on the patient can be used as a link between these systems, since they can be identified in both coordinate systems. In general, three different types of external reference points can be identified depending on the situation at hand: (i) anatomic landmarks, (ii) tattoos on the skin, and (iii) markings on external reference systems—such as shells or frames that are rigidly connected to the body.

Owing to the fact that the patient is not a rigid structure, all geometrical descriptions of anatomy should be expressed in a local or regional coordinate system. The local coordinate system of the patient is based on defined reference points, for example with one of the reference points as origin (see Fig. 2 and Appendix I for examples) and an orientation defined by a direction vector such as the spin and sternum or other reference points or alignment markings on the skin. This is schematically illustrated in Figs. 3, 4 and 5 for a cervix, a head and neck and a breast cancer patient, respectively.

Good patient fixation systems are the most effective means of getting an accurate and reproducible alignment. However good the fixation system is, there will always remain some internal organ and patient motions for which the reference points are needed to adjust the setup or even calculate the optimal dose delivery for the next treatment fraction (15, 23).

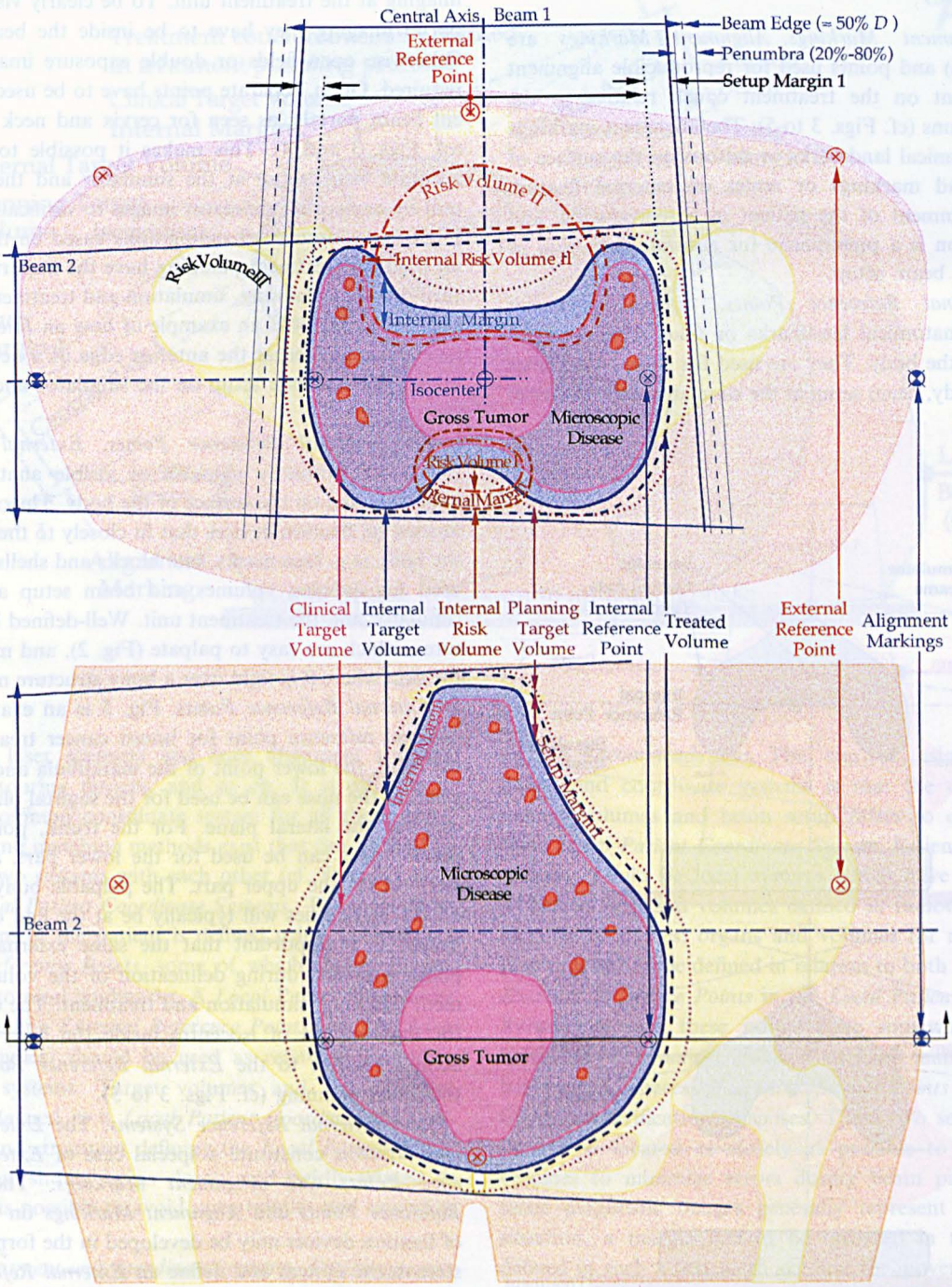

Fig. 3. Illustration of reference points, margins and volume concepts for an advanced cervix tumour. The *Internal Reference Points* are essential for simulations and portal verification, whereas the *External Reference Points* are primarily intended to improve the precision in patient and radiation beam setup. Please observe also that the *Internal Margin* is a margin on the target tissues and thus the *Clinical Target Volume*, whereas the *Setup Margin* 1 is a margin on the beam cross section, as clearly seen in the upper tomogram (see Sects. 3.2 and 3.3). In the lower frontal view the *Setup Margin* is more seen in a beam's eye view perspective and then surrounding the *Internal Target Volume*.

There are several coordinate systems that must be taken into account when planning and executing radiotherapy, and methods for transformations between the different systems are needed. The coordinate systems can be grouped depending on whether they relate to the diagnostic system, the patient or the treatment unit as defined below.

DEFINITIONS

3.2.1 Alignment Markings. Alignment Markings are lines (vectors) and points used for reproducible alignment of the patient on the treatment couch relative to the radiation beams (cf. Figs. 3 to 5). The alignment markings can be anatomical landmarks or tattoos on the surface of the body and markings or scales on external fixation devices. Alignment of the patient in a reproducible and stable position is a prerequisite for accurate definition of volumes and beam setup.

3.2.2 Internal Reference Points. Internal Reference Points are anatomical landmarks or fiducial markers located inside the body. They are used for defining volumes inside the body, beam setup at the simulator and for portal imaging at the treatment unit. To be clearly visible during portal imaging they have to be inside the beam portals. Otherwise open fields or double exposure images will be required. Often, separate points have to be used for different beam portals, as seen for cervix and neck treatments (cf. Figs. 3 and 4). This makes it possible to have very accurate beam setup at the simulator and the treatment unit by comparing simulator images to verification images. Digitally reconstructed radiographs based on the CT data set used for treatment planning have the important role of verifying that planning, simulation and treatment are all in agreement. Fig. 4 is an example of how an *Internal Reference Point* located at the anterior edge of a neck vertebra is used for accurate setup on the simulator and treatment unit.

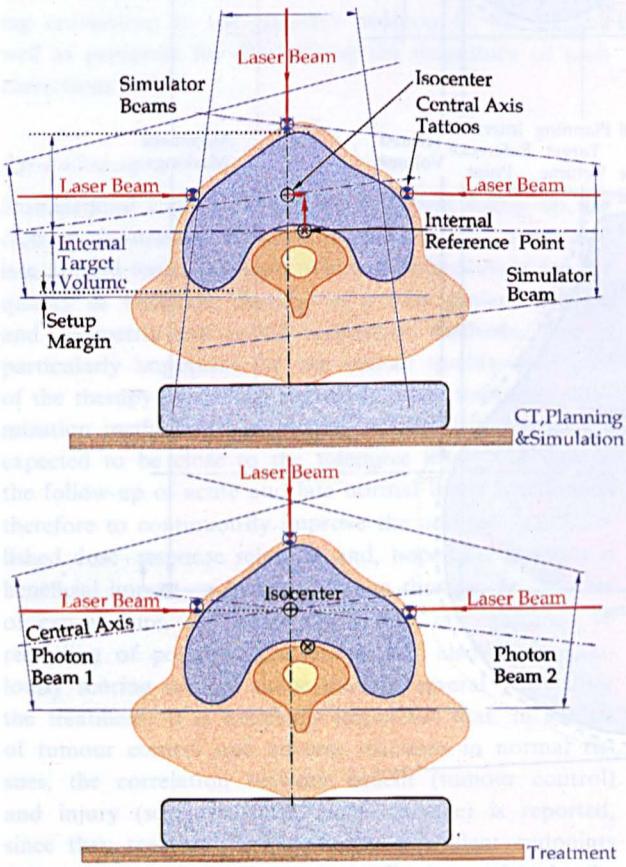

Fig. 4. Treatment simulation and radiation beam setup with *Alignment Markings* for a head and neck tumour. The upper panel illustrates the simulator work-up, where isocentre and alignment points are identified based on the *Internal Reference Point* and the dose plan. Beam's eye view verification films are also recorded for later comparison with the portal verification films recorded on the treatment unit during the therapy procedure. The location of the isocentre is also shown, and the motion of the couch top required to get a correct isocentric beam setup. The lower panel also illustrates the use of alignment tattoos for patient setup. In this case a small horizontal misalignment has minimal influence on the isocentre location.

3.2.3 External Reference Points. External Reference Points are primarily palpable or visible anatomic landmarks located on the surface of the body. They can also be located on fixation devices that fit closely to the exterior of the body (e.g. face-masks, bite blocks and shells). They are used for defining volumes and beam setup at both the simulator and the treatment unit. Well-defined bony structures, which are easy to palpate (Fig. 2), and markings on the skin where it is tight over a bony structure may be used as *External Reference Points*. Fig. 5 is an example of an external reference point for breast cancer treatment. For the head, the lower point of the mandibula and the upper point of the nose can be used for the sagittal plane and the ears for the lateral plane. For the trunk, points on the pelvic bones can be used for the lower part, and on the sternum for the upper part. The palpable bony structures on the extremities will typically be at the end of the large bones. It is important that the same external reference points are used during delineation of the volumes, treatment planning, simulation and treatment. The coordinates for the location of isocentre inside the body should be defined relative to the *External Reference Points* during treatment planning (cf. Figs. 3 to 5).

3.2.4 External Reference Systems. The *External Reference Systems* constitute a special case of *External Reference Points* and *Alignment Markings*. The *External Reference Points* and *Alignment Markings* on the surface of fixation devices may be developed in the form of a local stereotactic system and define an *External Reference System* in which the target and risk volumes can be described and defined. Several stereotactic systems have been used for the head, and reproducible systems for the thorax and abdominal area have also been developed (24). The *External Reference System* can serve as a bridge between the different coordinate systems employed in the clinic when used during diagnostic work-up, treatment planning, simulation and treatment.

3.2.5 Diagnostic coordinate systems. Different diagnostic units and treatment accessories have their own coordinate systems: diagnostic X-rays, CT, MRI, SPECT, PET,

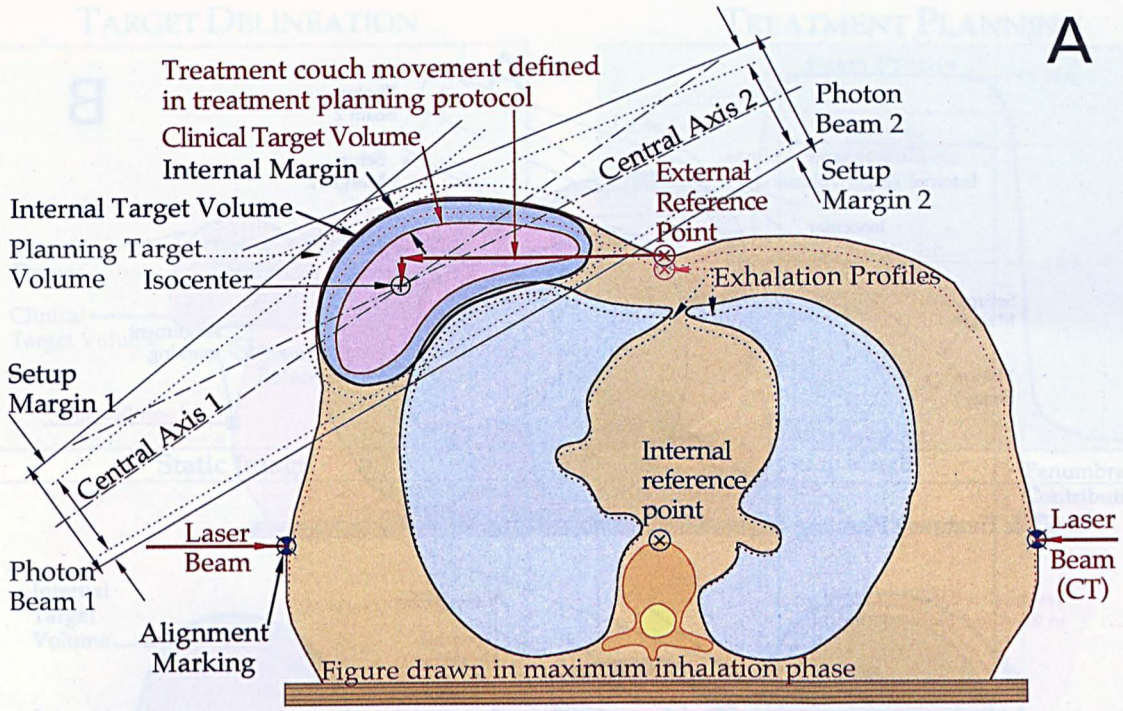

Fig. 5A

ultrasound, laser scanners and laser alignment systems, patient contouring devices, and so on. It is difficult to identify a common coordinate system for all these units, but fusion and matching methods exist that can be used to relate any two systems with each other (cf. Sect. 3.2.4).

3.2.6 Local Patient Coordinate Systems. The local coordinate system of the patient is defined using *Internal and External Reference Points*, some of which should preferably be anatomical landmarks. A *Local Patient Coordinate System* including *External Reference Points* (see Fig. 2 for typical examples) should be used as reference for other coordinate systems. Target volumes and risk volumes should be defined in a *Local Patient Coordinate System*. All points and structures defining the *Local Patient Coordinate System* should be as closely and rigidly related to each other as possible to avoid uncertainties and minimize margins.

3.2.7 Treatment unit coordinate systems. Treatment unit coordinate systems can be defined for many different parts of the unit, e.g. the rotary gantry, collimators, radiation beam, light beam, laser alignment beams and couch system. The light beam and customary laser based isocentre indication system are used for the beam-patient setup, and all other treatment unit coordinate systems should be accurately calibrated relative to these to avoid errors. The *External Reference Points* that are used to define the *Local Patient Coordinate System* should be setup relative to a well-aligned light beam and isocentre indication system to minimize the setup errors.

3.2.8 Recommendations. The aim of using reference points and coordinate systems is that the definition of patient volumes and beam setup refers to one and the same *Local Patient Coordinate System*. Patient coordinate systems should be local systems which have validity for tissues, organs and volumes defined in radiotherapy. The location of tissues, organs and volumes for radiotherapy planning should be defined in relation to both *Internal* and *External Reference Points* in the *Local Patient Coordinate System*, because these points have somewhat different functions. *External Reference Points* are mainly used for beam setup, whereas *Internal Reference Points* are used for treatment verification purposes. These two sets of points should be located as closely as possible to the defined volumes to minimize errors during beam patient setup. Since diagnostic images generally represent a "frozen" situation, a margin has to be included in the volumes defined in such a way as to account for movements of the tissues relative to the *Local Patient Coordinate System*. The reference points have to be as fixed as possible to the actual tissues to minimize treatment margins. Suggestions on the selection of anatomic reference points are given in Fig. 2 and Appendix I. These reference points should in turn be used for beam setup and portal verification (cf. Fig. 10). Because of inaccuracies in beam patient alignment and treatment unit coordinates, a margin has to be added to the beam periphery to account for uncertainties and variations in the beam alignment relative to the *External Reference Points* (cf. Fig. 6). For each external beam

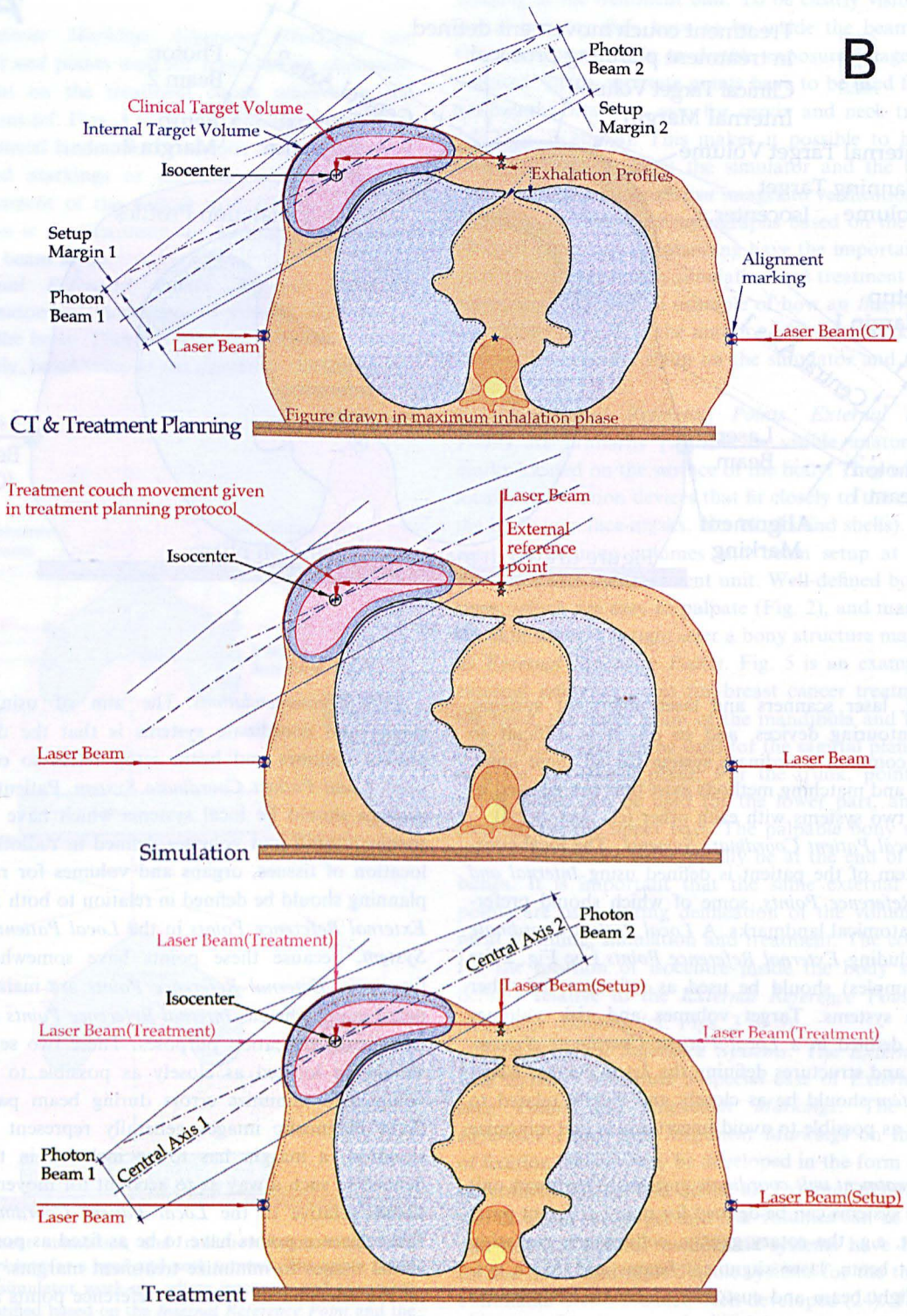

Fig. 5. Illustration of the patient setup using *Internal* and *External Reference Points* for the treatment of a mammary carcinoma by opposed photon beams. In (A) the patient alignment during CT imaging and the location of isocentre and *Setup Margins* during treatment planning are shown in close-up. The three figures in (B) represent treatment planning, simulation and radiation therapy, respectively. For this breast cancer patient the effect of breathing is substantial, as seen by the wide *Internal Margin* and the motion of *External* relative to the *Internal Reference Point*. The dashed lines represent the patient's cross section during maximum exhalation, showing that the chest wall and the *External Reference Point* move substantially, whereas the internal one remains almost fixed on the couch. This motion makes the *Setup Margin* in the beam coordinate system much larger for a tangential quasi parallel opposed photon technique (as shown in the figure) than for example for a perpendicular electron or proton beam irradiation. The *Internal Margin* towards the lung is largely determined by the lung movement, whereas the skin surface is the outer border. It is also seen that the outer *Setup Margin* is wider than that towards the lung, since there is no organ at risk outside the skin but the lung is very sensitive.

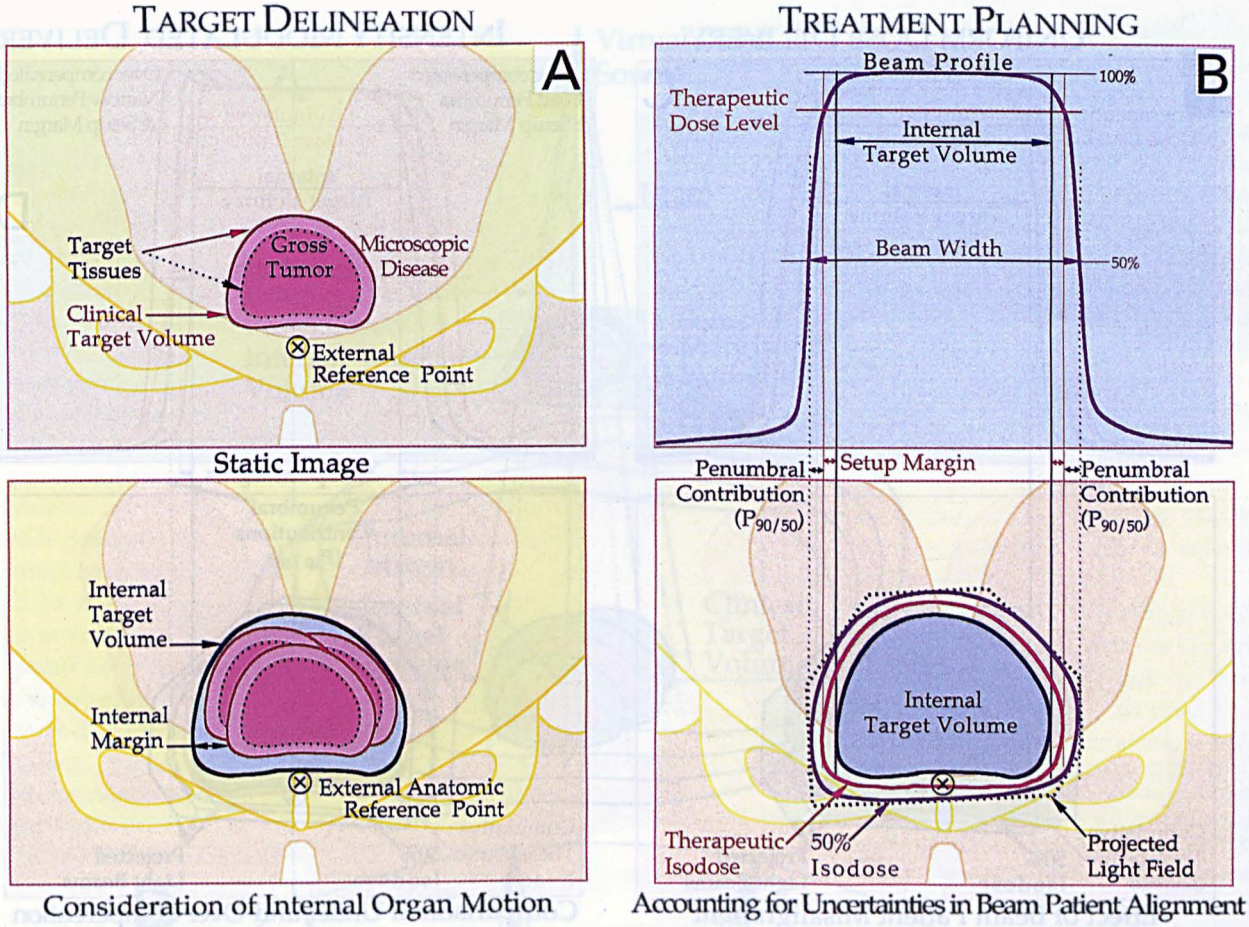

Fig. 6A, B

the treatment planning system should be able to add a margin in a beam's eye-view projection to account for these setup uncertainties, as illustrated in Figs. 7A and 6B (cf. (26) and Sect. 3.3.6).

For portal imaging it is sometimes difficult to find good internal reference points, e.g. for small beams in the abdominal region. Special action has to be taken to verify setup in such situations by using the double-exposure technique (low-dose image with increased field size) or by a beam in a different direction.

3.3 Treatment geometry

For *Curative Radiation Therapy*, the target tissues consist of all tissues that may contain clonogenic tumour cells. Therefore, the target tissues often have to include normal tissues, such as lymph vessels and supportive stroma, to ensure a curative dose to all clonogenic tumour cells. For *Postoperative Radiation Therapy* no gross tumour may be left, and the target tissues are those suspected of harbouring subclinical malignant disease. In some regions, e.g. in the head, the target tissues may be delineated partly by osseous barriers, partly by surfaces, or they may on clinical grounds include volumes with known probability of subclinical spread. Thus, by target tissues is understood tumour tissues or tissues with a sufficiently high probability of microscopic tumour spread to make it relevant for *Curative Radiation Therapy*.

Most target tissues are mobile in the *Local Patient Coordinate System* and thus cannot readily be defined as fixed volumes in the patient. However, by using *External Reference Points* for patient setup and a suitable internal margin around organs and target tissues for internal organ motions and changes of their shape and size, it is often possible to identify a well-defined internal volume which is fixed in the *Local Patient Coordinate System* and always includes the organs or target tissues. Fig. 5 illustrates a common difficult case where there is a substantial influence of breathing motions on the breast and the associated *External Reference Point*. In such a case it is recommended that the CT or MR images for treatment planning are recorded in the maximum inhalation phase to make sure that this extreme position of the target tissues can be fully considered. Also the maximum exhalation phase needs to be considered when estimating the required margins (see Fig. 5), unless the treatment is synchronized to the breathing motions. By adding a margin for internal organ mo-

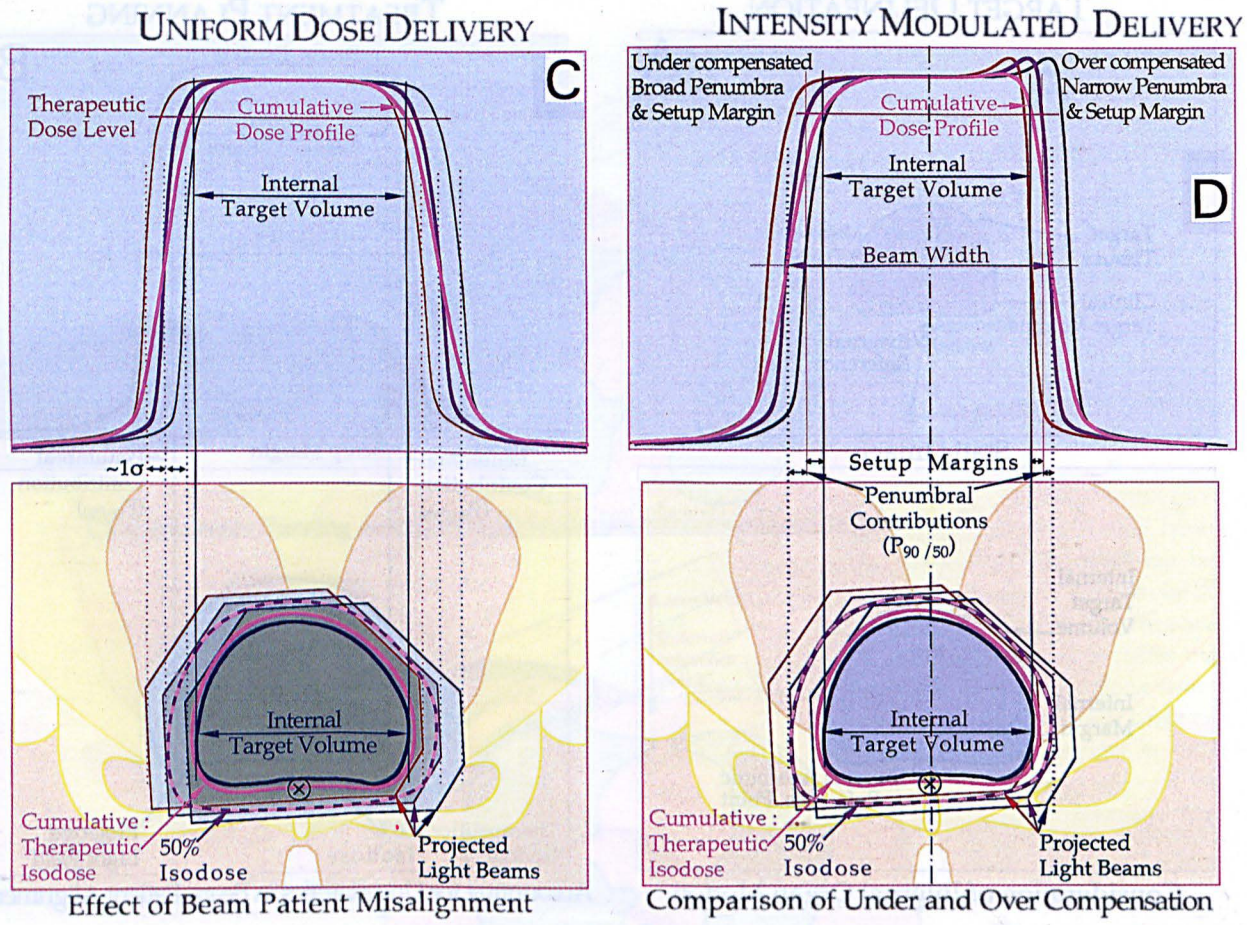

Fig. 6. Schematic illustration of the handling of internal organ motions and the setup uncertainty during target volume definition and treatment delivery. (A) Schematic image of a prostate tumour as it may appear in relation to the *External Reference Point* on a series of three digitally reconstructed radiographs, simulation or verification films (cf. also Fig. 10). During radiotherapy, the target tissues and the *Clinical Target Volume* move particularly due to varying rectal and bladder content, so an *Internal Margin* has to be added to it in order always to have a well-defined *Internal Target Volume* fixed in relation to the *External* and *Internal Reference Point*. Knowledge about the internal organ motions is thus required if the *Internal Margin* and the *Internal Target Volume* are to be accurately delineated. (B) The bony structures are never perfectly stationary in the coordinate system of the beam. The skin marks may also move relative to bony structures because of the elasticity of the skin. There are also movements of the radiation beam relative to the gantry coordinate setting and the light field. All these motions and uncertainties of the beam in relation to the *Internal Target Volume* may be considered by adding a *Setup Margin* to the beam cross section in beam's eye view during treatment planning (cf. also Fig. 7A). (C) During radiation therapy the total cumulative dose profile can be calculated by summing the dose profiles of the quasi randomly positioned beams corresponding to the actual dose delivery. The *Setup Margins* should thus be chosen during the dose planning process, such that the cumulative therapeutic isodose delivered during the whole treatment series really encloses the *Internal Target Volume*. The dashed 50% isodose is approximately coinciding for the most probable single beam and the cumulative dose distribution. (D) It can be shown, based on radiobiological arguments, that a somewhat better alternative to a uniform beam with a broad *Setup Margin* is to use an overcompensated beam with a narrow margin (23, 25). As illustrated in the upper dose profile and the lower isodose image a closer conformal treatment is possible by using overcompensated beams with a reduced *Setup Margin*.

tions around the target tissues, to get a target volume which is fixed in the local patient coordinate system, it is possible to use a single dose plan with stationary beams and always be sure that all target tissues receive full dose during treatment (cf. Figs. 5 and 6). However, the margin on the target tissues implies that normal tissues around the target tissues have to be irradiated. Therefore, one of the principal aims of radiation therapy will always be to make such margins as narrow as possible consistent with adequate target coverage. However, the goal to reduce margins can only be achieved by strenuous development of accurate treatment techniques and precise fixation methods. It is therefore important that all types of uncertainties are included in the margins such as aposteriori or random uncertainties and apriori or systematic uncertainties (5) and their combined effect as measured, for example, by their total equivalent variances (cf. Appendix II and 27).

There are a few cases when the internal margin can almost be disregarded, such as when the target tissues are closely connected to bony structures and cannot move, e.g.

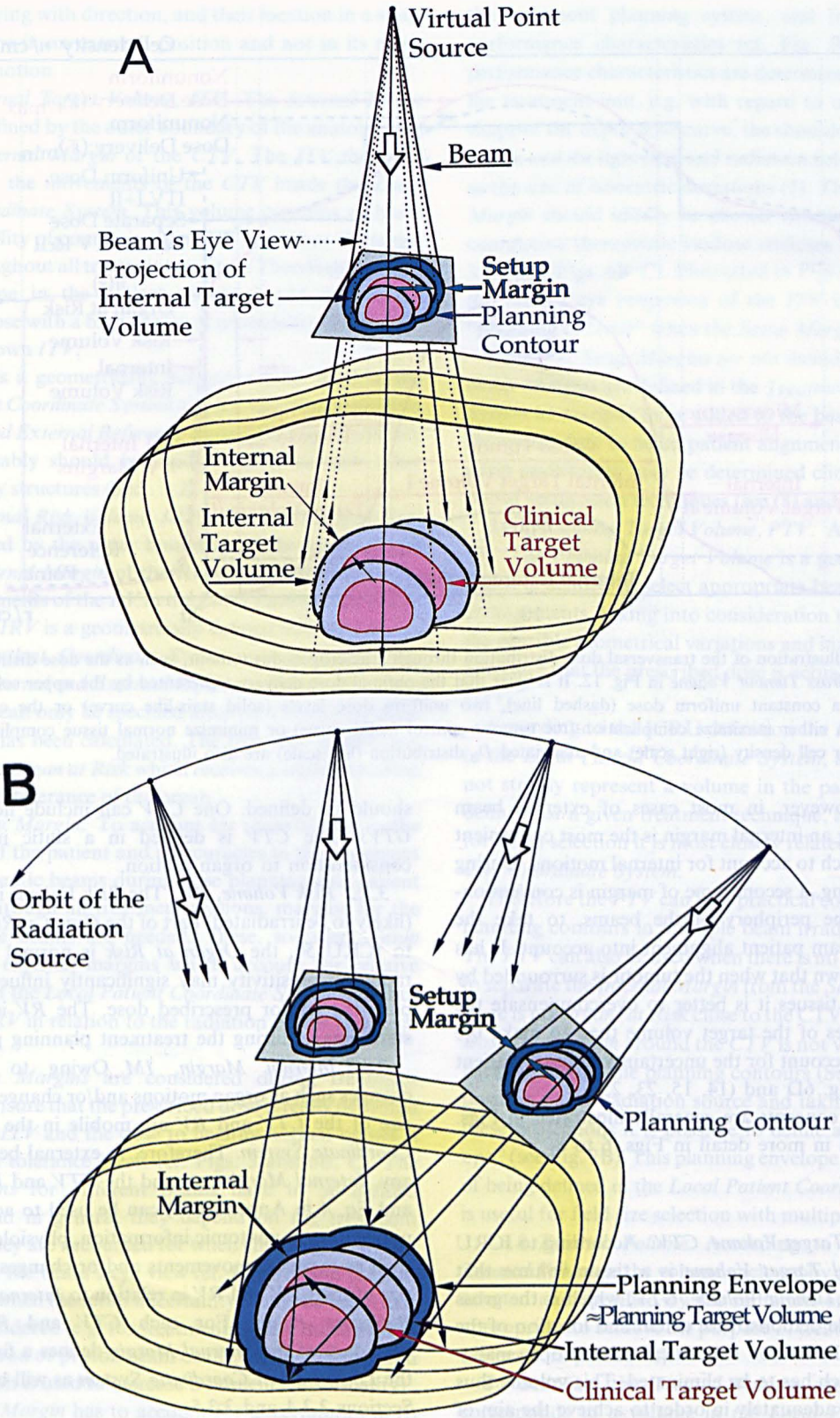

Fig. 7. (A) Illustration of how the *Setup Margin* is added to the beam's eye view projection of the *Internal Target Volume* (drawn on a stack of CT or MR slices) to get the Planning Contour of the therapeutic beam. (B) By back-projection of the planning contours from a set of conformal beams it is possible to define a planning envelope in the *Local Patient Coordinate System*, namely the envelope of all back-projected planning contours. This volume is closely related to the *Planning Target Volume*.

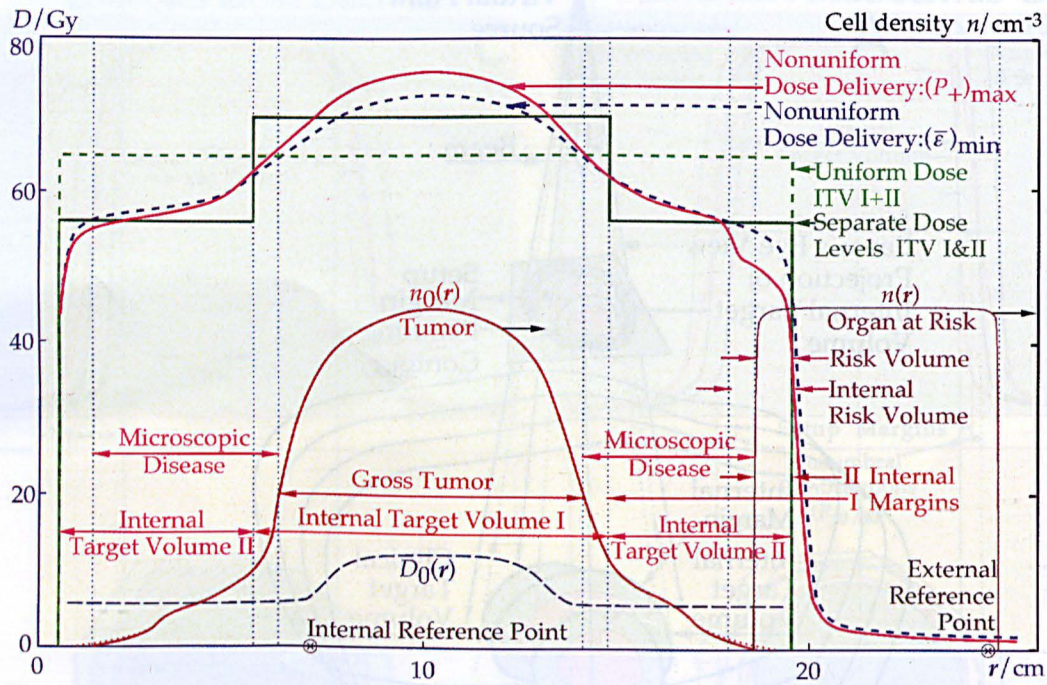

Fig. 8. Schematic illustration of the transversal dose distribution through a heterogeneous tumour, such as the dose distribution through the centre of the *Gross Tumour Volume* in Fig. 12. It is clear that the optimal dose delivery represented by the upper solid curve can be approximated by a constant uniform dose (dashed line), two uniform dose levels (solid stair-like curve) or the continuous dose distributions which either maximize complication-free tumour control (solid curve) or minimize normal tissue complications (dashed curve). The tumour cell density (right scale) and associated D_0 distribution (left scale) are also illustrated.

in the head. However, in most cases of external beam radiation therapy an internal margin is the most convenient technique by which to account for internal motions. During treatment planning, a second type of margin is conventionally added to the periphery of the beams, to take the uncertainty in beam patient alignment into account. It has recently been shown that when the tumour is surrounded by sensitive normal tissues it is better to overcompensate the beam at the edges of the target volume than to make the beams wider to account for the uncertainty in beam patient alignment (cf. Fig. 6D and (14, 15, 23, 25)).

The following concepts are generally illustrated in Figs. 3–5 and 12, and in more detail in Figs. 6 to 8.

DEFINITIONS

3.3.1 Clinical Target Volume, CTV. According to ICRU 50: "The *Clinical Target Volume* is a tissue volume that contains a *Gross Tumour Volume, GTV*, which is the gross palpable or visible/demonstrable extent and location of the malignant growth, and/or subclinical microscopic malignant disease, which has to be eliminated. This volume thus has to be treated adequately in order to achieve the aim of therapy: cure or palliation."

One or several *CTVs* can be specified in a patient at the same time. For each target tissue to be treated according to a prescribed dose fractionation schedule a separate *CTV* should be defined. One *CTV* can include none or several *GTVs*. The *CTV* is defined in a static image without consideration to organ motion.

3.3.2 Risk Volume, RV. The *Risk Volume* is the potential (likely to be irradiated) part of the *Organ at Risk*. According to ICRU 50, the *Organ at Risk* is normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed dose. The *RV* is defined in a static image during the treatment planning procedure.

3.3.3 Internal Margin, IM. Owing to physiological changes such as organ motions and/or changes in shape and size of the *CTV* and *RV* are mobile in the *Local Patient Coordinate System*. Therefore, in external beam radiotherapy, *Internal Margins* around the *CTV* and *RV* (see Fig. 3 and Eq. 4 in Appendix II) can be used to account for the uncertainty in anatomic information, physiological changes such as expected movements and/or changes of shape and size of the *CTV* and *RV* in relation to *Internal and External Reference Points*. For each *CTV* and *RV* the outer boundary of the *Internal Margin* defines a fixed volume in the *Local Patient Coordinate System* as will be discussed in Sections 3.3.4 and 3.3.5.

Since the *Internal Margin* should be anatomically adjusted, it is not recommended that a constant margin always be added around the *CTV* and *RV* in a static image. This is because the movements of the *CTV* and *RV* can be

strongly varying with direction, and their location in a static image may be in an extreme position and not in its mean position of motion.

3.3.4 Internal Target Volume, ITV. The *Internal Target Volume* is defined by the outer boundary of the anatomically adjusted *Internal Margin* of the *CTV*. The *ITV* therefore accounts for the movements of the *CTV* inside the *Local Patient Coordinate System*. This volume contains or has a high probability of containing the *CTV*, and thus the target tissues, throughout all treatment sessions. Therefore, the *ITV* is the volume in the patient which should receive the prescribed dose with a high degree of probability. Each *CTV* will have its own *ITV*.

The *ITV* is a geometrically defined volume fixed in the *Local Patient Coordinate System* and it is specified in relation to *Internal and External Reference Points* (see Figs. 3 and 12), which preferably should be rigidly related to each other through bony structures (Sect. 3.2).

3.3.5 Internal Risk Volume, IRV. The *Internal Risk Volume* is defined by the outer boundary of the anatomically adjusted *Internal Margin* of the *RV* and therefore accounts for the movements of the *RV* in the *Local Patient Coordinate System*. The *IRV* is a geometrically defined volume fixed in the *Local Patient Coordinate System* and is specified in relation to *Internal and External Reference Points*. Note that the true *IRV* can only be specified after the *Cumulative Dose Distribution* has been calculated. The true *IRV* is then that volume of the *Organ at Risk* which receives a significant dose with regard to tolerance of the organ.

3.3.6 Setup Margin. To account for uncertainties in the positioning of the patient and inaccuracies in the alignment of the therapeutic beams during dose planning and patient irradiation through all treatment sessions, margins for the setting of the beams are needed. These, so-called, *Setup Margins* are external margins which account for relative movements of the *Local Patient Coordinate System* and thus the *ITV* or *IRV* in relation to the radiation beams (see Sect. 3.2.8).

The *Setup Margins* are considered during treatment planning to ensure that the prescribed dose is really delivered to the whole *ITV* and the dose to healthy normal tissues is below agreed tolerance levels (cf. Figs. 3 and 6B, C). The *Setup Margins* for different beams have to be defined separately and in general they depend on the treatment technique. They are accounted for when choosing treatment beam sizes in the beam's eye view (cf. Fig. 7A and (28)) or beam energy when the setup uncertainty along the beam axis has to be considered (e.g. for treatments where the distal fall off in an electron or proton beam or the width of the photon build-up region is used to increase treatment conformality).

The *Setup Margin* has to account for uncertainties in (i) patient positioning (interfractional movements), (ii) movements of the patient during each treatment fraction (intrafractional movements), (iii) dose planning and treatment technique in general through the geometrical resolution of the treatment planning system, and (iv) treatment unit performance characteristics (cf. Fig. 5). Treatment unit performance characteristics are determined by the quality of the treatment unit, e.g. with regard to uncertainties in the shape of the depth dose curve, the shoulder of the penumbra region and the light field and radiation field alignment as well as the size of isocentric deviations (5). The size of the *Setup Margin* should ideally be chosen iteratively, such that the cumulative therapeutic isodose encloses the *ITV* (see Sect. 3.2.8 and Figs. 6B, C). Illustrated in Figs. 7A and 7B is how the beam's eye projection of the *ITV* is increased to the "planning contour" when the *Setup Margin* is added.

Note that *Setup Margins* are not included in the ITV. The *Setup Margins* are defined in the *Treatment Unit Coordinate System* as margins to be added to the beams to account for the uncertainty in beam patient alignment (cf. Fig. 11). The setup uncertainty may be determined clinically by repeated portal verification techniques (see (8) and Sect. 4.1).

3.3.7 Planning Target Volume, PTV. According to ICRU 50: "The *Planning Target Volume* is a geometrical concept, and it is defined to select appropriate beam sizes and beam arrangements, taking into consideration the net effect of all the possible geometrical variations and inaccuracies in order to ensure that the prescribed dose is actually absorbed in the *CTV*."

According to the ICRU definition the *PTV* is not defined in the *Local Patient Coordinate System*, and therefore does not strictly represent a volume in the patient. The *PTV* is defined for a given treatment technique, and since it is used for beam selection it is most closely related to the *Treatment Unit Coordinate System*.

Therefore the *PTV* can be a practical concept for selecting planning contours in multiple beam irradiation techniques. The *PTV* can also be used when there is no need or possibility to separate the *Internal Margin* from the *Setup Margin*, e.g. if there is no *Organs at Risk* close to the CTV or the *Cumulative Dose Distribution* around the *CTV* is not very important. By back-projecting the planning contours (Sect. 3.3.6) for each position of the radiation source and taking the envelope of these projections it is possible to define a "planning envelope" (see Fig. 7B). This planning envelope has the advantage of being defined in the *Local Patient Coordinate System* and is useful for field size selection with multiple beam portals.

3.3.8 Treated Volume. According to ICRU 50: "The *Treated Volume* is the volume enclosed by an isodose surface, selected and specified by the radiation oncologist as being appropriate to achieve the purpose of treatment (e.g. tumour eradication, palliation)."

To delineate the *Treated Volume* correctly, so that it corresponds to a volume in *the Local Patient Coordinate System*, the real *Cumulative Dose Distribution* should be used considering all possible movements of the *Local Patient Coordinate System* relative to the treatment beams delivered to the patient.

3.3.9 Irradiated Volume. According to ICRU 50: "The *Irradiated Volume* is that tissue volume which receives a dose that is considered significant in relation to normal tissue tolerance."

To specify the *Irradiated Volume* correctly, so that it corresponds to a tissue volume in the *Local Patient Coordinate System*, the *Cumulative Dose Distribution* should be used by considering the movements of the *Local Patient Coordinate System* relative to the treatment beams.

3.3.10 Cold Volume. A *Cold Volume* is a volume inside the *ITV* which receives a dose that is lower than the prescribed dose to the *CTV* by an amount that is larger than the tolerance limit (see Sect. 3.4). For practical purposes, a tolerance limit of 5% (one relative standard deviation) is generally recommended if nothing else is stated. To specify the size of the *Cold Volume* correctly, the *Cumulative Dose Distribution* really delivered to the patient should be considered (cf. Fig. 6C).

3.3.11 Hot Volume. A *Hot Volume* is a volume in the *Local Patient Coordinate System* which receives a dose larger than the prescribed dose by an amount larger than the tolerance limit. For practical purposes, an upper limit of the tolerance range of 5% is generally recommended if nothing else is stated. A *Hot Volume* outside the ITV is often called a *Hot Spot* (cf. ICRU 50). To specify the size of the *Hot Volume* (or *Hot Spot*) correctly, the *Cumulative Dose Distribution* should be considered (cf. Fig. 6C).

3.3.12 Recommendations

Determination of extent of disease and selection of treatment technique. For treatment planning, the *Gross Tumour Volume* can often be well localized by palpation, ultrasound, X-rays, CT, MR, gamma camera, SPECT, PET and/or other diagnostic techniques as discussed in Section 2.3. Sometimes also the extension of the subclinical malignant disease for delineation of the *Clinical Target Volume* can be estimated from the anatomy by some of these latter methods, but often its delineation has to be based on the accumulated clinical experience on the pattern of spread and recurrence of the disease by stage. From the point of view of dose delivery, the radiation therapy situation may therefore be schematically illustrated as shown in Fig. 8. The *GTV* is generally the primary tumour and its direct infiltration into surrounding tissues with a density of tumour cells above the detection limit for the diagnostic methods at hand. If the gross tumour extends continuously to identified macroscopic metastases such as in lymph nodes, these may be included in the same *GTV* as the primary tumour, depending on the clinical situation such as the prescribed dose level and other treatment options. Because a fairly homogeneous dose within a continuous tumour area is usually preferred, a single *GTV* is usually used. When the gross tumour alone is to be treated in accordance with a prescribed time dose pattern, the associated *Internal Target Volume* should also include an *Internal Margin* for the uncertainty of the diagnostic method and for the possible range of motion inside the body of the tissues concerned during the treatment schedule, as indicated in the lower part of Fig. 8. In this situation the *GTV* comprises *CTV I.* The situation is similar for the *Internal Margin* of the subclinical malignant disease (*CTV II*), but the margin due to the uncertainty in the extension of microscopic spread will generally be the dominating one. This is because of our lack of knowledge about the exact extent of microscopic spread, as illustrated in Fig. 8 by the dotted lines at low tumour cell densities and discussed more in detail in Appendix II. *ITVs* and *Internal Risk Volumes* should be specified by or under the supervision of a qualified medical expert (preferably a *radiation oncologist*).

When the *ITVs* and *IRVs* have been accurately delineated relative to the *Internal and External Reference Points*, the dose delivery technique has to be considered. If there is no reason to suspect different sensitivities for the verified gross tumour and its presumed subclinical extension, and the tumour cell densities are not too different, a uniform dose delivery and therefore a single *CTV* and *ITV* may be sufficient, as shown schematically by the dashed rectangular dose distribution in Fig. 8.

However, if the verified gross disease is known to contain more resistant cell compartments, such as hypoxic tumour cells, and/or if the density of tumour clonogens is considerably lower in the subclinical region, different dose levels may be desirable. The definition of two or more distinct *ITVs* is then called for and the most suitable dose level for each should be specified. This case corresponds to the solid two levelled dose distribution in Fig. 8, and it could be delivered by a shrinking field technique towards the end of the treatment schedule, by concomitant boosts during the course of treatment or even by non-uniform dose delivery during each and every treatment session. In a *Hot Volume*, both the dose and the dose per fraction are high and thus also the probability of complications being induced extra high, a phenomenon often referred to as double trouble (29). By the intensity modulation in Fig. 8 the double trouble problem is converted to a double or even triple advantage. This is so since the dose delivery is reduced where significant amounts of normal tissues can be damaged, and so the dose, the dose rate and the dose per fraction are low and the steepness of the dose response relation is high. These effects result in a significantly reduced risk of complications being induced ((18) and Sect. 4.6). In principle, the different *Internal Target Volumes* do not necessarily need to be associated with prescribed fixed mean doses. In the future, one could for example perform a biological optimization in many cases (23, 30, 31), resulting in an optimal non-uniform dose distribution in the target volume with lower dose at the border to organs at risk. The present definition of *Internal Target Volumes* will therefore be very suitable also in the future when the target may be defined more in terms of volumes of approximately

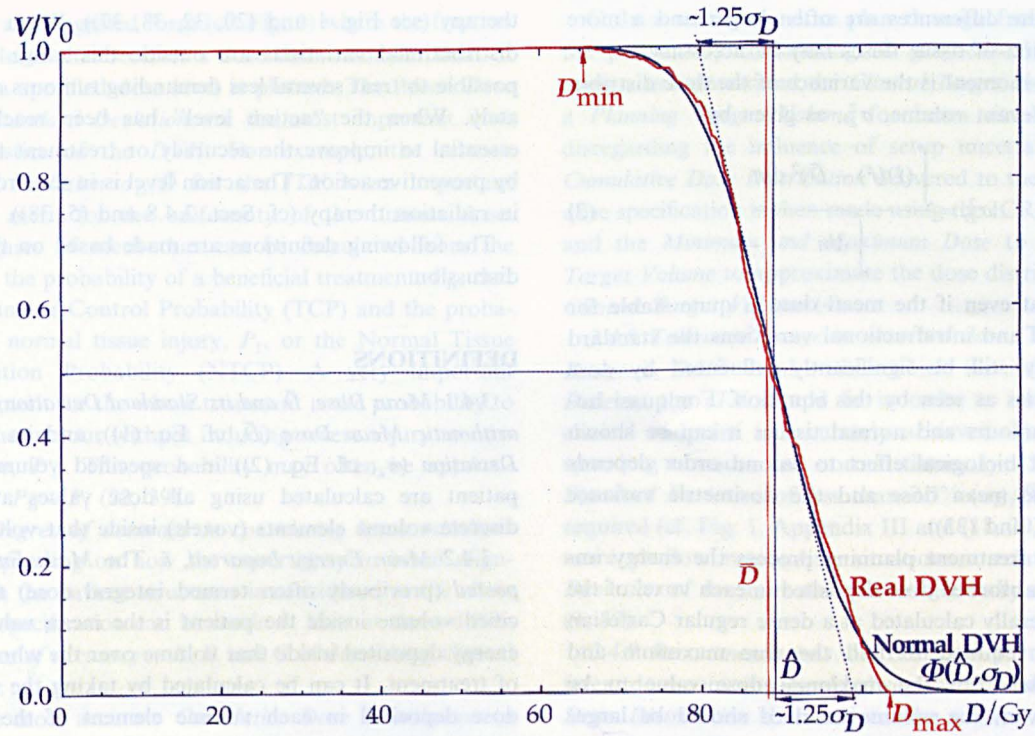

Fig. 9. Comparison of the *Dose Volume Histogram* for a biologically optimized treatment of the advanced cervix tumour in Fig. 3 (solid curve) with the curve expected for a pure Gaussian process with the right $\bar{D}$ and σ_D (dotted curve). It is seen that the main characteristics of the *Dose Volume Histogram* of the *Internal Target Volume* are quite well described by the *Mean Dose* and its *Standard Deviation* (34).

known tumour clonogen density and sensitivity rather than estimated dose prescriptions.

In brachytherapy, where the radiation sources move freely together with the target tissues, an *Internal Margin* may not be needed, and the *ITV* will include only the *CTV*. In such cases the radiation source or applicator could be regarded as an internal reference system (cf. Sect. 3.2.4).

3.4 Dose concepts

In order to quantify the radiotherapeutic effects of a delivered dose distribution, simple and relevant dose distribution parameters should be used. The time and dose fractionations are the most important characteristics of the delivered dose distribution in relevant volumes, and should be described to allow accurate quantification of radiation effects. In fractionated radiotherapy it is important to realize that the dose distribution in the patient will vary from fraction to fraction and even during each treatment fraction. Therefore, in addition to the time *Cumulative Dose Distributional* parameters these temporal variations have to be considered. For quasi uniform tumours the first two moments of the dose distribution (i.e. the mean dose Eq. (1) and its standard deviation Eq. (2)) are the most important quantifiers for the radiation effects in normal and malignant tissues (32, 33). In many cases these two measures of the dose delivery also describe the main characteristics of the dose volume histogram as illustrated in Fig. 9 (34).

The first moment is the mean dose, $\bar{D}$, deposited in the volume or organ in question. This quantity is important as it quantifies the mean energy imparted, $\bar{\varepsilon}$, to the tissue according to:

$$\bar{D} = \frac{\bar{\varepsilon}}{m} = \frac{\int D(\vec{r})\,\mathrm{d}m}{\int \mathrm{d}m} = \frac{\int D(\vec{r})\rho(\vec{r})\,\mathrm{d}v}{\int \rho(\vec{r})\,\mathrm{d}v} \approx \frac{\int D(\vec{r})\,\mathrm{d}v}{\int \mathrm{d}v} \quad (\text{if } \rho = 1) \tag{1}$$

Here $D(\vec{r})$ is the *Cumulative Dose Distribution* absorbed in the patient during the course of treatment.

It is not surprising that the mean dose is clinically relevant, since it quantifies the amount of energy absorbed locally and the associated biological effect (32, 35). For tissues that are closely water equivalent in density the mass-averaged and the volume-averaged absorbed dose values are almost the same according to the approximation in Eq. (1). To be more precise, for electron and photon beams the absorbed dose to a tissue is actually given as the absorbed dose to small volume elements of water inside the tissue in question, since the differences are generally less than 1% (5). However, for neutrons and other high

LET beams the differences are often larger and a more strict calculation of tissue doses may be necessary.

The second moment is the variance of the dose distribution in the relevant volume, σ_D^2, as given by:

$$\sigma_D^2 = \frac{\int (D(\vec{r}) - \bar{D})^2 \, dm}{\int dm} \qquad (2)$$

It is clear that even if the mean dose is quite stable for interfractional and intrafractional variations the standard deviation may still be significantly influenced by dose non-uniformities as seen by this equation. For quasi homogeneous tumours and normal tissues it can be shown that the exact biological effect to second order depends mainly on the mean dose and the dosimetric variance (Appendix III and (33)).

During the treatment planning process the energy imparted or the absorbed dose deposited in each voxel of the patient is generally calculated at a dense regular Cartesian grid. This is required to find the true maximum and minimum doses. For the maximum dose value to be clinically relevant the volume involved should be larger than 2 cm^3. In fact, from a clinical viewpoint it is important to report if the *Mean Energy Imparted* (cf. Eq. (1) and Sect. 3.4.2) is increased significantly in relation to the dosimetric precision requirements at hand and to the prescribed mean dose and thus the mean energy imparted to the tumour according to the dose plan. Thus an increase in the mean energy imparted of about 3–5% in general is clinically significant. This could be the case either by a dose increase of 10–15% in one-third of the *ITV* or by a still larger increase in a smaller portion of the *ITV* (33, 35, 36). In cases where only a 1D or 2D planning is made it is straightforward to simplify Eqs. (1) and (2) such that they are only averaged over the depth or the central slice of the patient. For example, the customary midline dose is closely related to the mean dose over a volume around the mid-point on the central axis. It is also possible to account more accurately for the missing dimension when the extension of the tumour or the organ at risk is approximately known in these directions.

The minimum dose is easier to define since there is always a finite risk of having many clonogenic tumour cells in any part of the *ITV* where the absorbed dose is low. Therefore the minimum dose in very small voxels or even at points may be of considerable clinical interest, and it is good practice to quote the minimum dose as the mean value in a volume element (voxel) not larger than 0.1 cm^3. It should therefore be pointed out that interfractional and intrafractional dose variations may have a significant influence on the minimum dose.

The range of acceptable dose variations for quasi uniform tumours is often called the *Tolerance Range* (see Sect. 3.4.8) and is in the order of 3% ($\sigma_D/\bar{D}$) in radiation therapy (see Fig. 1 and (20, 32, 33, 37)). When the dose distributional variations are outside this range it is still possible to treat several less demanding tumours appropriately. When the "action level" has been reached it is essential to improve the accuracy or treatment technique by preventive action. The action level is in the order of 5% in radiation therapy (cf. Sect. 3.4.8 and (5, 38)).

The following definitions are made based on the above discussion.

DEFINITIONS

3.4.1 Mean Dose, $\bar{D}$ and its Standard Deviation, σ_D. The *arithmetic Mean Dose* ($\bar{D}$, cf. Eq. (1)), and its *Standard Deviation* (σ_D cf. Eq. (2)) in a specified volume in the patient are calculated using all dose values at all the discrete volume elements (voxels) inside that volume.

3.4.2 Mean Energy Imparted, $\bar{\varepsilon}$. The *Mean Energy Imparted* (previously often termed integral dose) to a specified volume inside the patient is the mean value of the energy deposited inside that volume over the whole course of treatment. It can be calculated by taking the absorbed dose deposited in each volume element of the volume, multiplying it by the voxel mass and integrating the products over all voxels inside the volume of interest in the patient ($\bar{\varepsilon}$ cf. Eq. (1)).

3.4.3 Point Dose, D_p. The *absorbed dose at a point* (D_p) is a dose value calculated at a specified point or voxel in the patient. Of particular interest for compliance with the ICRU recommendations is the absorbed dose at the ICRU reference point (4).

3.4.4 Minimum Dose, D_{min}. The *Minimum Dose* in a specified volume in the patient is the lowest dose value in any of the voxels inside this volume.

3.4.5 Maximum Dose, D_{max}. The *Maximum Dose* in a specified volume in the patient is the highest dose value in any of the voxels inside this volume.

3.4.6 Cumulative Dose Distribution. The *Cumulative Dose Distribution* is most extensively defined by the dose distribution matrix describing the total absorbed dose delivered to each of the individual volume elements of the patient during fractionated radiotherapy. In this way the dose to various organs is accurately defined and linked to their respective volume elements. When precision in beam patient alignment and accuracy in dose delivery are very high it may be sufficient to use one fixed dose plan. In the general case it might be desirable to combine dose plans for a nominal beam, one where the alignment has been altered by one standard deviation up and down in relevant directions to account for positional uncertainties (26). When the geometric relation is of minor importance the *Dose Distribution* can be reduced to a *Dose Volume Histogram* (*DVH*) for an organ or volume of interest. Then the fractional volume of that organ is plotted against the absorbed dose value it receives. Often the *DVH* is pre-

sented in an integrated form (cf. Fig. 9) where the fraction of the volume that receives a dose that is smaller than or equal to a specified dose level is plotted. The *Mean Dose* and its *Standard Deviation* are the most important dose characteristics of the *DVH*. For example, the relative *Standard Deviation* $\sigma_D/\bar{D}$ for the *ITV* is an important figure of merit for the uniformity of the tumour dose. Other figures of merit that can be calculated from the *DVH* are the probability of a beneficial treatment, P_B, that is, the Tumour Control Probability (TCP) and the probability for normal tissue injury, P_I, or the Normal Tissue Complication Probability (NTCP). A very important figure of merit for the whole treatment is the probability to control the tumour without inducing severe injury to normal tissue, P_+. This probability may often be approximated by $P_B - P_I$ (22, 39).

3.4.7 Degree of accuracy in considering beam misalignment. Depending on how the uncertainty in beam alignment with the patient structures is considered at the clinic the dose specification can be made at least at three different *degrees of accuracy*—A, B and C of decreasing clinical relevance:

A. The most accurate *Cumulative Dose Distribution* to the *Clinical Target Volumes* and the *Risk Volumes* can be obtained using concomitant in vivo dosimetry, portal imaging and CT or MRI to determine the actual location of the target tissues and *Organs at Risk* in relation to all delivered treatment beams. With this quite complex method the most relevant dose distribution parameters can be determined (15, 23, 25). If the dose distribution in the *Internal Target Volume* is inside the *Tolerance Range* (see Sect. 3.4.8), this method will not increase the accuracy of different dose values in the *Clinical Target Volume* much, but the absorbed dose to and size of the *Internal Risk Volume* will always be more accurately determined by this method if the dose gradient in the *Risk Volume* is high. This degree of accuracy is achieved today mainly in research procedures and generally not in routine radiotherapy.

B. Taking internal organ motions and the influence of setup uncertainties on the *Cumulative Dose Distribution* delivered to the patient into account, by using the *Mean Dose* and its relative *Standard Deviation* in the *Internal Target Volume* and the true *Internal Risk Volume*.

When the relative *Standard Deviation* of the *Dose Distribution* is larger than the *Tolerance Range* (often 3–5%), the *Minimum Dose* in the *Internal Target Volume* and the *Mean Dose* in the *Hot* and *Cold Volumes* should be stated. For strongly serial tissues like spinal cord, esophagus and colon the *Maximum Dose* to the *Organ at Risk* should also be stated.

To allow a more detailed follow-up the complete dose plan and *Dose Volume Histograms* for *Internal Target Volumes* and *Internal Risk Volumes* and other volumes of interest should be recorded.

C. In a stationary dose plan through frozen images of the patient, by considering all geometrical uncertainties using a margin around the *Clinical Target Volume* to form a *Planning Target Volume* for beam size selection but disregarding the influence of setup uncertainties on the *Cumulative Dose Distribution* delivered to the patient. The dose specification is then made using the ICRU *Point Dose* and the *Minimum and Maximum Dose* to the *Planning Target Volume* to approximate the dose distribution to the *Clinical Target Volume* (4).

3.4.8 Tolerance Range in absorbed dose. The *Tolerance Range* is the interval within which the delivered *Mean Dose* to the *ITV* should be in order to ensure that the clinical endpoint is accurately achieved. For steeply responding tumours and normal tissues ($\gamma > 2.0$) a relative *Standard Deviation* of less than 2.5% ($\sigma_D/\bar{D}$) is generally required (cf. Fig. 1, Appendix III and (18, 20, 32, 33)). For more shallow responding situations a relative *Standard Deviation* of no more than 5% is generally recommended (9, 37).

3.4.9 Recommendations. In radiation therapy, the different dose concepts should always describe the *Cumulative Dose Distribution* delivered to the patient as closely as possible (see Fig. 6C and D). The present recommendations require specification at least at the B *Degree of Accuracy* (cf. Sect. 3.4.7) in considering the uncertainty in beam alignment with patient structures. This implies that the two basic dosimetric concepts, the *Mean Dose*, $\bar{D}$, and its *Standard Deviation*, σ_D, to the *Internal Target Volume* should be used both for treatment prescription and reporting of radiation therapy procedures. The prescribed absorbed dose is therefore the *Mean Dose* $\bar{D}$ to the *Internal Target Volume* required to induce the desired clinical endpoint. To indicate the degree of dose homogeneity in the *ITV* it is recommended that, in addition to the *Mean Dose* delivered to the *ITV*, one should also report the relative *Standard Deviation* around the *Mean Dose* ($\sigma_D/\bar{D}$) (cf. Eq. (2)). It is often assumed that the actually delivered dose should be within the *Tolerance Range* from the prescribed *Mean Dose*. The relative *Standard Deviation* is a measure of the degree of uniformity of the *Dose Distribution* in a volume and is therefore an important figure of merit for the dose delivery to the *ITV*. When the relative *Standard Deviation* of the *Dose Distribution* is larger than the *Tolerance Range*, also the *Minimum Dose* to the *ITV* and the *Mean Dose* delivered to the *Hot* and *Cold Volumes* (cf. Sect. 3.3.11) should be reported. To get a more detailed description of the *Dose Distribution* the whole *Dose Volume Histogram* for the *ITV* and the *Internal Risk Volumes* should be recorded. With multiple *ITVs* these quantities have to be given for each *ITV*.

To allow accurate comparison with the dose concepts of the ICRU recommendations, primarily the absorbed dose at the ICRU reference point—often located centrally in the *Internal Target Volume* or *Planning Target Volume*

near the intersection of beam axis—should be stated (4). The *Minimum* and *Maximum Doses* to the *PTV*, as recommended for reporting by the ICRU, are often good approximations to the *Minimum Dose* to the *ITV* and the *Mean Dose* to the *Hot Volume*, respectively. These latter dose concepts should ideally be determined for the *Cumulative Dose Distribution* delivered to the patient during the course of therapy (Degree of Accuracy B, cf. Sect. 3.4.7). This distribution could be approximated by considering the beam displacements during the course of treatment (as schematically indicated in Fig. 6C and D) or the method proposed by Goitein (26). If there are no methods at hand to calculate the *Cumulative Dose Distribution* the true *Minimum Dose* to the *ITV* may be approximated by the *Minimum Dose* to the *PTV* in a static situation (cf. Figs. 6B and C and Sect. 5: 2 and 3). For completeness and also for historical reasons it may be desirable over a transition period to use both the present recommendations and the concepts of the ICRU 50 or the upcoming ICRU report (17) (the *Minimum* and *Maximum Dose* to the *Planning Target Volume*). However, the present concepts are ideally suited for all practical clinical purposes since they are self-sufficient, clinically more relevant and sufficiently close to the corresponding ICRU concepts, considering the accuracy with which the latter could be determined.

To characterize the dose distribution to the *Organs at Risk*, the most relevant dose concepts will depend on the functional organization of the tissue. For strongly serial tissues like spinal cord, brain stem, brachial plexus, esophagus and small intestine the *Maximum Dose* to the organ is often most relevant. For parallel tissues like lung, liver and kidney the *Mean Dose* to the *Internal Risk Volume* is generally more relevant. When the tissue organization is unknown it is a good idea to report both the *Mean Dose* (and its *Standard Deviation*) to the *Internal Risk Volume* and the *Maximum Dose* to the *Organ at Risk*.

It is hoped that the present report will be found useful in clinical work and that it will stimulate the further development of improved treatment techniques and the collection of more accurate data in clinical trials.

3.5 Clinical and biological parameters

3.5.1 General. The influence of fractionation and dose rate on the biological effect of the prescribed dose has been intensively studied both experimentally and clinically. Over the years, a number of models have been proposed and used to estimate the biological effect of the delivered dose, depending on fractionation and dose rate. The Linear-Quadratic model (40, 41) and its extension to the Incomplete Repair Model (42), including an exponential function for the treatment time, is considered by many as the most relevant for clinical use. It is not the intention here to discuss various models, but parameters are defined below that are of importance for the biological effect and which should be considered and documented for each radiotherapy course.

The volume factor is also of fundamental interest. There are two aspects concerning the volume factor. First, the probability of cure for a certain dose decreases with increasing tumour size due to a larger number of clonogenic tumour cells. Secondly, the complication probability increases with increasing volume of the *Organ at Risk* that is irradiated (*Internal Risk Volume*). The increased probability of complications is dependent on the organization of cell populations and functional subunits of the *Organ at Risk*. It can be shown largely in agreement with clinical experience that serially organized tissues are mainly influenced by the *Maximum Dose*, whereas the effect in parallel tissues depends more on the volume irradiated and the *Mean Dose* (36, 39, 43, 44).

The intrinsic radiosensitivity of the relevant target cells is a strong determinant for tumour cure as well as acute and late normal tissue effects. Clonogenic assays offer a direct measurement of cell survival after various doses but are too slow for routine clinical use. Rapid methods are under development and will hopefully soon be available for the individual patient.

The influence of the overall treatment time on treatment outcome is strongly correlated to the cell proliferation rate of the tumour and normal tissues. For tumours, the S-phase fraction of the cell cycle was usually determined by the labelling index in vitro. However, the size of the S-phase fraction is not always strongly correlated to the proliferative capacity of the tissue. Therefore, today, it is replaced by determination of the potential doubling time, T_{pot}, using BudR or IudR labelling in vivo. A low T_{pot} value may indicate that a tumour will benefit from short radiotherapy courses using brachytherapy or accelerated fractionation with external beams. In this situation acute reacting tissues are dose limiting. Still, there is no routine clinical use of T_{pot} determinations.

Tumour hypoxia is certainly a problem for the eff ectiveness of radiotherapy. In spite of numerous studies in this field, it is still difficult to predict the influence of hypoxic clonogenic tumour cells on individual patients, as the possibility and degree of reoxygenation during fractionated treatment may vary from tumour to tumour. Recently, measuring oxygen tension in tumours using thin electrodes or PET imaging has been demonstrated as a feasible method, but one not yet in routine clinical use.

3.5.2 Radiation quality, dose and time factors. Parameters which influence the biological effect should be documented for each radiotherapy course. These are:

- Radiation qualities used
- Dose per fraction, constant or variable
- Interval between fractions
- Number of fractions
- Dose rate and treatment time for each dose fraction

- Rest periods
- Overall treatment time

In using multiple fractions per day one has to be aware that even interfraction intervals of 6–8 h are not enough for complete repair of sublethal damage in late responding tissues. This has been shown for spinal cord and vascular damage. Because of the importance of having complete repair of normal tissue damage between fractions, the long repair time has to be considered in the prescription of the total dose and its fractionation. With complex multiple field techniques the treatment time for the whole dose fraction may be long enough to allow for significant repair and therefore result in a reduced radiation effect. This may occur even if each radiation field is delivered at a high dose rate. From this point of view multiple beam devices may have a biological advantage.

Furthermore, the dose-rate dependence for tumour cure as well as for acute and late normal tissue effects has to be considered. Low dose rates are less effective per unit dose than high dose rates. In the range 1–0.2 Gy/min the dose rate effect becomes clinically relevant, and below 0.05 Gy/min the dose-rate dependence is pronounced. The dose-rate sensitivity is stronger for late reacting tissues than for acutely reacting tissues, and for the majority of tumours it is probably similar to that for acutely reacting tissues largely due to the different shapes of the shoulders of the associated cell survival curves.

In general, rest periods during the treatment course should be avoided as tumour cell repopulation may be large. The extra dose required to counteract cell proliferation in the tumour might be in the order 0.3–0.6 Gy/day. Furthermore, there is no sparing of damage in late-reacting tissues during the rest period. Therefore, increasing the dose in order to compensate for tumour regrowth will almost always raise late side effects.

3.5.3 Tumour volume and stage. The probability of tumour cure at a certain dose level depends on the tumour volume, or, more precisely, the number of clonogenic cells in the tumour. Usually the tumour volume is described by the T-stage, but the size of regional lymph nodes is seldom specified. In order to improve the accuracy of dose–volume–response relationships it is recommended that the volume of the primary tumour and pathological enlarged nodes should be defined in CT or MR images. 3D-treatment planning systems should allow definition of subvolumes and calculation of relevant volumes and *Dose Volume Histograms*. Also the size of the *Irradiated Volume* (see Sect. 3.3.9) and the *Internal Risk Volume* should be estimated (see Sect. 3.3.2).

3.5.4 Biological factors. Routine determination of the intrinsic radio-sensitivity in terms of the surviving fraction at 2 Gy (SF2), or assessment of the relative radio-sensitivity by rapid methods for tumour and normal tissues, will probably be possible in the near future. Such parameters should be documented, as they are of major importance for individual treatment optimization. It is also urgent to establish reliable routine methods for estimating the cell proliferation rate in the tumour. T_{pot} is considered the most relevant at the moment, but further studies may show that T_{pot} is correlated to proliferation parameters such as Ki-67 and PCNA, investigated in the histopathological examination. Techniques for measuring the degree of hypoxia in the tumour and the degree of abolishment by reoxygenation during treatment execution are established and it is hoped will soon come into clinical use.

During follow-up it is important not only to follow treatment-related complications, but to investigate their possible correlation to tumour control or recurrence. Such correlations may be a valuable clinical indication for identification of subgroups of radiation-sensitive or radiation-resistant patients (22).

3.6 Physical and technical parameters of therapy equipment

3.6.1 General. The physical and technical parameters cover all those properties of the equipment used in the therapy procedure that influence the radiation beam and its location relative to *the Local Patient Coordinate System*. All of these parameters are generally included in the treatment plan or in the treatment record. However, most data that specify the treatment unit, simulator, diagnostic X-ray, CT or MR machine or equipment used in portal verification and patient dosimetry are not considered in detail in the treatment records but may instead be documented centrally for the whole radiation therapy department. It is then good practice not only to record all pertinent data for the different types of equipment but also the dates when they have been taken into use and when they have been replaced to simplify retrospective studies.

3.6.2 External radiation beams. If the whole treatment plan cannot be saved it is important to record the type of treatment units employed and the irradiation technique, including the number and direction of beam portals and whether fixed SSD or isocentric technique is used. Furthermore, the beam modalities—such as electrons or photons, beam energy—and the use of possible beam modifiers—such as wedge filters, compensators, bolus, beam blockings, independent collimator jaws or multileaf configuration—together with patient positioning and possible fixation aids, etc., should be recorded. It is particularly important that the beam is specified in such a way that it can be used for accurate determination of the delivered dose at least when combined with the central documentation for the treatment units of the department.

3.6.3 Brachytherapy applicators and sources. Brachytherapy sources are used either as free sources or sources inside applicators. The type of isotope and source strength used in terms of reference air kerma rate have to be

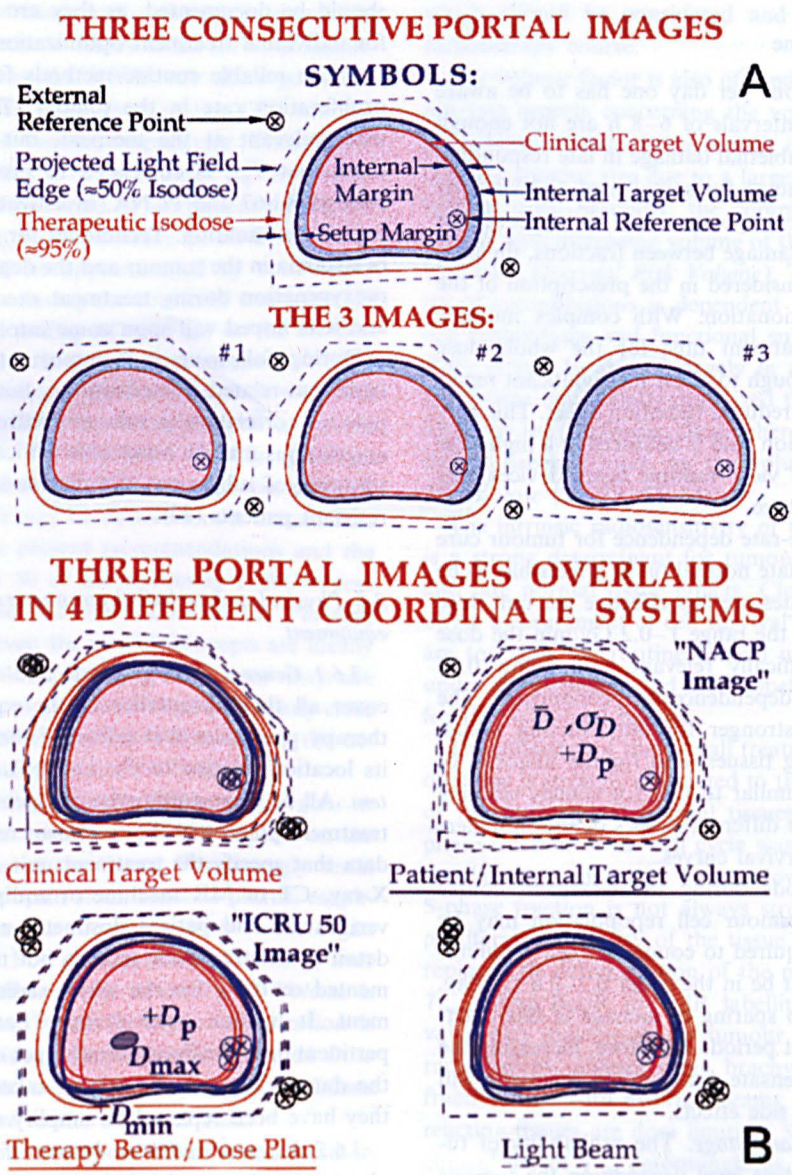

Fig. 10. Illustration of the appearance of three consecutive portal images overlaid in four different coordinate systems. In (A) the schematic images are shown with the symbols used for the targets and the beams. It is seen in (B) that the system defined by the *Internal* and *External Reference Points* is most simple with regard to the appearance of the *Internal Target Volume* and the cumulative dose delivered at completion of treatment (cf. Fig. 6C).

specified, together with a satisfactory geometrical description of sources and applicators. Most sources and applicators come from a few manufacturers, and commercial descriptions of them should be available. The number of sources, source positions and dwell times have to be clearly recorded. If an afterloading unit is used, it should be stated whether a source train, an oscillating source or a pulsed source technique is used. For rigid applicators the source positions can be derived from the location of the applicator inside the patient and the relative positions of the source in the applicator. For flexible applicators a more detailed description of applicator form and position is also needed.

3.6.4 Patient dosimetry. The type of dosemeter used in patient dosimetry (see Sect. 2.5) should be documented, either in the patient record or unambiguously in the general description of the dosimetric procedures used at the clinic. In patient dosimetry, there are often precalculated values from the treatment planning system. When measurements are carried out on the patient these values have to be compared with the precalculated values. The measured and precalculated values should be used for on-line quality assurance and recorded for later analysis of type of deviation and possible systematic variations. Deviations beyond the tolerance limit should be followed by an

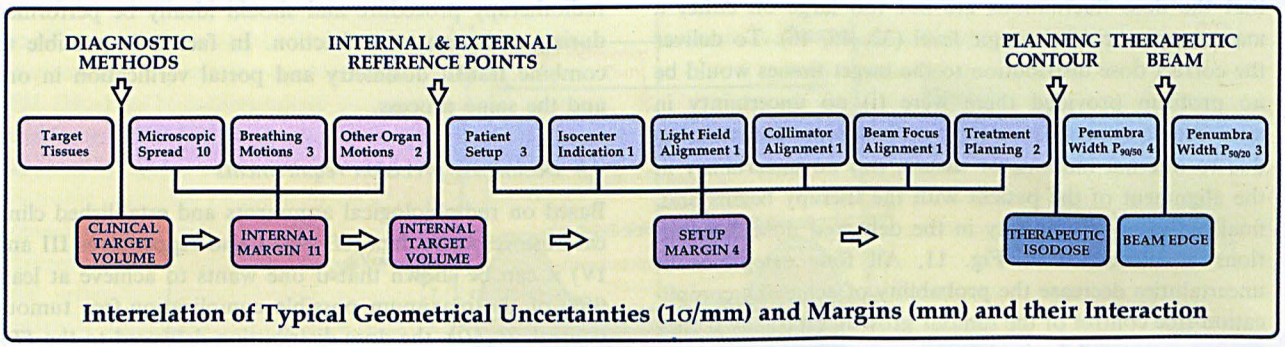

Fig. 11. Schematic illustration of the interaction of different groups of error sources during the radiation therapy process. The *Internal* and *External Reference Points* and the *Internal Target Volume* constitute the interface between the internal error sources linked to the motion of the *Target Tissues* and the external ones associated with the uncertainty in beam patient setup.

immediate analysis and a comment about the reason behind it.

4. GENERAL RECOMMENDATIONS

4.1 Portal verification

Portal imaging allows an accurate day-to-day determination of the position of *Internal Reference Points* in relation to the radiation beams (see Sects. 2.5 and 3.2.8). Traditionally, this has been done using X-ray film, but several new electronic on-line techniques are now in use and the technique should be stated. Portal verification is done by comparing portal images with simulator images and/or digital reconstructed radiographs from the treatment planning system. Deviations greater than stated tolerance limits should be recorded for shape and position of the beam relative to the *Local Patient Coordinate System* and possible rotation of the beam and the patient. Systematic errors between simulation and treatment can be discovered by portal imaging and corrected (13, 15). The magnitude of random errors can be detected from the portal images for a certain treatment technique and can be used to determine the required *Setup Margin* (see Sect. 3.3.6). When larger deviations are found it may be desirable to repeat the underlying CT or MR imaging and, if verified, a renewed dose plan may even be necessary.

The dose delivery and the relative location of *Clinical Target Volumes* and *Risk Volumes* will depend largely on the reference frame chosen, as shown schematically in Fig. 10. This problem is illustrated on a set of three consecutive portal verification films—nos. 1, 2 and 3 as seen in Fig. 10A. Besides the *Reference Points*, shown in all three images are the projection of the *CTV*, the *Internal Target Volume*, the therapeutic isodose of each dose fraction as well as of the entire treatment and, finally, the light field. In reliably estimating the dose delivered to the *ITV* and *Internal Risk Volume*, the influence of all these motions has to be considered (7). In principle, this could be done in any of the four coordinate systems illustrated in Fig. 10B: (i) the tumour or more specifically the *CTV*, (ii) the patient as specified by the *Internal* and *External Reference Points* and consequently also the *ITV*, (iii) the therapy beam and thus the dose plan, and, finally, (iv) the light field used to simulate the radiation beams.

The three portal images are assumed to be recorded relatively closely in time, so although the shape of the different volumes does not change much their relative positions do differ somewhat. However, in all three cases the *ITV* is inside the therapeutic isodose for each dose fraction. Through the definition of the *ITV* in relation to the *Internal* and *External Reference Points*, the *Local Patient Coordinate System* and consequently the coordinate system of the *ITV* is generally the clearest one, since both the *ITV* and the *Reference Points* by definition are linked together (see Fig. 10B the upper right image). In the other three coordinate systems, only one of the concepts remains essentially intact in the three verification films.

This illustrates the importance of using the *Internal and External Reference Points* in the definition of the *ITV*. Not only can the delivered dose distribution be calculated with greater ease and accuracy but also the dose delivery will be more accurate. Besides these advantages, the systematic use of *Internal* and *External Reference Points* will increase accuracy throughout the radiation therapy procedure from simulation and daily patient setups to treatment verification by portal imaging. With the recent increase in the use of real time portal verification devices, reference points on bony structures may play an important role in increasing the accuracy of checking the treatment field locations.

4.2 Consideration of geometrical uncertainties

The aim of *Curative Radiation Therapy* is to eradicate all clonogenic tumour cells. The principal goal during the course of treatment is therefore to ensure that the prescribed dose is imparted to all the target tissues. To be more precise, it is more important that the *Mean Energy Imparted* to the *CTV* is correct than that the absorbed dose everywhere in the *CTV* is equal to the prescribed mean value. This generalization rests on the assumption

that the dose fluctuations are not too large on either a macroscopic or microscopic level (32, 45, 46). To deliver the correct dose distribution to the target tissues would be no problem provided there were (i) no uncertainty in microscopic tumour spread, (ii) no positional uncertainties due to internal motions of tissues, (iii) no uncertainty in the alignment of the patient with the therapy beams and, finally, (iv) no uncertainty in the delivered dose distributions as illustrated in Fig. 11. All four categories of uncertainties decrease the probability of achieving complication-free control of the tumour growth, especially if they are not accounted for in the treatment planning procedure (7, 14, 15, 23, 25, 47).

Obviously, the best thing would be if one could eliminate as far as possible the patient beam setup uncertainties by good fixation techniques, possibly combined with synchronization of the irradiation with breathing or other internal motions. However, the uncertainty in microscopic spread is very hard to eliminate because of individual patterns of spread in different patients and also the finite resolution of diagnostic methods. In the first approximation one would think it did not matter much whether the uncertainty in the location of the *CTV* relative to the radiation beam was due to uncertainties in microscopic tumour spread, organ motions, or patient beam setup. However, as described in detail in Appendix II an accurate patient setup requires a systematic use of *External* and *Internal Reference Points*, and thus a separation of uncertainties due to internal organ motions and lack of information about the extent of microscopic spread and to external sources such as uncertainties in beam patient alignment and dose planning. This is one of the principal reasons why the *Internal Margin* and the *Setup Margin* must be clearly distinguished (cf. Appendixes II and IV). The other main reason is that the dosimetric concepts should be as relevant as possible for the target tissues that is the *Gross tumor* and the subclinical disease (see Sect. 3.3 and 5).

4.3 Patient dosimetry

Patient dose measurements, together with portal imaging, are effective checks of the entire patient setup (see Sects. 2.5 and 3.6.4). Both entrance and exit doses should be measured at points of interest in the beam, and compared with prescribed and precalculated dose values, at least at the beginning, half way through, and towards the end of the treatment. This will help to detect changes in patient anatomy, such as variations in patient thickness, and to detect errors in dose or patient beam alignment and setup. As part of the quality assurance programme it is a good idea to use patient dosimetry during every treatment session, and especially during conformal therapy (48).

Both dosimetric and geometric verification (cf. Sect. 4.1) of the radiotherapy technique are fundamental steps in the radiotherapy procedure and should ideally be performed during each treatment fraction. In fact it is possible to combine transit dosimetry and portal verification in one and the same process.

4.4 Dosimetric precision requirements

Based on radiobiological arguments and established clinical dose response data (cf. Fig. 1 and Appendixes III and IV) it can be shown that if one wants to achieve at least 95% of the maximum possible complication-free tumour control, $P_+(\hat{D})$, the dose distribution delivered to the *ITV* should be within ΔD from $\hat{D}$ as given by

$$\Delta D = \frac{\hat{D}}{10\gamma} \tag{3}$$

where $\hat{D}$ is the optimal mean dose to the patient and γ is the mean normalized slope of the dose response relation for the tumour and the normal tissue.

This means that for steep dose response gradients, γ, the clinically acceptable dose interval is quite narrow. For typical clinical data assuming $\hat{D} \approx 64$ Gy and $\gamma = 4$ the required accuracy in dose delivery is about 1.6 Gy or less than one dose fraction. This corresponds to an accuracy in dose delivery of about 2.5%, which is quite a demanding figure compared with what is generally achieved in clinical practice (cf. Sect. 4.4, Appendix IV and (5, 20, 32)). However, it is not unreasonable to interpret the classical figure of 5% precision in dose delivery stated by ICRU (3) as a maximal deviation (and thus approximately a 2σ value) and the agreement between these recommendations is perfect.

When a higher probability of severe complications than a few percent is unacceptable for clinical reasons, the higher doses should be avoided at all costs. This reduces the acceptable range of variations even further, as illustrated by the clinical data set of Fig. 1. A dose accuracy in the order of 1 Gy (1σ) is then not unusual for steep responding tumours.

4.5 Quality assurance

Since both the geometric and dosimetric precision requirements are quite strict in *Curative Radiation Therapy* it is essential to have a comprehensive quality control system to ensure a high clinical performance. Quality assurance is defined as procedures and systems for assuring that the quality parameters of a process are in accordance with the preset standards. These standards are in many situations defined by international standardization bodies like the International Standards Organization (ISO standards), International Electrotechnical Commission (IEC standards), or national authorities. The quality of healthcare is much less rigidly defined, and no general agreement exists regarding its assessment. Interpersonal and patient-doctor relationships, fear and doubts about treatment outcome

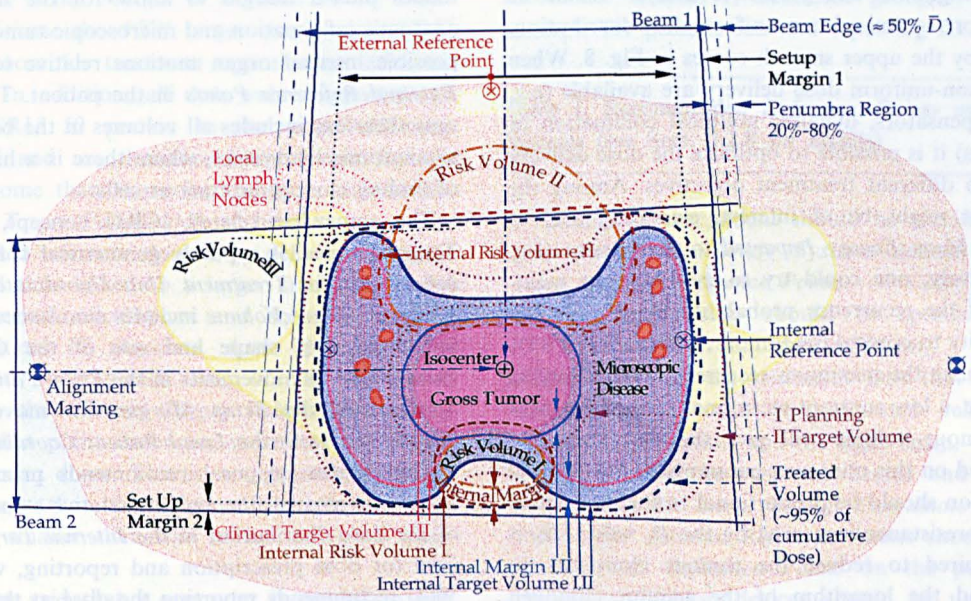

Fig. 12. Comparison of the present *Internal Target Volume* concept with the *Planning Target Volume* concept suggested by ICRU 50. It can be seen that the *Planning Target Volume* includes the treatment technique dependent *Setup Margin*, which in the present report is regarded as a margin on the treatment beams not as part of a special target volume concept. Dose concepts defined for the *Planning Target Volume* will therefore be less clinically relevant than for the *Internal Target Volume*, since the former include an unnecessarily large volume of non-target tissues whereas the latter are as close as possible to the *Clinical Target Volume*. In the case illustrated in the figure it is decided to prescribe different doses to the gross tumour and the subclinical malignant disease. Therefore two *Internal Target Volumes* are defined with somewhat different *Internal Margins*.

will constitute parts of the reference frame of quality concepts. Quality assurance of radiation therapy includes the whole range between these two extremes (5). It is important that the radiotherapy process is conducted with the accuracy required by national and international standards.

Quality assurance of the whole radiotherapy process implies strict requirements on the staff, the therapeutic procedures and the technical systems used to comply with selected standards. All categories of staff therefore need the relevant competence. Procedures for the different parts of the process have to be written unambiguously and kept up to date. Setting standards implies strict definitions, and those introduced above could be useful. All the parameters listed in these recommendations should be subject to meticulous checking and verification. All systems and devices have to be part of the quality assurance process: imaging devices, treatment planning systems, simulators, treatment units and verification systems. Checks of beam quality and homogeneity, portal images and clinical dose measurements form part of such quality assurance systems. Clinical quality assurance should include follow-up, chart-rounds, peer reviews and quality audits.

This report is mainly concerned with the conceptual basis which must exist before quality assurance programmes can be implemented. Quality assurance systems for radiotherapy are in use and under development in many places in the Nordic countries, and abroad (5, 6, 48, 49, 50).

4.6 Treatment optimization

During the last decade our knowledge about the radiation response of tumours and normal tissues has increased considerably. This is not just true of our understanding of the importance of the repair of radiation damage in normal and malignant tissues, and how it can be used to find the optimum dose fractionation schedule, but also for our knowledge about the steepness of the dose-response relationship of different organs and tumours to non-uniform fractionated irradiation, as illustrated in Fig. 1. This knowledge has led to an increased ability to quantify radiation effects by semi-empirical models like the $\alpha\beta\gamma\delta$ description of cell survival (the linear quadratic model with correction for tumour heterogeneity and cell proliferation) and by the use of Poisson and other statistical methods to describe the effect of radiation on structured conglomerates of normal and malignant cells (41). Some of the results of these methods are fairly general and can have an important bearing on the way we should quantify and document radiation therapy treatments and treatment outcome.

The ultimate step, when more accurate data on the tumour cell density and sensitivity are available—for example through clinical experience or through nuclear

medicine investigations and predictive assays—would be to deliver a more optimized non-uniform dose distribution, as illustrated by the upper smooth curves in Fig. 8. When methods for non-uniform dose delivery are available (e.g. by using compensators, dynamic multileaf collimation or scanned beams) it is possible to optimize the dose delivery with regard to different treatment objectives. Among the objectives that might be of interest, classically are, to minimize the *Mean Energy Imparted* to the patient (Eq. (1)). Alternatively, one could try to minimize the maximum value of the recurrence probability for a given desired probability to control the tumour, such as 90 or 95% (51, 52). To make the maximum recurrence probability as low as possible, a low constant recurrence probability over the entire tumour volume will give the best treatment outcome. Based on this mini-max assumption, the optimal dose distribution should be proportional to the product of the local radioresistance measured by the D_0 value (D_0 is the dose required to reduce the tumour clonogens to $1/e \approx 37\%$) and the logarithm of the tumour clonogen density (52). This procedure will compensate for the larger risk of missing clonogens where their density is high or their sensitivity is low (high D_0). A tenfold reduction of the tumour cell density then corresponds to a dose reduction in the order of 10%. To reduce the adverse reactions in normal tissues, instead the *Mean Energy Imparted* to the patient should be minimal to keep the integral dose low. It is then advantageous to give a higher dose where the local D_0 value is lowest. Then a given dose has a higher probability of eradicating tumour cells, as indicated by the dashed smooth curve in Fig. 8. This latter case is closer to classical radiation therapy with uniform radiation beams.

An even more stringent method would be to maximize probability to control the tumour without severe complications in normal tissues, as tried out extensively in recent years (36, 39, 53, 54). The optimal shape of the delivered dose distribution would then also depend on *Risk Volumes* in the neighbourhood of the *Internal Target Volume*, as indicated by the solid curve in the region, adjacent to and including the *Internal Margin*, near the right tumour border in Fig. 8. It is clear from this discussion that the ideal dose delivery can be approached gradually in several steps of increasing clinical advantage and complexity. It is also apparent that an accurate delineation of the target and risk volumes is of fundamental importance for a true optimization of the treatment. Recent reviews of this field have been published by Webb (55), Brahme (30, 56) Ågren Cronquist (39) and Söderström (31).

5. ADVANTAGES OF USING THE PRESENT APPROACH

The present recommendations define only one principal target volume, namely the *Internal Target Volume*. This volume includes all verified or presumed tumour-bearing tissues plus a margin to allow for the uncertainties in anatomic information and microscopic tumour spread and possible internal organ motions relative to *Internal* and *External Reference Points* in the patient. This target volume therefore includes all volumes in the body in relation to anatomic landmarks, where there is a high probability of finding clonogenic tumour cells.

The somewhat related ICRU concept, the *Planning Target Volume*, is a purely geometrical concept generally defined in the *Treatment Unit Coordinate System*. The *Planning Target Volume* includes simultaneously a margin for changes of shape and size of the *Clinical Target Volume* and its movements in the *Local Patient Coordinate System* and the *Setup Margins* for movements of the beams relative to the *Local Patient Coordinate System*.

The present proposal recommends primarily that the arithmetic mean value and the relative standard deviation of the dose distribution in the *Internal Target Volume* be used for dose prescription and reporting, whereas ICRU 50(4) recommends reporting the dose at the ICRU reference point and in addition the minimum and maximum dose to the more extended *Planning Target Volume*. According to ICRU recommendations the mean dose in the *Planning Target Volume* can also be used for reporting, but both its mean dose and particularly its minimum dose can differ significantly from those of the *Internal Target Volume* defined here. It is clear that the dose concepts of the *Internal Target Volume* are much more closely related to the clinical outcome in randomized trials as they do not include the dose delivery to the clinically unimportant *Setup Margin* (cf. Fig. 6).

The *Internal Target Volume* is similar to the Real Target Volume proposed by Onogi et al. (10). Similarly, the Mobile Target Volume defined by Urie et al. (7) accounts for organ motions, but it was defined in relation to the treatment machine and not to anatomic reference points on the patient. The differences between the present proposal and that of the ICRU are schematically illustrated in Fig. 12. The practical consequences of these differences are summarized below:

(i) The absorbed dose at the ICRU reference point often differs by several percent from the mean absorbed dose to the *Internal Target Volume*. In multiple field techniques, for example, the ICRU point dose may be a few percent higher than the mean dose to the *Internal Target Volume*. Therefore, doses reported using the two methods may differ by about this amount.

(ii) The *Planning Target Volume* is generally larger than the presently defined *Internal Target Volume* (see Sect. 3.3.7). Consequently, the minimum dose to the the *Planning Target Volume* may be significantly lower than the minimum dose in the present clinically more relevant *Internal Target Volume*. When the effect of setup uncertainties on the dose distribution in the *PTV* is disregarded (cf. 4) this difference is fortunately reduced.

(iii) Since the *Setup Margin* is included in the *Planning Target Volume* the *PTV* target concept of ICRU 50 gives less room for treatment optimization than the *ITV* (23, 25). In addition, all dose values reported according to ICRU 50 pertain to the larger *Planning Target Volume* and are therefore less relevant for the treatment outcome than those for the more clinical relevant *Internal Target Volume* defined here.

(iv) The ICRU reference dose is by definition a point dose value and thus linked to a larger statistical uncertainty in numerical calculations and according to the classical definition of absorbed dose (57, 58). The present method recommends use of the arithmetic Mean Dose in the *Internal Target Volume*. Sometimes it is claimed that point doses are more accurately calculated than mean doses. This is not generally true for the same reason that the standard deviation of the mean value is smaller than that of an individual measurement.

(v) It is often said that a computer is needed to calculate a mean dose value. This is certainly the case to obtain accurate point doses. However, the mean dose value in an extended volume can generally be calculated more accurately, since the influences of heterogeneities and interface effects tend to average out over larger volumes. The arithmetic mean dose is therefore a physically better defined quantity even though several point dose values have to be calculated to arrive at an accurate mean value.

(vi) The standard deviation and the mean dose to the *Internal Target Volume* may be calculated when multiple point dose data are available, and both these concepts are known to be of considerable clinical interest as they influence the probability of controlling the tumour (32, 33).

(vii) The present *Internal Target Volume* concept has the conceptually appealing property of being independent of the radiation treatment technique employed. The *Planning Target Volume*, on the other hand, depends considerably on the technique used to treat the patient. The *Internal Target Volume* is therefore ideally suited for comparing the clinical value of different treatment techniques. Furthermore, dosimetric quantities such as *Mean and Minimum Doses* and *Dose Volume Histograms* for the *Internal Target Volume* are more relevant for the clinical treatment outcome.

(viii) Finally, the present recommendations are sufficiently general to be applicable to all radiation modalities, not just to photons.

6. SUMMARY

The main steps that have to be considered when following the present recommendations are summarized in the three tables below, covering reference points and coordinate systems I, treatment geometry II and dose concepts for prescription and reporting III.

Table I. Recommended *Reference Points* and *Coordinate Systems* (see Sect. 3.2.8 for details)

* Volumes in the patient should be specified using *Local Patient Coordinate Systems* defined by *External* and *Internal Reference Points*.
  * The beam setup should be specified using the *Treatment Unit Coordinate System*.
* Those parts of the treatment unit that influence the beam setup should be calibrated relative to the isocentre indication and the light beam.
* To get a link between the beams and the volumes defined in the *Local Patient Coordinate System*, *External* and *Internal Reference Points* should be used:
  - *External Reference Points* on the patient surface or on fixation devices should be used for beam setup during patient imaging, simulation and treatment.
  - *Internal Reference Points* inside the body, and preferably inside the beam cross section, should be used as reference points on digitally reconstructed radiographs, for beam setup at the simulator and for portal verification during radiation therapy.
* All *Reference Points* should be:
  - as rigid as possible (e.g. on bony structures) to improve patient positioning
  - located as closely as possible to the target tissues to minimize patient beam setup errors
  - as rigidly related as possible to the target tissues to minimize the *Internal Margin*.

Table II Recommendations for *Description of Treatment Geometry* (see Sect. 3.3.12 for details)

* An *Internal Target Volume* should be specified in a *Local Patient Coordinate System* defined by *External* and *Internal Reference Points*. The *Internal Target Volume* includes a *Clinical Target Volume* and an *Internal Margin* if the *Clinical Target Volume* is mobile in the *Local Patient Coordinate System*.
* When different dose levels, and more generally when different time dose fractionation schedules, are prescribed for different regions of the disease, separate *Internal Target Volumes* should be specified for each.
* The *Internal Risk Volumes* should be specified in the *Local Patient Coordinate System*.
* *Internal Target Volumes* and *Internal Risk Volumes* should be specified by or under the super-vision of a qualified medical expert (preferably a radiation oncologist).

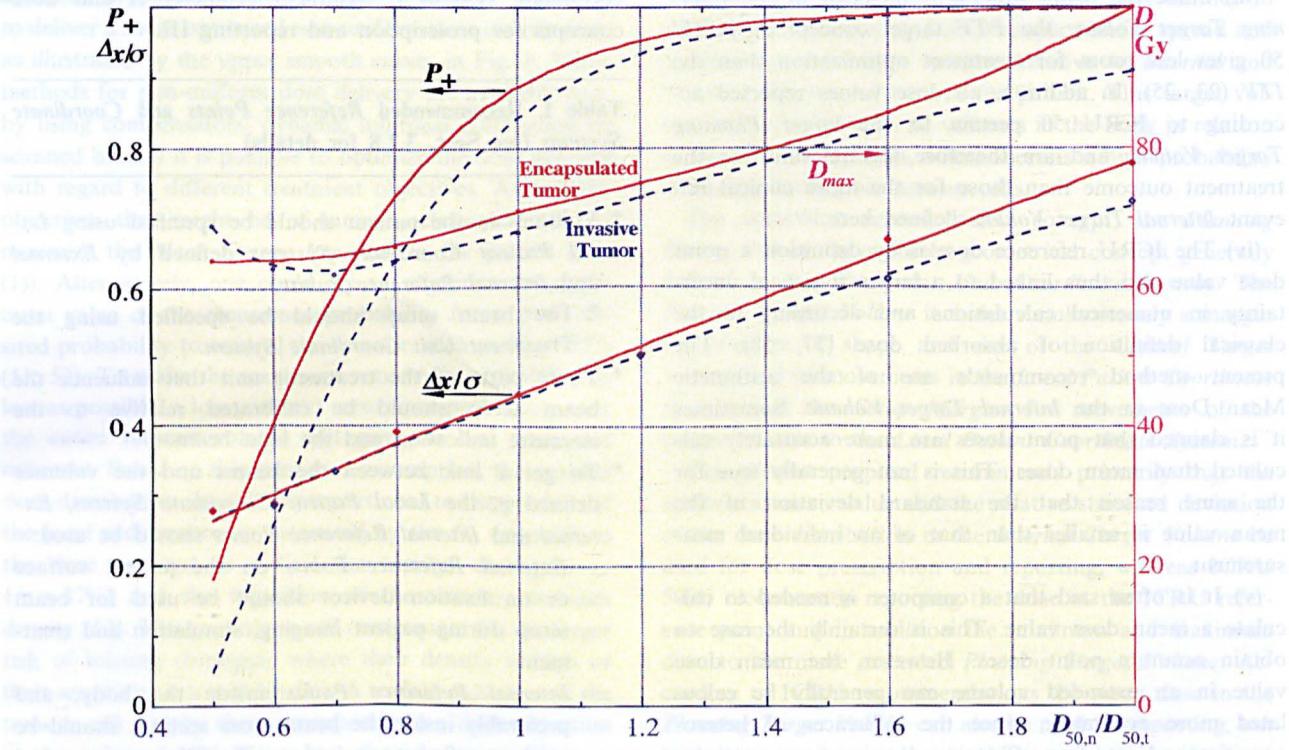

Fig. 13. Illustration of the increase of the optimal relative *Internal Margin* ($\Delta x/\sigma$) as a function of the sensitivity of the tumour relative to the surrounding normal tissues. Also shown are the concomitant increase in the complication free tumour control probability P_+ and the optimal maximum dose to the target tissues. The lower curves pertain to a more invasively growing tumour and are linked to a less advantageous outcome, as seen in the figure.

* A *Setup Margin* should be added to the projection of each *Internal Target Volume* and *Internal Risk Volume* during treatment planning to account for the uncertainty in beam patient alignment.

Table III. Recommended *Dose Concepts* for prescription and reporting radiation therapy (see Sect. 3.4.9 for details)

* The *Mean Dose* and the relative *Standard Deviation* of the *Cumulative Dose Distribution* delivered to the *Internal Target Volume* and the *true Internal Risk Volumes* should be stated.
* When the relative *Standard Deviation* of the *Dose Distribution* is larger than the *Tolerance Range* (often 3–5%), the *Minimum Dose* in the *Internal Target Volume* and the *Mean Dose* in the *Hot* and *Cold Volumes* should also be stated. For strongly serial tissues like spinal cord, esophagus and colon, in addition the *Maximum Dose* to the *Organ at Risk* should be stated.
* To allow a more detailed follow-up, the complete dose plan and *Dose Volume Histograms* for *Internal Target Volumes* and *Internal Risk Volumes* and other volumes of interest should be recorded.
* To ensure accurate comparison between the dose concepts of the present NACP recommenda-tions and those of the ICRU 50 report, the ICRU *Point Dose* and the *Minimum* and *Maximum Dose* to the *Planning Target Volume* should also be reported.

ACKNOWLEDGMENTS

It would not have been possible to complete the present report without the valuable collaboration of numerous colleagues in the Nordic countries and abroad. In particular, detailed constructive comments have been received from Shlomo Shalev, Hannu Järvinen, Björn Zackrisson, Michael Goitein, Ben Mijnheer and Ulrich Quast, who are all gratefully acknowledged. In addition to the indirect support of the departments of the working group members, important financial support for a Nordic Consensus Meeting by the Nordic Cancer Union and for the printing of the report by the King Gustaf V Jubilee Found are also gratefully acknowledged.

APPENDIX I. PATIENT POSITIONING AND PATIENT FIXATION

The position or movement of the skin is influenced by the thickness of the subcutaneous fat. The tension of the skin and subcutaneous fat is also influenced both by muscule tension and gravity and therefore changes with the body position. With respect to radiotherapy, different degrees of skin stretching may appear during the anatomic work-up and

patient positioning on the radiotherapy couch. A patient who positions himself, say, from the left side of the couch causes the skin to stretch in certain directions. The associated skin tension can be neutralized by having the patient sit up once and then reposition in order to achieve a comfortable and natural position. This procedure must be performed at the simulation, CT and in connection with every treatment if the skin markings are to be useful throughout the treatment.

Muscle tonus also affects the patient's body position from time to time, so it is important that the patient is placed in a comfortable and natural position. When positioning is performed at the simulator, one attempts to align the patient so that his or her central vertical axis coincides with a straight laser line. The patient undergoing simulation may not then be lying in a reproducible and comfortable natural position, and so unintentionally move from the aligned position due to muscle strains, etc. It is therefore important to allow the patient to find a relaxed and stable position already at the CT unit and the simulator.

Hence, it is important to let the patient be placed in a position that is comfortable and that is acceptable to the CT planning personnel. At the CT examination, a minimum of three points are tattooed on the patient's skin. Two of the points are located contralaterally in order to prevent and control possible rotation of the body.

To achieve as identical a patient position as possible at all stages of the treatment process, one normally has to use such accessories as laser alignment lights and patient fixation aids. Different types of patient fixation equipment exist with a great variety of properties, from pure immobilization equipment, like bite blocks and straps, to accessories that facilitate reproducible positioning, like masks, shells and frames. It is essential that the same accessory can follow the patient from the CT scanner, via the simulator to the treatment unit. This is necessary if patient position is to be reproduced throughout the entire treatment process.

Another important factor is that the fixation aids can be used without the planning images or dose delivery being distorted. Hence, they have to be manufactured from materials with low attenuation coefficients both for low and high energy photons, electrons and microwaves. If MRI or US are used, the materials also should not cause significant distortions with these imaging modalities. To combine information in a planning system from tomographic images recorded on different diagnostic modalities like CT and MRI, an external stereotactic system that follows the patient through the process is very useful. This makes it possible to scan in identical positions on all modalities and easier to accurately transfer information between different diagnostic units (24).

APPENDIX II. INTERACTION OF GEOMETRIC UNCERTAINTIES

The problem of accurate patient setup has recently been treated in detail using radiobiological models for the tumour and surrounding normal tissues (23, 25). With these models it was found that within a few percent the same treatment outcome could be achieved by increasing the field size proportional to the standard deviation, σ, of the associated positional uncertainty, as shown in Fig. 13. Depending on the relative sensitivity of the tumour and surrounding normal tissues, the required field size increase κ in units of σ on each side of the *Internal Target Volume* is in the range $\kappa = (0.40–0.80)$, where the larger values pertain to the situation with more resistant normal tissues outside the tumour. In these studies the treatment technique was parallel opposed beams and the dose level was actually increased somewhat in order to compensate for the decrease in dose at the border of the *Internal Target Volume* caused by the uncertainty in beam positioning (cf. D_{max} in Fig. 13). It should also be pointed out that the normal tissue end point should be as life-threatening as a recurrent tumour to make a balance between local tumour control and fatal complications relevant. The curves presented in Fig. 13 are based on such clinical data for head and neck tumours (22). For more invasive tumours, with microscopic tumour cells infiltrating further into the normal tissues, the loss in tumour control by just increasing the field size was larger as indicated by the lower dashed blue curves in Fig. 13. When the tumour is surrounded by non-critical normal tissues even larger margins may be called for, since the normal tissue end point is non-fatal for the patient. In such cases, κ values even larger than 1 may be desirable (47).

If we call the equivalent geometric standard deviation due to uncertainty in the extent of spread of the target tissues σ_T and the associated standard deviation due to internal organ motions in relation to the *Internal* and *External Reference Points* σ_M, their total contribution to the standard deviation associated with *Internal Margin* (cf. Sect. 3.3.3) may, when they are uncorrelated, be approximated by the relation:

$$\sigma_I^2 = \sigma_T^2 + \sigma_M^2 \qquad (4)$$

The uncertainty in the extent of spread of the target tissues (σ_T) may depend on the uncertainty of the detection method used for the verified disease but more often on the uncertainty in the pattern of microscopic spread of the presumed subclinical disease as given for example by the probability distribution for the tumour stage to recur locally if not treated. It is important that both a posteriori or random uncertainties as well as a priori or systematic variations are taken into account, preferably in the form of their total equivalent variances (5, 27). For example, both random peristaltic and breathing motions as well as more unusual systematic accumulations of bowel gas

should be accounted for when selecting margins in the pelvic region. The standard deviation due to organ motions (σ_M) can be determined by repeated measurements using some diagnostic technique. The width of the *Internal Margin* δ_I to be added around the target tissues may then be approximated by

$$\delta_I = \kappa\sigma_I \tag{5}$$

where κ generally varies over the interval 0.4–0.8 (cf. Fig. 13). When this margin has been added to the target tissues and thus to the *Clinical Target Volume*, the *Internal Target Volume* in the *Local Patient Coordinate System* is obtained (see Sects. 3.3.3 and 3.3.5).

In order to ensure that the prescribed dose is delivered to the *Internal Target Volume* during the whole course of treatment a *Setup Margin* for each beam has to be added around the beam's eye view projection of the *Internal Target Volume* (cf. Fig. 7). This is done during the treatment planning phase to get the sizes of the required treatment fields. The *Setup Margin* added to the projection of the *Internal Target Volume* will therefore be:

$$\delta_S = \kappa\sigma_S \tag{6}$$

In principle, also the standard deviation in the beam patient alignment due to setup uncertainties (σ_S) could be included in a total integrated geometrical uncertainty (σ_Σ) according to

$$\sigma_\Sigma^2 = \sigma_T^2 + \sigma_M^2 + \sigma_S^2 \tag{7}$$

However, this quantity has no operational meaning unless it is possible to set up the beam directly according to the location of the *Clinical Target Volume*. Such a procedure is rarely possible in clinical practice. One possible exception could be the stereotactic irradiation of small intracranial targets, or when using clips or fiducial markers to indicate the *Clinical Target Volume* after surgery. Therefore, generally in clinical practice a setup procedure is used which makes use of *External Reference Points*, as described above (see Sects. 3.2, 4.2). The sum of the two margins δ_I and δ_S is always larger than or equal to $\delta_\Sigma = \kappa\sigma_\Sigma$ as would be obtained by straightforward quadratic addition according to Eq. (7) and thus:

$$\delta_I + \delta_S \geq \delta_\Sigma \tag{8}$$

This extra margin (δ_S) is needed to ensure a safe patient setup using the *External Reference Points*. If a less strict patient setup was used without *Internal* and *External Reference Points* the *Setup Margin* would increase even more. To give a feeling for the relative importance of the above uncertainties some typical values could be stated. The standard deviation in the spread of the target tissues is σ_T often in the order of 10 mm or more for non-encapsulated tumours, σ_M may be in the order of 10 mm in the pelvic area and σ_S is in the order of 3–5 mm depending on the patient and the target volume location, the performance of the equipment and the experience of the personnel. Thus σ_I is around 14 mm and δ_I is around 8.5 mm with $\kappa = 0.6$, whereas $\delta_I + \delta_S$ is as high as 10–11.5 mm, which is close to clinically reported values for the pelvic area. For comparison δ_Σ in this case is about 9 mm and clearly less than $\delta_I + \delta_S$ according to Eq. (8) but not by a large amount.

It is thus clear that the a posteriori or random and a priori or systematic uncertainties can be taken into account by selection of suitable margins. However, the margins have to be applied with some reference system in mind if they are to be really meaningful. The *Internal* and *External Reference Points* defining the *Local Patient Coordinate System* are the most natural for this purpose, as described above. Both the selection of the *Internal Margin* on the target tissues and *Clinical Target Volume* and the selection of *Setup Margins* on the planning contours are basically inverse problems (14, 15, 23, 25). Even though the last cited reference lacks the strict use of a reference coordinate system they all indicate how margins should be used in an efficient and accurate way for treatment plan optimization in the future.

APPENDIX III. DOSE QUANTITIES FOR CHARACTERIZING THE RESPONSE OF TUMOURS AND NORMAL TISSUES

It can be shown that the probability for tumour control ($P_{Benefit}$) and normal tissue complications (P_{Injury}) is given in the first approximation by

$$P_B(D(\vec{r})) = P_B(\bar{D}) - \frac{\gamma^2/2}{P_B(\bar{D})}\left(\frac{\sigma_D}{\bar{D}}\right)^2 + \cdots \tag{9}$$

and

$$P_I(D(\vec{r})) = P_I(\bar{D}) + \frac{\gamma^2/2}{1 - P_I(\bar{D})}\left(\frac{\sigma_D}{\bar{D}}\right)^2 + \cdots \tag{10}$$

respectively, where γ is the normalized slope of the dose response relation (32, 33). Thus, in the first approximation, when dose variations are small the mean dose and the variance of the dose distribution determine the treatment outcome. When the dose fluctuations are larger than about 5% (1σ) the minimum dose, D_{min}, to the tumour may also be important for the treatment outcome. In fact it is possible to define an effective uniform dose D_{eff} which produces the same treatment outcome as the uniform dose distribution (33). This effective dose can be approximated by:

$$D_{eff} = \bar{D}\left(1 - \frac{\gamma}{2P(\bar{D})}\left(\frac{\sigma_D}{\bar{D}}\right)^2\right) \tag{11}$$

which clearly shows that the effective dose decreases below $\bar{D}$ as soon as the relative standard deviation of the dose distribution increases. A similar analysis was recently presented by Niemierko (35).

For strongly heterogeneous tumours the optimal dose distribution $\hat{D}(\vec{r})$ is no longer uniform and a higher dose should be delivered to resistant volumes and where the clonogen density is high. The tumour control probability may then be approximated by:

$$P_B(D(\vec{r})) = P_B(\hat{D}(\vec{r})) - \frac{\gamma^2/2}{P_B(\hat{D}(\vec{r}))}\left(\frac{\sigma_{\bar{D}}}{\bar{\hat{D}}}\right)^2 \qquad (12)$$

where

$$\left(\frac{\sigma_{\bar{D}}}{\bar{\hat{D}}}\right)^2 = \frac{\int (D(\vec{r}) - \hat{D}(\vec{r}))^2 \, \mathrm{d}m}{\bar{\hat{D}}^2 \int \mathrm{d}m} \qquad (13)$$

Now it is the dose deviations or the variance from the optimal distribution which have a negative influence on the tumour control, and thus separate quasi homogeneous target volumes should preferably be defined for heterogeneous tumours.

APPENDIX IV. PRECISION REQUIREMENTS ON DOSE DELIVERY

In Appendix III, expressions were given for the probability of achieving tumour control and for complications in normal tissues. One of the goals in radiation therapy is that the number of patients, or the probability, P_+, that patients achieve tumour control without severe complications in normal tissues, is as large as possible. As seen in Fig. 1 these patients follow a bell-shaped curve as a function of dose with a maximum approximately half way between the doses causing 50% probability of tumour control and that causing 50% normal tissue injury. It has recently been shown (18, 33) that this curve is well described by a Gaussian distribution according to

$$P_+ \approx P_+(\hat{D}) \exp\left[-\pi\gamma^2\left(\frac{D-\hat{D}}{\hat{D}}\right)^2\right] \qquad (14)$$

where $\hat{D}$ is the optimal dose to the Internal Volume and γ is the mean normalized slope of the dose-response relations for tumour control and normal tissue damage (in general these slopes are not very different). Based on the Gaussian shape of the peak of this relation it is straightforward to derive the required dosimetric accuracy for a given maximal acceptable percental loss of curable patients such as 5%. The simple result is given by Eq. (3) in Section 4.4.

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