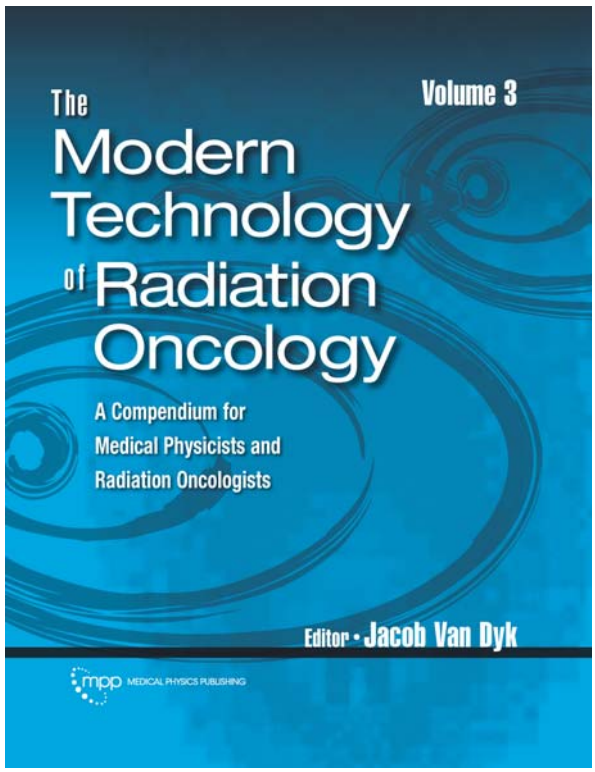

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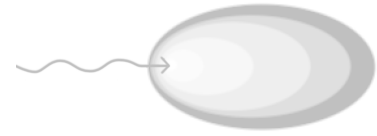
Chapter 11

Accuracy and Uncertainty Considerations in Modern Radiation Oncology



Jacob Van Dyk, Jerry J. Battista, and Glenn S. Bauman

11.1 Introduction

The evolution of the modern technology of radiation oncology has been very rapid, resulting in very significant escalation in treatment complexity, especially during the last decade (see Chapter 1). These increases in complexity have the primary aim of improved targeting of the malignant cells with greater radiation dose while minimizing dose to normal tissue, with the goal of improved tumor control or reduced side effects. This overarching goal of "hitting the tumor and missing the patient" drives the need for:

- improving patient immobilization,
- improving target definition and localization for treatment planning,
- accounting for target motion during a course of treatment,
- shaping the radiation beams to miss normal tissues,
- aiming the radiation beams accurately and adjusting their intensities to yield a desired dose pattern to the target cells,
- optimizing the prescription and dose delivery to maximize tumor control or reduce normal tissue response, and
- adapting daily treatments to account for changes in patient position and changes of anatomy.

Thus, the key features of this evolution include: immobilization, imaging for tumor staging and localization, treatment planning, motion control, and dose delivery combined with image guidance. The new buzzwords associated with this technological evolution are summarized in Table 11.1. Combined with the new technologies are changes in treatment dose prescriptions—often with higher doses per fraction or variable dose per fraction—for a specific number of treatment sites, including the major sites of lung, breast, and prostate. These principles reach their extreme in the precision delivery of particularly high doses per fraction in the context of intracranial and extracranial stereotactic radiosurgery/radiotherapy.

The underlying hypothesis for adopting these new and advanced technologies is that loco-regional control of cancer remains a significant barrier to cancer cure for many common cancers [50,125] and that better dose distributions will automatically translate into better clinical outcomes [184]. Controlled clinical trials are in progress to test this hypothesis for cancers of the prostate, lung, and brain. For cancer of the prostate, the local control and biochemical (PSA count) relapse-free survival rates are demonstrating significant improvements [27,162,230], and survival data are showing positive trends [71,72,123]. For cancer of the breast, loco-regional control through the use of adjuvant radiation therapy has been shown to provide an incremental survival benefit when used in addition to chemotherapy [19,39,220]. In addition, reduced normal tissue complications have been demonstrated for a number of clinical sites [25,27, 43,51,116,121,230].

Further clinical gains using these new technologies, however, may be limited by uncertainties associated with the entire treatment process. As indicated above, the process of radiation treatment is complex and involves multiple steps, including:

- patient evaluation and multidisciplinary treatment decision making;
- imaging for tumor staging and treatment planning;
- patient immobilization for reproducible setup for planning and treatment;
- acquisition of (increasingly multi-modality) volumetric imaging for treatment planning;
- definition of target volume and normal structures on planning images;
- radiation dose measurements for machine calibration and for input into dose computation algorithms;
- computerized dose computations;
- optimization of the treatment plan using "manual" forward planning or "automated" inverse planning, possibly with dose-volume or radiobiological objectives based on physician guidance and prior clinical experience;
- dose-fractionation prescription;
- verification imaging prior to each treatment fraction; and
- radiation treatment.

Each step of the process of radiation treatment involves uncertainties, both human and technology-based, which may compromise the potential advantages of the new, complex, and expensive technologies. Therefore, it is important not only to have a quantitative understanding of uncertainties, but also to consider the propagation of these uncertainties as part of the entire treatment optimization process. Ideally, we would all have a clear understanding of the levels of accuracy and uncertainties that exist in everyone's own facility for each treatment technique. Practically, this is a significant challenge. This chapter provides an overview of accuracy and uncertainty considerations, both from a historical perspective and in the context of today's treatments using the modern technology of radiation oncology. The strategies used in the past merit a fresh review and outlook if we are to attain the full clinical benefit of promising new technologies.

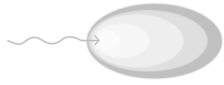


Table 11.1

Acronyms and jargon associated with recent developments in the modern technology of radiation oncology.

ACRONYM/"BUZZWORD"	BRIEF DESCRIPTION	ONE OR TWO MAJOR REFERENCES
2-D RT	Two-dimensional radiation therapy	[91]
3-D CRT	Three-dimensional conformal radiation therapy	[91]
MLC	Multi-leaf collimator	[20]
IMRT	Intensity-modulated radiation therapy	[20,91]
IMAT/VMAT	Intensity or volumetric- modulated arc therapy	[228]
IGRT	Image-guided radiation therapy	[101,102]
4-D	Four-dimensional. Imaging or treatment that considers or accounts for the effects of intra-fraction organ motion or deformation.	[32]
ART	Adaptive radiation therapy. Applying treatment changes during a course of therapy to adapt to anatomical changes in the patient.	[226]
DART	Dose-adaptive radiation therapy. Similar to ART but with dose re-optimization during a course of radiotherapy.	[103]
DRR	Digitally reconstructed radiograph (from CT scans)	[179]
BART	Biologically-adaptive radiation therapy	[128]
DVH	Dose-volume histograms	[48]
FMEA	Failure mode and effects analysis	[58,82]
GTV	Gross tumor volume	[95,96,97]
CTV	Clinical target volume	[95,96,97]
PTV	Planning target volume	[95,96,97]
PRV	Planning at risk volume	[96,97]
BTV	Biological target volume	[128]
Treatment margins	Margins as defined for CTV, PTV and PRV	[95,96,97]
Respiratory control/gating	Methods of accounting for breathing in radiation therapy	[111]
Tomotherapy	"Slice treatment" and CT scanning providing IMRT treatments along with IGRT	[132,154]
SRS	Stereotactic radiosurgery . . . usually intracranial, often single large dose fraction	[161]
SRT	Stereotactic radiation therapy . . . usually intracranial, multi-fractions	[161]
SBRT/SABR	Stereotactic body radiation therapy/stereotactic ablative radiotherapy . . . multi-fractions with large doses per fraction to non-cranial sites	[68,110]
TCP	Tumor control probability	[9,10]
NTCP	Normal tissue complication probability	[9,10]

11.2 Terminology

11.2.1 Measurement terminology

Many of the terms used in measurement terminology have been defined by international organizations such as the Bureau International des Poids et Mesures (BIPM) and the International Organization for Standardization (ISO), and their definitions are summarized in this chapter's appendix. Unfortunately, there is still some inconsistency in common usage of terms in radiation oncology versus what is recommended by international bodies. This section summarizes, in simplified language, some of the terms presented in detail in the appendix and some of the more common terminology associated with accuracy and uncertainties as used in radiation therapy. The goal is to encourage consistency in terminology between the professional jargon in the radiation oncology community and that used by the metrological organizations.

Accuracy is the closeness of agreement between a measured quantity and its "true value."

Trueness is the closeness of agreement between the average value obtained from a large series of test results and the accepted true value. While sometimes trueness is referred to as "accuracy of the mean," this usage is not recommended [99].

Precision is the closeness of agreement of the results when the same measurement is made repeatedly.

Error is the difference between the measured quantity and its reference value. Note that error in this context is not to be confused with a production error or mistake. In the radiation oncology context, however, the word "error" tends to be used for both measurement errors and mistakes.

Systematic error is a set of results of measurements that deviate by a consistent amount from the true value of the measurement. Once a systematic error is known, a correction can be applied to compensate for it.

Random error occurs when the same measurement is performed repeatedly and the resulting variations lead to the measurable values being inconsistent.

Uncertainty is a parameter that characterizes the dispersion of values that can be obtained for a particular measurement when it is performed repeatedly. For such repeated measurements, the results can be represented by a statistical distribution, which can be summarized by specific statistical quantities such as mean, mode, standard deviation, and variance.

Standard uncertainty is the standard deviation. The symbol often attributed to the standard uncertainty is u or u_c.

Combined standard uncertainty is the standard uncertainty of a quantity that is composed of various components, each of which has its own uncertainty. The combined standard uncertainty is obtained by combining the square of the sums of the individual standard deviations and taking the square root. This assumes a gaussian distribution for each of the contributing uncertainties. This mathematical procedure for combining uncertainties is generally known as "addition in quadrature." By way of a simple example, if s is the most probable value for the sum (or difference) of two measurements x and y, and if Δx and Δy are the probable uncertainties in x and y respectively, then the most probable uncertainty in s, Δs, is

$$\Delta s = \sqrt{(\Delta x)^2 + (\Delta y)^2} \tag{11.1}$$

Type A uncertainties are those that are evaluated by statistical methods.

Type B uncertainties are those that are determined by means other than statistical methods. While Type A and Type B uncertainties were classified in the past as random or systematic, it is now recognized that there is not always a simple correspondence between these classifications. Type B evaluations require critical thinking, intellectual honesty, and professional skill. [Note that Type A and B evaluations are distinct and different from the quantities α and β associated with thresholds when testing for statistical significance (i.e., t-test of two quantities).]

Expanded uncertainty is the standard uncertainty multiplied by a *coverage factor, k,* such that the statement of the expanded uncertainty gives a higher probability that the correct value lies within the range of the stated uncertainty. Often the expanded uncertainty is given the symbol U such that

$$U = k\,u \tag{11.2}$$

By way of example, let us assume that we would like to know with what level of certainty a particular quantity Y has when its mean is determined as y. The uncertainty statement could be written as

$$Y = y \pm U \tag{11.3}$$

Generally $k > 1$. For k equal to 1, 2, or 3, there is approximately a 67%, 95%, or 99% probability, respectively, that y lies between $\pm U$. Often we will see uncertainties quoted, for example, "at the $k = 2$ level" or "with $k = 2$".

Tolerance. The dictionary definition of tolerance is "the permitted variation in some measurement or other characteristic of an object or work piece" [46]. The BIPM does not recommend the use of "tolerance" [30]. However, in the world of engineering and quality control, tolerance is considered the permissible limit or lim-

its of variation in particular quantities or measurements, i.e., the range of acceptability beyond which corrective action is required. In the radiation oncology context, the practical definition of tolerance is generally used as the permissible limit beyond which corrective action is required. A more detailed discussion on "tolerances" and "criteria of acceptability" can be found in the International Atomic Energy Agency (IAEA) TRS-430 publication on the commissioning and quality assurance (QA) of treatment planning systems (TPSs) [90], as well in the European Society of Radiotherapy and Oncology (ESTRO) Booklet 10 [109] on independent dose calculations. The details of the terminology used in these two references are not totally consistent, neither with each other nor with the international agencies. Tolerance could get confused with the concept of "action level." Also, in radiation oncology, "tolerance" is often discussed in the context of normal tissue tolerance. Thus, from a QA or quality control (QC) perspective, it might be better to avoid the use of the term "tolerance."

Action level (maximum permissible level). If the difference between measured value and its expected or reference value exceeds the action level, then a response is required immediately. Ideally, the response would be to bring the system back to a state of functioning that meets the normally accepted range of values. If this is not immediately possible, then the use of the equipment or procedure must be restricted to clinical situations in which the identified inadequate performance either has no clinical significance or is acceptable and understood. Many QA/QC reports describe action levels. "Maximum permissible error" is effectively the same as action level and has been formally defined by the metrology organizations (see the appendix to this chapter).

11.2.2 Terminology related to patient safety

Issues related to patient safety are addressed in Chapter 12; however, because some terms such as "*error*" are used both in the accuracy/uncertainty context and the patient safety context, a brief discussion of these terms will be addressed here.

It is well known that in addition to expected and recognized uncertainties associated with patient treatments, there are also the occasional times when there is an unintended deviation from the intended delivery that falls outside of the inherent uncertainties of the process, possibly as a result of technology malfunction, human error, or miscommunication. Figure 1.7 of Chapter 1 in this volume shows how publications related to treatment errors have grown dramatically in the last decade. The Institute of Medicine's (IOM) 2000 report *To Err is Human: Building a Safer Health System* [115] has defined *error* to be "the failure of planned action to be completed as intended (i.e., error of execution) or the use of a wrong plan to achieve an aim (i.e., error of planning)." Similarly, the publication on a Canadian "adverse events" study [8] defined *adverse event* as "an unintended injury or complication that results in disability at the time of discharge, death or pro-longed hospital stay and that is caused by health care management rather than by the patient's underlying disease process." They defined *disability* as "temporary impairment of function lasting up to a year, permanent impairment of function or death." *Health care management* includes the actions of individual hospital staff, as well as the broader systems and care processes, and includes both acts of omission (failure to diagnose or treat) and acts of commission (incorrect diagnosis or treatment, or poor performance).

It should be noted that medical error definitions are subject to deliberation, since there are many types of medical errors, ranging from minor to major, and the causes of the errors are often poorly understood. Furthermore, there are many other terms that have been used both in the hospital context as well as in publications, including *accidents*, *incidents*, *events*, *mistakes*, *misadministrations*, *unusual occurrences*, and *discrepancies*.

There are two benefits of well-organized QA/QC programs in the radiation therapy department. The first is that it helps to minimize the uncertainty in radiation treatment, thereby providing good accuracy in the treatment process. The second is that it reduces the possibility of having "errors" or "adverse events" and provides a framework for the systematic evaluation, non-punitive reporting, and learning from "errors" when they occur. Adverse events are not addressed in this chapter, but they are addressed in Chapter 12. While issues related to accuracy and uncertainties are the topics covered in this chapter, inevitably there is some overlap in the process of minimizing uncertainties and reducing treatment errors; however, it is the assessment of individual and combined uncertainties in the overall process that is primarily addressed here.

11.2.3 Summary of accuracy and uncertainty terminology

Figure 11.1 illustrates and summarizes a number of the concepts and definitions described above. Error is the difference between the true value of the measured quantity and the measured value (upper left quadrant of Figure 11.1). The total error is a combination of both systematic and random errors. Generally (although not always) errors are summed in quadrature with assumptions about their underlying statistical distribution. Trueness is the closeness of agreement between the

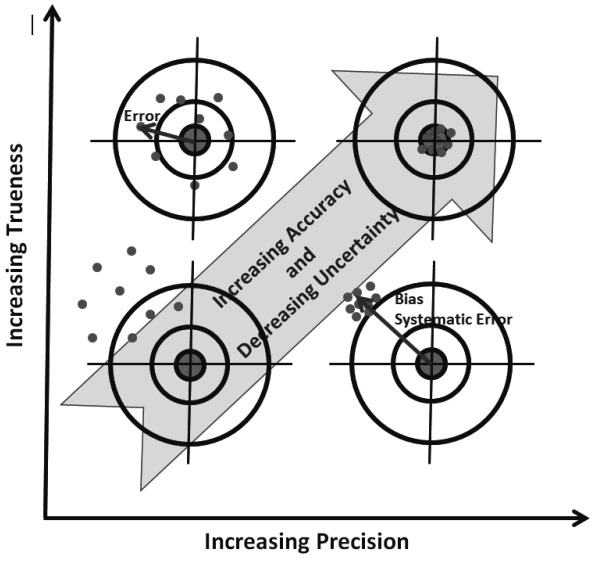


Figure 11.1
Sets of measurement data points (small dots) demonstrating some of the general concepts associated with measurements. The upper left quadrant shows large random error. The upper right quadrant shows small random error. The lower left shows both large systematic error and large random error. The lower right demonstrates a large systematic error (or bias) with a small random error. With increasing trueness and increasing precision, there is an increase in accuracy and a decrease in uncertainty. (Adapted from [151].) SEE COLOR PLATE 75.

average value obtained from a large series of test results and the accepted true value. Trueness is largely affected by systematic error. Precision is the closeness of agreement between repeated independent measurements. Precision is largely affected by random error. Accuracy is an expression of the lack of errors, both random and systematic. Uncertainty characterizes the range of values within which the true value is asserted to lie with some level of confidence.

The upper left quadrant of Figure 11.1 demonstrates a number of data points exhibiting large random error. The upper right quadrant contrasts this with a number of data points having small random error. The lower left quadrant demonstrates a set of data points having both large systematic and random error. The lower right quadrant shows points with significant systematic error (or bias) but small random error. The large, lightly shaded arrow in the figure from the lower left to the upper right demonstrates that with increasing trueness and increasing precision, there is increasing accuracy and decreasing uncertainty. If a third circle were to be drawn on each of these quadrants to define the maximum permissible error (action level), then any point falling outside of that circle would require evaluation and corrective action.

11.3 Historical Evolution of Accuracy Considerations

In 1969, Wambersie et al. [210], who quoted the radiobiological and clinical evidence of Flamant et al. [56], supported the thesis that dose deviations of 7 to 10% could be detected clinically. Subsequently, Herring and Compton in 1971 [76] addressed the question of what accuracy is required in *clinical* dosimetry. They concluded that, at least for some tumors, the probability of tumor control is a very steep function of dose. Using the cancer of the larynx data of Shukovsky [180], they determined that a drop of 10% in dose could precipitously change the probability of control from 70% to 10%. Normal tissue reactions were also considered to be sharply dependent on dose. A more detailed discussion on accuracy requirements was provided in Report 24 by the International Commission on Radiation Units and Measurements (ICRU) in 1976 [94]. The major conclusion in this report is that "the available evidence for certain types of tumor points to the need for an accuracy of ±5% in the delivery of an absorbed dose to a target volume if the eradication of the primary tumor is sought. Some clinicians have requested even closer limits such as ±2%, but at the present time it is virtually impossible to achieve such a standard." Subsequent to this report, there have been a number of analyses of accuracy requirements [22,23,49,143,185,209], with the general, common conclusion being that we should aim for an accuracy of ±5% in the delivery and determination of dose to tumors and normal tissues although in some cases "an absorbed dose delivery of 3.5% is proposed even though it is known that in many cases larger values are acceptable and in a few special cases an even smaller value should be aimed at" [143]. Brahme noted, "If the normalized dose response gradient is higher than 3 [% change in response per 1% change in dose], as is frequently the case, the relative standard deviation of mean dose in the target volume should be less than 3 per cent to achieve an absolute standard deviation in tumor control probability of less than 10 per cent" [23]. Most of these analyses were performed in the 1980s, the era of two-dimensional radiation treatment (2-D RT). No reports with recommendations on accuracy requirements have been published for the modern era in which we have 3-D conformal radiation therapy (CRT), IMRT, and IGRT, although the International Atomic Energy Agency (IAEA) is in the process of generating such a report for publication in 2013 [89].

One source of uncertainty information for the various steps of the radiation treatment process is from QA

programs conducted in the context of multi-institutional clinical trials or through international organizations. The European Organization for Research and Treatment of Cancer (EORTC) developed a simple process of testing the quality of various steps in the chain, from machine output calibration to the planning and delivery of therapy. Although their process was limited primarily to phantom geometries [78,79,107,117], they showed that variations in measured beam output will affect patients. From these data, Bentzen et al. [17] estimated a 7% to 8% loss in tumor control probability (TCP) for the 10% of the beams with the most severe underdosage and a 19% to 22% increase in mild morbidity due to the 10% of the beams with the greatest overdosage. By considering standard mathematical dose-response representations, Bentzen estimated that by improving the coefficient of variation (CV, i.e., the ratio of the standard deviation to the mean) in dose delivery from 10% to 5%, the TCP could be improved by 13%, and reducing the CV from 5% to 2% would gain another 4.3% in TCP. He argues for accuracy in dose delivery, noting that there would be significant gains in reducing the CV to 2%, but that there is not likely much more to be gained by reducing it even lower. Data from Leunens et al. [127] showed that for head and neck patients, the CV for dose delivery in 11 patients was 4.3%. A similar study performed 10 years later yielded similar results [26].

The incorporation of treatment uncertainty information in the treatment planning process has only recently become a topic of intense research. Early work was reported by Goitein [67] in 1985, followed a few years later by Boyer and Schultheiss [21], Shalev [178], and Urie et al. [198]. In more recent years, we and a number of other groups have addressed issues related to patient setup and organ motion uncertainties [6,7,13,34–38,73,81,133,163,171,172,175,183,204,205,229] as well as intra- and inter-physician variation in target volume definition for the same patient [31,54,84,126,129,188,199,218,225]. For example, clinically realistic positioning errors were predicted to decrease TCP by 5% for esophageal cancer [171] and by 11% for prostate cancer [172]. More recently, a method of displaying the "worst case" dose distribution along with the conventional treatment plan has been developed by Lomax for proton therapy [98]. Figure 11.2 shows an example of such a distribution with Figure 11.2(a) showing a conventional plan and 11.2(b) showing the worst case scenario. The latter is developed by calculating a number of dose distributions with slight alterations in specific parameters, such as translated or rotated CT data sets or altered CT numbers. Then a hybrid worst case dose distribution is calculated by considering the lowest dose for all points in the planning target volume (PTV) and the highest dose for all points outside of the PTV. Thus, this type

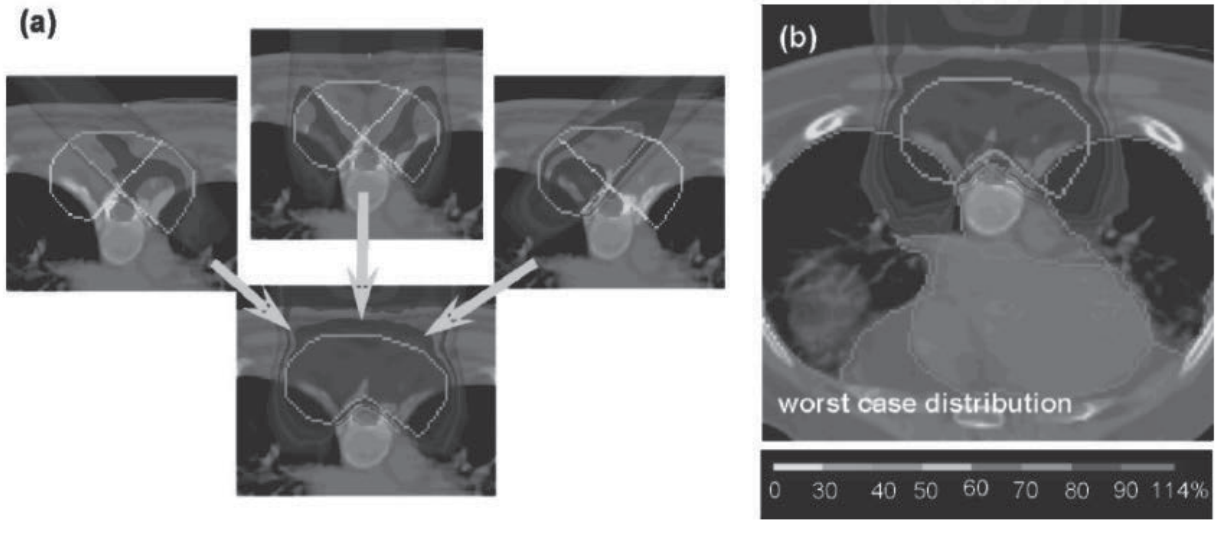


Figure 11.2
(a) Nominal dose distributions in a transverse CT section for three individual proton beams along with the composite distribution. (b) The worst case distribution in the same section. Potential cool region in the target corresponding to 10–20% dose reduction is shown in blue and may be due to possible junction problems with the three abutting beams. (Reproduced with permission from ICRU [98]). SEE COLOR PLATE 76.

of analysis and display shows potential zones for underdosing the target and potential overdoses within the normal tissues.

11.4 Considerations in the Need for Accuracy

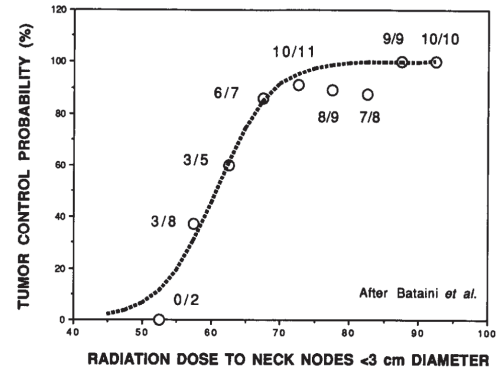
The need for accuracy is predicated by four major considerations: (1) the steepness (slopes) of dose-response curves, (2) the level of dose differences that can be detected by clinical observations in patients, (3) statistical consideration of level of accuracy needed for clinical trials, and (4) the level of dose accuracy that is practically achievable [158]. Each of these will now be addressed in more detail.

11.4.1 Slopes of dose-response curves

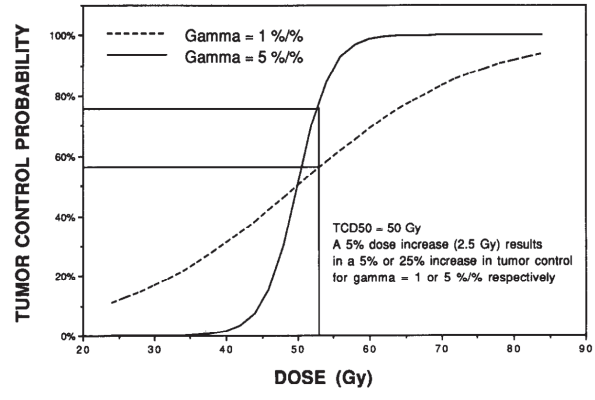
The biological response of cells, malignant tissues, and normal tissues is known to have a sigmoidal shape, with low doses yielding virtually no effect, while the response rises rapidly with an increase in dose and then saturates. Figure 11.3 shows sample clinical data from a publication by Okunieff et al. [153], who generated 90 dose-response curves of human tumors from multiple institutions. The dose that controls half the tumors is labelled as TCD_{50} and the γ_{50} is the percent change in tumor control probability (TCP) expected from a 1% change in dose at about the TCD_{50} (i.e., local maximum slope). The authors demonstrated that values of γ_{50} varied dramatically from as low as 0.04 to as high as 47, although they are quick to point out that the very high and the very low values are probably fortuitous, and the 25% to 75% ranges of γ_{50} are more representative. The data of Figure 11.3(b) show what can happen if γ_{50} ranges between 1 and 5—if the dose is increased by 5%, then the TCP could be increased by 5% for data with a γ_{50} of 1, and by 25% for γ_{50} of 5.

While the clinical data for tumors showed relatively shallow dose-response curves when based on a population of patients, the authors of this paper note that the steepness of the dose-response curves, and therefore the magnitude of γ_{50}, will be greater for individual patients. The reported curves are based on population statistics that include many sources of heterogeneity, including tumor response, clinical observation, and dose delivery.

Similar dose-response data are also available for normal tissue reactions. A recent review has been performed through the QUantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) project [18,136]. Generally, normal tissue dose-response curves are steeper than they are for tumors; thus γ_{50} values are expected to be higher. A sample set of clinical data from the QUANTEC review for radiation pneumonitis are shown in Figure 11.4 [138]. Lung is one of those organs that is considered to have a significant parallel tissue structure, thereby yielding a very significant volume effect. Thus,



(a)



(b)

Figure 11.3
(a) Example of dose-response data for local tumor control based on data from a single institution for patients with pyriform sinus primary tumors. Local control is based on neck nodes under 3 cm. (b) Idealized dose-response curves with TCD_{50} = 50 Gy and γ_{50} of values of 1% and 5% change in TCP per 1% change in dose. A 5% increase in dose at TCD_{50} (2.5 Gy increase) increases the TCP from 50% to almost 55% for γ_{50}=1 and from 50% to 75% for γ_{50}=5. Figures are reproduced with permission from [153].

dose-volume information is required to model lung response. In this context, dose-volume histograms (DVH) are generally used as an aid for treatment planning.

Very rarely do we find dose-response curves for both tumors and normal tissues in the same clinical study. Furthermore, clinical dose-response data are generally only available near the upper end of the dose-response curves for tumors and near the lower end for normal tissues. Roberts et al. [167] re-analyzed the results of caesium-137 low-dose-rate brachytherapy trials for stage I and II cervix carcinoma and were able to generate separate tumor-related dose-response data for local control, metastases as well as data for complications (see Figure 11.5). This is one study that has generated both tumor and normal tissue dose-response

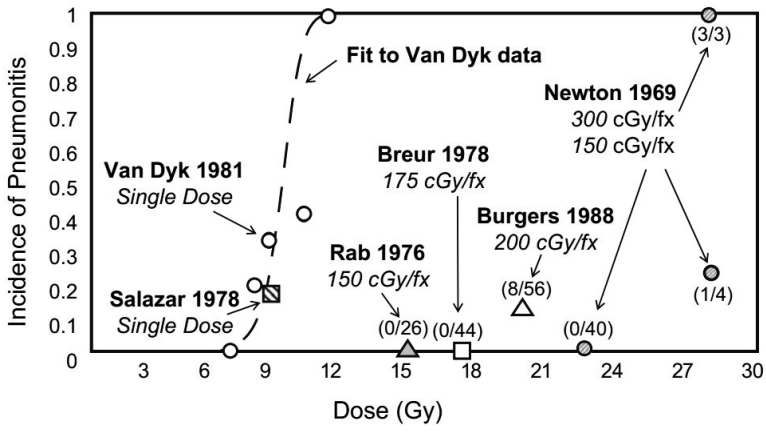


Figure 11.4
Dose-response data for radiation pneumonitis after whole lung irradiation. The numbers in parentheses give the incidence of radiation pneumonitis divided by the population at risk for each fractionation scheme. (Reproduced with permission from [138].)

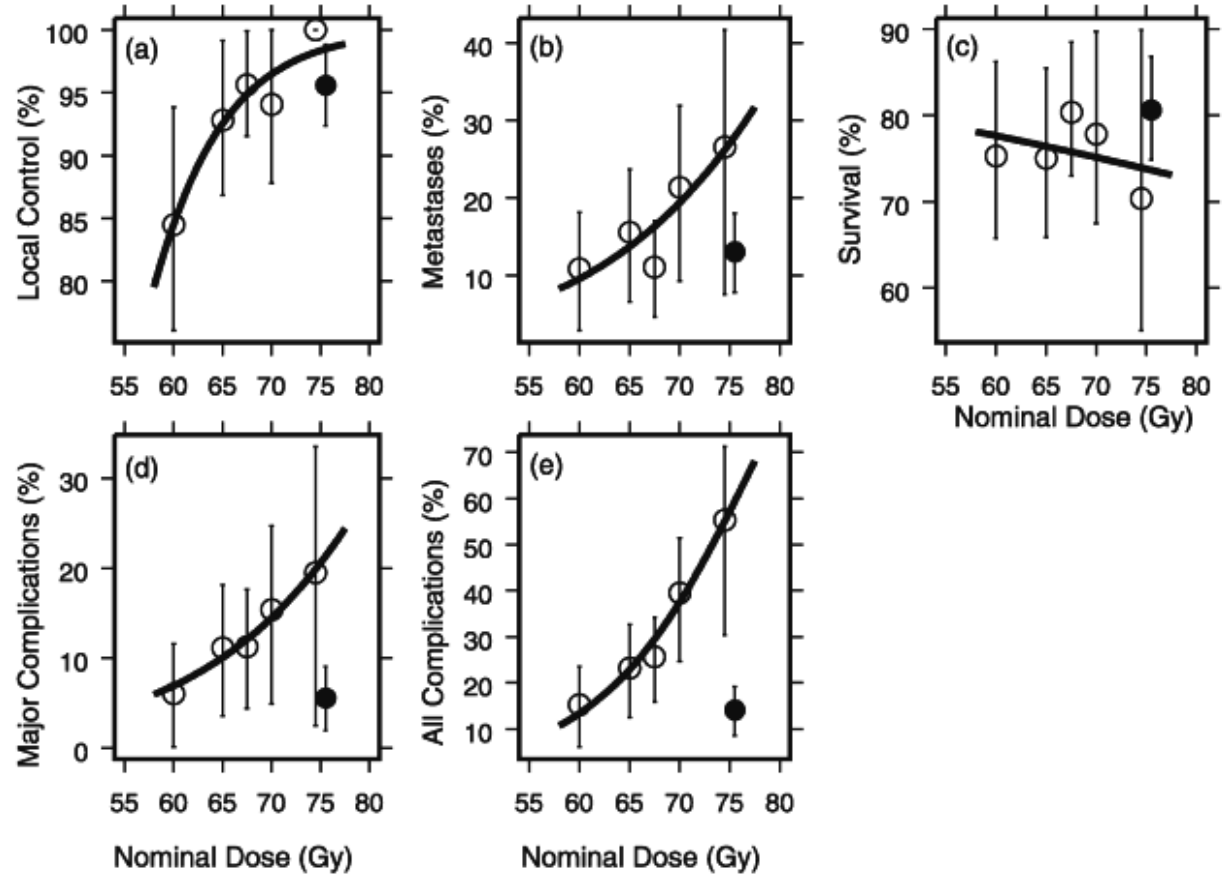


Figure 11.5
Dose-response curves for (a) local control, (b) metastases, (c) cancer-related deaths, (d) major complications and (e) all complications, following caesium low-dose-rate (LDR) brachytherapy. Kaplan–Meier estimates of recurrence/survival at five years were plotted with 95% confidence intervals, as a function of the nominal dose of the treatment group. Open symbols: Selectron LDR (1.6 Gy/hour); closed symbols: historical manual radium LDR (0.5 Gy/hour). The points at 75 Gy were offset for clarity, and fitted unweighted curves were added to aid interpretation. (Figure reproduced with permission from Roberts et al. [167].)

data. It also demonstrates that the data are found over a limited range of the dose-response curve. Furthermore, from the steepness of the dose-response data, it reinforces the importance of an accuracy of ~5%, both for external beam and brachytherapy.

The report by the IAEA [89] provides a quantitative analysis of the influence of accuracy on treatment outcome, providing insight as to how different types of inaccuracy affect outcome and a general impression of the accuracy required in radiation therapy. The analysis is based on the slopes of dose-response curves, but not only at the γ_{50} level, but also at other (less steep) response levels. The results demonstrate that a dosage bias of a few percent (slightly larger for NTCP than TCP) causes a change in both endpoints (TCP and NTCP) of 3%. This may be an indication of the maximum acceptable clinical uncertainty in dose delivery, especially for late-reacting tissues.

11.4.2 Level of dose differences that can be detected by clinical observation

It was already indicated earlier that Wambersie et al. [210] supported the thesis that dose deviations of 7% to 10% could be detected clinically by a radiation oncologist. Similarly, Dutreix [49] reported on two examples where a dose delivery difference of 7% in two different patient groups were discovered independently by a radiation oncologist, one relating to tumor regression and the other to normal tissue reactions. Thus, it appears reasonable that a 7% dose threshold exists for detectable clinical changes observed by a radiation oncologist. Also, Kuban et al. [119] have reported on the long-term results of a dose escalation trial of prostate cancer where the dose was increased from 70 to 78 Gy (i.e., 11% increase in dose). They were able to demonstrate a statistically significant improvement in clinical outcome, i.e., freedom from biochemical or clinical failure was superior for the 78 Gy arm (78% as compared with 59% for the 70 Gy arm, $p = 0.004$). An even greater benefit was seen in patients with initial PSA >10 ng/ml (78% vs. 39%, $p = 0.001$).

11.4.3 Statistical consideration of level of accuracy needed for clinical trials

Well-controlled clinical trials are very time- and cost-intensive. Several studies have illustrated the impact of dosimetric uncertainties on the sample size required for a clinical trial. Orton et al. [155], for example, demonstrated that 60% more patients would be required in a dose-escalation study if no corrections were made for lung density (creating a dose delivery range of 10% to 20%) compared to a study incorporating tissue inhomogeneity corrections with a reduced uncertainty of about 5%. Similarly, Pettersen et al. [160] investigated the impact of dosimetry QA (i.e., good accuracy in dose delivery versus poor accuracy) on the number of patients required in radiotherapy randomized control trials. They assumed underlying biological γ_{50} values (γ_{biol}) and determined the clinical γ_{50} (γ_{clin}) by a convolution which accounted for a distribution of technical and dosimetric factors. Table 11.2 shows the impact on the γ_{clin} derived from specific γ_{biol} and assuming different uncertainties (between 5% and 15%) in dose delivery.

Table 11.2

Observable γ_{clin} value for standard deviation (SD) in dose of 5%, 10%, and 15% assuming an underlying γ value, characteristic for the patient population and without any influence of variation in technical and dosimetric parameters, γ_{biol} of 3, 5, and 7. (From Pettersen et al. [160].)

	$\gamma_{biol} = 7$	$\gamma_{biol} = 5$	$\gamma_{biol} = 3$
$SD_{dose} = 5\%$	5.3	4.2	2.8
$SD_{dose} = 10\%$	3.5	3.1	2.4
$SD_{dose} = 15\%$	2.5	2.4	2.0

Figure 11.6 indicates the number of patients required with increasing steepness of dose-response curves, and it clearly shows that a decreasing number is required as the dosimetry uncertainty is reduced. Furthermore, the generation of accurate dose-response data (i.e., γ_{clin}) is much improved with reduced dose uncertainties.

11.4.4 Level of dose accuracy that is practically achievable

From the point of view of the steep nature of dose-response curves, the level of dose differences that can be detected as a change in clinical response by radiation oncologists—and the level of accuracy desired for optimizing the efficacy of clinical trials—one could propose that an accuracy of a few percent, i.e., 2% to 3% in the dose delivered to the patient, should be the goal of all of radiation therapy. However, the reality is that

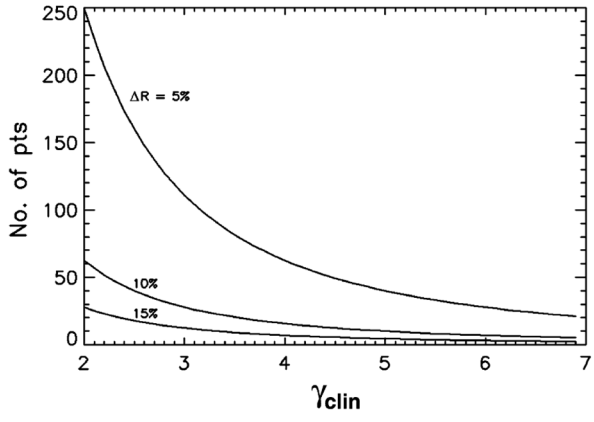


Figure 11.6
The number of patients required in each arm of a randomized controlled clinical trial calculated for various response differences and for increasing steepness of the clinical dose-response curve, γ_{clin}. ΔR% is relative change in response. (Reproduced with permission from Pettersen et al. [160].)

2% to 3% accuracy in the dose determined to points in the patient is actually extremely difficult, if not almost impossible, especially with today's increased complexity in technology and dose delivery. Statements on accuracy requirements need to take into account the reality of what is practically achievable in modern radiation therapy. Much of the remaining sections of this chapter address this, first by reviewing the steps in the radiation therapy process, and then by addressing the uncertainties associated with each of these steps. Uncertainties associated with commissioning of imaging and therapy machine hardware and associated dosimetry are also considered. The outcome of these reviews and the composite uncertainty is summarized in the final section of this chapter.

11.5 The Radiation Therapy Process

From the point of view of uncertainty analysis and uncertainty modeling, it is useful to sort uncertainties into two major categories: (1) *human-related (patient or personnel)* uncertainties and (2) *technology* or *dose-related* uncertainties. Human-related uncertainties can be analyzed by considering the radiation therapy process from a patient's perspective (i.e., patient's-eye view), whereas technology-related uncertainties can be addressed by considering a machine perspective (i.e., machine's-eye view), including dosimetry, commissioning, and quality control processes. Table 11.3

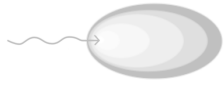


Table 11.3
Examples of human- and technology-related uncertainty components in the radiation treatment process. Note that these are not comprehensive lists but only some examples for illustration.

HUMAN-RELATED UNCERTAINTIES	TECHNOLOGY-RELATED UNCERTAINTIES
Target and organ-at-risk segmentation	Absolute dose determination
Patient repositioning	Machine calibration
Organ/tumour motion	Beam profiles
Interpretation of on-line image matching	Imaging quality/resolution
Deformation	Dose calculation
Couch position	Electron density
Organ full/empty	Beam energy
Weight change	Machine isocentricity
Contour change	Tissue inhomogeneity corrections
Source-to-surface distance	Beam modifiers
Immobilization devices	Leaf transit times
Accuracy of laser setup	Uncertainty in leaf position
Skin tattoo movement	Partial leaf transmission
Breathing motion	Optimization algorithm

summarizes some examples of the *human-related* versus *technology-related* uncertainties.

It is also worth noting that processes upstream of the radiation treatment process can impact negatively on the delivery and efficacy of radiation treatment. For example:

- Surgical practices with regard to lumpectomy (revision surgery or not for positive margins) will influence the need for a radiotherapy boost.
- Efficiency of diagnostic assessment pathways for tumors may influence the stage at which disease presents to the radiation oncologists for treatment.
- Differences exist in the philosophical approaches to treating malignancies.

Thus the radiation treatment team also needs to view itself as part of a larger system of care, associated with other human and technical uncertainties. Technical innovations within the radiation treatment pathways may not be sufficient to offset deficiencies at other levels of the system or factors limiting improved patient outcomes may be best addressed through system-level improvements. For example, delays in diagnostic assessment for lung cancer may result in advanced stage disease that will have a plateau in cure rates no matter what the improvements in the technology of radiotherapy delivery [156,208].

11.5.1 External beam radiation therapy

The various stages of external beam radiation therapy are outlined in column 1 of Table 11.4. While the details of the stages will vary to some extent depending on the clinical diagnosis and the technology available in a facility (e.g., 2-D RT versus 3-D CRT versus IMRT), the general process will include many, if not all, of these considerations. Column one describes the process, column two includes a brief description of each stage, column three outlines the equipment that might be involved, and column four lists some sources of uncertainty that are discussed in the next section.

11.5.2 The brachytherapy treatment process

Many of the stages of the brachytherapy process are analogous to the external beam therapy process. However, there are some distinct differences as well. Table 11.5 summarizes the steps in the brachytherapy process.

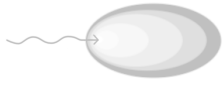


Table 11.4

The stages of the modern external beam radiation therapy process, the equipment involved and a summary of the accuracy and uncertainty issues in that stage.

PROCESS	BRIEF DESCRIPTION	EQUIPMENT	ACCURACY AND UNCERTAINTY ISSUES
Diagnosis and clinical evaluation.	Tumor pathology. Staging.	Cytology, pathology, molecular characterization imaging and other diagnostic equipment.	Uncertainty of lab results. Uncertainty of staging resulting in inappropriate treatment decisions.
Therapeutic decisions.	Cure/palliation/ treatment modalities.	Clinical and evidence based guidelines; nomograms and decision aids.	Inappropriate or inaccurate decisions could lead to inappropriate treatment approach. Decisions need to consider patient preferences/autonomy as well as physician judgement. Decision aids and guidelines subject to bias and quality evidence. Varying degrees of validation.
Treatment prescription/ directive.	Choice of general treatment modality or technique.	None, but decision depends on equipment available in the department and "culture" of the department; training of individual; decision aids and guidelines.	The absolutely "correct" prescription is not always known. Decrease in intra-centre variability in prescription practices achievable through centre guidelines and QA audits/reviews (e.g., 95% coverage of PTV by 95% of dose as an institutional planning standard versus other standards).

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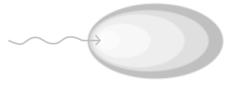

Table 11.4
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PROCESS	BRIEF DESCRIPTION	EQUIPMENT	ACCURACY AND UNCERTAINTY ISSUES
Patient positioning and immobilization for imaging (and treatment).	Laser positioning. Patient support and positioning.	Lasers. Head rests, arm or leg supports. Casts/moulds. Stereotactic devices.	Laser accuracy on CT simulator and congruence with therapy machine(s). Stability of immobilization devices. Patient comfort and compliance.
Imaging for treatment planning.	Set up patient. Generate images for target volume and normal tissue localization.	CT, MR, PET or PET-CT, SPECT or SPECT-CT, x-ray (e.g., simulator), ultrasound.	Limitations of imaging equipment, e.g., CT and MR have much better resolution than PET or SPECT. Accuracy of image fusion for multi-modality.
Determination (contouring) of target volumes and organs at risk (structure segmentation).	Use ICRU concepts of GTV, CTV and PTV.	Conventional simulator. CT-simulator, possibly combined with information from MRI, PET, SPECT, ultrasound.	Limitations of imaging technologies. Limited knowledge of microscopic spread to define the GTV-CTV margin. Limited knowledge of patient motion or setup uncertainties to define CTV-PTV margin. Intra- and inter-observer variation in delineation of region of interest boundaries. Should consider independent audit/review process possibly through QA rounds; adoption of consensus contouring guidelines and ongoing continuing education within institution to promote consistency of segmentation among professionals.
Treatment planning (forward or inverse).	Dose calculations and treatment optimization is performed based on the treatment prescription/directive.	Computerized treatment planning system . . . possibly more than one, e.g., 2-D, 3-D, IMRT, SRS, SBRT, TomoTherapy, CyberKnife.	Accuracy of dose calculations is dependent on the calculation algorithm and how well it has been implemented on the TPS. It is also dependent on the quality of the data measured for the commissioning of the TPS and how well the appropriate parameters for the calculation algorithm have been determined.
Physician approval of treatment plan.	Decision is made on whether the plan is acceptable especially regarding tumor dose uniformity or acceptable doses to OARs.	Plan display possibly at TPS, possibly in physician's office, or possibly elsewhere. May need some form of interconnectivity. Review of dose contours, DVH, radiobiology based comparisons (relative TCP/NTCP).	Physician's knowledge and experience regarding treatment planning system output and balance between target dose and acceptable normal tissue tolerances. Clarity of communication between treatment planner and physician. Institutional guidelines for dose volume constraints and objective metrics of plan "quality."

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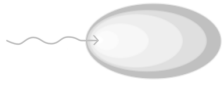

Table 11.4
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PROCESS	BRIEF DESCRIPTION	EQUIPMENT	ACCURACY AND UNCERTAINTY ISSUES
Data transfer and file management.	Data transfer may be done manually on paper, or it may be done through a department record-and-verify or oncology management system.	For 2-D RT, it is the manual transfer of information through the patient treatment sheet. For 3-D CRT, it may be through the treatment sheet or through a network interface. For IMRT, MLC data have to be transferred electronically, probably through a networked oncology management system.	Manual transfer of data needs clearly written information and instructions. Similarly proper QA protocols should be established for electronic data transfer.
Plan validation/ checking.	For 2-D RT, this would be a check of the MU calculation. For IMRT, this may require a phantom measurement of the patient specific procedure, or it may be a calculation performed by independent calculation software.	For 2-D, it would require data tables to perform the time or MU calculation. For IMRT, this would require phantoms and/or independent software.	There should be at least two independent checks of MU/time calculations. For IMRT patient specific QA measurements, clear protocols/ procedures need to be established as well as the definition of criteria of acceptability.
Treatment machine setup/ immobilization/ imaging.	The same patient immobilization used at the simulation or imaging stage will have to be transferred to the therapy machine.	Port films, electronic portal imaging, cone beam CT, MV CT, real time tracking.	Patient setup uncertainties need to be understood. Protocols with criteria of acceptability need to be established. Immobilization devices need to be checked. Patient changes should be monitored throughout the treatment course with on-line imaging. Training of oncologists and therapists in on-line image matching and characterization of observer uncertainty (or at least institutional guidelines for action level thresholds for corrective action).
Treatment dose delivery, possibly with *in vivo* dosimetry.	Dose is delivered with appropriate field sizes, gantry rotations, shielding, MLC settings, etc.	Treatment machine, e.g., cobalt-60, linear accelerator (possibly with MLC, EPID, IMRT capable, on-line-CT), TomoTherapy, CyberKnife, cyclotron for heavier particles.	Machine dosimetry calibration. Reproducibility of patient setup. Special considerations in dose computations (e.g., small irregular fields, tissue inhomogeneities). Accuracy of *in vivo* dosimetry system.

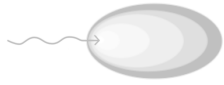

Table 11.5

The stages of the modern brachytherapy process, the equipment involved and a summary of the accuracy and uncertainty issues in that stage. Note that the order of the stages will vary from one procedure to another.

PROCESS STAGE	BRIEF DESCRIPTION	EQUIPMENT	ACCURACY AND UNCERTAINTY ISSUES
Diagnosis and clinical evaluation.	Tumor pathology. Staging.	Cytology, pathology, imaging and other diagnostic equipment.	Uncertainty of lab results. Uncertainty of staging resulting in inappropriate treatment decisions.
Therapeutic decisions.	Cure/palliation/ treatment modalities.	Clinical and evidence based guidelines; nomograms and decision aids.	Inappropriate or inaccurate decisions could lead to inappropriate treatment approach. Decisions need to consider patient preferences/autonomy as well as physician judgement. Decision aids and guidelines subject to bias and quality of evidence. Varying degrees of validation.
Treatment prescription/ directive.	Choice of general treatment approach and radiation sources to be used.	None, but decision depends on equipment available in the department.	The absolutely "correct" prescription is not always known. Well-established prescription or clinical trial protocols should be used where available. Should consider independent audit/review process possibly through QA rounds.
Purchase appropriate sources for permanent seed implants.	Permanent seed implants will use relatively short-lived isotopes such as I-125,Pd-103, Yb-169, Au-198.	None.	Accuracy of radioactive content. Usually a one source activity is used for all sources. There could be some variation in source activities. This will depend on the vendors' specifications and their ability to meet those specifications. Variations in source activities of more than 5% are plausible.
Placement of source applicators.	Different brachy-therapy procedures will require different applicators.	Applicators, needles.	Skill and experience of the brachytherapist; will vary by technique (i.e., pre-planned versus intra-operative planning for permanent prostate implant).
Patient positioning and setup for imaging (and treatment).	Patient support and positioning.	Leg supports/stirrups. Casts/moulds. Possible use of stereotactic device.	Imaging should include source/ catheter/applicator positioning within the body. Stability of source holding devices. Patient comfort.
Imaging for treatment planning.	Set up patient. Generate images for target volume and normal tissue localization.	CT, MR, PET or PET-CT, SPECT or SPECT-CT, x-ray (e.g., simulator), (transrectal) ultrasound. In-room versus "distant" imaging.	Limitations of imaging equipment, e.g., CT and MR have much better resolution than PET or SPECT. Transfer of patient between OR and imaging suites can introduce positioning error in applicators/sources (i.e., HDR techniques).

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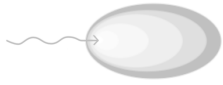

Table 11.5
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PROCESS STAGE	BRIEF DESCRIPTION	EQUIPMENT	ACCURACY AND UNCERTAINTY ISSUES
Determination (contouring) of target volumes and organs at risk (structure segmentation).	Use ICRU concepts of GTV, CTV and PTV.	AP/lateral radiographs. Conventional simulator. CT-simulator, possibly combined with information from MRI, PET, SPECT, ultrasound.	Limitations of imaging technologies. Limited knowledge of microscopic spread to define the GTV-CTV margin. Limited knowledge of patient motion or setup uncertainties to define CTV-PTV margin. Should consider independent audit/review process possibly through QA rounds. Evolving brachytherapy standards (i.e., classic Manchester point based to image and volume based techniques for cervix).
Treatment planning (forward or inverse).	Dose calculations and treatment optimization is performed based on the treatment prescription/ directive.	Computerized treatment planning system . . . possibly more than one, e.g., HDR brachytherapy, prostate brachytherapy.	Accuracy of dose calculations is dependent on the calculation algorithm and how well it has been implemented on the TPS. It is also dependent on the quality of the data measured for the commissioning of the TPS and how well the appropriate parameters for the calculation algorithm have been determined.
Physician approval of treatment plan.	Decision is made on whether the plan is acceptable especially regarding tumor dose uniformity or acceptable doses to OARs.	Plan display possibly at TPS or in OR, possibly in physician's office, or possibly elsewhere. May need some form of interconnectivity.	Physician's knowledge and experience regarding treatment planning system output and acceptable normal tissue tolerances. Clarity of communication between treatment planner and physician. Evolving brachytherapy standards (i.e., classic Manchester point based to volume based techniques for cervix). Institutional guidelines.
Data transfer and file management.	Data transfer may be done manually on paper, or it may be done through a department record-and-verify or oncology management system.	For manual techniques, the data may also be transferred manually possibly through the patient treatment sheet. For HDR, it may be through the treatment sheet or through a network interface. For LDR, the data could be transferred manually or electronically through a networked oncology management system.	Manual transfer of data needs clearly written information and instructions. Similarly proper QA protocols should be established for electronic data transfer.

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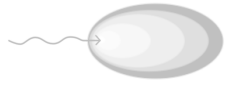

Table 11.5
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PROCESS STAGE	BRIEF DESCRIPTION	EQUIPMENT	ACCURACY AND UNCERTAINTY ISSUES
Plan validation/ checking.	Usually an independent check is performed. Sometimes *in vivo* dosimetry is used.	May require an independent brachytherapy calculation system. *In vivo* dosimetry system.	There should be at least two independent checks of calculations. Clear protocols/procedures need to be established as well as the definition of criteria of acceptability.
Preparation of brachytherapy sources.	Permanent seed implants: radioactive seeds loaded into insertion needles. Temporary implants: catheters, needles, or applicators need to be chosen and prepared for insertion.	For permanent implants: appropriate seed insertion appliances. For temporary implants: appropriate needles or catheters. LDR afterloading system. HDR afterloading system.	Positional uncertainties of sources within catheters or needles.
Brachytherapy procedure implementation.	Patient set-up procedures. Insertion of catheters/ applicators.	Verification imaging with x-ray or CT.	In-house patient setup uncertainties need to be understood. Protocols with criteria of acceptability need to be established. Immobilization devices need to be checked. Patient changes should be monitored throughout the treatment course.
Source loading either for manual LDR treatments or remote LDR / MDR / HDR treatments.	Dose is delivered with appropriate sources and source dwell times.	HDR remote afterloading unit. LDR remote afterloading unit. Imaging techniques such as ultrasound, x-ray, CT.	Machine dosimetry calibration. Reproducibility of patient setup. Accuracy of *in vivo* dosimetry system.
Follow-up imaging and production of post insertion plan.	This is commonly done for prostate brachytherapy.	CT scanner.	Serial imaging for multifraction HDR (e.g., cervix).

11.5.3 The generic radiation treatment process and human decision making

While Tables 11.4 and 11.5 clearly indicate the various steps in the radiation treatment process, they do not indicate very clearly the various levels of decisions and the professionals involved in making those decisions. Figure 11.7 shows a generic diagram of the radiation therapy process for either external beam or brachytherapy. Not only are the general steps in the process emphasized in this diagram, but also the individuals involved and the multiple stages of review that need to occur to generate an accurate and safe treatment for the patient.

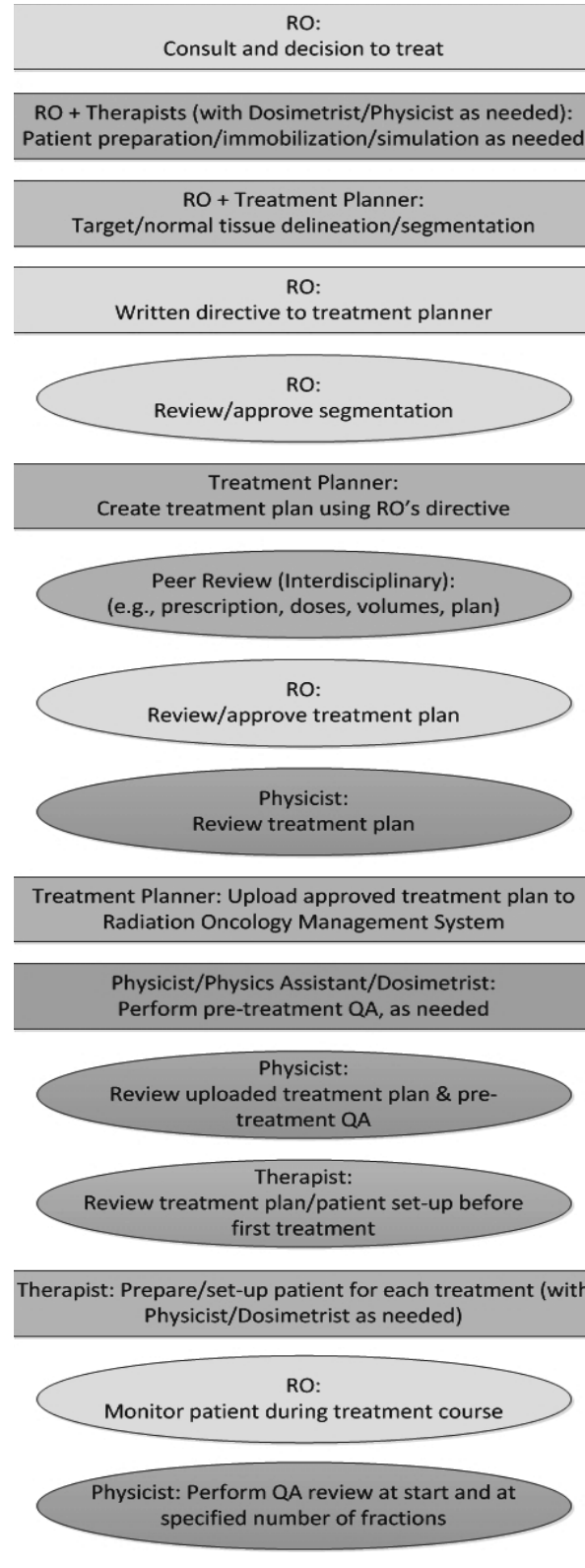


Figure 11.7
Schematic flow diagram of the steps in the radiation treatment process for either external beam or brachytherapy. The steps are in rectangular boxes whereas the review stages are shown in ovals. Different team members are represented by different colors. For this diagram a "treatment planner" could be a dosimetrist, a radiation therapist, or a medical physicist, as these roles vary quite significantly in different parts of the world. RO = radiation oncologist. (This figure was adapted/modified from a similar figure in [146] and can also be found in [89].) SEE COLOR PLATE 77.

11.6 Accuracy and Uncertainty Issues at Each Stage of the Radiation Therapy Process

11.6.1 Technology or dose-related uncertainties

11.6.1.1 Absolute dose determination at a reference point in a phantom

The determination of the absolute dose at a reference point in a phantom has probably had more analysis than any other component of the total dose delivery process, partly because this links directly with national and international calibration or standardization laboratories, and partly because this is the first stage of the entire dosimetry chain. The most recent published analysis of this was reported by Andreo [5]. The results are summarized in Table 11.6.

The estimates in the four columns in Table 11.6 are dependent on the nature of the calibration methodology used in the standards laboratory. For photon beams, the results demonstrate that the absolute dose to a reference depth in a water phantom is accurate to about 1.0% to 1.5% ($k=1$). The results for electrons are similar,

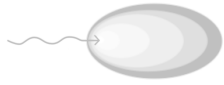


Table 11.6

Estimated combined standard uncertainty in D_w at the reference depth in water in megavoltage photon beams. From Andreo [5]. PSDL = primary standards laboratory, SSDL = secondary standards laboratory.

PHYSICAL QUANTITY OR PROCEDURE	RELATIVE STANDARD UNCERTAINTY (%)			
Step 1a: standards laboratory	SSDL ^{60}Co	PSDL ^{60}Co	PSDL ^{60}Co + accel.	PSDL accel.
$N_{D,w}$ calibration of the secondary standards	0.5	—	—	—
Long term stability of the secondary standard	0.1	—	—	—
$N_{D,w}$ calibration of the user dosimeter at the standards lab	0.4	0.5	0.5	0.5
Combined uncertainty of Step 1a	0.6	0.5	0.5	0.5
Step 1b: hospital				
Long term stability of user dosimeter	0.3	0.3	0.3	0.3
Establishment of reference conditions	0.4	0.4	0.4	0.4
Dosimeter reading M_Q relative to timer or beam monitor	0.6	0.6	0.6	0.6
Correction for influence quantities k_i	0.4	0.4	0.4	0.4
Beam quality correction, k_Q	1.0[a]	1.0[a]	0.7[b]	—
Combined uncertainty of Step 1b	1.3	1.3	1.1	0.9
Combined standard uncertainty in D_W (Steps 1a + 1b)	1.5	1.4	1.2	1.0

[a] Calculated values.
[b] Measured values normalized to ^{60}Co.

except for the case of plane-parallel chambers, which are calibrated in cobalt-60 beams where the estimate was around 2%. Note that these results represent best-case scenarios, with dosimetry performed meticulously by primary/secondary standards laboratory personnel.

The next question relates to the implemented overall accuracy of beam output determination when one uses different types of dosimeters. In work by Tailor et al. [190], they provided a comparison of absorbed dose determinations using 21 different makes and models of ionization chambers for low- and high-energy photon and electron beams, of which 13 models were cylindrical ion chambers and eight models were plane-parallel chambers. A high degree of precision (<0.25%) resulted from measurements with all chambers being done in a single setting. In all cases, the *maximum* spread in output from the various cylindrical chambers was <2%, implying a standard deviation of less than 0.5%. For plane-parallel chambers, the maximum spread was somewhat larger, up to 3%. A few chambers were identified as outliers, indicating the importance of independent calibration cross-checks to assure that one particular chamber in a department is not one of those outliers.

11.6.1.2 External audits of dose determination at a reference point in a phantom

The above estimations of beam calibration accuracy assume that the calibration process is performed accurately and consistently, using dosimeters that are functioning well and implementing calibration protocols strictly according to recommendations. As an independent check, several organizations—such as the IAEA, the Radiological Physics Center (RPC) in Houston, Texas, and ESTRO—have developed an independent, external auditing process using mailed dosimeters, such as thermoluminescent dosimeters (TLDs) or optically stimulated luminescence dosimeters (OSLDs). A typical set of results is shown in Figure 11.8 for the ESTRO-QUALity assurance network (EQUAL) of the

ratio of absorbed dose in water measured by the EQUAL measuring laboratory, Qm, and the absorbed dose in water stated by the participating centre, Qs, for cobalt-60 and x-ray beams [53]. The mean ratio is 0.994 with a standard deviation of 2.1% and an overall spread of ~17%. About 3% of the outputs in reference conditions showed deviations outside the tolerance level of ±5%. Again, these results must be viewed as the starting point of uncertainty in absolute dose, and it is disturbing that some facilities are "off on the wrong foot" with major discrepancy relative to their national calibration.

In 2009–2010, the RPC had similar results—the mean ratio of independent TLD measurement to an institution's stated photon dose was 0.999 ±0.016, and for electron beams it was 0.998 ±0.017 [89]. Note that known (obvious) irradiation errors were excluded from this analysis. The RPC has set a threshold of ±5% to identify calibration errors requiring further analysis and intervention. During the last few years (e.g., 2009–2010), approximately 3% to 5% of photon beams and 5% to 8% of electron beams continue to fall outside of this action level [89].

To gain a sense of the uncertainty in the "secondary" TLD process, the IAEA TLD dosimetry system has been compared by the BIPM and three primary standards laboratories (PSDLs) [100]. The results of 59 reference irradiations of D_{IAEA}/D_{PSDL} had a mean value of 0.998 ±0.6% (1SD) from 1998–99 and 1.004 ±0.9% from 2000–01. All data were between 0.982–1.016. Data from IAEA TLD irradiations in radiation therapy hospitals in developing countries from 1998–2001 (1317 beams) showed a ratio of D_{TLD}/D_{stat} of 1.010 ±7.2% (1SD), where D_{TLD} is TLD measured dose and D_{stat} is the dose stated by the user. In 84% of the cases, the results were within the IAEA acceptance limit of 5%, whereas 1.3% (17 beams) had discrepancies larger than 20%, pointing out major problems in the delivery of dose to the TLD. The authors note that the distribution of the results for 50 high-energy x-ray beams audited in Australia in 1998 had a mean ratio of 1.002 and a standard deviation of 1.1%, with no results outside the acceptance limit of 5% [100].

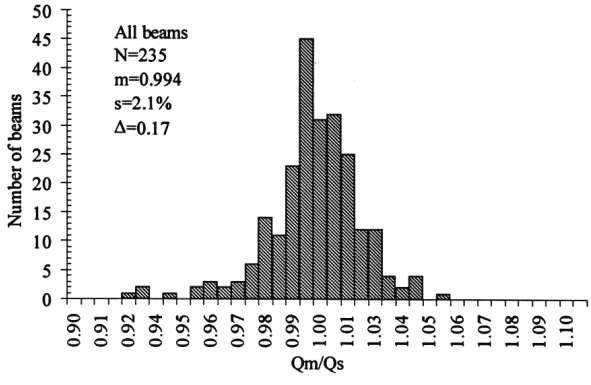


Figure 11.8
Results of the output checks under reference beam conditions for cobalt-60 and megavoltage x-ray beams expressed as a ratio of absorbed dose in water, Qm, as measured by the laboratory and the absorbed dose in water, Qs, as stated by the participating institution. *N* is the number of beams, *n* is the number of dosimeters, *m* is the mean of the distribution, *s* is the standard deviation, and Δ is the spread of the results (i.e., difference between highest and lowest Qm/Qs). (Reproduced with permission from [53].)

The overall conclusion from the above data is that in a well-resourced environment, the dose to a reference point in a water phantom can be delivered with an uncertainty of 2% (k=1), although in less-resourced environments, dose uncertainty was about 7%, with 16% of hospitals being outside the 5% acceptance limit around the year 2000. It is hoped that future audits will produce tighter compliance with national standards. This is particularly important as multi-center clinical trials—which rely on negligible uncertainty in local dose calibration of treatment machines—become more prevalent.

11.6.1.3 Dose determination in a phantom at points away from the reference point

The EQUAL project also audited data for percentage depth doses, beam output variation with collimator opening, and wedge transmission factors [53]. The results for ratios of measured-to-stated doses are summarized in Table 11.7. Findings indicate that percentage depth doses and outputs for open-field collimator variations can be determined with a similar uncertainty as the determination of the calibration dose at a reference point in the phantom, i.e., standard deviation of about 2%. However, wedged fields show much larger variations, with a standard deviation of 10% to 14%, with six deviations larger than ±10% for wedged output variations and 10 deviations outside of ±10% for wedge transmission factors.

11.6.1.4 Imaging system uncertainties

Imaging systems for treatment planning include conventional simulators with radiographic or fluoroscopic modes, computerized tomography (CT), positron emission tomography (PET) or PET-CT, magnetic resonance imaging (MRI) or single photon emission tomography (SPECT). PET-MRI scanners are also being introduced for treatment planning. The uncertainties for these systems are primarily geometric, although densitometric

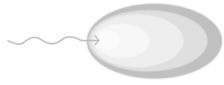


Table 11.7

Ratios of measured TLD dose to the stated dose, *Qm/Qs*, for percentage depth dose data (both 10 cm x 10 cm and 20 cm x 20 cm), output variation with collimator opening for open fields, output variation with collimator opening for wedged fields, and wedge transmission factors. *N* = number of beams, *m* = mean of the distribution, *s* = standard deviation, Δ = maximum spread of results. (Results extracted from [53].)

	PERCENTAGE DEPTH DOSE FOR 10CM X 10CM	PERCENTAGE DEPTH DOSE FOR 20CM X 20CM	OUTPUT VARIATION WITH COLLIMATOR OPENING (OPEN BEAMS)	OUTPUT VARIATION WITH COLLIMATOR OPENING (WEDGED BEAMS)	WEDGE TRANSMISSION FACTORS
N	217	217	642	208	405
m	0.996	0.994	1.003	1.006	1.007
s	1.5%	1.8%	1.8%	13.8%	10%
Δ	0.10	0.16	0.17	2.02	2.02

information is especially important for dose calculations. Table 11.8 summarizes some of the geometric and densitometric considerations for these various imaging modalities as used for therapy planning. The "overall geometric considerations" include imaging resolution combined with laser alignment, machine isocentricity (e.g., conventional simulators), couch motion, and image distortions (e.g., MRI). In reality, issues related to image registration should also be considered because on-line image data are often remapped to the images used for treatment planning.

An excellent review of uncertainties associated with molecular imaging systems can be found in Chapter 2 of this volume, especially Section 2.3.

11.6.1.5 Treatment planning systems (TPS)

There have been many reports on accuracy of dose calculation algorithms [203]. One of the more detailed reviews of such algorithms was produced by AAPM Task Group 65 [158]. In a recent cooperative research project [65] sponsored by the IAEA, some practical clinical tests were developed based on the IAEA TRS-430 report [90]. A semi-anthropomorphic phantom representing the human thorax (CIRS Thorax, CIRS Inc., Norfolk, Virginia) was scanned, planned, and irradiated in 17 different hospitals using 14 different algorithms and inhomogeneity correction methods implemented on different commercial TPSs. A total of 53 clinical test case datasets for different energies and calculation algorithms were produced. Criteria of acceptability had been defined based on IAEA TRS-430 and ranged between 2% to 5% in dose, depending on the location of the measurement point, the nature of the beam–patient treatment geometry, and the ancillary devices used in the treatment. The algorithms in the study were divided into three types:

- measurement-based algorithms, e.g., Clarkson integration;
- model-based algorithms using a pencil beam convolution model and primarily equivalent path length for tissue inhomogeneity corrections (lateral electron transport was not modeled); and
- model-based algorithms, which primarily use a point kernel convolution/superposition model and account for density variation in 3-D (changes in lateral electron and photon transport are modeled approximately).

Measurements were performed in the phantom with a small-volume (0.125 cc) ionization chamber in most hospitals, although in some cases a Farmer-type chamber was used. The results of the percentage of measurements outside of the agreement criteria are shown in Figure 11.9 as a function of algorithm type and beam energy. Dose differences of more than 20% were discovered with some of the simple algorithms and high-energy x-ray beams. The level of agreement decreased with energy and increased with sophistication of calculation algorithm.

Table 11.8

Summary of geometric uncertainties associated with imaging systems used for treatment planning. N/A = not applicable.

IMAGING MODALITY	SPATIAL RESOLUTION	OVERALL GEOMETRIC CONSIDERATIONS	DERIVATION OF ELECTRON DENSITY RELATIVE TO WATER
Simulator film radiography	≤ 0.1mm	0.5 – 2 mm	N/A
Simulator fluoroscopy	≤ 0.5 mm	0.5 – 2 mm	N/A
CT	≤ 1 mm	1 – 2 mm	0.02 after conversion of CT number to electron density relative to water (1.00)
MRI	≤ 1 mm	2 – 7 mm (can be reduced to ≤ 1 mm with corrections) [211,212]	N/A
PET	4 – 8 mm	4 – 8 mm	N/A
SPECT	8 – 20 mm	8 – 20 mm	N/A
Ultrasound	1 – 3 mm	1 – 3 mm	N/A

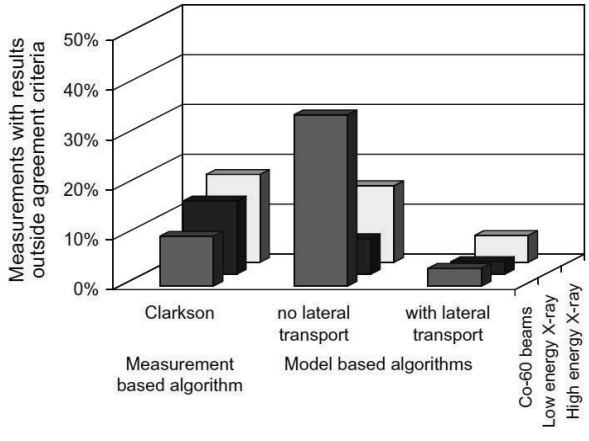


Figure 11.9
Percentage of measurements with results outside agreement criteria depending on algorithm type and energy. (Reproduced with permission from [65].) SEE COLOR PLATE 78.

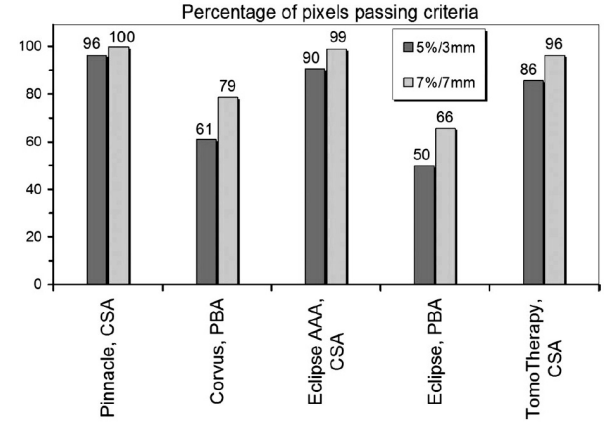


Figure 11.10
Percentage of pixels meeting criteria of 5%/3mm or 7%/7mm. (Reproduced with permission from [41].) SEE COLOR PLATE 79.

Another study by Davidson et al. [41] evaluated the accuracy of five commonly used IMRT TPSs—three using convolution/superposition algorithms (CSA) or the analytical anisotropic algorithm (AAA) and two using pencil beam algorithms (PBAs)—in calculating the absorbed dose within a low-density, heterogeneous region when compared with measurements made in an anthropomorphic thorax phantom. The results are shown in Figure 11.10. The dose predicted in the target center met the test criteria (5% of the dose normalization point or 3 mm distance to agreement) for all TPSs tested. However, at the tumor–lung interface and at the peripheral lung in the vicinity of the tumor, the CSA/AAAs performed better than the PBAs (85% and 50%, respec-

tively, of pixels meeting the 5%/3 mm test criteria). Doses distal to the PTV were more difficult to calculate accurately, with dose variations lying between an underestimation of 3.6% to an overestimation of 11.2%. Doses outside the PTV tended to have larger uncertainties because of inaccurate lateral scatter calculations.

A review of various publications on accuracy of dose calculations in anthropomorphic phantoms for conventional 3-D CRT treatments was performed by an ESTRO working group and is summarized in Table 11.9.

Similar results reviewed by the ESTRO group for IMRT are shown in Table 11.10.

In summary, the accuracy of dose calculations by commercial TPSs is dependent on various issues as summarized below:

1. Detector size used for performing measurements during commissioning of the TPS has a significant impact on the accuracy of beam profiles and small field outputs. Large ionization chambers could underestimate the central ray dose by a factor of two for small fields [3]. Large chambers also yield larger penumbras at field edges compared to small-diameter chambers [173].
2. The commissioning process implemented by the user of a TPS.
3. The sophistication of the physics algorithm used for dose calculations.
4. The location within the body where doses are calculated, especially in regions of low densities, such as lung and air cavities where lateral disequilibrium may occur [33,47].
5. The accuracy of calculations for specific beam configurations (e.g., IMRT) and beam modifiers such as wedges (real or virtual) and MLCs.
6. Appropriate commissioning of special, non-standard techniques, such as stereotactic radiosurgery, stereotactic body radiation therapy, total skin irradiation, and total body irradiation.

Because of these multiple variables, it is difficult to give simple statements about the accuracy of dose calculations with a computerized TPS. The data in Figure 11.9, Figure 11.10, Table 11.9, and Table 11.10 are very representative of achievable accuracies.

11.6.1.6 Dose delivery systems

In a very recent review, Moran and Ritter [145] summarized uncertainties associated with modern radiation therapy systems. Their results are summarized in Table 11.11.

11.6.2 Human-related external beam treatment uncertainties

The following discussion expands on the brief comments made on accuracy and uncertainty issues in column four of Table 11.4.

11.6.2.1 Clinical decisions

The first three stages of the total treatment process—"diagnosis and clinical evaluation," "therapeutic decisions," and "treatment prescription/directive"—relate to clinical decision making. Much could be said about

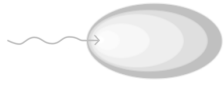


Table 11.9

Results from studies of the accuracy of dose determinations in anthropomorphic phantoms of conventional and 3-D CRT treatments. (Adapted with permission from ESTRO Booklet 9 [142].)

REFERENCE	REGION	SITE	NO.	AVERAGE	SD (%)
Johansson et al., 1987 [107]	Europe	Tonsil	19	1.035	3.2
Wittkämper et al., 1987 [222]	Netherlands	Prostate	18	1.015	1.5
Thwaites et al. 1992 [193]	United Kingdom (UK)	Pelvis-Homogeneous	62	1.008	2.7
		Lung-Inhomogeneous	62	1.011	3.4
Aird et al., 1995 [2]	UK	Head-and-neck	13	1.007	2.1
		Bronchus	13	0.989	2.4
Kron et al., 2002 [118]	Australasia	Head-and-neck	19	1.001	3.5
		Pelvis	21	0.996	3.3
Venables et al., 2003 [206]	UK	Breast	36	0.979	1.3
De Angelis et al., 2005 [42]	Italy	Pelvis	16	1.009	2.2

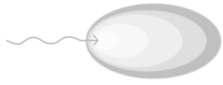


Table 11.10

Results from studies of the accuracy of dose determinations of IMRT treatments. (Adapted with permission from [142].)

REFERENCE	REGION	SITE	NO.	AVERAGE	SD (%)
Gillis et al., 2005 [66]	Europe	Pelvis	10		
ESTRO-QUASIMODO		PTV		1.014	1.6
		OAR		0.997	3.6
Tomsej et al., 2005 [196]	France and Belgium	Head-and-neck	16	0.992	3.9
GORTEC					
Ibbott et al., 2006 [86]	US	Head-and-neck			
RPC-RTOG		Primary PTV	450	0.99	8
		Secondary PTV	223	0.99	7
Tomsej et al., 2007 [195]	Europe	Fictitious volume	7	0.966	2.4
ESTRO-OECI		(after internal QA)		0.978	1.5
TomoTherapy					

ESTRO = European Society for Radiotherapy and Oncology
QUASIMODO = Quality ASsurance of Intensity MODulated radiation Oncology
GORTEC = Groupe d'Oncologie Radiothérapie des tumeurs de la TEte et du Cou
RPC = Radiological Physic Center
RTOG = Radiation Therapy Oncology Group
OECI = Organisation of European Cancer Institutes

this, but the details of these issues are beyond the scope of this chapter. Decisions at each of these stages determine the direction and strategy of the subsequent stages. While not much information is available on accuracy and uncertainties within these stages, one source of such information relates to compliance in clinical trials. Peters et al. [159] recently reported on the impact of radiation therapy quality on outcome in a large international phase III trial evaluating radiotherapy with concurrent chemotherapy for advanced head and neck cancer. Participating centers were required to submit diagnostic imaging and treatment plans for patients entered onto the trial to the Quality Assurance Review Center (QARC) by the end of the first week of radiotherapy. These materials were reviewed by QARC, and feedback was provided to the investigators to either confirm that the plan was protocol-compliant or to recommend modifications if the plan was noncompliant. Revised plans were further assessed and, if necessary, additional changes were recommended. Of the 820 evaluable patients, 208 (25.4%) were considered noncompliant with respect to protocol-specified criteria. Of the 208, 162 patients had significant deviations related to tumor criteria with or without associated normal tissue criteria, and 46 patients had significant deviations related to normal tissue criteria only. The results showed that those patients with compliant plans from the outset fared significantly better in terms of overall survival and time to loco-regional failure than those patients with significant protocol deviations. They also noted that centers treating only a few patients are the major source of quality problems. This analysis demonstrates powerfully the importance of quality radiation therapy in order to achieve optimal treatment outcomes in the combined modality (chemoradiotherapy) treatment of advanced head and neck cancer.

Brundage et al. [28] reported on a real-time audit of radiation therapy in a regional cancer center in which they reviewed the prescriptions and treatment plans of 3,052 cases. Due to errors in radiation planning or prescription, 4.1% of plans were not approved by the audit. Most of the plans were so identified because of insufficient coverage of the clinical target volume or because of risk to critical structures within the treatment volume. Some 3.6% were identified by the audit as being inconsistent with treatment policy, most of which were

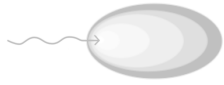


Table 11.11

Summary of estimated uncertainties and the ability to measure for components of linear accelerators (Table adapted from [145].)

COMPONENT	ESTIMATED UNCERTAINTY	NOTES WITH RESPECT TO MEASUREMENTS	DOSIMETRIC IMPACT	EXAMPLE REFERENCES
S_c, collimator output factor	0.5%–1%	Straightforward with correct equipment (S_c phantom, chamber, build-up caps)	Impact: minimal for large fields; larger for small fields	[216,231]
Jaw positioning accuracy	< 1 mm	Typically measured with graph paper, high resolution dosimetry to be used when assessing abutted fields	Impact: minimal impact on output for large fields; greater than 15% dose uncertainty for abutted fields with 1 mm gap or overlap	[113,122, 168]
Wedges	2%/2 mm	Estimated using AAPM TG-142 tolerances (monthly and annual tests)	Depends on depth, wedge angle, and distance off axis	[113]
MLC position - static	≤ 1 mm, leaf end/edge transmission highly variable	Straightforward relative check with picket fence test	Minimal impact with sufficient margins. Caution with field edge matching using MLCs (up to 20% discrepancy at match edge) and small field sizes/beamlets	[1,83]
MLC position - dynamic	Typically ≤ 1 mm	Measure output for narrow "sliding window"	Dose discrepancy highly dependent on gap between adjacent leaves	[131]
MLC transmission	Up to several percent with highly modulated IMRT fields	Discriminate between interleaf and intraleaf leakage or measure average value	Does not vary (but lack of modeling 1.5%–3% for static fields)	[52]
Tabletop (or couch)	Depends on angle, energy, and position. Attenuation up to 20% for extreme conditions	Can measure with ion chambers, EPIDs, and other methods	Beam attenuation: up to 13% for couch top; 15% for support rails. Can spoil skin sparing	[139] (and others, see [145])

not approved because the choice of target volume resulted from a shift in treatment philosophy toward omitting the clinically normal but undissected ipsilateral axilla from the radiation target volume. The means of developing consistency in these stages is aided by the development of departmental protocols based on the best information available from clinical trials and the literature. In addition, the development of site-specific quality assurance reviews and checklists can improve treatment consistency [24,80].

11.6.2.2 Patient positioning and immobilization for imaging and treatment

Accurate, comfortable, and reproducible patient setups are crucial to minimizing target volume margins. These immobilization procedures need to be implemented already at the stage of imaging for therapy planning. Many immobilization procedures have been developed. The most recent summary of various immobilization devices is shown in Table 11.12, along with quantitative estimates of expected uncertainties for different anatomic sites.

Daily image guidance allows for the reduction of both systematic and random uncertainties, as shown schematically in Figure 11.1. A sample of our experience with helical tomotherapy daily megavoltage CT is shown in Figure 11.11. Without daily image guidance, setup uncertainties could be as large as 20 mm for non-cranial tumors; however, with image guidance, these are reduced to less than a few millimeters. In addition to positioning correction, daily image guidance enabled the detection and corrections to account for significant anatomical changes due to tumor regression or weight loss.

11.6.2.3 Determination (contouring) of target volumes and organs at risk (structure segmentation)

Target volume delineation is recognized as having one of the largest uncertainties of all the steps in the radiation treatment process. Unfortunately, without invasive measures (e.g., surgical intervention or image-guided biopsy), it is difficult to establish the absolute "truth" of what the real target volume should be. Instead, many studies have been performed of inter- and intra-physician variations in target volume contouring, and the "correct" answer becomes some form of "consensus" (or "expert") average volume. An excellent review of various methods used for contouring in radiation oncology has been provided by Jameson et al. [104]. In a literature search, they identified 69 relevant studies (see Table 11.13). The most common tumor sites were prostate (26), lung (10), head and neck cancers (8), and breast (7). The most common metric of comparison was "volume" (used 59 times), followed by "dimension and shape" (used 36 times), and "centre of volume"(used 19 times). Of all 69 publications, 67 used a combination of metrics, and two used only one metric for comparison. Inconsistencies in methods of contour comparison may be addressed through the implementation of consensus guidelines and training. Once established, these could be included in software packages to set "alarms" when deviations occur.

To help minimize variations in target volume determinations, the ICRU has defined gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) through ICRU Reports 50, 62, and 83 [95–97]. However, the weakest link continued to be the starting point—GTV determination. Recently, the ICRU has added some sub-volume categories to account for the change in tumor dimensions during a course of treatment and to address the idea of adaptive radiation therapy. Thus, the concepts of "initial tumor volume" (iGTV), "residual gross tumor volume" (rGTV), and the "adaptive clinical target volume" (aCTV) are introduced in the new ICRU report on brachytherapy [92].

Hamilton and Ebert [70] have performed an interesting review of volumetric uncertainty in radiation therapy. Figure 11.12 provides a schematic summary of factors affecting volumetric uncertainty. Again they point out inter- and intra-physician variability is one of the significant components of uncertainty.

The issue of inconsistent metrics for comparing target volume delineation was addressed recently by Fotina et al. [59] who guided a study in which seven prostate and eight lung cases were contoured by eight experienced observers. The conclusion of the study was that a combination of descriptive statistics, overlap measures, and statistical measures of agreement or reliability analysis is required to fully report the inter-rater variability in delineation.

The clinical impact of variation in target volume or normal tissue contouring is unknown for most clinical situations, but the impact of variability in OAR volumes has been characterized for organs like rectum [55,57] and parotid [152]. Weiss and Hess [217] note that the geometric uncertainty as a result of contouring variation is larger than that of setup errors and organ motion for some tumor sites. In addition, they point out that the uncertainty due to contour variation is both systematic and random for the individual, but only random for a population. An individual may consistently define larger or smaller volumes with some intra-observer variation, but for large numbers of patients and observers, these contribute to an overall random error. This becomes important in multi-center clinical trials where a large variation in contouring processes between centers may have an impact on trial results. They make the following suggestions to reduce uncertainties in GTV and CTV determination:

- Clear instructions for defining GTVs, CTVs, and PTVs. This is especially relevant for multi-centre clinical trials.
- Selection of appropriate imaging and image display techniques. Image quality and window level settings can result in over- or under-estimation of tumor boundaries. Exploitation of available technical

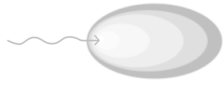


Table 11.12

Comparison of immobilization devices and expected uncertainties for various anatomic sites. Adapted with permission from [141].

ANATOMIC SITE	IMMOBILIZATION DEVICE	EXPECTED UNCERTAINTY (MEAN SETUP ERROR)	REFERENCES
Intracranial	Stereotactic head ring	1.0 mm	[176]
	TALON	1.38 ± 0.48 mm	[174]
	GTC frame	2.00 ± 1.04 mm	[11]
	HeadFIX bite plate	< 2.0 mm	[120,186,187]
	Thermoplastic mask systems	1.59 ± 0.84 mm	[61]
		2.1 ± 1.0 to 2.7 ± 1.5 mm	[197]
		3.17 ± 1.95 mm	[11]
Head and neck	Type S thermoplastic	3.1 ± 1.6 (sup landmarks)	[169]
		8.0 ± 4.5 (inf landmarks)	[169]
	Bear-claw board	2.8 ± 0.9 (sup landmarks)	[169]
		8.0 ± 5.5 (inf landmarks)	[169]
Spine	Screw fixation of spinous process	2 mm	[69]
	Body cast with stereotactic frame	≤ 3.6 mm	[130]
	Custom stereotactic frame	2 – 3 mm positioning accuracy	[227]
	Scotch cast torso and head masks	Cervical: 0.3 ± 0.8 mm AP, -0.1 ± 1.1 mm Lat, 0.1 ± 0.9 mm SI	[182]
		Thoracic: 0.3 ± 0.8 mm AP, 0.8 ± 1.1 mm Lat, 1.1 ± 1.3 mm SI	[182]
		Lumbar: 0.0 ± 0.9 mm AP, -0.7 ± 1.3 mm Lat, 0.5 ± 1.6 mm SI	[182]
Lung - SBRT	Abdominal compression (Elekta body frame)	5 – 8 mm	[124]
		3.4 mm AP, 3.3 mm Lat, 4.4 mm SI	[223]
		2 mm	[147]
		2 mm	[74]
		~ 5 mm	[194]
	Abdominal compression (Leibinger body frame)	1.8 – 4 mm	[77]
	BodyFIX	2.5 mm	[62]
		0.3 ± 1.8 mm AP, -1.8 ± 3.2 mm Lat, 1.5 ± 3.7 mm SI	[214]
Breast	Breast board with arm support	-1.7 ± 2.8 mm AP, 1.2 ± 3.7 mm SI	[148]
	Vac-Lok	-1.8 ± 2.9 mm AP, 0.4 ± 2.3 mm SI	[148]
Abdomen	BodyFIX	~2 mm AP, ~ 2 mm Lat, ~6 mm SI	[224]
	Elekta body frame	3.7 mm Lat, 5.7 mm SI,	[124]
	Leibinger body frame	1.8 – 4.4 mm	[75]
Prostate	Generic leg support	6.5 mm	[135]
	Full Alpha Cradle	6.0 mm	[135]
	HipFix (thermoplastic)	4.6 mm	[135]
	Vac-Lok	4.6 ± 3.5 mm (prostate)	[60]
		7.6 ± 4.7 mm (seminal vesicles)	[60]
	BodyFIX	3.0 ± 1.29 mm	[213]
Prone pelvis	Belly board	4.5 mm AP, 3.2 mm Lat, 4.2 mm SI	[4]

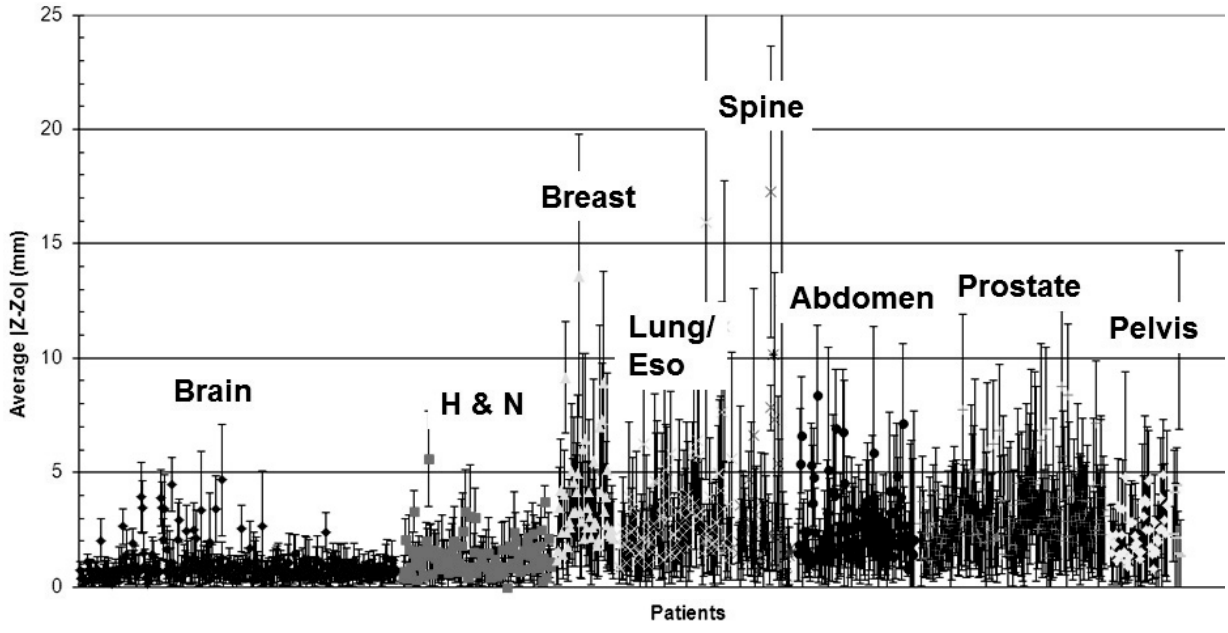


Figure 11.11
Daily anterior-posterior patient setup corrections relative to the average of the first two fractions for 889 helical tomotherapy patients by anatomic site (225 brain, 125 H&N (head and neck), 48 breast, 95 Lung/Eso (esophagus), 46 spine, 98 abdomen, 156 prostate, 47 other pelvis, and 7 extremities. The points represent average values, and the error bars are standard deviations. (Figure courtesy of Dr. S. Yartsev of the London Regional Cancer Program.) SEE COLOR PLATE 80.

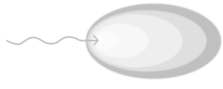


Table 11.13

Contouring metrics used for each tumor site as a ratio of the total publications for that site. Table adapted from [104]. All the references are included in the table in the Jameson et al. paper. CI = Concordance index

SITE	# PUBLICATIONS	VOLUME (%)	CI (%)	CENTER OF VOLUME (%)	SHAPE DIMENSION (%)
Lung	10	8 (81)	4 (40)	2 (20)	5 (50)
Breast	7	7 (101)	3 (42)	4 (57)	5 (72)
Brain	8	6 (76)	2 (25)	4 (50)	2 (25)
Prostate	26	21 (82)	5 (19)	4 (15)	16 (62)
Head and neck	8	8 (101)	3 (37)	1 (13)	2 (25)
Pancreas	1	1	0	0	0
Bladder	3	3	0	2	2
Rectum	1	0	0	0	1
Oesophagus	2	2	1	0	2
Cervix	3	3	1	2	1
Total	69	59 (86)	18 (26)	19 (28)	36 (52)

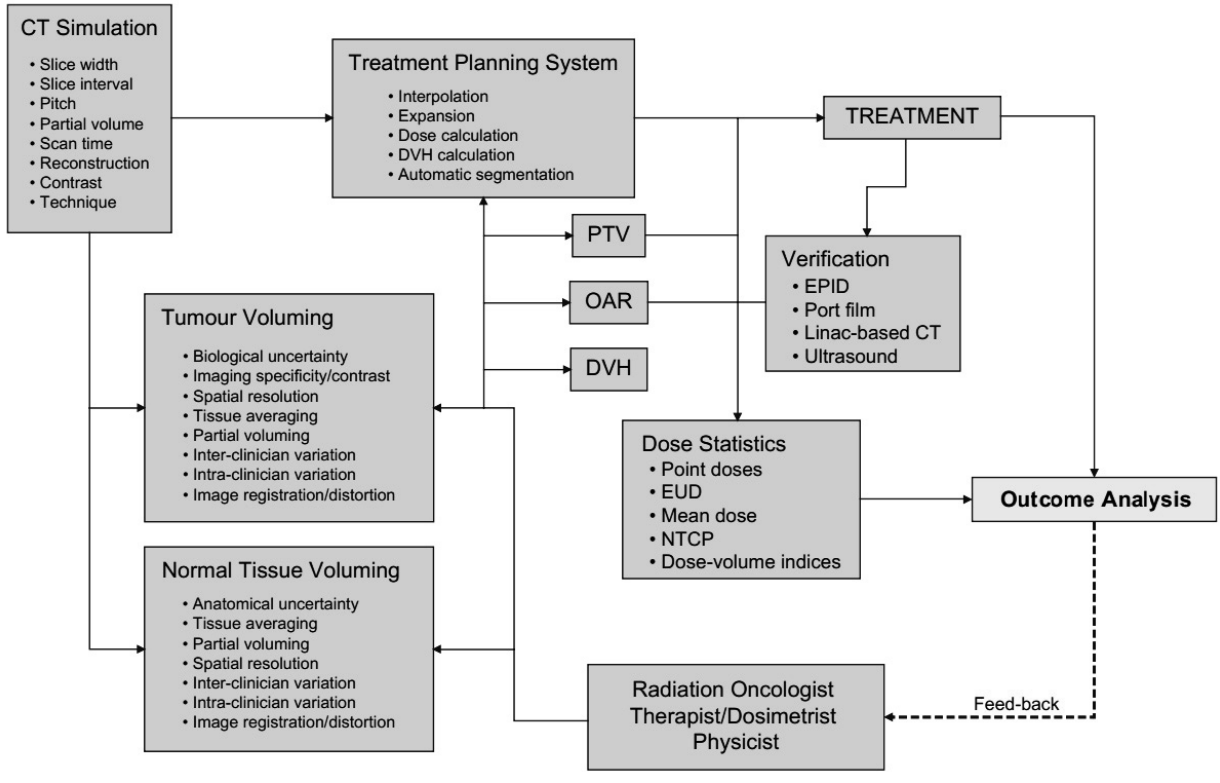


Figure 11.12
Factors involved in volumetric uncertainty in target volume delineation. The flowchart describes the chain of potential uncertainty in delineating gross tumor volume, planning target volume, clinical target volume, and organs at risk. It should be noted that this system has the facility to feed back information on volume delineation in relation to individual patients and global practice. CT = computed tomography; CTV = clinical target volume; DVH = dose-volume histogram; EPID = electronic portal imaging device; EUD = equivalent uniform dose; NTCP = normal tissue complication probability; OAR = organ at risk; PTV = planning target volume. (Reproduced with permission from [70].)

means for image registration and multimodality imaging are important components of minimizing target definition uncertainties.

- Close liaison with other specialists, particularly diagnostic radiologists and surgeons, is essential. Second opinions and the use of teleconferencing are useful. Each department should have well-planned QA procedures for the entire treatment planning process. For multicenter studies, trial runs and the establishment of central reviewing boards are suggested.

Even after their review, the definition of the "ideal" GTV and CTV remain unclear. Detailed analyses of clinical, radiologic, pathologic information together with data on the incidence and location of tumor edge recurrences are necessary to identify the "true" target volume boundary and pattern of spread. An example of co-registration of prostate digital histopathologic images to *in vivo* MR images was recently published by Ward et al. [215] and demonstrated a sufficient accuracy for co-registering the smallest clinically important lesions (0.2 cm^3) with 95% confidence.

For standardizing normal tissue contouring, the Radiation Therapy Oncology Group (RTOG) has developed a male and female pelvic contouring atlas by having 16 radiation oncologists contour specific normal tissue structures [64]. A computer program was used to determine the binomial distribution to generate 95% group consensus contours. These contours and definitions were then reviewed by the group and modified. There was general agreement among the panelists for most structures except for the adnexa, where there was great variability, and this subjectively posed the greatest difficulty in identification. Consensus guidelines for pelvic normal tissue contouring were reached and are available as a CT image atlas on the RTOG website.

This report serves as a template for the definition of the male and female pelvic normal tissue structures for radiation therapy planning, allows for uniformity in defining normal tissues for clinical trials delivering pelvic radiation, and will facilitate future normal tissue complication research. Automated aids (auto-segmentation, atlas-based libraries) for contouring can also potentially reduce variability in contouring. However, these tools are still under development and require the implementation of their own unique commissioning and quality assurance processes [63,85].

In addition, the trend toward multi-modality imaging treatment planning introduces additional sources of uncertainty, both in image registration as well as composite target volume delineation (e.g., registration of PET images and the selection of an SUV threshold to delineate a tumor boundary) [221]. Khoo et al. [112] demonstrated that a well-structured education program reduced both inter- and intra-observer prostate contouring variations. The impact was greater on MRI than on CT. The reduction in contouring variations among radiation oncologists with good education/training -programs was also found in other studies for other anatomic sub-sites, including the upper cervical esophagus [189], head and neck [12], and post-prostatectomy [144]. Clearly, with the ongoing implementation of new technologies into routine clinical practice, education programs for target contouring should be incorporated as part of the continuing medical education of radiation oncologists.

11.6.2.4 Treatment planning (forward or inverse)

Broadly speaking, treatment planning involves all the steps involved in preparing the patient for radiation treatment, including appropriate patient positioning, imaging, target volume and normal tissue localization, definition of dose-volume constraints and prescription, determination of beam arrangements and field-shaping requirements, physician approval of the plan, and transfer of data to make the therapy machine ready for irradiation. However, this section addresses the specifics associated with definition of dose-volume constraints and prescription, determination of beam arrangements, and field-shaping requirements. All of this activity is performed with a computerized treatment planning system. While uncertainties associated with the technology of treatment planning systems have been discussed in Section 11.6.1.5, the actual process of treatment planning has the goal of developing an optimal plan that meets the dose-volume constraints defined by the radiation oncologist. These dose-volume constraints have their own uncertainties and, furthermore, optimization algorithms do not necessarily yield a unique solution. These have been discussed in the QUANTEC papers that define dose-response considerations for all the significant tissues and organs in the body. A summary discussion of these data is provided by Marks et al. [136] and includes a discussion on the limitations of these data and the predictive models that are used. The data are extracted from the published literature—with different authors often presenting their data differently (e.g., actuarial versus crude complication rates)—and pooled data from multiple studies have the risk of being inaccurate.

In terms of the predictive power of DVH or radiobiological models, the predictions of clinical outcomes are limited by the available input data, which at times have been extrapolated beyond the original data range without validation. Furthermore, the models have their own limitations in terms of representing the radiobiological response for a variety of dose-volume-fractionation situations. DVHs reduce complex 3-D dose distributions such that spatial information is lost, and there is no knowledge of where the actual "cold" or "hot" spots are. These models also assume all regions within the organ have equal response, although some investigators have incorporated functional DVH information [137]. The data are generally based on one-time planning CT information, which does not account for patient intrafraction or inter-fraction changes. This process is shown schematically in Figure 11.13. The data include inter-institutional and physician differences in image segmentation, dose calculations, patient populations, and preferred beam arrangements.

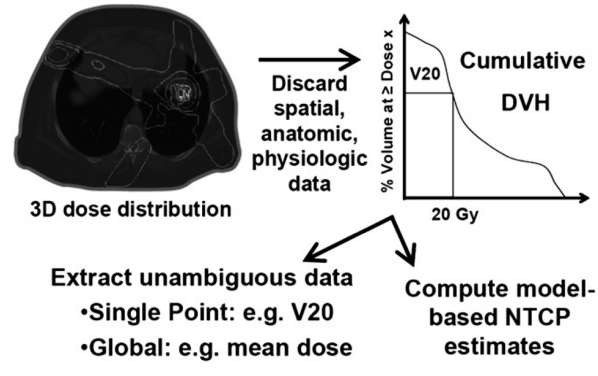


Figure 11.13
Schematic representation of the extraction of dose-volume parameters for NTCP modeling and the computation of NTCP. A 3-D dose distribution is reduced to a 2-D DVH by discarding all spatial, anatomic, and physiologic data. The 2-D graph is then further reduced to a single value of merit [e.g., mean dose, percent of the organ receiving ≥20 Gy (V20)], or a model-based NTCP. (Reproduced with permission from [136].)

In spite of these limitations, these models are a present-day reality, and their use—as well as the prescribed dose-volume constraints—are part of the computerized treatment planning and optimization process. Unfortunately, it is very difficult to make simple, quantitative statements about the accuracy and uncertainties of the radiobiological models and the dose-volume data that are used as part of the constraints for the treatment planning process. In many instances, the quantitative levels of these uncertainties are not even known. Accuracy may improve through future correlation of observed clinical outcomes with 3-D/4-D dose distribution data and model predictions. This obvious strategy would "calibrate" the TCP/NTCP models, now that we can provide tighter control of the dose variables. Complicating things further are the inherent uncertainties related to individual patient heterogeneities related to medical comorbidities, such as diabetes, cardiovascular disease, and underlying genetic sensitivity. Ultimately, the principles of personalized medicine—in terms of optimal drug selection, dosing, and prediction of response based on underlying genomic profiles—may also apply to the application of radiation therapy as a therapeutic modality. This may complement "traditional" evaluation criteria, such as those described above for the general patient population [219]. The future promise is delivering "the right dose at the right place for the right type of patient."

Once the dose volume constraints have been defined, the optimized treatment can be developed. For 3-D CRT, this is often done using a "manual" forward planning process. For most IMRT, "automated" inverse planning software is required. A discussion of optimization procedures is much beyond the scope of this chapter. However, the variation in quality of treatment plans developed by automated procedures needs to be evaluated, and that evaluation in itself has uncertainties. Knöös et al. [114] have addressed this and discuss evaluation uncertainties in three different categories as defined by SMART objectives, i.e., are they specific, measurable, and attainable? The question is, once a plan is developed, does another better solution exist (i.e., issues of local minima in optimization space)? If not specifically accounted for, anything can appear in structures that are not included in the optimization, e.g., if a structure is not outlined and included in the optimization process, it could inadvertently receive a high dose due to its omission in the optimization procedure. One means of improving that is to evaluate several plans with different weighting of the objectives for all the involved structures [114]. However, performing multiple plans for routine clinical treatment planning is very time consuming; thus automated procedures for doing this in a robust manner must be developed.

Research is also on-going to develop treatment plan optimization procedures that are robust to the presence of treatment-related uncertainties [140]. An important requirement for robust planning is that reasonable numerical models of the likely uncertainties and their effects on the delivered dose distribution and treatment outcomes must be available. This includes uncertainties such as tumor and normal tissue dose-response and target contouring. A first attempt at this was made by Goitein [67] in which he developed nominal plans, as well as two worst-case scenarios, i.e., overdose and underdose. While others have worked on this as well [178,198], very little of this research is used in clinical practice today. One of the problems is that the degree of uncertainty in various parameters is not well understood quantitatively [140], and practical means of their incorporation remain elusive.

In addition, given the physical limitations of dose delivery, there may be trade-offs that need to be resolved based on physician judgement or patient preference, and that is another source of uncertainty. For example, when there is an overlap between a target and OAR, which gets priority?

11.6.2.5 Physician approval of treatment plan

The above comments regarding uncertainty knowledge and display are very relevant for physicians when they have to review and approve a treatment plan. This part of the process requires good communication between the physician and the treatment planner. It also assumes the physician understands the details of the meaning of the information that is presented to him or her, be it by computer or word of mouth. Figure 11.7 highlights the many decision/review points between physicians and other staff. Part of the communication is often clarifying physician objectives and tacit assumptions, and sometimes there needs to be a reality check on what is actually possible. There is also room for improved display and evaluation tools for radiation oncologists, especially as technology evolves [15,16,221].

11.6.2.6 Data transfer and file management

In the 2-D radiation therapy days, the resulting treatment planning data were transferred manually, but 3-D CRT and IMRT treatments require some form of digital transfer since plans generally include information about multiple MLC configurations. The digital transfer is usually done by a record-and-verify system or a networked radiation oncology information system. If there are issues with data transfer, usually these involve "gross" errors rather than small uncertainties. This chapter does not really address errors or misadministrations, but rather accuracy and uncertainties. A recent report by the IAEA [88] on record-and-verify systems

gives some description of the errors/misadministrations that have been reported with record-and-verify systems, discussing how to minimize them. It notes that many of the errors are partially attributed to the lack of appropriate human control in terms of organization and interpretation of large amounts and types of digital data. Such errors can also occur as a result of lack of well-defined workflow and procedures, particularly at interfaces between systems and interfaces between manual/human processes and electronic processes.

11.6.2.7 Plan validation/checking

For 2-D radiation therapy, plan checking was straightforward and involved an independent monitor unit or time calculation for simple field configurations. For IMRT, this generally involves either a phantom measurement process or an independent calculation using software not related to the software that was used to calculate the treatment plan. Various independent plan check software packages have been developed, sometimes for generic accelerator technologies and sometimes for specialized procedures like helical tomotherapy [192]. By way of example, for helical tomotherapy and for ten head and neck patients, for the modified (which includes the TomoTherapy couch) and original CT, respectively, the mean difference between the original plan and the calculation with the independent software was +1.1% (range −0.4% to +3.1%) and 1.1% (range −0.4% to +3.0%) with 94.4% and 95.4% passing a gamma with 4%/4 mm criteria [192]. Siochi et al. [181] describe independent software used in a paperless clinic which covers 3-D CRT and IMRT, electrons, stereotactic radiosurgery, total body irradiation, and clinical setups with and without virtual simulation. The planning systems handled by this software were ADAC Pinnacle and Varian FASTPLAN, while the record-and-verify systems were LANTIS and VARIS. In clinical use, this software has caught discrepancies between MLC leaf positions in the record-and-verify database and those in the treatment plan. It has also found errors in table positions for fields with the same isocenter. Treatment fields that did not have assigned dose, but that should have been part of the dose tracking, have also been flagged, requiring the physicists to redistribute the assigned doses. Total body irradiation plans with wrong table positions have also been caught, as have other errors that are related to electron plans, such as missing applicator names, bolus thicknesses not indicated, MUs which did not match, and collimator angles which were incorrect. A large fraction of the errors detected were from electron plans, cone-beam Y jaw values, and table positions. This was because these data involved direct human manipulation of the database values. Automated checking of plan parameters reduces error rates by allowing a more thorough check of the record-and-verify database and the treatment plan. It greatly reduces the tedious one-to-one data correspondence checks and formalizes the checks for logical consistency.

11.6.2.8 Treatment setup, immobilization, imaging, and dose delivery

Patient setup prior to radiation dose delivery involves the use of the same immobilization devices discussed in Section 11.6.2.2 and which are used for patient imaging and simulation. Patient setup uncertainties are largely due to pliable patients with mobile and changeable organs who must be set up multiple times during a course of radiation treatment. Modern image-guidance technologies have allowed for quantifying such setup uncertainties and implementing corrective actions. The magnitudes of corrections for different regions within the body that are made with IGRT using helical tomotherapy were discussed in Section 11.6.2.2 and shown Figure 11.11.

The magnitude of setup and organ motion uncertainties determines the size of margins around the CTV to generate a PTV. A detailed report produced in the United Kingdom (UK) describes and recommends the best evidence-based practices for determining geometric uncertainties explains how CTV-to-PTV margins should be generated. They recommend that "each radiotherapy department should determine the verification protocols and planning margins required for their own practice. This is because the frequency of imaging, the tolerances and action levels used, and the planning margins will vary according to local use of techniques, processes, anatomical site, equipment and immobilisation" [170]. The report gives detailed information on how these margins should be determined.

11.6.2.9 End-to-end tests

To evaluate the quality of the total treatment process, "end-to-end" tests can be performed, usually on anthropomorphic phantoms which can be loaded with point dosimeters such as TLDs or OSLDs, or 2-D planes using films or 3-D gels [177]. These tests involve imaging the phantom, developing a full treatment plan by outlining the target volumes and OARs, defining the beam directions, calculating the optimized treatment plan with details of MLC configurations, transferring the data to the treatment machine, performing the actual irradiations, and determining resultant doses at particular locations in the phantom. The RPC has reported on such "end-to-end" tests that have been used for credentialing institutions to participate in specific clinical trials involving IMRT treatments. Results are shown in Table 11.14 for 128 institutions that irradiated the head

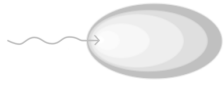


Table 11.14

Results of irradiations of the head-and-neck and pelvis phantoms by participating institutions. (Reproduced with permission from [86].)

PHANTOM	HEAD-AND-NECK	PELVIS
Irradiations	163	22
Pass	115 (71%)	14(64%)
Fail	48 (29%)	8 (36%)
Institutions represented	128	16

and neck phantom (some multiple times, for a total of 163 irradiations) and the pelvis phantom, which was irradiated 22 times by 16 institutions [86]. The pass rate was based on the ratio of measured dose (as determined from the TLDs) to the institution's stated dose, which was expected to agree within 7%. Also, the distance to agreement (DTA) in the high-dose gradient region near the OAR was expected to be no greater than 4 mm. Thus, nearly one third of all the head-and-neck phantom irradiations failed to meet these fairly liberal criteria on the first attempt. Twenty-eight of the failures were dose discrepancies as measured with TLD, seven were dose distribution discrepancies measured with radiochromic film, and 13 reflected disagreements in both TLD and film measurements. The discrepancies in the ratio of measured-to-calculated dose in the region of the primary target volume ranged from 0.78 to 1.13 (-22% to $+13\%$), with a mean of 0.99 and a standard deviation of 0.08. A similar result was seen at the location of the secondary target volume. The DTA measurements showed a range from -15 mm to $+8$ mm (where a positive sign indicates that the RPC measurement of a given dose level fell at a greater distance from the phantom center, or more posterior, than the institution's calculated value). The mean in DTA value was -0.7 mm with a standard deviation of 3.5 mm.

A review of the results revealed a number of errors made by the institutions. These included incorrect data input into the treatment planning system, inaccurate modeling by the treatment planning algorithm of small field sizes formed by MLC leaves with rounded leaf ends, indexing errors in the table movement system for serial tomographic IMRT, inaccurate phantom positioning, and some treatment delivery errors, such as the use of incorrect monitor unit settings. Clearly, when about one third of the results for IMRT irradiations are outside of the 7%/4mm criteria, this indicates that it is actually very difficult to achieve results that are preferred to be within 3%/3mm. Treatment complexity has introduced more procedures, more personnel, and more "hand-offs"; thus, error propagation is an issue that merits research and control.

In a review of the RPC's activities over 38 years, Ibbott et al. [87] evaluated the deviation rates of several trials that required credentialing for some or all participants. The results, shown in Table 11.15, indicated that trials requiring credentialing experienced low deviation rates. Three protocols for which credentialing was required of all participants had rates of deviation between 0% and 4%, whereas two protocols that had limited credentialing requirements had rates of deviation on the order of 7% to 17%. In another study, some institutions were credentialed for one technique but not for another. Credentialed institutions received no deviations on the protocol, whereas the remaining institutions had a deviation rate of 16%. Clearly, the frequency of deviations can be reduced for institutions that go through the credentialing process, demonstrating that there is improved accuracy for institutions taking extra care to abide by treatment protocols and that an

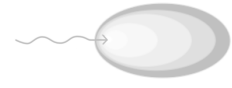


Table 11.15

The effect of credentialing on the deviation rate of several trials. (Reproduced with permission from [87].)

STUDY	MAJOR DEVIATIONS	MINOR DEVIATIONS	PATIENTS (*n*)
GOG 165, HDR cervix			
Credientialed institutions	0	15	70
Noncredentialed institutions	57	87	275
RTOG 95-17, HDR and LDR breast (all)	0	4	100
RTOG 00-19, LDR prostate	0	6	117

Abbreviations: GOG = Gynecologic Oncology Group; HDR = high dose rate; RTOG = Radiation Therapy Oncology Group; LDR = low dose rate

audit by an external agency is an excellent tool for improving treatment compliance.

Das et al. [40] examined the variation in IMRT dose prescription, treatment planning, dose recording, and dose delivery among 803 brain, head-and-neck, and prostate cancer patients who were treated with different treatment planning systems at five different medical institutions to assess variability in patient care. A total of 46% of the patients received a maximum dose that was more than 10% higher than the prescribed dose, and 63% of the patients received a dose that was more than 10% lower than the prescribed dose. At all five institutions, the prostate cancer cases had the smallest dosimetric variation, while the head-and-neck cancer cases had the largest variation. The median dose to the target varied from the prescribed dose by ±2% in 68% of the patients, by ±5% in 88% of the patients, and by ±10% in 96% of the patients. The recorded isocenter dose varied from prescription for all disease sites and treatment planning systems (see Figure 11.14). Thus, there was substantial variation in the prescribed and delivered doses among the institutions, raising concerns about the validity of comparing clinical outcomes for IMRT and suggesting the need for national or international guidelines for dose prescription, planning, and reporting for a meaningful clinical trial in IMRT.

In 2003, Palta et al. [157] proposed confidence limits and action levels for IMRT treatments where confidence limit is defined as the absolute value of the mean deviation plus 1.96 times the standard deviation. The factor of 1.96 implies that 5% (i.e., 95% confidence) of the individual points are outside of tolerance for that particular situation. The action level serves as a pass-fail criterion, and any points beyond that criterion require further investigation. The values shown in Table 11.16 were based on a questionnaire that was mailed to 30 institutions actively involved in IMRT treatments.

11.6.3 Brachytherapy-related uncertainties

While in some ways brachytherapy has been a mature treatment modality for many years, it appears that some

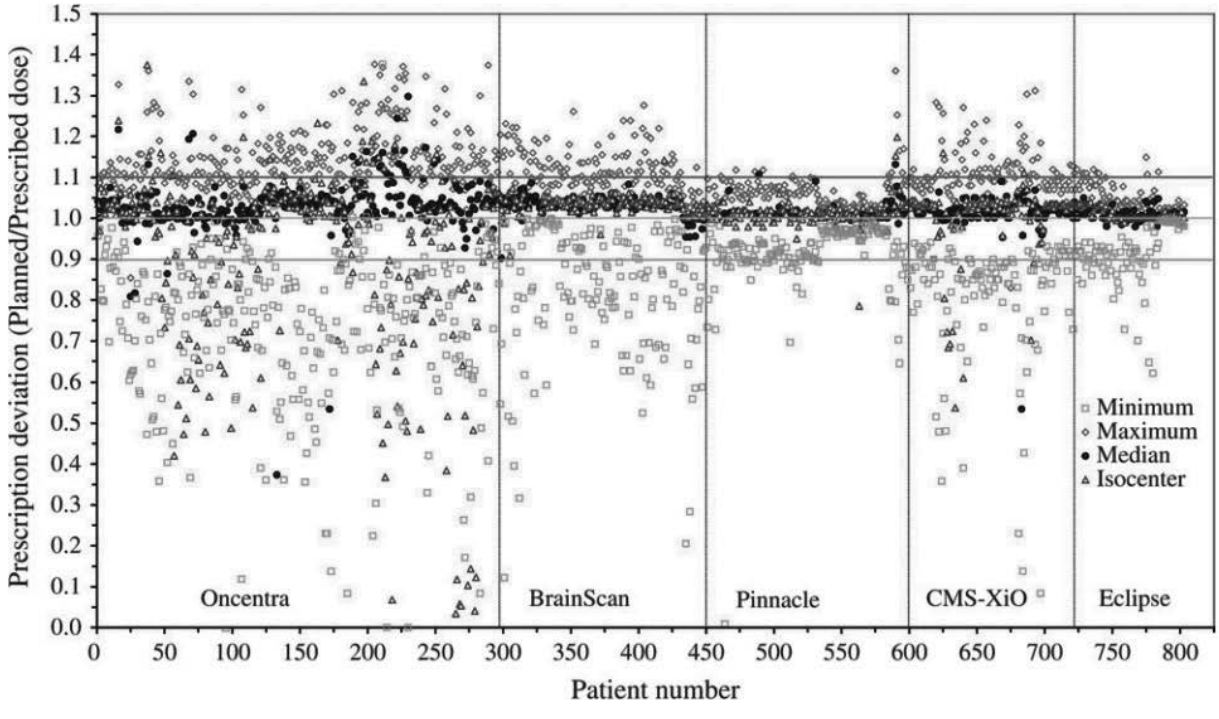


Figure 11.14
Dosimetric variations between the prescribed and delivered doses among 803 patients from five medical institutions with different treatment planning systems. Vertical lines separate the data according to treatment planning system (from left to right: Oncentra, BrainScan, Pinnacle, CMS-XiO, and Eclipse). The horizontal line at 1.0 represents no dose deviation; the horizontal lines at 1.1 and 0.9 represent dose deviations of +10% and −10%, respectively, between the planned dose and the prescribed dose. (Reproduced with permission from [40].) SEE COLOR PLATE 81.

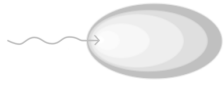


Table 11.16
Proposed confidence limits for IMRT treatments from Palta et al. [157].

REGION	CONFIDENCE LIMIT*	ACTION LEVEL
High dose, low dose gradient	±3%	±5%
High dose, high dose gradient	10% or 2 mm DTA	15% or 3 mm DTA
Low dose, low dose gradient	4%	7%
Dose fall off ($d_{90\text{-}50\%}$)	2 mm DTA	3 mm DTA

*The confidence limit is defined as the sum of the average deviation and 1.96 SD. The average deviation used in the calculation of confidence limit for all regions is expressed as a percentage of the prescribed dose according to the formula: $100\% \times (D_{calc} - D_{meas}/D_{prescribed})$.

aspects of brachytherapy have not advanced at the same rate as external beam radiation therapy, although treatment planning has advanced from simple look-up tables to complex, image-based, dose-calculation algorithms. Rivard et al. [165] have reviewed the evolution of brachytherapy treatment planning and note that the current approach is based on the AAPM TG-43 formalism [149,164,166]. In the meantime, dose calculations have improved and are based on Monte Carlo, collapsed cone, and Boltzmann transport equation methods. The newer planning systems also allow for tissue heterogeneity corrections, scatter conditions, radiobiology, and image guidance. Rivard et al. [165] point out that there are a number of limitations to the existing TG-43 formalism. These include:

1. The difference in absorbed dose between water and tissue. While this ratio is nearly 1 between 0.01 to 10 MeV, it does dip to 0.96 near 0.05 MeV due to higher photoelectric effect cross-sections of tissue compared to water. Thus, absorbed dose in water is about –4% to +2% compared to tissue for low- and high-energy photons, respectively.
2. Differences between radiation attenuation in water and tissue. This is quite significant (>5%) for energies below 0.03 MeV.
3. Source shielding or applicator radiation interactions. These effects could be quite large and are dependent on the type of applicators or shielding. Dose differences of 5% are possible for high-energy sources within 5 cm of the skin.
4. Differences between radiation data set acquisition and patient treatment. Limited phantom sizes could result in effects >5% for iridium-192 sources.
5. Dose, kerma, and electrons. Dose calculation subtleties may assume equivalence between absorbed dose and kerma. The breakdown of the charge-particle equilibrium assumption can also occur at material boundaries, especially at high-Z interfaces, and this can result in >5% differences within a few millimeters of high-energy, photon-emitting sources. Brachytherapy treatment planning systems also ignore the contribution of betas emitted from radionuclide disintegration.

Rivard et al. [165] provide a table in their report indicating the sensitivity of commonly treated anatomical sites to limitations in the currently available brachytherapy dose calculation algorithms. While the table shows which physical limitation is relevant for each clinical site, it does not add any quantitative information as to what the level of uncertainties might be for these sites.

Quantitative uncertainty estimates for brachytherapy have been provided by the Task Group 138 report of the AAPM jointly with Groupe Européen de Curiethérapie–European Society for Therapeutic Radiology and Oncology (GEC–ESTRO). Their uncertainty formalism was taken from the reference standards of the International Organization for Standardization (ISO) *Guide to the Expression of Uncertainty in Measurement* (GUM) [108] and the National Institute of Standards and Technology (NIST) Technical Note 1297 [191]. Tables 11.17 through 11.21 are taken from the Task Group 138 report and demonstrate the nature of the uncertainties associated with brachytherapy.

It is noted in the Task Group 138 report that there may be sources in which these dosimetric uncertainties

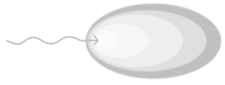


Table 11.17

Propagation of best practice uncertainties (k = 1 unless stated otherwise) associated with the transfer of air-kerma strength from NIST through the Accredited Dosimetry Calibration Laboratory (ADCL) to the clinic for low dose rate (LDR) low-energy brachytherapy sources. WAFAC = wide-angle free-air chamber. (Reproduced with permission from [45].)

ROW	MEASUREMENT DESCRIPTION	QUANTITY (UNITS)	RELATIVE PROPAGATED UNCERTAINTY (%)
1	NIST WAFAC calibration	$S_{K,\mathrm{NIST}}$ (U)	0.8
2	ADCL well ion chamber calibration	$S_{K,\mathrm{NIST}}/I_{\mathrm{ADCL}}$ (U/A)	0.9
3	ADCL calibration of source from manufacturer	$S_{K,\mathrm{ADCL}}$ (U)	1.1
4	ADCL calibration of clinic well ion chamber	$S_{K,\mathrm{ADCL}}/I_{\mathrm{CLINIC}}$ (U)	1.2
5	Clinic measures source air-kerma strength	$S_{K,\mathrm{CLINIC}}$ (U)	1.3
	Expanded uncertainty (k = 2)	$S_{K,\mathrm{CLINIC}}$ (U)	2.6

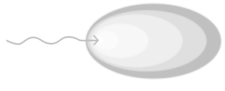


Table 11.18

Propagation of best practice uncertainties (k = 1 unless stated otherwise) associated with the transfer of air-kerma strength from NIST to the manufacturer for LDR low-energy brachytherapy sources. WAFAC = wide-angle free-air chamber. (Reproduced with permission from [45].)

ROW	MEASUREMENT DESCRIPTION	QUANTITY (UNITS)	RELATIVE PROPAGATED UNCERTAINTY (%)
1	NIST WAFAC calibration	$S_{K,\mathrm{NIST}}$ (U)	0.8
2	ADCL well ion chamber calibration	$S_{K,\mathrm{NIST}}/I_{M}$ (U/A)	0.9
3	ADCL calibration of source from manufacturer	$S_{K,\mathrm{M}}$ (U)	1.1
4	Manufacturer instrument calibration for assay	$S_{K,M}/I_{M}$ (U/A)	1.2
4	ADCL calibration of clinic well ion chamber	$S_{K,M}$ (U)	1.3
5	Clinic measures source air-kerma strength	$S_{K,M\ bin}$ (U)	1.4 or 2.4
	Expanded uncertainty (k = 2)	$S_{K,M\ bin}$ (U)	2.8 or 4.8

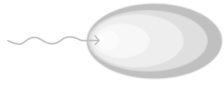


Table 11.19

Propagation of best practice uncertainties (k = 1 unless stated otherwise) associated with the transfer of air-kerma strength from NIST through the ADCL to the clinic for LDR high-energy brachytherapy sources. Well-chamber measurement uncertainty is estimated to be 0.5%. WAFAC = wide-angle free-air chamber. (Reproduced with permission from [45].)

ROW	MEASUREMENT DESCRIPTION	QUANTITY (UNITS)	RELATIVE PROPAGATED UNCERTAINTY (%)
1	NIST calibration	$S_{K,\mathrm{NIST}}$ (U)	1.0
2	ADCL well ion chamber calibration	$S_{K,\mathrm{NIST}}/I_{\mathrm{ADCL}}$ (U/A)	1.1
3	ADCL calibration of source from manufacturer	$S_{K,\mathrm{ADCL}}$ (U)	1.2
4	ADCL calibration of clinic well ion chamber	$S_{K,\mathrm{ADCL}}/I_{\mathrm{CLINIC}}$ (U)	1.3
5	Clinic measures source air-kerma strength	$S_{K,\mathrm{CLINIC}}$ (U)	1.4
	Expanded uncertainty (k = 2)	$S_{K,\mathrm{CLINIC}}$ (U)	2.8

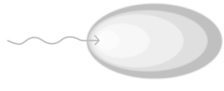


Table 11.20

Propagation of best practice uncertainties (k = 1 unless stated otherwise) associated with the transfer of air-kerma strength from a traceable NIST coefficient from the ADCL to the clinic for HDR high-energy brachytherapy sources. (Reproduced with permission from [45].)

ROW	MEASUREMENT DESCRIPTION	QUANTITY (UNITS)	RELATIVE PROPAGATED UNCERTAINTY (%)
1	ADCL calibration	$S_{K,\mathrm{NIST}}$ (U)	1.1
2	ADCL well ion chamber calibration	$S_{K,\mathrm{NIST}}/I_{\mathrm{ADCL}}$ (U/A)	1.2
3	ADCL calibration of source from manufacturer	$S_{K,\mathrm{ADCL}}$ (U)	1.3
4	ADCL calibration of clinic well ion chamber	$S_{K,\mathrm{ADCL}}/I_{\mathrm{CLINIC}}$ (U/A)	1.4
5	Clinic measures source air-kerma strength	$S_{K,\mathrm{CLINIC}}$ (U)	1.5
	Expanded uncertainty (k = 2)	$S_{K,\mathrm{CLINIC}}$ (U)	2.9

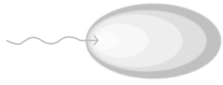


Table 11.21

Propagation of best practice uncertainties (k = 1 unless stated otherwise) in dose at 1 cm on the transverse plane associated with source-strength measurements at the clinic, brachytherapy dose measurements or simulation estimates, and treatment planning system dataset interpolation for low-energy (low-E) and high-energy (high-E) brachytherapy sources. (Reproduced with permission from [45].)

		RELATIVE PROPAGATED UNCERTAINTY (%)	
ROW	UNCERTAINTY COMPONENT	LOW-E	HIGH-E
1	S_K measurements from row 5 of Tables 11.17 and 11.20	1.3	1.5
2	Measured dose	3.6	3.0
3	Monte Carlo dose estimate	1.7	1.6
4	TPS interpolation uncertainties	3.8	2.6
5	Total dose calculation uncertainty	4.4	3.4
	Expanded uncertainty (k = 2)	8.7	6.8

are larger, such as when using investigational sources that lack a robust source-strength calibration traceable to a primary standards laboratory, or for sources whose calibration carries uncertainties larger than those in row 1 of Table 11.21 due to design variations and subsequent energy differences. If these uncertainties become greater than 20%, then implants should be performed with caution, preferably under Institutional Review Board (IRB) oversight with disclosure to patients about the uncertain aspects of the procedure.

Action levels described in ESTRO HDR brachytherapy QA guidelines are summarized in Table 11.22 and give an indication of the minimum accuracy levels that should be achievable. Improved guidance is needed, even for established procedures such as ultrasound-guided prostate implants.

For brachytherapy, there are no published data on end-to-end assessments. While it is possible to get the source outputs (air kerma rates) to within 5% for conventional sources, this is very difficult to do for the less common or new sources and source capsules. Furthermore, once treatment planning uncertainties are accounted for, it is not easy to determine the dose to tissues in the patient within 8% to 10%.

11.7 Uncertainty Propagation

Figure 11.7 and tables 11.3 through 11.5 demonstrate the many considerations that have to be addressed at various stages of the radiation therapy process for both external beam and brachytherapy. These considerations range from decision making regarding diagnoses and staging, imaging, target volume delineation, beam calibration, treatment planning, and dose delivery with or without image guidance. Some uncertainties relate to geometry (in mm) and others relate to dose (in Gy). Clearly the problem of propagating uncertainties throughout the multiple stages of the treatment process is very complex.

Only a few research groups have attempted to model uncertainty propagation as a means of assessing the impact of uncertainties at various stages of the treatment process and their resulting impact on clinical outcome. Van Dyk et al. [202] have described a computer model of the entire radiation therapy process chain, starting with imaging, that can forecast the delivered dose distribution and estimate radiobiological effects (TCP and NTCP). A first use of the prototype of this model has been described in the Proceedings of the International Conference on the Use of Computers in Radiation Therapy [202]. A sample result showed the impact of daily geometric image guidance for a prostate case. TCP values deteriorated from 94.4% (planned) to 90.3% (delivered) when image guidance was *not* used, and values were restored to 93.4% with MVCT image guidance.

In subsequent analysis, we simulated various combinations of scenarios for repositioning and replanning (Table 11.23) for different margin settings around the

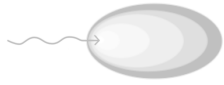


Table 11.22

Test frequencies and action levels for various brachytherapy procedures. HDR = high dose rate, PDR = pulsed dose rate, LDR = low dose rate, MDR = medium dose rate. (Adapted from [207].)

DESCRIPTION	MINIMUM REQUIREMENTS	
	TEST FREQUENCY	ACTION LEVEL
HDR/PDR		
Source calibration	Source exchange	5%
Source position	Daily/quarterly	2 mm
Length of treatment tubes	Annually	1 mm
Irradiation timer	Annually	1%
Date, time, source strength	Daily	-
Transit time effect	Annually	-
LDR/MDR		
Source calibration, mean of batch	Source exchange	3%
Source calibration, individual source, decay	Source exchange	5%
Linear uniformity	Source exchange	5%
Source position, source length	Half yearly	2 mm
Irradiation timer	Annually	2%
Date, time, source strength in treatment unit	Daily	-
Manual Afterloading		
Source calibration, decay calculation	Source exchange	5%
Linear uniformity, source length	Source exchange	5%
Source identification	Daily/annually	—

gross target volume (GTV) of the prostate: (a) traditional 10mm/7mm in the anterior and posterior directions, (b) tight 5 mm isotropic margins, and (c) adaptive margins based on initial setup displacements observed during the first seven treatment fractions. This seven-day sampling period was based on our previous analysis of setup shifts using on-line CT that demonstrate that shifts "stabilize" after this initial period of adaptation [14]. Table 11.23 lists a wide range of options, in order of increasing resources and investments required (from scenarios 1 to 5). For example, practical daily replanning (scenario 5) would require recontouring, re-optimization, and recomputation of dose distributions, ideally at the treatment console. This process is not easily implemented, but it will become possible via computational [44] and computer networking advances. The simulations we describe below can help justify the costs of additional resources when significant clinical advantages are to be expected.

The impact of various target margins, image guidance schedules, and replanning strategies on DVH metrics, averaged over 13 patients, is summarized in Figure 11.15 and Figure 11.16. Figure 11.15 shows tumor-related metrics, while Figure 11.16 shows results for the major critical structure, the rectum. It is best to review these data sets in two distinct groups based on target margin settings. For each margin set, we simulated different repositioning and replanning approaches to update the cumulative dose distribution. Within each margin group, the strategies are placed in order of greater complexity and resource consumption. Reviewing the first 10/7 mm margin group (Figure 11.15a), we

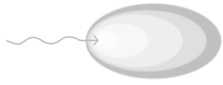


Table 11.23

Repositioning and replanning protocols for uncertainty propagation modelling.

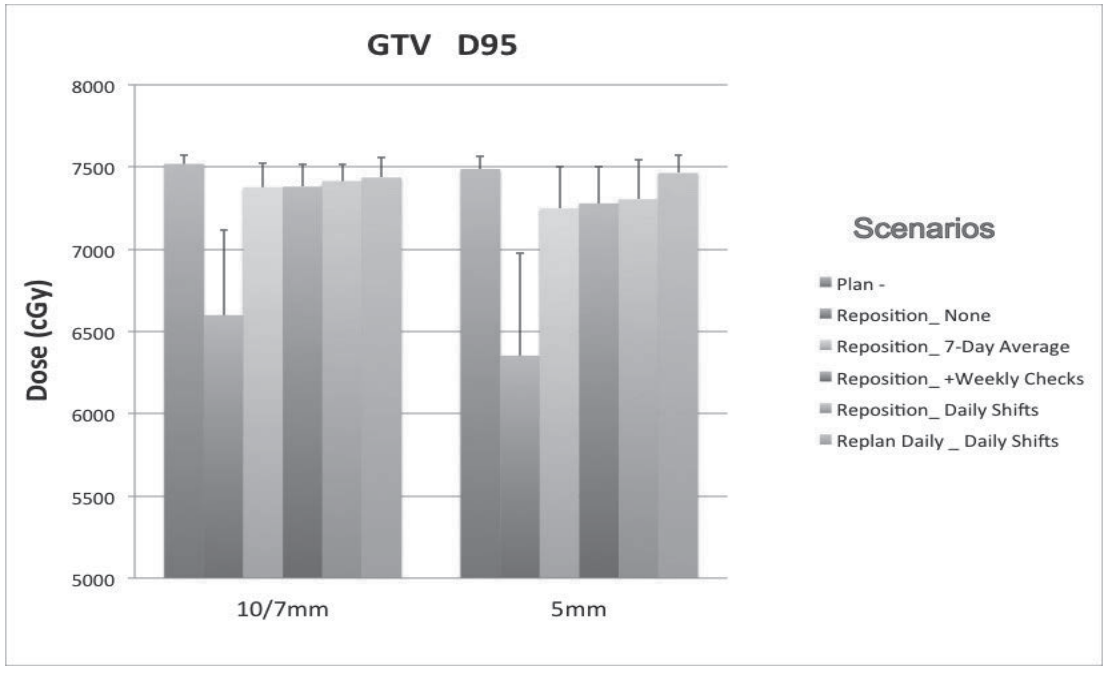
SCENARIO	ON-LINE REPOSITIONING	OFF-LINE REPLANNING		PTV MARGIN
1	No	a	No	10 mm (7 mm post)
		b	No	5 mm
2	—Daily imaging & repositioning for first 7 fractions —Daily repositioning for remaining fractions using average (ΔX, ΔY, ΔZ) of shifts over first 7 fractions	a	No	10 mm (7 mm post)
		b	No	5 mm
3	—Daily imaging & repositioning for first 7 fractions —Scheduled imaging & repositioning at every 5th fraction —For "in-between" 4 fractions, repositioning using the "running" average (ΔX, ΔY, ΔZ) of shifts	a	No	10 mm (7 mm post)
		b	No	5 mm
4	Daily imaging & repositioning	a	No	10 mm (7 mm post)
		b	No	5 mm
5	Daily imaging & repositioning	a	Daily Replan	10 mm (7 mm post)
		b	Daily Replan	5 mm

note that there is little gain in GTV targeting (D95) using more frequent repositioning beyond the first seven days of treatment. In fact, daily shifting of the patient causes an increase in dose to the nearby rectum (V70 in Figure 11.16a) because of consistent retargeting. For the 5 mm margin group, infrequent repositioning reduces target coverage (D95) but compensation is possible when daily dose replanning is also implemented. Again, the high-precision retargeting enhances the rectal dose, but the impact is generally within an acceptable mean risk of 5% (Figure 11.16b).

In summary, we have developed a computer simulation model that allows exploration of "what if" scenarios for assessing the potential benefits of image-guidance strategies, evaluated in terms of the multi-fraction dose distribution, DVH metrics, and TCP/NTCP predictions. For IMRT of the prostate, we have learned that: (1) the image-guidance schedule can be relaxed when generous GTV margins (10/7mm) are used, and (2) tighter margins (5 mm) reduce the dose to the rectum as expected, but daily replanning during therapy may be required to maintain target coverage as planned and, paradoxically, may increase the rectal dose as compared to the uncorrected plans.

Similarly, Jin et al. [105,106] have published a dose uncertainty model for IMRT delivery. For eight retrospectively selected patients, dose uncertainty maps were constructed using the dose uncertainty model at the 95% CL [106]. In addition to uncertainties inherent to the radiation TPS, four scenarios of spatial errors were considered: (1) machine only, (2) machine only + intrafraction, (3) machine only + interfraction, and (4) machine only + both intrafraction and interfraction errors. To evaluate the potential risks of the IMRT plans, three dose uncertainty-based plan evaluation tools were introduced: (1) confidence-weighted DVH, (2) confidence-weighted dose distribution, and (3) dose uncertainty volume histogram. They found that dose uncertainty caused by interfraction setup error was more significant than that of intrafraction motion error. The maximum dose uncertainty (95% confidence) of the CTV was smaller than 5% of the prescribed dose in all but two cases (13.9% and 10.2%). The dose uncertainty for 95% of the CTV volume ranged from 1.3% to

A.



B.

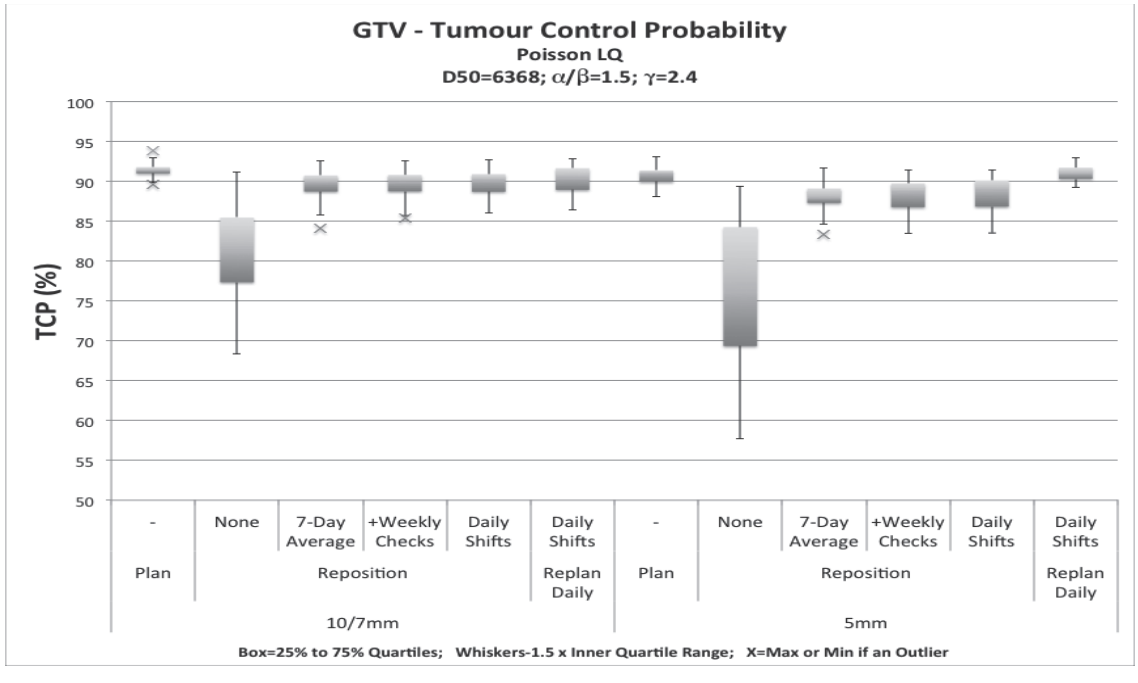
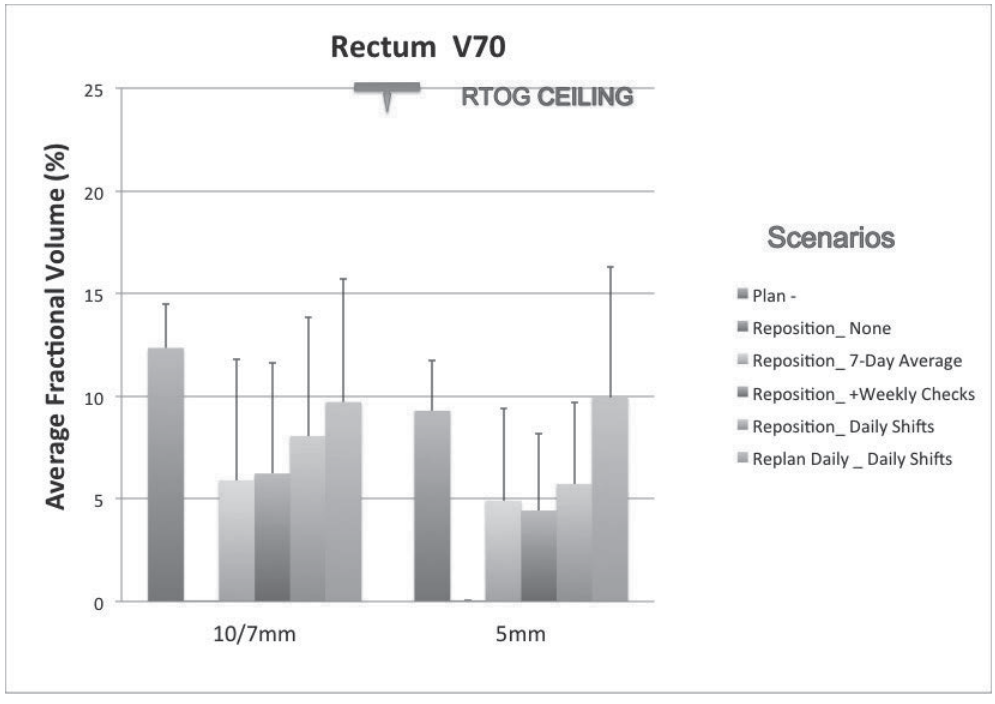


Figure 11.15
Prostate target coverage for various schedules of patient repositioning and dose re-planning using MVCT for the image guidance and adaptive therapy. The study was performed for 13 prostate patients and a 5-field IMRT treatment plan. Part A uses a dose metric (D95) and part B uses a radiobiological TCP metric. SEE COLOR PLATE 82.

A.



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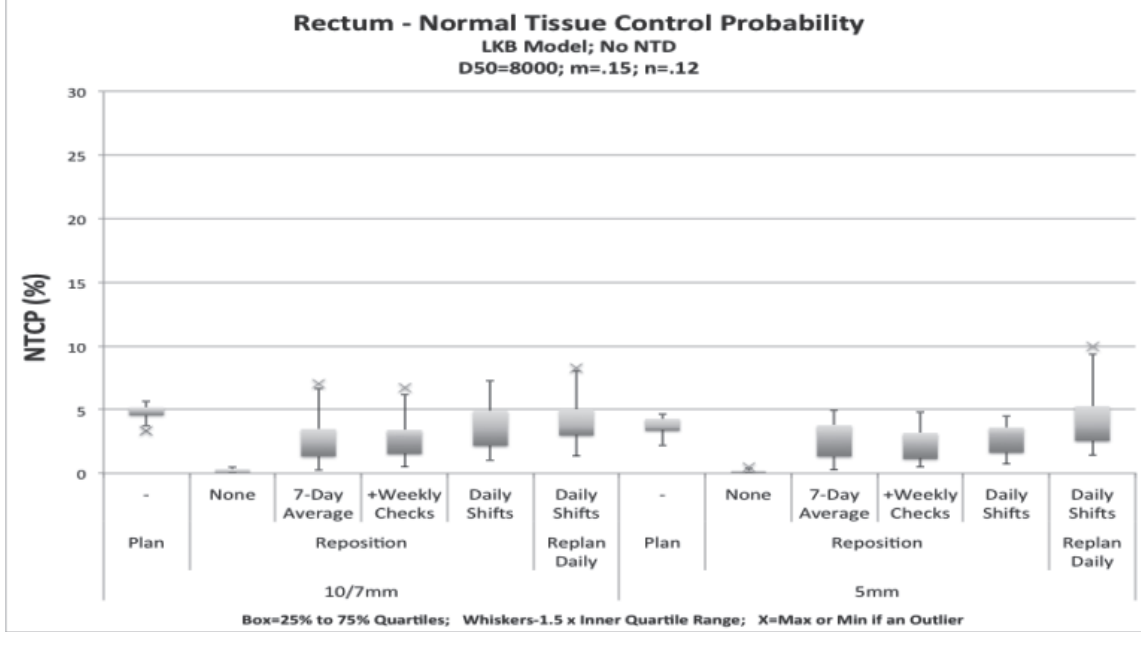

Figure 11.16
Rectal toxicity for IMRT of the prostate using MVCT image guidance. Treatment plan information is given in the caption to Figure 11.15. Part A uses a dose metric (V70) and part B a radiobiological NTCP metric. SEE COLOR PLATE 83.

2.9% of the prescribed dose. Thus, they concluded that prostate IMRT plans satisfying the same plan objectives could generate a significantly different dose uncertainty because of a complex interplay of many uncertainty sources.

Uncertainty propagation models demonstrate the feasibility of testing different "what if" scenarios to assess the impact of any variety and combination of uncertainties and to aid in the development of robust treatment plans. Such plans are designed to be minimally affected by treatment-related uncertainties. Robustness, for example, would be manifested as a reduction in the size of error bars in figures 11.15 and 11.16. Specific robust optimization algorithms have been reviewed by McQuaid et al. [140].

The type of modelling we describe here is still in its infancy. More research is required with prospective capture of clinical response data, incorporated with a database holding all the 3-D/4-D anatomical and dose data of each patient. Computer simulations of different procedures would then be optimized and applied prospectively to clinical decision making and to cost-effective resource acquisition and allocation.

11.8 Summary

This chapter has addressed some of the considerations associated with accuracy and uncertainties in radiation therapy. As is clear from the discussion in this chapter, it is not easy to make simple statements about dose delivery accuracy to a patient. Clearly, it is very dependent on an array of considerations, ranging from the technology that is used, the technique that is applied (e.g., small field versus large field versus 3-D CRT or IMRT with IGRT), the clinical site within the patient, the imaging that is used for treatment planning, and the imaging that is used for treatment guidance. The adoption of uncertainty propagation models with "end-to-end" experimental verification may be used to simulate the combinations and permutations of uncertainties and identify the key weak links in the overall radiotherapy process.

In the first recommendation in its report, the IAEA suggests the following as an advisory comment regarding accuracy and uncertainties [89]: "*All forms of radiation therapy should be applied as accurately as reasonably achievable (AAARA), technical and biological factors being taken into account.*"

Single-number statements, such as an accuracy requirement of ±5%, may be very difficult to achieve under some circumstances in modern radiotherapy. This is predicated on the fact that different techniques have different accuracy requirements and different accuracy capabilities, e.g., a radical course of small-field, hypofractionated SBRT has different accuracy requirements and different accuracy capabilities compared to total skin irradiation for mycosis fungoides. The AAARA principle has been discussed in Chapter 1 of the first volume of *The Modern Technology of Radiation Oncology* [201], as well as in a paper on magna-field irradiations [200], although in that paper it was referred to "as precise as reasonably achievable."

Ideally, every institution would develop its own uncertainty estimations for its patients using its specific techniques. This is certainly true for setup and treatment-related uncertainties since the CTV to PTV margin needs to be defined for the institution's specific immobilization techniques, available imaging, and treatment technologies. This is one area that requires further research and specific recommendations so that the concept can be implemented practically.

Appendix: Formal Measurement-related Terminology

Measurand is the "quantity intended to be measured" [30].

Accuracy (or measurement accuracy) is "closeness of agreement between a measured quantity value and a true value of a measurand" [30]. Note that according to the BIPM, the concept "measurement accuracy" is not a quantity and is not given a numerical value. A measurement is said to be more accurate when it offers a smaller measurement error.

Precision (or *measurement precision*) is "closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions" [30].

Trueness (or *measurement trueness*) is the "closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value"[30]. Note that measurement trueness is not a quantity and thus cannot be expressed numerically, but rather it allows for a comparative statement.

Error (or *measurement error*) is the "measured quantity minus a reference quantity value" [30]. Note that error in this context is not to be confused with production error or mistake (see Section 11.2.2). In the radiation oncology context, the word "error" tends to be used for both measurement error and mistakes.

Systematic error (or *systematic measurement error*) is the "component of measurement error that in replicate measurements remains constant or varies in a predictable manner" [30]. Systematic measurement

error and its causes can be known or unknown. A correction can be applied to compensate for a known systematic measurement error. Systematic measurement error equals measurement error minus random measurement error.

Bias (or *measurement bias*) is the "estimate of a systematic measurement error" [30].

Random error (or *random measurement error*) is the "component of measurement error that in replicate measurements varies in an unpredictable manner" [30]. A reference quantity value for a random measurement error is the average that would ensue from an infinite number of replicate measurements of the same measurand. Random measurement errors of a set of replicate measurements form a distribution that can be summarized by its expectation, which is generally assumed to be zero, and its variance. Random measurement error equals measurement error minus systematic measurement error.

Uncertainty (or *measurement uncertainty*) is a "non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used" [30]. For such repeated measurements, the results can be represented by a statistical distribution, which can be summarized by specific statistical quantities such as *mean*, *mode*, *standard deviation*, and *variance*. Since each measurement or procedure in radiation treatment, including dose calculations, cannot be performed perfectly, each has a corresponding uncertainty.

Standard uncertainty or *standard measurement uncertainty* is the "measurement uncertainty expressed as a standard deviation" [30]. The symbol often attributed to the standard uncertainty is u or u_c.

Combined standard uncertainty (or *combined standard measurement uncertainty*) is the "standard measurement uncertainty that is obtained using individual standard measurement uncertainties associated with the input quantities in a measurement model" [30]. ISO defines this as the "standard uncertainty of the result of a measurement when that result is obtained from the values of a number of other quantities, equal to the positive square root of a sum of terms being the variances or covariances of these other quantities weighted according to how the measurement result varies with changes in these quantities" [29].

Type A evaluation (or *Type A evaluation of measurement uncertainty*) incorporates a method of "evaluation of measurement uncertainty by a statistical analysis of measured quantity values obtained under defined measurement conditions" [30].

Type B evaluation (or *Type B evaluation of measurement uncertainty*) incorporates a "method of evaluation of a component of measurement uncertainty determined by means other than Type A evaluation of measurement uncertainty" [30,93]. This often involves scientific judgement or other information, e.g., uncertainty estimates of physical constants used in determining absolute doses. Type B evaluations require critical thinking, intellectual honesty, and professional skill. The value of uncertainty may be taken from a resultant value of a previous measurement, a reference value from the literature, or using the value of uncertainty associated with a standard for which a calibration certificate is available.

Uncertainty budget is a "statement of a measurement uncertainty, of the components of that measurement uncertainty, and of their calculation and combination" [30].

Maximum permissible error (or *maximum permissible measurement error*) is the "extreme value of measurement error, with respect to a known reference quantity value, permitted by specifications or regulations for a given measurement, measuring instrument, or measuring system" [30]. The BIPM points out that the term "tolerance" should not be used to designate "maximum permissible error."

Tolerance or *tolerance interval*. As indicated above under "maximum permissible error," the BIPM does not recommend the use of "tolerance" [30]. The ISO has a series of standards under the topic of "Tolerances, tolerance definitions and symbols (including GPS)," where GPS refers to "general product specifications." These standards relate to devices such as bearings of various forms. The U.S. National Institute of Standards and Technology (NIST) [150] defines *confidence interval* as follows:

> A confidence interval covers a population parameter with a stated confidence, that is, a certain proportion of the time. There is also a way to cover a fixed proportion of the population with a stated confidence. Such an interval is called a *tolerance interval*. The endpoints of a tolerance interval are called *tolerance limits*. An application of tolerance intervals to manufacturing involves comparing specification limits prescribed by the client with tolerance limits that cover a specified proportion of the population.

Thus, the NIST definition includes a statement of confidence or probability with its definition of "tolerance interval." In the radiation oncology context, the practical definition of tolerance is generally used as the permissible limit beyond which corrective action is required.

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