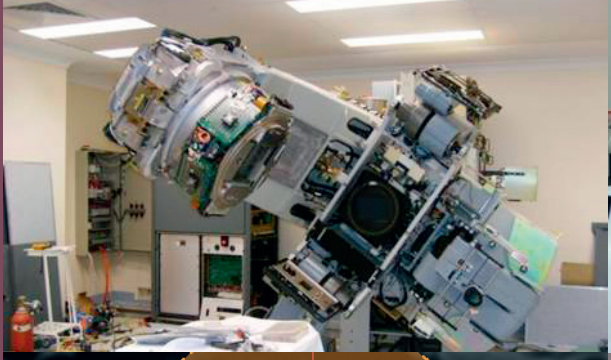

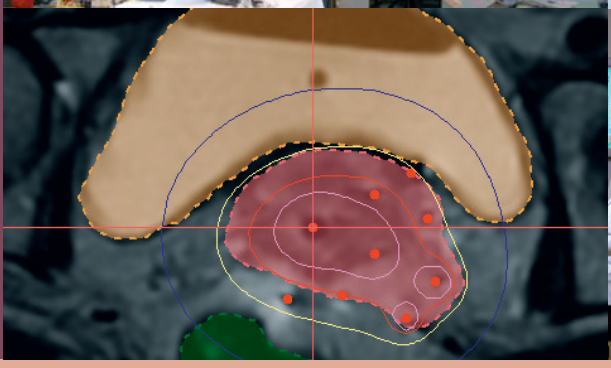


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No. 31

Accuracy Requirements and Uncertainties in Radiotherapy

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ACCURACY REQUIREMENTS AND UNCERTAINTIES IN RADIOTHERAPY

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IAEA HUMAN HEALTH SERIES No. 31

ACCURACY REQUIREMENTS AND UNCERTAINTIES IN RADIOTHERAPY

ENDORSED BY:
AMERICAN ASSOCIATION OF PHYSICISTS IN MEDICINE,
AMERICAN SOCIETY FOR RADIATION ONCOLOGY,
EUROPEAN FEDERATION OF MEDICAL PHYSICS,
EUROPEAN SOCIETY FOR RADIOTHERAPY AND ONCOLOGY

INTERNATIONAL ATOMIC ENERGY AGENCY
VIENNA, 2016

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Marketing and Sales Unit, Publishing Section
International Atomic Energy Agency
Vienna International Centre
PO Box 100
1400 Vienna, Austria
fax: +43 1 2600 29302
tel.: +43 1 2600 22417
email: sales.publications@iaea.org
http://www.iaea.org/books

Printed by the IAEA in Austria
November 2016
STI/PUB/1679

IAEA Library Cataloguing in Publication Data

Names: International Atomic Energy Agency.
Title: Accuracy requirements and uncertainties in radiation therapy / International Atomic Energy Agency.
Description: Vienna : International Atomic Energy Agency, 2016. | Series: IAEA human health series, ISSN 2075–3772 ; no. 31 | Includes bibliographical references.
Identifiers: IAEAL 16-01070 | ISBN 978–92–0–100815–2 (paperback : alk. paper)
Subjects: LCSH: Radiotherapy. | Cancer — Radiotherapy. | Radiation dosimetry.
Classification: UDC 615.849 | STI/PUB/1679

FOREWORD

Radiotherapy is a key treatment modality for cancer patients. In recent years, there have been major developments in external beam radiotherapy, which has developed from simple two dimensional techniques to three dimensional image based conformal radiotherapy, intensity modulated radiotherapy, image guided radiotherapy and four dimensional techniques. Similarly, brachytherapy has also seen an increase in the use of three dimensional image guided adaptive approaches. The underlying aim of these advances was improved patient outcome with normal tissue complications at acceptably low levels and reduced morbidity.

While multiple reports have defined accuracy needs in radiation oncology, most of these reports were developed in an earlier era in which different radiation technologies were in use. In the meantime, the situation regarding uncertainties in radiation dosimetry reference standards has improved, technology has evolved and more detailed patient outcome data are available. This publication addresses accuracy and uncertainty issues that will be relevant to the vast majority of radiotherapy departments, including both external beam radiotherapy and brachytherapy. Accuracy requirements pertaining to special techniques (e.g. on heavy particle therapy or robotic therapy) are not specifically addressed, although some of the broad comments and recommendations are also relevant to these techniques.

This publication begins with the assumption that a specified prescription is correct and addresses uncertainty issues associated with the fulfilment of that prescription. In terms of radiation incidents or near misses, it is recognized that a safety conscious department is also likely to be an accuracy conscious department. Quality assurance and accuracy are closely related. This publication is not intended as a quality assurance guide; rather, the focus is on generating an awareness of accuracy and uncertainty issues. Accuracy in relation to clinical outcome is not addressed in this report.

A description is given of the entire radiotherapy process, and accuracy issues are addressed from radiobiological, clinical, dosimetric and technical perspectives. Consideration is given to the degree of accuracy that is practically achievable. The management of uncertainties is discussed and specific recommendations are made. Advances and changes in health care delivery mean that the field of radiation oncology and its processes of care are continuously evolving, and statements in this report should be secondary to clinical judgement.

The intended audience of this report includes all those professionals working in radiotherapy who may have an impact on treatment accuracy and who are involved in the management of treatment uncertainties, including radiation oncologists, medical physicists and radiotherapy technologists.

This publication is endorsed by the American Association of Physicists in Medicine (AAPM), the American Society for Radiation Oncology (ASTRO), the European Federation of Medical Physics (EFOMP) and the European Society for Radiotherapy and Oncology (ESTRO). The important contribution of B. Mijnheer and J. Van Dyk is acknowledged. The IAEA officers responsible for this publication were B. Healy, D. van der Merwe, J. Izewska and E. Zubizarreta of the Division of Human Health.

CONTENTS

1. INTRODUCTION

1.1. BACKGROUND

Approximately one in three people will develop cancer during their lifetimes. Depending on the region of the world they live in, up to 65% of all cancer patients could benefit from radiotherapy as part of their treatment management. A much lower radiation treatment rate is feasible in the low income nations of the world, primarily owing to the lack of radiotherapy facilities [1].

There have been major advances in radiotherapy related technology in recent years. These technological developments have allowed for a transition from conventional two dimensional (2-D) radiotherapy to the implementation of three dimensional (3-D) conformal radiotherapy (CRT), intensity modulated radiotherapy (IMRT), image guided radiotherapy (IGRT), adaptive radiotherapy (ART) and four dimensional (4-D) imaging and motion management in radiotherapy [2–4]. Brachytherapy procedures have also evolved [5, 6], both for high dose rate (HDR) techniques as well as for permanent implants, especially for prostate cancer treatment. Multiple imaging modalities are now available for target volume and normal tissue delineation for radiation treatment planning, for both external beam radiotherapy (EBRT) and brachytherapy. These new technologies are often combined with an integrated computerized radiation information system, allowing cancer centres to become fully networked environments. The pace of new advances in technology and the expectation of improved outcomes in both EBRT and brachytherapy have resulted in a recognized need for greater accuracy and oversight in the radiation treatment process [7].

The degree of application of these technologies within radiotherapy varies dramatically across the world. These variations are not only found between nations; there are also considerable variations within individual nations. Independent of the level of technological sophistication, accuracy in radiotherapy and the means by which it is achieved and maintained remain central to the treatment process. In order to sustain the required accuracy in dose delivery, all steps of the radiotherapy process need to be covered by comprehensive quality assurance (QA) programmes. It is well recognized that there is a need to evaluate the influence of different factors affecting the accuracy of radiation dose delivery and to define the actions necessary to maintain treatment uncertainties at acceptable levels [8].

1.2. OBJECTIVE

While a number of reports and publications have defined accuracy needs for radiotherapy, most of these reports were developed in an era when different radiation technologies were in use [9–15]. In the meantime, there have also been improvements in dosimetry standards. Furthermore, published accuracy requirements were partially based on the clinical information and procedures available at that time, prior to the availability of image based 3-D CRT, IMRT or IGRT. In addition to technological changes and advances in dosimetry, significant data have been published from clinical studies using these new technologies (see Section 4.3.5). In view of new technologies and techniques, improvements in dosimetry methodologies and new clinical dose–volume data [16], an IAEA consultants meeting has recommended that an international guidance document on accuracy requirements and uncertainties in radiotherapy be developed in order to promote awareness and encourage quantification of uncertainties and to promote safer and more effective patient treatment.

Issues related to accuracy and uncertainties are relevant to all types of radiotherapy. However, as discussed later in this publication, the level of accuracy required depends on clinical and technological circumstances. Historically, as a compromise, the International Commission on Radiation Units and Measurements (ICRU) [17–20] has identified three levels of prescribing and reporting. The following is quoted from ICRU Report 83 [21]:

> *"Level 1 recommendations: minimum standards for prescribing and reporting.*
>
> "Prescribing and reporting at Level 1 is considered the minimum standard required in all centers, a standard below which radiotherapy should not be performed. Operating at Level 1 is sufficient for simple treatments and implies that knowledge of absorbed doses on the central beam axis is known and that simple two-dimensional (2D) absorbed-dose distributions at the central axis are available.
>
> *"Level 2 recommendations: prescribing and reporting state-of-the-art techniques.*
>
> "Level 2 prescribing and reporting implies that the treatments are performed using computational dosimetry and 3D imaging. At this level, it is assumed that all volumes of interest *e.g.,* gross tumor volume (GTV), clinical target volume (CTV), planning target volume (PTV), organs at risk (OAR) and planning organ-at-risk volume (PRV) (see Section 4), are defined using,

for example, a series of computed tomography (CT) or magnetic resonance imaging (MRI) sections and that 3D absorbed-dose distributions are available and include heterogeneity corrections.

"It is expected that dose–volume histograms (DVHs) for all volumes of interest are routinely computed. It is also assumed that a complete QA program is in place to ensure that the prescribed treatment is accurately delivered.

"Level 3 recommendations: optional research-and-development reporting.

"Reporting at Level 3 includes the development of new techniques and/or approaches for which reporting criteria are not yet established. Examples include the use of concepts such as tumor-control probability (TCP), normal tissue complication probability (NTCP) or equivalent uniform dose (EUD).

"It is recommended that all information required for Level 1 prescribing and reporting should be included in Level 2, and recommendations at Levels 1 and 2 should be incorporated when reporting at Level 3. It is recognized that procedures at Level 3 may be added to Level 2 in the future."

Guidance provided in this publication, describing good practices, represents expert opinion but does not constitute recommendations made on the basis of a consensus of Member States.

1.3. SCOPE

The present publication is limited to the radiotherapy procedures used in the vast majority of radiotherapy departments, including EBRT and brachytherapy, i.e. ICRU levels 1 and 2. Specialized delivery techniques such as robotic radiotherapy and modalities such as proton and heavy ion therapy are not the focus of this publication, although a brief mention is made of some of these where appropriate. The intended audience for this publication are professionals working in radiotherapy who are able to address issues related to treatment accuracy and who have an influence on treatment related uncertainties at any stage of the radiation treatment preparation and implementation process. These professionals include metrologists, radiation oncologists, medical physicists, radiotherapy technologists (RTTs) and dosimetrists [22]. In this publication, 'radiation oncologist' is used to describe physicians or radiological medical practitioners. Radiation therapists are also known as radiographers, medical

radiation technologists or RTTs. Dosimetrists specialize in treatment planning, although in some centres, this may be performed by medical physicists, radiation therapists or both.

While it is recognized that there can be significant variations in the dose prescriptions that physicians use even for the same disease site and stage, these variations are not considered part of the treatment uncertainties. The uncertainties addressed in this publication begin with the assumption of a specified prescription. Therefore, the questions are how accurately the prescription can be delivered and what the associated uncertainties in doses determined for the tumour and all relevant normal tissues are. For that reason, the importance of inter- and intraclinician volume delineation has been emphasized.

The concepts of GTV, CTV and PTV are often not as clearly defined for brachytherapy as they are for EBRT; the differences will be elucidated in this publication. The complexity of the external beam and brachytherapy procedures relates to the time period over which treatment is delivered, the multiple steps in the radiation treatment process that can exert a range of influences, and the knowledge, skills and attitudes of the members of the multidisciplinary team.

The radiation treatment stages include: patient identification; treatment directive (prescription), patient positioning and immobilization for simulation or imaging; target volume and organ at risk delineations; treatment planning; patient immobilization, positioning and imaging for treatment delivery; and finally, dose delivery. The process for brachytherapy is similar in terms of imaging and delineation of targets and OAR, but different in patient set-up and immobilization procedures. Brachytherapy, however, has different dose rate considerations.

1.3.1. Terminology

Consistent terminology is important for good communication. The term ‘uncertainty’ is defined as a parameter that characterizes the dispersion of values that can be obtained for a particular measurement when it is performed repeatedly. More recently, terms such as ‘expanded uncertainty’ and ‘coverage factor’ have been introduced. Standard uncertainty is generally considered to be equivalent to one standard deviation, although, at times, an overall uncertainty is stated at another level of confidence, e.g. 95%. This rescaling can be performed using a coverage factor, k. Multiplying the combined standard uncertainty by k gives a result known as the expanded uncertainty.

Type A and Type B uncertainties are preferred terms in metrology laboratories (further discussion of these terms can be found in Section 3). It should be noted that Type A and B uncertainties are not to be confused with random and systematic errors. The terms random error and systematic error continue to be used in the radiotherapy literature. Random errors vary arbitrarily in direction

and magnitude, while systematic errors tend toward a similar direction and magnitude. Uncertainties can be combined in quadrature to obtain the overall uncertainty. However, margin recipes have been developed that use different weights for combining systematic and random uncertainties in radiotherapy.

'Accuracy' refers to the closeness of agreement between a result and the true value. 'Precision' is the closeness of agreement between repeated independent measurement results obtained under stipulated conditions. The term 'tolerance' is somewhat ambiguous in its application. One definition of tolerance is a range of acceptability, beyond which corrective action is required. However, this can be confused with 'action level'. Thus, the use of tolerance is avoided in the recommendations of this publication. It is assumed that readers of this publication will have a basic medical radiation physics or radiation oncology background such that detailed definitions of commonly used terms are not required.

1.3.2. Radiobiological considerations

A radiobiological and clinical framework for making rational decisions on the required level of accuracy in radiotherapy is provided. Dose–response curves describe the relationship between dose and the incidence of a specific type of radiotherapy end point, be it tumour or normal tissue related. For demonstrative purposes, a logistic expression is used to model the dose–response relationship in γ_{50}, the normalized dose–response gradient, and D_{50}, the dose to generate 50% response, which are generally parameters used to generate fits to the clinical data. The normalized dose gradient (or the steepness of the dose–response curve), γ, is used to represent the absolute change in response, in per cent, for a 1% change in dose anywhere along the dose–response curve. Summary data are provided for γ_{50} and show that late responding normal tissues have a steeper γ_{50} (e.g. 2–6) compared with tumours (e.g. 1.5–2.5). Quite often, values of 4 and 2, respectively, are used for illustrative purposes. Caveats regarding published steepness estimates include:

(a) Patient series with heterogeneity in patient, tumour and dose characteristics will result in shallower dose–response curves.
(b) Bias in non-randomized studies appear to yield higher γ_{50} values compared with randomized trials.
(c) γ values for adjuvant therapy are much lower than those derived in a definitive treatment setting.

In a relatively heterogeneous population, reduced accuracy will have relatively less impact than uncertainty at the individual patient level. Selected examples are used to illustrate how different types of accuracy affect outcome,

and to provide a general impression of the required accuracy in radiotherapy. While no simple, hard rules can be given, modelling shows that it is reasonable to strive for accuracies in systematic bias of 1–2%. For random uncertainties, modelling shows that if the aim is to limit the increase in toxicity to <3%, the dose uncertainties (σ_D) would need to be kept to <5% and <3% for γ_{50} equal to 4 and 6, respectively. To ensure a reasonably low loss of tumour control, an increase in toxicity, or both, a realistic goal would be to aim for a <5% random σ_D. In well stratified patient populations, such as those that could be found in clinical trials, this limit should probably be tightened to σ_D <3% to meet a 3% maximum deterioration of outcome. Based on modelling of geometric uncertainty, aiming again for <3% loss in tumour control probability, the volume receiving <90% of the planned dose should be <12% and <6% for γ_{50} = 1.8 and 4.0, respectively. The number of patients required in randomized controlled clinical trials is strongly dependent on the steepness of the dose–response curve and the uncertainty in dose delivery, with many more patients being required for inaccurate systems.

1.3.3. Clinical radiotherapy

In addition to accuracy in dose delivery, accuracy considerations in the specification and delineation of the relevant tumour, target and normal tissue volumes are considered. The ICRU volumes are reviewed and should be used. The patient care plan should be formulated based on uniform staging and international classifications of diseases, evidence based medicine or consensus guidelines, or a combination of these. Radiotherapy outcomes should be based on uniform and well defined toxicity end points. Radiotherapy institutional policies and guidelines should have an embedded anatomical consensus atlas. Clinicians should undertake training in site specific volume delineation. An interdisciplinary review and reporting consensus on interclinician and intraclinician variation should be pursued.

The levels of accuracy that are practically achievable in clinics are reviewed in this publication. For air kerma and absorbed dose to water determinations, secondary standards dosimetry laboratories should maintain reference standards in ^{60}Co, with a relative standard uncertainty of 0.7% (k = 1). When comparing reference standards, an action level of 1.5% at the intercomparison level is recommended. Under reference conditions in hospitals, a dose can generally be delivered with an accuracy of 2% (k = 1). Relative dose parameters such as dose ratios, output factors and off-axis factors can be measured to an accuracy of 1% (k = 1), and published recommendations advise maintaining relative dose parameters at the 2% level. The daily output constancy of modern clinical linear accelerators (linacs) varies within 2% (k = 1). Dosimetry considerations for special techniques such as IMRT, stereotactic radiosurgery (SRS), stereotactic

body radiotherapy (SBRT) and total body irradiation are briefly addressed. For brachytherapy remote afterloaders, the temporal accuracy is <0.5% (k = 1), the source strength should be known within an uncertainty of 1.5% (k = 1), and a dose accuracy of <5% (k = 1) is achievable at 10–50 mm distances from most sources. Dose calculations should have a numerical accuracy of 2% (k = 1) for water type dose calculations, while for lower density heterogeneities, 1-D algorithms are accurate to about 10% (k = 1).

For external beam calculations, treatment planning system accuracies are extremely variable depending on the nature of the algorithm. For simple dose calculation algorithms, differences between calculations and measurements as large as 20% have been observed for high energy photon beams. Model based dose calculation algorithms using convolution or superposition principles, which include lateral transport considerations, are generally able to yield results within 3.5% (k = 1).

Treatment accuracy can be affected by the tumour site, available staff and technology resources, staff shift schedule, staff vigilance and the number of treatment breaks. Treatment accuracy begins by verifying that the patient, site and procedures are correct. The implementation of QA is essential for accurate radiation treatment, both for EBRT and brachytherapy. In vivo dosimetry (IVD) adds an additional safeguard for accurate radiation treatments and, in EBRT, it has an accuracy of 2–3% (k = 1).

Geometric accuracy and accuracy considerations in the dose delivered to a volume are reviewed for EBRT based on ICRU Report 83 [21]. End to end tests with anthropomorphic phantoms have yielded an uncertainty in dose of 5% (k = 1); thus, considering additional patient related uncertainties (e.g. set-up, respiratory motion), 5% uncertainty is likely to be an underestimate for real patients.

Precision and accuracy in radiotherapy are dependent on many factors, including appropriate training, adequate staffing, suitable QA programmes and quality control tools related to specific techniques or technologies, and proper quality control (QC) procedures. A good QA programme needs to include: a set of procedures that covers all key processes in the organization; monitoring processes to ensure the procedures are effective; adequate record keeping procedures; recording incidents and near misses, with appropriate and corrective action where necessary; regular reviews of individual processes and the quality system itself for effectiveness; and the facilitation of continual improvement.

With rapid change in technology and its increasing complexity, the cost of QA is also increasing. The literature analysing the cost–benefit relationship in QA is increasing; however, it is too early to make quantitative recommendations. Participation in multi-institutional clinical trials may improve and harmonize

evidence based QA, and thereby the accuracy of radiation treatments; however, this relationship requires further research.

With the effect of the increasing costs of QA and the accuracy and use of radiobiological models for treatment planning, further research is required on the cost–benefit relationship in QA. In principle, each clinic should determine patient and treatment related uncertainties in their own departments. In a British Institute of Radiology report [23], a process for determining geometric uncertainties is outlined. The report includes a description of imaging procedures and margin recipes. The display of uncertainties in the treatment planning process remains a challenge, with no methods being implemented in commercial treatment planning systems. This remains an area for research and implementation. Considerations for reducing uncertainties include the implementation of clear policies, guidelines and procedures; good documentation of both the policies and procedures as well as the results of acceptance, commissioning and QC tests; and ongoing education and training for routine procedures and technologies, new technologies and brachytherapy.

Factors to consider in the prevention and mitigation of errors include the extent to which the information transfer between the various professionals involved in the patient's treatment process is clear; internal and external audits; second checks; peer review of individual cases; an incident reporting system; and ongoing, up-to-date training.

Specific examples of reducing uncertainties are given for brachytherapy, for head and neck treatments using IMRT, for SBRT and for pelvis and breast treatments. A brief discussion is provided on adapting treatments to patient changes measured with image guided radiotherapy, although it is recognized that no clearly defined protocols exist, and this remains an area for further research.

This publication provides a summary of external beam audits using mailed dosimeters. For the Imaging and Radiation Oncology Core Houston Quality Assurance Center (IROC Houston), the variation in dose stated by the institution versus the IROC Houston measured dose is about 1.7% ($k = 1$), although 3%–5% of photon beams and 5%–8% of electron beams fall outside the IROC Houston acceptability threshold of 5%. For IMRT, based on a series of early trial runs, the IROC Houston has developed criteria of acceptability of 7% in dose and 4 mm distance-to-agreement (DTA). Even with these relatively broad criteria, a 30% failure rate was initially reported for IMRT using the IROC Houston spine and pelvic phantoms on the first attempt. After ten years of IMRT implementation and experience, the current failure rate is still at 10–15%. Nevertheless, it should be possible to achieve a mean dose accuracy of 3% at the centre of the target volume with more than 95% of pixels achieving a gamma index of 3% and 3 mm DTA.

The IAEA dose and clinical auditing programme is described in this publication, including the comprehensive clinical audits which are provided through the IAEA Quality Assurance Team for Radiation Oncology (QUATRO) programme. The requirement for clinical audit has been enshrined in European legislation through the Medical Exposures Directive 97/43/EURATOM [24].

Clinical audits are considered a means of improving patient treatment quality. They should include a feedback process and well defined criteria for assessing the appropriateness of decisions and actions with reference to infrastructure and resources. These criteria are required for processes and outcomes and can be specific or generic. Clinical audits are usually process measures rather than clinical outcome measures, and they are often centred on resources, waiting lists, logistics and infrastructure. Clinical audits can be comprehensive or partial, internal or external, proactive or reactive, or a combination of these. The clinical audit process includes the following phases: pre-audit preparation by both the local and auditing teams; conduct of the audit (entrance briefing, the audit itself including observation, interview, document and record review, physical measurements and exit briefing including recommendations), and reporting.

1.3.4. Safety and quality

In summary, there are two significant considerations that determine the need for accuracy in radiotherapy. As described in more detail in Section 4.2, the first consideration relates to the nature of radiation dose–response for both tumours and normal tissues [10–13]. Dose–response curves are known to have S shaped or sigmoidal relationships with a relatively steep slope near the 50% response level. It is generally recognized that tumours have a shallower dose–response relationship in comparison with normal tissues. In either case, a small inaccuracy in dose could result in a significant deviation from the planned response. For tumours, a slight underdose could yield a decrease in the probability of tumour control while, for normal tissues, a slight overdose could yield a significantly higher probability of morbidity. The second consideration relates to providing safe patient treatment with the avoidance of treatment errors in a very complex multistepped radiation treatment process [25]. Some recent widely reported incidents and near misses have yet again confirmed the importance of having effective quality and safety programmes in place [26]. They have also resulted in an increased awareness of the importance of a safety reporting system, and how to use the resulting data from such a system for learning and improvement [27]. Creating a culture where accuracy is an integral component of every professional's practice is one of the tools by which these two considerations can be addressed. This publication primarily addresses accuracy concerns from the perspective of the first consideration, which is radiobiological. The issue of

patient related treatment errors has its own unique requirements and could be the subject of a separate comprehensive report. Only minor consideration is given in this publication to treatment related incidents or near misses, although it is recognized that a safety conscious department is likely to be more concerned about accuracy issues.

Inevitably, as part of an accuracy and uncertainty discussion, QA issues will also be raised. However, the focus of this publication is not on QA programmes, codes of practice or guidelines, many of which have been well documented by various societies and organizations. The focus is on raising an awareness of accuracy and uncertainty issues such that the treatment process can be optimized and appropriately communicated, to the ultimate benefit of the patient. Inevitably, some discussion of QA and its management will be part of the process of ensuring that treatments are as accurate as reasonably achievable.

While it is well recognized that uncertainties in the radiation dose delivery process have an impact on clinical outcome, the actual measurement of that outcome has its own uncertainties. One component of accuracy requirements that is beyond the scope of this publication has to do with clinical outcome assessment. While it is clear that there are uncertainties associated with determining a particular level of tumour control or a specific type of normal tissue response, the quantification of these uncertainties requires further study.

1.4. STRUCTURE

This publication begins with a brief description of the entire radiotherapy process for EBRT and brachytherapy, followed by a section on the terminology relevant to accuracy considerations. The rationale for determining accuracy requirements is then outlined in detail from radiobiological and clinical perspectives. The next section is devoted to what level of accuracy is practically attainable both in EBRT and in brachytherapy. The section on managing uncertainties is followed by specific recommendations arising from this publication. Throughout the report, summary statements on accuracy requirements and uncertainties are provided at the end of each section. Some of the recommendations at the end of this publication are gleaned from these summaries.

2. THE RADIOTHERAPY PROCESS

2.1. PROCESS OVERVIEW

The cancer treatment pathway can vary significantly from one patient to another. Radiation treatment can be given either as a single modality or in combination with other therapies, typically including chemotherapy, surgery or both. Several multidisciplinary teams are generally involved in defining the treatment approach. Within the radiotherapy process itself, a further multidisciplinary team comprising a radiation oncologist, a medical physicist and an RTT, and in some countries a dosimetrist, is necessary. Each member of this team is responsible for different aspects of the entire radiotherapy process. The accurate delivery of multiple radiation treatment fractions is influenced largely by the reproducibility of patient set-up and the dosimetric and technical accuracy of the radiation treatment machines, associated accessories and the treatment planning process. Furthermore, the accurate clinical implementation of the treatment plan is dependent on the accuracy and completeness of the documentation and the knowledge, skills and attitudes of all the members of the radiotherapy multidisciplinary team. What is crucial in radiotherapy is the co-existence of equipment QC procedures with best clinical practice; independently, they will not achieve the required outcome.

The patient pathway through the radiotherapy department has several discrete but interlinked stages. Figure 1 shows a schematic block diagram of the steps in the EBRT process. Brachytherapy considerations will be addressed later in this section. The remainder of this publication will consider the various aspects of the treatment process and the corresponding uncertainties for each of these stages.

2.2. PATIENT IDENTIFICATION

Proper radiation treatment starts with patient identification and includes three critical components — correct patient, correct site and correct procedure [29]. Misidentification is a problem that still occurs in radiotherapy departments. “The potential for misidentification errors is greatest in acute care hospitals where a wide range of patient interventions are carried out in various locations on patients by staff who work in shifts” [30]. Incidents relating to misidentification have been reported to the Radiation Oncology Safety Information System (ROSIS) [31] and the IAEA’s web based Safety in Radiation Oncology database

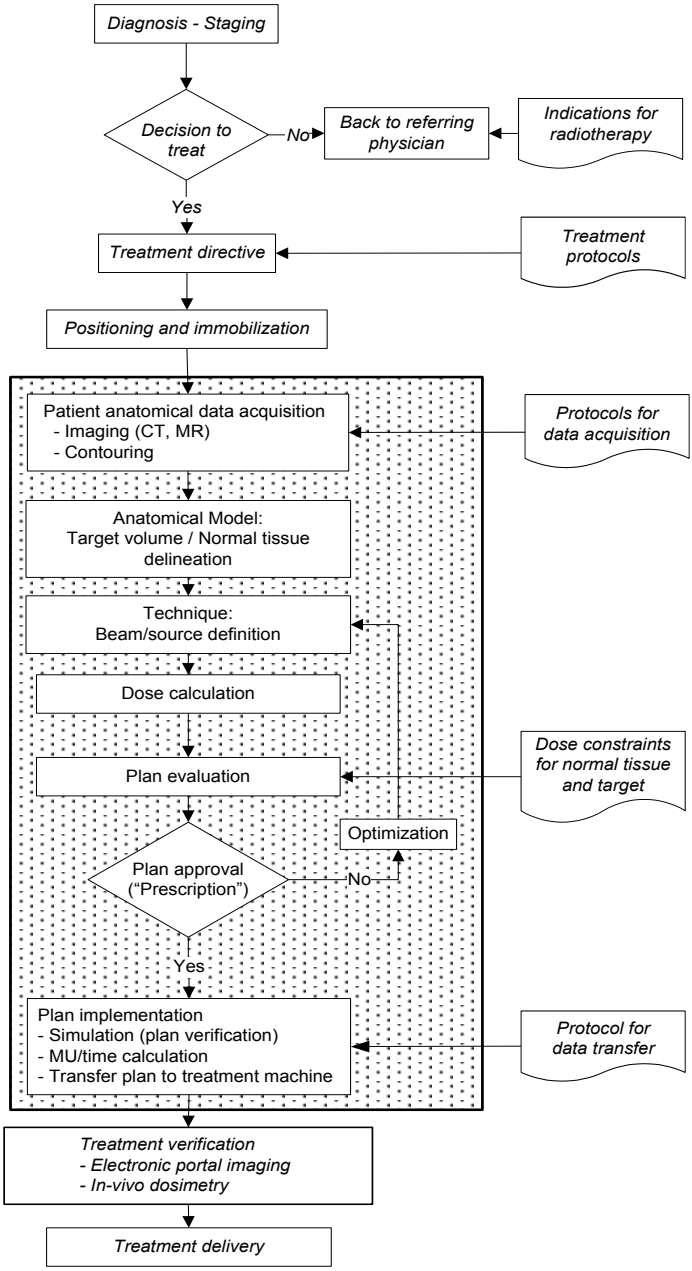

FIG. 1. Flow chart illustrating the steps in the EBRT process, starting with diagnosis and ending with treatment delivery. The shaded background refers to the sub-processes that are considered part of treatment planning. The elements shown on the right refer to guidelines, practices or protocols that inform the process (adapted from Ref. [28]).

(SAFRON) [32, 33], and were also clearly identified as one of the significant sources of treatment misadministrations by the IAEA [34].

2.3. TREATMENT DIRECTIVE

Based on all the diagnostic information available to the radiation oncologist as well as to medical colleagues in other disciplines (e.g. medical oncologists, surgical oncologists, radiologists, nuclear medicine physicians or pathologists), the specific disease stage [35] will be determined in a multidisciplinary clinic and the appropriate treatment directive will be implemented by the radiation oncologist. This directive includes the dose prescription for the target volumes as well as the dose limitations for normal tissues. Examples of details of the information to be included in treatment prescriptions can be found in a policy directive from Australia [36].

2.4. POSITIONING AND IMMOBILIZATION FOR TREATMENT PLANNING

Reproducible positioning with a high degree of immobilization is critical. The initial definition of the position and the ability to reproduce this position on a daily basis is essential for the accurate delivery of a course of treatment. The optimum patient position and the method of immobilization are based on the clinical site, the extent of the target volume and the location of the OAR, and are dependent on the type of treatment and the status of the patient. Positioning accuracy in stereotactic treatments requires (sub)millimetre precision, but achieving the highest level of accuracy needs to be balanced by the level of discomfort caused to the patient, while not compromising the desired outcome.

2.5. TARGET AND ORGAN AT RISK VOLUME DELINEATION

Once the decision to use radiotherapy has been made, the volume for treatment must be carefully defined for the patient. This can involve clinical localization or the use of radiographic bony landmarks relative to surface anatomy using a radiotherapy simulator. Alternatively, the extent of the GTV observed on images derived from CT can be graphically outlined on virtual simulation or treatment planning workstations. To account for microscopic disease that may exist in the normal tissue around the GTV, an appropriate margin is used to define the CTV. Any critical organ with a high sensitivity to

radiation that is in proximity to the defined target volume must also be noted and taken into account to prepare the optimum treatment plan. Cross-sectional multiplanar information can be obtained from a range of diagnostic imaging techniques, primarily CT in EBRT, but multiple imaging modalities (e.g. CT, MRI, PET, single photon emission computed tomography (SPECT) and ultrasound) can be used to aid in tumour, target or OAR volume delineation, or in all of these [37]. Failure to use consistent positioning (including flat table tops and immobilization devices) throughout may result in difficult or incorrect image registration and consequently in less accurate volume delineation. Wide bore CT scanners facilitate the physical positioning of the patient for imaging in the actual treatment position. Image acquisition for treatment planning purposes should be carried out by RTTs familiar with the simulation and treatment process, and should be of high quality so that clear definition of the volumes and structures of interest is facilitated. The same patient-specific positioning and immobilization devices should be used during imaging for treatment planning as will be used later during the treatment delivery.

2.6. TREATMENT PLANNING

The non-graphical, planar or cross-sectional imaging data are then transferred to the treatment planning team and an optimum treatment plan is produced. This may include defined margins for the target volume and OAR, beam type, energy, field arrangement, total dose and fractionation. The final plan is then approved by the radiation oncologist. Uncertainties are intrinsic to the treatment planning process, e.g. tumour delineation and dose calculation, and, especially if tissue inhomogeneities are involved, may affect the treatment outcome. The input of data into the record and verify system (RVS) should be by direct network transfer rather than manual entry wherever possible. However, there is still potential for errors in the data transfer to the RVS and, whether data are transferred manually or electronically, they should be double checked by independent professionals.

2.7. PATIENT IMMOBILIZATION AND POSITIONING FOR TREATMENT DELIVERY

In some centres, once the treatment plan has been completed and additional ancillary devices such as shielding blocks or boluses have been produced, the patient is set up in the treatment position either on a simulator or on a treatment unit, and consistency in the positioning is confirmed before treatment starts. Use

of inconsistent immobilization devices may result in the incorrect application of treatment and should be detected through this procedure. Note that imaging on treatment machines with different couch sags will result in inaccuracies associated with the treatment, with the potential for a systematic displacement. Regular checks of accessory equipment should be carried out in accordance with policies and procedures. Several studies have shown, for instance, that head and neck support shape can change over time and with variation in usage [38]. Individual customized head rests are an alternative. Extensive reuse of thermoplastics could result in loss of rigidity and poor immobilization; therefore, reuse should be limited or avoided. Portal image registration (either manually or automatically) can also be a source of uncertainty, particularly where staff is unfamiliar with the detailed anatomy or transformation protocols.

2.8. TREATMENT DELIVERY

Daily treatments are given in fractions, from as as few as a single fraction to as many as 40 or more fractions. Regular checks on the output and performance accuracy of the treatment units must be carried out routinely. Care taken with accurate positioning is only effective if the equipment performance and function are accurate to within the agreed limits. In addition to verifying dosimetric beam characteristics, there should also be checks of the laser lights, field defining lights, gantry angles and other mechanical parameters.

Over the course of the treatment, changes in patient anatomy can occur, such as tumour shrinkage or growth, or the patient could suffer from adverse effects such as weight loss, weight gain, pain or fatigue. These conditions must also be monitored as they can significantly alter the patient position and subsequent accuracy of the treatment delivery. On-line daily imaging has shown shifts in patient set-up from about 2 mm in the head and neck region to 6–8 mm in the pelvic region [39]. Patient weight loss or gain or tumour shrinkage may result in incorrect fitting of immobilization devices with a subsequent change in patient position.

Currently, a wide range of fractionation schemes are routinely applied, and reduced treatment volumes facilitate higher doses. Patients may receive a fractionated course of treatment for up to two months, with modern IGRT techniques allowing for biologically effective higher doses by varying the overall treatment time. Hyperfractionated treatments have an impact on the scheduling of patients and may involve more than one treatment team in the daily delivery process. Maintaining accuracy is more complex in settings where different teams are involved in routine treatment delivery and patient monitoring. Hypofractionated high dose per fraction treatments may require even greater

clinical, dosimetric and geometric accuracy. Gaps or delays in treatment can be critical in maintaining clinical accuracy and may affect the overall outcome.

Technical developments have increased the complexity of the radiotherapy treatment process and have resulted in a shift in types and levels of responsibility taken by the members of the team. Staff may not have the necessary knowledge level to undertake this responsibility. For instance, image matching is more routinely becoming the responsibility of the RTT, and image matching protocols require an ability to identify the relevant structures, interpret the images and make the appropriate changes. Bony anatomy or other landmarks can be used to verify positioning, but soft tissue matching can be more relevant to some targets or critical structures. Discernment of the appropriate methodology requires a higher level skill set and adherence to well developed imaging registration protocols.

Accuracy throughout the treatment pathway, ensuring reproducibility, is heavily dependent on the standard and clarity of the related documentation. Clear and detailed recording of the patient chart, diagnostic information, treatment prescription, pretreatment processes and patient monitoring throughout treatment is essential. Prescriptions should be based on institutional policy, with documentation of the reason for any deviation. Any changes or amendments to the prescription or plan should be clearly documented, giving the reason for the changes. This documentation helps to minimize inaccuracies in dose delivery, even if frequent changes in members of the treatment team are unavoidable. Ultimately, appropriate documentation of a patient's treatment also gives an accurate picture of the patient treatment summary for the clinician and enables investigation of any adverse reaction to the treatment. Good communication between the team members where all disciplines feel able to comment on the treatment process also encourages an overall commitment to and culture of accuracy in a department.

2.9. BRACHYTHERAPY CONSIDERATIONS

Brachytherapy can be applied to most anatomical sites of the body. It can be used either alone or, more commonly, as part of a multimodality approach with EBRT, surgery or chemotherapy, or a combination of these. Brachytherapy allows local delivery of an equivalent dose of radiation in a smaller number of fractions than is possible with conventional EBRT. For example, in treating low risk prostate cancer, an 8 week course of 40 fractions of IMRT radiation can be replaced by 4 fractions (or fewer) of HDR brachytherapy given over 2 days, or by a single low dose rate (LDR) seed implant. Brachytherapy is a mandatory component of curative treatment of cervical cancer using temporary intracavitary or combined intracavitary and interstitial applications.

The process for brachytherapy (Fig. 2 [40]) is similar to EBRT. Similarities occur in that CT and MR based imaging can be used for 3-D target and OAR volume delineation, and the definitions of GTV and CTV apply as well. However, other procedures are sufficiently dissimilar in that the patient set-up and immobilization considerations are quite different, and there is also a need for applicator reconstruction. Part of the planning process includes the selection of the most suitable type of brachytherapy, such as permanent seeds versus temporary implants, and intracavitary versus interstitial implants. Other important decisions include dose rate (i.e. LDR versus HDR), the type and activity of the radionuclide to be used, and the best treatment applicator to fit the clinical situation. The delineation of the target volume should take into account the need for an anatomical margin of safety in the positioning of the therapeutic device. The nature and complexity of the required patient preparations for the process are also specific to the treatment site and the type of brachytherapy used. For example, the scheduling of permanent LDR brachytherapy procedures should be coordinated with the delivery of the necessary sources, taking into consideration the time necessary for source and applicator preparation and sterilization. In addition, for some cases, such as permanent seed prostate implants, not only is a plan produced before treatment, but a CT scan is often made 3 to 4 weeks after the insertion of the implant, and a post plan is developed to determine the actual (recorded and reported) dose delivered to the prostate [41, 42].

The accuracy of the dose delivery with brachytherapy is very much dependent on the type of technique that is used. A permanent implant such as is used with prostate treatments has the possibility of some seed mobility and a change in prostate volume, whereas a HDR brachytherapy treatment is given over a short time (typically 20 to 40 minutes) and the applicator needs to be held stable for that time to avoid the likelihood of volume changes during the treatment. However, when a single applicator is used for multiple HDR fractions (e.g. a course of 3 fractions delivered in a period of 24 hours), interfraction applicator and OAR movement relative to the applicator are most likely to be the largest uncertainties for the dose delivery. On the other hand, repeated procedures (e.g. weekly fractionation) may result in applicator placement differences. Other uncertainties in afterloading brachytherapy include applicator reconstruction, image fusion and source positioning.

The quality and accuracy of a brachytherapy programme is dependent on three broad components: (1) open consultation between the radiation oncologist and the medical physicist to assure optimal preparation and management of the individual patient's treatment, (2) a quality management programme that includes the procedures for imaging and contouring and ensures the correct functioning of all related devices (e.g. sources, applicators and computer assisted planning and programmes) and the correct integration of physics supervision into the treatment

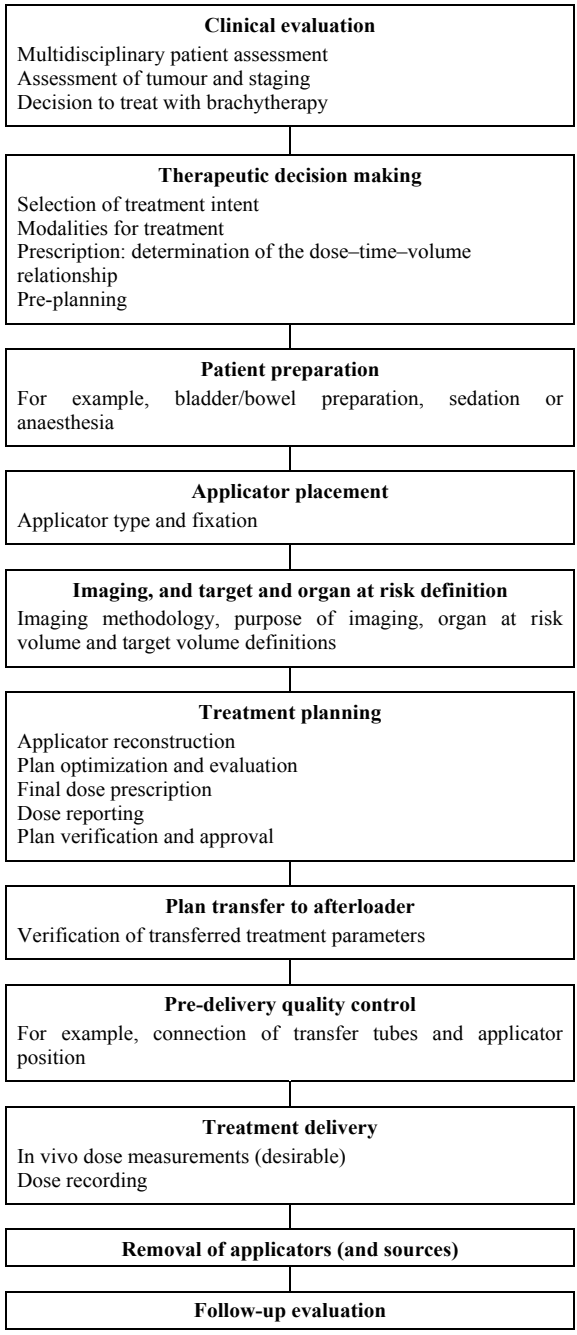

FIG. 2. One example of the procedure flow in brachytherapy, identifying each major activity. (Adapted from Ref. [40]).

delivery process, and (3) a well designed treatment delivery programme that will ensure an accurate and safe application of the radioactive sources [43]. As will be discussed in Section 6.5.8, some sources of uncertainty are shared by all types of brachytherapy applications to some extent, but many others will differ considerably from one another, as they are dependent on the location in the body (deep seated or superficial); the tissue composition (influence on energy of the radiation); the application, fixation and localization techniques used; and user variability.

2.10. SUMMARY

This section discusses the radiotherapy process, including EBRT and brachytherapy, in the context of accuracy and uncertainties. It has been established that:

— Radiotherapy is a complex process of treatment planning and treatment delivery.
— Steps in the process include patient identification, preparation of a treatment directive, patient positioning and immobilization for planning and treatment, volume delineation from patient images, treatment planning and review, and treatment delivery.
— The complexity of radiotherapy is due to:
  • The time period (up to 40 fractions) over which treatment is delivered;
  • The various elements described in this section which, over time, can exert a range of influences;
  • The number of different staff groups required for radiotherapy, and their knowledge, skills and perspectives.
— For brachytherapy, whether intracavitary, interstitial, permanent or temporary implant, some processes that are different from those in EBRT are found, including applicator or catheter placement, reconstruction and removal. Brachytherapy can involve additional medical disciplines, including surgical specialities and anaesthesiology.
— Accuracy in radiotherapy can be achieved through well designed delivery processes, minimizing gaps or delays in treatment, and promoting QA processes, thorough documentation and staff communication.

Finally, it is emphasized that there is a need for a culture of safety in radiotherapy [44], particularly for advanced techniques in which most process steps are linked to professional review, followed by a decision that could lead

to restarting the process. Multiple stages of review need to occur to generate an accurate and safe treatment for the patient.

3. DEFINITIONS AND TERMINOLOGY

3.1. INTRODUCTION

When discussing terms such as ‘accuracy’, ‘precision’, ‘uncertainty’ and ‘error’, it is important to use clear and consistent terminology. These terms are often used ambiguously in the radiotherapy literature. To maintain a focus on accuracy and uncertainties, the emphasis in this publication is on measurement terminology. The term ‘error’, as used in the context of patient safety and standardized incident reporting taxonomies, is not applied here. Various relevant documents have been published by several groups, including the International Organization for Standardization (ISO) [45–47] and the International Bureau of Weights and Measures (BIPM, Bureau International des Poids et Mesures) [48]. A few important terms will be reviewed in this Section since these terms are used throughout this publication, as well as in the medical and scientific literature on radiotherapy.

3.2. BASIC TERMS

3.2.1. Uncertainty

There is no measurement (or procedure) in the radiation treatment process that can be performed perfectly; each step has a corresponding uncertainty. A recognition and understanding of the uncertainties associated with the various stages of the radiation treatment process is necessary to determine the resultant uncertainty of the dose delivered to specific tissues within the body, whether they be cancerous or healthy normal tissues. Quantitatively, this uncertainty is a parameter that characterizes the dispersion of values that can be obtained for a particular measurement when it is performed repeatedly [47]. For such measurements, the results can be described by a statistical distribution, which can be summarized by specific statistical quantities such as mean, mode and standard deviation. Figure 3(a) shows an example of a Gaussian (normal) distribution and the corresponding standard deviation.

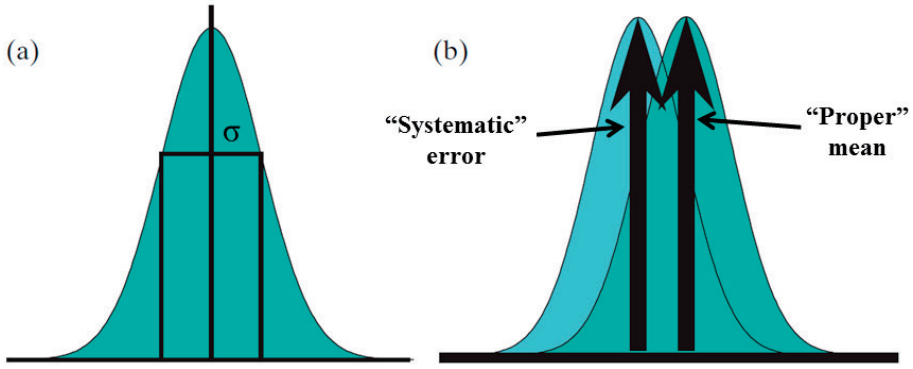

FIG. 3 (a) Uncertainty distribution for a particular measurement. (The vertical axis shows frequency; the horizontal axis shows the measurement value.) The standard deviation is shown by σ. (b) Comparison of two uncertainty distributions, one about the proper mean and the other with a systematic error. (Adapted from Ref. [28].)

The uncertainty of the result of a particular measurement generally consists of several components that the International Committee for Weights and Measures [49] groups into two categories according to the method used to estimate their numerical values: Type A uncertainties are those that are evaluated by statistical methods, and Type B uncertainties are those evaluated by other means (see also ICRU Report 76 [9]). While in some situations, Type A and Type B uncertainties were classified as random or systematic, it is now recognized that there is not always a simple correspondence between these classifications. The radiotherapy literature still uses the terms 'random' and 'systematic' frequently, usually to describe errors. These terms will be used, recognizing that the use of the term error in this context is not strictly correct. Random radiotherapy field placement errors vary in direction and magnitude, whereas systematic errors tend toward a similar direction and magnitude. Indeed, systematic errors, as related to patient set-up, can be determined by statistical means, in both 2-D and 3-D [50], and can be corrected (e.g. by the use of on-line imaging measurements). Figure 3 (b) demonstrates an example of two uncertainty distributions, one of which has a systematic error.

Figure 4 [51] shows set-up deviations for a group of five patients and demonstrates the difference between random and systematic uncertainties in individual patient data as well as in population based data. Generally, measurements that combine various Type A uncertainties can be combined in quadrature to provide an estimate of overall uncertainty. The combination of Type A and Type B uncertainties may also be done in quadrature [12, 49], although

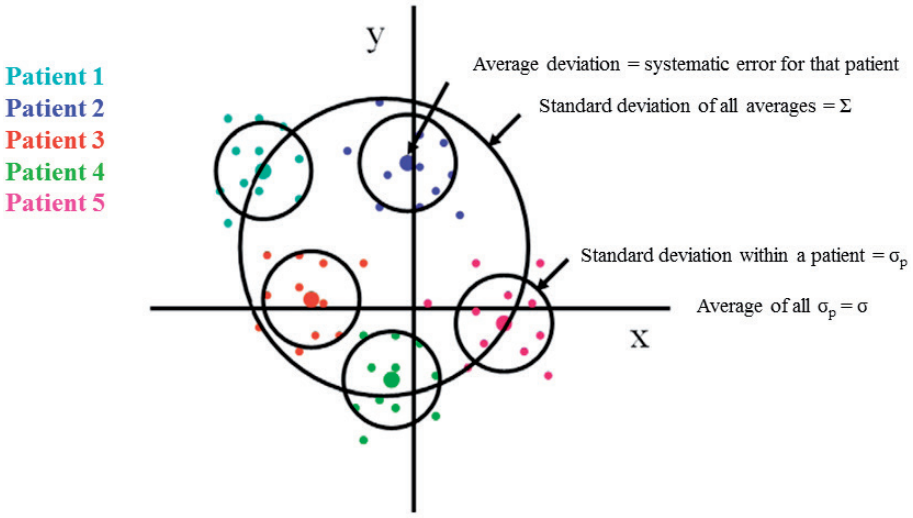

FIG. 4. Graphical presentation of systematic and random set-up errors in a group of five patients. Note the set-up error for each measurement in small coloured dots, the average systematic error per patient in large dots, the standard deviation of the set-up error for each patient in small circles and the standard deviation of all averages in the large circle. The figure illustrates that detailed knowledge of the set-up error for a given patient can reduce the required margin compared with margins based on group statistics. (Adapted from Ref. [51].)

for geometric uncertainties in radiation treatment, various margin recipes have been developed which provide different weights to the combination of systematic versus random uncertainties [52] (see Section 7.4).

It is worth noting that not all uncertainties in radiation treatment can be described by a Gaussian distribution. Uncertainties associated with breathing provide an example of a non-symmetrical uncertainty distribution. Target volume delineation uncertainties related to biological factors, such as hypoxic volume, imaging limitations, changes in target position and shape, and intra- or interclinician variability tend to be distributed in a skewed, bimodal or highly variable manner and are also not usually analysable in this way [53, 54].

3.2.1.1. Expanded uncertainty and coverage factor

The following two paragraphs are adapted from the web site of the National Institute of Science and Technology of the United States of Ameria [55] as well as from Ref. [47] (see also ICRU Report 76 [9]).

The combined standard uncertainty (u_c) is used to express the uncertainty of many measurement results. However, some applications (e.g. those concerned

with health and safety) require instead a measure of uncertainty that defines an interval about the measurement result (y) within which the value of the measurand (Y) can confidently be asserted to lie. The measure of uncertainty intended to meet this requirement is termed expanded uncertainty, with the suggested symbol U, and is obtained by multiplying $u_c(y)$ by a coverage factor, with the suggested symbol k. Thus $U = ku_c(y)$ and it is confidently believed that Y is greater than or equal to $y - U$, and is less than or equal to $y + U$, which is commonly written as $Y = y \pm U$.

In general, the value of the coverage factor k is chosen on the basis of the desired level of confidence to be associated with the interval defined by $U = ku_c$. Typically, k is in the range of 2 to 3. When the normal distribution applies and u_c is a reliable estimate of the standard deviation of y, $U = 2u_c$ (i.e. $k = 2$) defines an interval with a level of confidence of approximately 95%, and $U = 3u_c$ (i.e. $k = 3$) defines an interval with a level of confidence greater than 99%.

Recently, a joint report by the AAPM and the Groupe Européen de Curiethérapie — European Society for Radiotherapy and Oncology (GEC-ESTRO) on dosimetric uncertainty analysis has described these concepts in some detail and has provided uncertainty estimates of single radioactive source dosimetry preceding clinical delivery [56].

3.2.2. Error

The error (or deviation) of a measured or calculated result is the difference between its value and the expected value obtained by some other method that is considered to be a reference. In the case of dose calculations, the reference data are often obtained from measurements or from Monte Carlo calculations. Contrary to measurements, which are subject to both Type A and Type B uncertainties, calculations are, in most cases, subject only to Type B uncertainties; for example, if one evaluates the dose calculated at one point then one will find that the calculation will be completely repeatable, assuming that the calculation parameters are identical (the same grid spacing, the same geometry, identical calculation point, identical calculation algorithm, etc.). However, when one performs a measurement at the same location in a phantom on a number of occasions, one will find a distribution of results. Thus the comparison is a calculation with zero random uncertainty with a measurement that will have a noticeable statistical distribution. If the calculation deviates significantly from the mean of the measured data, it is considered to have a systematic error. In some cases, calculations can also be subject to Type A uncertainties if they are based on a statistical method (e.g. Monte Carlo calculations) that makes use of random starting points (seeds) for the generation of random numbers. In addition, one can also compare a number of calculation points (different spatial locations,

for example, central axis per cent depth doses) with a number of different measurements at the same spatial locations. It is then necessary to statistically combine the individual deviations to make an overall assessment of the quality of the calculation.

Unfortunately, the term error is also used in the context of mistakes. For example, the Institute of Medicine defines an error as "the failure of a 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)" [57]. Errors may be errors of commission or omission, and usually reflect deficiencies in the systems of care. These types of errors are not overtly addressed in this publication, although in places, suggestions are made to minimize them.

3.2.3. Accuracy

Accuracy refers to the closeness of agreement between a result (calculated or measured) and the true value [45], where the true value is generally the accepted reference value. Accuracy involves a combination of random and systematic components. It also combines the concepts of trueness and precision.

3.2.4. Precision

Precision is the closeness of agreement between repeated independent tests or measurement results obtained under stipulated conditions [45]. Note that precision depends only on the distribution of random errors and does not relate to the true value or to the reference value. Precision is usually quantified as a standard deviation of the test results. Less precision is reflected by a larger standard deviation. Quantitative measures of precision depend critically on the stipulated conditions. Figure 5 shows an example of the relationship between accuracy and precision.

FIG. 5. Demonstration of the concepts of accuracy and precision where the aim is for the blue bullet to be in the centre of the target. (Adapted from Ref. [58].)

3.2.5. Tolerance

The concept of tolerance is generally applied in the context of QC. One definition of tolerance is the range of acceptability beyond which corrective action is required. Thus, if a measurement, e.g. the source to surface distance (SSD), is given a tolerance of 5 mm, then any measurement outside the SSD ± 5 mm range cannot be tolerated (i.e. it is unacceptable and needs corrective action). However, when considering treatment planning systems (TPSs), the situation is not straightforward and a less restrictive approach is often used. The choice of a tolerance value can be dependent on the uncertainty attributed to the reference data. It should be larger for larger uncertainties and can also be dependent on the specific application. For example, radiosurgery will have a smaller tolerance in dose and geometry than conventional radiation treatments. It should be noted that a defined tolerance level within the radiotherapy context could be dependent on the clinical situation. Thus the tolerance levels associated with small field treatments as used for SRS will be substantially tighter than those for conventional or large field treatments, since stereotactic treatments involve very high doses given in a single fraction (or a few fractions for stereotactic radiotherapy), usually close to very radiosensitive normal tissues.

A more detailed discussion is given in IAEA Technical Report Series No. 430 [28] on tolerances and criteria of acceptability in the context of dose calculations using computerized radiation TPSs. It is noted that the accuracy of dose calculations depends on the algorithm, the region within the beam (e.g. central, uniform dose region, buildup region, penumbra region and out-of-field region) and the region within the patient (eg. muscle, bone, lung and interface region).

In some reports, tolerance levels and action levels have different meanings. Indeed, the BIPM, in a discussion of the ‘maximum permissible error’, recommended that the term ‘tolerance’ be used [59]. A series of standards is issued by ISO on the topic of tolerances, tolerance definitions and symbols (including GPS), where GPS refers to general product specifications. A definition given by NIST in the USA [60] states that:

> “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 end points 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. The primary context of both the ISO and NIST definitions is the manufacturing industry. In the context of radiotherapy, there is a recent comprehensive discussion of the difference between tolerance and action level in the ESTRO Booklet No. 10 [61], Independent Dose Calculations. Because an independent determination of a parameter has an intrinsic uncertainty, a complex relationship exists between the chance that the true value of that parameter is outside the tolerance level and the uncertainty in the measurement procedure. In Ref. [61], formulas are given for calculating action limits based on the probability of patients having a dose value exceeding a tolerance limit, as a function of observed dose deviation and uncertainty in the dose verification method.

The word tolerance has an independent meaning in the context of normal tissue tolerance, where it represents a specified clinical reaction to a particular dose level, possibly defined by a dose–volume histogram.

3.2.6. Action level (maximum permissible error)

Because of the different definitions of tolerance and the recommendation by the BIPM that the term be avoided, the recommendations of this publication will not include this term. Rather, Section 8, which contains the recommendations of this publication, shows examples of some representative dose and spatial uncertainties and suggests an action level. An action level for "any measurable quantity" is the "level above which intervention should be undertaken" [62]. The BIPM provides a formal definition for the maximum permissible error as 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" [59]. In this publication, action level and maximum permissible error are assumed to be the same. Thus, if the difference between a measured value and its expected value, based on typical uncertainty estimates, exceeds the action level or the maximum permissible error, then a response is required immediately. Ideally, this response would bring the system back to a state of function that meets expected uncertainty levels. If this is not immediately possible, then the use of the procedures or equipment should be restricted to clinical situations in which the identified inadequate performance is of no clinical significance, or is of a clinical significance that is acceptable and understood.

3.3. OTHER COMMENTS ON TERMINOLOGY

The terms described above have been clearly defined in separate subsections of this publication because they are crucial to the description of accuracy and uncertainties in radiotherapy. In addition, there are many concepts in medical physics and radiation oncology that are part of the science and practice of these disciplines. It is assumed that readers of this publication will have a basic background such that detailed definitions are not required. Hence, concepts such as absorbed dose, dose–volume histograms, various target volumes and so on, are assumed to be clearly understood. Detailed guidelines on the management of error and uncertainty in a clinical setting are found in Refs [63, 64].

3.4. SUMMARY

This section discusses the terminology used when reporting on the level of accuracy in radiotherapy.

— Consistent terminology is important for good communication.
— The term ‘uncertainty’ is defined along with more recent terminology such as ‘expanded uncertainty’ and ‘coverage factor’:
  • Uncertainty is a parameter that characterizes the dispersion of values that can be obtained for a particular measurement when it is performed repeatedly.
  • A standard uncertainty is generally considered to be equivalent to one standard deviation; however, at times it may be desirable to state an overall uncertainty at another level of confidence, e.g. 95%. This rescaling can be done using a coverage factor, k. Multiplying the combined standard uncertainty, u_c, by a coverage factor gives a result which is called the expanded uncertainty, and is usually represented by the symbol U.
— While Type A and Type B uncertainties are preferred terms in metrology laboratories, the terms random errors and systematic errors continue to be used in the radiotherapy literature. Type A and B uncertainties should not be confused with random and systematic errors.
— Random errors vary randomly in direction and magnitude, while systematic errors tend toward a similar direction and magnitude.
— Uncertainties can be combined in quadrature to obtain the overall uncertainty, assuming the uncertainties behave according to a (near) Gaussian distribution.
— Margin recipes have been developed and use different weights for combining systematic and random uncertainties in radiotherapy.

— Accuracy refers to the closeness of agreement between a result and the true value.
— Precision is the closeness of agreement between repeated independent tests or measurement results obtained under stipulated conditions.
— The term tolerance is somewhat ambiguous in its application. One definition of tolerance is the range of acceptability beyond which corrective action is required. However, this can be confused with the term action level. Thus, the use of tolerance is avoided in the recommendations of this publication. It is assumed that action level is equivalent to the more formal metrological definition of maximum permissible error.
— It is assumed that readers of this publication will have a basic medical radiation physics or radiation oncology background such that detailed definitions of commonly used terms are not required.

4. RADIOBIOLOGICAL FRAMEWORK FOR CONSIDERING ACCURACY REQUIREMENTS

4.1. INTRODUCTION

Logically, patients inadvertently receiving a higher than intended dose to OAR will have an increased risk of developing toxicity; patients receiving a lower than intended dose to the target volume will have an increased risk of local failure [12]. Studies trying to compare outcome in patients with and without major deviations between intended and delivered radiotherapy are subject to the concern that patients with such deviations may not constitute a random subset of all cases; in other words, this comparison may be biased towards a better outcome in patients without deviations, as discussed, for example, in Ref. [65]. Owing to limited clinical evidence, a number of authors have tried to consider the effect of accuracy on outcome based on empirically derived dose–response models [12, 13, 66, 67]. These studies are important not only as a means to quantify the likely consequences of poor accuracy but also as a means of identifying what level of accuracy is required in radiotherapy. It may seem logical to aim for taking the accuracy of each step in the overall treatment planning and delivery process to the highest (reasonably) achievable level. In practice, however, there is a limit beyond which further improvement would have no clinically meaningful effect on treatment outcome. It is the purpose of this section to discuss the framework and evidence base for making rational decisions on the required level of accuracy in radiotherapy.

4.2. SOURCES OF DEVIATIONS FROM PRESCRIBED DOSE

It is important to establish a framework and a terminology for a systematic discussion of uncertainties in radiotherapy planning and delivery. The actual physical dose delivered to a reference point in a patient can be written as:

$$\hat{D} = D_{\mathrm{I}} + b + \varepsilon \tag{1}$$

where D_{I} is the intended (prescribed) dose, b is a bias (often called systematic error) introduced by baseline deviations between intended and delivered dose, and ε is a random variable describing the residual variation in the delivered dose (often called random error). An example of b would be a beam calibration error causing an output variation that is assumed to be constant over extended periods and would, in principle, introduce a bias in the dose delivered to all patients treated in this period. Note that b may vary over longer periods, for instance, if beam output is recalibrated or if set-up lasers are adjusted.

The random component ε has a mean value of zero and a variance that can be resolved into two components:

$$\sigma_{\mathrm{D}}^2 = \sigma_{\mathrm{pop}}^2 + \sigma_{\mathrm{F}}^2 = \sigma_{\mathrm{pop}}^2 + \sigma_f^2 / N \tag{2}$$

where σ_{pop}^2 is the patient to patient or patient level variability in a population of treated patients, σ_{F}^2 is the variation resulting from interfraction or fraction level variability over a full course of N treatment fractions and σ_{f}^2 is the variation between fractions. Patient level variability could, for example, arise from deviations introduced at the stage of the planning CT scan or at simulation. Fraction level variability arises from deviations occurring at the time of therapy, such as set-up variability or the degree of bladder filling in a patient receiving pelvic radiotherapy.

4.2.1. Geometrical uncertainties

Increasing use of 3-D CRT and IMRT has effectively extended the problem of accuracy in radiotherapy to the consideration of geometrical uncertainties. These uncertainties were less of an issue when parallel opposed fields with rather liberal margins around the target volume were commonly used. Relatively little has been published in terms of modelling the effect of geometrical uncertainties, but some simple model considerations will be presented in this section.

4.3. DESCRIPTION OF DOSE–RESPONSE CURVES

A radiation effect or end point is a specific observable effect in a tissue or organ that could occur at some time after irradiation and can reasonably be attributed to the radiation. For normal tissues, the effect can be an early or late change in normal tissue morphology or function, e.g. xerostomia after head and neck radiotherapy. With increasing radiation dose, radiation effects may increase in severity (so in the case, of xerostomia, its grade), probability of incidence (i.e. the proportion of irradiated individuals developing a specific grade, e.g. grade 3 xerostomia) or both. The terminology and grading of normal tissue effects of radiotherapy have been defined in various dictionaries or toxicity scales, e.g. by the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) [68], the RTOG Late Effects Working Group [69] or the Common Terminology Criteria for Adverse Events [70] dictionaries. In the case of tumours, the preferred end point in radiotherapy studies is typically persistent tumour control, often defined as the absence of tumour progression at a specified time, e.g. 5 years after radiotherapy.

In this section, as is the general convention in the published literature, the term dose–response relationship or curve is used for the relationship between dose and incidence of a specific radiotherapy end point. The dose–response curve is generally sigmoid in shape, with the incidence rising gradually from zero to 100% as dose increases from zero to infinity. For an individual case, the incidence is interpreted as the probability that this patient achieves the specific end point.

The assessment of radiotherapy outcome requires prolonged observation of the patient, as tumour recurrence or late side effects may occur several years after the end of therapy [71]. As patients will be subject to the competing risk of dying from cancer progression, or will have an incomplete follow-up because they were alive without toxicity or tumour recurrence at the last follow-up, actuarial methods, such as the Kaplan-Meier estimate, are needed to adjust for the number of cases at risk over time [72]. Clinical dose–response curves will then be fitted to the actuarial estimates of incidence of toxicity and of tumour control. Some studies have demonstrated that late effects may continue to develop 10 or even 20 years after radiotherapy [73–75]. However, 5 year estimates are generally accepted as a reasonable indication of the late toxicity associated with radiotherapy alone, or combined with other modalities, except for very late effects such as radiation related second malignant neoplasms. In terms of picking up the clinical effect of changed radiotherapy, a recent analysis by Yarnold et al. [76] showed that 5 year estimates of the relative risk of late effects after two different dose fractionation schedules for whole breast irradiation after tumour resection were significantly higher than 10 year estimates for 10 specific late side effects. This suggests that the ability to resolve the effect of modified therapy after 5 years is actually higher

than after 10 years. In other words, the fact that late effects continue to occur in a population of irradiated individuals does not prove that a very long follow-up period is required to describe the relative toxicity of treatments.

4.3.1. Quantitative analysis of dose–response relationships

Several mathematical functions have been used in the literature to link exposure to the NTCP of a specific end point or to TCP, including the Poisson, logistic and error link functions [77]. For simplicity, and following a general trend in the literature, the logistic dose–response relationship will be discussed here.

The general mathematical form of the logistic dose–response model is:

$$\text{NTCP or TCP} = \frac{\exp(\beta_{0+}\beta_1 D + \beta_2 Dd + \beta_3 z...)}{1 + \exp(\beta_{0+}\beta_1 D + \beta_2 Dd + \beta_3 z...)} \quad (3)$$

where D and d denote the total dose and dose per fraction, respectively, and z is any other patient or treatment characteristic modifying the risk of expressing the end point. The ratio β_1/β_2 is an estimate of the α/β value of the linear quadratic model. The coefficients, β_i, are estimated by logistic regression, a procedure available in many standard statistical software packages.

In the present context, it is useful to parameterize the logistic dose–response relationship in terms of γ_{50} and the dose required for 50% response, D_{50}:

$$\text{NTCP or TCP} = \frac{1}{1 + \exp\left[4\gamma_{50}\left(1 - D/D_{50}\right)\right]} \quad (4)$$

γ_{50} is the normalized dose–response gradient or simply the γ value, a parameter characterizing the steepness of the dose–response curve (see Section 4.3.2). Any other patient or treatment characteristic influencing the NTCP or the TCP is generally assumed to modify the position, i.e. the D_{50}, rather than the steepness of the dose–response curve. One minor issue with the logistic dose–response model is that NTCP or TCP at zero dose is not exactly equal to zero. However, for practical values of γ_{50} with NTCP or TCP < 0.02, and in terms of fitting clinical data, this does not cause problems.

4.3.2. Quantifying steepness of the dose–response curve

One description of the steepness of dose–response curves, used in the past, is the percentage increase in dose required to improve the TCP from 50 to 75% (Δ75/50 (%)) or, for NTCP, the percentage decrease in dose required to reduce the complication rate from 50 to 25% (Δ50/25 (%)). Data for the latter descriptors are summarized in ICRU Report 76 [9] based on data reviews by Mijnheer et al. [12] and Wambersie [10]. These data show large variations in the reported slopes of dose–effect curves for different tumours and normal tissues, depending on their radiobiological characteristics, as well as uncertainties associated with the generation of these parameter values. The mid-range represents the steepest portion of this curve, and at this point, a 5% change in dose may result in a 10% to 20% change in TCP, at a TCP of 50%. Similarly, a 5% change in dose may result in a 20% to 30% change in complication rates in normal tissues.

A more recent and commonly used measure of the steepness of dose–response curves is the normalized dose–response gradient, γ, defined as:

$$\gamma = D\frac{\mathrm{d}P(D)}{\mathrm{d}D} = DP'(D) \tag{5}$$

where $P(D)$ is the dose–response function. Intuitively, γ is the (absolute) change in percentage points for a 1% relative increase in dose (see Fig. 6 [78]). For simplicity, γ will be referred to as the steepness of the dose–response curve in the remainder of this publication.

The S shape of the dose–response curve implies that the value of γ will vary with dose. This is indicated by an index: the notation γ_x indicates that this is the γ value at the dose corresponding to a response probability of x%. For a logistic dose–response curve, the γ value is specified at the 50% response level, γ_{50}. This is the point where the logistic curve attains its maximum steepness (but not necessarily its maximum γ value, owing to the multiplication with dose in Eq. (5)). Mathematically, the steepness at any other response level can be calculated once γ_{50} is known, as shown in Section 4.3.3. This is very practical in terms of tabulating steepness parameters for the dose–response relationship for various end points. For any practical application, however, it is important to use the local value of γ at the actual clinical response level, as shown below.

For a relatively small change in total dose, ΔD, the resulting absolute change in response, ΔP, can be calculated using the approximation

$$\Delta P \approx \gamma_x \frac{\Delta D}{D} \tag{6}$$

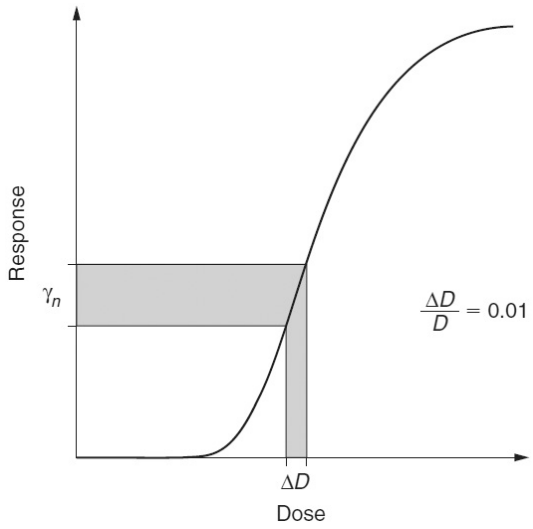

FIG. 6. Geometrical interpretation of the normalized dose–response gradient: γ_n is the absolute change in response in percentage points for a 1% relative increase in dose. γ_n varies along the dose–response curve, resulting in the S shape of the curve. It is generally tabulated at the 50% response level. The full dose–response curve is defined by two parameters, D_{50}, the dose for 50% response and γ_{50}. If these parameters are known, the response probability for any other dose as well as the γ-value for any other response level can be calculated. (From Ref. [78]).

where γ_x is the local steepness of the dose–response curve and x is the response at dose D. This corresponds to approximating the dose–response curve with the tangent to the curve; if larger dose perturbations are investigated, it is necessary to work with the actual mathematical expression for the dose–response relationship.

4.3.3. Slope and dose–effect level

In practice, the incidence of severe adverse effects is generally very much lower than the frequency of tumour control. As a consequence, γ_{50} is often not a very meaningful parameter for characterizing the slope at a lower response level. For example, in the case of $\gamma_{50} = 4$ for severe adverse effects, the γ value for an effect occurring in 5% of the cases, γ_{05}, is 0.62, or about 7 times lower than γ_{50}, and hence the relative steepness of the dose–response curve for tumour and normal tissues are reversed, assuming that tumour control is between 15% and 90%, and γ_{50} for the tumour control curve is 2. Table 1 tabulates local γ values for a range of response levels for dose–response curves with varying steepness.

The γ value for other combinations of response level and γ_{50} may be found by bivariate interpolation in the table.

TABLE 1. LOCAL γ VALUE AS A FUNCTION OF γ_{50} AND THE RESPONSE LEVEL FOR A LOGISTIC DOSE–RESPONSE CURVE

	Response level											
γ_{50}	5%	10%	15%	20%	30%	40%	50%	60%	70%	80%	85%	90%
1	0.05	0.16	0.29	0.42	0.66	0.86	1.00	1.06	1.02	0.86	0.73	0.56
2	0.24	0.52	0.80	1.06	1.50	1.82	2.00	2.02	1.86	1.50	1.24	0.92
3	0.43	0.88	1.31	1.70	2.34	2.78	3.00	2.98	2.70	2.14	1.75	1.28
4	0.62	1.24	1.82	2.34	3.18	3.74	4.00	3.94	3.54	2.78	2.26	1.64
5	0.81	1.60	2.33	2.98	4.02	4.70	5.00	4.90	4.38	3.42	2.77	2.00

This table also produces a useful, albeit informal, impression of the validity of the linear approximation (Eq. (6)) to the dose–response curve: over a range of response levels, where the local γ values are roughly constant, the linear approximation is likely to give a satisfactory accuracy.

4.3.4. Constant dose per fraction versus constant number of fractions

If the dose–response slope is generated by using increasing numbers of equal sized fractions then, in this case, one of the benefits of using the γ parameter is that it is independent of fraction size. However, the steepness of a dose–response curve is greater if the data are generated by varying the dose while keeping the number of fractions constant, rather than by varying the number of fractions using a fixed dose per fraction. Intuitively, this is a consequence of Withers' 'double trouble' effect [79]: as dose is increased and fraction number is kept constant, the dose per fraction also increases. Thus, the dose–response curve will be steeper in this situation. The notation $\gamma_{N,50}$ is used to indicate the response level, in this case 50%, with the N indicating that the number of fractions is fixed. The relative steepness of the dose–response curve generated with a fixed number of fractions γ_N compared with that of a curve generated with a fixed fraction size, γ_d, depends on the α/β ratio as well as the dose per fraction, d_r, at the relevant point of the curve [80]:

$$\gamma_N = \gamma_d \frac{\alpha/\beta + 2d_r}{\alpha/\beta + d_r} \quad (7)$$

In practical radiotherapy, the number of fractions is generally fixed by the treatment prescription. As can be seen below, in many situations, the accuracy requirements in radiotherapy depend directly on the steepness of the dose–response curve — but the relevant steepness will be that of the dose–response curve with a fixed fraction number. One implication of the fraction–size dependence of γ_N is that the patient level accuracy requirement will increase for a hypofractionated regimen, albeit relatively modestly. For late responding normal tissue with a high fractionation sensitivity, e.g. $\alpha/\beta = 2$ Gy, the relative change in γ_N (and hence in required accuracy) when increasing dose per fraction from 2 Gy to, for example, 5 Gy, is only 14% and this value approaches 33% at very high doses per fraction [80].

4.3.5. Slopes of dose–response curves

Bentzen and Overgaard estimated and summarized values for γ_{50} pertaining to tumours and normal tissues [78, 80, 81]. Dose–response curves for late normal tissue end points tend to be steeper (Fig. 7), with typical γ_{50} values ranging from 2 to 6, than the dose–response curves for local control of squamous cell carcinoma of the head and neck (Fig. 8), which have typical γ_{50} values between 1.5 and 2.5. For illustrative purposes, values of 4 and 2, respectively, are sometimes used in these cases. Although recent overviews such as the QUANTEC reviews (quantitative analysis of normal tissue effects in the clinic) [16, 82] have summarized a considerable amount of new clinical data for many normal tissue end points, these general estimates still hold.

There are a few important caveats regarding published steepness estimates. Firstly, series with considerable heterogeneity in patient and tumour characteristics as well as dosimetric heterogeneity will show a larger variability in response between patients, and this will make the dose–response curve shallower (see Section 4.3.6). Secondly, γ_{50} estimates from randomized controlled trials of dose escalation in radiotherapy for prostate cancer were found to be statistically significantly lower than estimates from retrospective case studies [83]. This is most likely the result of several types of bias in non-randomized studies, as discussed by Diez et al. [83]. As most current γ value estimates arise from non-randomized designs, this is an important limitation to our current knowledge. Thirdly, the apparent γ value for adjuvant radiotherapy will typically be much lower than that estimated from the definitive setting; an example is post-operative whole breast irradiation for breast cancer [84]. This is probably not primarily a

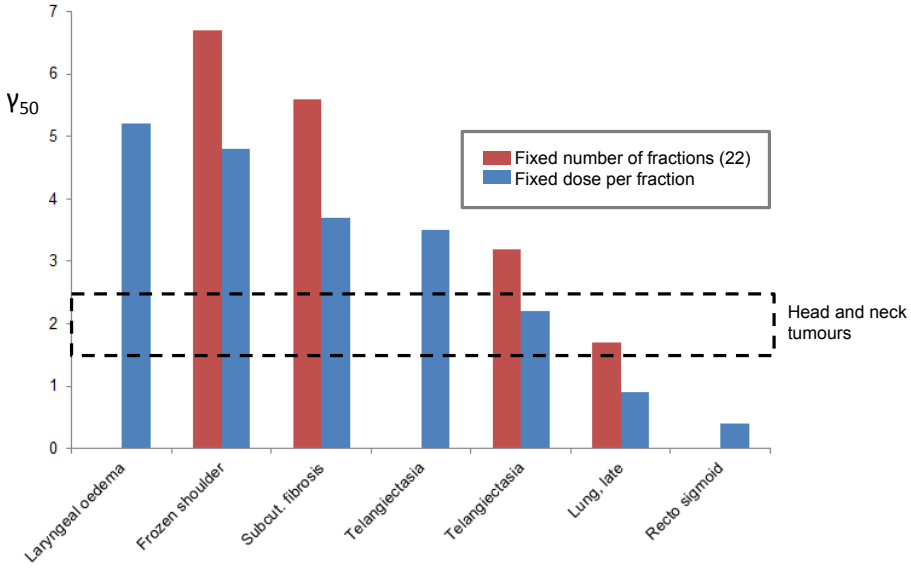

FIG. 7. Estimated γ values for various late normal tissue end points. Estimates are shown both for treatment with a fixed dose per fraction and for a fixed number of fractions. The shaded horizontal band corresponds to the typical values at the point of maximum steepness for dose–response curves with head and neck tumours. (Adapted from Ref. [78].)

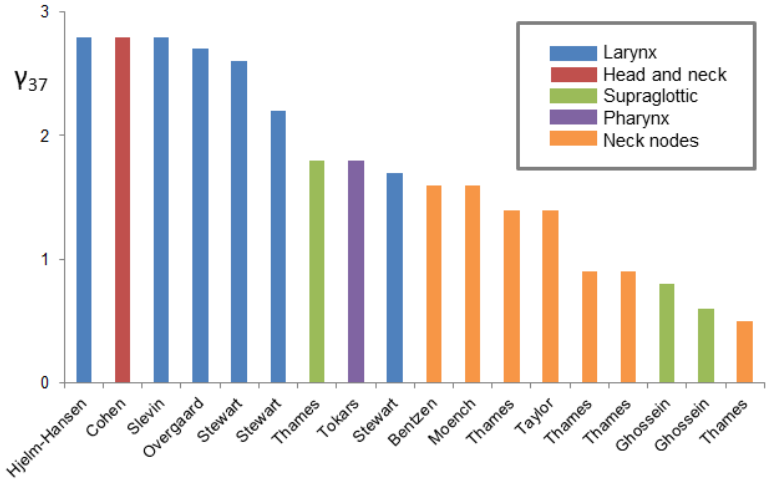

FIG. 8. Estimated γ values from a number of studies on dose–response relationships for squamous cell carcinoma in various sites of the head and neck. Note that the relative difference between γ_{37} on the ordinate and γ_{50} as used in the present calculations is less than 4% over the range of many of the clinical values. (Adapted from Ref. [78].)

consequence of heterogeneity among patients but results from the fact that a large proportion of the irradiated individuals have no residual cancer at the time of therapy; for a discussion see Yarnold et al. [76].

4.3.6. Patient to patient variability and stratification

Patient to patient variability in response to radiotherapy will cause the population dose–response curve to become shallower [85–88]. A direct demonstration of this effect in experimental animal tumours was provided by Khalil et al. [89]. Levegrun et al. [90] showed how stratification for risk group increased the steepness of the dose–response curve for biopsy outcome after radiotherapy for prostate cancer from $\gamma_{50} = 2.9$ to $\gamma_{50} = 3.4–5.2$ after stratification, when analysing the whole population. A similar effect of stratification has been seen for normal tissue end points. For example, Honore et al. [91] found that the dose–response curve for sensorineural hearing loss after radiotherapy for nasopharyngeal carcinoma was relatively shallow, with $\gamma_{50} = 0.7$ (with 95% confidence limits 0.2 and 1.2). However, in a multivariate model, adjusting for patient's age and pretreatment hearing level, a steeper dose–response curve was estimated: $\gamma_{50} = 3.4$ with 95% confidence limits 0.3 and 6.5. All of this means that in a relatively heterogeneous population, a reduced accuracy will have relatively less impact than uncertainty at the individual patient level. However, in a relatively homogeneous population, as might be found in a clinical trial with specific eligibility requirements, a reduced accuracy may have a greater impact.

4.4. THE INFLUENCE OF ACCURACY ON TREATMENT OUTCOME

A comprehensive analysis of evidence based accuracy requirements is beyond the scope of this publication. Instead, it will demonstrate how various components of accuracy affect therapeutic outcome in selected examples. By doing so, the aims are twofold: (1) to provide an insight into how different types of inaccuracy affect outcome and (2) to provide a general impression of the required level of accuracy in radiotherapy.

4.4.1. Bias in delivered dose

The simplest case, and indeed the case considered in most of the literature in the 1970s and 1980s, is a systematic bias, i.e. a systematic deviation between prescribed and delivered dose in a whole population of patients. This could be introduced at multiple levels, e.g. errors in machine output calibration, inaccurate beam data in a TPS, imprecision in co-registration of treatment planning data

and actual patient geometry. The net effect of all these factors on the delivered dose in a population of (identical) patients treated on a specific machine with a specific beam energy, treatment planning software etc. is represented by the component b in Eq. (1). Estimating the effect on outcome is straightforward: a bias b in dose delivery will give rise to a change in the probability of a specific treatment outcome, ΔP, given by Eq. (6):

$$\Delta P = \gamma_x \frac{b}{D_I} \tag{8}$$

where D_I is the intended dose and x is the NTCP or TCP after that dose.

As an example, assume that γ_{50} for tumour control is 2, and a 30% TCP is expected for a given patient; using Table 1, γ_{30} is 1.5. A bias resulting in the delivery of a 5% lower dose than intended, that is, $b/D_I = -5\%$, will result in a $\Delta P = -7.5$ percentage points. Or, put differently, the TCP will be reduced from 30% to 22.5%, a clinically significant decrease.

Similarly, for a normal tissue with $\gamma_{50} = 4$ and an incidence of grade 3 oral mucositis of 70%, $\gamma_{70} = 3.54$. A 5% over dosage, i.e. $b/D_I = +5\%$ will increase the mucositis risk by 18%, i.e. from 70% to approximately 88%. This is approaching the range where the linear approximation starts to break down. For a relatively rare side effect, e.g. grade 4 mucositis with an expected NTCP of 5%, $\gamma_{05} = 0.62$, ΔP becomes 3%, i.e. the risk increases from 5% to 8%.

Systematic bias in delivered dose should be minimized as far as reasonably achievable. This kind of inaccuracy affects a large population of patients. In case of overdosage, the risk of adverse effects increases rapidly, especially for relatively frequent normal tissue effects. This will also be the case for vulnerable patients, i.e. patients with comorbidities or other factors increasing the risk of side effects. While these patients will have a theoretical advantage in terms of tumour control probability, any attempt to improve tumour outcome should clearly come from a rational clinical decision to escalate dose rather than as a consequence of an (unknown!) inaccuracy in treatment planning and delivery.

The exact conversion of bias into change in treatment outcome depends on the risk of side effects, probability of tumour control and the steepness of the underlying dose–response curve. Some side effects will vary in terms of the γ_{50} of the underlying dose–response curve and in incidence for a given dose — and therefore in the local γ_x. No hard rule can be given as this will be a continuum of effects, but in view of the relatively marked change in response rates it is reasonable to strive for accuracies in systematic bias in the order of 1–2%.

4.4.2. Random uncertainty in delivered dose

The effect of a random deviation between intended and delivered dose, ε in Eq. (1), is very different from a systematic bias. By definition, the mean value of ε in a population of patients is zero; if it were different from zero, that component of the variation would be included in the b term in Eq. (1). Intuitively, this means that the probability of erring on the 'hot' side will be balanced by the probability of erring on the 'cold' side. For simplicity, we make the — generally quite reasonable — assumption that ε has a normal distribution with mean zero and variance σ_D^2. The variance can usefully be decomposed as in Eq. (2) into a patient level or baseline variation and a fraction to fraction variation. Uncertainty, arising during delivery of each fraction, will again have a zero mean and will tend to cancel out even in the individual patient as the number of fractions increases. An example of a patient level inaccuracy could be an inaccuracy in a patient's anteroposterior diameter for a parallel opposed field technique measured at the time of simulation. This would affect the dose delivered during the whole course of radiotherapy (if the possibility of a systematic change in anterior-posterior (AP) diameter during therapy is disregarded). But it will randomly vary from patient to patient and have a mean value of zero over a large sample of patients. A fraction level uncertainty could be variation in the actual daily SSD for an SSD based technique. Clearly, this variation would result in a random sequence of positive and negative deviation of a given magnitude from fraction to fraction. This variance component will decrease inversely with the number of fractions, N, which is to say that the standard deviation will decrease with the square root of N. This is one reason why fractionation schedules employing a large number of fractions are inherently more 'forgiving' than schedules treating in fewer fractions. Of course, the chance of having patient changes with longer times is larger for schedules with more fractions and longer overall treatment times.

If the dose–response relationship were linear, or, as is the case around the 50% response level, if the approximation of the dose–response curve by the tangent of the curve were valid over the range of uncertainty (i.e. a range corresponding to, e.g. $\pm 3x\sigma_D$), the positive and negative deviations would balance out from patient to patient and indeed, for a single patient, from fraction to fraction. It follows from this argument that the response level where the effect of random deviations would be largest is where the curvature of the dose–response curve is maximal, i.e. near the foot and the top of the curve. Intuitively, if one looks at the foot of the curve, this is because the right hand tail of the distribution of deviations will move up the dose–response curve, resulting in a larger gain in response than the corresponding change from moving down the curve as a result of deviation in the left hand tail.

Formally, the response probability in the presence of a random deviation in delivered dose, $\tilde{P}(D)$, is the convolution of (*N*)TCP(*D*) with a normal distribution with mean *D* and standard deviation σ_D:

$$\tilde{P}(D) = \int_{-\infty}^{\infty} (\mathrm{N})\mathrm{TCP}(x) \cdot nd(D, \sigma_D; x)\, \mathrm{d}x \tag{9}$$

where $nd(D, \sigma_D; x)$ is the normal distribution density function evaluated at dose *x*.

Figure 9 shows how increasing variability in the delivered dose will lead to a decrease in TCP at the point of the curve where the effect is largest. For a dose–response curve with γ_{50} = 1.8, which is a typical value for unselected head and neck cases, even a 10% patient-level standard deviation of ε will lead to <3% loss of tumour control in a population of patients. In well stratified patient populations where γ_{50} may be around 4, the standard deviation of ε will have to be <5% in order to ensure < 3% loss of tumour control owing to patient to patient variability in dose delivery.

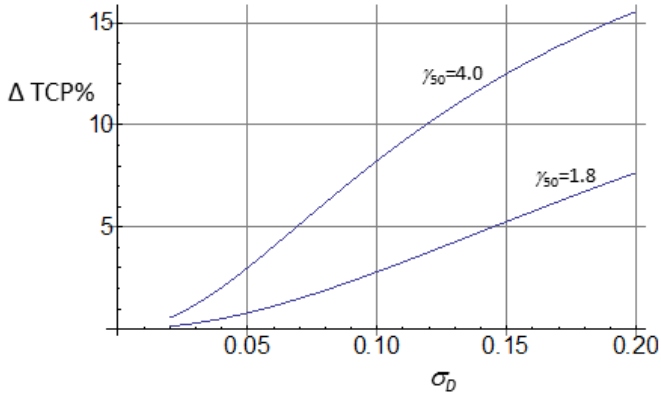

FIG. 9. Loss of tumour control probability with increasing random deviation between intended and delivered dose for two dose–response curves with differing steepness. The calculation is performed at the point of maximum curvature of the dose–response curve corresponding to a TCP of 79%. σ_D is the standard deviation of ε.

For normal tissue complications, the maximum effect of random variation in delivered dose will be seen at the foot of the dose–response curve, corresponding to an NTCP of 21%. Again, as we are operating on a dose–response curve

delivering treatment with a fixed number of fractions, γ_N is the relevant steepness measure. For normal tissues this can be as high as 4–6 in clinical series. In this case, if we aim to limit the increase in toxicity to <3%, we would need to keep σ_D at <5% and <3% for γ_{50} equal to 4 and 6, respectively (see Fig. 10).

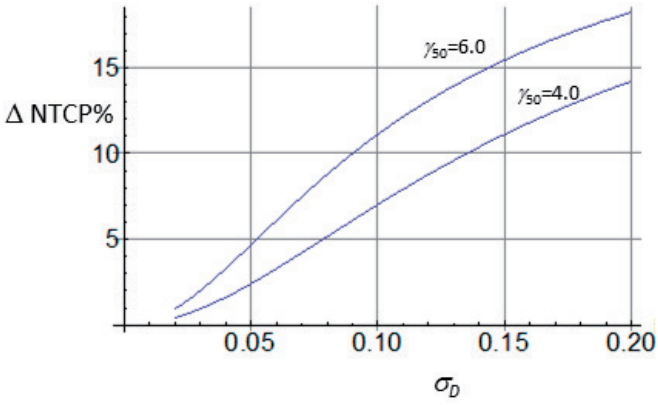

FIG. 10. Increase in normal tissue complication probability with increasing random deviation between intended and delivered dose for two dose–response curves of differing steepness. The calculation is performed at the point of maximum curvature of the dose–response curve corresponding to an NTCP of 21%. σ_D is the standard deviation for ε.

Also, in the case of random deviations between intended and delivered dose, it is difficult to provide a rational, hard constraint on required accuracy. Several parameters enter the calculation, in particular, the steepness of the underlying dose–response curve and the local response level being considered. To ensure a reasonably low loss of tumour control and increase in toxicity, a reasonable target would be to aim for a σ_D <5% in random uncertainty. In well stratified patient populations, such as those that may be found in clinical trials, this limit should probably be tightened to σ_D <3% to meet a 3% maximum deterioration of outcome.

4.4.3. Geometrical uncertainty in treatment delivery

Relatively little research has been performed on the clinical effect of geometrical uncertainties in radiotherapy. Tomé and Fowler [92] considered the effect of cold spots based on a population heterogeneity model. Again, a full treatment of this issue is beyond the scope of this publication, but a simple

formulation based on the dose–response curve and an assumption of statistical independence of the TCP in two separate tumour subvolumes is the following:

$$\Delta P = P(D) - P(D)^{1-\Delta V} P(D - \Delta V)^{\Delta V} \tag{10}$$

where ΔV is the fractional volume (taking values from 0 to 1) and ΔD is the dose missed owing to geometrical uncertainty. If model parameters are selected to reflect clinical dose–response relationships, this simpler model produces estimates in rough agreement with Tomé and Fowler's model. The penalty for missing a certain number of the fractions or, equivalently, a percentage of the prescribed dose will again depend on the steepness of the dose–response curve and will attain its maximum at the steepest part of the curve. Intuitively, this is because missing, for example, 3 out of 35 fractions will lead to a reduced dose to a subvolume of the tumour, but in this case there is no compensation from the remaining 32 fractions.

Also in this case, the number of degrees of freedom is large, and it is impossible to come up with a hard constraint on the required geometrical accuracy when delivering radiotherapy. However, aiming again for <3% loss in TCP, the volume receiving less than 90% of the planned dose should be kept to <12% and <6% for γ_{50} = 1.8 and 4.0, respectively (see Fig. 11).

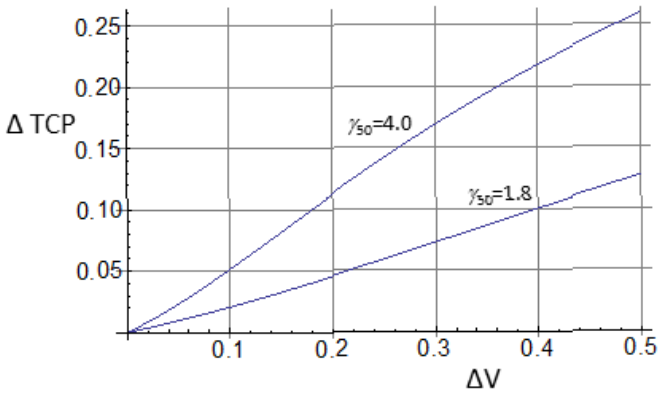

FIG. 11. Loss of TCP from missing 10% of the prescribed tumour dose to varying fractions of the target volume for two dose–response curves of differing steepness. The calculation is performed at the 50% response level where the steepness of the dose–response curve is maximal.

The above results are summarized in Table 2. A dosage bias of a few per cent, slightly larger concerning NTCP than regarding TCP, causes a change in both end points by 3 percentage points. This amount may be about the maximum acceptable clinically, especially for late adverse events. Also, if hypofractionation were to be used (a fixed number of fractions higher than 2 Gy), those dosage biases are slightly smaller for the same 3% change in effect because the dose–response curves are steeper.

TABLE 2. DOSAGE/VOLUME UNCERTAINTIES ARISING FROM DIFFERENT SOURCES, RESULTING IN <3% LOSS IN TCP OR <3% INCREASE IN NTCP, CALCULATED USING GENERIC MODEL PARAMETER VALUES

Source of uncertainty	Dosage/volume uncertainties resulting in:	
	<3% loss in TCP from TCP = 30% (γ_{50} = 1.8, γ_{30} = 1.5)	<3% increase in NTCP from NTCP = 5% (γ_{50} = 4.0, γ_{05} = 0.62)
Dosage bias, using 2 Gy fractions	<2% less dose	<5% more dose
Dosage bias, using 3 Gy/fraction hypo (fixed *N*)	<1.5% less dose (α/β = 10 Gy)	<3% more dose (α/β = 2 Gy)
Random uncertainty in delivered dose	σ_D < 10% (σ_D < 5% in well stratified patients, γ_{50} = 4.0)	σ_D < 5% (σ_D < 3% in well stratified patients, γ_{50} = 6.0)
Volume receiving <90% of planned dose	<12% of volume (<6% if γ_{50} = 4.0)	—

A random uncertainty in delivered dose has a greater effect in patient groups that are better stratified, because dose–response curves are also steeper in this case. Present evidence indicates that about a twofold reduction in the variability of dose delivery would have the same changes of effect in such groups compared with less well stratified patient groups.

Regarding the required accuracy of dose delivery in relation to tolerance for late adverse events, the feature of the minimum 1:1 association ($\sigma_D \leq x\% : \leq x\%$ effect) for conventional fractionation with well stratified patients should probably

be used as a basis. The accuracy of delineation of tumour volumes with respect to dose distributions is another important issue (as discussed in Section 5.1).

It should be emphasized that the present calculations are based on generic values of dose–response slope and fractionation sensitivity. There are marked differences in parameter values between specific tumour types and sites (as can be seen in Figs 7 and 8) and this will modify some of the present conclusions in particular cases. Furthermore, it needs to be noted that the above modelling is interesting for determining trends in assessing the impact of treatment related uncertainties. Recent work by Moiseenko et al. [93] where they compare radiobiological parameter determination for four different models found that statements regarding normal tissue radiosensitivity and steepness of dose–response, based on model parameters, should be made with caution as the latter are not only model dependent but are also sensitive to the range of complication incidence data exhibited by the clinical data.

Further discussion of the radiobiological principles involved in clinical treatments and their accuracy can be found: (a) regarding the heterogeneity and detriment of treatment interruptions, in Section 6.5.3; (b) on resistant hypoxic areas of tumours, in Section 5.2.1; (c) on OAR volumes and slopes of dose–response curves, in Section 5.2.4; and on the need for radiobiological models that calculate TCP and NTCP in commercial planning systems, in Section 7.5.

4.5. STATISTICAL CONSIDERATIONS OF THE ACCURACY NEEDED IN CLINICAL STUDIES

When designing clinical trials, sample size is an important factor — the ability to detect a difference in outcome in two arms is dependent on the number of patients in the trial. Furthermore, the level of treatment accuracy will impact the steepness of the measured dose–response curve, with lower accuracy resulting in a shallower curve, which in turn results in the need for more patients in the trial to detect a significant difference in results. Orton et al. [94] have evaluated the difference in the number of patients required in two-armed clinical trials and its dependence on the level of uncertainty in delivered dose. This study concluded that 60% more cancer patients would be required for a dose escalation lung study if no corrections were made for lung density (creating an uncertainty in dose delivery of 10–20%) compared with a study incorporating inhomogeneity corrections (reduced uncertainty of ~5%).

In 1994, Bentzen [78] reviewed some general problems in calculating the required number of patients in a trial with a radiobiological rationale. One crucial factor he found in calculating the size of a trial is the steepness of the dose–response curve for both tumours and normal tissues. He concluded that fairly

large trials, typically comprising 300 or more patients, are necessary, unless efficient stratification of the patients is possible according to the risk for some specific type of recurrence.

In 2008, Pettersen et al. [95] investigated the impact of appropriate dosimetry QA on the patient number required in radiotherapy randomized controlled trials. The steepness of clinical dose–response curves, γ_{clin}, was calculated by convolving a biological dose–response distribution and the distribution of technical and dosimetric factors. Population size calculations were performed, taking into account the γ_{50} and expected difference in outcome between two arms of a randomized clinical trial, for different levels of variation in dose to the patient population. They found that uncertainties in dose reduce the γ_{50} to the greatest extent when the initial gamma value is high, and to a lesser extent for low gamma values. Table 3 shows that the impact of increasing the uncertainty in dose on the clinically derived gamma value, γ_{clin}, is more pronounced if the underlying biological gamma value, γ_{biol}, is larger.

TABLE 3. OBSERVABLE γ_{CLIN} VALUES
(from Pettersen et al.[95])

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

Note: The calculation assumes an underlying γ value that is characteristic for the patient population and not influenced by variation in the technical and dosimetric parameters.

Figure 12 shows the number of patients required in each arm of a randomized controlled clinical trial as a function of increasing steepness of the clinical dose–response curve. Reduced uncertainty in dose leads to a significant reduction in the number of patients required in a clinical trial if the expected difference between the experimental and conventional arm is small. The reduction in patient numbers is smaller when the differences between the conventional and experimental arm are larger. Thus, the number of patients required in a randomized clinical trial may be reduced by introducing appropriate dosimetry QA, since the risk of underpowering the study is minimized. Clearly, dosimetry QA and minimizing uncertainties in clinical studies is cost effective.

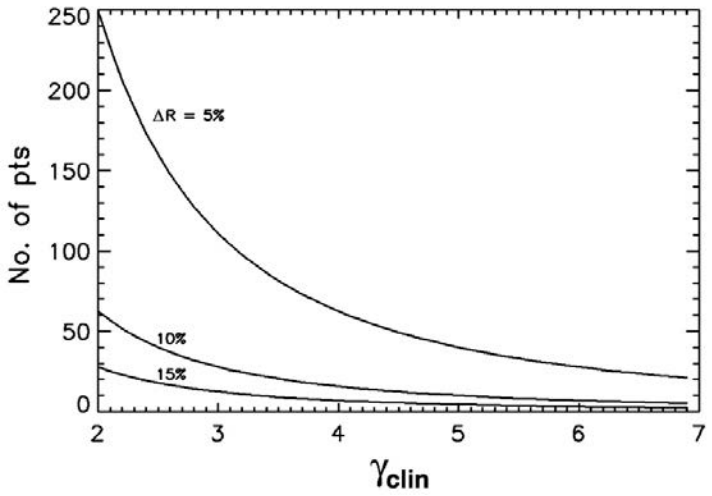

FIG. 12. The number of patients (pts) required in each arm of a randomized controlled clinical trial calculated for various response differences and for increasing steepness of the clinical dose–response curve, γ_{clin} (from Ref. [95]).

4.6. SUMMARY

— This section discusses the radiobiological framework for making rational decisions on the required level of accuracy in radiotherapy.
— Dose–response curves describe the relationship between dose and the incidence of a specific type of radiotherapy end point, be it tumour or normal tissue related.
— For demonstrative purposes, a logistic expression is used to model the dose–response relationship with parameters γ_{50} and D_{50}, i.e. the normalized dose–response gradient and the dose to generate 50% response, being parameters to generate fits to the clinical data. The normalized dose gradient (or the steepness of the dose–response curve), γ, represents the absolute change in response, in per cent, for a 1% change in dose anywhere along the dose–response curve, e.g. at 50% response (γ_{50}).
— Summary data are provided for γ_{50} and show that late responding normal tissues have a steeper γ_{50} (2–6) compared with tumours (1.5–2.5). Quite often, values of 4 and 2, respectively, are used for illustrative purposes.
— Caveats regarding published steepness estimates include:
  • Patient series with heterogeneity in patient, tumour and dose characteristics will result in shallower dose–response curves.

- Bias in non-randomized studies appears to yield higher γ_{50} values compared with randomized studies.
- γ values for adjuvant therapy are much lower than those derived from a definitive setting.

— In a relatively heterogeneous population, reduced accuracy will have relatively less impact than uncertainty at the individual patient level.
— Selected examples are used to illustrate how different types of inaccuracy affect outcome, and a general impression of the required accuracy in radiotherapy is given.
— While no simple hard rules can be given, the modelling shows that it is reasonable to strive for accuracies in systematic bias of 1–2%.
— For random uncertainties, the modelling shows that if we aim to limit the increase in toxicity to <3% we would need to keep the dose uncertainties (σ_D) to <5% and <3% for γ_{50} equal to 4 and 6, respectively.
— To ensure a reasonably low loss of tumour control and increase in toxicity, a reasonable goal would be to aim for a <5% in random uncertainty (σ_D). In well stratified patient populations, such as might be found in clinical trials, this limit should probably be tightened to σ_D <3% to meet a 3% maximum deterioration of outcome.
— Based on modelling of geometric uncertainty, aiming for <3% loss in TCP, the volume receiving <90% of the planned dose should be kept at <12% and <6% for γ_{50} = 1.8 and 4.0, respectively.
— The number of patients required in randomized controlled clinical trials is strongly dependent on the steepness of the dose–response curve and the uncertainty in dose delivery, with trials that have larger uncertainties requiring many more patients.

5. CLINICAL FRAMEWORK FOR CONSIDERING ACCURACY REQUIREMENTS

The evidence supporting a clear link between radiotherapy dosimetric and volumetric quality and common measurable clinical outcomes for tumour and normal tissue end points is relatively limited. In 1993, Dische et al. [96] reported that in head and neck cancer, dose differences as small as 5% may compromise tumour cure and normal tissue morbidity (note that this was 2-D dose reporting). They urged the use of consistent international reporting guidelines for dose accuracy in order to provide a credible international evidence base. In the first decades of the twenty-first century, the ability to display and report accurate

3-D dosimetric datasets, the development of harmonized scoring systems for toxicity and the conduct of high quality Phase II and III trials have made possible the collection of evidence that accurate, high quality radiotherapy positively influences clinical outcome.

The aim for any treatment course for any given patient is to maximize the probability of an optimal outcome and minimize the probability of a sub-optimal outcome due to failure to control the tumour and/or OAR complications. Producing the best outcomes for individual patients (irrespective of whether they receive a course of radiotherapy) requires careful adherence to the fundamental principles of good medical practice. Each patient should have a full history and examination, with particular reference to the oncological history, and to the genetic, social and emotional needs of the patient. Particular care must be given to viewing and understanding all appropriate imaging for that patient in a multidisciplinary environment, taking the surgical anatomy and surgical pathology into consideration. It is only after integrating all these factors that a radiotherapy care plan can be formulated and presented to the patient and the radiotherapy team. The radiation oncologist in charge of the case must take ultimate responsibility for the care plan, the radiotherapy prescription and the institutional guidelines on which they are based. This should be embedded in a clearly defined governance and QA structure covering the entire team involved in patient care.

There are a large number of non-malignant medical conditions that impact on both tumour and normal tissue radiation responses and affect the patient's own physiology and response to any given course of radiotherapy or chemoradiotherapy [97]. For example, the use of neoadjuvant hormone therapy and high dose radiotherapy in men with localized prostate cancer has significant implications for their cardiovascular health and the development of metabolic syndrome [98]. A number of groups have now begun to routinely include a variety of medical, physiological and surgical factors in predictive nomograms for radiotherapy outcomes [99, 100]. Sometimes, seemingly routine medications such as anticoagulants can impact on radiotherapy normal tissue toxicity [101]. In the practice of clinical oncology, managing these risks for various types of outcome in the individual patient is more complex than following guidelines or simply evaluating a dose distribution, nomogram or hazard ratio in isolation [99, 100, 102–104]. Radiotherapy outcome should be conceptualized as resulting from a matrix of probabilities, each with a given temporal risk function. For example, acute and late reactions have differing time density curves and should always be assessed in actuarial, or cumulative terms, or both, rather than as crude risks (see Section 4.3) [105, 106].

5.1. MEDICAL ASPECTS: HARMONIZING CLINICAL DATA

The exchange of relevant information is essential for any progress in cancer therapy. Selection of the treatment modalities is based to a large extent on the comparison of the previous results and results from other centres (local control rates and side effects). This is particularly important when altering protocols, modifying techniques, introducing new techniques or when performing a combination of these. These medical aspects for reporting are often underestimated or neglected. To avoid bias in recruitment, international staging systems such as the Union for International Cancer Control's TNM cancer staging system should be used [35]. The impact of potential bias in recruitment is illustrated in Fig. 13.

To assess, compare and avoid bias in the evaluation of outcome, international scoring systems for toxicity (e.g. EORTC-RTOG, Common Terminology Criteria for Adverse Events [68, 70]) should be used. Prescription and treatment delivery should be reported, published and described in a way that can be interpreted and understood by the general community. This means an agreement on several definitions, concepts and terminology. The ICRU has been involved for several decades in a constant effort towards harmonization in reporting treatments in order to facilitate a useful exchange of information [17–21, 107]. Accuracy in radiotherapy implies not only accuracy in absorbed dose evaluation at reference points and volumes (dose level) but also accuracy in

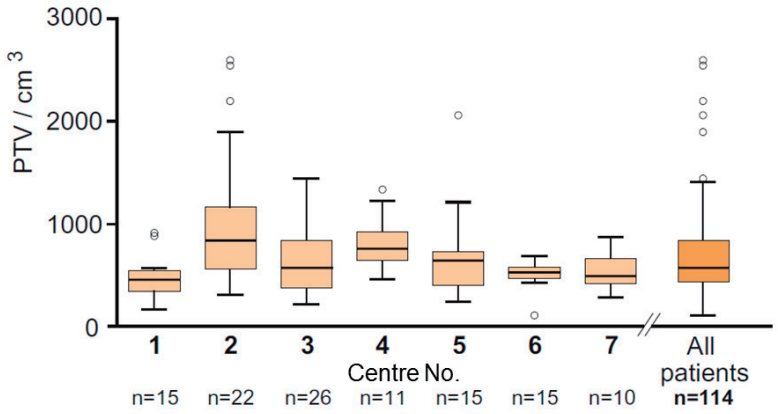

FIG. 13. Box plot illustrating the variation in PTV size in 114 patients recruited from 7 centres participating in a non-small-cell lung cancer (stage III) trial. There is a clear systematic difference between centres, presumably due to patient selection bias and different interpretation of the definition of the PTV by the radiation oncologists. Key: PTV, planning target volume. (Reproduced with permission from ICRU Report 71 [19].)

the specification and delineation of the relevant volumes. Inter- and intraclinician variation in target volume delineation was first quantified in the 1990s [108]. This is a crucial, extensive topic and full coverage of it is beyond the scope of this publication. The causes for this variation are numerous and range from the inherent biological variation in metastatic disease patterns [109] to local institutional policies (e.g. Fig. 13). Although the concept of GTV itself is simple and straightforward, accurate delineation of the GTV may be difficult for obvious pathological reasons (lack of clear borders). As a consequence, different observers may define different contours (Fig. 14).

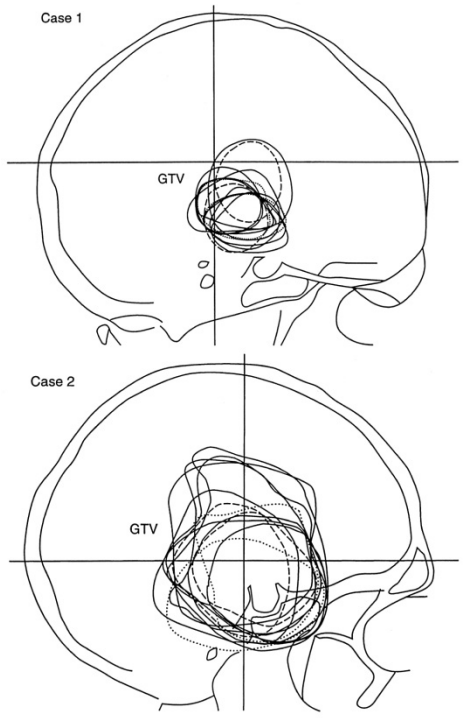

FIG. 14. Schematic drawings on lateral radiographs for two patients with brain tumours, where the GTV was delineated by: 8 radiation oncologists (solid line), 2 radiodiagnosticians (dotted line), 2 neurosurgeons (dashed line). (Adapted from Ref. [110].)

No consistent terminology has yet been developed to measure and report inter- and intraclinician variability. A wide variety of qualitative and quantitative descriptors have been used [111–122]. A sample of these descriptors includes:

— Simple volumetric measures;
— Concordance and disconcordance measures;
— Dissimilarity coefficients;
— Conformity indices;
— Dose–volume population histogram measures;
— Polar coordinate measures.

There is a need for consensus of terminology and methods in this area.

5.2. VOLUMES IN RADIOTHERAPY: CONCEPTS, DEFINITIONS AND TERMINOLOGY

A series of ICRU reports on "prescribing, recording and reporting" external photon, electron, IMRT and proton beam therapy were published between 1993 and 2010 [17–21]. They contain fundamental and well accepted terms and concepts. Similar reports have been published on dose and volume specifications for reporting intracavitary therapy in gynaecology [123] and interstitial therapy [124]. Important modifications are continuously introduced in practice because of developments in engineering, computer technology and imaging, but also owing to improved radio-oncological and radiobiological understanding.

In these sections on oncological and radio-oncological volume concepts, three groups of volumes are identified: (1) general oncological volumes, (2) radiation oncological volumes related to the target and (3) volumes related to normal tissues.

The general oncological volume concepts include the GTV and the CTV; they are based on general clinical oncological principles and are applicable to all forms of cancer therapy. For radiotherapy, it is important for several reasons not to let the intended irradiation technique affect how the GTV and CTV volumes are delineated. For example, it is essential to be able to compare and evaluate various treatment techniques for a given CTV. In precision radiotherapy, tumour volumes are often repeatedly imaged during therapy to allow for the adjustment of the volume to be treated, which is often referred to as adaptive therapy. Either anatomical, e.g. CT or MRI, or functional, e.g. MRI or PET, imaging is used. A subscript should indicate at what dose level or time and by which imaging or clinical modality the GTV was determined, e.g. $GTV_{30Gy,\ PET}$. For OAR typical morbidity end points are defined which require specific volume definitions.

This approach is consistent with the growing tendency towards comprehensive cancer diagnosis and treatment centres combining the different diagnostic and therapeutic strategies and modalities of surgery, chemotherapy and radiotherapy. The final aim is to use a comprehensive approach to control the disease in the GTV and the overall CTV (local, regional and distant spread) taking into account adverse side effects and impairments in quality of life. Such a comprehensive approach requires common terminology, concepts and definitions for diagnosis and staging, treatment strategy and evaluation of outcomes. In this publication the definitions of GTV and CTV proposed in ICRU reports for EBRT are further elaborated for the general adaptive treatment approach with the introduction of rGTV and adaptive CTV.

The PTV and the PRV are concepts introduced to ensure that the absorbed doses delivered to the corresponding GTV or rGTV, the CTV or the adaptive CTV and the OAR match the prescription constraints. In contrast to the GTV and CTV, selection of the PTV depends largely on technical aspects of the various radiation modalities.

5.2.1. Oncological volume concept: the gross tumour volume

The initial GTV is the gross demonstrable extent and location of the tumour at diagnosis, before any radiation treatment has been given. ICRU Report 83 [21] states that:

> "the GTV may consist of a primary tumour (primary tumour GTV or GTV-T), metastatic regional node(s) (nodal GTV or GTV-N), or distant metastases (metastatic GTV, or GTV-M). Typically, different GTVs are defined for the primary tumour and the regional node(s). But in some particular clinical situations, it might well be that the metastatic node cannot be distinguished from the primary tumour at diagnosis, e.g. a nasopharyngeal undifferentiated carcinoma infiltrating postero-laterally into the retropharyngeal space, including possible infiltrated nodes. In such situations, a single GTV encompassing both the primary tumour and the node(s) may be delineated [for the primary radiochemotherapy.]"

This single GTV approach may be adapted during the course of treatment according to the response of both the macroscopic primary and nodal tumour.

For a complete and accurate GTV and stage definition, it is necessary to specify the tumour location, its extent in all dimensions, its volume and its growth pattern. As examples, for cancer of the cervix, this would include the parametria and pelvic wall, and for uterine corpus, the vagina and the adjacent organs. The dimensions and anatomical location of the GTV still form the major basis of the

TNM classification systems [35] and the World Health Organization (WHO) International Code for Disease in Oncology [125]. The stage classification represents a major prognostic factor.

Although the concept of GTV itself is straightforward, accurate delineation of the GTV may be difficult, mainly due to difficulties in discrimination between the malignant tumour and normal tissue.

5.2.1.1. The GTV and the investigation technique

Volumetric imaging such as CT, MRI and ultrasound has been the most commonly used imaging technique in radiotherapy to define the anatomical extent of the GTV, in addition to clinical examination, where feasible. More recently, PET/CT and functional MRI (fMRI) have been increasingly introduced to add a functional dimension into the evaluation of the GTV.

As different examination methods may produce different GTVs, as has been reported for CT, MRI and PET [126, 127], the method(s) used to delineate the GTV have to be specified and reported. Therefore, it is recommended to link the GTV designation to the modality of imaging used, e.g. GTV_{CT}, GTV_{MRI}, $GTV_{PET/CT}$, as already proposed in ICRU Report 83 [21]. In disease sites that are directly accessible to endoscopic (light imaging), clinical examination, or both (e.g. head and neck or gynaecological sites), the GTV information may also be specified as $GTV_{endoscopy}$ or $GTV_{clinical}$. In general, any clinical imaging will lack the accuracy possible after surgery, where the assessment can be based on a pathological specimen.

5.2.1.2. Identification of functional sub-GTV(s)

The use of functional imaging with PET using various tracers, or with fMRI, can add functional aspects to the delineation of the GTV that may be likely to have an impact on the treatment outcome [128–131]. The identification of functional sub-GTV(s) will avoid the introduction of new or potentially confusing terminology, such as biological target volume or hypoxic target volume [132]. It may also be used as repetitive imaging, which could show the change in functional (sub)-GTV during the course of treatment. It is important that the method used to evaluate the size and shape of the sub-GTV be specified, as different imaging methods may result in different delineated sub-GTVs.

5.2.1.3. The composite GTV

The information provided by a given imaging method may be complementary to other imaging modalities as stated before, e.g. to MRI,

CT or clinical examination, or a combination of these. It is essential for the communication of oncological results to indicate the final GTV that has been used for planning the various forms of oncological treatments. If different methods for the definition of the GTV have been used to provide complementary information, the oncologist should use a composite GTV. This composite GTV ($GTV_{composite}$) is the GTV that has been used for the oncological treatment planning. The different imaging methods contributing to such composite definition should be described. As pointed out above, the dimensions of the GTV should be reported as comprehensively as possible, together with its topographical relationships. Analogue specifications can also be applied to the CTV corresponding to a given GTV (see Section 5.2.2).

5.2.1.4. Change in tumours during treatment: The initial GTV (iGTV) and the residual GTV (rGTV)

Radiotherapy, often combined with chemotherapy, takes place over an extended period of time, which results in a change of the tumour characteristics, dimensions, volume and topography, and allows for treatment adaptation (or 'boost' treatment), according to tumour response. It must be noted that the application of this principle to adaptive therapy, based on daily imaging, is currently an active area of research, and often the same terminology is used in studies investigating aspects of this issue.

For a considerable number of tumours, significant tumour response and regression have been observed during (the first weeks of) radiotherapy, and this may be even more enhanced during combined radiochemotherapy. While this clinical response has been known for a long time, it can now be better depicted and quantified by precise 3-D and 4-D repetitive CT and MRI, and, more recently, by functional imaging, e.g. PET/CT or MRI.

When the various tumour changes seem to be significant, it is suggested that the detectable tumour after a certain amount of treatment be called 'residual gross tumour volume' (rGTV). According to current evidence, e.g. from preoperative rectal cancer treatment (radiotherapy or radiochemotherapy) and consecutive surgery, such rGTV may contain macroscopic or microscopic disease, or even no disease. Analogous to the term GTV used at diagnosis, the term for clinical rGTV contains the attribution of macroscopic or gross malignant disease, which may be depicted by using the same clinical and diagnostic means. This makes an assessment of macroscopic tumour response possible. However, it is evident that the clinical validity of rGTV is less compared with initial GTV (iGTV) at diagnosis, which is established by biopsy.

To distinguish clearly between the proven GTV at the initiation of treatment and the residual volume after a certain amount of treatment, the concept of rGTV

is proposed as a specific terminology. The time and dose point during the course of treatment when this assessment is performed should be specified.

In addition to the changes to the whole GTV, parts of the GTV may resolve completely or change in appearance. After considerable treatment, these parts may no longer carry the major tumour characteristics noted at diagnosis, but may have become fibrotic, for example. These findings may be detectable by clinical means, by endoscopy or by imaging. An example of such typical imaging findings is a grey zone that had previously been signal intensive in the proximity of the iGTV.

5.2.1.5. Uncertainties in selection and contouring of initial GTV and residual GTV

Uncertainties in the selection and contouring of the GTV have been recognized for a long time for all tumour sites (see Section 5.1). The size and configuration of the GTV depend strongly on the method of investigation applied. The least variations in overall assessment are seen in patho histological investigations, which are indicated in the TNM classification [35] as, e.g. 'pT2' (for pathological macroscopic and microscopic tumour assessment). Any other form of clinical investigation results in more variation in clinical tumour assessment, indicated, for example, as 'cT2'. Furthermore, for different clinical investigations and imaging methods, a significant variation in precision can be observed, which results in different uncertainties for GTV assessment.

The amount of variation is mainly dependent on the tumour type and the method of investigation applied. In general, a gold standard for a certain type of clinical imaging for a given tumour is evident from clinical imaging and pathological studies. Such gold standards are accepted in the international scientific community according to the level of evidence provided. Their strengths and limitations are well recognized and may continuously change with progress in imaging. For example, within the context of head and neck and lung oncology, the various uncertainties for GTV assessment have recently been shown, comparing CT, MRI and PET/CT with the gold standard from pathological findings [133, 134]. GTV contouring comparisons have only been performed to a limited extent so far, and then mainly in the context of radiotherapy related research.

ICRU reports have been referring to differences between investigation methods at diagnosis for a long time, e.g. in ICRU Report 62 [18] when comparing pathological specimen and radiological imaging for breast cancer. With regard to rGTV and residual pathological findings during or after radiochemotherapy, the validity and reliability of clinical imaging is (even) less straightforward, with only limited pathological or clinical proof so far [135]. Major uncertainties exist in what has to be regarded as residual disease within the rGTV. Even more

uncertainties are observed with regard to the presence of residual microscopic disease in the area of adjacent residual pathological tissue. Much research is therefore needed to validate the assessment of the rGTV and the residual adjacent pathologic tissue, which will include morphological and functional imaging and, in the future, maybe also pathohistological mapping.

For future development of iGTV and rGTV orientated radiotherapy treatment approaches, the investigation and reporting of uncertainties in GTV assessment is needed. The evaluation and the reporting of systematic and random variations of iGTV/rGTV contouring are therefore encouraged both for iGTV/rGTV selection and for iGTV/rGTV contouring.

5.2.2. Oncological volume concept: the clinical target volume

The CTV is a volume of tissue that contains a demonstrable GTV and assumed subclinical malignant disease with a given probability. Following (radical) surgical resection, the CTV may contain only subclinical disease. The treatment aim may be cure or palliation but always includes considerations with regard to treatment related adverse side effects and impairments in quality of life.

The CTV, or parts of it, may be identified for treatment using surgery, radiotherapy or chemotherapy, or some combination of these modalities. This is a joint decision of the clinical oncology board. For defining the general cancer strategy and selecting the CTV for radiotherapy (alone or in combination), the type of malignancy, the potential of combined treatment strategies, the consequence of loco-regional failure and the expected feasibility of salvage treatment may need to be taken into account.

For radiotherapy and for surgery, the notion of subclinical malignant disease takes into account:

— The microscopic tumour spread at the boundary of the primary tumour GTV (CTV-T). It is a kind of shell outside what can be observed, palpated or visualized using a particular imaging modality.
— The possible regional infiltration into lymph nodes (CTV-N) and the microscopic tumour spread around a macroscopically involved node.

For systemic treatment (including chemotherapy), the potential metastatic involvement of other organs needs to be considered, which may also include a certain site for radiotherapy (e.g. the brain), despite their normal appearance on clinical and radiological examinations (CTV-M).

5.2.2.1. Selection of the CTV-T and CTV-N

The selection of the tissues that bear risk for microscopic infiltration outside of the GTV is a probabilistic assessment integrating the biological and clinical behaviour of the various tumour entities and the knowledge of the surrounding anatomy, including structures that are barriers to tissue infiltration, or on the contrary, by structures that are easy conduits for tumour dissemination.

The probability of the presence of malignant cells and their density in the margin around the GTV decreases with the distance from the border of the GTV. In addition, there may be specific local routes of spread which may give specific adjacent locations a higher probability of malignant cells being present. The various lymphatic routes of spread carry specific probabilities for involved lymph nodes in certain areas, mainly dependent on the tumour location and biological behaviour. One practical consequence is, for example, that different CTV-Ts (CTV-T_1, CTV-T_2, CTV-T_3, etc.) may be selected according to their assumed probability of tumour cell load.

In the literature and in ICRU reports, recommendations for various CTV-N areas have been estimated based on clinical and pathohistological observations on the pattern of spread [21]. These concepts have been widely employed for a long time and have been redesigned for 3-D imaging, e.g. in head and neck cancer [136], in lung cancer [137] and in Hodgkin's disease [138, 139].

The concept of different CTVs is increasingly being investigated and applied for both tumour and lymph-node related CTVs, using different imaging modalities with regard to suspicious areas of involvement based on morphological and functional imaging, e.g. in head and neck cancer and in prostate cancer [140]. Similar studies are in preparation for lung cancer and Hodgkin's disease.

In principle, the size and configuration of the CTV-T results from the selection of either a large or a narrow margin around the GTV and depends on various conditions. The CTV-T may also include the whole tumour bearing organ (e.g. in prostate cancer, the prostate). In the case of limited disease cervical cancer, the cervix itself is regarded as the GTV and the related CTV-T has margins between the boundaries of the cervix and the GTV. There may even be a second CTV-T with a margin around the cervix indicating a certain probability of tumour cells being present, as proposed in the GEC-ESTRO recommendations and as practised in cervical cancer surgery.

The CTV selection should take into account the target selection and contouring uncertainties. However, the CTV does not include the range of motion of internal anatomy (see Section 5.2.3). The selection of the CTV(s) is currently based on personal clinical experience, on departmental experience and on exchanged and published information providing different levels of evidence. The selection of the CTV(s) is the responsibility of the radiation oncologist. The 3-D

delineation of the CTVs for the primary tumour, the nodal site, or both, will often be guided by published recommendations, which aim to translate the regions at risk for microscopic spread (both at the primary tumour site and in lymph node areas) into boundaries identifiable on planning CT or MRI.

5.2.2.2. Response related adaptive clinical target volume (aCTV)

The GTV may change and shrink during the course of treatment. This leads to a residual tumour volume at a given time of treatment. This may then become the starting point for an adaptation of the initial GTV related CTV, which is then called the adaptive clinical target volume (aCTV). Such target adaptation takes into account the individual morphological and/or functional response to treatment and the initial GTV. This adaptive CTV is based on the size and the configuration of the rGTV as it presents at a given time during treatment. This rGTV is defined according to agreed upon diagnostic characteristics for GTV assessment, and after treatment it may contain macroscopic or microscopic disease, or both, or neither. Around this rGTV, residual microscopic tumour cells may be suspected, in particular in areas with residual (macroscopic) pathological tissue, i.e. in grey zones, which may be located in the area of the initial GTV. Therefore, the aCTV may include a margin around the rGTV, or no margin, according to the type of response and the suspected residual tumour cells. The margin may reflect residual grey zones in the area where the initial GTV was located. Even a subunit of the rGTV which is considered to bear a specific tumour load may be selected to become the aCTV.

The adaptive target volume concept implies that residual tumour (macroscopic or microscopic) after a certain treatment (radiotherapy, chemotherapy, surgery, or a combination of these) needs additional treatment compared with that applied to the CTV-T that is related to the initial GTV. This additional treatment may be (boost) radiotherapy, chemotherapy (targeted therapy), surgery or any combination of these. Whereas traditional practice has mainly focused on providing additional treatment to the GTV related CTV-T at diagnosis, there is increasing evidence that many situations may require additional treatment to an adaptive CTV based on the rGTV only.

More aggressive treatment may become possible for such volumes, which may be significantly smaller, resulting in improvement of local control. Treatment related morbidity can be minimized if surgery is less radical or if high dose radiotherapy is focused on small volumes. The radiotherapy boost concept and the underlying CTV-T concepts have so far referred to the initial GTV plus margins for potential microscopic spread. The response related adaptive boost concept, including the adaptive CTV-T concept, focuses on the situation as it presents after initial treatment, which will have resulted in a significant change of

GTV and topography. These topographical (geometrical) changes may also lead to considerable dosimetric changes and have received major attention in the recent era of repetitive imaging. So far, these geometrical changes have been subsumed under ART. In the tumour response related adaptive approach as presented here, individual tumour biology, as shown by the individual response, is taken as the reference frame into which the adaptive (boost) radiotherapy has to be integrated. At present, this may be accomplished through morphological repetitive imaging, which can provide major information, but in the future, increasingly functional imaging may also provide valuable additional information.

Various clinical scenarios are given below to illustrate the initial and the adaptive CTV-T approaches based on the initial GTV and the residual response related GTV, respectively. This tumour response related concept of adaptive CTV-T can also be applied to macroscopic nodal and metastatic disease which would then result in an adaptive CTV-N or an adaptive CTV-M, or both.

Whereas the selection of the CTV-T based on the initial GTV follows the pathways of traditional CTV-T with some modification, the CTV-T selection based on the rGTV represents the new adaptive CTV-T approach. The adaptive CTV definition in radiotherapy has so far been mainly based on morphological repetitive imaging such as CT, MRI, ultrasound, endoscopy and clinical examination. The volume findings and the resulting selection of adaptive target volumes may be different depending on the imaging modality applied [126, 141]. Functional imaging is also being investigated for defining volumes for specific biological characteristics, which are often smaller compared with those based on morphological imaging [127].

Response related adaptive target concepts for defining boost treatments in radiotherapy have been successfully used in traditional treatment guidelines, e.g. in Hodgkin's disease (lymph nodes), small cell lung cancer (tumour and lymph nodes), anal cancer (tumour), Ewing's sarcoma (tumour) and in selected cases of head and neck cancer (tumour and lymph nodes). Treatment approaches including response related adaptive target concepts have been widespread in multidisciplinary oncology for various cancer sites and often apply different treatment modalities, e.g. ablative hormonal therapy followed by definitive brachytherapy to the residual target volume.

5.2.3. Planning target volume

The recent developments in defining concepts and terminology for reporting volumes [20, 21, 142] reflect the progress in the multimodality approach that is used in determining the general oncological treatment strategy. On the other hand, specific volumes need to be considered as tools to achieve the radiotherapy objectives in the context of the overall cancer strategy. In Sections 5.2.1 and 5.2.2,

the general oncological concepts of GTV and CTV have been considered as applicable to any kind of cancer treatment strategy using surgery, radiotherapy, medical chemotherapy or a combination of these. The different modalities may be applied simultaneously or successively; the tumour response or tolerance to one treatment modality may influence the selection and parameters of the following treatment modality. These situations make the introduction of new volume concepts in radiotherapy necessary: the rGTV and the aCTV.

The present section deals with concepts related specifically to radiotherapy. The overall treatment prescription includes the definition of the place of radiotherapy within the overall oncological strategy, e.g. radical surgery, (neo)adjuvant, simultaneous or successive anti-neoplastic drugs. This implies the definition of all CTVs that should be irradiated (including adaptive CTVs), their extent and location, the dose and dose distribution, fractionation and time–dose distribution.

The concept of PTV was initially introduced for external photon beam therapy in ICRU Report 50 [17]. It has been developed (and slightly adapted) in successive ICRU reports [18–21]. So far, it has not been explicitly adapted for brachytherapy [123, 124]. The PTV concept of EBRT cannot be directly applied to brachytherapy. A brachytherapy PTV concept needs certain adaptations owing to the dose distributions, which have completely different characteristics compared with EBRT (see Section 5.3.2).

Within the frame of the global (multimodality) anti-cancer strategy, the specific goal of the radiation therapy contribution to the treatment is to deliver the prescribed dose to every selected CTV with a clinically acceptable probability. To achieve this goal, a volume, PTV, is defined as the volume planned to be irradiated at the appropriate dose in order to ensure that all parts of the CTV receive the prescribed dose with the clinically accepted probability and within the constraints of the OAR.

There is thus a PTV each time radiotherapy of a CTV is planned for curative, postoperative or palliative intent. However, the approach to delineate the PTV, its size and shape may be very different depending on the technique. Unlike the volume concepts for GTV and CTV, which are mainly based on clinical situations and oncological principles, radiotherapy PTV additionally depends to a large extent on the treatment conditions and technical possibilities of radiotherapy. Depending on the global treatment strategy, there can be one or several PTVs irradiated simultaneously or successively.

The PTV includes the CTV and a margin that accounts for involuntary organ motion and filling, and geometrical uncertainties in dose administration. The PTV is generally larger than the CTV; it may be much larger, slightly larger or sometimes equal (e.g. in some brachytherapy applications). In certain common situations, specifically, the use of SRS or SBRT for cranial or extracranial targets,

the concept of CTV is not applied and the PTV is created from an expansion of the GTV or internal target volume (ITV).

The PTV is thus a geometrical concept introduced for treatment planning, dose prescription, dose–volume reporting and evaluation. For EBRT, it is the recommended tool to shape dose distributions to ensure that the goal of the radiation treatment will actually be reached despite geometrical uncertainties such as organ motion and set-up variations [21].

5.2.3.1. Uncertainties in delineating the PTV

The delineation of a PTV has to take into account essentially two types of uncertainties:

(1) The size and shape of the CTV and its position or physiological movements and shape within the patient;
(2) Irradiation delivery that depends largely on the irradiation technique.

The margin that takes into account the first set of uncertainties surrounds the CTV in EBRT like a shell and is called the internal margin, and defines the ITV. The second set of uncertainties related to beam delivery conditions leads to the definition of the set-up or external margin and is again added like a shell to the CTV in EBRT.

The combination of these two types of margins around the CTV forms the PTV. In ICRU Report 62 [18], it was recommended that for EBRT, internal and external margins should be added quadratically. The ITV concept is particularly important in clinical situations where uncertainty about the position or movement of the CTV dominates over set-up uncertainties.

The additional volume irradiated when adding a PTV margin to a CTV depends on tumour location and radiation treatment technique. In some cases, such margins may become small, e.g. in high precision IGRT or in techniques where the radiation applicator is fixed to the target, such as in intracavitary and interstitial brachytherapy.

In some brachytherapy applications, the radiation source is attached to or is in contact with the tumour and moves with the coordinate system of the tumour. Therefore, according to current knowledge, set-up errors or motion uncertainties seem to be very limited. The main uncertainty remains the delineation of the (residual) GTV and judgement of the extent of microscopic involvement, e.g. the spread from cervix to the body of the uterus and/or to the parametria.

Whereas delineation and dose prescription for the GTV(s) and CTV(s) is the responsibility of the radiation oncologist within the oncological multidisciplinary team, delineation and dose prescription of PTV is the responsibility of the

radiation oncologist and the medical physics team, who together develop the planning aim which is then subjected to a feasibility evaluation.

5.2.4. Normal tissue related concepts and volumes

Treatment related morbidity and associated impairment in quality of life are essential issues to be taken into account in cancer treatment, and relate to any treatment modality, e.g. surgery, radiotherapy or anti-neoplastic/targeted drug treatment, or any combination of these. There are typical patterns of early and/or late morbidity associated with any of these treatment modalities. These may interact and can be increased when combining these modalities. Hence, the decision on a treatment strategy must be based on balancing the curative potential of each modality and the probability of inducing early or late adverse side effects, based on the available evidence.

5.2.4.1. Morbidity end points and volumes in organs at risk

The OAR or critical normal structures are tissues which, if irradiated, could suffer significant morbidity and thus influence the treatment planning and the dose prescription [21]. In principle, all non-target tissues could be considered OAR, if they have an impact on treatment and outcome. However, which normal tissues are considered OAR typically depends on the location of the CTV/PTV, the prescribed dose or both.

There are OAR specific or OAR subvolume specific types of morbidity. For bladder morbidity, urgency and frequency pattern can be related to the dose to the bladder trigone and neck, which establish the bladder emptying and closing functions. Bladder fibrosis and volume shrinkage may occur if the whole bladder (wall) is in the high dose volume. For rectal and sigmoid morbidity, bleeding is linked to different grades of telangiectasia, often in small volumes. A change in bowel habits is a consequence of the circumferential dose, and urgency and continence problems are a consequence of damage to the overall recto-anal wall and nerve plexus structures regulating the recto-anal discharge.

OAR subvolume location, as defined by reference points, also represents a possibility to assess morbidity, such as rectal bleeding. The locations of such reference points may correlate to the location of reference volumes to different degrees; the advantage is that the location is at a defined point in the organ, such as the bladder point for the bladder neck.

The appropriate dose–volume constraints in the OAR will evolve further with time, based on clinical research and further understanding of underlying biological mechanisms through experimental research. Such progress will be

associated with the development of experimental, (bio-)imaging and treatment techniques.

Regarding tissue organization, the ICRU Report 83 [21] states that "from a functional point of view, tissue organization has been conceptually divided into "serial," "parallel," or "serial–parallel" [17, 143]. Serial organs, or serial-like organs (e.g. spinal cord, nerve, the gastro-intestinal tract), consist of a chain of functional units, which all need to be preserved to guarantee the functionality of the tissue. However, more recently, this concept has further evolved to address tissue organization, also within certain organs, which is often a mixture of parallel and serial organization [144].

5.2.4.2. Geometric uncertainties in OAR assessment

Variations in the position of the OAR during treatment must be considered. The major determinant seems to be variation in organ geometry and motion in relation to radiation beams or sources, which may occur during or between fractions of radiotherapy, and may result in a considerable dose variation. However, contouring uncertainties have also not been comprehensively resolved so far, in particular for organs such as the mobile bowel. Furthermore, depending on various morbidity end points and biological targets for adverse side effects within a given organ structure, different subvolumes for contouring may need to be defined, e.g. for urinary bleeding (telangiectasia) and urinary urgency symptoms (trigonum vesicae).

In the context of EBRT, the concept of the PRV has been developed [18–21]. This is analogous to the PTV in that margins are added to the OAR to compensate for variations and uncertainties. ICRU Report 83 recommends that "a margin around an OAR with a serial-like structure (e.g. spinal cord) is more clinically relevant than around an OAR with parallel-like structure (e.g. liver, lung, parotid)" [21]. Note that is important to contour the whole organ of a parallel-like structure, since tolerance depends more on the percentage of the whole organ volume irradiated.

As for the PTV, several authors have proposed approaches to calculate the OAR-PRV margins on the basis of systematic and random uncertainties [21, 145–147]. With such a margin concept, OAR dose assessment has so far only seen limited applications in the radiotherapy community. It has been implemented at specific organ sites, such as the spinal cord in head and neck radiotherapy. A major new direction for more accurate dose–volume assessment for OAR seems to be repetitive imaging in the framework of IGRT and advanced image registration methods.

ICRU Report 83 discusses tissue organization in regard to dose constraints for organs at risk and their delineation:

"The concept of tissue organization is operationally useful for determining dose-volume constraints and for the evaluation of the DVHs. Indeed, for serial-like organs showing a threshold-binary response, the dose at or close to the maximum dose to a given volume is typically the best predictor of loss of function. In contrast, for parallel-like organs showing graded absorbed-dose responses, the mean absorbed dose or the volume that receives an absorbed dose in excess of some defined value have been used as predictors of loss of function.

…….

"This concept of tissue organization is also useful for the delineation of OARs. For instance, for the retina or tubular-type organs such as the rectum, it is preferred (but more time consuming) to delineate the wall or surface rather than the full organ. For serial-like organs, as the volume irradiated may have less impact on the assessment of the organ tolerance, the extent to which these organs are delineated will probably have lesser importance for the patient's treatment. However, to allow comparison between centers, it is very useful to follow guidelines, e.g., to delineate the spinal cord for head-and-neck tumors from its junction with the brain stem to the first dorsal vertebra, and for prostate cancer to delineate the rectum starting at the anus up to the position at which the rectum turns horizontally into the sigmoid colon. In contrast, for parallel-like organs, the volume assessment is crucial, and complete organ delineation is required. In all instances, the volume of the organ delineated should be recorded. This is particularly important when DVHs are reported in terms of relative volumes" [21].

Some treatment modalities (e.g. photon IMRT and particle scanning beam techniques) may:

"result in a more heterogeneous absorbed-dose distribution in normal tissues and larger volumes of normal tissues irradiated, each tissue presenting with different responses. Thus, the optimization process requires enhanced consideration of biological response of normal tissues. Dose-volume constraints for OARs are mainly derived from retrospective clinical observations, which have been translated into NTCP curves [148–150]. The majority of the data come from the clinical literature of the 1970s and 1980s, *i.e.*, from the pre-3D-imaging photon era and therefore with less reliable dose and volume information. It is only more recently that prospective studies have systematically looked at the relationship between

absorbed dose, volume, and normal-tissue complications from patients treated with 3D-CRT or IMRT" [21, 148–150].

Recent data from breast IMRT trials demonstrate that acute skin erythema is strongly correlated with dosimetric hot spots within breast parenchyma rather than skin dose per se [151]. This suggests that local anatomy, physiology and cytokine effects may play a large role over and above simple mechanistic models. Examples of dose constraint and outcome data have also been published for other body sites and normal tissue and OAR (albeit with the above limitations) as both single institution and multi-institution data [102, 106, 152–157].

The planning team should use an evidence based set of dose constraints for normal tissues in the context of a clinical trial or routine practice, which is embedded as part of the QA framework and institutional clinical policy library for their department. Careful evaluation of dose constraint parameters and cumulative and differential (or direct) DVHs should be performed in the context of the known clinical scenario for that patient. Other measures of PTV coverage such as the conformity or homogeneity index, tail EUD or Sigma Index can also form part of the dose constraint library [158, 159]. Figure 15 shows an example of a template for an ICRU based departmental policy library. Ease of access, authorship, revision dates and an audit trail are important requirements for any policy storage system.

Regarding margins for the OAR, ICRU Report 83 states that:

"A margin around an OAR with a serial-like structure (e.g., spinal cord) is more clinically relevant than that around an OAR with a parallel-like structure (e.g., liver, lung, parotid). Note that delineation of the PTV and the PRV will often result in one or more overlap regions. It is recommended that the margins not be compromised for the PTV or PRV even if overlaps occur. To ensure sufficient normal-tissue sparing, priority rules in the planning system can be used or the PTV or PRV can be subdivided into regions with different absorbed dose constraints" [21].

The ICRU currently recommends that the dose to the full PTV be reported (see Fig. 16). For reporting of the PRV, the ICRU states that:

"it is recommended that, as for the PTV, the PRV be described by including the size of the margins applied to the OAR in different directions. As for the PTV, many authors have proposed approaches to calculate the OAR–PRV margins on the basis of systematic and random uncertainties" [21].

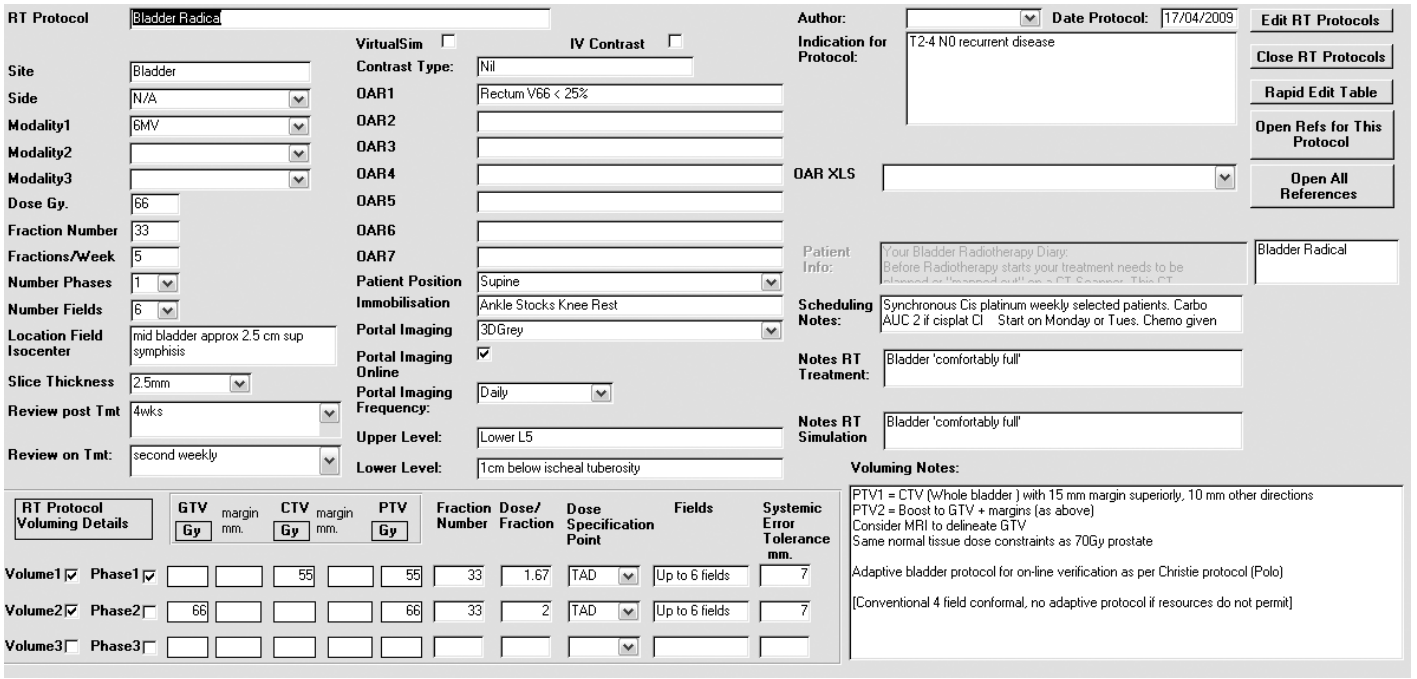

FIG. 15. An example template for a site or technique specific ICRU based institutional clinical policy library. (Image courtesy of C. Hamilton.)

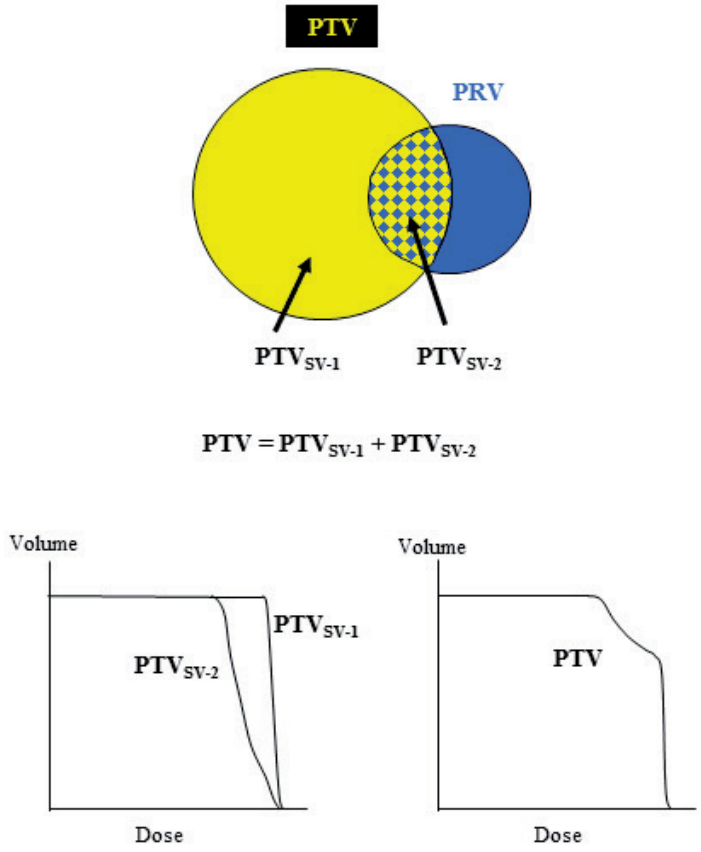

FIG. 16. Schematic description of PTV subvolumes delineated in case of overlap between PTV and PRV. (Key: PTV, planning target volume; PRV, planning organ at risk volume; SV, subvolume; CTV, clinical target volume. (Reproduced with permission of the ICRU (ICRU Report 83 [21]).)

The PTV_{SV-1} and PTV_{SV-2} may be used for planning purposes (beam arrangement and dose prescription), but the dose distribution should be reported in the whole PTV (bottom right figure). In case of a compromise on dose in the overlapping region between the PTV and the PRV, reporting the dose in the sub PTV (i.e. PTV_{SV-1}, left figure) may wrongly represent the dose to the underlying CTV. For example, if the prescribed near minimal dose to the PTV is 65 Gy and the dose to the PRV should not exceed 50 Gy, the planned dose in PTV_{SV-2} should range between 70 and 50 Gy. It is the responsibility of the radiation oncologist in charge of the patient to select and prescribe the best dose variation in that

volume. (Using modern techniques such as IMRT and beam scanning makes 'dose painting' possible.)

5.2.4.3. Remaining volume at risk and OAR

The remaining volume at risk (RVR) is defined as the volume that is outside all delineated OARs and CTVs but within the imaged region of the patient [21]. Doses to the RVR as well as the OAR and PTV should be reviewed during the plan evaluation stage to ensure regions of high dose outside the PTV do not go undetected. Also, the dose to the RVR could be useful in predicting late effects such as carcinogenesis.

5.2.5. Treated volume

The treated volume (TV) is defined in ICRU Report 83 as:

> "the volume of tissue enclosed within a specific isodose envelope, with the absorbed dose specified by the radiation oncology team as appropriate to achieve tumour eradication or palliation, within the bounds of acceptable complications" [21].

Also,

> "the value of the isodose surface selected to define the TV treated volume should be quoted either relative to the prescribed absorbed dose or in absolute terms. It is important to identify the shape, size and position of the treated volume in relation to the PTV for several reasons. One reason is to provide information to evaluate causes for local recurrences (inside or outside the TV)" [21].

The TV is required:

> "because of the limitations of irradiation techniques, the volume receiving the prescribed dose may be different than the PTV; it might be larger (sometimes much larger) or smaller, and in general more simply shaped (less with IMRT or scanning- beam techniques than with conventional radiation therapy techniques)" [21].

The dose level defining the TV is specified in terms of the (physical) absorbed dose, and, when appropriate, the biologically weighted doses (i.e. isoeffective doses that take into account factors such as the dose per fraction,

overall time, radiation quality, but also the biological system and effect, and other relevant factors).

The TV can be derived from the computed DVH curve. For example, $D_{98\%}$ could be selected as the dose level defining the TV as proposed for photon and proton therapy [20, 21]. The anatomical location, extent, volume and dimensions of the TV (three orthogonal dimensions) should be reported and the corresponding PTV should be specified. The TV should (in principle) completely cover the PTV but include as few normal tissues as possible outside the PTV. This leads to the concept of the conformity index which is defined in ICRU Report 62 as the ratio between the TV and the PTV.

5.2.5.1. Reference volume(s)

Other reference volumes have been defined specific to particular studies and are mainly used to facilitate comparisons and to make such comparisons more objective.

5.3. PTV DOSE ESCALATION

There now exists a large amount of Level 1 evidence supporting the value of dose escalation in improving local control, survival or both in a large number of malignancies [160–163]. The importance of achieving local control in terms of overall quality of life and survival remains a central tenet in the good quality practice of radiotherapy [164]. More detailed knowledge of the 3-D dose distribution within the PTV associated with functional imaging co-registration (so-called dose-sculpting, e.g. for dominant intraprostatic lesions) is now possible given new imaging modalities and fusion software. Van Vulpen et al. [165] have correlated the actual dose distribution in the prostate with local recurrences in prostate cancer using functional imaging. Even in tumour sites where dose heterogeneity is significant, the relationship between cold spots and clinical recurrence still remains largely theoretical [165, 166].

It is likely for many tumour sites that failure to appreciate local region extension and to adequately cover this with GTV and CTV will be responsible for a significant proportion of clinical failures [120, 167, 168]. The routine use by radiation oncologists and their departments of evidence based GTV and CTV volume delineation institutional guidelines in both clinical trial and routine settings is mandatory to minimize this source of variation and uncertainty among clinicians. For example, Giraud et al. [169] compared the size of lung tumours measured on the resection specimen with the real size of the tumour, including microscopic extension, determined by the pathologist, in a series of 70 patients

with non-small-cell carcinoma of the lung. The mean value of microscopic extension measured by the pathologist was 2.7 mm for adenocarcinomas and 1.5 mm for squamous cell carcinomas. An 8 mm margin for adenocarcinomas and a 6 mm margin for squamous cell carcinomas includes microscopic extension in 95% of cases.

Figure 17 demonstrates an example of the type of evidence required to define the GTV and possibly the sub-GTV and CTV for prostate cancer. Preoperative imaging with CT and carbon-11 choline PET can be matched to the pathological volume of invasive disease.

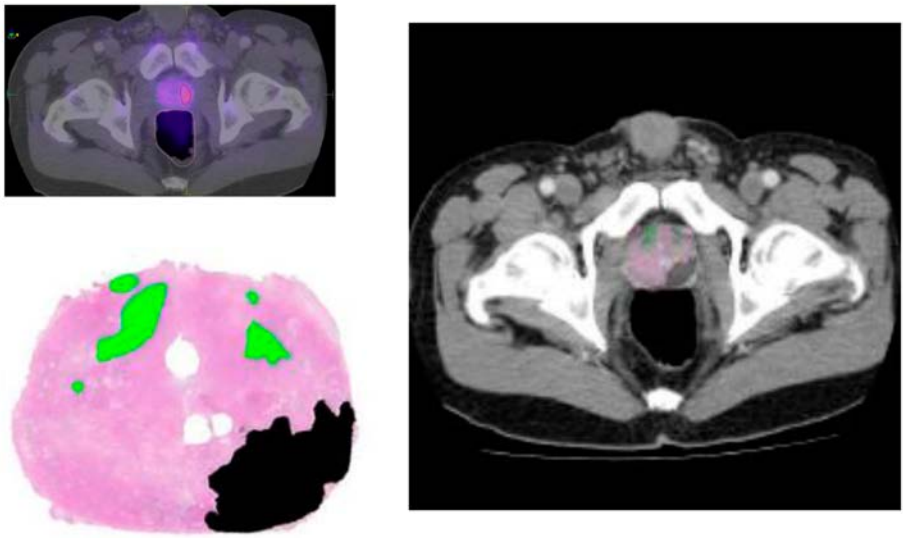

FIG. 17. Upper left: Fused carbon-11 choline PET scan and planning CT simulation image. Lower left: Haematoxylin and eosin stained section from prostatectomy specimen. In black: invasive disease, in green: prostatic intra epithelial neoplasia. Right: Superimposed prostatectomy haematoxylin and eosin stained section on the preoperative diagnostic CT image. (Adapted from Ref. [170].)

5.3.1. Application of the PTV concept in external photon beam therapy

In EBRT, the PTV usually surrounds the representation of the CTV with a margin (like a shell) such that the planned dose is delivered to the CTV. The width of the margin takes into account both the internal and set-up uncertainties. The internal margin takes into account the (possible) changes of the CTV in size,

shape and position during treatment. The set-up margin accounts specifically for uncertainties in patient positioning and alignment of the therapeutic beams during the treatment planning and all treatment sessions. The goal of IGRT is to reduce this margin such that less normal tissue will be irradiated.

5.3.2. Application of the PTV concept in brachytherapy

In recent years, brachytherapy has significantly benefited from advanced imaging technologies. GTV and CTV are used in brachytherapy in the same way as in EBRT, since these volumes are anatomical and clinical concepts applicable to any radiotherapy technique. For gynaecological brachytherapy, the recommendations by the Gynaecological GEC-ESTRO working group [171, 172] introduced the adaptive concepts of high risk CTV (HR-CTV) and intermediate risk CTV. They also took into account the tumour spread at the time of brachytherapy and at the time of diagnosis. These concepts have been widely accepted and have become the framework for the development of this adaptive image guided treatment approach. This treatment approach, which enables individual 4-D target volume optimization based on MRI with appropriate dose–volume constraints for target and OAR, is being increasingly translated into clinical practice.

The application of PTV in brachytherapy has not yet been specifically dealt with in ICRU reports. For gynaecological brachytherapy, the cervix and the sources have been assumed to be bound or fixed together, and thus it has been assumed that the PTV equals the CTV. This was also the approach taken in the United States based Image-Guided Brachytherapy Working Group recommendations [173] and the GYN GEC-ESTRO working group recommendations, where the CTV concept based on 3-D imaging was introduced, and in which the PTV was assumed to be equal to the CTV [171]. However, this assumption is unfounded because there are indeed uncertainties in brachytherapy related to the source location relative to the target. Such uncertainties are source positioning, applicator reconstruction, image fusion, stability of applicators relative to target (e.g. needles in prostate implants) and target contouring. In the GEC-ESTRO Handbook of Brachytherapy [174], the following definition is given:

> “In brachytherapy, the PTV is defined to select appropriate source arrangement, positioning and/or movement control. The dose distribution to the PTV has to be considered as representative of the dose distribution to the CTV.”

Tanderup et al.[175] have questioned whether it is actually possible to draw such a PTV and whether the PTV dose is actually representative of the CTV dose. One has to consider how CTV and PTV doses are related to each other in the inhomogeneous brachytherapy dose distribution. The brachytherapy dose distribution is different along the axis of source catheters (longitudinal direction — e.g. along tandem and needles) from the direction perpendicular to these (orthogonal direction). In the longitudinal direction, the dose distribution may be elongated by loading extra source positions just at the edge, outside the target, or both, and in this way, a dose plateau can be created which extends beyond the CTV. This approach will make the dose distribution more robust towards uncertainties in the direction along source catheters. The dose distribution in the central region of the implant is typically almost unaffected by such modifications of dwell positions at the edge of or outside the target. The orthogonal dose fall-off is almost exclusively determined by physics and cannot be manipulated to become less steep by modifying the loading pattern. This is fundamentally different from the situation in EBRT where the dose plateau is increased in size by application of a margin, but no dose escalation is performed (Fig. 18).

A PTV concept has been developed within the frame of endovascular brachytherapy [176], which includes a margin along the catheter axis compensating for catheter movements relative to the defined target. This

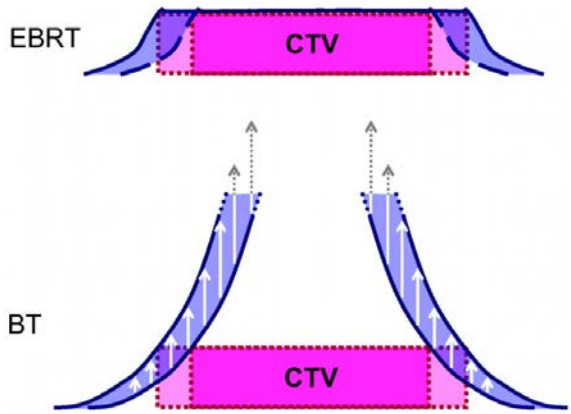

FIG. 18. Effect of margins on dose distribution in EBRT and in intracavitary cervix cancer brachytherapy. In EBRT (above), a PTV margin will result in an increase of the volume irradiated to a high dose. The dose plateau becomes larger in size, but the CTV dose remains unchanged. In brachytherapy (below), a PTV margin into the lateral and anterior–posterior direction and a renormalization of dose according to the PTV will result in a general dose escalation. The dose throughout the CTV and OAR will systematically increase from inner to outer dose profile. (Adapted from Ref. [175].)

longitudinal wall concept has also been applied for intraluminal brachytherapy. These concepts do not include margins in the orthogonal direction. A similar approach is applicable in intracavitary brachytherapy where a selected margin along the tandem can be applied [175]. The application of a PTV concept in interstitial brachytherapy is similar, but is slightly more complicated and needs more development to understand and define exactly which role a PTV can play [177]. Of specific interest for brachytherapy is the possibility to apply a pre-planning PTV concept which addresses the need to think in terms of margins before and during the brachytherapy application. This is a different PTV concept because it is not applied during treatment planning, but is applied for up front management of uncertainties.

Application of margins should be based on a systematic evaluation of uncertainties. Currently, only a few studies have been published on uncertainties in 3-D image guided intracavitary brachytherapy. Further work on this is clearly warranted. Specifically, it would be of great interest to analyse the stability of different applicators and fixation techniques [171].

In summary, uncertainties in brachytherapy can only be partially compensated for by adding PTV safety margins. It appears that the PTV concept is not useful for routine dose reporting, although it may play a role for reporting worst case scenarios (such as the minimum target dose) in the presence of uncertainties. Dose normalization to the PTV is strongly discouraged since it can lead to dose escalation (see Fig. 18) [175].

5.3.3. Proton and carbon ion beam therapy

In photon beam therapy, as indicated earlier, the PTV is primarily used to determine the lateral beam margins. In the case of protons and carbon ions, delineation of the PTV requires a different approach: in addition to the lateral margins, some margin in depth must be left to allow for uncertainties in the knowledge of where the distal (e.g. 90 %) isodose would fall.

The beam energy (i.e. penetration) should be chosen such that the CTV is within the TV, taking into account both motion and range uncertainties (see Section 5.2.5 on the definition of the TV). Thus for protons and ions, the lateral margins and the margins in depth (relative to the proximal and distal surfaces) solve different problems and will virtually always be numerically different. As a consequence, for each beam orientation being considered, in principle, a separate PTV with different margins would be needed laterally and along the direction of each beam.

An alternative approach is to determine the treatment parameters using the CTV, rather than the PTV, and to place the burden of adding appropriate lateral and range margins to the computer algorithm. This means that both lateral and

depth margins are computed in designing each beam. In the case of scattered beam treatments, the lateral margins would be designed into the aperture in the beam's eye view, and the depth margin would be designed into the compensator. For scanned beams, and intensity modulated proton therapy in general, these margins would influence which pencil beams would be used, and the depth of penetration of each one.

When a single beam is used, the beam sizes are enlarged to cover uncertainties in set-up and the beam penetration is increased to compensate for other uncertainties, as mentioned. The issue is more complex when more than one (non-parallel) beam is used. The PTVs for each beam could be reported individually, but they cannot be added because they correspond to different processes.

Regarding the reporting of dose to the PTV, ICRU Report 78 states that:

> "it is required that the dose distribution within the 'PTV' be recorded and reported. This would be unworkable if there were a separate PTV for each beam employed, and impossible if separate lateral and depth margins were built into the computer's beam-design algorithm. It is therefore proposed that, in proton therapy, the PTV be defined relative to the CTV on the basis of lateral uncertainties alone. An adjustment must then be made within the beam-design algorithm to take into account the differences, if any, between the margins needed to account for uncertainties along the beam direction (i.e., range uncertainties) and those included in the so-defined PTV (i.e., based on lateral uncertainties)" [20].

The same approach can be extended to carbon ion therapy. For reporting, the anatomical location, extent, volume and dimensions (three orthogonal dimensions) of the PTV should be indicated.

5.4. VOLUME AND DOSE DISTRIBUTION EFFECTS

The outcome of a treatment of an individual patient is determined by the overall dose distribution in the irradiated volume in that patient and the patient specific radiation sensitivity. Dose–response curves of a group of patients are based on average values of a number of individual patients, which may have variations in dose delivery and intrinsic radiosensitivity. In order to separate these two variables and to obtain the optimum dose distribution for an individual patient, it is necessary to assess the actual dose delivery in the target volume and OAR. This may differ from the planned dose distribution, and methods are

therefore needed to assess the actual dose distribution over a complete course of radiotherapy.

5.4.1. Dose in organs with varying volume

If the target volume or the volume of an OAR varies during treatment, the delivered dose distribution may differ from the planned dose distribution in that volume. These variations may occur rather rapidly, i.e. during a single fraction, or gradually over the complete course of radiotherapy. The effect of volume variations on the dose delivered to that volume depends on the magnitude of the variation, the treatment technique and the margins applied, i.e. the CTV-PTV margin and the margin around an OAR. With the implementation of 3-D CRT and IMRT techniques, and the accompanying trend to reduce these margins, the chances of having areas in the target volume that receive a lower dose than planned, or parts of an OAR that receive a higher dose than desired, are not zero [178].

In order to determine the dosimetric consequences of these variations in volume, the following information is needed: (a) a time dependent description of the volume changes, (b) a calculation of the (static) dose distribution at relevant time intervals and (c) the generation of cumulative dose distributions over the course of therapy of each subvolume of a specific tissue or organ.

5.4.1.1. Time dependent description

As discussed in Section 6.4, a number of volumetric imaging tools are now available to describe the patient anatomy in 3-D either as a function of time during one treatment fraction or during a series of fractions. The main purpose of these tools is to ensure that the position of relevant patient anatomy is the same during each treatment, or just before, compared with the planned position. By applying in-room imaging, the patient position, the patient treatment or both can be adapted, if necessary, to keep the dose in specific volumes the same within specified uncertainties compared with the planned values. However, if the volume is variable, simple couch position shifts are not always sufficient and more sophisticated methods of using this imaging information are necessary, such as using it to perform image guided adaptive radiotherapy. One of the main problems when dealing with organs with varying volume in fields with steep dose gradients is the tracking of the position of specific subvolumes in that organ. For that purpose, a number of groups have developed deformable registration algorithms [179, 180]. Furthermore, making a new plan based on the modified position of the PTV and OAR requires a lot of effort in contouring all relevant

structures. In order to reduce that laborious task, automated contouring tools, in combination with atlases of patient anatomy, are under development.

5.4.1.2. (Static) dose distribution

The next step is to calculate the 3-D dose distribution for each time point at which a relevant change in anatomy has been observed. Using the conventional dose calculation procedure by combining a new set of CT data with existing treatment parameters in the clinical treatment planning system would make such a procedure very cumbersome. For that reason, new approaches are under development, such as designing robust treatment techniques that produce dose distributions that are less sensitive to volume variation, or the use of atlases of precalculated dose distributions. A conceptually simple, but in practice still rather cumbersome approach, is the use of 'plan of the day' adaptive radiotherapy. Multiple IMRT plans of a particular patient are generated for various possible positions of the PTV and OAR. By using in-room imaging, the optimal plan of the day is chosen, an on-line set-up correction is applied, and the corresponding treatment plan is irradiated. Other image guided adaptive radiotherapy methods under investigation try to adapt the treatment technique automatically, for instance, by changing leaf positions or collimator angle, to maintain adequate dose coverage of target volume and sparing of OAR. It is obvious that these techniques should be fast to make them clinically useful, while the accuracy should be comparable to results of existing dose calculation algorithms.

5.4.1.3. Cumulative dose distribution

The assessment of the accumulated dose in moving subvolumes of tissue or an organ requires the combination of a time dependent description of the volume variation and a dose calculation for each time point. Various approaches are under development to make such an approach useful for routine application in the clinic [181, 182]. Modelling the movement of the organ due, for instance, to breathing, as a function of time during one fraction, in combination with predetermined dose distributions, might result in a more reliable actual dose distribution than using the planning results. In order to get the cumulative dose distribution, assumptions still have to be made about the constancy of the movement during a series of fractions. The development of deformable registration tools will certainly help in determining the cumulative dose distribution in mobile tissues that only change in position or shape. However, an as yet unsolved problem is how to take changes in the volume and position of subvolumes of these tissues, e.g. of the PTV or of OAR, into account in regions with a large dose gradient.

A detailed discussion of these elements to achieve the determination of the actual dose distribution delivered to normal tissues during a course of radiotherapy has been given by Jaffray et al. [183]. That paper also describes a number of future developments to achieve a high accuracy of the dose within tissues with varying volume.

The impact of dose and volume uncertainties on the generation of dose–response data has been analysed in recent work by Kurjewicz [184]. Using the Lyman-Kutcher model for lung response, an analysis of 200 virtual experiments was performed, and it was found that uncertainties of 10% in dose and volume resulted in a significant increase in the derivation of the *m* parameter (slope related parameter) in the model, in addition to yielding large 95% confidence limits in the resulting parameter. The mean value and the 95% confidence levels of the *n* parameter (volume dependent parameter) were hardly affected.

Better knowledge of the actual dose distribution in the target volume and OAR, incorporating variations in volume in the accumulated dose determination, will allow the assessment of more accurate dose–response curves, and consequently, will yield improved input data for TCP and NTCP models. That knowledge can then be used to design and deliver the optimum treatment to an individual patient.

It should be noted that the total dose map may not be representative for the overall radiobiological effect of the dose, as fractionated dose values can theoretically not be accumulated in a linear way. The effect will be more pronounced for strategies with strong dose variations, for instance, when applying a high dose per fraction. However, in a theoretical study for some typical radiotherapy techniques, Bortfeld and Paganetti [185] showed that a standard deviation of the daily dose fraction of 10% leads to a dose accumulation error due to radiobiological effects of less than 1%. Also, a recent study of the evaluation of the radiobiological impact of anatomical modifications during radiotherapy for head and neck cancer showed that taking radiobiological effects into account while accumulating total dose leads to very small differences compared with a simple linear sum of the dose fractions [186]. For adaptive strategies that make use of the total dose in a limited number of voxels instead of the whole target volume, it might be worthwhile to take radiobiological effects into account.

The level of accuracy of the dose in a volume achievable in practice will be elucidated in Section 6.6, while in Section 7.6.4 the various aspects related to the decision of when to replan a patient will be discussed in more detail.

5.5. SUMMARY

This section discusses the clinical framework and evidence base for making rational decisions on the required level of accuracy in radiotherapy.

— ICRU definitions and processes should be embedded in departmental training, workflow, QA and reporting. ICRU volumes are clearly separated into oncological volumes (GTV, CTV) and geometrical volumes (PTV, PRV).
— A patient care plan should be formulated based on a uniform staging and international classification of diseases system and audited in a multidisciplinary setting.
— The radiotherapy prescription, dosimetry, delivery and verification should be formulated and audited in a multidisciplinary setting.
— Radiotherapy institutional policies should be based on evidence based medicine, consensus guidelines or both.
— Radiotherapy outcomes should be based on published toxicity scoring systems.
— Radiotherapy institutional clinical policies should have an embedded anatomical consensus atlas.
— Clinicians should undertake training in site specific volume delineation.
— Modern high resolution visual displays and tools should be used for volume delineation.
— Large scale high quality 3-D dose–volume outcome data should be pooled by cooperative groups.
— An interdisciplinary review and reporting consensus on interclinician and intraclinician variation should be pursued.
— Further site specific studies on correlation of imaging and pathology should be pursued.
— For repeated imaging during adaptive therapy, the dose level and imaging modality should be indicated on the revised GTV, e.g. $GTV_{20Gy,\ MRI}$.

6. PRACTICALLY ACHIEVABLE LEVELS OF ACCURACY

6.1. REFERENCE DOSIMETRY

6.1.1. The international measurement system

The international measurement system for radiation metrology provides the framework for consistency in radiation dosimetry by disseminating to users calibrated radiation instruments that are traceable to primary standards (Fig. 19). The BIPM was set up by the Convention of the Metre (Convention du Mètre, signed in 1875) with the aim of ensuring worldwide uniformity in metrology [48].

In radiation dosimetry, the primary standards dosimetry laboratories (PSDLs) of many States of the Metre Convention have developed primary standards for radiation measurements. Primary standards are instruments of the highest metrological quality that permit determination of the unit of a quantity according to its definition, the accuracy of which has been verified by comparison with standards of other institutions of the same level, i.e. with those of the BIPM and other PSDLs.

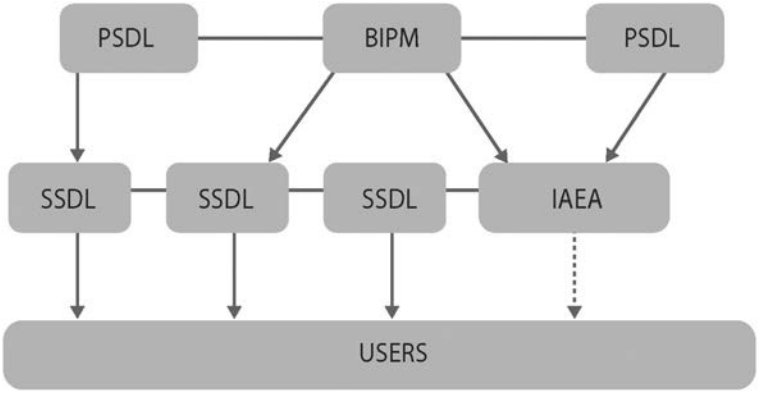

FIG. 19. A simplified representation of the international measurement system for radiation dosimetry. The dotted lines represent comparisons of primary and secondary standards and the arrows represent calibrations traceable to primary standards. It can be seen that an secondary standards dosimetry laboratory (SSDL) can obtain traceability either from the BIPM (if it is a National Metrology Institute of the Metre Convention), a PSDL or the IAEA. The dashed arrow represents exceptional calibration of a user instrument by the IAEA in the event that a country has no SSDL and limited resources.

Ionization chambers used in hospitals for reference dosimetry must have a calibration traceable (directly or indirectly) to a primary standard. Primary standards are not used for routine calibrations, since they represent the unit for the quantity at all times. Instead, the PSDLs calibrate secondary standard dosimeters for secondary standards dosimetry laboratories (SSDLs) that in turn are used for calibrating the reference instruments of users, such as therapy level ionization chambers used at hospitals.

6.1.2. The BIPM and PSDLs

Primary dosimetry standards are realized by the PSDLs in about twenty countries worldwide. The PSDLs have developed various experimental approaches to establish them.

Free-air ionization chambers are the primary standard for air kerma in air for superficial and orthovoltage X rays (up to 300 kV). They cannot function as a primary standard for ^{60}Co beams, since the air column surrounding the sensitive volume (for establishing the condition of electron equilibrium in air) would have to be very long. This would make the chamber very bulky and the various required corrections and their uncertainties would also become problematic. At ^{60}Co energy, graphite cavity ionization chambers with an accurately known chamber volume are used as the primary standard.

The standards for absorbed dose to water enable therapy level ionization chambers to be calibrated directly in terms of absorbed dose to water instead of air kerma in air. This simplifies the dose determination procedure at the hospital level and improves accuracy compared with the air kerma based formalism. Standards for absorbed dose to water calibration are now available for ^{60}Co beams in several PSDLs, and some have extended their calibration services to high energy photon and electron beams from accelerators.

Comparisons of air kerma and absorbed dose to water primary and secondary standards have been carried out for several years. Comparisons of primary standards of air kerma and absorbed dose to water for ^{60}Co gamma radiation between the PSDLs have been organized by the BIPM as well as by Regional Metrology Organizations. The key comparison reference values have been established by the primary standards at the BIPM for both quantities. The comparison results and degrees of equivalence are consistent for both quantities, except in a few cases [187]. The largest deviation from the key comparison reference values are 0.84% and 0.74% for air kerma and absorbed dose to water, respectively.

6.1.3. EBRT standards

The main role of the SSDLs is to bridge the gap between PSDLs and the users of ionizing radiation by enabling the transfer of dosimeter calibrations from the primary standard to user instruments [188]. In 1969, a network of SSDLs was established as a joint effort by the IAEA and WHO in order to disseminate calibrations to users by providing the link between users and primary standards, mainly for countries that are not members of the Metre Convention. By 2013, the network included 84 laboratories in 67 IAEA Member States, of which over half are in low and middle income countries. The SSDL network also includes 20 affiliated members, among them the BIPM, several national PSDLs, the ICRU and other international organizations that provide support to the network [189]. As the organizer of the network, the IAEA has the responsibility to verify that the services provided by the SSDL member laboratories follow internationally accepted metrological standards. The first step in this process is the dissemination of dosimeter calibrations from the BIPM or PSDLs through the IAEA to the SSDLs. In the second step, follow-up programmes and dose quality audits are implemented by the IAEA for the SSDLs to guarantee that the standards disseminated to users are kept within the levels of accuracy required by the international measurement system [189].

One of the principal goals of the SSDL network in the field of radiotherapy dosimetry is to ensure that the dose delivered to patients undergoing radiation treatment is within internationally accepted levels of accuracy. A first step to accomplishing this is to ensure that the calibrations of instruments provided by the SSDLs are correct, emphasizing the participation of the SSDLs in QA programmes for radiotherapy, promoting the contribution of the SSDLs to support dosimetry quality audits in radiotherapy centres and assisting if needed in performing the calibration of radiotherapy equipment in hospitals.

6.1.3.1. Comparison of ionization chamber calibration coefficients for absorbed dose to water and air kerma for ^{60}Co

In the programme initiated in 1995, an SSDL calibrates a transfer ionization chamber, sends it to the IAEA for calibration and repeats the calibration once the chamber has been returned to the SSDL. Assuming a typical relative standard uncertainty for air kerma and absorbed dose to water calibration for ^{60}Co of an ionization chamber at an SSDL of about 0.75% (at $k = 1$), as recommended in IAEA Technical Report Series No. 374 (TRS 374) [190], an action level of ±1.5% is applied.

Forty-seven SSDLs (i.e. those with therapy level capabilities) participated in the comparison programme in the period 1999–2012. Some discrepancies

outside the action level were identified in the early years, mainly prior to 2001. There were a few borderline cases in subsequent years for air kerma. In recent years, the absorbed dose to water data appear to be more accurate than the air kerma data. The results are shown in Fig. 20.

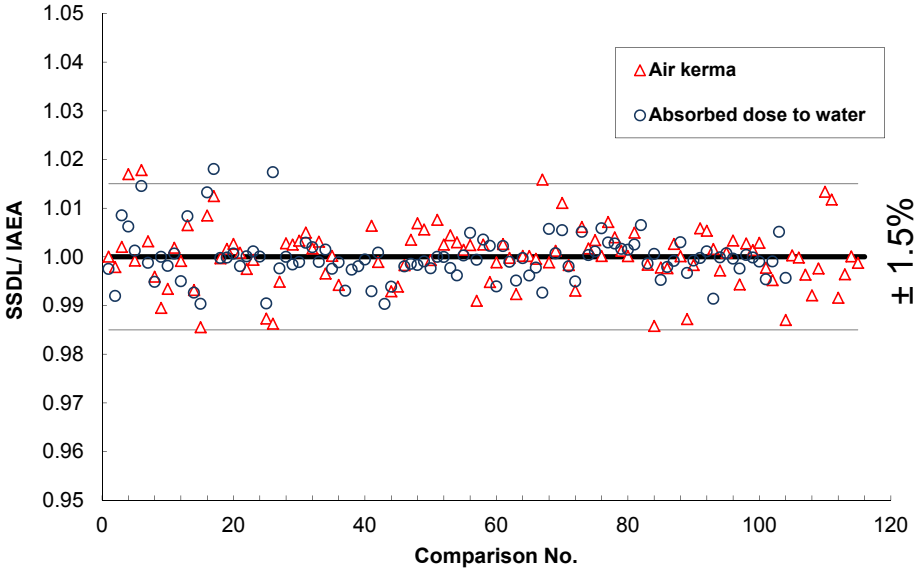

FIG. 20. Ratios of ionization chamber calibration coefficients supplied by the SSDLs to those measured by the IAEA in 1991–2012. Triangles correspond to air kerma for ^{60}Co and circles correspond to absorbed dose to water coefficients.

6.1.3.2. Kilovoltage X ray beams

Air kerma standards for kilovoltage X ray beams are established at PSDLs and are transferred to SSDLs by a calibrated reference-quality ionization chamber. PSDLs can calibrate ionization chambers with an uncertainty of 0.75%, as indicated in the previous section. Once received by the SSDL, the calibrated ionization chamber becomes the local standard, and its calibration coefficient is transferred by the lab to other instruments, including those submitted by customers. The uncertainty of transfer of kilovoltage air kerma calibration coefficients is dependent upon laboratory procedures but has been determined at several laboratories to be about 0.5% [191].

6.1.3.3. High energy X ray and electron beams

Because megavoltage (MV) X ray beams are often calibrated relative to a ^{60}Co standard, standards for higher energy photon beams are not routinely transferred from PSDLs to SSDLs. For the relatively few labs with high energy photon beams, direct transfers are possible and a slightly improved accuracy will be obtained (see Table 4).

TABLE 4. ESTIMATED COMBINED STANDARD UNCERTAINTY IN D_W AT THE REFERENCE DEPTH IN WATER IN MV PHOTON BEAMS
(Adapted from Ref. [192])

Physical quantity or procedure	Relative standard uncertainty (%)			
	SSDL Co-60	PSDL Co-60	PSDL Co-60 and accelerator	PSDL accelerator
Step 1: Standards laboratory				
$N_{D,w}$ calibration of the secondary standard	0.5	—	—	—
Long term stability of the secondary standard	0.1	—	—	—
$N_{D,w}$ calibration of the user dosimeter at the standards laboratory	0.4	0.5	0.5	0.5
Combined uncertainty of Step 1	0.6	0.5	0.5	0.5
Step 2: 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 relative to timer or beam monitor	0.6	0.6	0.6	0.6
Correction for influence quantities	0.4	0.4	0.4	0.4
Beam quality correction	1.0 [a]	1.0 [a]	0.7[b]	—
Combined uncertainty of Step 2	1.3	1.3	1.1	0.9
Combined standard uncertainty in D_w (Steps 1 and 2)	*1.5*	*1.4*	*1.2*	*1.0*

Note: $N_{D,w}$ — absorbed dose to water; D_w — absorbed dose to water.

[a] calculated values

[b] measured values normalized to ^{60}Co

On the other hand, MV electron beams are calibrated relative to a ^{60}Co standard, and standards for high energy electron beams are therefore not routinely transferred from PSDLs to SSDLs.

6.1.4. Brachytherapy standards

Brachytherapy standards have been developed at several PSDLs [193, 56]. Recommendations for establishing and maintaining air kerma strength standards for low energy photon emitting sources have been published [193]. These recommendations call for the regular circulation of sources of each model to the PSDLs and to the SSDLs, and back to the manufacturer, to assure the constancy of the reference standard.

Prerequisites for the determination of reliable data to characterize brachytherapy sources for dosimetry have been published [194, 195]. These prerequisites call for the determination by either measurement, calculation or both, of the AAPM Task Group (TG) 43 [196] dosimetry parameters in a manner that supports the assembly of a set of consensus data for each source model to be used in treatment planning. Before such sources are used in cooperative group clinical trials, it is advised that they meet these dosimetric prerequisites.

Early systems of dosimetry (i.e. rules for application) relied on the source specification from the manufacturers (usually in terms of mg Ra or mg Ra equivalent, then later, activity). Often the physicists did not have the proper means for an in-house verification of the source strengths. Source decay was ignored owing to the fact that the long half-life of ^{226}Ra (1602 years) has no influence on the source strength over the clinical lifespan of a source, and thus has no influence on the overall outcome. In general, for all shorter lived sources, a correction is applied to the treatment times in order to take into account the decay of the radionuclide, based on its half-life. For very short lived sources, corrections are used for decay even *during* treatment.

Much more sophisticated and individualized systems of dosimetry are available at the present time. All these are based on the source strength of each source expressed as the result of an air kerma measurement, usually in terms of the quantity reference air kerma rate (RAKR) expressed in Gy (μGy or mGy) per hour at 1 m, or as air kerma strength, S_K, expressed in the units U, with 1 U = 1 $\mu Gy \cdot m^2 \cdot h^{-1}$ = 1 $cGy \cdot cm^2 \cdot h^{-1}$. This immediately improves accuracy since it eliminates the uncertainties introduced when the quantity ‘activity’ (or

'effective' or 'apparent activity') is used. However, errors or uncertainties are still possible, for the following reasons:

(1) It is sometimes difficult for the user to check every source, e.g. for multiple seeds or ^{137}Cs beads that are used in LDR brachytherapy systems, or for sources that are delivered under sterile conditions for permanent implants.
(2) The RAKR needs to be linked accurately to the dose rates close to the sources using an absorbed dose rate constant, Λ. Values of Λ have usually been measured by several investigators for all source designs, mostly with thermoluminescent dosimetry (TLD), but more recently, Monte Carlo calculations have been used [197].
(3) If older TPSs are still in use that contain algorithms that include source activity, users need to be aware that, when they convert from a stated or measured RAKR to the quantity 'activity', they need to use the same conversion factor that is used in the algorithm. The user manual for the TPS should provide such information.

For HDR, a great deal of effort has been made to improve accuracy. In order to trace the source strength of an individual source to a primary standard, a thimble ion chamber or a well-type ionization chamber can be recommended, depending on national guidelines [198]. The accuracy of HDR source calibration has been investigated by a number of authors, for example:

(1) The RAKR for HDR ^{192}Ir brachytherapy sources based on the United Kingdom's National Physical Laboratory air kerma standard was found to be accurate to 2.6% and 1.2%, respectively, for the conservative and optimized estimates of the calibration coefficient (based on the expanded uncertainties (k = 2)) [199].
(2) An audit of 14 Swedish centres using a well-type chamber calibrated both at the Wisconsin and at the National Physical Laboratory resulted in an accuracy estimate of 2.5% for vendors and 1.3% for hospitals, respectively (k = 2) [200].
(3) Van Dijk et al.[201]: overall uncertainty 1.0% (k = 1).
(4) Stump et al.[202]: expanded uncertainty of 2.15% (k = 2).

In a report on a dosimetric analysis for photon emitting brachytherapy sources by the AAPM TG138 and GEC-ESTRO, the available literature has been reviewed and an estimate was presented for the standard uncertainty of the secondary laboratory calibration and the transfer to the clinical well chamber of 1.3% for low energy LDR brachytherapy sources (at the k = 1 level). For high

energy LDR sources the number 1.5% and for high energy HDR sources the number of 1.3% was associated, respectively [56].

The in-house source strength verification must be performed according to a national or international code of practice (e.g. Refs [203–205]). The outcome of this measurement for a single source should be within 5% of the certificate presented by the supplier and within 3% for the mean result of a batch of sources. If not, the calibration should be repeated, preferably with an independent system. If this result is also outside 3%, then the RAKR (or equivalent) within the HDR planning system should be altered. If measured source strengths for newly acquired sources continue to show a significant difference from the manufacturer's figures, the system needs thorough investigation and a discussion should take place with the supplier. An independent audit is also of value (see, for example, Ref. [200]).

6.1.4.1. Calibration of a hospital's dosimetry system: example brachytherapy uncertainty budget

A source is measured at the primary lab to determine the air kerma strength S_K (the quantity recommended by the AAPM) or RAKR (recommended by the IAEA [206]). The source is sent to an SSDL, where it is placed in the SSDL's standard well-ionization chamber, and a measurement of ionization current is made. This transfers the primary standard to the SSDL. The customer then sends a well chamber to the SSDL, where the process is repeated: a source of the appropriate model is placed in the SSDL's well chamber and its air kerma strength determined. The source is then transferred to the customer's chamber and the ionization current determined. This process transfers the calibration coefficient of the reference to the customer's dosimetry system, with an expanded uncertainty ($k = 2$) of between 6.8% and 8.7%, depending on the energy of the source [56].

6.1.4.2. Dose to water calibration for brachytherapy sources

The source strength expressed in terms of air kerma strength S_K or RAKR needs to be multiplied by the dose rate constant Λ to obtain the quantity of dose to water at the specified calibration distance (see Section 6.2.3.2). Dose to water is the quantity of interest for dose prescription and recording, but has been difficult to measure directly. Therefore, the existing generally accepted recommendations of national and international societies have included the concept of the intermediate step of measurement of air kerma rates for brachytherapy sources.

Within the European Association of National Metrology Institutes**,** several European national metrological institutes have recently participated in the joint research project 'T2 J06 Brachytherapy' on the development of

methodologies to provide a direct dose to water calibration in terms of $\dot{D}_{W,\,1\,cm}$ for brachytherapy sources with calibration transfer to SSDLs. Several standards have been developed. The standards for LDR sources were developed at the Istituto Nazionale di Metrologia delle Radiazioni Ionizzanti (Italy), the Laboratoire National Henri Becquerel (France) and the Physikalisch-Technische Bundesanstalt (Germany). The standards for HDR ^{192}Ir sources were developed at the Physikalisch-Technische Bundesanstalt (Germany), the Italian National Agency for New Technologies, Energy and Sustainable Economic Development, the Van Swinden Laboratory (the Netherlands), and the National Physical Laboratory (UK) [207, 208]. Direct $D_{W,\,1\,cm}$ calibrations are in principle now possible for specified conditions and could slightly reduce the dose calculation uncertainty by eliminating the combined steps of determining S_K and Λ.

The introduction of a $D_{W,\,1\,cm}$ calibration standard for brachytherapy sources into codes of practice and the clinical routine requires an action plan and resources to guide the brachytherapy community to the proposed new calibration standard. Professional societies must therefore develop new recommendations for this introduction in order to avoid errors and misunderstandings at the level of the clinical user. Slight but clear modifications must be made in the treatment planning software used worldwide to allow the direct insertion of a $D_{W,\,1\,cm}$ source strength value into the module of source strength definition, which is the responsibility of the vendors of such systems. From the perspective of harmonization with EBRT reference dosimetry, it is expected that ultimately a dose to water concept in brachytherapy will be introduced. However, in the present context it is too early to discuss this in depth since there are suggestions that it may be more appropriate to consider a dose to medium approach (see Section 6.2.3.2). The influence of these changes on the overall uncertainty budget of brachytherapy dosimetry is not taken into account in this publication. It is noted, however, that this step is intended to obtain a smaller uncertainty budget in the calibration chain of sources used in brachytherapy.

6.1.5. Clinical dosimetry

6.1.5.1. Dose to a reference point in a clinical radiotherapy beam

Several sources of uncertainty contribute to the accuracy of dose delivered to radiotherapy patients. A principal source of uncertainty is related to the calibration of the reference dosimetry standard used for reference dosimetry. In most institutions, the calibration of the hospital reference standard is performed at a national SSDL or PSDL. Also, in most cases, calibrations are based on a ^{60}Co standard. Only a few laboratories offer calibrations in terms of absorbed dose to water for high energy photons or electrons. Currently, according to the

BIPM Key Comparison Database [187], the uncertainty of calibrations in terms of absorbed dose to water for ^{60}Co radiation is on average equal to 0.5% (less than 0.8% at $k = 1$) for PSDLs and 0.7% (less than 1.2% at $k = 1$) for SSDLs.

The uncertainty of calibrations at SSDLs in the USA was analysed by Ibbott et al. [191]. This evaluation considered the uncertainties associated with every step of the process of transferring a calibration standard from the laboratory's standard instrument to a customer's instrument, and combined this with the stated uncertainty of the PSDL. As part of the requirements for accreditation, the USA SSDLs are required to estimate the uncertainties of each component of calibration of a customer's instrument. Mitch et al. [209] have reported this uncertainty to be of the order of 1.5% ($k = 2$).

In most clinics, the annual calibration of the treatment equipment is performed with the local standard, whose calibration is made by a SSDL with an uncertainty stated in the calibration report. However, the continued calibration constancy of the treatment equipment is monitored through the use of a field instrument, whose calibration is determined by comparison with the local standard, with an estimated uncertainty of 1.0%. Therefore, the calibration of the field instrument, when combined in quadrature with that of the local standard, might be as much as 1.25% ($k = 1$). Note that this calculation considers only the calibration of the instrument and overlooks other aspects of performance such as linearity, energy dependence and dose rate effects.

When a reference dosimeter is used for the determination of absorbed dose to water in the hospital beam, the uncertainties in the different physical quantities or procedures that contribute to the dose determination have to be combined. The uncertainty in the calibration of an ionization chamber must be combined with other sources of uncertainty, including uncertainties in establishing the reference conditions (instrument positioning at the reference depth in a phantom, influence quantities), beam quality correction, uncertainties introduced by the use of phantom materials other than water, and the stability of the instrument.

The analysis of uncertainties in reference dosimetry based on absorbed dose to water standards at the hospital level is given in Technical Reports Series No. 398 [210]. For ^{60}Co, the combined standard uncertainty for the determination of the absorbed dose to water at the reference point has been estimated to be 0.9% ($k = 1$). For high energy photon beams, the estimated relative standard uncertainty of $D_{w,Q}$ (where D is dose, w is water and Q is beam quality) at the reference depth in water, based on the ionization chamber calibration in ^{60}Co gamma radiation, is 1.5%. For high energy electron beams, the estimated relative standard uncertainty of $D_{w,Q}$ at the reference depth in water varies between 1.4% and 2.1%, depending on the ionization chamber used and its calibration with a smaller value corresponding to the chamber cross-calibration in a high energy electron beam. In a recent review, Andreo [192] summarizes the estimated

combined uncertainty in D_w at the reference depth in water in MV photon beams. The results are shown in Table 4.

To summarize, the dose at a reference depth in a water phantom for MV photon beams is accurate to about 1.0 to 1.5% ($k = 1$) and between 1.4 to 2.1% in high energy electron beams.

6.1.5.2. Thermoluminescent dosimetry audit of clinical beams

Several authors have determined the uncertainty of calibration of treatment machines through measurement. The IROC Houston TLD audit indicates that in the USA, the output calibration of MV photon beams has a standard deviation of 1.7% [191].

The IAEA and WHO TLD programme provides audits of the calibration of high energy photon beams in radiotherapy centres worldwide, mostly in low and middle income countries. Figure 21 shows the mean and standard deviation of the

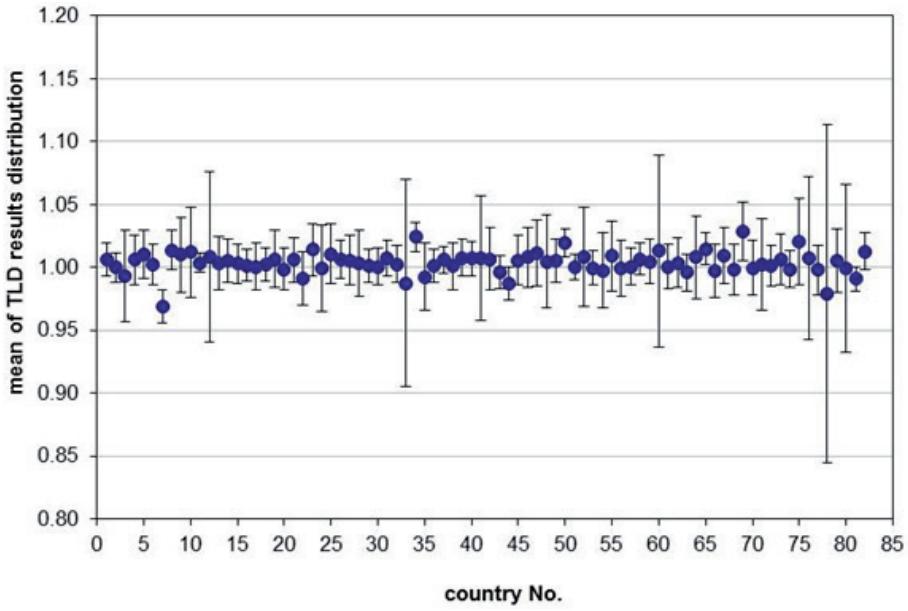

FIG. 21. Results in the IAEA and WHO TLD postal dose audit presented as the mean of TLD results distribution per country for 82 countries participating at least 5 times in TLD audits in 2001–2010. The error bars correspond to the standard deviation of the results distribution for individual countries. Extreme deviations exceeding 20% have not been excluded from these statistics.

distribution of the TLD results by country for 82 countries that have participated in the IAEA and WHO TLD audits at least 5 times between 2001 and 2010.

The snapshot of current dosimetry practices in radiotherapy centres of low and middle income countries presented in Fig. 21 illustrates large differences in quality of beam output measurements between different countries in the world. The mean of the results distribution in a particular country reflects upon the traceability to SI of the dose measurements and the standard deviation is related to the consistency in the dose delivery among hospitals in the country. Overall, most countries maintain adequate levels of quality in beam output dosimetry in radiotherapy, with the mean of the results distribution equal or close to 1.00 and a low scatter of results. About 80% of countries in the graph have a mean within 0.99–1.01, and approximately 95% of the countries within 0.98–1.02. The standard deviation of TLD results distribution is smaller than 2% for nearly half of the countries, which may be considered the reflection of the best dosimetry practices in radiotherapy centres achievable today. For over 80% of the countries, the standard deviation is smaller than 3%, which may not be considered optimal, but shows a reasonably consistent pattern of the dose delivery at centres in these countries. However, as shown in Fig. 21, there are some countries where beam output measurements in radiotherapy are less than adequate. Particularly poor quality of beam calibration can be noted in six countries, shown in Fig. 21, where the standard deviation of the TLD results distribution is larger than 5%; this can be attributed to persistent deviations in TLD results that have affected these statistics. It should be noted that poor dosimetry practices in some countries may result in unacceptably large uncertainties in the doses delivered to cancer patients.

The participants of the IAEA and WHO TLD postal dose audit programme [211] provided information on the dosimetry codes of practice used, including numerical values of the correction coefficients applied for the calculation of absorbed dose to water from ionization chamber measurements. The statistical evaluation of the distribution of results (in terms of dose to TLD over the stated dose, D_{TLD}/D_{stat}) for hospitals using different dosimetry codes of practice is given in Table 5.

The results for hospitals using absorbed dose based ($N_{D,w}$) or air kerma based (N_K) codes of practice show a smaller standard deviation than the results for the hospitals that use older dosimetry recommendations based on exposure based calibrations (N_X) or where the code of practice was not reported. The $N_{D,w}$ based codes of practice (mostly IAEA Technical Report Series No. 398 (TRS 398) and AAPM TG51 [210, 212]) and the N_K based codes of practice (IAEA Technical Report Series No. 277 (TRS 277) [213]) are the main dosimetry codes of practice used for radiotherapy beam calibration. The last row of Table 5 gives the results from the hospitals that did not supply sufficient information.

TABLE 5. RATIO OF TLD MEASURED DOSE TO THE DOSE, D_{TLD}/D_{STAT}, AND SD

Code of practice	*N*	Mean D_{TLD}/D_{stat}	SD (%)
Absorbed dose based ($N_{Dw)}$	2188	1.003	2.2%
Air kerma based ($N_{K)}$	1064	1.006	2.4%
Exposure based calibrations (N_X)	302	1.012	3.4%
Unknown	930	1.008	4.1%

Note: The ratios in Table 5 were reported by participants in IAEA and WHO TLD audits in 2001–2010 and are grouped according to dosimetry codes of practice. Extreme deviations exceeding 20% were excluded from these statistics.

The analysis of TLD results of the IAEA and WHO TLD audit [214] has shown that the percentage of discrepancies in the beam calibration is higher for users of ^{60}Co teletherapy units than for those using high energy photon beams from linacs. In 2001–2010, radiotherapy centres using modern dosimetry codes of practice had TLD results with a standard deviation of 2.0% for MV X ray beams, and 2.4% for ^{60}Co gamma beams [211].

6.1.6. Propagation of uncertainties in reference beam dosimetry

An example of propagation of uncertainties for reference beam dosimetry is available from the analysis of the results of the IAEA and WHO TLD postal dose audit network (see Fig. 22). Results of reference TLD irradiations by the BIPM and six PSDLs and audit results of SSDLs and reference radiotherapy centres were analysed for 2001–2010. The standard deviation of the TLD results distribution is 0.7% for BIPM and PSDLs, it increases to 1.1% for SSDLs and is at the level of 2.2% for radiotherapy centres following modern $N_{D,w}$ based dosimetry codes of practice.

The uncertainty in the ratio of the TLD dose evaluated by the IAEA to the dose stated by the participating centre, $u_c(D_{TLD}/D_{stat})$, is analysed below in order to derive the uncertainty in the dose delivery by radiotherapy centres, as recorded through TLD audits. The $u_c(D_{TLD}/D_{stat})$ can be expressed as the standard deviation of the statistical distribution of a large number of TLD results, as shown in Fig. 22. On the other hand, the uncertainty $u_c(D_{TLD}/D_{stat})$, depends on the uncertainty $u_c(D_{TLD})$ in the dose evaluated from the TLD measurements and on

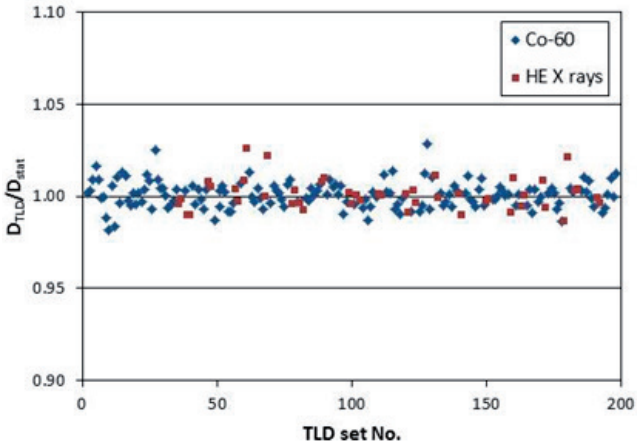

FIG. 22(a). Results of reference irradiations provided by the BIPM and six PSDLs during 2001–2010 in support of the IAEA and WHO TLD postal audits. Each data point represents the average of three dosimeters, and the results of 197 reference irradiations are shown. The graph includes data points for 151 ^{60}Co and 46 high energy X ray beams. The mean is 1.001 and the standard deviation is 0.7%. For ^{60}Co beams, the mean is 1.001 and the standard deviation is 0.7%. For high energy X rays, the mean is 1.001 and the standard deviation is 0.8%.

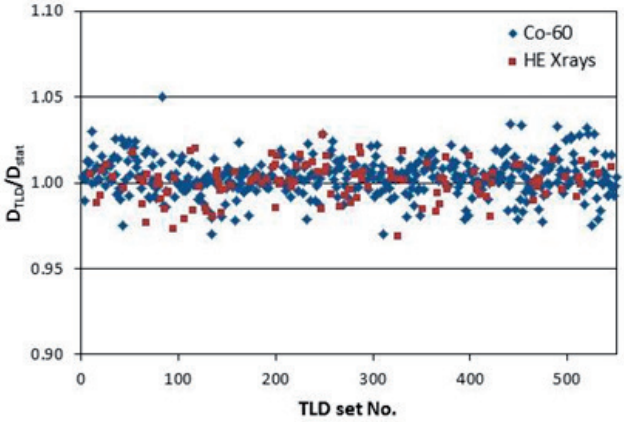

FIG. 22(b). Results of the IAEA and WHO TLD audits at SSDLs during 2001–2010. Only results from SSDLs using the absorbed dose to water based dosimetry codes of practice are included. Each data point represents the average of three dosimeters, and the results of 550 beam checks are shown. The mean is 1.003 and the standard deviation 1.1%. The graph includes data for 424 ^{60}Co beams and 126 high energy X ray beams. For ^{60}Co, the mean is 1.004 and the standard deviation is 1.1%. For high energy X rays, the mean is 1.001 and the standard deviation is 1.1%.

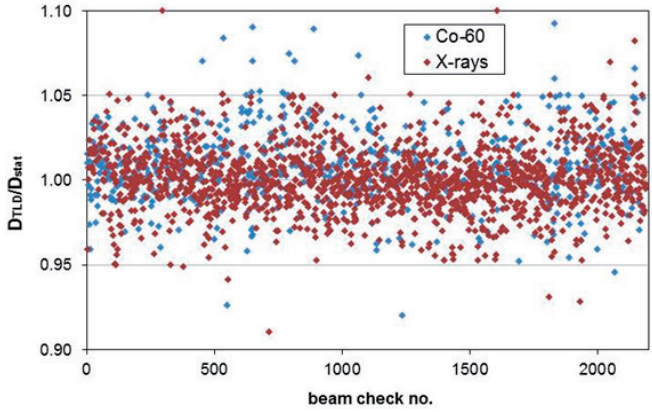

FIG. 22(c). Results of hospital beam checks during 2001–2010. Only results from hospitals using $N_{D,w}$ based dosimetry codes of practice are included. The results of 2188 beam checks are shown. The mean is 1.003 and the standard deviation 2.2%. The graph includes data for 631 ^{60}Co beams and 1557 high energy X ray beams. For ^{60}Co, the mean is 1.008 and the standard deviation is 2.4%. For high energy X rays, the mean is 1.002 and the standard deviation is 2.0%. Seven results outside 10% are not shown in the graph, including two results outside 20% that were excluded from these statistics.

the uncertainty $u_c(D_{stat})$ in the dose stated by the participant. Thus the uncertainty $u_c(D_{TLD}/D_{stat})$ is equal to:

$$u_c\left(\frac{D_{TLD}}{D_{stat}}\right)=\sqrt{\frac{u_c(D_{TLD})^2+u_c(D_{stat})^2}{L}} \quad (11)$$

where L is the number of thermoluminescent dosimeters used in the determination of the TLD dose.

From this equation, the uncertainty $u_c(D_{stat})$ in the dose delivered to TLD by audit participants can be derived using the data shown in Fig. 22(c) and the intrinsic uncertainty $u_c(D_{TLD})$ of the IAEA TLD system. The resulting $u_c(D_{stat})$ equals 3.0% (k = 1) for ^{60}Co beams and 2.3% (k = 1) for high energy X ray beams for the centres participating in the IAEA and WHO TLD postal dose audits in 2001–2010 that follow modern dosimetry protocols (see Fig. 22(c)). As discussed above (see Section 6.1.5.1), the TRS 398 code of practice [210] suggests that the relative standard uncertainty of the dose D_w at the reference depth in water should be 0.9% for a ^{60}Co beam and 1.5% for high energy X rays. Thus the TRS 398 values are lower than those derived from TLD results, in particular for ^{60}Co beams. This indicates that dosimetry practices in radiotherapy

centres participating in the IAEA and WHO TLD postal dose audits involve uncertainties related to the dose delivery additional to those described in the TRS 398 code of practice [210]. The uncertainties in calibration of the local dosimetry standards by some national SSDLs may have contributed to this effect. Another contributing factor might be related to uncertainties in the set-up of TLDs for irradiation and sub-optimal equipment performance, in particular for ^{60}Co units in some radiotherapy centres, due to inadequate maintenance programmes.

Table 6 is taken from the ESTRO Booklet 9 [215] and summarizes results from multiple reports published in the last 20 years on audits or comparisons between delivered and calculated dose values under reference conditions for high energy photon beams. In summary, under standard reference conditions (broad uniform beam (e.g. 10 cm × 10 cm) at a reference depth), the dose can generally be delivered with an accuracy of about 2.0% (k = 1).

TABLE 6. RESULTS FROM STUDIES OF THE ACCURACY OF DOSE DETERMINATIONS UNDER REFERENCE CONDITIONS FOR HIGH ENERGY PHOTON BEAMS
(Adapted from Ref. [215])

Region or country	Number of beams	Average	SD (%)
Scandinavia	50	1.017	2.3
Europe	16	1.024	3.3
Netherlands	40	1.008	2.0
International (mainly USA)	740[a]	1.008	1.9
UK	100	1.003	1.5
Europe	125 119[a]	0.970 0.985[a]	9.5 2.5[b]
Poland	22	1.004	3.8
Ireland	13	1.002	1.2
Germany	114[a]	0.996	2.1
Czech Republic	362[a]	1.000	2.8
Italy	16	1.009	1.6

[a] Including ^{60}Co
[b] Excluding deviations >12%

6.2. RELATIVE DOSIMETRY AND DOSE CALCULATION

This section addresses data needed for treatment planning, but does not consider the irradiation of the patient.

Many measurements of ionizing radiation made in the clinic are relative measurements, i.e. they are measurements comparing the doses delivered under different circumstances. As an example, measurements of percentage depth dose compare the doses at depths in a phantom to the dose at a reference point, usually the depth of maximum dose (d_{max}). Similarly, measurements of output factors compare the doses at d_{max} in different field sizes to the dose at the same depth in a 10 cm × 10 cm reference field.

Relative doses are generally calculated by treatment planning computers for patient dosimetry, although this may be followed by an absolute dose calculation to generate the number of monitor units (MUs) per beam (or time per beam on a ^{60}Co teletherapy machine) that have to be set on the treatment machine. Such relative dose calculations are based, at least in part, on measured data. Regardless of the calculation method, it is essential that the calculations be validated against measurements for the specific treatment machine being modelled.

Relative measurements require similar attention to accuracy as that required for absolute measurements, except that the reference to standards laboratories is not required. However, the uncertainty of relative measurements must be kept small because any uncertainty in the measurements has the potential to be incorporated into patient dose calculations, and ultimately into the dose delivery process.

6.2.1. Commissioning of dosimetry measurement equipment

Few recommendations exist for the commissioning of dosimetry equipment [216, 217], and in reality, most medical physicists assume that dosimetry equipment works as intended. It is not common for ionization chambers, for example, to be subjected to commissioning tests other than those performed by a calibration laboratory.

Instruments used to perform QA procedures should be incorporated into a comprehensive QA programme. The QA programme should address not only the equipment used for primary calibrations, but also the devices used for relative measurements and routine QA, such as water phantom scanning systems, film scanners, diodes and TLD dosimetry systems.

The AAPM has published recommendations [218] advising that dosimetry equipment be evaluated upon initial use and regularly thereafter. Recommendations exist for local standards as well as for field instruments.

Dosimetry systems such as automated water phantom scanners also require commissioning. In this case, a key performance issue is the reproducibility of the positioning of the detector. The AAPM has estimated the achievable positioning accuracy as 1 mm, but this value is likely an overestimate for modern equipment. A better estimate might be to consider 1 mm to be the 3 sigma value, yielding an effective uncertainty of 0.3 mm ($k = 1$).

The dosimeters used with such systems need not be calibrated, but tests should be conducted to determine their reliability and the constancy of their response. These detectors should be evaluated to determine that their response is constant over the course of a standard set of measurements, that they are not subject to water leakage and that electrical leakage remains below acceptable levels. The linearity and stem effect of such instruments should be tested annually. Mechanical integrity should be tested at each use.

Devices used for relative dose measurements (e.g. ionization chambers, diodes and TLDs) or for measuring dose distributions (e.g. ionization chambers and film) do not require calibration. However, relevant aspects of their performance (e.g. linearity, leakage) must be evaluated at commissioning as part of a QA programme. Their sensitivity should be measured frequently, especially if there is the intention of comparing measurements taken at different times. The linearity of these devices should be evaluated frequently, as should other factors such as dose rate dependence. AAPM TG106 [219] on beam data commissioning and TG120 [220] on dosimetry for IMRT provide details of the correct use of dosimeters for different tasks.

6.2.2. Commissioning of treatment machines

6.2.2.1. Dose and geometry in EBRT machines

Moran and Ritter [221] have provided a summary of estimated uncertainties ($k = 1$) associated with measurements on modern linacs. The following summarizes some of the data from this chapter, which includes ample references for justifying these numbers.

— Output ratios can be measured with an uncertainty of 0.5–1.0%.
— Machine jaw position has an uncertainty of less than 1 mm.
— Estimated uncertainties for wedge measurements are approximately 2% or 2 mm (the latter refers to wedge placement accuracy).
— Multileaf collimator (MLC) static position has an uncertainty of less than 1 mm, although leaf end and edge transmission are highly variable.
— MLC dynamic position has an uncertainty of less than 1 mm.

— MLC transmission can be several per cent with highly modulated IMRT fields.
— The table top and couch attenuation uncertainties are highly variable and depend on angle, energy and position. Attenuation through the couch supports can be as much as 20% for extreme conditions.

In 2007, the IAEA developed an auditing process for dose determination under reference and non-reference conditions using new procedures for TLD irradiation in hospitals [222]. The off-axis measurement methodology for photon beams was tested in a multinational pilot study. The results are shown in Fig. 23 and indicate a statistical distribution of dosimetric parameters (off-axis ratios for open and wedge beam profiles, output factors and wedge transmission factors) in 146 measurements of 0.999 ± 0.012 ($k = 1$).

The achievable accuracy in treatment machine geometry is dependent upon the QA applied and the action levels that are accepted. For modern treatment equipment used for advanced technologies such as IMRT and SBRT, the AAPM recommends [223] that linear positioning be maintained at the 1 mm level, and that angular parameters be maintained at 1°.

However, Li et al. [224], and others, have estimated that for IMRT, much smaller criteria for acceptability are required, especially in the positioning of the MLC leaves. Li et al. showed that a leaf positioning error of 1 mm could lead to a mean dose discrepancy of the order of 7% [224]. Cadman et al. [225] also showed that leaf positioning errors introduced significant dosimetric errors. In their system, a reduction in leaf position of 1.4 mm was necessary to avoid dosimetric errors of 12%.

Generally, relative dose parameters, such as percentage depth dose, tissue–maximum (tissue–phantom) ratios, relative output factors and relative off-axis factors, can be measured to an accuracy of about 1%. Published recommendations advise maintaining relative dose parameters at the 2% level. AAPM TG142 [223] recommends that monthly output checks confirm output constancy to be better than 2%, and daily checks should have an acceptability criterion of 3%. This suggests that the output constancy of clinical linacs has an uncertainty of 2% or better at the $k = 1$ level.

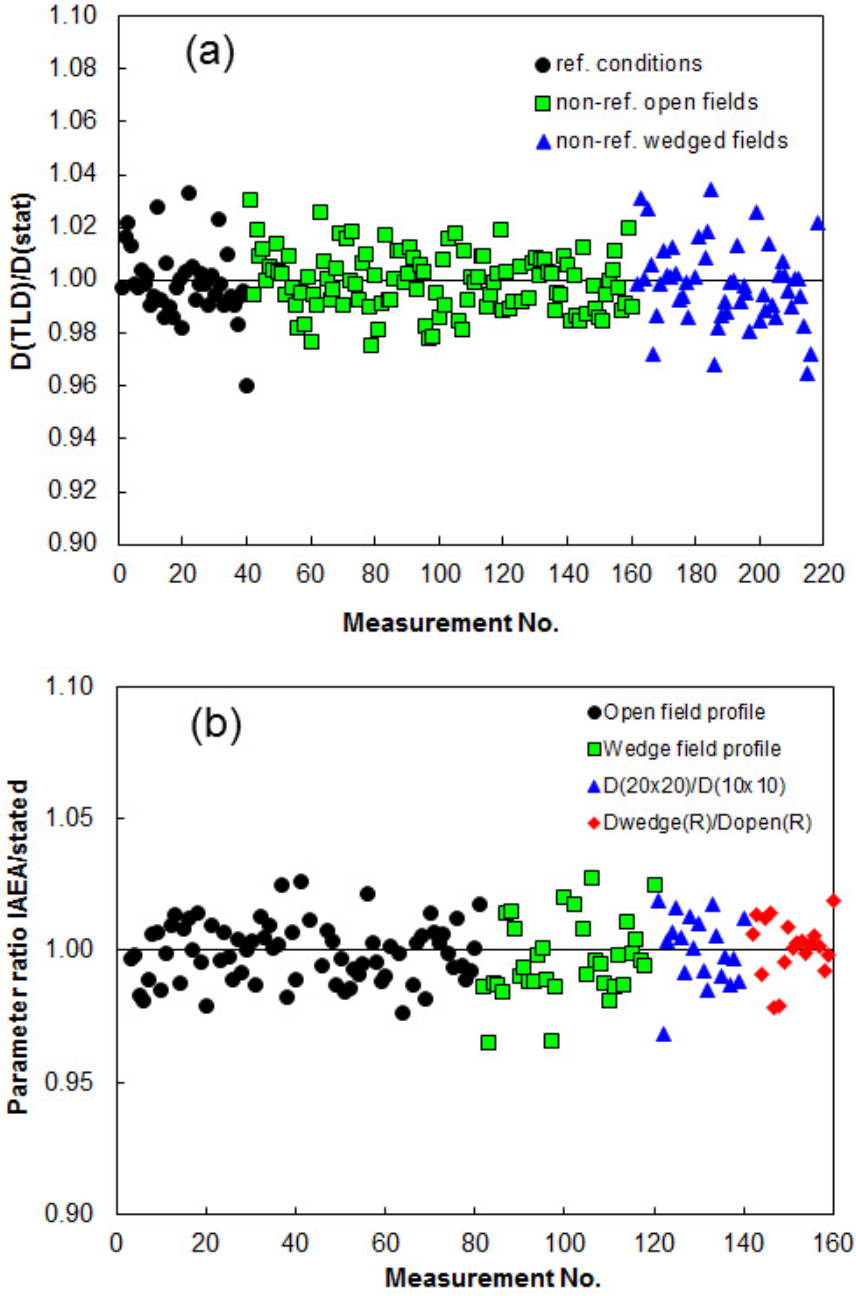

FIG. 23. The results of the multicentre pilot study: (a) doses, i.e. ratios of the IAEA TLD measured dose to the participant stated dose; (b) beam parameters, i.e. ratios of the TLD measured beam parameter to those stated by the participant.

6.2.2.2. Special considerations for dedicated systems such as IMRT, SRS, SBRT and total body irradiation

Treatment equipment specifically designed for stereotactic use demands considerably tighter specifications of geometric uncertainty than equipment used for conventional, i.e. non-IMRT, radiotherapy [223, 224, 226]. The manufacturers of such dedicated devices specify their positional accuracy as less than 0.5 mm. The dosimetry systems are comparable to those of conventional linacs and it is reasonable to expect constancy of 2% or better ($k = 1$ level).

A dedicated accelerator system for helical tomotherapy is different in that while the physicist can and should measure the output regularly, this output is not used directly for patient treatments. Instead, for planning purposes, a standard output value is integrated in the treatment planning software as part of the commissioning process, and it is this value that must be compared with measurements. Moreover, the output of the device is known to vary with rotation angle, and consequently, both the angular variation and the average value must be compared with the integrated value [227].

For some techniques, such as stereotactic treatments and helical tomotherapy, conventional calibration field sizes are not available. Such techniques, along with IMRT procedures, have increased the uncertainty of clinical dosimetry and its link to reference dosimetry using conventional dosimetry codes of practice. As a result, dosimetry uncertainties have become considerably larger than those applicable when conventional beams are used [228]. It is a clear that there is need for a methodology that complements dosimetry in the reference conditions recommended in existing calibration codes of practice. A joint IAEA and AAPM working group has been set up with the aim of developing such a code of practice, which will be based on the general formalism published in 2008 [228]. The formalism introduced the concept of two new intermediate calibration fields: (1) a static machine specific reference field for those modalities that cannot establish conventional reference conditions, and (2) a plan class specific reference field closer to the patient specific clinical fields, thereby facilitating standardization of composite field dosimetry. This work is ongoing and includes uncertainty estimates in the new code of practice.

A more recent report on small field MV photon fields has been produced by the Institute of Physics and Engineering in Medicine in the UK [229]. In their discussion on the estimation of uncertainty in small field measurements, they point out that the selection of a suitable detector (considering its size, water equivalence, energy dependence and other characteristics) together with careful experimental set-up and the application of the appropriate corrections to the detector readings will ensure that Type B uncertainties are kept as low as possible. They indicate that a detailed study of uncertainty contributions in the

determination of absorbed dose to water in small fields still needs to be carried out. It is generally expected that the overall (combined) uncertainty in small field dosimetric measurements will be higher than those from measurements in broader fields because of the higher uncertainties (Type B) in the values of detector perturbation factors, mass stopping power and mass energy absorption coefficient ratios of detector medium to water. It is suggested that further research is needed to establish values for these factors and their uncertainties in small fields for the detectors used. These uncertainties should then be used as input into determining combined uncertainties in treatment delivery.

Total body irradiation has different considerations. Many treatment techniques have been developed and treatment geometries tend to be at extended distances with very large field sizes [230, 231]. Reports making recommendations on total body irradiation dosimetry consistently advise performing dosimetric measurements under the conditions that the patient will be treated [230–232]. They also indicate that, with a significant effort, a total body dose uniformity of approximately 5% and 10%, respectively, can be achieved in young paediatric cases and in adults.

6.2.2.3. Brachytherapy remote afterloaders

Several AAPM reports have been written describing brachytherapy considerations, including a detailed dosimetry protocol (AAPM TG43) [196], a code of practice considering all aspects of brachytherapy physics (AAPM TG56) [203], a report describing brachytherapy delivery procedures in which both systematic and random errors as well as treatment misadministrations are minimized (AAPM TG59) [233] and a dosimetric uncertainty analysis (AAPM TG138) [56]. The TG56 report provides a description of a comprehensive QA programme that addresses each of three basic processes: (1) the applicator insertion process, (2) the implant design and evaluation process, and (3) the treatment delivery process. It points out that the variability in brachytherapy device features and clinical practice standards precludes the development of a fixed QA programme. The ESTRO Booklet No. 8 [204] provides detailed QC methods, test frequencies and action levels for all types of afterloaders. The action levels are thought to reflect the upper limit of acceptability in clinical conditions and are similar to the QC limits given in the AAPM reports. Using recommendations such as those found in the reports cited here, each institution must develop a programme specifically suited to the local clinical environment. One of the major challenges is to identify the relevant quantitative end points and the accuracy with which they must be realized to carry out the radiation oncologist's clinical intent in a practical and reasonable fashion. These reports provide guidance for implementing a QA programme and the values they list for

physical end points can generally be considered as clinical uncertainties at the $k = 1$ level.

Several observations are made in the AAPM TG56 report regarding quantitative accuracy statements.

(a) Positional accuracy

In most clinical applications of remote afterloaders, a source positional accuracy of ±2 mm relative to the applicator system (not to anatomical landmarks in the patient) is achievable.

(b) Temporal accuracy

A temporal accuracy criterion of ±2% seems easily achievable both by manual and commercially available remote control afterloading systems.

(c) Dose delivery accuracy

For dose delivery accuracy, it is useful to subdivide dose delivery into physical and clinical aspects. According to TG56, a source strength calibration accuracy of ±3% appears reasonable. This is consistent with the more recent, and more detailed analysis by TG138 [56]. The best practice values for uncertainties in dose determination at 1 cm from the brachytherapy source in the clinic, including the steps from the full chain of source calibration, up to the dose calculation using the treatment planning system dataset interpolation for low energy sources, is 8.7% and for high energy sources 6.8% (at the $k = 2$ level). These data relate to the use of the TG43 formalism for dose calculation in a water medium. For the same conditions, TG56 estimates that for LDR delivery, a physical dose delivery accuracy of 5 to 10% is achievable at distances of 1 to 5 cm from most common LDR sources. TG56 also estimates that computer assisted dose calculations should have a numerical accuracy of ±2%, although for the lower density heterogeneities such as air and fat, they suggested that one dimensional algorithms have an accuracy of the order of 10% depending on the energy. This was further analysed with several examples by Rivard et al. [5] in 2009. More recently, the situation with a modern model based dose calculation algorithm was reported [234] and this is discussed further in Section 6.2.3.2.

Clinical dose delivery accuracy is much more difficult to determine since it involves an array of issues that are difficult to solve. Factors to consider include the accuracy with which the treatment planner and the treatment planning computer can reconstruct the 3-D geometry of the applicators and the source dwell positions within the applicators. Anatomical reference points are often

required, e.g. bladder and rectal reference points for intracavitary brachytherapy. In addition to achieving the desired dose distribution, dwell times may have to be optimized and careful attention will then have to be applied to optimization end points, prescription criteria and the quality of the resultant implant. Along with this, as in EBRT, are the difficulties of defining the target volume and critical organ margins relative to the applicators in addition to the consideration of controlling or compensating for patient motion. Because of the variability of procedures, action levels will have to be determined by each user based on practical considerations.

6.2.3. TPSs (uncertainty in the dose calculation)

TPSs require the entry of data to model the radiation beams. The amount of data required depends on the computational algorithm, and can vary from very few measurements to thousands of measurements that completely map the radiation beams for a range of field sizes. Systems that require little measured data rely upon a comprehensive description of the design of the accelerator head, collimator and accessories. The accuracy of any TPS is finally determined through a comparison of calculations with measured data. Complete validation of a TPS requires comparison between calculations and measurements over a wide variety of treatment conditions, necessitating a large volume of measured data.

Systems that require the measurement and transfer of tables of data might tempt the user to reduce the number of data points in an attempt to speed up the process. This should be resisted, as deviating from the spatial or numerical resolution of the measured data could increase the uncertainty of calculated dose rates.

6.2.3.1. Dose calculations (EBRT)

The determination of the dose delivered to the patient involves a complex process. Generally, the process begins with a set of measurements in a water phantom under idealized conditions. Dose calculation algorithms often require these water based measurements as input data. The algorithm then makes appropriate corrections for different tissues, variable beam and patient arrangements, and relevant machine geometries and energies. Multiple algorithms exist on various commercial TPSs. Some systems use correction based algorithms in which the dose to the patient is first calculated as though the patient consisted of a uniform water density, and corrections are then made for tissue inhomogeneities [235]. Other algorithms are model based and calculate the dose directly using tissue density information generally obtained from CT scans [235]. The latter generally use convolution or superposition algorithms. Even

when the physics is more comprehensive, the accuracy of the calculations is dependent on how well the physics algorithm has been translated into computer code. Thus, just because it is a model based algorithm does not automatically mean that it provides the correct answer. Because of the multiple variables, the multiple algorithms, the multiple beam geometries and the multiple therapy machine related parameters, it becomes difficult to make simple statements about accuracy and uncertainties in the dose calculation procedure.

Much has been published on dose calculation algorithms. Indeed, these algorithms continue to evolve as new physics information becomes available and as computer technology allows more sophisticated algorithms to be practically implemented on commercial TPSs. As an estimate of the accuracy capabilities of TPS calculations for 3-D CRT, one of the more complete studies was published in 2014 [236]. The IAEA developed a set of practical clinical tests for TPSs based on its TRS 430 report [28]. The methodology was based on a semi-anthropomorphic phantom representing the human thorax and the simulation of the chain of external beam treatment planning activities. The phantom was scanned using CT. The CT data were transferred to the TPS where planning of the clinical test cases and dose calculations were performed. The planning tests covered a range of conformal radiotherapy techniques. These irradiation procedures were then delivered to the phantom on the treatment machine. Doses to specific points in the phantom were measured with an ionization chamber. The results give an indication as to the accuracy and uncertainties associated with modern TPSs.

The pilot procedure was carried out in 17 different hospitals which used 14 different algorithms, inhomogeneity correction methods or both, implemented on different commercial TPSs [237]. A total of 53 clinical test case datasets for different energies and calculation algorithms were produced. Criteria of acceptability had been defined in IAEA TRS 430 [28] and ranged between 2 and 5% depending on the nature of the beam–patient treatment geometry and the ancillary devices used in the treatment. Figure 24 gives a high level summary of the results. In this study, algorithms were divided into three types:

(1) Measurement based algorithms.
(2) Model based algorithms which use a pencil beam convolution model and primarily equivalent path length corrections to account for inhomogeneities. Changes in lateral electron transport are not modelled.
(3) 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 modelled approximately.

Dose differences of more than 20% were discovered for some of the simple algorithms and high energy X ray beams. The number of deviations outside

the criteria of agreement increases with the beam energy and decreases with sophistication of the calculation algorithm. For the type 3 algorithms (point kernel convolution/superposition), the deviations between the calculated and measured doses were within the stated agreement criteria (i.e. 2–5%) for nearly all TPSs tested.

Discrepancies between measurement and calculation may arise due to a number of factors. These include: (1) TPS beam data input, (2) beam model fitting, (3) dose calculation algorithm, (4) verification measurement set-up and (5) dosimeter measurement uncertainty. Some of the deviations are related to systematic errors associated with algorithm limitations, while others may indicate deficiencies in the different parts of the treatment planning process chain.

In a more recent report describing the extension to this study [238], 186 datasets (combination of algorithm and beam energy) were collected in 59 hospitals in 8 European countries (Estonia, Hungary, Latvia, Lithuania, Serbia, Slovakia, Poland and Portugal). Dosimetry problems (outside the criteria of acceptability of 2% to 5% depending on the specific test) were identified in 10% of the datasets and a summary of the reasons for the deviations is shown in Fig. 25. The CT number to relative electron density conversion curves needed adjustment in about two thirds of the centres (based on the following criteria of acceptability: ±5 HU for water; ±50 HU for bone-like material and ±20 HU for

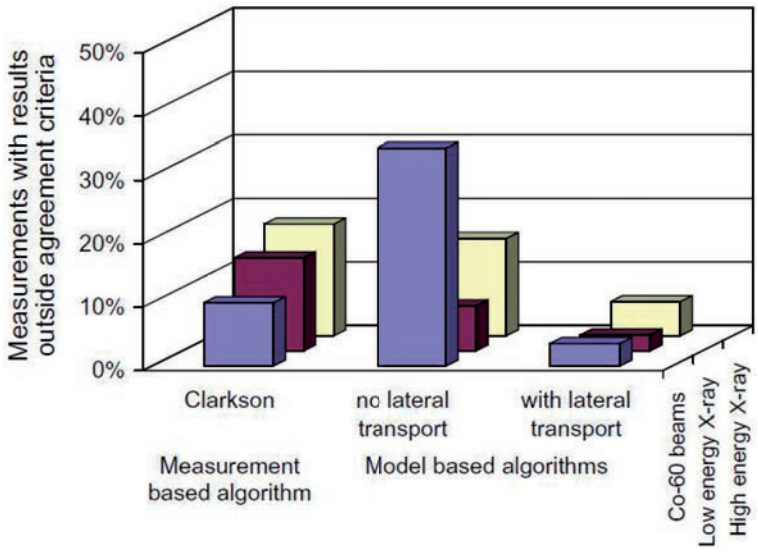

FIG. 24. Percentage of measurements with results outside agreement criteria depending on algorithm type and energy. (From Ref. [237].)

all other materials). Again, the largest deviations were for the simpler algorithms, with the poorest performance occurring with ^{60}Co beams and model based algorithms not accounting for lateral transport (e.g. pencil beam convolution).

Analogous results have been published in other reports. For example, Davidson et al. [239, 240] determined the accuracy of five commonly used IMRT TPSs, three using a convolution/superposition algorithm (CSA) and two using a pencil beam algorithm (PBA) in calculating the absorbed dose within a low density, heterogeneous region in an anthropomorphic lung phantom. The predicted dose in the centre of the target volume was within 5% of the measured dose or within 3 mm DTA for all TPSs tested. For more challenging locations at the tumour–lung interface and at the peripheral lung in the vicinity of the tumour, the CSAs gave better results than the PBAs with 86–96% and 50–61%, respectively, of calculation points within the 5%/3 mm criteria (see Fig. 26).

Another recent report [241] provided an evaluation of inhomogeneity corrections and monitor unit calculations for treatment planning. They looked at two accelerator vendors, 4 different energies and various algorithms. The measurements confirm that Pinnacle CSA predicts doses mostly to within ±5%, even near lung–tissue interfaces over the full range of energies and field sizes tested. The Eclipse modified Batho and equivalent tissue maximum ratio algorithms overpredicted doses by 10% or more in the lung and near the lung–tissue interfaces if the field size was less than 10 cm × 10 cm when the energy was 18 MV or higher. At lower energies, the field size had to be at least 6 cm × 6 cm for calculated doses to be within 10% of the measurements. For bone–tissue interfaces, doses were

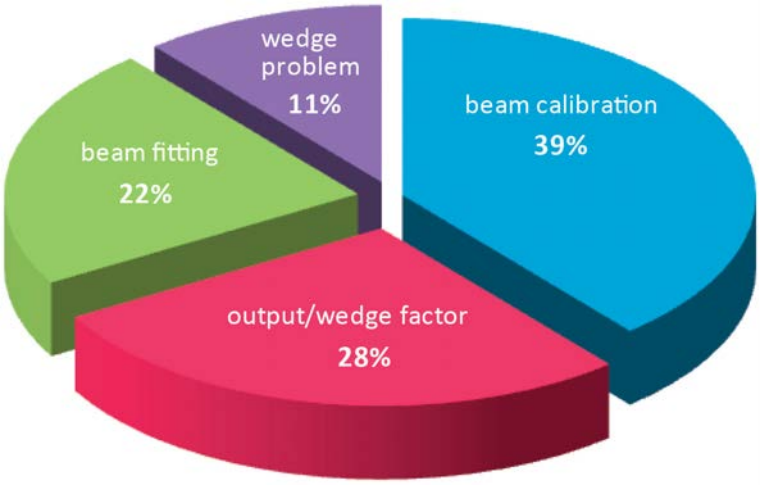

FIG. 25. Reasons for deviations that occurred in the IAEA audits of TPSs. (From Ref. [238].)

generally underestimated by 5 to 10% or more by all calculation methods over the range of field sizes and energies reviewed. Results from studies of the accuracy of dose determination in anthropomorphic phantoms of conventional 3-D CRT treatments are summarized in Table 7 [215]. These variations have a standard deviation up to 3.5%. Part of the variation is attributed to the dosimetry method used during these audits. Another part relates to interinstitutional variation.

Monte Carlo methods, which mimic the radiation transport process, are capable of providing more accurate dose calculations. They tend to involve long calculation times and therefore are often used for research and benchmarking purposes in both external beam [242] and brachytherapy dosimetry [243]. Several Monte Carlo codes have been developed. In an effort to speed up the calculations, they are based on a number of different approximations and assumptions. There are several commercial planning systems that offer a Monte Carlo code as an option to calculate the absorbed dose in the patient as part of their normal routine application (e.g. Refs [244, 245]).

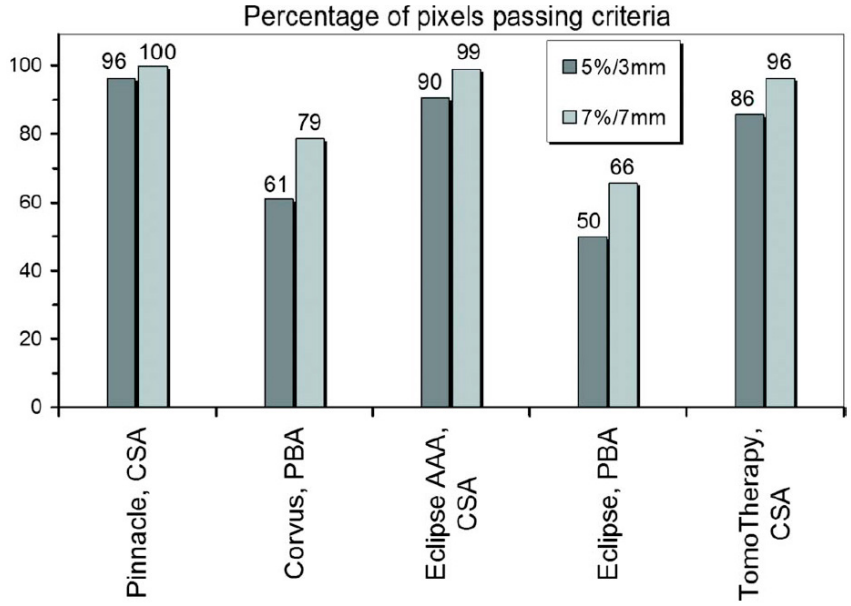

FIG. 26. Percentage of pixels meeting criteria at the tumour–lung interface and at the peripheral lung in the vicinity of the tumour, at both levels tested for all TPSs (Key: 5%/3 mm, percentage of pixels falling within 5% of the calculated dose or within 3 mm DTA; 7%/7 mm, percentage of pixels falling within 7% of the calculated dose or within 7 mm DTA.) (From Ref. [239].)

TABLE 7. RESULTS FROM STUDIES ON THE ACCURACY OF DOSE DETERMINATIONS IN ANTHROPOMORPHIC PHANTOMS FOR CONVENTIONAL AND 3-D CRT TREATMENTS
(Adapted from Ref. [215])

Region or country	Site	*N*	Average	SD (%)
Europe	Tonsil	19	1.035	3.2
Netherlands	Prostate	18	1.015	1.5
UK	Pelvis, homogeneous	62	1.008	2.7
	Lung, inhomogeneous	62	1.011	3.4
UK	Head and neck	13	1.007	2.1
	Bronchus	13	0.989	2.4
Australasia	Head and neck	19	1.001	3.5
	Pelvis	21	0.996	3.3
UK	Breast	36	0.979	1.3
Italy	Pelvis	16	1.009	2.2

For treatment planning with electron beams, Monte Carlo based algorithms have a higher accuracy than conventional dose calculation algorithms and are therefore sometimes preferred (e.g. Ref. [244]). Their accuracy is dependent on Poisson statistics and the number of histories used in the calculation, thus yielding Type A uncertainties. In addition, Type B uncertainties occur as a result of the various assumptions (e.g. variance reduction strategies) and input data (e.g. source geometry, cross-sections) that are required to perform the calculations. AAPM Task Group 105 [242] points out that deviations of up to 10% have been observed between two different Monte Carlo codes. These discrepancies were attributed to differences in the modelling of the machine MLC and were not caused by particle transport in the patient, thus demonstrating the importance of careful modelling of the MLC in IMRT treatment planning. Studies from photon Monte Carlo algorithms showed calculated output ratios to be within 1.5% of measurements over a range of field sizes. Similar results (1–2%) were reported for electron beam output ratios for field size specific applicators. The task group suggests that 2% statistical uncertainty should be the goal for patient fields that have irregular shapes.

6.2.3.2. Dose calculations (brachytherapy)

The early efforts within the Manchester System [246] using Sievert integrals went someway to calculating dose along a series of lines parallel to the axis of the source. The main brachytherapy TPSs currently in use for most brachytherapy applications are based on the formalism of the AAPM TG43 [196, 247], which brings each aspect of the problem of dose calculation into a parameterized equation. The method is based on the air kerma strength of the source (from in-house measurements or from the source certificate), the conversion factor Λ being the dose rate constant in water providing the dose rate to water conversion at the reference point at 1 cm on the transverse axis of the source, the radial dose function accounting for scatter and absorption and the geometry function accounting for the activity distribution of the physical source along the transverse axis, and an anisotropy function for calculation at points off the transverse axis. The data of the parameters and functions are specific for a given source design and must be available (or entered manually) in the TPS.

There are a large number of papers comparing TG43 dose rates for several different ^{125}I and ^{103}Pd sources with Monte Carlo calculations [248–255]. For HDR sources, the value of the dose rate constant Λ is known at a higher level of accuracy. The source strength can be traced to a primary standard of air kerma rate.

The medical physicist is responsible for entering the data and validating the calculations of the TPS for the applications used clinically. The data required under TG43 formalism have been analysed by several expert groups from the many papers in the literature and should comply with the prerequisites [194, 195, 256]. Internet access to comprehensive databases of TG43 data can be very helpful for the individual user and it is therefore recommended to use such data, e.g. at the Carleton University [257] and ESTRO [258] websites.

The uncertainty of these data can be estimated on the basis of the techniques for performing the measurements (e.g. TLD) and calculations (Monte Carlo) and are of the order of 3.0–3.6% and 1.6–1.7%, respectively, according to the TG138 report [56]. This results in the propagation of best practice uncertainties in the absorbed dose rate to water at 1 cm on the transverse plane of 4.4% for low energy sources and 3.4% for high energy sources (at k = 1 level), as shown in table V of Ref. [56]. The factors included in the uncertainty analysis were the source strength measurements at the clinic, the determination of dose parameters by measurement and/or calculation and treatment planning system dataset interpolation.

It is noted that, although this widespread use of the TG43 formalism for dose calculation in brachytherapy is the standard at the time of writing, it has several limitations. In fact, TG43 is a superposition of single source dose distributions calculated with data obtained in a liquid water phantom with a fixed volume for radiation scattering. Several effects of clinical brachytherapy cases are therefore not included, with varying influence on overall accuracy.

When the actual patient is considered, more uncertainty comes into play. This arises in particular from:

(a) Tissue inhomogeneities, elemental composition, density changes and lack of scatter;
(b) Attenuation in the actual applicator materials holding the source, effects of protective shielding and intersource shielding;
(c) Imaging processes and the transfer of image data to the treatment planning computer;
(d) Target definition and contouring;
(e) Variations at clinical dose delivery.

Some of these issues yield relatively small uncertainties (mostly less than 1.5%); however, applicator attenuation and tissue inhomogeneities could yield significant uncertainties under some conditions and these are discussed below. Also, several other examples of clinical uncertainties in brachytherapy procedures are presented in the following sections.

A recent review by GEC-ESTRO and the AAPM resulted in guidelines [259] in which several aspects of brachytherapy dose delivery not accounted for in the TG43 formalism were analysed for their influence on the total dosimetric uncertainty, e.g. inter- and intrafraction changes, and lack of full scatter in some applications.

Dose delivery in a permanent prostate implant is to some extent affected by the intersource shielding, for instance. The aforementioned report [259] showed this effect depends on the seed type and radionuclide used, the seed spacing and size of the implant. Monte Carlo studies with low energy seed sources used in such implants showed results which ranged between a negligible effect and a CTV D_{90} overestimation of 1% to 5% depending on the implant geometry, volume and seed density and seed model.

While tissue density can be obtained from CT imaging datasets, tissue composition is not currently available with conventional CT scanning. In prostate implants, low energy radiation dose deposition is influenced by the presence of calcifications, whereas in breast implants, the ratio of adipose/gland tissue determines the effects on delivered dose. The sensitivity of the dosimetry for these effects was studied by Landry et al. [260] with Monte Carlo methods using 4 prostate and 4 breast cases with different seed types. The effect of composition on prostate dosimetry varied from negligible to an average D_{90} increase of 3.2% compared with water, while the lower Z_{eff} in breast tissue led to a 30% increase in D_{90}. Smaller effects were connected with density variations.

With high energy sources, the Compton effect in dose delivery decreases the concern with heterogeneity in tissue composition when compared with the use of lower energy photon radiation, though effects with density, interface effects and high Z shielded applicators can be apparent. The effects of partly shielding a region of the implant are both distance and position dependent and therefore not constant. Patient scatter conditions in breast cancer implants using an HDR ^{192}Ir source were shown to overestimate the dose at the tissue–air interface by 14%, but a much lower effect was found at the higher isodose areas near to or in the implanted volume [261].

When using contrast medium in a breast balloon catheter with HDR ^{192}Ir, the prescription dose may be overestimated by 4%–10% depending on the concentration of the contrast medium for the given balloon size of 4.5 cm diameter. These effects will vary for other balloon sizes, and distances other than the dose prescription distance.

Owing to the dependence of so many factors, types of applications, variations from patient to patient, etc., the uncertainty budget of brachytherapy cannot simply be summarized in one single number. Each treatment technique will have to be analysed separately (e.g. for prostate, breast, gynaecology) and even more so for specific applicator techniques.

Model based dose calculation algorithms (MBDCAs) have recently been incorporated into commercial brachytherapy TPSs. This has been made possible by increases in computing power, so that approaches based on fundamental physics processes or physics models, such as the linear Boltzmann transport equation, are now available in a clinical setting. An MBDCA will improve treatment planning compared with the implementation of the traditional TG43 formalism by accounting for individualized, patient specific radiation scatter conditions, and the radiological effect of material heterogeneities differing from water.

The first studies comparing the potential of such algorithms are under way and guidance on implementation and parallel reporting during the transition phase have been published by the AAPM TG186 [234]. The analysis of the Varian Acuros software versus benchmark Monte Carlo calculation showed agreement in general within 2% [262, 263].

Introduction of new formalisms into the clinical setting has had a major influence on the quality management of radiotherapy departments. Comparisons with Monte Carlo methods are well beyond the capabilities of the average medical physics service and require additional resources and guidance. In two Vision 20/20 publications in the journal Medical Physics, ideas for possible guidance were described [5, 243]. It was suggested in Ref. [243] that the introduction of MBDCAs in clinical practice will require new QA standards to supplement current recommendations on TPS QA, that consideration should be given to new dose specifications such as dose to medium in medium, and that radiotherapy departments should consider the additional infrastructure needed to uniformly introduce these new algorithms.

It is expected that widespread use of these new MBDCAs will increase the overall accuracy in dosimetry, but will also necessitate joint efforts to critically appraise the new methods.

An excellent review of brachytherapy TPS QA is given by Rivard et al. [5]. This article points out that manufacturers are making progress in developing MBDCAs, brachytherapy sources and brachytherapy delivery systems which go well beyond the current QA guidelines. The role of intraoperative and multimodality image based planning is growing. However, many institutions still perform conventional brachytherapy. Williamson et al. [8] point out that published guidelines on brachytherapy QA emphasize the QA of the equipment itself rather than the clinical processes involved in brachytherapy, and that the individual QC tests recommended are based on equipment performance specifications rather than on the basis of a thorough risk assessment. For non-image-based brachytherapy, the AAPM TG Reports 56 and 59 [203, 233] provide reasonable guidance on procedure specific process flow and QA. Quantitative accuracy requirements described in the TG56 report have been summarized above. The action levels described in the ESTRO HDR brachytherapy QA guidelines [204] are summarized in Table 8 and give an indication of minimum accuracy levels that should be achievable. Improved guidance is needed even for established procedures such as ultrasound guided prostate implants.

TABLE 8. TEST FREQUENCIES AND ACTION LEVELS FOR VARIOUS BRACHYTHERAPY PROCEDURES
(Adapted from Ref. [204])

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	—

Note: HDR — high dose rate; PDR — pulsed dose rate; LDR — low dose rate; MDR — medium dose rate.

6.3. PATIENT POSITIONING AND IMMOBILIZATION

The initial definition of the patient position and the ability to accurately reproduce this position on a daily basis is crucial for the accurate delivery of a course of treatment. With the current trend towards higher overall dose, higher dose per fraction and smaller volumes, care and attention to patient preparation is of even greater significance.

The optimum patient position and method of immobilization is based on the clinical site and the extent of the tumour volume. This can be one of the most effective methods of minimizing dose to the OAR. The physical status of the patient and the stage of disease should be considered when deciding on the most appropriate immobilization method. Patients may suffer with comorbidities that may affect their ability to achieve and maintain the required position and this must be taken into account. In the case of palliative treatment, patient comfort may be considered a priority but accuracy, within agreed parameters, must be maintained.

The implementation of immobilization devices includes detailed documentation of reference points. There should be an institutional reference system for associating the table position with the immobilization and positioning devices. Indexed systems facilitate this process but require compatibility between the devices and the table top (usually all indexed immobilization devices will also then need to be purchased from a single supplier). Patient repositioning uncertainties are dependent on the body site and the immobilization devices used. For example, treatment to treatment variation for immobilized head and neck set-ups of up to 3 mm has been observed. For unimmobilized pelvic set-ups, variations of 6–8 mm are common. These variations can be even larger in the thoracic region. Daily on-line imaging data for treatment set-ups indicate variations in anatomy that can range over a couple of millimetres for head and neck treatments to 10–20 mm in the pelvis [264, 265]. Incorrect positioning of head and neck patients could potentially result in the unwanted inclusion of the spinal cord in the high dose volume. An important aspect of positioning and immobilization is the clarity of the information given to the patient and the level of their understanding of the importance of maintaining their position. Good cooperation on the part of the patient is essential. A detailed explanation should be given to patients of topics such as bladder or bowel preparation. Care must be taken in achieving a balance between maintaining patient privacy and not compromising positioning.

An acceptable level of accuracy can be achieved even without sophisticated systems by care and attention when carrying out positioning and immobilization based on an understanding of the underlying principles and not simply the technical application. Ensuring as much patient comfort as possible and taking

care with preparation and application of immobilization devices will minimize patient movement and reduce non-acceptable deviations. Patients who are uncomfortable are more likely to try to adjust their position and to find the treatment procedure more distressing than is necessary. Patient positional change can be avoided by using a single position (rather than turning patients over between fields, for instance) for treatment of all fields. The knowledge and skill of the RTTs carrying out the preparation of immobilization devices is also a factor, as demonstrated by Malone et al. [266], who found that the effectiveness of any immobilization device was improved as the RTTs became more familiar with it, resulting in a decrease in the overall error rate with the increase in the number of patients treated. It is good practice to use visual verification of the light field with respect to the target volume and healthy tissue sparing where static fields are used. For advanced techniques using small or dynamic fields, composite fields could be used as a guide instead.

6.3.1. Methods commonly used for daily patient set-up verification

6.3.1.1. External markings

Accurate marking of reference points and field delineation, whether directly on the patient skin or on the immobilization device, are essential. For many years, skin markings were used to define the full field area for treatment, and, in many centres across the world, they are still used in this way. The difficulty of over-reliance on skin marks is their inherent unreliability. Skin, particularly in the more obese patient, is mobile with respect to the underlying organs, and a shift in skin mark position can lead to a failure to adequately cover the intended internal volume. Many centres are now routinely using couch height for positioning rather than relying on skin marks and lateral lasers. This method defines the location of the isocentre at a height relative to the table. A clearly marked rigid ruler must be used. In conjunction with a rigid table, couch height has been shown to significantly improve accuracy in the anterior/posterior direction when compared with alignment of skin marks and laser lights [267, 268].

The moisture content of skin also varies with time and this can cause marks to become blurred or faded. Tattoos are ideal but may not be acceptable in some cultures. Dependent on the skill of the RTT, it may also be difficult to differentiate the tattoo from skin blemishes. Various commercial products are now available that can help to overcome this problem.

Marks on both skin and immobilization devices must be clear and not too thick. Thick lines are open to significant uncertainty in field positioning, and over a course of treatment can lead to a substantial shift in field borders. When re-marking is required due to fading skin marks, great care must be taken

to reproduce the position exactly. Here, the width of the initial and subsequent markings is critical as significant positional change can be introduced. Tape used to mark field information on the immobilization devices must be secured with minimum creasing to facilitate clear marking.

Where there is a second treatment phase or integrated boost, care must be taken to differentiate the two phases. Some centres use a different colour in these instances.

6.3.1.2. Bone matching

With increasing potential for imaging the treatment volume at the time of treatment, the reliance on external skin marks changes. Skin marks are now more commonly used to denote isocentres and reference points for positioning with subsequent imaging and field verification prior to treatment. Bony anatomy is now used in many centres to match the daily treatment volume with the original digitally reconstructed radiograph (DRR). Bony anatomy is stable in comparison with skin and therefore constitutes an improvement in daily positioning accuracy. With respect to prostate treatment, Liu et al. [269] refer to skin marks as normally associated with a planning margin of 10 mm and a 6–7 mm margin in the posterior direction. They found that skin mark alignment led to under-dosage of the PTV in more than 50% of all cases in both supine and prone positions and they found that there was a significant improvement with the use of bony alignment in both positions. This was further improved when soft tissue matching was used.

6.3.1.3. Soft tissue matching

Bony anatomy matching is perhaps most accurate in the head and neck area. However, although bone is far more stable than skin, it is still not ideal in situations where the organs contained within the bony cavity are subject to variation in position. Van Haaren et al. [270] determined for prostate treatments that margins of 8 mm would be insufficient if treatment was carried out without position verification and set-up corrections, or based on bony anatomy matching alone.

Soft tissue matching is now commonly used but is dependent on the availability of the technology and the ability of staff to interpret the images correctly. Van der Vight et al. [271] found that bony anatomy did not represent the prostate position, as organ motion was considerable and bony matching could result in a significant, non-acceptable deviation. They recommend the use of gold fiducial markers with an off-line correction protocol to track prostate position prior to treatment delivery to reduce systematic set-up error, and an on-line correction protocol to reduce random error. Fiducial markers are not suitable in

all settings and can also be subject to shift of position within the implanted area. The advent of IGRT has now made daily imaging possible and a greater level of accuracy than ever before can now be achieved [272].

With IGRT, margins can be reduced and, correspondingly, the PTV volume. This was demonstrated by Tournel et al. [273], who were able to reduce their CTV-PTV margins in rectal cancer patients treated with tomotherapy from 10–15 mm to 8 mm in the lateral directions, 11 mm in the anterior direction, 7 mm in the posterior direction, 10 mm in the cranial direction and 12 mm in the caudal direction.

6.3.1.4. Organ motion

Even with direct soft tissue matching, internal organs are subject to change within the time of individual fraction delivery. This can be related to physiological processes such as breathing, swallowing, heartbeat, bowel or bladder filling. In circumstances where care and attention to positioning and immobilization can greatly increase the level of accuracy, efforts have focused on minimizing organ motion as much as possible, as it can also have a significant impact on accuracy, particularly with 3-D CRT or IMRT where there is very little margin for error. Prostate displacement occurs as a result of bladder or bowel filling and organ deformation can be quite significant. Bayley et al. [274] found that prostate motion during a fractionated course of treatment could be as much as 5–10 mm in the AP direction, 1–2 mm in the lateral direction and up to 10 mm in the superior-inferior direction. Muren et al. [275] documented both a large internal motion of the bladder and a substantial patient set-up variation as a result of bladder filling in radical radiotherapy of urinary bladder cancer. In the thorax, normal breathing can result in a significant shift in position of both lung and breast volumes. For instance, McNair et al. [276] found that organ motion during breathing could range between 6 and 18 mm resulting in PTV margins of 15–20 mm. In the head and neck region, changes to the larynx position are regularly observed due to swallowing.

6.3.1.5. Reference points

When the initial reference point identified at CT acquisition requires a shift of the isocentre, this must be recorded with great care to avoid misinterpretation of the table translation. The isocentre position should be verified against the DRR at the time of first treatment. In a paper by Klein et al. [277], incorrect coordinate use, not necessarily always as a result of a shift, was the most common error detected. They also pointed out that if the coordinates are derived incorrectly and entered into the RVS, the error is perpetuated. The Royal College of Radiologists,

as well as the ICRU, recommend the use of a single coordinate system in a department. This should specify the isocentre position relative to a set-up point giving translational directions and rotation around the axes [18, 278]. Again, most errors relating to coordinate systems can be detected and corrected by imaging at the initial treatment. The in-room imaging method used can be portal imaging with film, electronic portal imaging devices (EPIDs) or any other device for IGRT, depending on the specific situation and the local resources. These images should be reviewed according to institutional policies defined by a team including both radiation oncologists and RTTs, while medical physicists would coordinate the implementation of the image analysis methodology.

When preparing a patient for treatment, all the individual factors must be considered to ensure maximum stability and reproducibility over the full course of treatment. Care at this stage of the process will maximize the use of often scarce resources, reduce set-up difficulties and keep the need for repeat procedures to a minimum.

6.3.2. Site specific positioning and immobilization

6.3.2.1. Pelvic region

For patients treated in the pelvic area without immobilization set-up, variations of 6–8 mm are common. The optimum immobilization method, however, remains a subject of debate, with a study by Song et al. in 1996 finding no significant variation in position with no immobilization but with very careful set-up procedures [279], and Malone et al. [266] demonstrating a decrease in overall uncertainty with the increase in the number of patients treated within any one immobilization system. Care and attention as part of the patient set-up is a crucial step in accurate preparation and treatment delivery, saves time subsequently and reduces the risk of non-acceptable deviations. Efficiency is further improved by familiarization with the immobilization systems.

Several studies have shown that a simple footrest system is effective in minimizing pelvic movement, and that care and attention to initial positioning can be cost effective while achieving good results. A 1995 study by van Herk et al. [280] found that leg rotation was the second most important factor in maintaining position when treating prostate cancer patients. Baumert et al. confirmed that lower leg immobilization and fixation decreased rotation in the frontal plane [281].

Debate relating to the use of a belly board is ongoing. There are advantages to treatment in the prone position with respect to the dose delivered to the rectum and bowel, but these are often mitigated by the difficulty in set-up, position stability and reproducibility. Robertson et al. [282] found that the prone position

required significantly more pretreatment corrections even when the patient was immobilized, and this should be taken into consideration when treatment appointment times are being allocated. Bayley et al. [274] found no difference in uncertainty between prone and supine but observed considerably less prostate motion in the supine position and an increased number of pretreatment corrections in the prone position, which required a larger PTV to compensate. In this study, they found statistically significant improvement at all dose levels for the OAR following corrections related to organ motion. The optimum position is still under debate with different studies often reaching different conclusions. It is important to assess each patient individually and to preselect only those patients for prone treatment who will be able to maintain stability in the prone position.

A comfortable arm position when patients are supine helps to maintain stability [283]. When using a vacuum cast, it should be long enough to fully support the patient's spine; it should not stretch the patient's skin and the sides should be sufficiently low to ensure that lateral tattoos are visible [284].

Patient weight may vary over the course of treatment and this may have an impact on the dose distribution. There may be weight loss due to the disease or side effects, or perhaps weight gain if the patient has had hormonal therapy as part of the treatment regime. It is useful to have a baseline weight taken at time of simulation for comparison if necessary. Such weight changes are subject to volume changes over time and could lead to positional shifts.

Where a bladder filling policy is in place, the simulation must be carried out under the same conditions. The policy should achieve the desired dose constraints while ensuring the patient is comfortable enough to maintain position. The filling capability of the bladder may change towards the end of the treatment. This is also true for rectal filling. A significant relationship exists between rectal distension at the time of planning and the NTCP/TCP, resulting in a significantly higher incidence of biochemical failure and poorer patient outcome [285]. Heemsbergen et al. [286] confirmed this and found a significant decrease in tumour control for a subgroup of patients in their study with a large rectum (volume $\geq$90 cm^3) at the time of the planning CT scan.

6.3.2.2. Thoracic region

Variations in position with patients treated in the thoracic region are even greater than in other parts of the body, and an immobilization device is essential in these cases. A higher degree of patient comfort with limited immobilization may be possible with the introduction of IGRT and the ability to image patients daily prior to treatment delivery. However, this must be carefully considered in the context of resources and staff ability. Swallowing, respiration and diaphragm motion must all be considered. It is advisable to use breast and lung boards

and to accurately record the reference positions of all elements. The boards should be referenced to the treatment couch and preferably fixed in position. In a study of three immobilization devices for intrathoracic treatment, O'Shea et al. [287] found that non-acceptable deviations were increased when the patient was positioned with a head support only. Stability in the position of the arm is necessary to ensure accurate reproducibility in the thoracic region.

The use of a breast board is recommended to ensure position stability and reproducibility for breast radiotherapy. Difficulties with arm position may be encountered with a small bore CT scanner but CT planning with a breast board is advisable to ensure lung and heart doses are kept to the minimum. Canney et al. [288] demonstrated a 60% reduction in the mean cardiac dose and a 32% reduction in maximum dose for left-sided treatment when they used a breast board with the arm raised over the head, compared with no breast board and the ipsilateral arm abducted and flexed by 90°. Breath-holding techniques have also been used to achieve cardiac dose reduction in left breast irradiation [289].

6.3.2.3. Head and neck region

Patient repositioning uncertainties are dependent on the body site and the immobilization devices used. Mean set-up errors for immobilized head and neck patients of up to 10 mm have been reported [290]. When treating the head and neck region, a 3–5 point fixation immobilization mask system should be used. A 5 point immobilization mask would cover the top of the head to improve stability. The site for treatment must be considered when preparing the immobilization device.

A 5 point fixation mask is recommended when the supraclavicular nodes in the lower neck region are included in the treatment volume. Skin reactions, particularly in the thinner neck area, can be very severe and are increased by the immobilization device. In some centres, it is common practice to cut out the mask where the direct treatment is incident on the skin. With such cut-outs, care should be taken not to compromise overall mask stability. This procedure is, however, not feasible with rotational IMRT techniques and attention must be paid to the additional skin dose that may be delivered with these techniques. It should also be noted that scans for treatment planning should be performed with the identical mask configuration to that used on the treatment machine.

Individual, customized head rests are an option. Houweling et al. [291] compared standard with individual head supports and demonstrated a significant improvement in reproducibility and stability using the individual support. They found a decrease in both systematic and random error of interfraction variation with statistically significant reductions in vertebral rotation at C1 to C3.

6.3.2.4. Limbs

Irradiation of the limbs presents specific positioning and immobilization concerns. It is important to spare a strip of skin and subcutaneous tissue to maintain adequate lymphatic drainage and minimize side effects following treatment. In the case of lower limb avoidance, the second limb can create additional difficulties. Rotation of the limb can be avoided by appropriate immobilization.

6.3.2.5. Preparation and storage of immobilization devices

Immobilization masks should be rigid to afford maximum stability and reproducibility and should be carefully stored to prevent distortion. All accessory equipment used, including immobilization masks, should be marked with patient details clearly visible. Preparation of the immobilization devices must include detailed documentation of the reference points used. Policies should be developed for the institutional reference system based on table position and indexing or marking of any immobilization and positioning devices. The reuse of thermoplastic materials should be limited to their useful lifespan, as reusing them too often results in loss of rigidity and poor immobilization.

6.3.3. The treatment couch or table

The treatment couch can, of itself, be a source of non-acceptable deviation. The most stable material currently used for the table top is carbon fibre. Flexible inserts should be avoided as their shape can change with extensive use [268, 271, 292]. Rigid devices can be used to provide skin sparing and maintain the patient's contour. Foam mattresses should in general be avoided, but a thin mattress may be useful in the case of prone single spinal field treatment, for instance, where the rigid table may cause severe pain or discomfort.

In terms of the dosimetric effect of the treatment couch, Pulliam et al. [293] evaluated the impact of the couch and rails for five patients with both eight field IMRT and two arc volumetric modulated arc therapy (VMAT) treatments of the prostate. The couch caused average prescription dose losses (relative to plans that ignored the couch) to the prostate of 4.2% and 2.0% for IMRT with the rails out and in, respectively, and 3.2% and 2.9% for VMAT with the rails out and in, respectively. These losses are clinically unacceptable for treatment planning approval. The overall impact of these losses was explored using TCP modelling and showed an up to 10.5% reduction in TCP attributable to neglecting the couch during treatment. These effects are relatively large and should be accounted for in treatment planning, not only of IMRT and VMAT but for all types of treatments.

6.3.4. Laser light system

An accurate laser light system is crucial to accurate positioning and reproducibility. A centrally mounted sagittal laser with two lateral lasers is the conventional arrangement for straightening the patient and avoiding rotational error. Routine daily checks should include simple tests of the accuracy of the laser system. Quoted specifications range between 1–2 mm accuracy in laser alignment with an action level of 2 mm [223, 264, 294, 295].

6.3.5. Summary of immobilization procedures and related uncertainties

As described above, many immobilization procedures have been developed. The most recent published summary of various immobilization devices is shown in Table 9 with quantitative estimates of expected uncertainties for different anatomical sites.

TABLE 9. COMPARISON OF IMMOBILIZATION DEVICES AND EXPECTED UNCERTAINTIES FOR VARIOUS ANATOMICAL SITES

(Adapted from Ref. [296])

Anatomical site	Immobilization device	Expected uncertainty (Mean set-up error)	References
Intracranial	Stereotactic head ring	1.0 mm	[297]
	TALON	1.38 ± 0.48 mm	[298]
	GTC frame	2.00 ± 1.04 mm	[299]
	HeadFIX bite plate	<2.0 mm	[300–302]
	Thermoplastic mask systems	1.59 ± 0.84 mm	[303]
		2.1 ± 1.0 to 2.7 ± 1.5 mm	[304]
		3.17 ± 1.95 mm	[299]
Head and neck	Type S thermoplastic	3.1 ± 1.6 (sup. landmarks) and 8.0 ± 4.5 (inf. landmarks)	[305]
	Bear claw board	2.8 ± 0.9 (sup. landmarks) and 8.0 ± 5.5 (inf. landmarks)	

TABLE 9. COMPARISON OF IMMOBILIZATION DEVICES AND EXPECTED UNCERTAINTIES FOR VARIOUS ANATOMICAL SITES (cont.)

Anatomical site	Immobilization device	Expected uncertainty (Mean set-up error)	References
Spine	Screw fixation of spinous process	2 mm	[306]
	Body cast with stereotactic frame	≤3.6 mm	[307]
	Custom stereotactic frame	2–3 mm positioning accuracy	[308]
	Scotch cast torso and head masks	Cervical: 0.3 ± 0.8 mm ant. pos., −0.1 ± 1.1 mm lat., 0.1 ± 0.9 mm sup. inf. Thoracic: 0.3 ± 0.8 mm ant. pos., 0.8 ± 1.1 mm lat., 1.1 ± 1.3 mm sup. inf. Lumbar: 0.0 ± 0.9 mm ant. pos., −0.7 ± 1.3 mm lat., 0.5 ± 1.6 mm sup. inf.	[309]
Lung	Alpha cradle/Vac-Lok	5–9 mm	[310–312]
Lung SBRT	Abdominal compression	5–8 mm	[313]
	(Elekta body frame)	3.4 mm Ant. pos., 3.3 mm lat., 4.4 mm sup. inf.	[314]
		2 mm	[315]
		2 mm	[316]
		~5 mm	[317]
	Abdominal compression (Leibinger body frame)	1.8–4 mm	[318]
	BodyFIX	2.5 mm	[319]
		0.3 ± 1.8 mm ant. pos., −1.8 ± 3.2 mm lat., 1.5 ± 3.7 mm sup. inf.	[320]

TABLE 9. COMPARISON OF IMMOBILIZATION DEVICES AND EXPECTED UNCERTAINTIES FOR VARIOUS ANATOMICAL SITES (cont.)

Anatomical site	Immobilization device	Expected uncertainty (Mean set-up error)	References
Breast	Breast board with arm support	−1.7 ± 2.8 mm ant. pos., 1.2 ± 3.7 mm sup. inf.	[321]
	Vac-Lok	−1.8 ± 2.9 mm ant. pos., 0.4 ± 2.3 mm sup. inf.	
Abdomen	BodyFIX	~2 mm ant. pos., ~2 mm lat., ~6 mm sup. inf.	[322]
	Elekta body frame	3.7 mm lat., 5.7 mm sup. inf.	[313]
	Leibinger body frame	1.8–4.4 mm	[323]
Prostate	Generic leg support	6.5 mm	[266]
	Full Alpha Cradle	6.0 mm	
	HipFix (thermoplastic)	4.6 mm	
	Vac-Lok	4.6 ± 3.5 mm (prostate) and 7.6 ± 4.7 mm (seminal vesicles)	[324]
	BodyFIX	3.0 ± 1.29 mm	[325]
Prone pelvis	Belly board	4.5 mm ant. pos., 3.2 mm lat., 4.2 mm sup. inf.	[326]

Note: sup. — superior; inf. — inferior; ant. pos. — anterior-posterior; sup. inf. — superior-inferior; lat — lateral.

6.4. IMAGING SYSTEMS

Imaging for radiotherapy is generally performed for treatment planning purposes before the treatment is started and for positioning, verification, evaluation and replanning purposes during the course of treatment. Imaging for treatment planning purposes is often performed at dedicated facilities such as CT or PET/CT and MRI scanners and (CT) simulators in detached rooms. Imaging

performed during treatment for positioning and verification purposes is usually performed using equipment in the treatment room.

The uncertainties related to imaging in the radiotherapy process are primarily of a geometric nature, as the primary aim of the imaging is to target the beam accurately in both treatment planning and treatment delivery. The contributions to the uncertainties related to imaging fall mostly in two categories depending on their origin:

— Geometric calibration and consistency of the imaging systems;
— Reconstruction and registration of images.

Another important issue is the sensitivity and specificity of the imaging system(s) in delineating (as part of the treatment planning process) or identifying (as part of the treatment delivery process) both the target volumes as well as the OAR. While some of these issues were discussed in Section 5, some additional comments will be given here. Identifying and delineating anatomical regions of interest (ROIs) is one of the most challenging aspects in 3-D CRT and IMRT. In the latter, the optimization process has no ability to constrain the dose to structures that have not been delineated properly.

This section describes in more detail the sources of uncertainty in imaging for radiotherapy and their nature for the various types of imaging systems used in the radiotherapy chain.

6.4.1. Image quality, sensitivity and specificity

Specification of the image quality requirements largely depends on the purpose of the images. When used for target delineation and identification of OAR, the image quality should provide sufficient sensitivity and specificity to identify the different structures in a unique and accurate way. (Sensitivity is given by the number of true positives divided by the number of true positives plus the number of false negatives, and specificity by the number of true negatives divided by the number of true negatives plus the number of false negatives.) Reduced image quality will inevitably result in large intra- and interobserver variations in target delineation. Using planning CT data only, Van de Steene et al. [327] reported large interobserver variations in GTV definition for lung tumours, and for the determination of its clinical relevance. One solution to reduce these variations is to combine several imaging modalities [114, 328], provided a reliable image registration has been performed and the interpretive skills of the radiation oncologist are adequate for the different imaging modalities, as each imaging modality displays different information and has its own limitations. These clinical aspects have been discussed in more detail in Sections 5.1 and 5.2.

Sensitivity and specificity should also be assessed for imaging techniques used for in-room image guidance. Poor image quality will hamper the observer's capability to register the images of the day to the reference image (e.g. large interobserver variability in the cranio-caudal positioning of prostate patients when using poor quality EPID images [329]), but might also influence the accuracy of automated registration tools and autodetection of implanted fiducials. When using automated registration or detection algorithms, the user is advised to evaluate the system's performance for different image acquisition settings (e.g. identifying image quality limits beyond which the algorithm fails) and to establish appropriate institutional imaging protocols.

6.4.2. Geometric calibration of imaging systems

Whether inside or outside the treatment room, the imaging systems are effectively intended to provide a representation of the treatment machine's isocentre, except in cases when the actual treatment beam is used for imaging. One of the most important factors in the accuracy of an imaging system is its geometric calibration with respect to the corresponding geometry of the treatment system. This includes calibration of the imaging isocentre (or for non-isocentric systems, more generally, the beam to patient alignment), of the beam collimation, of movable parts for positioning, of the readout scales or rulers, of any secondary positioning systems used in conjunction with the imaging system (such as independent lasers or light fields) and of the system's accuracy in guiding the treatment beam (e.g. respiratory synchronized gating or tracking). In the case of imaging for treatment planning, the essential feature is to establish an accurate and known geometric representation of the patient, upon which the treatment geometry can be accurately superimposed. In the case of imaging for positioning and verification during treatment, the aim is to reproduce the treatment geometry with the imaging system as accurately as possible.

Geometric calibration is mostly performed using phantoms with well defined geometries suitable for visualization. Often, an imaging system will be delivered from the manufacturer with custom-made phantom(s) for calibration. The phantom will most often contain one or more radio-opaque markers arranged in a pattern facilitating calibration to the relevant geometry in 2-, 3- or 4-D (the fourth dimension being time). Examples of phantoms with embedded ball bearing fiducials for 3-D geometric calibration of a stereoscopic imaging system and an isocentric rotational monoscopic imaging system are shown in Fig. 27. The calibration process could, for instance, involve positioning the phantom in the geometrical centre of the treatment system (either by imaging using the treatment beam or by using a secondary positioning system already calibrated to the treatment system), taking at least two images of the phantom, from

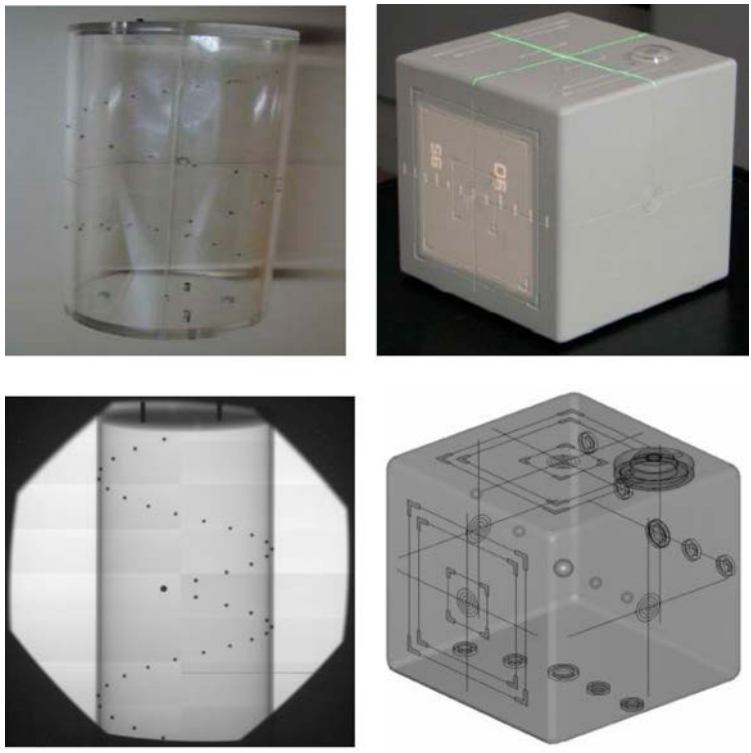

FIG. 27. Phantoms for 3-D geometrical calibration using known external features and interior structures. (Courtesy of U. Oelfke and J. P. Bissonnette.)

orthogonal angles for instance, calculating the corresponding geometrical centre of the imaging system and then calibrating this to the geometrical centre of the treatment system.

Quantification of the geometrical accuracy of an imaging system based on phantom calibration can include, for instance, for a cone beam CT on board imaging system: the distance between the radiological isocentre of the imaging system and the mechanical isocentre of the treatment system, diameters of the imaging system isocentre ellipsoid, standard deviations of beam collimator jaw positions (at isocentre distance), standard deviations of positions of extended beam generator and detector plate, and standard deviations of gantry rotational positions. Some systems use the phantom data to recalibrate the imaging isocentre with respect to the treatment isocentre (e.g. room mounted imaging systems, see Section 6.4.10.2). Others use the acquired information in the image reconstruction process (e.g. on board cone beam CT (CBCT) systems, as in Section 6.4.10.1).

6.4.3. Image reconstruction

All X ray imaging systems basically consist of a beam generator and a detector device, either in a fan beam solution or in a cone beam solution. The image displayed to the user will be a processed image rather than the raw data from the detector device. The level of processing needed in order to obtain a useful image depends on several factors, such as the dimension of the beam and detector (fan or cone beam, line or array detector), whether the resulting image is 2-, 3- or 4-D, the detector type (e.g. diodes, ionization chambers, film or flat panel detectors), accessory inserts (filters), the beam quality and the contrast desired in the image. The processing (i.e. image reconstruction) affects the quality of the image both with respect to spatial dimensions and with respect to contrast and noise in the image, and these factors again affect the accuracy related to the use of the image.

The image quality in terms of spatial dimensions includes the spatial resolution of the image (related both to detector size and to distance between detectors) and spatial distortions in the image. The image quality furthermore includes the signal to noise ratio, the image contrast and artefacts in the image. Image artefacts can be a severe source of decreased image quality (and hence decreased accuracy), and include, for instance, streaking artefacts caused by high Z objects for kilovoltage (kV) X ray CT imaging, ghosting effects caused by detector relaxation and updating time mismatch, patient breathing and changes in anatomy during image acquisition (e.g. typical CBCT artefacts), and cupping effects in cone beam CT caused by patient thickness variation. A typical example of the influence of image reconstruction is given in Fig. 28, where a radio-opaque marker embedded in an anthropomorphic phantom is imaged in two different ways (sequential and helical CT scanning). A poor reconstruction in the latter hampers accurate definition on the marker's geometric centre. Current reconstruction algorithms have filters to correct for these artefacts and the user is advised to evaluate these effects for the different procedures that are being used clinically.

Optimization and calibration of image reconstruction parameters will often be performed using phantoms with specialized features suitable for the purpose, such as phantoms containing volumes of varying density and atomic composition, and spatial patterns of varying resolution (for instance, stripe patterns with varying stripe width and distance). Figure 29 shows an example of a phantom used for CT imaging containing well defined regions of both varying density and composition and varying spatial patterns. The phantom can be imaged with a range of settings of image acquisition and processing parameters for image quality optimization under varying conditions.

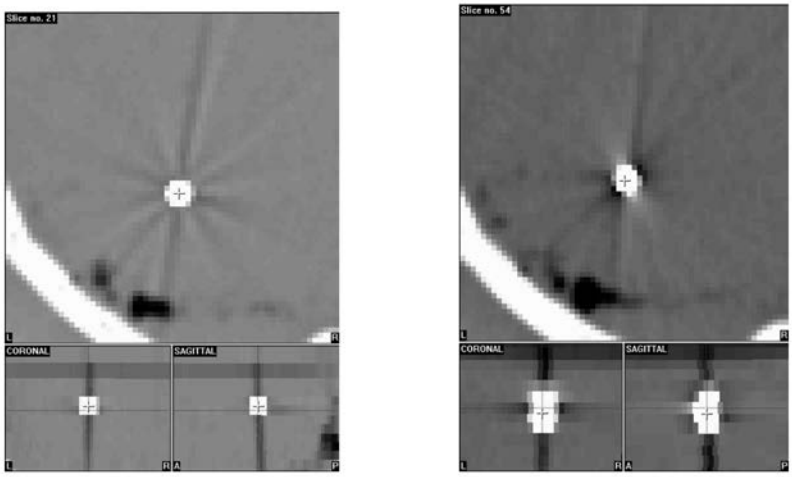

FIG. 28. (Left) An axial reconstruction of a 0.2 cm lead bead based on CT data from an anthropomorphic phantom using a sequential scanning mode with a slice thickness and feed of 0.2 cm. (Right) A similar axial reconstruction of the same lead bead using a helical scanning mode (slice and feed of 0.2 cm) illustrating the enlarged streaking artefact. (Images courtesy of D. Verellen.)

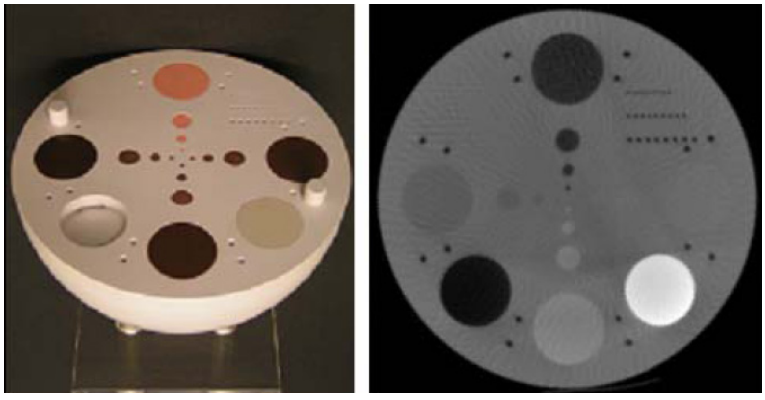

FIG. 29. Picture of a phantom used for image quality optimization (left) and an axial CT image of the phantom (right). (Images courtesy of Siemens.)

The optimization of image quality can result in a tabulation of settings optimal for various imaging purposes, to be included (preferably automatically integrated) in the imaging techniques for the device. The calibration should ideally result in a quantification of accuracies related to the different imaging

procedures. Such a quantification, however, is rarely carried out in practice, one reason being that this would imply an extensive assessment of accuracies related to different geometries, contrasts and techniques used, and would therefore have limited practical use. For imaging systems used for positioning purposes, the limiting factor in reality becomes the overall registration and evaluation process accuracy, whether this is carried out automatically or manually (see Section 6.4.9).

A related issue is the quality of DRRs generated by TPSs, as these DRRs might be used by several image guidance systems to reference the patient's position on the treatment couch to the ideal position as assessed by the TPS. It is important to understand the influence of the CT image quality (e.g. spatial resolution and slice thickness) as well as the reconstruction algorithm on the geometric accuracy and visibility of pertinent information on the DRR. Institutional imaging protocols should be developed for different disease sites, anatomy and techniques. Specific tests in the QA programme of a TPS are needed to guarantee the quality of DRRs [28].

6.4.4. Imaging dose

Acquisition of X ray images implies the delivery of a dose of ionizing radiation to the patient in the imaged volume. The importance of the imaging dose in a setting where the patient will receive a large therapeutic dose is a much disputed issue. The validity of the as low as reasonably achievable (ALARA) principle should be seen in the light of the ability of the increased imaging dose to enhance the therapeutic effect. Also, it should be considered that the use of extensive imaging may yield a potential for decreasing the volume irradiated to therapeutic doses, and thereby decrease the overall integral dose to the patient, thus reducing potentially toxic doses to healthy tissues.

Nevertheless, it is of importance to provide a good assessment of the delivered dose when imaging in radiotherapy, so that the actual imaging dose delivered to the patient is well known. This might not necessarily influence the quality of the therapeutically delivered dose (unless the imaging dose is incorporated into the treatment plan, which is seldom the case), but it is a radiation protection measure. The management of imaging dose during IGRT has been evaluated extensively in the AAPM TG75 report [330], and more recently in the AAPM TG179 report [331]. Again, it is difficult to generate objective data as the imaging dose is related to the required image quality, and it is the user's responsibility to respect the ALARA principle. For instance, if the images are to be used to localize bony structures in a CBCT scan prior to treatment (e.g. a head and neck treatment), the image quality requirements are less stringent compared with a situation where soft tissue contrast is needed (e.g. in

the prostate and rectum). The former case can be realized with reduced image quality, and thus much less dose, compared with the latter for the same geometric accuracy. Another issue to be considered is the required frequency for imaging. In some cases, a weekly scan in combination with an appropriate positioning policy and PTV margin definition can be sufficient; in other cases, daily imaging will be required, and in the case of 4-D respiration correlated treatment, many images will be acquired during the treatment. It should be recognized that some imaging techniques primarily induce superficial or skin dose (e.g. kV X ray systems), whereas others will deliver dose deeper within the patient's volume (e.g. MV CT).

A recent investigation showed the feasibility of commissioning a kV X ray source in a commercial TPS to calculate the dose to patient resulting from IGRT procedures [332]. The modelled profiles agreed with the measured ones to within 5%. Thus, this might become a procedure that could incorporate the total imaging and treatment dose as part of optimization of the treatment technique in the treatment planning process. Monte Carlo studies [333–335] have noted that the dose to bone is three to four times higher than dose to tissue in kV CBCT procedures, and this can become an important consideration when this dose is accumulated over a multifraction daily image guidance treatment course. In short, the radiation oncologist is expected to justify the benefit with respect to the additional imaging dose. In order to make an accurate evaluation, the dose to the patient generated by the system and the influence of different image acquisition settings and techniques should be established.

6.4.5. X ray simulator

The simulator is used in a separate room for either direct planning of 2-D treatments, or for verification of a prepared treatment plan through imaging the beam's eye view of the composite treatment fields. The simulator consists of a C arm gantry in an isocentric geometry and beam collimation similar to that of the treatment machine. Imaging can usually be performed in both radiographic and fluoroscopic imaging mode, and the simulator is equipped with automated brightness control to optimize image quality during beam-on time.

The most recent simulators include anatomy based technique selection, automatic correction for image distortion, last image hold, MLC verification, a variety of image viewing and manipulation tools with annotation, image printing to film or paper, DICOM (Digital Imaging and Communications in Medicine) export to TPS, EPID, RVS and patient management systems. The image manipulation tools enable adjustments to be made to field parameters and image quality on the last held image, which reduces the screening time and hence patient dose. Some models are equipped with wide aperture (typically 90 cm)

CBCT options allowing volumetric imaging in the treatment position. However, because of the restriction on gantry rotation speed, acquisition times are still slow and the reconstruction time and image quality do not match that of a diagnostic CT scanner.

A detailed description of QC tests and acceptability criteria for conventional simulation and their recommended frequency is given by Mayles et al. [198] and Van Dyk and Munro [336]. Typically, the isocentre ellipsoid of a simulator can have diameters down to between 0.5 and 2.0 mm over the rotation of the gantry. It is important to realize that the simulator and the treatment machine are in different locations and that the translation from one isocentre to the other can only be performed by the patient's skin marks, fiducials attached to the patient, immobilization devices or a combination of these. Immobilization devices will inevitably introduce an additional uncertainty in the process and, more importantly, a deviation in the mechanical settings will introduce a systematic deviation throughout the entire treatment.

An alternative to using the X ray simulator with a CBCT option to acquire a volume dataset of the patient in the treatment position is to modify CT scanners to meet the needs of radiotherapy and add software to perform the simulation function, known as virtual simulation. In some clinics, all treatment planning takes place using CT images that are either transferred to the TPS or to the virtual simulation workstation. In this case, QC programmes adapted to the approach are required (e.g. identifying the shift in isocentre between two positions of the table due to sag at imaging inside the bore of the machine relative to the table position at the time of marking the laser lines outside the bore).

6.4.5.1. Simulator use for brachytherapy

Treatment planning for brachytherapy requires the acquisition of geometrical information for the implant, applicator or both, and the patient anatomy. In many centres, this is performed using a simulator with orthogonal views or a CT scanner. Sometimes, images from the C arm fluoroscopy unit in the operating suite during patient preparation can be used. For this option, fiducial markers, e.g. a reconstruction box, need to be used in order to correctly reconstruct the application. Another approach is to use known geometries for the fluoroscopic images and to digitally transfer the images to the TPS. Image distortions can be corrected and applicator positions can be reconstructed to an accuracy of 2 mm [337]. This provides an alternative to the orthogonal film method.

One study investigated the accuracy of implant reconstruction and dose delivery in 33 radiotherapy institutions in Belgium and the Netherlands [338]. The average reconstruction accuracy was −0.07 mm (±0.4 mm, 1 SD) for 41 localizers, 33 of which were simulators.

A geometric check procedure of the reconstruction techniques used in brachytherapy TPSs was developed by the European Quality Assurance Laboratory in the framework of the ESTRO project 'ESQUIRE' (Education Science and Quality Assurance in Radiotherapy in Europe) [339]. Four levels of deviation were defined using Δ as the confidence limit, where Δ is equal to the absolute mean +2 SD:

— Within the optimal level, when the mean deviation is ≤ ±0.5 mm and when Δ ≤ 1.0 mm;
— Outside the optimal level but within the action level, when the mean deviation is > ±0.5 mm and ≤ ±1.0 mm, or when Δ > 1.0 mm and ≤ 2.0 mm;
— Outside the action level, when the mean deviation is > ±1.0 mm and ≤ ±2.0 mm; or when Δ > 2.0 mm and ≤ 3.0 mm;
— In the emergency level, when the mean deviation is > ± 2.0 mm; or when Δ > 3.0 mm.

The results of 152 checks from 75 radiotherapy centres in 18 European countries during 2002–2005 are shown in Fig. 30. Eighty-six per cent of the results are within an acceptance level after the first check. For the remaining 14%, a second check was implemented. The results of the re-checks are in most cases within an acceptance level, except for 2% of the reconstructions. The overall results indicate the type of accuracy that is achievable, and the decrease

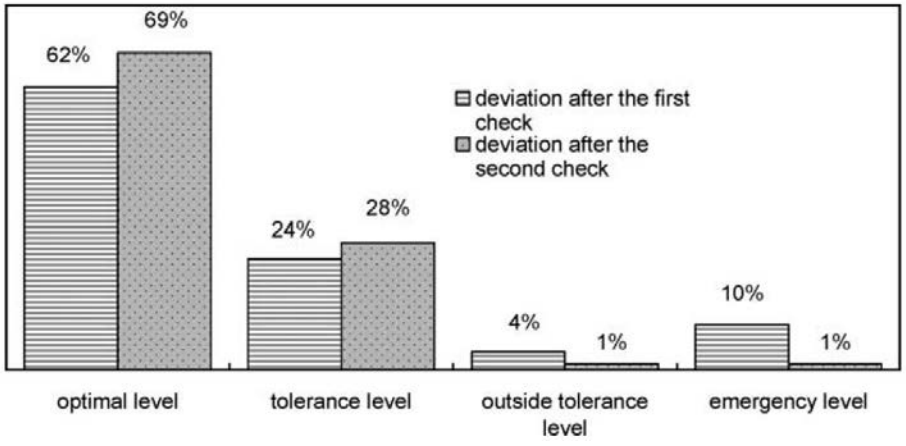

FIG. 30. The levels of deviation obtained from an external audit of geometric reconstruction in brachytherapy TPSs. The first and second checks are shown. This evaluation includes 152 checks. (From Ref. [339].)

of the deviations observed between the two checks demonstrates once again the importance of this kind of external audit, as some errors were revealed.

6.4.6. CT scanner

In radiotherapy, CT scanners are primarily used for treatment planning purposes, in a process where a pretreatment scan is performed, structures and targets are delineated in the image, the beam arrangement is optimized, and the radiation dose is calculated using the electron densities for the patient derived from the images. In the case of inverse optimization (e.g. as used in IMRT), the pretreatment scan is used to derive the optimal treatment parameters based on similar dose calculations.

The development of the concept of the beam's eye view into the transmission image from CT scans that would result from any beam orientation paved the way to producing images from CT data that correspond to conventional simulator images [340–342]. These DRRs could be overlaid with the outlines of anatomical structures, field shapes and cross-wires, and hence could display images similar to simulator radiographs. However, the spatial resolution of DRRs is limited by the voxel size of the CT scans and cannot match that of a simulator radiograph taken with a small focal spot and a short exposure. Nevertheless, successful implementation of 3-D CRT, IMRT and, more particularly, rotational IMRT cannot be achieved without 3-D information on the location and extent of the target volume and the position of adjacent OAR. The 3-D aspect of virtual simulation is essential to visualize the coverage of the target volume and the avoidance of OAR in these highly complex treatment plans. The term 'virtual simulation' was introduced by Sherouse et al. in 1987 [343], and Aird and Conway [294] described in detail the process of using computer aided design and DRRs to replace the process of physical simulation. An excellent overview of comparative studies between physical and virtual simulation can be found in the paper by Baker [344]. These studies support the observation that the precision of set-up evaluations using virtual simulation and DRRs was similar to that using simulator images, providing improved coverage of GTV and avoidance of OAR, and a reduction of systematic deviations in the treatment process by omission of the simulation stage.

When no prior physical simulation is performed, immobilization and patient positioning is performed at the CT scanner, with definition of a (tentative) isocentre, and (if relevant) placing of skin tattoos. Therefore, a laser alignment system will also often be installed at the CT scanner. Needless to say, the patient's position should be reproducible in the treatment room (or vice versa: the patient's position on the CT scanner should reflect the patient's position in the treatment room) and identical supports and immobilization devices should be

used. Special attention should be given to the treatment couch since CT scanners are usually equipped with curved, soft couch tops, whereas in radiotherapy, flat couch tops need to be used. As the CT data will be used for dose calculations, the attenuation of the table top (e.g. for posterior beams) needs to be incorporated in the dose calculation. Again, it is advisable to use identical table tops for imaging and treatment. It should be noted that in some TPSs, the dose calculation can account for the treatment couch attenuation by replacing the image of the CT couch by an image of the treatment couch in the CT data. Verification takes place on the treatment unit with the EPID or the on board IGRT system. Either the portal images acquired are compared with the DRRs produced by the virtual simulation software (in the TPS), or the CT data of the day is compared with the reference CT data. Mutic et al. [295] provide a comprehensive guide to the QA of CT simulators. They stress the need for frequent audit and review of the process as CT simulation and treatment techniques evolve.

The CT scanner has a non-isocentric O ring gantry geometry, and (almost always) has a fan beam and a row based detector system. The reconstruction of the 3-D image may introduce errors depending on scanner settings and on the reconstruction algorithm used. A specific issue of image artefacts in the reconstructed image is that when high *Z* material is present, this will produce streaking artefacts deteriorating the image quality. The latter has a twofold effect on treatment planning: (a) the reduced image quality will hamper accurate volume delineation, and (b) the electron densities will be affected resulting in erroneous dose calculations. The spatial resolution of the image is approximately 1 mm, except in the longitudinal direction where resolution is reflected by the distance between reconstructed slices, i.e. the slice thickness and the pitch.

Of special interest with CT scans is the conversion of CT numbers to electron density, which is required for accurate dose calculation. While CT scanners are generally calibrated with air and water values, the conversion of CT numbers to relative electron density values is dependent on the atomic number of the tissues. This conversion depends on the particular scanner and on its calibration and software. Ideally, these conversion curves need to be acquired using phantoms with multiple density inserts at a regular basis (ensuring long term reproducibility), after technical interventions, and each time new acquisition techniques are introduced. If multiple CT scanners are used for treatment planning, then the specific conversion curves must be configured correctly for each scanner. During the dose calculation process, the user should be able to select the appropriate conversion curve.

It is also noteworthy to mention the use of high *Z* contrast agents. Contrast is usually introduced to identify target volumes or for diagnostic reasons. Unfortunately, these contrast agents will not be present during the treatment delivery but will influence the dose calculation during the treatment planning.

This could result in high absorption of high energy photon beams and thus could affect the dose calculation significantly. The relative dose differences increase linearly with the HU value as well as with the volume diameter. A typical bolus diameter of 3 cm and HU values of 1400 could cause an estimated overdose of up to 7.4% and 5.4% for single 6 MV and 25 MV photon beams, respectively [345]. When the number of incident beams is increased, e.g. for a four field box technique, contrast agents cause a difference of 2.7% for 6 MV and 1.8% for 25 MV photon beams [345]. Thus, the impact of the contrast agent is very dependent on the treatment technique that will be used. In general, when contrast is deemed necessary, it is advised to acquire two consecutive scans of the patient, one without contrast, followed by one with contrast administered. Alternatively, the user can delineate the tissue with contrast capture (e.g. bladder) and force a new electron density to this delineated volume in the planning software.

It is good practice to scan a phantom with known geometry and density inserts and transfer the data to the TPS on a regular basis to verify the consistency of the scanner and the transfer procedure. Agreement within 2 mm is reasonable for distances. Agreement within 0.02 is reasonable for relative electron densities (i.e. CT numbers for a given object should not vary by more than ±20 HU) [28]. Typical CT scanner doses range from about 1 to 4 cGy within the scanned volume per CT study.

6.4.6.1. CT scanner for brachytherapy reconstruction

As an example of the use of CT in brachytherapy, the American Brachytherapy Society recommends that post-implant dosimetry should be performed on all patients undergoing permanent prostate brachytherapy for optimal patient care [346]. CT based dosimetry is recommended, based on availability, cost and the ability to image the prostate as well as the seeds. Additional planar radiographs should be obtained to verify the seed count. Dosimetric evaluation of prostate implants is usually performed 3–4 weeks post-implant. Also, Kolotas et al. [347] describe CT based interstitial HDR brachytherapy techniques for recurrent malignant gliomas. For these treatments, HDR provides a much shorter treatment time resulting in better patient comfort and better individualized optimization of the treatment than LDR.

In an analysis of dose uncertainty due to CT slice thickness in CT based HDR brachytherapy of prostate cancer, Kim et al. [348] found that dose uncertainties due to the finite slice thickness increase linearly with the slice spacing, from 3% and 8% for the slice thickness values ranging from 2 and 5 mm, respectively, in scenarios where there was a systematic displacement of the catheters. However, the more realistic scenario of a random displacement yielded average errors from 0.7%–1.7%. The apex and the base show larger and more variable dose errors

than the remainder of the prostate volume. No statistical difference was observed among different transverse sections of the prostate. A CT slice thickness of 3 mm appeared to be a good compromise, showing an acceptable average dose uncertainty of 1%, without unduly increasing the number of slices.

The GYN GEC-ESTRO Working Group published a paper on the considerations and pitfalls in commissioning and applicator reconstruction in 3-D image based treatment planning of cervical cancer brachytherapy [349]. Owing to the steep brachytherapy dose gradients, reconstruction errors can lead to major dose deviations in targets and OAR. Hence, appropriate applicator commissioning and reconstruction methods must be implemented in order to minimize random and systematic uncertainties and to avoid accidental errors.

6.4.7. PET/CT

PET/CT systems combine a PET detector with a CT scanner and can provide geometrically aligned anatomical data (the basis of the current treatment planning process) and functional information at the molecular level [350]. There are a number of different ways in which PET images can be used for treatment planning purposes. PET images could be available purely as a diagnostic aid; PET and CT images from separate scanners can be registered in software; PET/CT images from a combined scanner could be registered to a planning CT scan; or a planning PET/CT scan could be carried out on a combined scanner. Effective doses from FDG PET/CT scans are typically 15–25 mSv [351] and their resolution is 4–7 mm, depending on the examination and whether one is looking in the axial or transaxial plane, respectively [37].

The delineation of volumes is ideally based on all the diagnostic information and knowledge available of the anatomy, pathology and physiology of disease. As PET can be integrated into this knowledge base, it can aid decisions on treatment modification based upon probabilities of false positive and negative data within particular structures and locations. The accurate staging of some cancers using PET is known to be essential for the appropriate management of the patient [352]. Several studies have shown that the inclusion of PET data reduces interobserver variability [328, 353, 354]. Although this is a welcomed outcome, it does not necessarily mean that the volumes are being defined more accurately [355]. The introduction of any new imaging modality for treatment planning requires the adaptation of scanning procedures for use with that modality. Close liaison between radiotherapy and nuclear medicine staff will be required to develop these institutional guidelines. Acquiring the PET/CT dataset in the treatment position requires the direct involvement of RTTs to ensure that techniques are consistent across the planning and treatment processes. This has been quantified by a group from Nijmegen, the Netherlands, as demonstrated in Fig. 31, which shows that

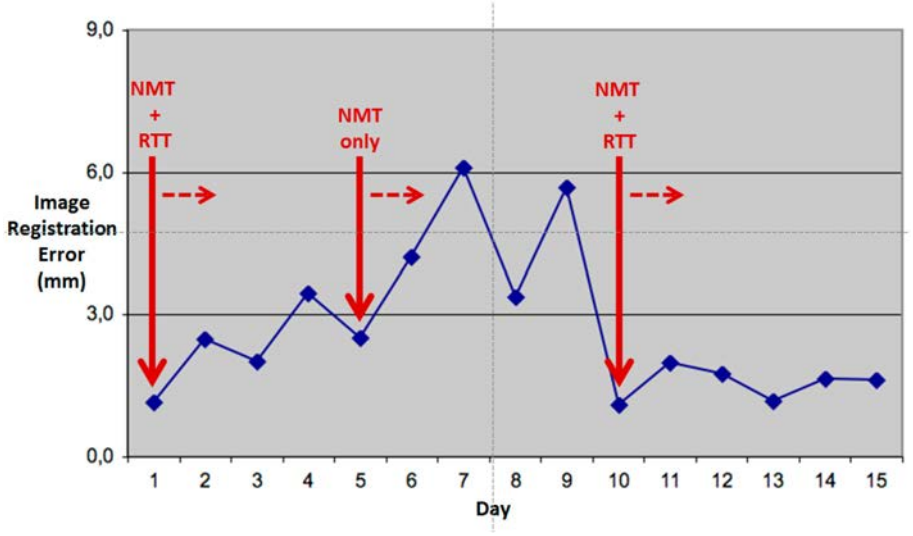

FIG. 31. Image registration errors with and without an RTT present. (Key: NMT, nuclear medicine technologist. (Data courtesy of W.V. Vogel)).

inaccuracies in patient set-up increase when nuclear medicine technologists set up the patient without an RTT present. Set-up of the patient for treatment is a time consuming process and, if undertaken for PET scanning, it will be necessary to develop procedures that minimize contact between the therapy radiographers and the patient after the patient has been injected with the radioactive tracer, in order to minimize radiation dose to staff. PET scanning times are relatively long, depending on the acquisition protocol, and patient compliance may be an issue in terms of maintaining the position throughout the scan. An editorial by Gregoire [356] highlights the issues in relation to false positive and false negative rates for detection of disease. The use of tracers will not be covered in this overview as the primary focus is on accuracy issues.

Initial studies [357] of the use of PET images in treatment planning used PET and CT images acquired on different scanners and registered subsequently. In general, these studies were performed with the patient in the treatment position. Software fusion of the PET and CT images has the advantage that the acquisition of the PET data does not necessarily need to be conducted in the treatment position and might be obtained from the diagnostic scan. The disadvantage is that the simulation scans and the PET scans will be acquired at different times, possibly on different couch tops (flat-top compared with a concave top) and with the patient potentially in different positions. In a review of organ motion and its management, Langen and Jones [358] refer to such position related organ motion

and the potential problems associated with imaging and treating the patient in different positions.

While the delineation of volumes on CT images may present some difficulties, the definition of volumes on PET images is likely to be more problematic owing to the poorer resolution and higher noise levels. There are a number of different options for defining lesion volumes using PET images. Volumes can be defined manually as for conventional CT planning, or alternatively, automated outlining methods can be used. Thresholding is the most widely used method to determine volumes automatically from PET images [359, 360]. It is well known in nuclear medicine that the selection of the threshold depends on the lesion size, shape and contrast (Fig. 32) and that the threshold can influence the assessment of the lesion's size and shape. Other factors such as lesion volumes, reconstruction software, tracer sensitivity and specificity should all be accounted for.

In defining a volume on the PET image it is essential to understand the acquisition process, especially in relation to physiological motion. More

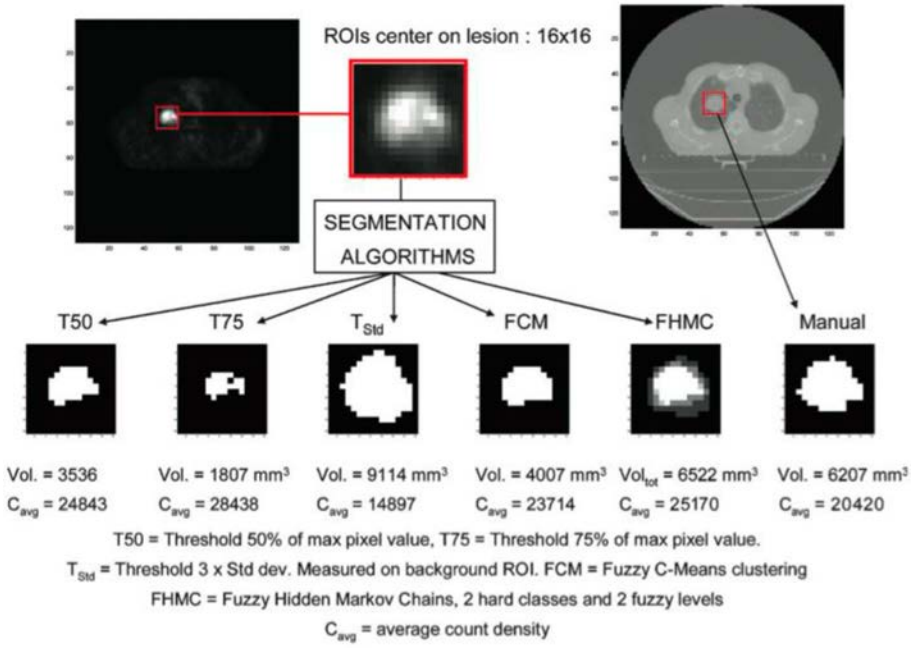

FIG. 32. An example of the variations in segmented volumes for a lung lesion using different threshold and analysis techniques. (Key: ROI; region of interest.) (Images courtesy of M. Hatt.)

information on motion management and attenuation correction can be found in Section 6.4.11.

Finally, it is important that the consistency of the scanning data is maintained in time as well as between different centres. The European Association of Nuclear Medicine has defined guidelines to ensure these issues. Boellaard et al. [361] and Velasquez et al. [362] showed the importance of centralized and uniform QA procedures on the variation in the data for multicentre trials.

6.4.8. MRI

MRI can add to the radiotherapy treatment planning process by providing improved characterization of soft tissues compared with CT. The contrast from soft tissue structures can be varied by manipulating the imaging parameters, such as tissue relaxation times (spin–lattice or T_1, and spin–spin or T_2). Another feature of the increased functionality of MRI is its true multiplanar capability reducing the partial volume imaging effect that often results from conventional axial CT imaging, particularly where the 3-D shape of the target is extreme or changes substantially between conventional CT slices. Furthermore, MRI can provide functional and biological information for tumour regions that may improve target definition and permit new opportunities for novel radiotherapy strategies. However, as for PET imaging, it is important to be aware that radiation oncologists should have appropriate training to interpret magnetic resonance (MR) images and understand how to use them for defining volumes of interest [363].

In principle, MR images cannot be used for EBRT treatment planning without accompanying CT images because the image data contains no information on tissue electron density or attenuation coefficients. The preferred methodology is to integrate MR images with CT data by coregistering the image sets in order to create the most appropriate volume of interest.

In brachytherapy, MRI may be used without performing additional CT acquisition since dose calculation in brachytherapy normally relies on dose calculation according to water equivalent tissue (see Section 6.2.3.2). For 3-D reconstruction of applicators directly in MRI, the procedures and uncertainties are slightly different from the situation in CT, owing to the different visualization of applicators in MRI compared with CT. However, similar procedures are used and described in detail in the GEC-ESTRO recommendations on applicator reconstruction [349].

Before image co-registration can occur (see Section 6.4.9), it is important to ensure that the MR data are suitable. MR image distortion is one potential concern, which can be divided into two main categories: system related and object induced. System related distortions are due to the imperfections of the

magnetic field (magnetic field inhomogeneity, gradient field non-linearities and eddy currents), its operating system and imaging sequences. In general, the effects of system related distortion are smallest at the centre of the magnet and worsen with increasing distance from the magnet's centre (i.e. at the periphery of the field of view). Caldwell and Mah [37] have indicated that these distortions could be as large as 15 mm at the edge of a 40 cm field of view; however,with correction, these can be reduced to less than 1 mm. System related distortion is best quantified and mapped using a phantom (linearity test object) with a known array of markers in 3-D to provide spatial assessments of the whole imaging volume used for treatment planning. Object induced distortion arises when any object (in this case, the patient) is placed within a magnetic field. This type of distortion results from magnetic susceptibility and chemical shift effects causing artefacts that are most pronounced at tissue boundaries, such as between air cavities and soft tissues. Chemical shift effects result from the different behaviour of protons in different tissues. Fat protons precess at a slower rate than water protons, and this can result in a chemical shift effect where the positions of fat and water protons are shifted from their true spatial locations. In order to utilize MR images for treatment planning, these image distortions must be evaluated, minimized, corrected for or a combination of these; otherwise, a systematic error may be incorporated into the treatment plan [364–366]. It is important to evaluate the imaging protocols to be used and to identify those sequences that offer the best combination of image quality and resolution and minimal image distortion. These sequences will differ depending on the anatomical site being imaged and treated.

Manipulation of the relaxation times of protons in tissues provides the two basic T_1 and T_2 weighted MR sequences. While this provides superior imaging of soft tissues, the imaging parameters can also be manipulated to benefit the treatment planning process by providing ultrafast imaging, volumetric sequences and cine mode acquisition. These sequences can be used to provide information on target motion and OAR displacement to help modify planning margins and to initiate image guided radiotherapy strategies. As with PET imaging, MRI for treatment planning should also mimic the CT planning procedures such as scanning the patient in the treatment position with a flat couch top insert; using the same immobilization devices, if they are MR compatible, where specified; providing the same instructions to the patient (e.g. full or empty bladder and minimizing internal organ motion by breath held procedures or bowel relaxants); and reducing the scanning time whenever indicated and possible.

Between 2005 and 2015, there were many advances in MRI technology that could further aid the definition of volumes for both EBRT and brachytherapy. The field strengths of MRI scanners have been increasing since their initial development, to 1.5–3.0 T at the time of writing. The image quality or resolution

improves when the signal is increased and the noise lowered. The signal to noise ratio approximately increases in a linear manner with field strength. Three tesla (T) scanners not only provide higher resolution images for better tissue definition but also improve MR spectroscopy applications. There are several issues associated with 3.0 T MR scanners that may limit their use for radiotherapy treatment planning. Among these is the exacerbation of magnetic susceptibility effects, doubling of the chemical shift effect, patient safety and engineering challenges. Ultra small superparamagnetic iron oxide particle contrast agents can assist in the evaluation of pathological lymph nodes for treatment. MR techniques using MR spectroscopy, dynamic contrast enhanced MRI, diffusion weighted MRI and diffusion tensor imaging can be used to further assess target volumes with improved and complementary morphological, functional and biological data. These techniques may also be combined with PET to further increase diagnostic sensitivity and specificity.

6.4.9. Image registration

In order to integrate information from multiple imaging studies, the data must be geometrically registered to a common coordinate system. This process is called image registration. Once different datasets are registered, information such as tissue boundaries, computed dose distributions and other image or image derived information can be mapped between these datasets and combined. This process is called data fusion [367]. A detailed overview of the different techniques has been reported by Maintz et. al. [368]. Image registration refers to a geometric transformation that maps the coordinates of corresponding points between two imaging datasets. In general, the image registration process involves three basic components [367]:

(1) The transformation model itself, which can range from a single global linear transformation for handling rotations and translations (6 degrees of freedom, 3 rotations and 3 translations) to a completely free form deformation model where the transformation is represented by independent displacement vectors for each voxel in the image data (degrees of freedom can reach 3 times the number of voxels).
(2) The metric used to measure how well the images are or are not registered.
(3) The optimizer and optimization process used to bring the imaging data into alignment.

In radiotherapy, a common strategy is to register each of the imaging studies to the treatment planning CT, as it is used as the primary dataset for treatment planning, dose calculation and as reference patient positioning for in-room image

guidance. These tools, however, cannot replace clinical judgement. Different imaging modalities image the same tissues differently and, although registration tools may help to better understand and differentiate between tumour and non-tumour tissue, they cannot yet make the ultimate decision (during treatment planning as well as at the time of treatment) of what to treat and what not to treat. The end result requires careful review by the user and evaluation tools must be present to enable this review process efficiently.

For volumes defined by the rigid skull, a rotate–translate model specified by 3 rotation angles and 3 translations can be accurately applied to map points from one image dataset to another. A more general linear transformation is the so-called affine transform, which is a composition of rotations, translations, scaling and shearing. A property of affine transformations is that they preserve colinearity ('parallel lines remain parallel'; in other words the patient's shape and posture remain unchanged). Both of these approaches are classified as rigid registrations. Rigid or affine transformations currently predominate but are challenged by non-linear deformations associated with treatment response, weight change, variation of organ position and volume between examinations, uncontrolled physiological motion (e.g. breathing) and more frequently, differences in patient pose (e.g. differences in the flex of the neck region). In some cases, where local rigid motion can be assumed, this problem can be solved by determining ROIs or subvolumes to optimize the registration process (if possible, appointing different weights of importance to different anatomical regions). However, this local rigid registration will not suffice in most clinical situations and non-rigid or deformable models must be introduced [369]. Deformable transformation models range in complexity from a simple extension of a global affine transformation using higher order polynomials with relatively few parameters, to a completely local or free form model where each point or voxel in the image volume can move independently. Between these two extremes, transformation models have been designed to handle various degrees of semi-local deformations using a moderate number of parameters, such as splines [179, 370]. An excellent overview of the different methods for image co-registration can be found in the work of Kessler et al. [367, 371]. In most registration algorithms, the parameters of a transformation model that bring two datasets into geometric alignment are the result of an optimization process based on the registration metric (a measure of the similarity or dissimilarity of the two image datasets). Most registration metrics in use today can be classified as either geometry based (using features such as anatomical or artificial landmarks and organ boundaries extracted from the image) or intensity based (using the image data directly). The optimization process is common to those used in inverse planning algorithms, in that it iteratively registers successive steps based on, for example, a gradient based descent method.

In addition to registering and fusing image data, 3-D dose distributions computed in the coordinate system of one imaging study can be mapped to another. With the introduction of volumetric imaging on the treatment units, CT data of the day can now be acquired to more accurately determine the actual doses delivered. By acquiring these studies over the course of therapy and registering them to a reference dataset, doses from consecutive treatment fractions can be recalculated and accumulated to provide a more likely estimate of the overall delivered dose to specific tissue voxels.

As mentioned before, it is important to validate the results of a registration before making clinical decisions based on the results. Usually, some kind of visual verification tool (split screen displays, fast toggling between image sets or colour coding) will help the user to assess the quality of registration. In addition to visually comparing how well the images from one study correspond to another at the periphery of anatomical tissues and organs, outlines from one study can be displayed over the images of the other. However, the accuracy of the calculated correction parameters needs to be verified in phantom studies. Typically, phantoms with embedded radio-opaque markers can be used for these image localization and position correction tests. Methodologies have been provided by Kashani et al. [372, 373]. These investigators introduced a deformable phantom, embedded with small identifiable reference marks, to apply a known deformation to a simple geometry and quantitatively evaluate the outcome of registration algorithms by comparing the measured and estimated location of a series of points. Most verification studies of registration algorithms have been performed on particular systems, and no general comparison or QA tools are available. In general, guidelines for QA of image registration tools in SRS and treatment planning are appropriate for CRT and IGRT. A typical example is the recommendations of the IAEA for the assessment of the technical principles, possible bias to a particular modality, constraints imposed on image acquisition, the degree and behaviour of automation, the registration model (rigid or deformable) and dependence on image acquisition parameters [28]. The AAPM has formed TG132 to review techniques for image registration, identify issues related to clinical implementation, assess accuracy and discuss acceptance and QA.

6.4.10. In-room imaging

Given a reference patient model (typically containing information from a CT scan), the primary goal of alignment in radiotherapy is to relate the position of the patient at treatment to that intended in planning. In-room IGRT has been defined as the process of frequent imaging in the treatment room during a course of radiation delivery, with decisions made on the basis of this imaging [374].

IGRT refers to the process of using imaging information acquired in the treatment room to verify patient set-up and account for inter- or intrafractional organ motion. Image guidance protocols include three stages of imaging: (1) imaging after initial set-up; (2) imaging after correction; and (3) imaging during or after treatment, or both. In addition to imaging, the process involves both comparison between reference and in-room images (manually or automated) and judgement. As these so-called registration algorithms will be used for patient localization and set-up, not only the translation from the imaging coordinate reference system to the treatment coordinate reference system, but also the reliability of the positional correction parameters requires careful verification. These registration results may be influenced by the imaging acquisition settings (image quality: spatial resolution, contrast, noise etc.), the available anatomical information (e.g. scanned region), as well as settings of the registration algorithm itself (most software packages offer user defined parameters such as ROIs, soft tissue versus bone registration). A complicating factor is that the patient representations in the original planning CT and the CT of the day may not be the same.

6.4.10.1. In-room imaging: Gantry mounted systems

(a) Planar imaging (MV portal imaging, kV imaging (radiographs, fluoroscopy))

A good history and overview of the use of port films has been provided by Munro [375], who reviews various film cassette combinations that allow for the best possible portal images recognizing the limitations of the technology for MV imaging. Another in depth review of this technology can be found in the report of AAPM TG28 [376]. Port films are used either as localization films, where only a fraction of an individual treatment is used to form an image, or verification films, where the film cassette is left in place for the entire duration of the treatment irradiation. Thus the dose range at the film for appropriate exposure is very large, from as low as 1 cGy (verification imaging) to 80–100 cGy (treatment irradiation). Quite often, double exposures have been used to show the radiation treatment field within a larger field so that the surrounding anatomy is more clearly visible. Interobserver variability studies suggest that human observers had difficulty accurately identifying field placement errors when the errors were 5 mm or smaller [375].

While portal imaging using radiographic films or EPIDs has been around for a long time, the ability to automatically acquire images in real time and the tools for semi-automatic quantification of set-up errors is more recent, thus creating an environment for in-room image guidance [39, 377]. The philosophy of portal imaging has in the past focused on QA of major errors in treatment ports

or set-up errors, with less emphasis on daily image guidance for more accurate treatment delivery. The clinical introduction of on-line EPIDs [378] has provided a semi-automated means of quantifying uncertainties in set-up and treatment delivery. The major advantage of MV based imaging is the fact that the actual treatment beam is used. As such, there is a direct alignment of patient position in the treatment beam, avoiding the need for additional calibration procedures for the IGRT system. Moreover, as the treatment beam is used, it allows for verification of the beam shaping, the possibility to verify field outline with respect to patient anatomy, and assessment of the transmission dose.

When used for evaluation of treatment set-up, the information obtained from the portal image is usually compared with that extracted from a reference gold standard of treatment set-up, e.g. a reference simulation radiograph or a DRR extracted from the reference CT data (including field borders and shape). Both single as well as double exposures can be obtained to combine the treatment field outline with anatomical information of the surroundings in one image. With the introduction of EPIDs, two classes of strategies have been introduced, the so-called off-line [280, 378–380] and on-line [378, 381, 382] approaches. The former monitors the position of the individual patient during a limited number of fractions and subsequently adapts the safety margins, treatment plan or both accordingly. The on-line approach may be as simple as adjusting the couch position daily (offering the possibility of reducing both systematic and random uncertainties) or as complex as informing the full re-optimization of the treatment parameters based on changes in the shape and relative position of target and normal structures.

Most EPID systems require some form of image and mechanical calibration. Calibration provides correction factors and measures accelerator and EPID characteristics that are used to produce the highest quality image in routine use. Often, background signals are subtracted and inhomogeneity of response is divided out. The EPID may even require gantry angle calibration, if the mechanical stability of the EPID is such that a mechanical shift offsets the calibration of a flat field, or the treatment machine characteristics change significantly with gantry angle. The user is encouraged to determine which characteristics will ensure optimal operation. Simple mechanical phantoms with square grids of pins to test for distortions are available from manufacturers or can be easily fabricated. The use of fiducial markers or field edges to quantify patient set-up errors can eliminate mechanical instability effects. Frequent (e.g. daily) QA procedures include safety features such as mechanical integrity and collision interlocks. Operational and image checks are accomplished by imaging a fixed phantom in a fixed geometry with a given dose. This allows rapid assessment of operability and image quality. Field edge detection is another important concern. There are two reasons to find the radiation field on the image. As most

imagers do not maintain a rigid and reproducible relationship with respect to the central axis of the treatment unit, the location of the radiation field can be used to establish a coordinate system within which the variation of the location of patient anatomy can be determined. In the absence of a shaped radiation field, or when a field extends beyond the borders of the image, a graticule projection may also serve this purpose. A second important role for portal field border extraction is verification of the shape and orientation of the treatment portal.

The use of EPIDs is limited in that it is a planar imaging technique requiring at least two gantry positions to provide an indication of the patient set-up in 3-D. Moreover, the image quality from MV beams is inferior to that obtained from kV for some sites, and surrogates are then required to locate the target volume, such as bony structures or implanted radio-opaque markers. A full report on EPIDs can be found in the AAPM TG58 Report [378]. The most recent acceptability criteria for EPID QA can be found in the report by AAPM TG142 [223]. Geometric action levels should be <1–2 mm and the resolution should be <1 mm.

In an attempt to improve on the image quality, kV imaging has been introduced as an add-on to treatment machines [383–385]. The concept is based on integrating a kV X ray source and a large area flat panel detector on a standard linac allowing fluoroscopy, radiography and volumetric kV CBCT. The kV imaging chain can be mounted orthogonal to the treatment beam or in-line with the treatment beam. The former has the advantage in that stereoscopic planar imaging is possible with one gantry position by applying hybrid kV and MV imaging, provided that an EPID is also installed. A second advantage is that the kV imaging system cannot be blocked by the head of the treatment unit. The in-line approach has the advantage in that the kV imaging axis coincides with the axis of the treatment beam, providing on-line image data in the beam axis. Again, it should be noted that the images are planar, and often more than two images are required for 3-D information. All systems share the principle that the kV imaging isocentre and the MV treatment isocentre are independent and might not coincide exactly. The QA for geometric accuracy needs to account for this feature.

The integration of both on board kV diagnostic imaging together with MV EPIDs on linacs can allow for real time 3-D tumour position monitoring during treatment delivery [386, 387]. The geometric accuracy of such a system has been found to be of the order of less than 1 mm in all three spatial dimensions when using fiducial markers.

(b) Volumetric imaging (kV and MV CBCT, MV CT)

Jaffray et al. [388] were among the first to explore the kV CBCT concept integrated with existing treatment machines, and several manufacturers have adopted this approach in recent releases of their equipment. As with on board

kV imaging systems for planar imaging, the concept is based on integrating a kV X ray source and a large area flat panel detector. The kV CBCT allows a volumetric CT image to be reconstructed from data collected during a single gantry rotation. Because the gantry rotation of a linac is much slower than a CT ring gantry, flat panel detectors are introduced to acquire so-called cone beam CT or volume CT images. The design of currently available on board kV CBCT systems is adversely influenced by many factors, such as scatter, beam hardening, mechanical instability and intrascanning organ motion.

As with the planar gantry mounted kV systems, systematic geometrical uncertainties are introduced, and no perfect geometry can be achieved for the image acquisition, owing to X ray tube and detector sagging during gantry rotation and projection angle uncertainties. A correction can be introduced into the image reconstruction algorithm in order to account for the existence of mechanical flex, assuming that it is both reproducible and stable in time. The QA procedure, therefore, primarily focuses on verifying the reproducibility of this mechanical flex [389, 390]. Based on phantom studies, Jaffray et al. [388] illustrated the full volumetric nature of the cone beam CT data, showing excellent spatial resolution in all three dimensions (as opposed to conventional fan beam CT where the cranio-caudal resolution depends on the slice thickness and pitch). The system provided submillimetre spatial resolution (approximately 0.7 mm full width at half maximum of the line spread function) and a lowest readily detectable contrast at 47 HU. Sharpe et al. [390] performed phantom measurements to assess the alignment of the centre of kV CBCT reconstruction to MV radiation isocentre to image and localize a 1 cm diameter steel ball bearing. Data from 21 treatment sessions over a 3 month period, acquired on a linac in routine clinical use, demonstrated that the system was able to relocate the object (the kV CBCT data was registered to the planning data to assess couch corrections) within less than 1 mm of the prescribed location. The mechanical isocentre of the kV system was found to be within ± 0.5 mm of the MV radiation isocentre. The remaining set-up accuracy depended on the mechanical precision of the different components of the delivery system. Sharpe et al. also presented a simple method for geometric calibration using the above mentioned ball bearing. In a first phase, the ball bearing (initially placed at the isocentre with the help of room lasers) is aligned with respect to the treatment isocentre based on orthogonal MV portal images acquired with an EPID. Consequently, look-up tables are generated by calculating the centroid of the ball bearing in each projection of the kV CBCT acquisition as a function of gantry angle. These look-up tables are stored for subsequent use and employed during the reconstruction process to relate each projection to the reconstructed voxel array, thereby ensuring that the centre of the reconstructed volume is coincident with the estimated treatment isocentre (based on MV imaging). Again, this procedure assumes that

the mechanical characteristics of the system are systematic and reproducible. A similar approach has been reported by Oelfke et al. [389]. Yoo et al. [391] reported a multi-institutional verification of a volumetric IGRT solution based on ball bearing measurements, and a mechanical isocentre accuracy of less than 1.5 mm ± 1.0 mm was reported for 60 measurements spanning a time period of 6 months.

With respect to CT number accuracy, Rong et al. [392] showed that for adipose tissue, the HU discrepancy from the baseline was 20 HU in a small phantom, but 5 times larger in a large phantom. Ding et al. [333] looked in detail at the additional doses to the normal tissues of a patient from a typical kV CBCT acquisition. They determined dose distributions to patient anatomies from a typical CBCT acquisition for different treatment sites, such as head and neck, lung and pelvis. Their results have shown that, from a typical head and neck CBCT scan, doses to soft tissues, such as eye, spinal cord and brain, can be up to 8, 6 and 5 cGy, respectively. The dose to the bone, due to the photoelectric effect, can be as much as 25 cGy, about three times the dose to the soft tissue.

Similar to kV CBCT approaches, fixed isocentric geometry and a fixed source–detector relationship may not be rigid in the MV CBCT approach. And again, this approach requires a correction to be included in the reconstruction algorithm. One such example in the literature reports vertical sag of more than 15 mm between gantry angles of 90° and 270° due to the additional weight of a flat panel detector within an experimental set-up [393]. At first hand, a deviation of 15 mm from the ideal imaging geometry may present an extreme value. However, it needs to be borne in mind that it is not the absolute value of this deviation which is of vital importance but rather that the observed gravitational sag is reproducible and stable over QA relevant timescales. As long as the non-ideal irradiation geometry is stable in time, the devised calibration methods can reliably correct for any related artefacts in the cone beam CT images. To eliminate the need for measuring the physical parameters for each gantry angle, the geometrical factors relevant for MV CBCT acquisition are measured and defined in a series of transformations that are determined by a simple calibration procedure. Projection matrices can then be introduced to be directly used in the filtered back projection algorithm. Pouliot et al. [393] demonstrated the use of a cylindrical phantom with 108 radio-opaque spheres embedded in a unique helical pattern to perform the geometrical calibration. This procedure includes source–detector distance, detector plane orientation, gantry and detector sagging, and image distortion. The same group also reported the possibility of using the beam parameters to generate a composite plan in the regular TPS combining the MV CBCT dose distribution with the planned treatment dose distribution [394]. The estimated geometric accuracy and resolution was 1–2 mm, while the dose per MV CBCT study was between 5 and 10 cGy [393–395].

The helical tomotherapy approach (introduced by the manufacturer TomoTherapy) is an example of an integrated system [396, 397] where the concept of an add on sequential tomotherapy [398, 399] device has been combined with helical CT scanning resulting in a two in one concept. The continuously rotating gantry combined with a CT detector array system allows MV CT imaging and can, in principle, be used for in vivo dose transmission measurements for dose verification. Basically, it is a CT scanner where the diagnostic X ray tube has been replaced with a 6 MV linac and the collimating jaws (or shutters) replaced with a binary collimator consisting of small high density metal leaves. In a manner similar to diagnostic helical CT, the patient is treated in slices by a narrow photon beam. CT image acquisition, using a somewhat lower energy than for treatment, is accomplished with all leaves open prior to treatment. As the imaging system is integrated with the treatment system (the same beam delivery device and couch synchrony) the MV CT acquisition and geometric QA are inherently included in the treatment delivery QA, the latter being far more important and sensitive to small errors. In contrast to the CBCT approach, where geometric uncertainties need to be corrected in the reconstruction algorithm, these uncertainties are physically and mechanically minimized. Examples of QA issues include field width, collimator twist, MLC centring, isocentre consistency with rotation, couch velocity and accuracy, and synchrony with the gantry rotation. An overview of typical QA procedures is given by Fenwick et al. [400] and, more recently, by AAPM TG148 [227]. The issue of image registration accuracy (kV CT versus MV CT) has been investigated by Boswell et al. [401] and Woodford et al. [402, 403]. The latter performed a study investigating the influence of different image acquisition settings on set-up accuracy and consistency in order to optimize these settings in a clinical environment.

Apart from mechanical instability, motion artefacts caused by breathing or peristalsis during the enhanced scanning times can compromise image quality for on board volumetric imaging solutions. Furthermore, the combination of an imaging cone beam with flat panel detection system inevitably leads to intensified scatter artefacts. Scatter correction methods were developed to solve the problem of scatter artefacts [404]. Specific calibration and image reconstruction tools warrant sufficient image quality for a wide range of IGRT procedures at moderate doses [405–408].

The field of view is limited in the longitudinal direction for CBCT solutions, but not for the fan beam solutions, where the patient is moved with respect to the beam throughout the length of the chosen field of view. The lateral field of view is limited by the size of the detector array, but for the CBCT solutions, the array may be displaced for so-called offset half-fan scans extending the lateral field of view. For fan beam solutions, the longitudinal spatial resolution must be set via a slice thickness combined with a pitch magnitude, while for the cone

beam solutions, the longitudinal spatial resolution is given by the detector array resolution combined with the source–patient–detector distances. The spatial resolution in the two other directions is given solely by the detector resolution and set-up geometry for all solutions. Insertion of a bow-tie filter, which works for optimal image quality by counteracting the variation in patient thickness in the lateral direction, may be required (for offset geometry, a half-bow-tie filter may be available). The rotation arc required for the reconstruction of images may be variable both in the fan beam and in the cone beam solutions, whereas in the cone beam solutions, the number of projections over the rotation arc may also be variable.

In summary, the major advantage of volumetric imaging is providing anatomical data that is available on a daily basis for the positioning process. This 3-D data can be used for dose reconstruction strategies allowing the verification of the dose of the day [179, 393, 409–411].

In the future, it can be expected that it will be possible to perform a treatment planning calculation on the images of the day. This suggests the possibility of on-line ART where the treatment technique is re-optimized throughout the course of treatment. This introduces both new opportunities and uncertainties which will require careful consideration.

6.4.10.2. In-room imaging: room mounted systems

(a) Planar imaging

Room mounted planar imaging systems have kV source detector assemblies mounted onto the walls, ceiling or floor of the treatment room. These systems are designed for stereoscopic radiographic or fluoroscopic projection imaging. In general, ceiling or floor mounted systems are efficient and generate low dose in terms of clinical applications, of the order of 0.5 mGy, as reported by AAPM TG75 and Verellen et al. [330, 412]. Similar to EPIDs, target localization requires surrogates such as bony landmarks or implanted radio-opaque markers. The absence of 3-D volume based target verification does not allow for quantitative monitoring of tumour or organ deformation and volumetric changes, but as the imaging system is independent of the treatment system, this approach is well suited to real time monitoring during treatment (e.g. respiratory synchronized treatments) [330, 374]. The commercially available systems usually combine stereoscopic X ray imaging with a real time optical tracking device (based on infrared (IR) reflective markers, such as BrainLAB's ExacTrack system, or on active LEDs, such as Accuray's Cyberknife). Both systems combine imaging technology with an automated (robotic) 6-degrees-of-freedom correction (robotic couch, robot mounted linac assembly or both).

The stereoscopic X ray approach provides an automatic 2-D or 3-D rigid body fusion method. Two projection kV images are acquired and automatically fused to DRRs generated from the 3-D CT reference set to determine relative shifts and rotations in all three orthogonal axes. Three dimensional anatomical information can then be inferred from the registered simulation images [412, 413]. When accessible and tolerable, implanted radio-opaque markers can be used as surrogates for soft tissue, albeit with the caveats of an invasive procedure and potential marker migration [414]. Generally, more than three seeds or markers are needed to correlate 3-D locations between them in the stereo images and to identify potential translations and rotations, assuming a rigid body model [415]. The markers can be identified for both static and moving objects. Gating software is used to define which respiratory phase the images are acquired at based on real time information obtained from the optical tracking devices, and in addition, the system can be used to trigger the linac for respiratory gated treatment [416] (see Section 6.4.11). For verification, snapshot stereoscopic images can be acquired during treatment for direct verification of gated delivery relative to the reflective marker surrogates for intrafraction motion. Intrafraction set-up variability in hypofractionated cranial and body radiotherapy was investigated by Spadea et al. [417] using integrated IR optical localization and stereoscopic kV X ray imaging. They found that according to the optical measurements, the size of intrafraction motion[1] was (median ± quartile) 0.3 ± 0.3 mm, 0.6 ± 0.6 mm and 0.7 ± 0.6 mm for cranial, abdominal and lung patients, respectively. X ray image registration estimated larger intrafraction motion, equal to 0.9 ± 0.8 mm, 1.3 ± 1.2 mm and 1.8 ± 2.2 mm, correspondingly.

Proper target localization with room mounted X ray systems requires calibration of the spatial relationship of the X ray tubes, the detectors and the real time optical tracking device with the isocentre of the treatment machine. The position of the detector with respect to the tube is based on edge detection of the radiation field borders. The spatial relationship with respect to the treatment isocentre is established using a calibration phantom with internal radio-opaque markers for kV imaging and external IR reflective markers or light emitting diodes for optical tracking. The specific kV configuration geometry is then stored in the planning system. An illustration of the calibration procedure is given in Fig. 33 and details of the QA of such a system are given by Verellen et al. in Ref. [412]. Likewise, the positioning accuracy (translational and rotational) for a Novalis Body system, incorporating two IR cameras, a video camera and two kV imaging devices, was determined using phantom studies by Yan et al. [418].

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[1] The expression of the size of intrafraction motion in terms of median ± quartile is specific to Ref. [417]. It is not possible to change the expression of these results because of lack of information on the uncertainty distribution.

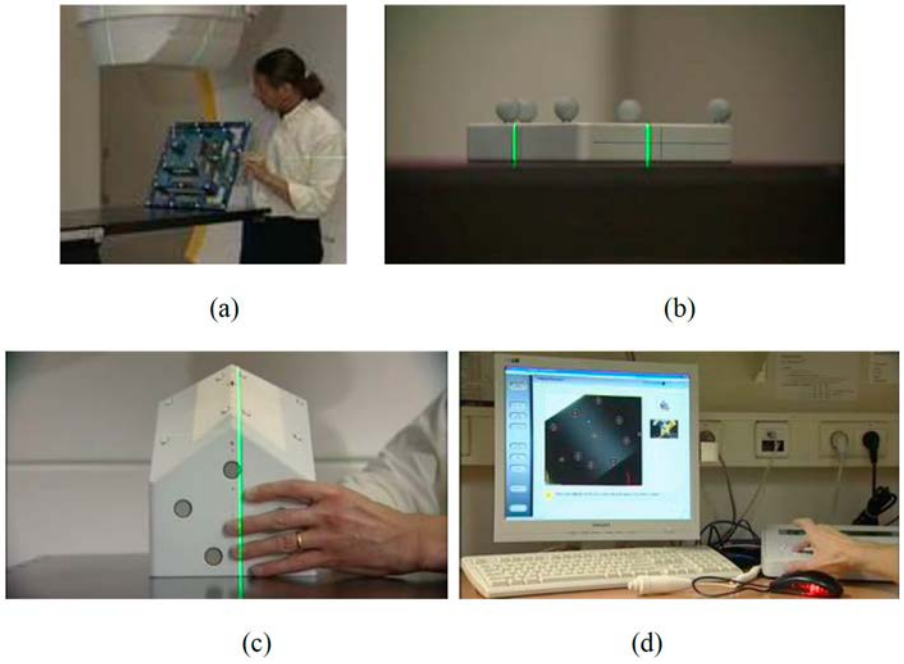

FIG. 33. An example of the calibration procedure for a target localization system: (a) Referencing video and IR system; (b) Calibrating IR system with respect to treatment isocentre using room lasers; (c) Phantom with IR reflective markers and radio-opaque imbedded markers; (d) Software tool to calibrate the X ray system with respect to the IR system referencing the IR markers and radio-opaque markers from the previous phantom. (Courtesy of D. Verellen.)

X ray systems in general are not presently capable of locating and registering soft tissue tumour volumes via their 2-D imaging systems. Some offer the option of tracking soft tissue tumours in the lung under certain conditions. Consequently, soft tissue tumour sites are normally marked with several fiducials in the same manner as for the spine. It is assumed that the fiducials maintain fixed positions within the tissue from the time that the treatment planning CT study is acquired until treatment is completed. This assumption is verified by measuring the relative spacing of the fiducials in the alignment images during treatment. If the relative fiducial spacing is unchanged from the CT study, it is assumed that the fiducials have not migrated. Room mounted X ray systems can potentially generate images more efficiently than other types of X ray imaging systems mainly owing to their fixed configurations relative to the beam delivery unit,

and hence can acquire images without mechanical movement. A full review of in-room kV imaging systems can be found in the report by AAPM TG104 [419].

(b) Volumetric imaging

An obvious approach to visualizing soft tissue prior to treatment and defining the spatial relationship between target and OAR is a high end diagnostic CT scanner inside the treatment room. Court et al. [420] reported the mechanical precision and alignment uncertainties for an integrated CT and linac system. The system integrates a high speed CT scanner on rails and a linac. The CT scanner is placed in close proximity to the medical linac, allowing a single couch to be moved from the imaging position to the treatment position. These systems vary in the amount of motion and degrees of freedom required to move the patient from one position to the other. If the CT images are acquired while the CT gantry is sliding over the static patient couch (CT on rails), the differences in couch deflection at different couch extensions are minimized [421]. Because CT imaging is not performed at the treatment isocentre, identification of the isocentre in the acquired CT image set is important for image guided treatment. Radio-opaque fiducial markers can be used to transfer the isocentre information between the linac and the CT scanner. The radio-opaque markers can be aligned to the lasers at the linac side first and attached to the patient's skin surface or the immobilization device as a temporary reference for the imaging session and treatment set-up. If the couch sags or moves differently at the CT side, the attached radio-opaque markers will move with the patient and therefore will not be affected by the uncertainties associated with the couch support device. Using external markers showed improved accuracy (<1 mm) for repositioning [420].

Concerning geometric accuracy, Court et al. [420] identified the following sources of uncertainty:

> "(1) the patient couch position on the linac side after a rotation; (2) the patient couch position on the CT side after a rotation; (3) the patient couch position as indicated by the digital readout; (4) the difference in couch sag between CT and linac positions; (5) the precision of the CT coordinates; (6) the identification of fiducial markers from CT images; (7) the alignment of contours with structures in the CT images; (8) the alignment of set-up lasers. All sources of uncertainty were less than 0.3 mm (1 SD) apart from the couch position on the CT side after a rotation (0.5 mm in the lateral direction) and the alignment of contours in the CT images (0.4 mm in the cranio-caudal direction)."

The major advantage of this approach is the availability of a high end CT scanner with optimal image quality. The rail track mounted tomographic imaging systems combine completely conventional CT technology with high image quality and clinical robustness [422]. Kuriyama et al. [421] reported a positional accuracy of under 0.5 mm, while Court et al. [420] reported an accuracy of 0.7 mm that can be further reduced to 0.4 mm (i.e. approaching the resolution of the CT scanner itself) when using radio-opaque fiducial markers with a solid phantom.

Owen et al. [423] investigated the agreement between CT on rails and planar EPID imaging and found considerable differences between the two as a result of slice thicknesses, which affected the accuracy of localization in the superior-inferior plane, and a couch sag that occurs at the CT on rails gantry, which could not be totally corrected for in the AP plane. Differences of >3 mm in the localization of fiducial markers were noted for 3.1–14.2% of the time, depending on the plane of observation. Furthermore, systematic errors of 1 to 3 mm were noted.

A 2011 study [424] described individual daily total error shift patterns in post-prostatectomy patients from a diagnostic quality CT on rails IGRT system. The temporal vector trends confirmed complex behaviours and unpredictable changes in magnitude and direction. These findings highlight the importance of using daily IGRT in post-prostatectomy patients. Such accuracy, in combination with excellent image quality, promises excellent management of interfraction set-up errors and organ motion. However, the issue of intrafractional motion between the imaging and delivery systems still remains and will have to be accommodated through the appropriate selection of PTV margins.

An alternative approach has been investigated by Sorensen et al. [425]: introducing a flat panel mobile C arm, capable of kV CBCT, into the treatment room. A commercial optical IR tracking system was introduced to define the relationship between the C arm image coordinates and the treatment machine isocentre, so as to obtain the appropriate reference frame for the reconstructed images. The system can rotate in synchrony with the linac allowing image acquisition in the treatment position while avoiding collisions between the devices. A default IR isocentre calibration phantom is introduced to define the linac isocentre within the IR tracking system reference frame. This enables accurate location of any IR reflecting object in treatment room coordinates, allowing the tracking of the C arm within the treatment room. Localizing reflective markers on a phantom with both the IR tracking device and transforming the reconstructed CT images to calculate room coordinates, the authors reported a mean absolute difference of 1.4 mm ± 0.5 mm (1 SD). As the calibration procedure is based on room–laser alignment, a fundamental assumption of this approach is that the room lasers are aligned with the linac isocentre. The same approach has been

introduced at Heidelberg University, where a CBCT imaging system controlled by a robotic arm was installed for its heavy particle facility treatment room [426]. These systems were required for particle treatment because the treatment beams do not exit the patient and cannot therefore provide a portal image.

A review of in-room CT based volumetric imaging systems can be found in the ESTRO-European Institute of Radiotherapy report [51].

6.4.10.3. Non-radiographic solutions

(a) Ultrasound

Daily ultrasound positioning for external beam prostate treatment is an attractive method for image guidance because no radiation is involved and the prostate itself is positioned without the need for implanted markers. However, with ultrasound positioning there are concerns about interobserver variability and the possible introduction of errors during image acquisition from the pressure to the patient's lower abdomen [427–429]. Reports of acceptable images and acceptable alignments range from 68% to 97% [429]. Despite questionable accuracy in this modality, it is still in widespread clinical use for image guidance.

(b) Radiofrequency markers

A system has been developed for patient positioning based on real time, continuous localization of implanted electromagnetic transponders (beacons). The transponders can be used as magnetic intraprostatic fiducials. Clinical evaluation of this 4-D non-ionizing electromagnetic localization system with transponders indicates a comparable localization accuracy to the isocentre (within 2 mm) compared with X ray localization [430, 431].

6.4.11. 4-D imaging hardware and software

Four dimensional imaging, as used in adaptive radiotherapy, has two different uses associated with it: (1) following tumour response during a course of treatment and adapting the treatment accordingly, or (2) managing tumour motion during each individual treatment fraction. The imaging of motion requires special attention, and the overall accuracy is a combination of the spatial accuracy of the imaging modality used (of the above described techniques) and the temporal aspects related to the use of a 4-D modality. Special phantoms are designed for calibration and accuracy measurements of motion imaging.

6.4.11.1. 4-D imaging for treatment preparation

It is important to understand that the breathing patterns and, hence, tumour motion will change over time (between simulation or imaging sessions and treatment sessions) and are inherently irreproducible. When measuring tumour motion, the motion should be observed over several breathing cycles.

(a) 4-D or respiration correlated CT(RC-CT)

Before embarking on the 4-D concept in CT scanning, it should be mentioned that in order to assess tumour motion, in many cases fluoroscopy using conventional simulators can be used to quantify displacements and evaluate reliable PTV margins. Assessment of motion is only one aspect of tumour motion; artefacts introduced in the image reconstruction are also to be considered. Basically there are three options possible for CT imaging that can include the entire range of tumour motion for respiration. Listed in order of increased workload they can be classified as: (1) slow CT; (2) inhalation and exhalation breath hold CT; and (3) 4-D or RC-CT.

With the previous generation of CT scanners with relatively slow data acquisition times, the image of the tumour was smeared out owing to breathing motion. In this case, tumour volume and organ delineation will include at least part of the internal margin, which is inappropriate in 4-D imaging. This technique yields a tumour encompassing volume, with the limitation that the respiratory motion will change between imaging and treatment. Moreover, motion may cause localization errors and, in some cases, disappearance of small tumours that should be detectable. The fast helical multi-slice CT scanners actually freeze the image of the tumour at one location at one particular moment in the breathing cycle, thus offering a more anatomically relevant representation of the tumour at a single point in time. As this is not necessarily the average tumour position, however, this fast acquisition might introduce large systematic errors with respect to beam–tumour alignment when used inappropriately. Several strategies have been investigated to solve this problem, such as inhalation and exhalation breath hold techniques, respiratory gating [432] and respiration correlated or 4-D CT (RC-CT) [433–436]. Inhalation and exhalation breath hold CT scans can also be applied to obtain a tumour encompassing volume. The advantage of this approach over the slow scanning technique mentioned above is that the blurring caused by motion is significantly reduced. Dose calculation, however, should be performed on the CT dataset that is most appropriate for that particular treatment and patient. One option could be to use a free breathing CT for dose calculation, and to use the inhalation and exhalation scans to determine the range of motion and achieve more accurate tumour delineation.

Four dimensional CT or RC-CT is a relatively new technology, made possible by the introduction of faster CT scanners with multiple row detectors. Basically, it is an oversampled or low pitch CT scan during which the respiration signal is recorded. The latter can be obtained with different methods, of which abdominal straps with a pressure sensor [435, 437, 438], IR markers placed on the patient's chest [436] and measuring airflow with thermocouples or spirometers in a mouth mask [439–441] are the most common. Afterwards, the CT images can be binned (sorted) according to the phase or amplitude of the external respiratory signal (phase angle or amplitude sorting) [441, 442]. Most commercially available systems are based on the phase of the external breathing signal; however, Lu et al. [441] have observed that the relationship to internal motion seems to be strongest with the amplitude of the external signal. These and other investigators showed that images generated using amplitude sorting displayed smoother lung–diaphragm boundaries and minimal reconstruction artefacts compared with phase angle sorted imaging [441, 443–445]. In short, phase angle sorting regards a shallow breath as being the same as a normal and a deep breath. Image binning itself can be performed prospectively or retrospectively. In prospective techniques, acquisition is synchronized with the patient's breathing, and all the projections are acquired during the same respiratory phase by means of a trigger produced by real time tracking of the respiratory signal [446]. On the other hand, retrospective algorithms [447–450] do not require any trigger signal during the acquisition, although they are constrained by the need to acquire several complete respiratory cycles per slice to avoid any empty phase bins. Therefore, the acquisition protocol usually requires multiple frames from every projection angle, each one corresponding to a different point during the breathing cycle.

Instead of one CT dataset, in 4-D CT or RC-CT several datasets, according to the number of bins, are available for tumour delineation and treatment planning. A limitation of 4-D CT is that it is affected by variations in respiratory patterns during acquisition. Based on these 4-D CT datasets, videos can be generated to visualize and quantify the tumour's motion. However, one should realize that a video loop generated from a 4-D CT scan is not representative for the patient's breathing during treatment as it represents only a few breathing cycles acquired several days prior to treatment repeated in a continuous loop. The patient's breathing during scanning or treatment can be irregular, and can also be affected by the patient gradually becoming more comfortable during the course of treatment or as a result of the response to treatment. Again, this emphasizes the importance of the imaging technique being chosen with regard to the radiotherapy technique that will be used to treat the patient (motion encompassing technique, immobilization, gating, tracking etc.).

Incorporating the 4-D information into treatment planning is possible in different ways, again based on the treatment technique. One option is to use only

one phase of the respiration, e.g. the mid-ventilation phase, as being the phase where the tumour is at its average position, in combination with a margin recipe (based on the extent of motion observed from the other datasets) to account for the motion [451]. Some investigators use maximum intensity projections, which reflect the highest pixel value encountered from all CT images along the viewing ray for each pixel, giving rise to an artificial intensity display of the brightest object along each ray on the projection image [452]. Another option is to contour each phase separately, or alternatively, contour one phase and use deformable registration to obtain the contours in the other phases, and use the union of the contours obtained from these datasets to obtain a margin recipe. In the case of respiratory gated radiotherapy, one might decide to delineate the tumour volume in the treatment phase angle or amplitude sorted dataset only (provided a similar technique is used to obtain the external breathing signal). Again, it is important to note that the patient's breathing during CT scanning might not be representative of the breathing during treatment and the correlation between the external signal and internal tumour motion is prone to changes (irregular breathing, tumour response, baseline shifts etc.). Respiratory gated or tracking techniques thus require IGRT during treatment to validate and update the correlation between the external breathing signal and the internal tumour motion.

(b) Respiratory correlated PET/CT

As mentioned earlier, inter- and intraobserver variability in tumour delineation can be improved with the combination of PET and CT. As RC-CT has been shown to be beneficial in imaging moving tumours, the effect of respiration on PET and the possibility of respiration correlated PET/CT [440, 453] needs careful consideration in radiotherapy treatment planning. PET imaging is a slow imaging technique requiring several minutes to obtain a reasonable signal to noise ratio. Therefore, several respiration cycles are covered by the images, obviously blurring the objects. Basically, motion artefacts in PET lead to two major effects: (1) they affect the accuracy of quantification, scrambling the measured standard uptake values, and (2) the apparent lesion volume is overestimated. Needless to say, the blurring artefact hampers possible registration with fast CT images. Caldwell et al. [454] suggested actually using this information to derive an individualized ITV [18], the hypothesis being that the respiration is taken into account in the imaging process and the visible lesion represents a probability distribution of the tumour's position. However, some arguments can be raised against this approach. Firstly, PET images are extremely sensitive to window and level settings and some kind of automated delineation software should be applied to define the PET based GTV [127, 455, 456]. The latter should be correlated with pathology data [127, 457, 458], which is extremely difficult with

blurred PET images. Moreover, the resulting intensity as observed in the images is a complicated combination of metabolic uptake heterogeneity and motion (typically yielding a high intensity at the average position and low intensity at the extreme positions). Secondly, accurate information on several parameters such as the maximal standardized uptake value (SUV_{max}) is hampered, and SUV values are only reliable when no or little movement of the target is present [459]. Thirdly, the attenuation correction could be wrongly performed when combining the fast CT scan with the slow PET scan. And finally, the information on intratumour heterogeneity in tracer uptake that would be needed for dose painting by numbers is completely lost because of the respiration motion. For these reasons, 4-D or respiration correlated PET imaging has been developed in a similar way to RC-CT.

Motion artefacts can be reduced by gating PET images in correlation with respiration. Nehmeh et al. [459] have shown that respiratory gating can reduce the degrading effect of breathing motion on PET images, allowing a more complete recovery of the true counts within the lesion and a more accurate estimation of the lesion volume. Based on phantom studies, these investigators showed a dependence of the reduction in the smearing effect on lesion size, motion amplitude and bin size. Respiration correlated PET (RC-PET) yielded an increase in the signal to noise ratio, as well as a recovery of the SUV values. Application to a patient study demonstrated that the technique was successful in reducing the smearing effect and correcting the SUV [459]. In these phantom studies, however, the PET data were acquired in gated mode and binned prospectively into 10 bins. This approach is sensitive to irregular breathing patterns as the bins have predefined time lengths. In an attempt to account for varying breathing frequencies, Nagel et al. [460] have investigated RC-PET based on continuous acquisition of the data in list mode and retrospective phase binning. Retrospective binning offers an advantage in that the time length of the bins is determined individually for each period of respiration. After binning the CT and uncorrected PET data into corresponding phases, the tumour and tissue positions on PET and CT match more closely, reducing motion artefacts introduced to the PET reconstruction with CT based attenuation correction. Using a moving lollipop phantom with a 3.2 cm diameter sphere filled with ^{18}F FDG, Nagel et al. observed that with a standard non-RC-CT-PET, the volume as measured in CT and PET datasets was underestimated by as much as 46% and overestimated by 370%, respectively. Volumes obtained from RC-CT-PET had average deviations of 1.9% (±4.8%) and 1.5% (±3.4%) from the actual volume for the CT and PET derived volumes, respectively [460]. Images with non-RC attenuation correction showed clear misplacement of the maximum activity, which would result in incorrect localization of the tumour in clinical practice. However, these investigators acknowledged that the sphere was

imaged in air with little occurrence of attenuation, which might overestimate the effects. It is interesting to note that a small phase shift could be observed in some experiments because the respiratory signals were recorded with different devices. Synchronization of both modalities (CT and PET) with a single device for respiration correlation is assumed to eliminate this phase difference. To overcome some of these problems, the same group performed a simulation with real patient data based on respiratory gated CT studies of five patients using conventional PET, non-gated PET with gated CT, gated PET with non-gated CT and phase matched PET and CT [461]. As expected, phase matched gated PET and CT gave essentially superior PET reconstructions. Gating of the PET alone (non-gated CT) gave the correct tumour shape but was not quantitative. Gating of the CT only (non-gated PET) resulted in blurred tumours and was again not quantitative, which was also true for the conventional PET.

(c) MRI

Ultrafast, volumetric and cine MRI can provide non-invasive means to evaluate not only variability in target volume positioning during radiotherapy but also the temporal variation in target volume deformation that may occur interfractionally and intrafractionally. These are pertinent issues that currently limit precision radiotherapy and justify the development of IGRT. Cine MRI can evaluate intrathoracic tumour mobility for patient individualization of treatment margins [462] and determination of the efficacy of free breathing gating techniques for lung radiotherapy [463]. Cine MR has been used to assess intrafraction motion in prostate cancer [464, 465]. This intrafraction information can be used not only to determine internal margin size for treatment planning but also to estimate the degree of organ deformation that may occur during radiotherapy [466].

6.4.11.2. 4-D in-room and feedback to treatment beam (gating, tracking)

For SBRT, the use of image guidance, gating and real time tumour tracking has been shown to be a method to improve the accuracy of treatment [467]. Guckenberger et al. [467] calculated safety margins for compensation of inter- and intrafractional uncertainties of the target position using pre- and post-treatment CBCT imaging. Safety margins for compensation of breathing motion were also evaluated for pulmonary tumours using respiratory correlated CT, model based segmentation of 4-D CT images and voxel based dose accumulation. The target in the mid-ventilation position was the reference. Because of large interfractional baseline shifts of the tumour, stereotactic patient positioning and image guidance based on the bony anatomy required safety margins of 12 mm

and 9 mm, respectively. Four dimensional image guidance targeting the tumour itself and intrafractional tumour tracking reduced margins to <5 mm and <3 mm, respectively. Additional safety margins were required to compensate for breathing motion. A quadratic relationship between tumour motion and margins for motion compensation was observed: safety margins of 2.4 mm and 6 mm were calculated for compensation of 10 mm and 20 mm motion amplitudes in the cranio–caudal direction, respectively. Thus, 4-D image guidance with pretreatment verification of the target position and on-line correction of errors reduced safety margins most effectively in pulmonary SBRT. The same principal investigator also developed a novel respiratory motion compensation strategy and found that for pulmonary targets with motion amplitudes >10–15 mm, the combination of gating and the mean target position concept allowed small safety margins with simultaneous long duty cycles [468]. Similar concepts have also been reviewed by Verellen et al. [469].

VERO is a new platform for image guided stereotactic body radiotherapy. Orthogonal gimbals hold the linac MLC assembly allowing real time movement to achieve tumour tracking. Systematic tracking errors were found to be below 0.14 mm. Two dimensional tumour trajectories were tracked with an average (90% percentile) tracking error of 0.54 mm, and tracking error standard deviations of 0.20 mm for pan and 0.22 mm for tilt [470].

CyberKnife is a linac on a robotic arm that is capable of tracking the tumour while the beam is on. In one study [471], the errors in the correlation model, which relates the internal target motion to the external breathing motion, were quantified. It was found that the mean correlation model errors were less than 0.3 mm. Standard deviations describing intrafraction variations around the whole fraction mean error were 0.2–1.9 mm for cranio–caudal, 0.1–1.9 mm for left–right and 0.2–2.5 mm for anterior–posterior directions. Without the use of respiratory tracking, these variations would have been 0.2–8.1 mm, 0.2–5.5 mm and 0.2–4.4 mm. The overall mean prediction error was very small (0.0 ± 0.0 mm) for all directions.

6.5. TREATMENT DELIVERY

Treatment delivery is the final stage of implementation of the prescription and, as such, the final step of the process of radiotherapy. During the preparatory phase, the optimum patient position, dose levels and tumour and OAR volumes have been carefully defined. The highest level of accuracy achievable at the time of treatment delivery will help to ensure an optimum outcome for all patients.

It is important to consider the technical developments that have taken place in radiotherapy over the past decades, which are continually evolving. The

complexity inherent in modern radiotherapy relates to the equipment available, the time period over which treatment is delivered, the elements that, over time, can exert a range of influences, and the knowledge, skills and attitudes of the multidisciplinary team. Accuracy is always important but the level of accuracy required increases with reduced volumes and increased doses which have been greatly facilitated by equipment developments and medical evidence (e.g. Ref. [472]).

6.5.1. Defining the levels of accuracy achievable

In this context, and given the wide diversity of resources currently available globally, it is important for a department to define the levels of accuracy that can be realistically achieved and to use this information both to inform current practice and to identify future improvements. In this way, more complex techniques will be introduced when an appropriate environment exists. The level of accuracy that can be achieved will be influenced by the factors previously identified. In defining the level of accuracy achievable, sources of uncertainty such as equipment, patient related procedures, staffing levels and working hours should be reviewed, the weak links identified and consideration given as to how they will be addressed.

A wide range of publications describe the levels of accuracy that are desirable and achievable. Acceptable levels of accuracy in the dose delivered to the dose specification point vary between 3.5% and 5% (k = 1) [10–12, 14, 28, 473]. The levels quoted, of course, relate to all elements of the radiotherapy process. Many of the uncertainties associated with treatment delivery are random and, when incorporating them into an acceptable accuracy level, can only be estimated.

6.5.2. Resources and working practices

To define the level of accuracy realistically achievable, a department should review its resources and working practices and calculate the number of patients who can be treated accurately within a given time frame and the level of complexity that can be safely implemented into daily practice. The implementation of IMRT, for instance, should only be considered when the department is satisfied that routine practice in 3-D CRT is being carried out to a sufficiently high standard and that the necessary resources are in place to support the delivery of more complex techniques. The same applies to transitioning to volumetric image based 3-D brachytherapy.

Currently, a wide range of fractionation schemes are routinely used in radiotherapy departments. With smaller volumes and higher doses, patients

may be prescribed a fractionated course of treatment for up to two months. Hyperfractionated regimes may also be used and will have an impact on the daily treatment unit schedule. This approach may also involve more than one treatment team in the daily delivery process. Hypofractionated, high dose per fraction treatments may require even greater clinical, dosimetric and geometric accuracy. Maintaining accuracy is more complex in these settings where different teams are routinely involved in treatment delivery and patient monitoring with a resulting lack of staff continuity.

The impact of working practices on the quality and safety of the department should be carefully considered. Where staff rotate between units or firms, and different working shift systems are unavoidable, time should be allocated for appropriate change-over and discussion of any important factors relating to the patients in treatment or being prepared for treatment.

Staff responsible for treatment delivery should understand the scientific basis of radiotherapy and the importance, therefore, of accurate delivery. They should be conscious of what they are doing, consider how best to do it and be aware of the consequences of not doing it correctly. Only in this way can a culture of accuracy in treatment delivery, irrespective of resource constraints, be assured. Any repetitive procedure can quickly become routine, which may result in diminished attention to detail, and a culture of working with awareness and alertness should be encouraged to avoid this. The clinical aspects of QA, including routine peer review meetings and regular chart rounds, can lessen the likelihood of errors in routine tasks. All staff should therefore be encouraged to participate in a comprehensive QA programme.

6.5.3. Interruptions to treatment and unscheduled gaps

Gaps or delays in treatment for any reason can be detrimental to maintaining accuracy and may affect the overall outcome. Patients should be categorized so that, in case of treatment unit breakdown, high priority patients can be treated preferentially. An understanding of the radiobiological principles is essential to prevent misinterpretation and misapplication of the treatment prescription. The Royal College of Radiologists (UK) states that interruptions to a course of treatment that result in an overall extension of the treatment time increases the risk of local recurrence, particularly for fast growing tumours. Using mathematical modelling, they calculate that an unscheduled gap of one day can result in an absolute reduction of local control of 1–1.4% for laryngeal cancer, with longer gaps significantly affecting treatment outcome for head and neck, cervical and lung cancer [474].

It is important that the staff understand the radiobiological significance of treatment interruptions if they are to ensure that these are managed effectively

in the department. Consideration must be given to the timing of the start of treatment and this should ideally be at the beginning of the working week. Starting treatment just before a break for a weekend, for example, adds at least two days to the overall treatment time. A policy must be developed to manage unscheduled gaps and all staff should be involved in this process if it is to be implemented successfully. The policy should include recommendations on scheduling, managing scheduled downtime and its impact and how to compensate for interruptions in treatment for whatever reason.

Gaps may also result from patient related factors and the RTTs on the treatment unit must be aware of anything that is causing difficulty in patient attendance. These may be social factors, transport related problems or issues related to side effects from treatment, which are often enhanced with chemoradiotherapy regimes. Carefully monitoring the patient on a daily basis will identify problems early. Regular audits of interruptions should be carried out and linked to the outcomes for the department. Unscheduled downtime of equipment should also be minimized by a thorough and regular preventative maintenance programme. Plans should also be developed for the possibility of backup treatment on other therapy machines in the department if at all possible.

6.5.4. Identification

Accurate treatment delivery starts with patient identification which has three central components — correct patient, correct site and correct procedure [29].

6.5.4.1. Correct patient

As indicated in Section 2.2, misidentification is a problem that still occurs in many radiotherapy departments and is acknowledged to be greater in acute care hospitals involving procedures in several locations and where staff work shifts [475]. Incidents relating to misidentification have been regularly reported to ROSIS [31]. Many departments now routinely ask patients to state their name, address and date of birth before entering the treatment room. Other options include the use of bar-coding, which has the added benefit of enabling more efficient management of the patient flow through the department, or photographic identification. Patient privacy must, however, be considered and the system used must be defined by the department based on their resources and the cultural values of the population. Irrespective of the method used, policies and procedures should be developed for patient identification and these should be followed.

It is also important to check that the patient is fit for treatment, e.g. has the patient been checked for any side effects, or are there specific tests such as

blood counts or clinical review which need to be carried out before treatment commences?

6.5.4.2. Correct site

The RTTs should check that the correct treatment plan is uploaded for the patient and that any amendments have been correctly entered, checked and signed. Where a treatment plan has more than one phase or a boost there must be a clear differentiation in instructions (both electronic and paper based) and markings used for set-up. Single redundancy in topography specification in the prescription is good practice.

6.5.4.3. Correct procedure

Where the patient needs specific pretreatment preparation such as bladder filling, sufficient time for such preparation must be allocated and the patient treated promptly to avoid unnecessary discomfort or distress. If the patient is receiving other concurrent treatment, then a specific timing schedule may be necessary and this must be incorporated into the treatment schedule.

6.5.5. Treatment documentation

The treatment charts contain both the instructions to allow the treatment to be carried out correctly and the permanent record of the treatment delivered to the patient. The treatment chart must therefore record all the information that pertains to the prescription. The treatment chart should be sufficiently comprehensive to facilitate an independent accurate check, and enable reconstruction, recalculation and review of the treatment delivered to the patient. There should be a policy within the department for regular checks of the treatment charts by the appropriate staff.

6.5.6. Incident and near miss reporting

A safety reporting and learning system should be in place with regular feedback and action plans. This should be consistent with national policy on radiation incident reporting, if such a policy exists. In many countries, reporting of significant incidents is mandatory. Local reporting systems should be designed as learning and improvement tools. The focus is to raise awareness of the potential for incidents and to encourage staff to always be conscious of this. Reporting of incidents and near misses should be seen as a positive aspect of treatment delivery, and this should be followed with good feedback and action

implementation involving the staff in raising the standard and accuracy of treatment delivery. Incident reporting is further discussed in Section 7.6.2.

6.5.7. EBRT

6.5.7.1. Patient positioning

The position of the patient defined at the preparatory stage has been selected as the ideal to achieve the prescription. The position must be accurately reproduced on a daily basis throughout the duration of a course of EBRT to identify any changes that will compromise this goal. Any variation in the patient position should be checked by referring back to the (CT) simulator images. RTTs need to be familiar with the process of image matching and may require additional training in this area. Portal images often have poor contrast and can be difficult to match; much will depend on the experience and expertise of the reviewer.

6.5.7.2. Reference point and field marking

Accuracy in setting field parameters, e.g. gantry and collimator angles, is also important. Particularly on some older treatment units, the gantry angle can be somewhat unstable and may take some time to set. In a busy department, small deviations may be accepted in the interest of saving time. It is important to remember that a series of small deviations can result in a very significant overall deviation.

Care with matching fields that have borders that are close to one another or touching is critical. Where fields are adjacent, such as tangential and supraclavicular fields in breast or craniospinal techniques, extra care must be taken and, if necessary, the borders should be marked or imaged daily to ensure that the correct movements between the fields have been made.

6.5.7.3. Quality assurance (QA) and quality control (QC) of treatment delivery

There should be an independent double check of all set-up parameters within the treatment room and an independent verification of the monitor unit or timer setting at the time of actual dose delivery. Double signatures should be recorded. A system of weekly chart reviews should be established. This should be carried out in accordance with local policies and procedures and these should include checks of the calculations, any amendments to treatment and whether they have been implemented, and all other safety critical parameters. As part of

a system of clinical audit, all aspects of treatment delivery should be reviewed regularly.

Considerable improvement in accuracy can be achieved by using pretreatment portal imaging. If RTTs are expected to make changes to patient position based on the images, institutional procedures must be developed with clear action levels. In addition to positional verification, imaging can also identify a range of other inaccuracies related to the beam, such as incorrect field orientation or incorrect MLC settings [277]. Observation of very small variations in field parameters, however, requires vigilance in the actual set-up.

6.5.8. Brachytherapy

There are many different types of procedures for introducing brachytherapy sources into the body. These have developed over many years from the library based brachytherapy techniques, in gynaecological therapy for instance, where LDR sources were placed manually into applicators (stabilized with some packing materials) into the uterus and vagina, to volumetric image based 3-D HDR brachytherapy [476, 477].

6.5.8.1. Dosimetry and prescription

It is not possible to quantify in a general way the effect on overall accuracy of the implementation into clinical routine of the rules of systems such as the Manchester, Stockholm or Paris system for gynaecology or the Manchester, Quimby or Paris system for interstitial applications. Similarly, the influence of international recommendations for dose recording and reporting, such as those published by ICRU on clinical outcome, is not known. Still, defining written institutional directives and policies will lead to consistency of dosimetry over larger groups of treated patients in the institution, and when based on such international recommendations, will also allow the comparison of clinical data from one institution to another and with published clinical results. It is only logical to conclude that, in the end, such multi-institutional intercomparisons will lead to the avoidance of gross errors and to a decrease of overall uncertainty in dose delivery. The following paragraphs discuss some aspects of the use of such systems.

The earlier types of brachytherapy used simple systems for calculating treatment times from standard tables developed by medical physicists and mathematicians. For example, for prescribing a treatment for cancer of the cervix under the Manchester System [478], the dose to a standard pair of points (point A) would be specified and achieved (as long as the dose to the rectum was not too high). For interstitial treatments, the Manchester System [246], and later the

Paris system [479], was developed. In order to ensure standards of recording and reporting in brachytherapy, the ICRU produced reports on Dose and Volume Specification for Reporting Intracavitary Therapy in Gynecology [123] and Dose and Volume Specification for Reporting Interstitial Therapy [124]. Since 2000, GEC-ESTRO has become involved in this work of standardization and has issued recommendations in its reports for both LDR and HDR brachytherapy [56, 171, 172, 174, 349, 480].

Whenever possible, treatment prescriptions and assessments of treatment administered should be stated in terms of absorbed dose in water. Where appropriate, e.g. for many interstitial implants, prescribed and reported doses should be based upon minimum dose to a target volume anatomically defined by 3-D imaging. As alternatives to the absolute minimum dose, which is difficult to evaluate reproducibly, the minimum dose to a specified fraction of the target volume, e.g. $D_{90\%}$ and $D_{98\%}$ determined from the DVH is acceptable [43, 346]. It is noted that $D_{100\%}$ has been shown to be too case dependent, whereas lower values such as $D_{98\%}$ and $D_{90\%}$ are more stable and are therefore a better choice. Similarly, dose heterogeneity in the TV can be specified volumetrically (e.g. the fraction of the target volume receiving greater than a given percentage of the prescribed dose, such as $V_{150\%}$ or $V_{200\%}$), as well as dose administered to critical organs to enable prospective correlation with morbidity. For OAR, values of the dose given to 2 cm^3 and 0.1 cm^3, D_{2cc} and $D_{0.1cc}$, are assumed to be indicative of complications. Dose reporting specifically for HDR prostate brachytherapy is discussed below.

However, dose specification based on anatomical landmarks is often not possible or useful. In these cases, dose has traditionally been specified to surfaces or points relative to the applicator geometry. For intracavitary treatments, where total source strength and the product of source strength and treatment time are well established prescription parameters, air kerma strength ($\mu Gy \cdot m^2 \cdot h^{-1}$) and integrated or total reference air kerma (TRAK) ($\mu \cdot Gy \cdot m^2$), should be used in place of the outdated mg Ra equivalent and mg/h, respectively. ICRU Report 58 [124] contains many suggestions on how to report dose homogeneity and other implant quality parameters in the absence of volumetric imaging or DVH capabilities. Similarly, ICRU Report 38 [123] makes many useful suggestions for recording dose in intracavitary brachytherapy.

Regardless of the dose specification criteria adopted by an institution, the following are to be noted:

— Dose specification criteria for prescribing treatment, quantifying administered treatment or quantifying normal tissue doses should be clearly defined and documented in the appropriate written procedures or the patient's treatment record. The description must clearly indicate how the

specified volume, surface or points are spatially localized, e.g. how point A coordinates are determined from orthogonal radiographs or 3-D images.

— The function of specified doses, e.g. vaginal vault surface dose, in constraining treatment or modifying the written directive should be documented.
— All personnel involved in planning treatments must understand the importance of consistently and reproducibly applying dose specification criteria to the treatment. For brachytherapy treatments that have been empirically validated by patient outcome studies, new dose specification parameters should not be implemented until the correspondence between the old and the new criteria is well understood. Similarly, when attempting to reproduce a clinical experience from another institution, the relationship between its dose specification criteria and those to be implemented must be clearly understood. This includes the understanding of the radiobiological effects of time, dose and fractionation when different treatment modes and schemes are compared.
— Where practical and appropriate, dose specification criteria endorsed by recognized consensus groups (e.g. ICRU, American Brachytherapy Society, GEC-ESTRO and AAPM) should be used to facilitate interinstitutional communication. It is expected that in the near future, the above mentioned GEC-ESTRO recommendations will form the basis of an update of ICRU Report 38 [123].

6.5.8.2. Imaging during brachytherapy

Even for the early forms of brachytherapy using a few radium (and later caesium) tubes, medical physicists have insisted on the use of a minimum of one pair of orthogonal radiographs in order to check and make further calculations of the source insertions in relationship to the surrounding tissues. Modern brachytherapy still uses orthogonal radiographs as well as many other different forms of imaging such as CT, MRI, ultrasound or conventional radiology systems [6, 173, 481].

Contouring volumes on cross-sectional images for brachytherapy is a field which has not been fully investigated. Interobserver variability may be considerable, as shown in studies for EBRT. It is therefore very difficult to provide an estimation of the dosimetric consequences of this issue.

One of the limitations of imaging derived information is that imaging is performed at one instant in time while treatment takes place over a finite duration. Movement may occur in the meantime. This may require corrective action, e.g. for HDR prostate brachytherapy, adjusting the position of the needles for subsequent treatments [6]. Simnor et al. [482] found that interfraction

correction for catheter movement in between a 3 fraction HDR scheme for prostate implants using pretreatment imaging is critical to maintain the quality of an implant. Without movement correction, there is significant risk of tumour under-dosage and normal tissue overdosage. The findings of this study justify additional imaging between fractions in order to carry out correction. For a PDR scheme of cervical cancer treatment, de Leeuw et al. [483] found occasional applicator displacements resulting in considerable changes in target dose for individual outliers. Mean changes for 18 applications in bladder and rectum dose were found to be 4% ±12% and 4% ±23%, respectively. Nesvacil et al. [484] compared intra- and interfraction variation data for 123 locally advanced cervical cancer patients from different centres. The standard deviations for both intra- and interfraction uncertainties were about 20% for OAR and around 13% for HR-CTV. Contouring and reconstruction uncertainties are inevitably included in the analysis, and therefore the variation corresponding to organ motion will be smaller.

It may be stated here that clinical procedures in which no attention is paid to possible intrafraction movements may lead to very serious under- or overdose of tissue volumes. These deviations should not be considered uncertainties, but rather treatment errors. Inspection of the applicator position in between fractions, visually, with imaging or using IVD should be considered mandatory for specific types of application. If not performed properly, deviations of intended dose may be of the order of several tens of per cent.

Imaging may not represent the target organ or tumour, e.g. a CT of the prostate ROI may actually represent the prostate, periprostatic venous plexus, urogenital diaphragm, puboprostatic muscle or neurovascular bundle. Better differentiation is provided by ultrasound or MRI. Similarly, the mass in the cervical area seen in a CT represents not only the tumour, but also includes the cervix, part of the adjacent vagina, the parametrium, part of the rectum and part of the bladder. Again, this can be better differentiated using MRI. Margins to the treatment volume are sometimes used to account for these uncertainties in target contouring, e.g. 3–5 mm [485].

Compared with EBRT, some patient movement may be allowed. The important thing is the applicator position in relation to tumour and target rather than in relation to bony landmarks, the treatment couch or the patient's external anatomy. The introduction of brachytherapy applicators (e.g. needles, catheters, tandems) causes displacement of the target organ in relation to the bony landmarks. Organ deformation (change in position, shape and volume) due to haemorrhage, oedema and the volume of the applicator itself may also be present. Hence, treatment planning has to take into account these organ deformations and target displacements caused by the introduction of the applicator, and imaging needs to be performed with the applicator in place. Technological limitations

usually prevent intraoperative planning with real time navigation in most clinical localizations, with the exception of prostate brachytherapy [486].

6.5.8.3. Applicator and source reconstruction

Simple manual systems for LDR brachytherapy and planar image based 2-D brachytherapy often use an orthogonal pair of radiographs to localize the sources, e.g. from X ray catheters placed into the applicators, and then use this information to determine the dose at reference points and to critical structures, e.g. for treatment of cervix, to the rectum. More complex systems, e.g. those using volumetric image based 3-D HDR, also rely on applicator reconstruction or reconstruction of the set of needles or catheters from CT or MRI. The accuracy with which an implant can be reconstructed and the dose delivered in a phantom has been published for a range of systems and techniques [338]. However, in intracavitary 3-D image based brachytherapy, it is interesting to note that "Systematic errors of a few mm can lead to significant deviation in dose" and that "by avoiding systematic reconstruction errors, uncertainties in DVH parameters can be kept below 10% in 90% of the patient population", according to Tanderup et al. [487].

As a conclusion of this Section, an estimated value of 5% (k = 1) is suggested as an expert consensus for dosimetric effects as a result of applicator reconstructions or volume interpretations in clinical brachytherapy practice.

6.5.8.4. Accuracy of brachytherapy delivery systems

In the practical clinical environment, the technical components of the delivery systems used for brachytherapy, including remote controlled afterloaders with single or multiple sources, each have their own sources of uncertainties. These are related to the type of procedure, the dwell time and the source positioning, while the dosimetric uncertainties are related to the strength of the source. For HDR applications, offsets in source position related to distortions in the source path due to the curvature of applicators or implants should be checked during the commissioning process in order to avoid uncertainties arising from differences in the planned and the actual treatment source position [488]. A good QA system in the department can ensure that over the clinical lifetime of delivery systems, the temporal and positioning accuracy can be held within rather strict limits. Frequent checks of system features based on written QC procedures should ensure the safe and reliable use of such systems. Methods, frequencies and action levels for such control procedures for brachytherapy equipment have been published in several national and international reports, e.g. Refs [203, 204].

A reasonable estimate of uncertainty can thus be derived from the levels defined in these reports.

6.5.9. In vivo dosimetry (IVD)

There are many steps in the chain affecting the dose delivery to a patient undergoing radiotherapy. Each of these steps introduces an uncertainty. It is therefore worthwhile, and maybe even necessary, to have an independent check of the actual dose given to patients treated with radiotherapy by means of IVD, as elucidated in several reports [489, 490]. In vivo dose measurements are an additional safeguard against various errors that could have been missed if only a pretreatment set-up verification or portal imaging were performed. In vivo dose measurements also document that the treatment was correctly delivered within well defined action levels.

Many types of IVD systems are available, but point detectors such as TLDs and diodes [491–493] are the most popular dosimeters. More recently, the use of metal oxide field effect transistors (MOSFETs) and optically stimulated luminescence dosimeters (OSLDs) for routine IVD purposes have also been investigated [490, 494, 495]. Although the use of point detectors for the verification of conventional radiotherapy techniques including 2-D and 3-D CRT has proven to be very useful, their application as in vivo dosimeters during treatment with techniques such as IMRT is generally more difficult because of the sharp dose gradients in those fields. For these techniques, single point detectors are not sufficient, and multi-point detector systems, such as EPIDs, have been explored to verify treatment delivery in 2-D and 3-D [496].

Various types of errors can be detected using IVD [491]. These errors can be due to the wrong SSD, a missing wedge, wrong fractionation of the total dose and limitations of the dose calculation algorithm in the TPS. Off-axis measurements can also be useful to verify wedge orientation. Wedge angles and orientation, incorrect placement of bolus or misuse of positioning aids are less easily detected and are more dependent on vigilance by RTTs.

EPID dosimetry methodologies (in vivo and in aqua) for IMRT and VMAT have made it possible to identify a number of serious errors related to the dose calculation in the TPS, the position of the leaves or to changes in the anatomy of the patient between treatment planning and dose delivery [496, 497]. Owing to their origin, most of these errors would not have been detected with pretreatment phantom or fluence verification.

For brachytherapy, IVD has been used for many years with a number of different detectors. However, difficulties have been encountered in the use of IVD in brachytherapy, mainly due to the high dose gradients encountered in brachytherapy and the large dynamic range of dose and dose rate [498]. There is

a significant variation in the difference between calculated and measured dose, and discrepancies larger than 30% are frequently seen [498]. Owing to these challenges, IVD has mainly been implemented in brachytherapy to detect gross errors in clinical practice, and it is associated with concerns regarding the limited sensitivity and specificity of error detection. Therefore, the routine use of IVD is currently limited. Brachytherapy is usually delivered without an independent verification of treatment delivery, although the impact of brachytherapy errors may be detrimental since brachytherapy is typically delivered in large fractions and with high gradient dose distributions. Improvement of the safety of brachytherapy may be possible by further development of IVD.

There is no general consensus among radiotherapy centres on the cost effectiveness of IVD, and, until recently, its routine implementation has not been widespread. However, some major incidents in radiotherapy would have been prevented if IVD systems were in place, and this has strengthened the reasoning in favour of IVD. It is now more broadly considered that the efforts and costs of IVD programmes are justified as part of a QA programme [498 , 499].

There is, however, another important application of IVD. If performed properly, the workload involved with IVD is limited, and errors of a few per cent can be detected. For that reason, IVD is now used more as a tool for an independent end to end check of the planned versus the delivered dose to the patient. In this way, even small systematic uncertainties in the dose calculation and dose delivery process can be traced. Some examples of uncertainties in treatment delivery that were reduced by using IVD are given in Section 7.6.3.

IVD is a relatively easy and accurate way to perform QC of dose delivery and it is the only method to trace a number of errors during the actual dose delivery. For patient groups where a high accuracy in dose delivery is required, such as in 3-D CRT, IMRT or in dose escalation studies, IVD during a few treatment sessions is highly recommended. After every change in the treatment procedure, IVD should again be performed. IVD has therefore been recommended, both as a QA tool and a safety measure, by the IAEA, major professional societies in radiotherapy and several national regulatory bodies. The estimated dose uncertainty of IVD in EBRT using regularly calibrated detectors, relative to calibrated ionization chamber dose measurements, is about 3% ($k = 1$), and is somewhat higher for MOSFETs (5%) [499]. Further developments in detector technology, as well as implementation and investigation of routine IVD is needed in order to quantify its impact on accuracy in brachytherapy.

6.6. COMBINED ACCURACY CONSIDERATIONS

6.6.1. Overview

As described earlier, the process of radiotherapy involves multiple steps including imaging of targets and critical structures, computations of radiation dose distributions and repeated patient set-ups during a fractionated course of treatment, possibly delivered over multiple weeks. With image guidance, more precise daily treatment is achievable using 3-D imaging of the anatomy of the day in the treatment room [500]. Imaging during a course of treatment has revealed complex patterns of tumour shrinkage and tissue displacements [501], both interfraction and intrafraction, the latter mainly due to respiration. However, the theoretical advantages of better retargeting must be considered within the context of uncertainties associated with this multi-step radiotherapy process. Specifically, a combination of uncertainties in the treatment chain, including initial target imaging, may neutralize any potential gains from single stage downstream improvements. For example, incorrect delineation of a target could result in a geographic miss that cannot be compensated by subsequent adjustments of the patient set-up. Conversely, accurate targeting may enable dose escalation when combined with frequently applied image guidance. While radiotherapy is now in a position to reach a new plateau in precision and accuracy, all combinations of uncertainties must be considered in order to realize this potential. While precision and accuracy of some individual procedural steps are known to some extent, the compounding effects are poorly understood and very difficult to model.

In terms of uncertainty propagation, it was indicated in Section 3.2.1 that generally, Type A uncertainties can be combined in quadrature to provide an estimate of overall uncertainty and that the combination of Type A and Type B uncertainties may also be performed in quadrature [12, 49]. This is true when considering one quantity such as absorbed dose to a point within the patient. However, it was also indicated that for geometric uncertainties in radiation treatment, various margin recipes have been developed which provide different weights to the combination of systematic versus random uncertainties [52]. Thus, the propagation of both dosimetric and geometric uncertainties in combination is a much more complex problem.

Van Dyk et al. [502] have described a computer model of the entire radiotherapy 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 was also described and 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 were restored to 93.4% with MV CT image guidance. However,

this type of modelling is still in its infancy and further research will be required in this area before it can be applied routinely in the clinic.

Similarly, Jin et al. [503, 504] 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% confidence level [504]. In addition to uncertainties inherent to the 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 set-up 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 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 sources of uncertainty.

Practically, end to end testing is currently performed with phantoms using clinical imaging, treatment planning and dose delivery procedures. QA groups for clinical trials such as the IROC Houston have performed multiple tests for various clinical sites, as discussed in Section 7.7.3.3. However, such procedures are generally performed on phantoms that are solid and do not move; hence they do not yet account for the impact of patient set-up related uncertainties and variations as might occur as a result of a multifraction treatment. Also, dose delivery during end to end testing with phantoms is often performed by medical physicists and not the RTTs. The results of end to end phantom studies have shown some very significant and disturbing deviations from the desired outcome, especially in the context of new technolgies that are supposed to provide improved treatment capabilities. Clearly, end to end testing needs to continue to be performed so that a better understanding can be gained regarding the appropriate implementation of both existing and improved radiotherapy techniques.

Since uncertainty propagation modelling is such a complex process, perhaps the practical way to generate improvements is to consider improvements in each step of the process individually. These have already been described throughout this publication. Summary recommendations will be made in Section 8 of this publication.

6.6.2. Geometric accuracy considerations

Delivering dose to the intended anatomical structures needs both an accurate description of the position of the anatomy and an accurate deposition of the dose. The uncertainty in this process is covered in the concept of the set-up margin described in ICRU Reports 50, 62 and 83 [17, 18, 21]. A detailed review of geometric uncertainties in radiotherapy can be found in two reports from the UK [23, 278].

Well established QA programmes, both nationally and internationally, are in place to make sure that simulators, CT scanners, TPSs and treatment units have an effective level of geometric integrity. They represent a base level of quality every system should have. In special treatment applications such as SRS, SBRT and brachytherapy, the requirements are different and are covered by special policies and procedures.

In the process of radiotherapy, new imaging systems (MRI/PET) have been introduced to reduce uncertainty in the size and position of the anatomical target as well as the OAR. In-room imaging systems aid in the delivery of the intended dose distribution to the intended volume of the patient. The geometrical integrity of these systems, both individually and in the total treatment chain with other systems, is a matter of concern. Assessment of the overall geometrical accuracy in specific treatment techniques and in specific institutions is important to validate margin recipes and the data on position uncertainties used in these recipes [23, 278]. The geometrical accuracy of individual systems and the propagation of their uncertainty throughout the total treatment chain is a complicated problem, both to understand and to handle in practice. Ongoing education and training of radiation oncologists, medical physicists and RTTs in these aspects is crucial to the ability of an institution to organize a comprehensive programme in this area.

Similar considerations exist for brachytherapy, especially since there is such a rapid fall-off of dose with distance. The emergence of image guided adaptive brachytherapy may allow geometric uncertainties to be further reduced.

6.6.3. Accuracy of dose delivered to a volume

Until recently, the ICRU recommended that the dose delivered to the patient should be prescribed to a specific point, known as the ICRU reference point, which is generally near the centre of the PTV [17, 18, 107]. Along with this, it was suggested to report the minimum and maximum dose to the PTV as well as an average and a median dose. In its recent report on radiotherapy dose prescription, recording and reporting [21], the ICRU makes suggestions specifically for modern technology providing IMRT treatments. The report indicates that point based reporting is inadequate for 3-D CRT and IMRT since a single point may not

be representative of the dose delivered to a volume, especially if there happens to be significant dose gradients in that volume. It recommends that, rather than prescribing to a point, dose–volume based prescriptions and reporting should be used. IMRT treatments require comprehensive dose computation capabilities since most IMRT techniques require inverse planning that is usually guided by dose–volume constraints. Thus, DVH calculation capabilities are inherent to the IMRT process. Figure 34 is taken from ICRU Report 83 [21] and shows DVHs with the suggested prescription and reporting points. The report recommends the use of an absorbed dose that covers a specified fractional volume V, i.e. D_V, although it does not recommend any particular value of V in the D_V for a prescription; however, it suggests that the median absorbed dose, i.e. $D_{50\%}$, is likely to be a good measure of a typical absorbed dose in a relatively uniformly irradiated tumour. Indeed, $D_{50\%}$ is very similar to the dose that was defined as the ICRU Reference Dose in earlier ICRU recommendations.

The reporting of several other D_V values gives an improved perspective on the absorbed dose heterogeneity in the target volume compared with a single point or volume parameter. $D_{98\%}$ and $D_{2\%}$ are representative of the near minimum and near maximum PTV doses, respectively.

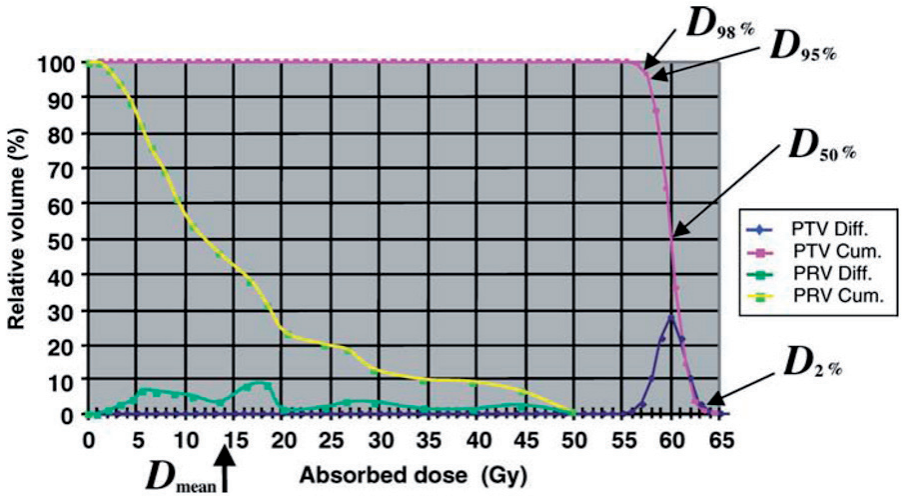

FIG. 34. Typical differential (Diff.) and cumulative (Cum.) DVHs of a PTV and PRV. The new metrics that can be used for prescription, recording and reporting are shown. Adapted from Ref. [21].

As in this publication, the ICRU [21] reviewed various considerations and reports addressing accuracy issues in IMRT delivery. Based on their review, they propose:

— For a low dose gradient (< 20%/cm) region, the difference between the measured (or independently computed) absorbed dose and the treatment planning absorbed dose, normalized to the absorbed dose prescription (e.g. $D_{50\%}$) should be no more than 3.5%. If the differential absorbed dose deviation–volume histogram is approximately a normal distribution with a standard deviation of 3.5%, with respect to the prescription absorbed dose, it means that about 85% of the points should be within the desired value (normalized to the prescription absorbed dose). The value of 5% was the original ICRU requirement for accuracy of delivery at the ICRU reference point [17].
— For a high dose gradient (> 20%/cm) region, the accuracy of DTA should be 3.5 mm, which, if the DTA histogram is normally distributed, means that 85% of the samples should be within a 5 mm DTA.

The ICRU points out that in the future, the recommended criteria might be more stringent since reductions in absorbed dose calculation uncertainty are possible with the use of advanced dose calculation algorithms such as direct Monte Carlo simulations.

6.6.4. End to end verification tests

The accuracy of delivery of dose to a volume of tissue in a patient includes a number of sources of uncertainty, as described previously. The accuracy of delivery of patient doses has been estimated by several groups through the use of mathematical techniques and phantom irradiations. Ibbott et al. [505, 506] have reported that the uncertainty in dose delivered with IMRT techniques to an anthropomorphic phantom in approximately 163 irradiations at 128 institutions was 5% (1 SD). The use of an anthropomorphic phantom simplifies set-up procedures and eliminates the uncertainty of patient motion; consequently, the 5% value is likely to be an underestimate in terms of dose uncertainty to the patient.

6.6.5. Other considerations impacting clinical outcome

There are some other considerations that have the potential to impact patient outcome as part of the radiation treatment. The biological effects of having to wait for radiation treatment could be significant since tumour cells are likely to

be dividing during the wait [507, 508]. The impact of this will vary dramatically for different tumour types, but in some cases, the negative effects are significant. While this is not an issue related to the treatment process itself, it is an issue that should be recognized as potentially having very serious consequences for the success of the treatment and therefore, appropriate resources should be in place to assure the shortest time possible between diagnosis and treatment. Similarly, the impact of gaps during a course of treatment will also have radiobiological consequences; hence, unplanned gaps should be minimized where possible (see Section 6.5.3).

6.7. SUMMARY

This Section addresses the levels of accuracy that are practically achievable in the clinic and is largely based on published data.

Currently, according to the BIPM Key Comparison Database [187], the uncertainty of calibrations in terms of absorbed dose to water for ^{60}Co radiation is on average equal to 0.5% (less than 0.8% at $k = 1$) for PSDLs and 0.7% (less than 1.2% at $k = 1$) for SSDLs.

For air kerma and absorbed dose to water determinations, assuming that the SSDLs have a relative standard uncertainty of about 0.75% ($k = 1$), an action level of ±1.5% is recommended by the IAEA.

The uncertainty of transfer of kilovoltage air kerma calibration coefficients is dependent upon laboratory procedures but has been determined at several laboratories to be about 0.5%.

The dose at a reference depth in a water phantom for MV photon beams is accurate to about 1.0 to 1.5% ($k = 1$) and between 1.4 to 2.1% in high energy electron beams.

Dosimetry systems such as automated water phantom scanners also require commissioning, and a key performance issue is the reproducibility of the positioning of the detector. The estimated achievable positioning accuracy is 1 mm, but this value is likely to be an overestimate for modern equipment. Relative dose parameters such as percentage depth dose, tissue–maximum (tissue–phantom) ratios, relative output factors and relative off-axis factors can be measured to an accuracy of 1%. Published recommendations advise maintaining relative dose parameters at the 2% level.

The performance of modern teletherapy equipment can be summarized as follows:

— Output constancy of clinical linacs generally has an uncertainty of 2% or better at the $k = 1$ level.
— Output ratios can be measured with an uncertainty of 0.5–1.0%.
— Machine jaw position has an uncertainty of less than 1 mm.
— Estimated uncertainties for wedge measurements are approximately 2% or 2 mm (the latter refers to wedge placement accuracy).
— Multileaf collimator (MLC) static position has an uncertainty of less than 1 mm, although leaf end and edge transmission are highly variable.
— MLC dynamic position has an uncertainty of less than 1 mm.
— MLC transmission can be several per cent with highly modulated IMRT fields.

The table top and couch attenuation uncertainties are highly variable and depend on angle, energy and position. Attenuation through the couch supports can be as much as 20% for extreme conditions.

For modern treatment equipment used for advanced technologies such as IMRT and SBRT, the AAPM recommends that linear positioning be maintained at the 1 mm level, while angular parameters are maintained at 1°. Dosimetry considerations for special techniques such as IMRT, SRS, SBRT and total body irradiation may differ.

For external beam calculations, the treatment planning system accuracies are extremely variable depending on the nature of the algorithm. For simple algorithms, inaccuracies of as large as 20% have been observed for high energy photon beams. Model based algorithms using convolution and superposition principles which include lateral transport considerations are able to yield results within 3.5% ($k = 1$). For bone–tissue interfaces, doses were generally underestimated by 5–10% or more by all calculation methods over the range of field sizes and energies reviewed.

For brachytherapy, the uncertainty of the consensus data used in the TG43 formalism [196] for low and high energy brachytherapy sources is of the order of 3.0–3.6% and 1.6–1.7%, respectively, according to the TG138 report [56]. This results in the propagation of best practice uncertainties in the absorbed dose rate to water at 1 cm on the transverse plane (associated with source strength measurements at the clinic, determination of the parameters by measurement, calculation or both, and treatment planning system dataset interpolation) for low energy sources to a total dose calculation uncertainty of 4.4% and, for high energy sources, 3.4% (at $k = 1$ level), as shown in the Table V of that task group report [56].

Owing to the dependence of so many factors, types of applications, variations from patient to patient etc., the uncertainty budget of brachytherapy cannot simply be summarized into one single number, and a wide range of achievable accuracy prevails at each step of the process. Recent guidelines have suggested that each brachytherapy treatment technique should be analysed separately (e.g. prostate, breast and gynaecological), that all factors that could influence the total dosimetric uncertainty over the entire treatment course should be considered, and that uniformity in uncertainty reporting should be adopted [259].

For imaging for treatment planning, the isocentre ellipsoid of a simulator can have diameters between 0.5 and 2.0 mm over the rotation of the gantry.

For CT simulation, the precision of set-up evaluations using DRRs is similar to that of simulator images, although the resolution in the longitudinal direction is dependent on the distance between the CT slices. The spatial resolution of the image is approximately 1 mm, except in the longitudinal direction where resolution is reflected by the distance between reconstructed slices, i.e. the slice thickness and the pitch. When CT scanning a phantom with known geometry and density inserts, agreement within 2 mm is reasonable for distances, and agreement within 0.02 is reasonable for electron densities relative to water. Typical CT scanner doses range from about 1–4 cGy within the scanned volume per CT study. For treatment planning, CT slice thicknesses of 3 mm appear to be a good compromise, yielding an average dose calculation uncertainty of about 1%.

PET scans have a resolution of 4–7 mm and result in total effective doses of 15–25 mSv. Close collaboration is required between radiotherapy and imaging staff to ensure proper patient set-up when imaging for treatment planning.

MRI distortions could be as large as 15 mm at the edge of a 400 mm field of view; however, with corrections these can be reduced to <1 mm.

For verification imaging and IVD, double exposures with film have been used to show the radiation treatment field within a larger field so that the surrounding anatomy is more clearly visible. Interobserver variability studies suggest that human observers have difficulty identifying field placement errors accurately when the errors were 5 mm or smaller. Geometric action levels for EPID should be <1–2 mm and the resolution should be <1 mm. The geometric accuracy of such a system was found to be of the order of less than 1 mm in all three spatial dimensions when using fiducial markers.

Kilovoltage CBCT provided submillimetre spatial resolution (approximately 0.7 mm full width at half maximum of the line spread function) and a lowest readily detectable contrast at 47 HU. When registering kV CBCT data to the planning data to assess the need for couch corrections, it was found to be within <1 mm of the prescribed location. The mechanical isocentre of the kV system was found to be accurate to less than 1.5 mm ± 1.0 mm. With

respect to CT number accuracy, Rong et al. [392] showed that for adipose tissue, the HU discrepancy from the baseline was 20 HU in a small phantom, but 5 times larger in a large phantom. A typical head and neck CBCT scan delivers doses to soft tissues, such as eye, spinal cord and brain of up to 8, 6 and 5 cGy, respectively. The dose to the bone, due to the photoelectric effect, can be as much as 25 cGy, about three times the dose to the soft tissue.

In MV CBCT, a vertical sag in the gantry of as much as 15 mm has been reported due to the additional weight of a flat panel detector for in-room cone beam CT. Specialized in-room imaging systems yield intrafraction motion measurements and target localization capabilities within 1.5 mm. The estimated geometric accuracy and resolution was 1–2 mm, while the dose per MV CBCT study was between 5 and 10 cGy.

The rail track mounted tomographic imaging systems use fully conventional CT technology with high image quality and clinical robustness. Kuriyama et al. [421] reported a positional accuracy of under 0.5 mm, while Court et al. [420] reported an accuracy of 0.7 mm that can be further reduced to 0.4 mm (i.e. approaching the resolution of the CT scanner itself) when using radio-opaque fiducial markers with a solid phantom

While a viable image guidance option, ultrasound suffers from interobserver variability. Comparisons of CT and ultrasound alignments have standard deviations of 4–5 mm in all directions. Real time localization with implanted electromagnetic transponders can yield accuracy within 2 mm.

Using planar imaging, the size of intrafraction motion was found to be (median ± quartile) 0.3 ± 0.3 mm, 0.6 ± 0.6 mm and 0.7 ± 0.6 mm for cranial, abdominal and lung patients, respectively. X ray image registration estimated larger intrafraction motion, equal to 0.9 ± 0.8 mm, 1.3 ± 1.2 mm and 1.8 ± 2.2 mm, correspondingly [417].

4-D imaging (respiration correlated CT) allows treatment adaptation for tumour response throughout a course of radiation treatment, and it allows for managing motion during individual treatment fractions. Respiration correlated PET imaging improves PET reconstructions. The use of tumour tracking technologies (such as VERO and CyberKnife) can track tumours to within a fraction of a milimetre.

Inter- and intrafraction uncertainties of 20% ($k = 1$) for OAR and 13% ($k = 1$) for target are typical in 3-D image guided gynaecological brachytherapy. By definition, these estimates include also uncertainty components from reconstruction of applicators and contouring.

Daily on-line imaging data indicate variations in anatomy that can range from a few milimetres for head and neck treatments to 10–20 mm in the pelvic and thoracic region.

IVD adds an additional safeguard for accurate radiation treatments. The estimated dose uncertainty of IVD in EBRT using carefully calibrated detectors, relative to calibrated ionization chamber dose measurements, is about 3% ($k = 1$) and somewhat less accurate for MOSFETs (5%).

Treatment accuracy can be affected by tumour site within the body, available staff and technology resources, shift schedule and staff interruption frequency. Treatment accuracy begins by ensuring that the patient, site and procedure are correct. The implementation of QC policies and procedures is essential for accurate radiation treatment. A wide range of publications describe the levels of accuracy that are desirable and achievable. Acceptable levels of accuracy in the dose delivered to the dose specification point vary between 3.5% and 5%. End to end tests with anthropomorphic phantoms have yielded uncertainty in dose of 5% ($k = 1$); thus, considering additional patient related uncertainties (e.g. set-up and respiratory motion), 5% is likely an underestimate for real patients.

7. MANAGING UNCERTAINTY

7.1. QUALITY MANAGEMENT VERSUS MANAGING QUALITY

Precision and accuracy in radiotherapy are dependent on many factors including appropriate training, adequate staffing, suitable QA and QC tools related to specific techniques or technologies, and proper QA and QC procedures. All these factors are especially relevant for the more complex technologies and procedures that are being implemented in the modern clinic. Quality management (QM) is directly linked to QA and QC.

> "Quality management, as the words imply, refers to all management issues of the quality system or the quality process. Quality management must be initiated and continuously encouraged from the top down. It must be a process that infiltrates the entire management structure of the organization for it to work successfully" [509].

Thus, QM is an administrative, organizational issue. The management of quality is also an ongoing concern and is a task that belongs to everyone in the organization. With increasing treatment complexity in radiotherapy, there is an inherent desire, or even a need, to continuously increase QA procedures. This ever increasing demand on resources is unsustainable. Every step in the radiotherapy process can, in principle, be tested for the cost as well as the desired benefit.

For instance, when a decision is made by the radiation oncologist to deliver a radiation dose to a patient, the oncologist has implicitly or explicitly justified the dose by weighing the benefit (tumour control or palliation of symptoms) against the detriment (risk of normal tissue complications or induction of new malignancy). If there is a greater demand for treating patients with a given treatment modality than a radiotherapy centre can provide (for instance, to achieve greater accuracy by using some form of motion management in the radiation treatment, or IGRT using CBCT on a linac), then one approach which can be applied neutrally, consistently and transparently is to use a cost–benefit analysis. In this sense, cost–benefit analysis is used to identify the most efficient way to maintain accuracy under these circumstances. The current problem is the practicality of doing this in each individual radiotherapy facility.

The analysis of managing quality may also be applied off-line in the radiotherapy process. For example, it may be used to optimize QC processes in terms of efficiency in maintaining geometric and dosimetric standards in radiotherapy equipment with a minimal use of resources, including time on the linac and the cost of personnel. The considerations that are common to any cost–benefit analysis of any activity in radiotherapy include:

(1) The benefit to the patient in terms of the probability that the activity will give extra years of life to that patient, and in terms of the likely quality of life of those years (e.g. increased accuracy leading to increased TCP and reduced NTCP);
(2) The detriment to the patient taking into account the following factors:
    (a) Increased NTCP (e.g. resulting from dose escalation);
    (b) The possibility of new radiation induced malignancies (e.g. from concomitant radiation dose arising from daily in-room imaging or the increased number of MUs from IMRT).
(3) The cost to other patients if there is limited access to resources, which are being used for patients receiving more sophisticated treatments.

The level of detail with which a cost–benefit analysis is applied will depend upon knowledge of parameters specific to the problem. Several approaches exist or are in preparation, such as the systems engineering use of failure modes and effects analysis (FMEA) suggested by AAPM TG100 [510]. These working groups consider some or all of the above issues, which can potentially also be expressed in terms of risk probability number (which FMEA refers to as RPN), quality adjusted life years (QALYs) or costs of resources in units of currency.

A QM process is critical for new techniques and technologies. This is especially true with staff turn-over since complex procedures require adequate documentation that can be readily reviewed and understood by new staff in the

department. Hence, an ongoing system of QA becomes critical for accurate and safe procedures. This is also true for clinical trial activities since there will be a greater likelihood of compliance with protocols when appropriate QM procedures are in place. As indicated in IAEA-TECDOC-1588 [511], if appropriate QA cannot be performed, then new technology or techniques should not be implemented since there may be a risk of inaccurate or even unsafe treatment.

In some locations, QM or QA procedures, or both, are legislated or imposed by regulatory bodies generally associated with the licensing of radiation related technologies. Such regulations could be implemented at the local, state, national or even international (e.g. European Union) level. Many national or international organizations have developed QA guidelines for specific techniques or technologies. Organizations such as the IAEA, ESTRO, AAPM, Australasian College of Physical Scientists in Medicine and the Canadian Organization of Medical Physicists have produced comprehensive guidelines on QA and QC procedures to be implemented with radiation related technologies.

One form of implementing a voluntary QM system is guided by ISO through its standards. ISO certification can be obtained by demonstrating implementation of the ISO standards. Some of the requirements in ISO 9001:2008 [512] (which is one of the standards in the ISO 9000 family) include:

— Having a set of procedures that cover all key processes in the organization;
— Monitoring processes to ensure they are effective;
— Keeping adequate records;
— Checking output for defects, with appropriate and corrective action where necessary;
— Regularly reviewing individual processes and the quality system itself for effectiveness;
— Facilitating continual improvement.

In summary, a QM programme is an essential component of the activities of a radiotherapy department. While it does not guarantee accuracy in radiation treatment, it does improve the likelihood that accurate treatments will be provided.

7.1.1. Quality management in HDR brachytherapy

In HDR brachytherapy, quality management (QM) is particularly important because the procedures are carried out quickly with high doses given in a short time period, with little opportunity for correction.

The QM programme should consider clinical aspects of HDR brachytherapy (patient selection criteria, dose determination and specification, fractionation,

quality of insertions, tumour volume and treatment volume), the physical aspects of dosimetry (checks of the computer information input, sources, strength and dose at different distances), QA of the treatment unit, applicators, the treatment planning system and the imaging system.

The description of a complete QM programme and details of the individual QA steps are beyond the scope of this publication, and the reader should consult other references (e.g. Refs [123, 124, 233, 513]) before starting an HDR programme or when seeking guidance for an existing HDR programme.

QA of treatment plans has been described in various reports. It is particularly important to have systems for checking computer plans generated for HDR. Work by Das et al. [514] proposes an efficient, precise and easy method for checking the complex computer calculation. AAPM TG59 [233] suggests that the ratio of the source strength multiplied by the dwell time to the dose or the TRAK/dose ratio should fall within the range expected for the given implant geometry. Quantitative verification of computer generated dwell time calculations is also reviewed in that report. Generally, these simplified methods require that the implant dimensions be determined independently from the localization radiographs and the source strength be taken from a precalculated table. With such methods, it is possible to verify that the total treatment time to within 3% of the TPS calculated value for 95% of cases.

Practice guidelines for HDR brachytherapy have recently been published by ASTRO and ACR [515].

7.1.1.1. Other aspects of QA in brachytherapy

A paper by Williamson [516] addresses concerns about aspects of brachytherapy QA that had not previously been addressed well in the literature. He points out that all the documents that existed at that time (i.e. 2008) distinguished between device QA (commissioning and periodic testing of planning, delivery and imaging systems) and clinical process QA (QA of patient specific treatment procedures). The AAPM TG reports 53 [517], 56 [203] and 59 [233] provide the most detailed conceptual frameworks for brachytherapy QA programmes. However, Williamson identified several issues that had not previously been addressed. From his analysis, and based on the comprehensive QA report of AAPM TG56, he suggested that for any brachytherapy procedure, QA should be included in the basic design of the process using the following steps:

(1) Define the anticipated or actual procedure flow, including patient preparation, applicator placement, imaging, treatment planning, etc. (Fig. 2). At each step, identify the critical activities to be performed, the required personnel and the information to be captured.

(2) Develop forms for capturing and documenting all critical information, including the implant drawing, applicator type, catheter numbering system, target localization data and written prescription.
(3) Identify vulnerable steps in the treatment delivery process, at which mistakes, misjudgements or inaccurate transmission of data could jeopardize the procedure outcome.
(4) For each such step, develop redundant checks, specifying who performs the check and actions to be undertaken in the event of an unacceptable outcome. Both the severity and the likelihood of the target error can be taken into account in deciding how to distribute the available QA resources.
(5) Develop a written procedure that outlines the procedure chronology, team member functions, QA checks and so forth.

A further point is that no documents exist that provide detailed guidance for image guided 3-D brachytherapy procedures, including permanent seed implants. Issues that remain to be addressed include:

— Indications for staffing levels, roles and responsibilities during volume definition studies and implant procedures, including critical QA functions.
— Processes for ensuring adequate transrectal ultrasound probe positioning and image quality during the procedure.
— Verifying target volumes manually segmented from intraoperative or volume-study images (approximately 40% of the permanent brachytherapy medical events and misadministrations in the Nuclear Materials Events Database [518] involved implanting the wrong organ because of poor transrectal ultrasound image quality, image misinterpretation or failure to verify the needle position).
— Review procedures for image based treatment plans, including checks of manual dose calculation and target localization accuracy.
— Improving operator performance by post-procedure implant quality assessment.

7.2. COST–BENEFIT

The cost of radiotherapy continues to increase as new technologies are implemented. The University Hospitals in Leuven developed an activity based costing model to quantify the changes in radiotherapy costs occurring in a decade of medical technological evolution [519]. They observed a considerable increase in total radiotherapy costs resulting from higher capital investments (96%) and personnel costs (103%), with the latter dominating the total picture. They

concluded that treatment delivery remains the most costly activity, boosted by the cost of improved QA, which represented 23% of total product costs associated with more advanced radiotherapy techniques. Cost increases are most obvious for complex treatments such as IMRT, representing cost increments of between 38% and 88% compared with conformal approaches.

Cost effective analyses of QA procedures yielding improvements in treatment accuracy are rare. Malicki et al. [520] performed an evaluation of the cost effectiveness of QA program modifications associated with increasing demands on accuracy and reliability in radiotherapy, using IVD as the example of a change in technical procedures. They analysed 6864 patients treated between 2001 and 2005 for tumours in the head and neck, breast, pelvis or lung. The quality of radiotherapy was expressed as the accuracy of dose delivery and the cost was estimated from labour, equipment and materials. Mean deviations between measured and calculated doses were reduced from −1.5 to 0.5%, 3.4% to 1.4%, 3.9% to 0.1% and −2.1% to 1.8% for head and neck, breast, pelvis and lung, respectively. The standard deviations of the measured values also decreased consistently. The predominant cost component of IVD was labour, limited at first to physics staff and later extended to QA personnel and technicians.

While accuracy is thought to improve with increased QC procedures, the question remains as to whether the effort in relation of the magnitude of the improvement is justified. McKenzie [521] has looked at this from the point of view of QALYs. The concept of using QALYs as a means of health technology assessment has been described by the UK's National Health Service [522]. McKenzie provides some specific examples of how benefit can be quantified in terms of cost of QALYs, using the assumption that society is willing to pay £30,000 (pounds sterling; ~US $44,000) per QALY (or £1 million (US $1.5 million) per human life). While it is possible to do a cost–benefit analysis objectively and equitably to all patients, it is much more difficult to perform such an analysis evaluating the impact of catastrophic errors. Since the concepts are new, the question remains as to what the reliability of such an analysis can be.

Recently, the AAPM has used a systems engineering approach to the cost–benefit of QA issues by considering FMEA. A preliminary report of AAPM TG100 was published [510]. Practical examples of detailed FMEA analysis have been published by Ford et al. [523], Sawant et al. [524] and Ciocca et al. [525]. The full impact of these publications on the field has yet to be felt, and it is therefore still too premature to make quantitative recommendations on such analysis procedures. Thus, for the time being, the best professional judgement based on the quantitative information that is available should be used.

7.3. RESEARCH

One of the significant concerns regarding accuracies and uncertainties in radiotherapy is the question of how much time, energy and effort needs to be put into improving accuracy and reducing uncertainties in radiotherapy. This concern has already been addressed under Section 7.2 where activities regarding cost–benefit analyses were discussed. While it is well recognized that previous statements on accuracy requirements were predicated both on dose–response considerations and on what accuracy is reasonably achievable, the issue of quantifying what is reasonable is in its infancy.

Recent technological advances appear to be moving forward at an ever increasing pace. The underlying assumption is that with improved dose delivery and better image guidance we will be able to escalate the dose to the target and reduce clinical morbidity. The question is how high can we go and at what cost? As indicated by Ling et al. [526], the cost is relatively easy to quantify; however, quantification of benefit is much more difficult. Of course, the most relevant metric is clinical outcome. However, outcome can only be determined through clinical trials and, as discussed earlier in this publication, clinical trial successes themselves are dependent on the accuracy and uncertainties of dose delivery. Furthermore, clinical trials take a significant amount of time. Then, as pointed out by Ling et al. [526], we are left with the surrogates of reduction of set-up uncertainties, minimizing the effect of organ motion in addition to delivering a dose as accurately as is reasonably achievable.

Ling et al. [526], in their commentary, raise many questions concerning the IGRT process and the difficulties in quantifying its clinical benefit. They also address some issues regarding the move towards higher doses per fraction. In a similar vein, Bentzen [527] points out that working in a technology and science based medical discipline, radiation oncology researchers need to further develop methodology for critical assessment of health technologies as a complement to randomized controlled trials.

What was not raised in either of these commentaries is the issue of radiobiological modelling in the context of routine treatment planning. The quantification of accuracy and uncertainties in radiobiological model predictions is very complex. Some would argue that radiobiological models provide predictive trends [528] although it has been shown that this is not always the case [104]. Generally, it is agreed that these models are probably not very accurate in predicting outcomes in an absolute sense. More research and more results from clinical studies are required to assess the capabilities of radiobiological models to predict clinical outcome. In the meantime, such models and their parameters should be used knowledgeably and with extreme caution, especially if they are implemented clinically in treatment planning.

7.3.1. Clinical trials

One of the most influential factors in improving treatment quality, monitoring outcomes, education and technological competence in any department of radiotherapy is the participation in large, appropriately designed randomized clinical trials. Similarly, well designed phase I and phase II studies may also have significant benefits for the entire department and patient population, provided trial design, implementation, conduct and analysis is legitimate, independently scrutinized and approved in terms of ethics.

The first and most obvious impact on treatment accuracy and quality in relation to trials is the adoption of evidence based practice. Where evidence is controversial or trial results are awaited, expert consensus guidelines should be followed [529]. Introduction of new technology in radiotherapy is particularly suited to a clinical trial environment where governance, technical procedures, clinical indications, clinical monitoring and outcomes are rigorously assessed [506, 530, 531]. Experience from both clinical trials and elsewhere indicates significant variation across departments in relation to technique, field size, dose and fractionation [532]. A recent review from Fairchild et al. of 17 multicentre trials that were centrally reviewed for protocol compliance suggests that improved compliance may result in more favourable clinical outcomes [533]. More robust, universal methodologies are needed to quantify the degree of protocol compliance (or the lack thereof), and factors that affect the quality and accuracy of radiotherapy as described in Sections 4 to 6 of this publication, should be included.

Participation in a randomized clinical trial and subsequent intercentre audits and source data verification (with penalties for non-compliance) provide very strong incentives for evidence based protocol adherence [534–536]. Many trial groups provide opportunity for learning, education and protocol development in the context of a so-called dummy run [537]. This allows a collaborative development of a skill base in departments prior to clinical implementation of new protocols. Participation in clinical trials provides valuable resourcing, infrastructure and quality outcome information at both national and international levels [538]. Randomized clinical trials provide the only large scale environment for completing the radiotherapy ‘quality loop’. In this environment, it is possible to be statistically confident in relation to clinical quality inputs and their correlation to important common cancer outcomes (e.g. survival, disease free survival, quality of life, OAR toxicity). Participating in a reasonable menu of contemporary randomized clinical trials usually provides the participating department with a ready made standardized set of protocol guidelines, contouring related atlases and outcome measures. The necessary conduct of clinical trials within a rigorous governance framework (e.g. good clinical reporting practice,

the Declaration of Helsinki, harmonization efforts) means no other QA activity in radiotherapy can provide the scope, depth and veracity of data generated both by the trial itself and by individual departments significantly contributing to studies [81, 539, 540].

In brachytherapy, an international study on MRI guided brachytherapy in locally advanced cervical cancer (EMBRACE) is in progress. MRI guided 3-D brachytherapy is increasingly being used in several centres [541, 542], and the results reported so far are very promising.

> "Based on the experience collected so far, the image based BT [brachytherapy] approach significantly improves the DVH parameters and the improved dose delivered seems to have a major impact on the clinical outcome with a concomitant decrease in the rates of both local failure and morbidity. The aim of the EMBRACE protocol is to introduce MRI based brachytherapy in a multicenter setting within the frame of a prospective observational study and to correlate image based DVH parameters for the clinical target volume and for organs at risk with outcome.
>
> "Based on these results, we hope to develop prognostic and predictive statistical models for clinical outcomes including volumetric, dosimetric, clinical and biological risk factors as well as radiobiological parameter estimates that will allow a precise risk assessment in individual patients and aid in the development of new treatment protocols" [543] .

7.4. DETERMINING UNCERTAINTIES IN THE CLINIC

In order to minimize the clinical impact of dose and treatment related uncertainties, the professionals involved must have some understanding of the magnitude of the uncertainties that exist within their own clinical context and for their specific treatment procedures. For beam dosimetry and other aspects of treatment technologies, such uncertainties are generally derived from commissioning and QA procedures. A proper recording of the data will give variations in the results over time. Third party independent calibration procedures will give a sense of accuracy in absolute beam dosimetry. However, what are much more difficult to determine are patient and treatment related uncertainties. Uncertainties related to patient positioning and daily repositioning, organ motion and organ deformations, and tumour and patient related changes are much more difficult to determine. It is the magnitude of these uncertainties that allows determination of the margin to go from CTV to PTV.

IAEA-TECDOC-1588 [511] indicates that one of the milestones to transition from 2-D radiotherapy to 3-D CRT or to IMRT is to perform an audit of set-up uncertainties so that 3-D margins can be determined. A means of determining treatment related uncertainties is by some form of verification and imaging of the patient in the treatment position on the treatment machine. This imaging could be performed using port films or EPIDs and extended to full daily in-room image guidance. Increased levels of sophistication should aim to provide greater accuracy in patient position in order to allow a reduction in the CTV to PTV margin.

Perhaps the best description of determining patient related geometric uncertainties can be found in sections 3 and 4 of a report published by the Royal College of Radiologists (UK) [278]. In summary, they describe the geometric verification process in terms of the following issues:

— Equipment and technical infrastructure;
— Personnel, responsibilities and training;
— Imaging protocols:
  • Image acquisition;
  • Frequency and timing of imaging.
— Measurement of set-up errors:
  • Gross error;
  • Systematic and random error.
— Action levels and correction strategies;
— Dose considerations — concomitant exposure;
— Audit.

Each of these issues is addressed in detail in the report, which includes mathematical descriptions of how to combine the uncertainties. The report also addresses how random and systematic errors may be derived from portal images and further discusses the interrelationship between CTV to PTV margins and verification imaging. The general principle is illustrated in Fig. 35.

The magnitude of the CTV to PTV margin is largely governed by the combined systematic errors. An off-line portal imaging strategy can be used to verify the patient set-up. An on-line correction strategy capable of detecting target position can additionally monitor and control both the systematic and random errors associated with organ motion.

The report includes a description of the equipment needed for geometric verification and it addresses clinical site specific procedures for geometric verification. These are excellent guides that can be used for developing in-house treatment geometric verification procedures and for the determination of clinical treatment margins for each clinic.

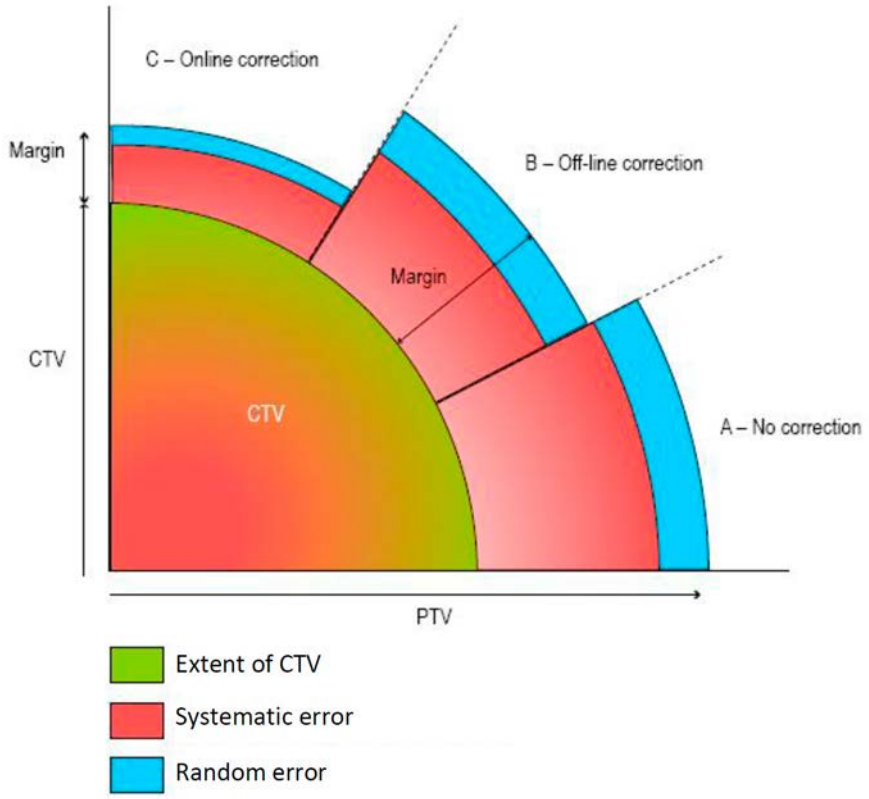

FIG. 35. The CTV to PTV margin is governed by combined systematic and random errors from all possible sources. The application of treatment verification with imaging protocols designed to quantify and reduce some of these contributing sources can provide justification to reduce the applied margin. (Adapted from Ref. [278].)

The most recent discussion on margins and margin recipes has been reported by van Herk at the 2011 AAPM summer school [147]. He provides an example of a margin calculation spreadsheet. An adapted version of this is shown in Fig. 36.

The margin recipe used in the example of Fig. 36 is:

$$CTV - PTV_{\text{margin}} = 2.5\Sigma + 0.7\sigma \tag{12}$$

where Σ is the root mean square of systematic uncertainties and σ is the root mean square of random uncertainties.

Type of uncertainty	Systematic (mm)	Systematic squared (mm^2)	Random (mm)	Random squared (mm^2)	Total margin (mm)
GTV delineation	2.5	6.25	0.0	0.0	
Organ motion	3	9	3	9.0	
Set-up error	1	1	2	4.0	
Intrafraction motion		0	1	1.0	
Total error	4.0	16.25	3.7	14.0	
	Times 2.5		Times 0.7		
Margin	10.1		2.6		12.7

FIG. 36. A typical margin recipe calculation spreadsheet for EBRT. This example calculates the margin for prostate irradiation with an off-line decision policy based on bony anatomy. Note that the margin shown is intended to guarantee a 90% probability that the 95% isodose line of the cumulative dose encompasses the CTV. (Adapted from Ref. [147].)

Similarly, McKenzie et al. [145] have derived an OAR-PRV margin for OAR which are small, serial or both in low (+) or high (−) dose regions

$$CTV - PTV_{\text{margin}} = 1.3\Sigma \pm 0.5\sigma \tag{13}$$

The derivation of margins to account for patient related systematic and random uncertainties is very difficult using phantoms. However, many of the other physical aspects of the treatment process can be assessed by using end to end phantom tests. End to end here means scanning a phantom, performing treatment planning on the phantom images and then irradiating the phantom as a patient would be treated, with dosimeters in the phantom. Results of such tests as performed by auditing groups such as the IROC Houston are described in Section 7.7.3. Similar end to end tests should be performed in-house.

7.5. PRESENTATION OF UNCERTAINTIES

The display and presentation of uncertainties of 3-D dose distributions continues to be a challenge [20], partly because of the large amount of data that exists within a 3-D dose distribution, and partly because of the complexity of different magnitudes of uncertainties within different regions of the irradiated

patient. In 1988, Shalev et al. [544, 545] described an objective method using a prescription file to define the clinician's requirements in terms of the area of each organ (on individual CT slices) which may be treated to predefined tolerance doses. A computer programme compared the predicted dose distribution with the prescribed limits, and displayed regions of non-compliance as coloured "areas of regret". In addition, score functions were used to provide a quantitative measure of the acceptability of dose distributions within the target and each OAR.

Examples of methods of display have also been provided by Goitein [546] and by Urie et al. [547]. They used a technique for estimating the uncertainty by performing a series of three calculations. The first calculation of dose uses nominal values for the patient and radiation beam, while the second and third calculations use extreme values (upper and lower limits) of the dependent parameters. The calculations result in an estimate, at some specified confidence level, of the range of dose within the patient. This is a way to demonstrate the magnitude of potential concerns as a result of treatment related uncertainties. Techniques for displaying uncertainty bands in DVHs have also been described [548]; however, since uncertainties in different locations can be highly correlated, this makes the estimation of the net effect very difficult. For this reason, van Herk [549] developed a Monte Carlo technique that allowed estimation of uncertainty in any dose related quantity, such as minimum dose in the CTV, EUD and TCP. The multiple instance geometry approach by McShan et al. [550] is similar, although more correct; however, computationally, it is much slower. Such approaches allow for the comparison of rival plans in terms of robustness for dosimetric or geometric uncertainties [551].

Another approach was developed by Lomax and was summarized in ICRU Report 78 [20]. In this method, dose distributions are calculated for a number of different scenarios (e.g. CT datasets translated or rotated, or altered CT numbers). A hybrid dose distribution is generated, which indicates the worst case situation. It allows for the identification of cold spots in the tumour or hot spots within OAR. The display is somewhat analogous to Shalev's images of regret.

As mentioned above, techniques for estimating and displaying uncertainty bands for DVHs have been reported that can demonstrate the region within which the true DVH lies [547, 552]. Similarly McQuaid, et al. [553] have suggested the use of confidence intervals in DVH displays so that plans can be compared based on different models of the known or predicted uncertainties in the process.

Kupchak et al. [554] developed a method for mapping NTCP onto regions of dose–volume space and included in the maps statistical considerations of risk. The generated maps can identify high risk regions for normal tissue complications, which is an advantage compared with single point dose–volume constraints. The maps "help select safe and robust treatment plans and open the

possibility for improving the efficiency of biologically based plan optimization by focusing on the more critical sections of DVH curves" [554].

So far, none of the methods of uncertainty estimation and uncertainty display have become routine in the treatment planning process, nor are any of them available in commercial treatment planning software. The implementation and practical evaluation of such procedures remains an area for research and further development. It is clear, however, that uncertainty estimation for specific treatment plans and techniques should be part of the standard practice within the treatment planning process. This type of information will help develop treatment plans that are more robust and less affected by uncertainties in the treatment process.

7.6. REDUCING UNCERTAINTIES

As elucidated in Section 6 of this publication, various types of dosimetric as well as geometric uncertainties exist in the delivery of radiotherapy. Dosimetric uncertainties are introduced during the calibration of the reference ionization chamber used for absolute dosimetry, during the relative dose measurements, in the dose calculation by the TPS and in the actual dose delivered during the irradiation of the patient. The main sources of geometric uncertainties are related to target delineation, set-up and physiological changes. In this section, various approaches will be discussed and examples given of how to reduce each of these uncertainties in clinical practice. The examples are taken from various institutions to which the contributors to this publication belong and reflect a variety of methods to improve the accuracy of specific radiotherapy techniques. The magnitude of these improvements will differ in each centre and depends on many factors, including the level of sophistication of the QA method and the treatment technique.

7.6.1. Approaches to reducing uncertainty

As discussed earlier, radiotherapy is a multidisciplinary process; responsibilities are shared between the different disciplines and must be clearly defined. Each group has an important part in the output of the entire process and their roles are interdependent, requiring close cooperation. For this purpose, a quality system should be introduced in each radiotherapy department, which should encompass a comprehensive approach to all activities in the radiotherapy department starting from the moment a patient enters it until the moment he or she leaves, and also continuing in the follow-up period.

A prerequisite for managing uncertainties is the presence of a comprehensive quality system, as discussed in Section 7.7.2.2. In order to determine and reduce uncertainties in the clinic, it is essential that written directives, guidelines and procedures exist for those issues that have an influence on the accuracy of patient treatment. Furthermore, documentation and communication should be unambiguous to guarantee optimal treatment and to avoid incidents and near misses. Finally, it should be emphasized that education, training and continuing education of the radiotherapy team members are of critical importance for a successful quality system.

7.6.1.1. Policies, guidelines and procedures

Radiotherapy departments generally produce directives for the many steps in the treatment of a patient. This leads to consistency of patient treatment and stimulates communication about the various processes that take place in the centre. Obvious candidates for policy development are clinical guidelines for tumour specific sites, planning objectives, positioning and immobilization, and QA programmes for equipment. These policies and procedures are often part of the QM system of the department and can be considered as an enforced level of oversight and review of already existing procedures. A team approach is often taken to defining policies and procedures because many aspects — clinical, technical and practical — are involved. Policies should be regularly reviewed, for instance, if new equipment has been installed, or if data in the literature seem to recommend new guidelines. Possible methods of improvement, for instance, by regular policy and procedure review meetings, should be identified. By including these directives in education and training programmes, junior staff members may become aware of the various procedures applied in their department for the optimal treatment of a patient with a specific disease. Such policies and procedures should specify any circumstances which might arise where a responsible staff member (‘operator’) must refer to another before proceeding with the treatment. Regular multidisciplinary peer review is required to ensure adherence to accepted institutional policy.

One of the most important steps in a radiotherapeutic procedure is the delineation of target volumes and internal risk structures for treatment planning purposes. Large uncertainties may exist in volume definition, as elucidated in Sections 6.6.2 and 7.4, which can be reduced by having well defined guidelines, based on multimodality imaging and other clinical information. Extensive training in volume delineation as well as special courses on this topic should be part of the medical education (continuing professional development) of each resident and radiation oncologist. In this way, inter- and intraclinician variation should be reduced, and smaller margins may result, based on well defined margin

recipes. These guidelines should be based on consensus documents drafted by expert groups either locally or internationally, e.g. as recently provided for target volume definition in postoperative radiotherapy for prostate cancer by the EORTC [555] and RTOG [556]. Consensus reports may include a CT image atlas available on a web site. These guidelines will allow uniformity in defining volumes for clinical trials and may also be used for internal consistency in a department.

Guidelines may vary in the description of details of the process. They may, however, have links to more specific information e.g. web sites, hyperlinks or custom document storage programs that are used to store and provide more detailed procedures. This is particularly useful for the numerous QA tests of radiotherapy equipment performed by the physics staff. Such a QA programme is based on a number of QC tests that should specify the parameters to be tested, the tests to be performed, the specific equipment to be used, the geometry and frequency of the tests, and the staff performing and supervising the tests. Such a QA programme should furthermore specify the expected results and the action levels, as well as the procedures required when the action levels are exceeded. It should be kept as simple as possible in order to optimize the time and effort required. QA programmes should be tailored to the specific equipment and departmental situation.

7.6.1.2. Documentation

Guidelines of all steps and procedures in a radiotherapy department should be well documented and are often part of an oncology information system. One way to maintain this documentation is to develop a quality system, as discussed in Section 7.1, since this ensures that all documentation is kept in one place and updated regularly (reviewed at least annually). These documents should specify what the composition, tasks and responsibilities of a multidisciplinary QA team in a radiotherapy department are and how QA programmes should be structured. Clarity of documentation and communication is a prerequisite for optimal patient treatment. Various organizations have designed documents for specific purposes, e.g. simulator, prescription and treatment sheets, which could serve as templates for a department. Examples of worksheets for a number of QC tests of dosimetry equipment, TPSs and treatment delivery equipment have been provided by several national and international organizations, often in the national language. For instance, section 12 in the IAEA radiation oncology physics handbook [557] provides details on how an external beam equipment related QA programme should be structured, and gives a number of examples of QA programmes for radiotherapy equipment. Regular control of QA records is needed to trace any

deviation of the reference conditions. Early observation of discrepancies will reduce uncertainties and could even avoid incidents or near misses.

An important part of the documentation of a course of radiotherapy is the reporting of the dose prescription. Although for 2-D and 3-D CRT, the recommendations provided by the older ICRU reports are generally followed, this is not yet the case for IMRT, where the ICRU has developed some new recommendations, as discussed in Section 6.6. Several publications have showed that large variations in prescribed and delivered IMRT dose values exist between institutions [558, 559]. The latter authors reviewed criteria for dose prescription applied in current IMRT trials. Guidelines for use of IMRT in trials generally allow each institution to define its own dose specification criteria, which has led to differences in IMRT prescriptions. They concluded that dose prescription and specification standards for IMRT clinical trials do not currently exist in the same way they are available for 2-D and 3-D CRT treatments. For that reason, ASTRO has recently provided recommendations for documenting IMRT treatments [560]. Because some of these recommendations are ambiguous, further discussion of these proposals is needed before they can be universally adopted.

Not only the reporting of the dose prescription should be unambiguous, but all aspects related to the treatment should also be well documented. Details of the actual treatment data should be recorded in a clear and easily accessible way by all people involved in the management of the patient, thus reducing the chance of misunderstandings and the incidence of errors. The performance of an external audit is a good way of tracing insufficiencies in the documentation system, as discussed in Section 7.7.

7.6.1.3. Education and training

The role of education and training of all staff members in a rapidly evolving field such as radiotherapy cannot be overemphasized. It is evident that radiotherapy requires well trained professionals for all the steps involved in a patient treatment. Inadequate training may not only result in a non-optimal treatment, but significant risks for patients also occur if the users of radiotherapy equipment are insufficiently trained. Recent analysis of a large number of incidents and near misses has shown that all staff members, radiation oncologists, medical physicists and RTTs can be involved in the occurrence of these events [25, 27, 561, 562]. It is therefore of the utmost importance that all staff members are aware of the caveats of the part of a patient treatment which they are performing. In other words, each staff member should have adequate education and training in those aspects of the treatment procedure for which they are responsible, including knowledge about how accuracy requirements and uncertainties are influenced by those procedures.

All professionals working in radiotherapy departments must be specialized in their discipline and must have met the particular requirements for education, training and competence in their speciality before they are allowed to influence patient treatment [563]. Unfortunately, this is not always the case, e.g. for RTTs in many countries it is not a prerequisite to have formal radiotherapy training before treating patients. In principle, the level and content of the training programme of the treatment team should be appropriate for the type of treatments performed in that particular institution.

It is recognized that education programmes vary internationally both in terms of content and duration. To aid standardization, the IAEA has developed a number of syllabuses for professionals working in radiotherapy, describing in detail the contents of academic education programmes, as well as other training material [557, 564–570], including some training videos [571]. These syllabuses and clinical training programmes include both academic education and practical, clinical, on-the-job training. The latter is of great importance for optimal and accurate patient treatment and the avoidance of incidents. On-the-job training, supervised by experienced radiotherapy professionals, in addition to university education, is the recommended approach.

For specialization as well as for continuous medical education activities, on-line access to textbooks, journals, courses or other resources is a prerequisite in a modern radiotherapy department. Generally, a vast amount of information can be found on a specific topic using the Internet. All staff members should therefore be trained in literature searching skills and have the possibility to take advantage of formal continuing professional development activities.

It is worthwhile studying UK legislation [572], which recommends the simple means of competency charts and matrices, together with training records, to aid the manager in maintaining competency throughout a skill mixed workforce. Associated with training is the issue of supervision. For instance, in most work within brachytherapy, direct supervision is preferable, as formulated, for instance, in the Royal College of Radiologists (UK) document [63]: “A trainee can undertake treatment planning under direct supervision of an entitled operator who is responsible for the task being completed correctly.” Indirect supervision requires careful rules to be followed by the supervisor to ensure that no critical piece of work proceeds along the chain unchecked.

Implementation of new equipment depends on the resources and expertise present in a department, and should incorporate a multidisciplinary approach where radiation oncologists, physicists and RTTs are well integrated. Education and training are therefore critical issues for the safe implementation of new equipment, and should be well thought-out before the new tools are installed. Although it is obvious that institutions must ensure staff are properly trained before using new equipment, it is often difficult to determine when the training

is sufficient to start actual patient treatment. It is therefore important, particularly during the initial phase of using new equipment, that a comprehensive QA programme is in place. In addition to learning the theoretical background of using new equipment from the literature and at courses, interactive teaching sessions, focused on situations in practice, should be an important part of training in the various aspects of new technology.

From the analysis of a number of recent incidents (and near misses) occurring in radiotherapy institutions after the introduction of new technology, it has become evident that a considerable number of these incidents were due to insufficient training of the responsible individuals (e.g. see Ref. [561]). For instance, in one recent incident, the treatment planner made an error in the use of the TPS, while in another incident, a physicist did not measure the output of small fields correctly [26]. In both cases, additional training in the use of the new option of the TPS, or the dosimetry of SRS beams, respectively, might have avoided these errors.

Several documents provide guidance on the specific training required for brachytherapy [34, 204, 233, 573]. Often, within this guidance, HDR training is singled out for more extensive discussion, mainly because it is considered the type of brachytherapy where the risks are highest. It is evident from various reports concerning incidents, near misses and errors in brachytherapy (and in radiotherapy generally) that insufficient training is often identified as a weakness. For all members of the brachytherapy team, the rules for training are the same: fundamental qualifications (forming the underpinning knowledge base), specialist knowledge base (from lectures and self-study), specific training and understanding of all procedures that the individual is planned to be responsible for.

Understanding the precise meaning of responsibility for a task, and what an individual member of the team is signing for at the end of the task, has been discussed in a number of publications, e.g. Ref. [63]. According to UK legislation [572], "An operator is personally responsible for his/her own contribution to the patient's treatment", and "Treatment planning can only be carried out by an adequately trained, entitled operator."

Associated with training are the subjects of QM and audit (see Sections 7.1 and 7.7). These subjects can be considered as a continuation of the same theme, i.e. ensuring accuracy in dose delivery and the safety of the patient through various essential components: commissioning of equipment, basic training, continuous professional development, procedures and particularly the checking of performance and procedure by audit.

All staff should also have some degree of understanding of the responsibilities of the other members of the team. Both internal and external audit (as required by a quality system) help the team develop this understanding.

Audit of the paper (or electronic) pathways by following each step of the process, from the patient arriving in the clinic to the patient's departure from the clinic, is a very valuable tool. Not only does this uncover any risky shortcuts but it also demonstrates where the actual procedural document is weak or not working appropriately. This type of audit is a requirement of any quality system (see Section 7.7).

7.6.2. Prevention and mitigation of incidents and near misses

From various analyses of incidents and near misses in radiotherapy it has become evident that human errors were the main causes [34, 561, 562]. In this respect, radiotherapy is no different from other types of technology such as commercial air traffic, the chemical industry and road transport. In these reports, it was concluded that one of the factors contributing to many of the reported incidents and near misses in radiotherapy was the lack of information transfer between the various professionals involved in a course of radiotherapy of a cancer patient. Each centre should therefore have a safety reporting and learning system, which is a legal requirement in many countries, and continuous analysis of the events reported in that centre is necessary. The extensiveness and reliability of such a reporting system will strongly depend on the readiness to report errors and to discuss them openly. First, different categories need to be defined to account for the severity of the incident. For example, a first level of incident could be established for those incidents which result in a deviation of the delivered dose from the prescribed dose of less than 5% or where the incident resulted in a geometric miss of no clinical consequence. The severity of the incident will have a large influence on the follow-up procedure. An important prerequisite of a safety reporting and learning system is therefore that all information should be handled confidentially.

The next step is that the analysis of incidents and near misses should lead to recommendations on how, when and under which circumstances they should be rectified. Incidents should be considered a weakness of a system and an opportunity to improve procedures rather than to judge an individual's behaviour. The attitude of staff and their awareness and alertness regarding procedural errors play an important role in preventing future incidents and near misses. The lessons that should be learned from these incidents and near misses should be the topic of staff meetings. The various factors that may cause incidents and may harm the cure rate or quality of life of a patient should be evaluated continuously. In that respect, it may be helpful that the information provided in the reports of organizations that have analysed errors in radiotherapy institutions, such as the IAEA and International Commission on Radiological Protection (ICRP) reports [34, 473], as well as the report on the ROSIS experience [574], is available in

each institution with an incident reporting system. Although the local situations are different, the causes and frequency of the incidents and near misses described in these reports give an indication of what may happen in each clinic. Table 10, which is taken from the IAEA Safety Reports Series No. 17 [34], summarizes the causes and frequency of a number of incidents that occurred in radiotherapy departments before the year 2000.

TABLE 10. EXAMPLES OF CAUSE AND FREQUENCY OF OCCURRENCE OF ERRORS MADE DURING A COURSE OF RADIOTHERAPY OF CANCER PATIENTS
(Adapted from Ref. [34])

Cause	Number of incidents
Calculation error of exposure time or dose	15
Inadequate review of patient chart	9
Error in anatomical area to be treated	8
Error in identifying the correct patient	4
Error involving lack of or misuse of a wedge	4
Error in calibration of a Co-60 source	3
Transcription error of prescribed dose	3
Decommissioning of teletherapy source error	2
Human error during simulation	2
Error in commissioning of the treatment planning system	2
Technologist misread the treatment time or monitor unit setting	2
Malfunction of the accelerator	1
Treatment unit mechanical failure	1
Accelerator control software error	1
Wrong repair followed by human error	1

Audits are another way of getting useful information about the quality of current clinical practice in a department and receiving advice about prevention of errors in the future. Audits can be performed in different ways but should preferably be carried out by an independent organization or group of observers (see Section 7.7). An important and, in some countries, a legal requirement is participating in an audit of the output and other beam characteristics of irradiation equipment. Generally, a limited number of parameters are verified during such an audit, which can be performed by post (e.g. Ref. [214]) or by a visit from a team of experts (e.g. Ref. [575]). Analysis of the results of these audits is of direct importance for the daily work in the department and essential for high quality treatment.

7.6.2.1. Incidents, near misses and errors in brachytherapy

Over the last ten years, various publications and studies concerning radiotherapy incidents have been published, foremost among them the IAEA's Safety Report Series No. 17 [34] and ICRP Publications 86 [473] and 112 [561]. Brachytherapy, however, has its own particular peculiarities that mean that this modality of radiotherapy requires that incidents and near misses related to it be considered separately. Indeed, much of the literature on safety in brachytherapy refers to one particular event in the USA where an HDR source was left in a patient who was then returned to the ward [576]. A further set of documents was published by the United States Nuclear Regulatory Commission [577] entitled Human Factors Evaluation of Remote Afterloading Brachytherapy. This very large document contains 13 page executive summaries, demonstrating the seriousness with which these incidents were taken by the regulatory authorities.

As shown in Section 6.5.8, brachytherapy using HDR is associated with complex imaging and planning, for which training and detailing of procedures is an essential part of QM. However, because it involves radioactive sources, brachytherapy is also heavily regulated. In particular, the high activity of an HDR source means that it is subject to special anti-terrorist regulation. For example, in the UK, the Environmental Agency [578] requires that sources are carefully looked after during their entire lifetime. This particularly includes the time they spend in a clinical environment: from delivery to storage, installation (within a safe treatment room, which may incorporate special features such as a radioactive safe for storage, special strong lockable doors and a movement sensor alarm), use and return.

The IAEA's Safety Report Series No. 17 [34] stresses the need for an emergency plan if a source becomes lodged in the patient, for instance because of a kink in the catheter or the source becoming dislodged from the driving mechanism. Emergency procedures have the objective of avoiding unnecessary

radiation doses to patients, staff and the public by returning the source quickly to its shielded position or lead pot. Initial training and regular exercising of this procedure are essential for the whole HDR brachytherapy team.

When surveying the literature, it also becomes obvious that the general view is that HDR is the most hazardous form of brachytherapy. The ICRP reinforces this concept in their report Prevention of High-dose-rate Brachytherapy Accidents [579]. Even though incidents and near misses are assumed to be greatly under-reported, more than 500 HDR events have been recorded. The most frequent cause is human error. Examples of some specific events associated with treatment itself are as follows:

(a) Wrong patient — see Section 6.5.4.1.
(b) Reverse order of entry of dwell positions. This has resulted in a patient receiving an 8.0 Gy dose at the prescription point instead of the prescribed 5.0 Gy. The regulatory authority required the following corrective actions: (1) modifying the annual retraining programme for oncologists and physicists; (2) modifying the procedure for the second physicist check; (3) modifying the procedures for the oncologist check.
(c) Inadequate default position for the start of dwell sites resulting in a radiation dose in an unintended part of the oesophagus.
(d) Kink in a catheter. A sharp curve in the catheter trapped the source for a period of time resulting in a high dose in the trachea instead of the bronchus.
(e) Dwell position error. The wrong step length was entered into the HDR system (5 mm instead of 2.5 mm) resulting in a dose that was too low.
(f) Catheter of the wrong length. This resulted in parts of body, the right eye particularly, receiving an unnecessary dose of radiation.

ICRP Publication 97 [579] makes a series of recommendations to reduce the number of incidents and near misses in brachytherapy, including:

(a) A comprehensive QA programme;
(b) An external audit, which includes both the physical aspects of dosimetry and procedural aspects within a quality system;
(c) A second check and verification of all significant steps from prescription to final delivery of treatment by a second competent person;
(d) Peer review of each case to improve quality;
(e) Reporting of every incident to the appropriate authority.

Reference [579] also gives a few very specific recommendations, such as the need for training in specific areas of HDR brachytherapy, keeping the source step size constant, having a dedicated suite and appointing permanent senior staff.

AAPM TG59 Report [233] has a similar approach to other publications on this subject, but also identifies the difference between systematic and random errors. Systematic errors are mainly associated with commissioning of equipment. Random errors are due to individual mistakes, slips, lack of judgement and occasionally to machine malfunction. Such errors may be due to: (1) transient malfunction of a device; (2) failure of a team member to follow established procedures; (3) making a mistake when following a procedure; (4) relying on procedures which inadequately define each team member's duties and responsibilities (adequate definition in procedures is of vital importance). The TG59 Report reinforces some of these concepts, but identifies a "misadventure" as a treatment which deviates from the safety or accuracy criteria set by the individual institution; it is an error or incident with potential to compromise the patient's clinical outcome. It should be noted that good clinical judgement must be used to identify a misadventure; it is neither useful nor possible to set exact criteria for such events. Most misadventures are due to human errors or misjudgements rather than failure or malfunction of equipment. Inadequate training and supervision, as discussed in Section 7.6.1.3, excessive time pressures and inadequate documentation have all been identified as causes of errors.

It is worth mentioning that a completely different set of rules apply to LDR brachytherapy using ^{125}I or ^{103}Pd seeds for prostate radiotherapy. For these treatments, the risks of misadventure are not so great at the time of treatment. However, after the patient has been discharged from the hospital, other medical professionals or members of the public can be put at risk, although this is generally a relatively minor risk. Particularly where environmental regulations may be contravened, e.g. when the patient dies or a further operation is needed, special attention is required. It is essential that all persons are made aware, for at least 2 years for ^{125}I seeds, that an individual contains these seeds, by making use of a wallet card or other means of warning surgeons, autopsy and crematorium staff or others of the risks.

7.6.3. Examples to show how to reduce different uncertainties for a range of situations

In this section, a number of examples are given of how a reduction in geometric or dosimetric uncertainties can be obtained in clinical practice. Each example represents the experience in the clinic of one of the contributors to this publication and is meant as an illustration of the approaches discussed earlier in this section. These cases should not be considered a recommendation for clinical implementation in other institutions, because they are specific to the local situation.

7.6.3.1. IMRT

Patient anatomy can change during a course of treatment and such changes might introduce clinically significant dosimetric deviations. This is important for IMRT of the head and neck, for instance, in which fields may pass through a sinal cavity (e.g. Ref. [580]). In vivo EPID dosimetry is used to confirm the correct delivery of IMRT fields [581]. Figure 37 shows the results of in vivo EPID dosimetry of an IMRT treatment of a head and neck cancer patient, where the exit dose of each beam has been back projected to a plane through the isocentre and compared with the planned dose distribution in these planes. The deviation of the dose at the isocentre was considered to be clinically unacceptable. Further analysis using a CBCT verification scan showed that the emptying of a postoperative cavity that was filled during the planning CT caused the difference. By repeat CT imaging and IMRT replanning, the uncertainty could be reduced.

In ESTRO Booklet No. 9 [215], a number of other examples are given of pitfalls, potential errors and possible actions to solve specific problems when applying IMRT.

7.6.3.2. Frameless stereotactic body radiotherapy of the lung

In order to guarantee the localization accuracy and intrafraction stability of the target during frameless stereotactic body radiotherapy, 4-D CBCT can be used [582]. A bone match can then be performed to the reference CT scan, for which the time weighted mean tumour position can be chosen. The respiration cycle is also derived from the reconstructed 4-D CBCT scan. Following this, a soft tissue match on the moving tumour is performed for each phase in the breathing cycle. Figure 38 shows that if the bony anatomy is chosen as a surrogate for tumour position, a considerably larger margin between the GTV (red line) and PTV (purple line) would be required compared with a soft tissue match.

7.6.3.3. Pelvis

Figure 39 shows that a considerable improvement in patient set-up accuracy can be achieved by applying portal imaging for patients treated in the pelvic region. Careful analysis of the results of a portal imaging programme can trace several systematic errors such as the imperfect alignment of lasers or differences in couch sag during CT scanning and actual patient treatment. Portal imaging may also lead to various strategies to improve treatment accuracy in a department even further, for instance with respect to patient immobilization and patient positioning techniques by the RTTs. Knowledge of the random and systematic uncertainties of patient set-up for a specific treatment technique can

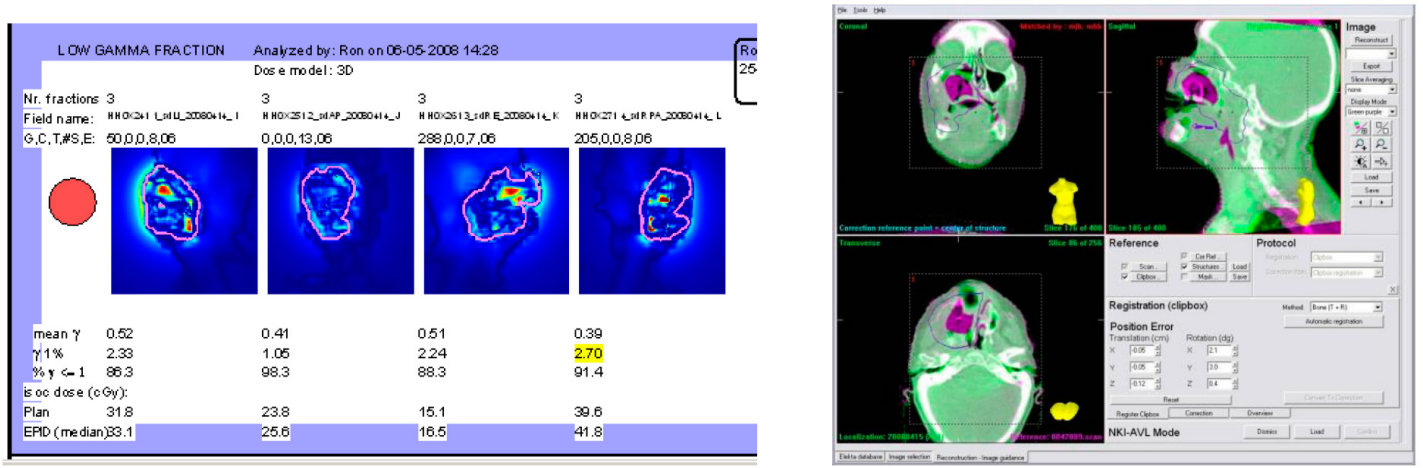

FIG. 37. Left: Results of in vivo EPID dosimetry of an IMRT treatment of a head and neck cancer patient. Right: Verification of the patient position by comparing a CBCT scan (green) with the planning CT scan (purple). The red spot in the gamma images on the left indicates that the fluid with which the postoperative cavity was filled when the planning CT scan was made was removed during treatment, resulting in the purple area in the cone beam CT scan, indicating an air cavity. (Images courtesy of C. Hamilton.)

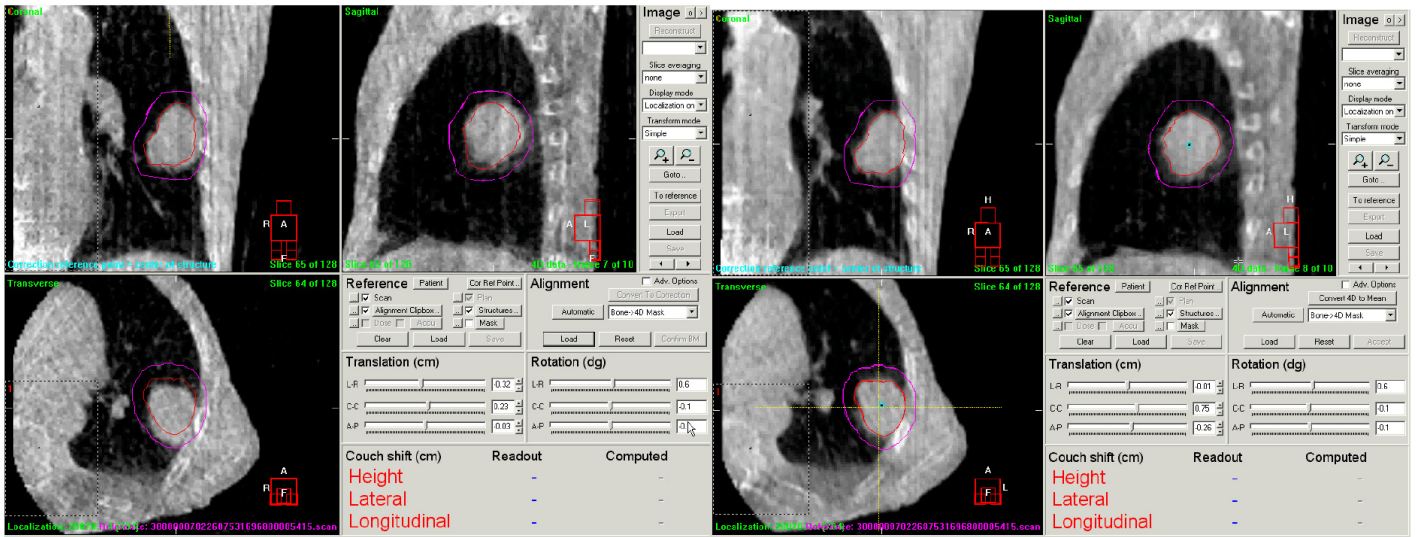

FIG. 38. Results of bone matching (left) and tumour matching (right) of a frameless stereotactic lung cancer treatment verified with 4-D CBCT. (Images courtesy of C. Hamilton.)

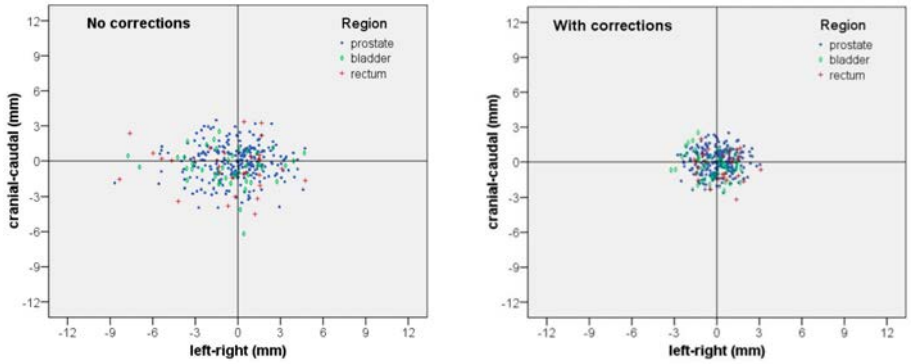

FIG. 39. Results of routine portal imaging of patients treated in the pelvic region. (Figures courtesy of C. Hamilton.)

be used for the adjustment of margins for a specific patient group, for instance, in combination with dose escalation, as discussed in Section 5.3.

Figure 40 shows the results of IVD applied during 3-D CRT of prostate cancer patients entering a clinical trial. The average ratio of measured and prescribed dose was 1.009 ± 0.012 (1 SD) for the total prostate trial group treated on two accelerators. When the results were analysed per accelerator, the ratios were 1.002 ± 0.015 (1 SD) for accelerator A and 1.015 ± 0.008 (1 SD) for accelerator B. This difference could be attributed to the cumulative effect of three

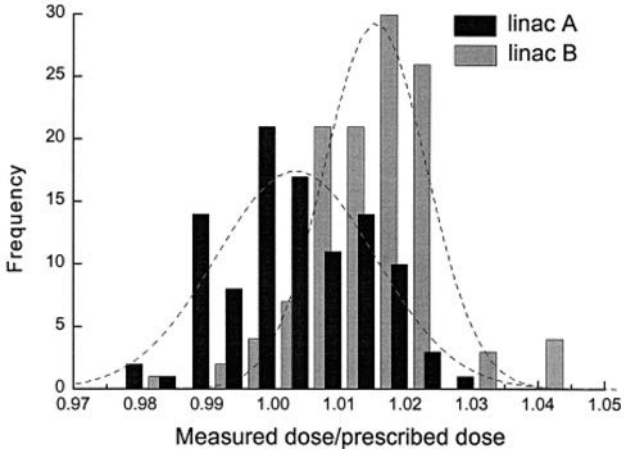

FIG. 40. Frequency distributions of the IVD results of 3-D CRT of prostate treatment on two different linacs. (Figure courtesy of C. Hamilton.)

small imperfections in the performance of accelerator B (output factor 0.5%; gantry angle output dependence 0.5%; calibration factor 0.2%) that were well within the limits of the QA programme. The overall uncertainty could be reduced by applying a more accurate output of accelerator B.

7.6.3.4. Breast

The geometric accuracy of a standard 3 field mono-isocentric technique (tangential breast and oblique supraclavicular fields) may be improved by adopting a daily pretreatment anterior on-line 'check field' on the supraclavicular field using an EPID. An action level of 5 mm resulted in a field shift in approximately 50% of fractions and a highly significant reduction in field placement error ($P < 0.026$ left to right and $P < 0.0000021$ superior to inferior), as shown in Fig. 41. An additional 3 to 7 MUs per image is given and is accounted for in the total dose.

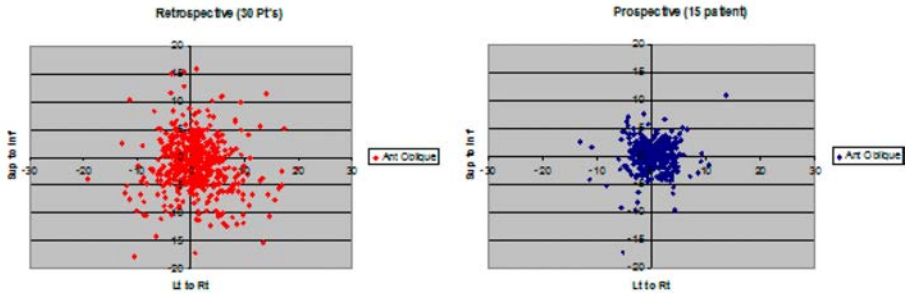

FIG. 41. Scatter plot of 3-D field placement errors before and after the use of a daily on-line check field for the supraclavicular field. (Figures courtesy of C. Hamilton.)

7.6.4. The decision to replan a patient

During a series of radiotherapeutic treatments, considerable volume changes may occur. As a consequence, the dose in the target volume may decrease, and the dose in OAR may increase without replanning. Several methods have been developed to alert the clinician if shrinkage of the tumour or changes in anatomy might result in an under-dosage of the target volume or excessive irradiation of OAR. In these situations, image guidance often provides information to predict the need for dose adjustment. Criteria for replanning are currently based mainly on deviations in position between planning CT and verification imaging.

In order to ensure adequate dose distributions in target volume and safe dose values in normal tissues, it is essential to quantify these geometric variations, expressed as length, into changes in dose values, a quantification which currently requires repeat CT imaging, repeat delineation of target volume(s) and OAR, and replanning. Because this is a time consuming process, replanning is only applied in a limited number of situations. Instead, a more robust approach is often chosen that incorporates changes in geometry that are already possible, for instance, by adopting a rather generous CTV to PTV margin.

Various groups are investigating faster methods that would allow more frequent replanning, if possible, accompanied by margin reduction. One of the problems that need to be solved is how dose distributions should be combined if volume variations occur. For this purpose, deformable organ registration tools are developed to track organ shape changes. These algorithms are, however, still in a research phase and need further development before they can be implemented for routine clinical applications [180]. Once developed, they lead to the possibility of adaptive radiation treatment in which treatment variations are monitored and incorporated in re-optimizing the treatment plan early on during the course of treatment [583, 584].

One example of adaptive planning was performed by Woodford et al. [501], who reviewed the daily MV CT scans from a helical tomotherapy machine of 17 patients with non-small-cell lung cancer. With a prescription of 30 fractions, they found that if the GTV decreases by more than 30% at any point in the first 20 fractions of treatment, adaptive replanning is appropriate to further improve the therapeutic ratio.

A number of techniques are available for in-room verification imaging, applying both on-line and off-line approaches. However, not all techniques provide sufficient anatomical information to decide if replanning is necessary. For instance, imaging of bony anatomy by using portal imaging might not reflect the actual position of the tumour volume. A tool to visualize soft tissue is often essential to allow for adaptations of the treatment plan. In-room image guidance provides sufficient imaging information to reliably predict the need for dose adjustment in many situations. The implementation of in-room image guidance in many centres will probably increase the demand for replanning. On the other hand, an increase in the use of hypofractionated schemes and thus shorter overall treatment times might reduce the chance that volume changes occur.

Many patients with head and neck or lung cancer have tumour shrinkage, weight loss or both during the course of radiotherapy. Careful ongoing observation of the patient's condition during clinical review by the radiation oncologist is at this moment probably the most widely used criterion for replanning. Often the radiation technologists have already observed changes in the immobilization or increased set-up uncertainties. Repeat simulation or CT imaging and replanning

using the same beam set-up, followed by analysis of initial and adapted dose–volume parameters, can then be used to assess if the resulting new plan differs to a degree considered clinically significant. If so, continued treatment of the patient with a new, adapted plan might be necessary.

In lung cancer, several types of anatomical changes during the course of radiotherapy may occur. For instance, in-room imaging during an irradiation course may show that the lung appears to be filled with fluids which were not there at the time of planning, or re-expansion of the lung after atelectasis may occur. Also, the tumour position may differ between the time of making the planning CT scan and the actual treatment (a good example of this is shown in Ref. [585]). These situations may cause the tumour to shift out of the intended dose region, necessitating replanning of the treatment. Careful analysis of each individual case is required to decide if replanning is necessary.

Replanning may not always result in a considerable improvement of the actual plan compared with the initial plan. Even with significant anatomical and volumetric changes, the dose differences might be relatively small and depend on the volume and position of the target relative to that of the OAR. Also, the treatment technique plays an important role in the decision to replan. For instance, if parallel opposed fields are used, then changes of the external contour will have only a moderate, and easily predictable, effect on the mid-line dose distribution. If, however, IMRT is used, then volume changes are more critical with respect to target coverage or dose in OAR, which are less easy to predict without replanning. Additionally, with IMRT, tumour shrinkage does not always result in significant dosimetric differences in targets and critical structures. The benefit of replanning might, for instance, only be a moderate improved sparing of the parotid gland, while the dose in the spinal cord, brainstem and mandible remains unchanged. More studies with various groups of tumour sites are needed to determine criteria for repeat CT imaging and IMRT replanning for cancer patients undergoing radiotherapy.

Adaptive radiotherapy has different meanings for different people. For some, it means replanning as a result of volume changes during a course of radiotherapy. For others, it includes the ability to identify and correct interfractional patient treatment variations. Thus, it not only takes changes of anatomy into account, but it also accounts for patient misalignments and deviations during intrafraction organ movements, e.g. due to respiration motion.

It can be concluded that, currently, replanning is mainly performed after clinical indications that significant volumetric changes in the irradiated area of a patient have occurred. That information is mainly based on repeated imaging during a course of treatment. Observed geometric changes are, however, not related to variations in dose distribution in a straightforward way and consequently, no simple criteria for replanning can be given. Substantial

technological advancements are needed in the automation of planning, in combination with set-up error correction, before replanning can be conducted more frequently in the clinic. A further discussion of the effect of dose in tumours of varying volume on dose–response curves can be found in Section 4.4.

Specific aspects related to replanning in brachytherapy have been discussed in Section 6.5.8. It is particularly important for HDR patients to whom several fractions may be delivered following a single insertion of needles (under anaesthetic) that the positions of these needles with respect to the target volume and critical structures are checked immediately prior to each treatment delivery.

7.7. AUDITS IN RADIATION ONCOLOGY

7.7.1. External audits (EBRT and brachytherapy)

Audits can be very helpful in identifying gross deviations from standards, and especially in determining systematic errors in institutional procedures. At least three organizations conduct regular remote audits of treatment machine output calibration with mailed dosimeters. Such programmes are conducted by the IROC Houston in the USA, the IAEA and the National Cancer Center of Japan. Of these centres, the IROC Houston has the largest programme and monitors all the institutions that participate in the United States National Cancer Institute sponsored clinical trials (1888 institutions as of early 2012), both within the USA and internationally. The IROC Houston initiated its audit programme using TLD for photon beams in 1977 [586, 587]. In 1982, electron beams were included, and in 2007, measurements of proton beams were initiated. The IAEA monitors about the same number of institutions as the IROC Houston, approximately 1800. However, they measure fewer beams per year, and reported measuring 1228 clinical beams in 2010–2011, whereas the IROC Houston measures approximately 14 000 beams annually.

7.7.2. IAEA quality audits in radiotherapy

7.7.2.1. Dosimetry audits

The audits of radiation dose have a long tradition [214, 588]. Both on-site audit systems and mailed dosimetry programmes exist in parallel. Typically, on-site audits review local dosimetry systems, test dosimetric, electrical, mechanical and safety parameters of radiotherapy equipment, test TPSs and review the clinical dosimetry records. Many on-site review programmes operate at a national level for a limited number of hospitals, whereas mailed systems

provide cost effective audits at a larger scale, involving hundreds or thousands of radiotherapy facilities [588–591].

Dosimetry audits are an effective tool in identifying problems in practice, bringing these to the attention of the medical physicists concerned and providing support to find the source of the problems and therefore to rectify them. Audits have improved practice and the accuracy of dosimetry in a wide range of radiotherapy centres and over time, and help in maintaining these levels (see Fig. 42). Audits help in reducing uncertainties and in increasing the precision and consistency of radiotherapy dosimetry between centres. Altogether, dosimetry audit has improved consistency in radiotherapy results and outcomes for patients and provided clinicians with confidence in the dosimetry supporting their practice.

Typically, postal dose audit programmes have a limited scope and are capable of providing verification of a few selected dose points or beam parameters. A four level flexible audit system may be adapted for such audits in EBRT [590]:

— Level 1. Postal dose audits for photon beams in reference conditions [214, 588, 591]. This is the basic level, recommended for all radiotherapy centres and mandatory in several countries.

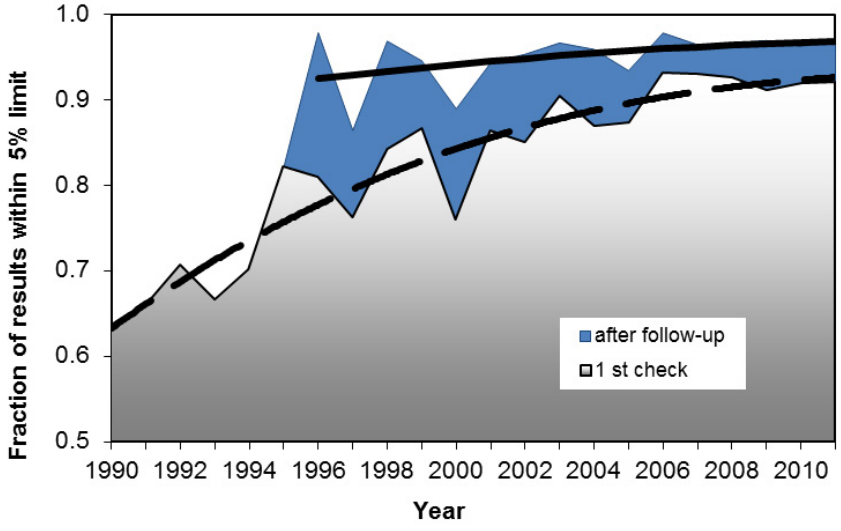

FIG. 42. Fraction of TLD results within 5% acceptable limit in the IAEA and WHO TLD postal dose audit programme. After a regular follow-up of poor TLD results was introduced in 1996, the fraction of acceptable results steadily increased.

— Level 2. Postal dose audits for photon and electron beams in reference and non-reference conditions on the beam axis [589].
— Level 3. Audits for photon beams in reference and non-reference conditions, off-axis and dose at depth on the beam axis for electron beams [222].
— Level 4. Audits for photon and electron beams in non-homogeneous or anthropomorphic phantoms. This step is used to verify the dose distribution for more realistic treatment situations, such as breast, prostate or lung [237] or special treatment techniques, such as IMRT of head and neck [592].

The gradual development and extension of the scope of dosimetry audits, initially from beams in reference conditions only, to include more parameters of dosimetry, equipment performance, complex irradiations, combined beams, treatment planning, new technology and so on, continues to increase their potential benefits. As the complexity of radiotherapy evolves, the scope of what can be included in dosimetry and wider radiotherapy quality audits also needs to continue to increase. This increased scope should also include brachytherapy procedures.

7.7.2.2. Comprehensive clinical audits (QUATRO)

As a response to requests for assistance to perform comprehensive audits in radiotherapy, the IAEA introduced comprehensive clinical audits (QUATRO) [593]. The objective of QUATRO auditing is to review and evaluate the quality of the practice of radiotherapy at a cancer centre to define how best to improve the practice. A guideline document [575] has defined how to conduct the audit. The IAEA organized several workshops to train QUATRO auditors and auditees, and multiple missions have been completed (70 between 2006 and 2013).

In order to optimize outcomes of radiation treatment, it is equally important that the clinical aspects as well as the physical and technical aspects of patient treatment are audited because, although it is essential for the radiotherapy process, accurate beam dosimetry and treatment planning alone cannot guarantee the required outcome. The comprehensive audit methodology has been described by the IAEA [575] and in a European Commission guidance document [594]. The IAEA QUATRO audit methodology puts emphasis on radiotherapy structure and process rather than treatment outcome. It includes assessment of infrastructure as well as of patient related and equipment related procedures involving radiation safety and patient protection aspects, where appropriate. Staffing levels and professional training programmes for radiation oncologists, medical radiation physicists and RTTs are also reviewed. The QUATRO procedures have been

endorsed by EFOMP, ESTRO and the International Organization for Medical Physics.

The objective of QUATRO is to evaluate the quality of all of the components of the practice of radiotherapy at a centre, including its professional competence, with a view to improve quality and provide a general audit methodology that can be applied in a range of economic settings. The audit includes an assessment of the ability of a centre to maintain its radiotherapy practices at the level corresponding to the best clinical practice in the specific economic setting (related to the ability of a country to sustain that technology).

QUATRO audits are organized by the IAEA in response to voluntary requests by radiation oncology centres in IAEA Member States in Africa, Asia, Europe and Latin America. The reason for the audit must be clearly articulated by the requestor. The audit is carried out by a multidisciplinary team of high level experts comprising a radiation oncologist, radiotherapy physicist and an RTT. The team spends one week in the radiotherapy department and reviews all aspects of the patient pathway from referral to follow-up. The audit starts with an entrance meeting with the management of the centre followed by a complete tour of the facility. Auditors observe aspects of working practices and procedures, interview staff, review and evaluate procedures and documentation and carry out practical measurements and performance tests. Radiation treatments for a range of anatomical sites are evaluated through review of a randomly selected patient files and treatment records.

A detailed set of checklists has been prepared to assist the audit team during the course of the audit and with the subsequent preparation of the report. These checklists are made available to the radiotherapy department prior to the audit in order to familiarize its staff with the audit methodology and to facilitate the audit.

The interpretation of audit results is made against the criteria of evidence based good radiotherapy practices. As an example of such criteria, the IAEA has given a description of the design and implementation of a radiotherapy programme regarding clinical, medical physics, radiation protection and safety aspects [513]. Audit reports document areas for the improvement of current services in audited centres, and centres receive advice for further development. Some centres have been acknowledged to operate at a high level of competence. Based on the audit results, it was possible for the IAEA to identify and address items that commonly need improvement at centres across the world, for example, staff training.

7.7.3. Imaging and Radiation Oncology Core Houston Quality Assurance Center (IROC Houston) dosimetry system

The IROC Houston's remote dosimetry audit system (Fig. 43) comprises a package with a lightweight platform and an acrylic mini-phantom containing several dosimeters for each radiation beam for both photons and electrons.

FIG. 43. IROC Houston irradiation phantoms for QA audit.

The uncertainty of the TLD system in measuring the output of accelerators remotely has been evaluated and found to be 1.5% [587]. This uncertainty is expressed as the standard deviation of measurements of dose with the IROC Houston's TLD system. Consequently, the IROC Houston's measurement of an institution's output can be stated at an uncertainty of less than 5% using a 99% confidence interval. The IROC Houston has established ±5% as a threshold for acceptability. In mid-2010, the IROC Houston discontinued the use of TLDs for routine annual audits of photon and electron beams, and adopted OSLD technology.

7.7.3.1. Results of the IROC Houston's annual audits

The histogram shown in Fig. 44 displays the results of audit measurements with TLDs in photon and electron beams between June 2009 and March 2010. The mean ratio of TLD measurement to the institution's stated photon dose was

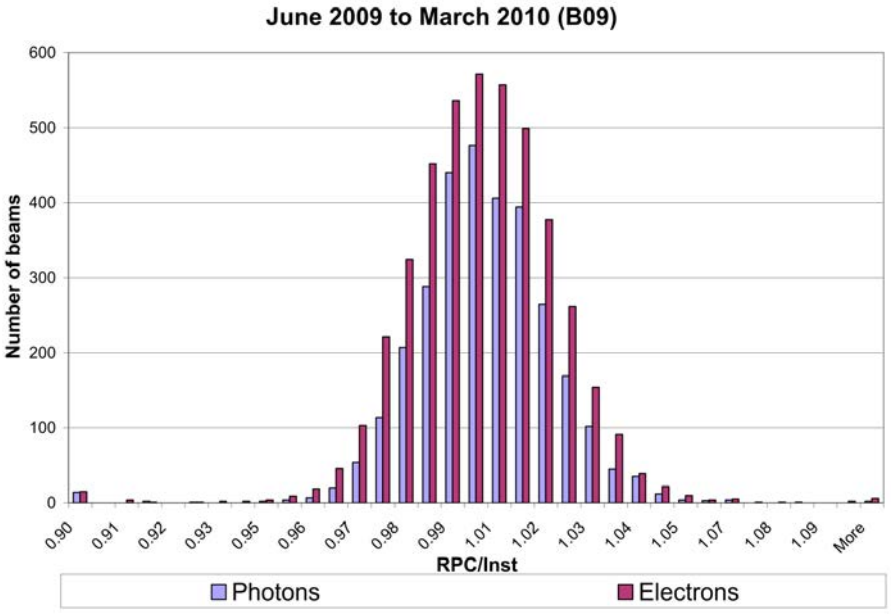

FIG. 44. The spread in results of the ratio of the IROC Houston-measured dose to the institution-stated dose, for audit measurements with TLD in photon and electron beams over approximately 9 months.

0.999 ± 0.016, and for electron beams it was 0.998 ± 0.017. (Known irradiation errors, excluding calibration errors, were excluded from the analysis.) The IROC Houston has set a threshold of ±5% to identify calibration errors requiring further analysis. During the last few years, approximately 3% of photon beams and 5% of electron beams fell outside this threshold. The vast majority of the IROC Houston's audit results correspond to radiotherapy sites in North America and Western Europe. The standard deviation of approximately 1.6–1.7% corresponds well with the estimated uncertainty derived from the recommendations of organizations such as the AAPM.

7.7.3.2. Remote audits under non-reference conditions

Considering that the IAEA found a significant number of deviations in non-reference situations, such as those used clinically on patients, in 2001 it developed a coordinated research project to audit measurements in a variety of clinically relevant irradiation geometries, including those under new and modern radiotherapy techniques. At the time of writing, these audits included

measurements of beam profiles, with and without wedges, for symmetrical and asymmetric fields for photon beams with and without MLC.

7.7.3.3. Audits of advanced technology procedures

The IROC Houston, as part of its mandate from the United States National Cancer Institute, also conducts remote audits of advanced technology procedures. The IROC Houston conducts an end to end test through the use of anthropomorphic phantoms. Several phantoms of different designs have been constructed. Currently, these phantoms simulate the head, thorax, abdomen and pelvis and are designed to evaluate IMRT treatments to the head and neck, prostate or lung, and stereotactic treatments to the brain, lung, spine and liver.

Evaluation of the phantom irradiation consisted of a comparison between the measured dosimetry data and the institution's calculated dose distribution. The calculated dose distribution information on the TLD volume and isodose information was provided either by hard copies of the treatment plans or electronic DICOM RT or RTOG data submitted to the Image-guided Therapy QA Center and subsequently made available to the IROC Houston. The results from the IROC Houston TLD and film were compared with the data provided by the institution. The criteria for an acceptable phantom irradiation were based on a statistical analysis of the first 10 phantom irradiations and approved by the RTOG. The established criteria were ±7% for absolute dose in the PTVs and ±4 mm for DTA in the high dose gradient region between the primary PTV and the OAR [592]. For the lung and spine phantoms, a 2-D gamma index evaluation is performed, and the criteria are shown in Table 11. The gamma index was introduced by Low et al. [595]. It provides a means of comparing 2-D measured and calculated dose

TABLE 11. RESULTS OF IROC HOUSTON PHANTOM IRRADIATIONS FOR ADVANCED TREATMENT PROCEDURES

Phantom	Head and neck	Prostate	Spine	Lung	Liver
Irradiations	752	174	19	174	23
Pass	585	143	13	124	12
Pass %	78%	82%	68%	71%	52%
Criteria	7%/4 mm	7%/4 mm	5%/3 mm	5%/5 mm	7%/4 mm
Year introduced	2001	2004	2009	2004	2005

maps. At each point in 2-D space, the gamma index is calculated using predefined values for the dose difference and DTA. If the gamma index value is greater than unity, it indicates a position where the agreement between the measured and calculated dose maps do not meet the predefined criteria.

The dose comparison results in Table 12 represent 475 phantom irradiations yielding 3337 TLD/institution ratios. These were reported as the ratio of the measured IROC Houston TLD dose to the mean dose to the TLD as calculated by the institution's TPS. The average TLD/institution ratio for the PTV structures was 0.99 with a standard deviation of ±5%. The range of the ratios was quite large, from a ratio of 0.44 up to 1.26.

Table 12 shows values of the DTA measured in the high dose gradient region between the primary PTV and the OAR. The average displacement was 0.2 mm with a standard deviation of 3.1 mm. The majority of the irradiations met the 4 mm criterion, with only 59 of the 475 results exceeding the criterion. The range of the DTAs was from −15 mm to +17 mm. A negative DTA meant that an institution delivered dose posteriorly beyond the planned distribution, i.e. the delivered dose fell more gradually than the planned dose and generally delivered a higher than intended dose to the OAR.

TABLE 12. ANALYSIS OF TLD AND FILM MEASUREMENTS FROM THE IROC HOUSTON HEAD AND NECK PHANTOM (2001–2008)

	PTV 1 (Dose: IROC Houston/Institution)	PTV 2 (Dose: IROC Houston/Institution)	Organ at risk (Dose: IROC Houston/Institution)	DTA (mm)
Mean	0.99	0.98	1.00	0.2
SD	0.056	0.046	0.20	3.1
Number of measurements	1671	834	832	475
Range	0.44–1.26	0.57–1.23	0.27–2.24	−15 to +17

To correlate the phantom irradiation pass rate with institutional demographics, analyses of the pass rate versus the number of MV therapy machines is shown is shown in Fig. 45. These results indicate that have a significant influence personnel resources and the size of the radiotherapy department on the pass rate.

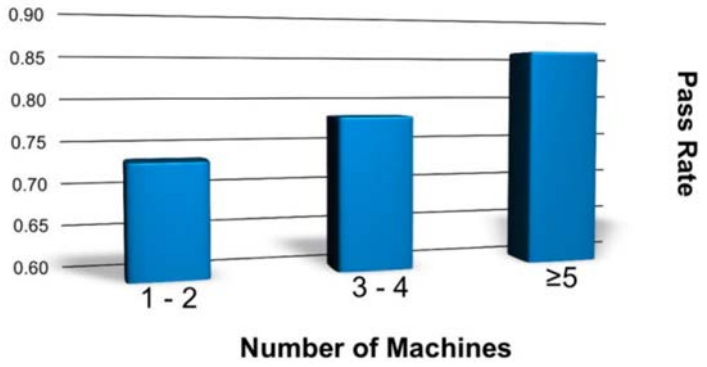

FIG. 45. Rate at which institutions passed the head and neck phantom irradiation as a function of the size of the radiotherapy department.

Results of audits that have been performed for IMRT treatments were also summarized in the ESTRO Booklet No. 9 [215]. These results of dose comparisons in anthropomorphic phantoms irradiated with IMRT beams are reproduced in Table 13.

TABLE 13. RESULTS FROM STUDIES OF THE ACCURACY OF DOSE DETERMINATIONS OF IMRT TREATMENTS
(Adapted from Ref. [215])

Audit group	Region	Site	No.	Average dose ratio	SD (%)
ESTRO-QUASIMODO	Europe	Pelvis	10		
		PTV		1.014	1.6
		OAR		0.997	3.6
GORTEC	France and Belgium	Head and neck	16	0.992	3.9
IROC Houston-RTOG	USA	Head and neck			
		Primary PTV	450	0.99	8
		Secondary PTV	223	0.99	7
ESTRO-OECI	Europe	Fictitious volume	7	0.966	2.4
TomoTherapy		(after internal QA)		0.978	1.5

Note: QUASIMODO — Quality Assurance of Intensity Modulated Radiation Oncology; GORTEC — Groupe d'oncologie radiothérapie tête et cou; OECI — Organisation of European Cancer Institutes.

ESTRO Booklet No. 9 points out that tests for IMRT verification can be separated into three components: (1) verification of equipment for IMRT delivery, (2) verification of IMRT treatment planning and (3) verification of patient specific IMRT techniques, i.e. the combined planning and delivery process of individual patient treatments based on both relative and absolute dosimetry. Proposed values for leaf position accuracy, leaf position reproducibility, gap reproducibility and leaf speed have been given by Palta et al. [596] for both step-and-shoot and sliding window techniques. Table 14 summarizes the suggested confidence limits and action levels for IMRT treatments.

TABLE 14. PROPOSED CONFIDENCE LIMITS AND ACTION LEVELS FOR IMRT TREATMENTS
(Adapted from Ref. [596])

Region	Confidence limit[a]	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 ($D_{90–50\%}$)	2 mm DTA	3 mm DTA

[a] 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 $100\% \times (D_{calc} - D_{meas}/D_{prescribed})$.

7.7.3.4. On-site dosimetry review visits

An on-site audit has been recommended by several organizations, including the AAPM and the IAEA [597, 598]. An independent audit is especially important for solo practitioners (i.e. people who are the only physicist at their institution) but it is also a valuable exercise for all practising medical physicists. It need not be extensive, but it should address key activities such as basic calibrations, the overall QA programme and documentation.

The IROC Houston's audits include a measurement of reference calibration. Figure 46 shows the percentage of institutions that are within the 3% acceptance criterion for beam calibrations. Several observations can be made. First, the results are better for photons than for electrons. Second, changes in calibration codes of practice result in more institutions being unable to stay within the

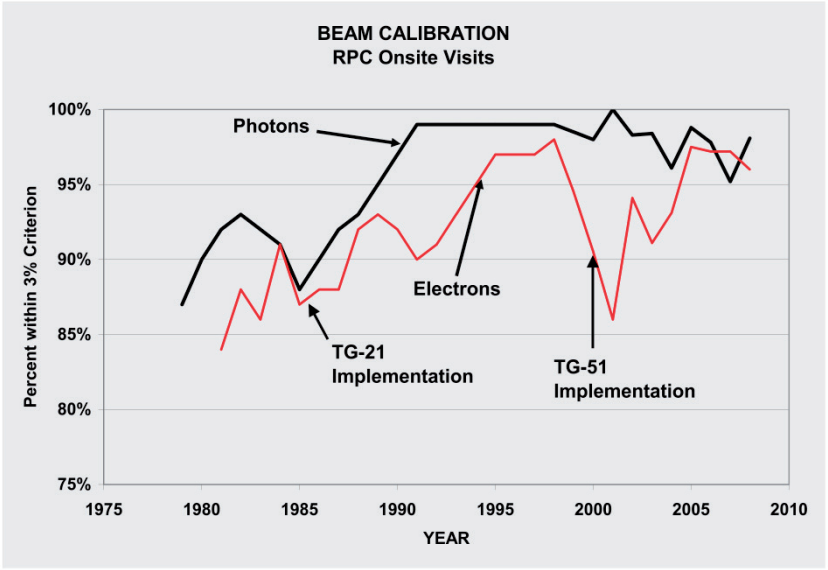

FIG. 46. Results of IROC Houston's on-site visits for beam calibrations.

acceptance criterion. Third, there is a general trend towards improvement such that the results are approaching a 97–98% compliance rate.

7.7.4. European Commission guideline on clinical audits

The requirement for clinical audit has been enshrined in European Atomic Energy Community (EURATOM) legislation through the Medical Exposures Directive: 97/43/EURATOM [24]. Following the publication of the Directive, a review was conducted within the European Union to assess the extent of implementation of clinical audit in practice, since it appeared to be very low. The survey results highlighted a low level of understanding of the actual meaning of clinical audit. To address this situation, a set of guidelines that would assist medical centres in implementing clinical audit in medical radiological practices was drafted [594].

The 97/43/EURATOM Directive gives European Union Member States freedom in interpreting the contents and practical organization of the clinical audit procedures. The principles of the European Commission and QUATRO guidelines [575] are the same, and are consistent with other clinical audit practices in individual countries. The methodology incorporated in both guidelines can be applied in a wide range of economic and cultural settings. What is important is that the centre has the ability to maintain their structure and processes at the

level corresponding to best clinical practice in the area. Also, the European Commission audit should cover all interrelated stages of the clinical pathway as they contribute to the overall quality of care.

It is important to clarify that clinical audit, as defined by the European Commission and in a similar way by QUATRO, is not a regulatory inspection and should not be undertaken by the regulatory authority. The authority can offer help and advice in initiating the process but should not use the audit as an enforcement tool. A national approach to clinical audit is recommended by both the European Commission and by QUATRO projects to ensure continuity.

Clinical audit as outlined in the European Commission guidelines includes some measure of clinical outcome. It is appreciated that this may be difficult and will vary between the three disciplines of radiology, nuclear medicine and radiotherapy, but at a minimum there should be a clear indication as to how outcomes are measured within the medical centre. The department's QA and QC manuals should contain elements of this information and should be available to the audit team.

A few important points need to be emphasized: the clinical audit should promote the development and use of international standards of practice, be applicable in all areas of health care, reflect the available resources, foster exchange of knowledge and information, help to develop standards of performance in radiology, nuclear medicine and radiotherapy, ensure compliance with the European Union Directive in terms of justification and optimization and foster an environment of good professional relationships and multidisciplinary approach to best patient care.

7.7.5. Clinical audit concept and objectives

Over the last 20–30 years, the role of clinical audit in medicine has become an established part of the health care framework. The UK National Institute for Health and Clinical Excellence[2] [599] has defined a clinical audit as:

> "a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change. Aspects of the structure, processes and outcomes of care are selected and systematically evaluated against explicit criteria. Where indicated, changes are implemented at an individual team

[2] On 1 April 2013, the name of this organization was changed to the National Institute for Health and Care Excellence.

or service level and further monitoring is used to confirm improvement in health care delivery."

In the practice of radiation oncology, clinical audit is usually taken to cover a variety of patient based care processes and outcomes in the routine delivery of treatment (usually excluding clinical trials). In 1989, the National Health Service (UK) defined clinical audit in a working paper as "the systematic and critical analysis of the quality of care including procedures used for diagnosis and treatment; the use of resources and the resulting outcome and quality of care for the patient" [600].

Clinical audit is therefore a measure of practices, procedures and outcomes against agreed standards of good practice and international comparisons. It should be a systematic and continuing activity combining internal and external components in order to achieve optimum outcomes. It should be part of an ongoing learning curve to bring about personal and professional improvement, with the results encouraging good practice and improved patient care. Clinical audit essentially means getting involved in a learning curve without expecting anything other than improvement. Performance cannot be improved if it is not measured. The ultimate objective of the quality audit is quality improvement, and the tool used is an assessment of a practice, or an activity, by an independent body. The quality audit is equivalent to peer review or independent evaluation of the practice.

The quality audit is recognized as an essential element of QA systems in radiotherapy. It is a method of checking that the quality of activities in a radiotherapy centre adheres to the standards of good practice. The standards may be recommended nationally or internationally, and should be derived from up-to-date evidence based data for cancer management. Good practice changes and evolves as research including clinical trials produce results, evidence based medicine evolves and technology develops. For clinical audit, good practice must first be defined, together with the standards against which the audit is to be carried out.

The audit involves fact finding and the interpretation of findings in the context of evidence based criteria for good practice. Deficiencies in structure, gaps in technology or deviations in procedures are identified by the auditors in the review process. In this way, the areas for improvement are documented and a set of recommendations are formulated for implementation by the audited centre. It is generally considered that the findings of the audit and its outcome are confidential between the auditing body and the audited centre.

It is worth mentioning that the quality audit in radiotherapy is not designed for regulatory purposes and the auditors have no power to enforce any actions based on their findings; they can just report their findings and

give recommendations. The audit should be understood solely as an impartial source of advice on quality improvement [575]. Therefore, it is the audited centre that decides on any actions required for the implementation of the audit recommendations.

Clinical audit is not evaluating research, but the ability and commitment to do research within the audited centre should be evaluated in the process of audit. The two processes (clinical audit and research) are complementary and systems need to be in place to assess clinical process and outcomes against research based best practice. Clinical audit should be seen as part of a continuous, dynamic learning and supportive process encouraging a culture and environment where continuous improvement is the goal of all concerned. Altogether, clinical audit stems from a requirement to enhance the overall quality of care given to patients. It is a quality improvement process, as quality is an ethical, professional and legal requirement and should constitute a core part of clinical governance. Clinical audit contributes to the quality of clinical care, gives confidence and provides assurance to the health care professionals, patients, the general public and managers that the best practice is planned.

7.7.6. Clinical audit criteria

Audit includes a quality cycles process which involves defining standards, collecting data or sample data to measure current practice against those standards and implementing any changes deemed necessary. A feedback system incorporated in the audit scheme monitors the changes and calls for re-audit when appropriate. With this approach, the auditing cycle stimulates and promotes continuous improvement for the benefit of the patient.

Criteria against which the audit will be carried out must be well defined. In general, any criterion must relate to a standard by which practice undergoing an audit can be assessed and evaluated. In the clinical context, audit criteria refer to a systematically developed statement that can be used to assess the appropriateness of specific health care decisions, services and outcomes [601].

Criteria can be developed for infrastructure and resources, the processes and the outcomes. Criteria can be generic, to cover a wide range of situations, or can be specific to the individual audit situation. They can help to carry out a more detailed analysis of a problem if this is required. Criteria may be rate based and are typically arrived at through expert consensus and focus groups in order to derive the best measure of service quality. They are typically process measures rather than clinical outcome measures. In the practice of radiotherapy or clinical oncology, the use of typical cancer outcome measures (survival, disease free survival, complication rates or population outcomes) is particularly difficult owing to the large number of geographical, selection, biological and therapeutic

biases, which occur in any typical clinical sample [602, 603]. Criteria for outcomes assessment are practical when outcomes can be easily measured and occur in closer proximity to care delivery. The simplest and most straightforward key performance indicators in radiotherapy are typically centred on resource, waiting list, logistics and infrastructure issues, rather than being directly related to patient focused or clinically relevant outcomes [604, 605].

Various sets of recommendations exist for infrastructure and resources required for operating radiotherapy services [513, 606]. The clinical process refers to the actions and decisions taken, and the process criteria encourage the clinical team to concentrate on the aspects of their work that contribute directly to improved health outcomes. Setting criteria for auditing the radiotherapy process can be difficult and should be based on evidence that may be available through literature search, high quality articles and good quality systematic review, or by formal consensus of high level experts in all aspects of radiotherapy.

Several authors have recently begun defining a quality framework in radiotherapy by outlining the major domains (both clinical and non-clinical) requiring education, consensus, definitions and methodologies in the practice of radiotherapy [8, 25, 510, 607–611]. Of particular importance in this regard is the adoption of a common set of definitions, which will cover both clinical and non-clinical aspects of a discipline that is rapidly changing in terms of its 3-D technology [612–614]. Valuable lessons may be drawn from the last 30 years' research in the existing working area of medical QA [615].

7.7.7. Clinical audit scope and focus

Quality audits can be of a wide range of types and levels, either reviewing the whole radiotherapy practice (comprehensive audit) or selected important parts of the practice (partial audit). In general, clinical audits can be comprehensive or partial, internal or external, proactive or reactive, or a combination of these.

Comprehensive audit in radiotherapy typically covers the whole clinical pathway of the patient including all interconnected stages of radiotherapy. In contrast, partial audit has a limited scope and only specific parts of radiotherapy practice are reviewed. This may be a partial audit of structure, for example, staffing levels and qualifications, or a process, for example, a dosimetry audit checking the beam calibration in EBRT [506]. Another example of a partial audit is credentialling for entry into cooperative clinical research studies [592, 616], which examines the compliance of a centre's procedures with a specific clinical protocol for a selected group of patients.

Partial audits may take the form of an external survey or questionnaire, for example, relating to resources, infrastructure, documentation and technical procedures. Audits may also include measures of the degree of adherence to

agreed clinical guidelines or protocols. Evidence from general medicine and radiation oncology suggest that the reasons for adherence or non-adherence to guidelines are complex, and this may not be a good measure of clinical quality under some circumstances [617, 618].

Partial audit is useful for examining individual sections of radiotherapy services and can be carried out as part of the continuum of a QA programme. It is about setting goals and achieving them through a series of small steps.

Internal and external audits typically have different focuses and scopes, but they can complement each other. For example, an internal audit or a self-assessment may be used as a preparation for an external audit and to monitor the implementation of the audit recommendations. Also, the internal audit rather than the external audit, especially in the national and international context, would be more suitable for the review of the radiotherapy outcome mostly owing to the fact that the outcome data reflect the past practice of the centre, not the current practice that is being audited. It is accepted that outcome, the effects of care on the health status of the patient or population, cannot be measured effectively by an external audit team; instead, the team should ensure that methods to measure outcome are in place and that outcome is regularly monitored. Outcome measurement has a stronger base in research than in audit. The external audit, therefore, would typically focus on the structure or setting in which care is given, including the equipment, facilities and human resources, and processes.

Internal audit is usually carried out by a team from within the hospital but outside the department and is useful in monitoring adherence to standards and guidelines and for introducing change. For instance, the internal audit could address a range of individual topics on an ongoing basis, and the external audit the full clinical pathway. This type of approach is consistent with the analogy of a learning curve and continuous rather than spasmodic improvement. For a local clinical audit of a specific element of practice, data collection forms can be developed and used to collect data prospectively for analysis over a defined period of time. This can then be used to analyse the effectiveness and outcomes of a process.

One example of the more common methods of assessing quality of clinical care through an internal audit is the so-called chart round or, in surgical units, the morbidity and mortality audit. In this setting, individual cases are discussed by clinical peers (either only with physicians or in a multidisciplinary context) in order to assess retrospectively whether the best care was given. These meetings may be relatively ad hoc or follow a regularized template with guidelines, minutes and defined outcomes [617, 619, 620]. It is recommended that internal audits be carried out on a regular basis.

External audits should be independent and are carried out by bodies external to the audited centre. Typically, external audits are carried out less frequently than internal audits.

A cycle of routine ongoing internal audits complemented by an external audit has been shown by some centres to be an effective and less onerous system. It may be worth mentioning that having a system of regular clinical audits in place reduces the efforts needed in regulatory control.

Quality audits may be proactive, consisting of a review of ongoing procedures with the aim of improving quality and preventing or reducing the probability of incidents or near misses, or they may be reactive, i.e. focused on a response to a suspected or reported incident or near miss. Examples of proactive and reactive quality audits are the IROC Houston [505] and IAEA and WHO TLD mailed dose programme [214], and on-site review visits to radiotherapy institutions by IAEA experts, respectively [575].

Reactive audit is closely related to incident monitoring, which is a process of reporting and peer review of clinical cases where there is concern regarding an unexpected adverse or potentially adverse outcome. This process may take the form of a local hospital or departmental audit process of so-called significant or sentinel events, a regional or national process [621–624] or an international process [625, 626]. Similar to registries for other medical disciplines including emergency medicine and anaesthesiology [627, 628] that have taken a more comprehensive approach to incident monitoring and error analysis with the introduction of anonymous incident reporting schemes, a registry of radiotherapy incidents and near misses is available through the ROSIS and SAFRON systems [31, 32]. There is now significant evidence to support the view that error, incident and near miss analyses require highly specialized taxonomic skills and a large national or international database of incidents to enable meaningful conclusions to be drawn [628–630]. Despite radiation oncology having a complex technological, physiological and digital systems control interface, similar to activities in anaesthesiology, intensive and emergency care, such programmes have not yet been widely applied [631]; however, there is ongoing work employing specialized approaches of risk management techniques in radiotherapy, such as probabilistic safety assessment, FMEA, events trees and risk analysis matrices [510, 523].

7.7.8. Carrying out the clinical audit

The clinical audit process includes the following phases: pre-audit preparation by both the local and auditing teams, conduct of the audit (entrance briefing, the audit itself including observation, interview, document and record review, physical measurements and exit briefing including recommendations) and the reporting.

7.7.8.1. The preparatory phase

Clinical audit purpose, coverage and scope need to be defined. Specifying the purpose of the audit will have an impact on the audit preparation, process, outcome and acceptance; therefore, it has to be clearly formulated. Clinical audit can cover all or part of the clinical or patient pathway through the health care system, from referral to follow-up, outlining a course of care provided to a patient. It should include the relevant services, departments and professions, as well as individuals involved in the process. Basing the audit on the care pathway [599] or the patient pathway [575] is the most comprehensive approach and will then incorporate all elements of care. The structure and design of the clinical audit also has an impact and must be carefully considered by the institution organizing an audit.

For the radiotherapy centre inviting an audit, it is necessary to collect the high quality data needed for a particular audit. It is also necessary to develop a concept for the management of the implementation of the recommendations generated by the audit, dedicate time to bring about the change, prepare a re-audit plan, allocate sufficient resources and responsibilities and provide means to monitor the change and document improvements.

7.7.8.2. The clinical audit teams

Clinical audit must be a collaborative process between those being audited and the audit team. Clinical audit is a team approach to the evaluation of care and this team approach should be taken by both the centre to be audited and the auditors. Team members will vary depending on the type of audit to be carried out and should be appropriate to the task. For radiotherapy, for example, the external clinical audit team should, therefore, comprise a radiation oncologist, a medical physicist and an RTT, all with extensive experience in their fields.

The local team should be put in place representing all relevant professional groups who will prepare the documentation necessary for the audit, inform all staff of the forthcoming audit and arrange the practical aspects of the audit. It should also ensure that relevant records and findings from partial and internal audits are available for the external audit team to review.

The audit team should have the necessary skills to reflect the purpose and carry out the process of audit with sensitivity, high level knowledge and understanding of the area and the issues that may arise. The team must be independent of the audited organization. It is worth emphasizing that the team has no power to enforce any actions or requirements on the basis of its findings. It must set ground rules and a pre-agreed plan of how to carry out the audit. The auditors must ensure that all conclusions drawn or recommendations made

are based on analysis of all the facts (e.g. poor outcomes may relate to a higher percentage of patients with advanced disease or comorbid disease) substantiated by accurate records of the audit documentation. The auditors must produce an independent assessment and report the findings and recommendations to the audited organization.

For clinical audit to be successful, the correct environment must exist. To be effective, the audit requires access to expertise in the specialist area and any patient related documentation considered necessary in order to review the practice. All staff in the audited department or area must be aware of the audit, its aims and purpose, how and when it will be carried out and what will happen subsequently. Staff must feel comfortable and safe with the audit process in order to fully engage with it. It should be seen as an open and collaborative exploration of any difficulties driven by a genuine desire to understand, appreciate and address problems.

7.7.8.3. Conducting the audit

At the beginning of the audit, the audit team should meet with as many of the staff who will be participating in the audit as possible. At the very least, the heads of each section involved in the audit should be present. The audit team should introduce themselves and give an outline of how they will carry out the audit, the staff they would like to meet and the documentation they require. This should also be a forum for the staff to ask any questions and clarify any misunderstandings of the purpose and process of the audit.

Comprehensive clinical audit should review the overall performance of the centre throughout the patient pathway. In cancer care, this will include diagnosis, decision to treat, treatment prescription, planning and preparation for radiotherapy, delivery of treatment and follow-up. All services, departments, equipment, professions and professionals should be involved in the process, as appropriate. It is essential that the audit team is given access to all relevant areas within the hospital and is able to speak with individuals directly and indirectly involved with the patient care process.

The use of audit checklists is recommended in the National Institute for Clinical Excellence report [599] for the preparation, design and carrying out of clinical audit, and to enable review and change. The IAEA QUATRO guidelines [575] also include a set of comprehensive checklists to assist the team in carrying out the audit and formulating the final report.

An exit meeting should be arranged between the audit team and the staff of the audited institution who had participated in the audit. The audit team should give a detailed and open account of the findings of their audit and invite comment, discussion and clarification of any points raised.

7.7.8.4. The audit report and post audit

A comprehensive report of the findings of the audit should be prepared and circulated within the project team for clarification and agreement. This publication should be completed within an acceptable time frame and should be forwarded to the lead member of the local team for clarification and correction of any factual inaccuracies. Recommendations on actions to take should be given.

Following the audit and receipt of the report, the local team should meet to evaluate the findings and decide on how to act on them. In particular, points to be considered and discussed would need to identify the items that need to be changed and related barriers, taking into account that increased workload or greater responsibility without associated reward or recognition may be required, and on some occasions, perceived loss of power, control or status may arise. These barriers need to be overcome, and this may involve creating an environment for changes: behavioural and attitudinal and changes to the workplace culture, with the latter possibly the most difficult to bring about.

Occasionally, audits may fail to achieve their purpose. There may be many reasons and pitfalls, but the most typical are related to poor communication and organizational problems, for example, failure to engage with all staff and to give sufficient information and feedback, poor relationships between professional groups and within the team, or the lack of a supportive relationship between clinicians and managers. Other problems may be structural, resource related or managerial, for example, insufficient expertise in project design and analysis, lack of an overall plan for the audit, lack of resources [632], improper prioritization, addressing issues that are perceived as less important or setting unrealistic goals.

Sustaining improvement is an important part of the follow-up of the audit. In order to achieve this, continuous monitoring should be in place; in particular, regular internal audits in specific areas need to be organized, with a less frequently scheduled external audit. The follow-up process should also include developing performance indicators and measuring adherence to policies. This process should be dynamic and informed by new developments, research results and new evidence; therefore, a regular clinical protocol review based on new evidence should be encouraged. Also, the value of learning from incidents and near misses cannot be underestimated. Supporting a dynamic and motivated approach to practice improvement among staff is another important aspect for creating an environment that will sustain change. Another point to consider is a combination of retrospective and prospective analysis using the retrospective information to give a historical benchmark enabling the definition of a prospective plan based on fact.

7.8. SUMMARY

This section discusses the management of uncertainties in radiotherapy including strategies for their reduction. Accuracy and precision in radiotherapy are dependent on many factors including appropriate training, adequate staffing, suitable QA and QC tools related to specific techniques or technologies and proper QA and QC procedures.

Requirements of a good QA programme, as stated in ISO 9001:2008 [512], include:

— A set of procedures that cover all key processes in the organization;
— Monitoring processes to ensure they are effective;
— Keeping adequate records;
— Checking output for defects, with appropriate and corrective action where necessary;
— Regularly reviewing individual processes and the quality system itself for effectiveness;
— Facilitating continual improvement.

With the rapid change in technology and increase in complexity, the cost of QA is also increasing. The literature on cost–benefit analysis is increasing; however, it is too early to make quantitative recommendations. Participation in clinical trials influences improvements in evidence based QA procedures and accuracy of radiation treatments. Further research is required in cost–benefit analysis associated with the increasing costs of QA. The accuracy and use of radiobiological model parameters for treatment planning needs further investigation.

In principle, each clinic should determine patient and treatment related uncertainties in their own departments. Based on a UK report [278], a process for determining geometric uncertainties is outlined. It includes a description of imaging procedures and margin recipes.

The display of uncertainties in TPSs remains a challenge with no methods yet implemented on commercial TPSs. This remains an area of research and implementation.

The following should be considered for reducing uncertainties:

— Implementation of clear policies, guidelines and procedures;
— Good documentation both of the policies and procedures as well as the results of acceptance, commissioning and QC test;
— Ongoing education and training for routine procedures and technologies, for new technologies and for brachytherapy.

Factors to consider in the prevention and mitigation of errors:

— Clear information transfer between the various professionals involved in the patient's treatment process;
— Internal and external audits;
— Second checks;
— Peer review of individual cases;
— Incident reporting system;
— Ongoing, up-to-date training.

Specific examples of reducing uncertainties are given for brachytherapy, for head and neck treatments using IMRT, for SBRT and for pelvis and breast treatments.

A brief discussion was provided on adapting treatments to patient changes measured with IGRT, although it is recognized that no clearly defined guidelines exist and that this remains an area for further research.

A summary was provided of external beam audits using TLD or OSLD.

— For the IROC Houston, the uncertainty in dose stated by the institution versus the IROC Houston measured dose is about 1.7% (k = 1), although 3%–5% of photon beams and 5%–8% of electron beams fell outside of the IROC Houston acceptability threshold of 5%.
— For IMRT, based on a series of early trial runs, the IROC Houston has developed criteria of acceptability of 7% in dose and 4 mm DTA. Even with these relatively broad criteria, about 30% of institutions failed to meet these criteria on first attempt.

The IAEA has introduced QUATRO for comprehensive audits. The IAEA dose and clinical auditing programme was reviewed. The requirement for clinical audit has been enshrined in European legislation through the Medical Exposures Directive 97/43/EURATOM.

Clinical audits are considered as a means of improving patient treatment quality. They should include:

— A feedback process.
— Well defined criteria for assessing appropriateness of decisions and actions:
  • For infrastructure and resources;
  • For processes and outcomes.
— Criteria could be specific or generic.

They are usually process measures rather than clinical outcome measures and they are often centred on resources, waiting lists, logistics and infrastructure. Clinical audits can be comprehensive or partial, internal or external, proactive or reactive or a combination of these.

The clinical audit process includes the following phases:

— Pre-audit preparation by both the local and auditing teams;
— Conduct of the audit (entrance briefing, the audit itself including observation, interview, document and record review, physical measurements and exit briefing including recommendations);
— Reporting.

8. RECOMMENDATIONS

This publication has reviewed the total radiotherapy process for both EBRT and brachytherapy. The rationale for determining accuracy requirements is described in detail from radiobiological, clinical, technical and dosimetric perspectives. A review is provided of what baseline levels of accuracy are practically attainable both in EBRT and in brachytherapy. Some discussion is provided on how to manage uncertainties to maintain them at acceptable levels.

This section makes some specific recommendations, which may in many instances be relevant at all three levels of dose prescription and reporting.

It is clear from discussion earlier in this publication and in the corresponding medical and scientific literature that radiotherapy is a very complex process which involves complex technologies — technologies which have considerable risk of doing harm if not handled appropriately. Furthermore, there is a tremendous worldwide variation in the availability and application of these technologies. In some locations, relatively simple 2-D EBRT and brachytherapy is the standard of practice. In other locations, a combination of 2-D radiotherapy and image based 3-D CRT is used. Yet other institutions may have the full range of capabilities, including various brachytherapy procedures as well as IMRT and IGRT. It is clear from the discussion on clinical considerations and levels of accuracy practically achievable that no single number will suffice to describe accuracy requirements in all of radiotherapy. However, general recommendations are applicable to all aspects of radiotherapy.

RECOMMENDATION 1: AS ACCURATELY AS REASONABLY ACHIEVABLE (AAARA)

All forms of radiotherapy should be applied as accurately as reasonably achievable (AAARA), technical and biological factors being taken into account.

The following comments provide a brief perspective on this recommendation:

— The acceptable risk versus benefit (and hence OAR tolerances) may be very different in, for example, early stage cancer of the larynx than in salvage radiotherapy for relapsed Hodgkin's lymphoma. Both are curative treatments but may have very different accuracy requirements to achieve optimal outcomes.
— SRS, SBRT and IMRT have significantly different dosimetric and spatial accuracy requirements and constraints compared with total body irradiation used in conjunction with a bone marrow transplant or total skin electron irradiation for mycosis fungoides.
— Owing to the placement of radioactive sources and the nature of the rapid dose fall-off, brachytherapy treatments have different considerations in terms of accuracy and uncertainties from EBRT.
— Two dimensional radiotherapy with minimal resources has different accuracy considerations compared with IMRT combined with IGRT.
— A high dose treatment involving a target volume near a critical normal tissue such as the eye or spinal cord might involve a substantially greater time and effort for planning and delivery compared with a low dose treatment for an emergency relief of spinal cord compression.

In all circumstances, normal tissue tolerance considerations should be recognized. Any treatment plan which approaches the potential for any clinical complication requires appropriate QA and corrective effort.

Based on these considerations, it is clear that a single statement about accuracy requirements, i.e. 5% in radiotherapy, is an oversimplification. The accuracy requirements are dependent on both technological considerations as well as biological and clinical concerns. Ultimately, the cost in terms of effort, likelihood of possible complications, the possibility of a recurrence and the impact on other patients in an environment of limited resources must be balanced against the benefit that will be gained for the patient in terms of cure and improved quality of life.

RECOMMENDATION 2: ICRU RECOMMENDATIONS

For consistency in prescribing, recording and reporting of EBRT and brachytherapy, the recommendations of the ICRU should be implemented. When relevant, the recommendations of other recognized consensus groups should be implemented.

For EBRT, the ICRU concepts of GTV, CTV and PTV should be used as part of the treatment planning process [17–21]. GTV and CTV are used in brachytherapy in the same way as in EBRT, since these volumes are anatomical and clinical concepts applicable to any radiotherapy technique. For gynaecological brachytherapy, the Gynaecological GEC-ESTRO working group [171, 172] introduced the adaptive concepts of high risk CTV and intermediate risk CTV. The application of PTV in brachytherapy is more controversial and has not yet been specifically dealt with in the ICRU reports. PTV safety margins can only be selectively applied in certain directions, whereas it is not possible to compensate for uncertainties in other directions at the time of dose planning. The dose distribution in the PTV is not representative of the dose distribution in the CTV. The role of the PTV in brachytherapy remains to be clarified as image guided brachytherapy becomes more mature.

For brachytherapy, ICRU Report 58 [124] contains many suggestions on how to report dose homogeneity and other implant quality parameters in the absence of 3-D imaging or DVH capabilities. Similarly, ICRU Report 38 [123] makes many useful suggestions for specifying dose in intracavitary brachytherapy. Where practical and appropriate, dose specification criteria endorsed by recognized consensus groups in their reports (e.g. ICRU, American Brachytherapy Society, AAPM and GEC-ESTRO) in the most recent form should be used to facilitate interinstitutional communication.

For image based EBRT where DVHs are available, ICRU Report 83 [21] should be used as guidance. Generally, this will involve prescriptions based on D_V in which the $D_{50\%}$ and $D_{98\%}$ and $D_{2\%}$ would also be recorded. Where image based radiotherapy is not yet available, prescriptions should be to the ICRU reference point and minimum and maximum doses should be reported [17, 18]. For special circumstances, where the dose distribution is less uniform, such as in SRS, other prescription methods may be necessary, such as '95% of the PTV should get at least a dose of *x* Gy'. Recommendations of clinical trials groups or other consensus bodies should also be taken into account.

RECOMMENDATION 3: LEVELS OF ACCURACY THAT ARE PRACTICALLY ACHIEVABLE

The data found in Tables 15 and 16 for EBRT and brachytherapy, respectively, should be used as a guide for estimating the levels of accuracy that are practically achievable. The tables also provide suggested action levels in cases where deviations occur that are significantly beyond the normal range of values.

Tables 15 and 16 contain 4 columns, with column 1 defining the specific quantity being evaluated. Column 2 indicates the dose related uncertainty estimate at the $k = 1$ level (conventionally indicated as the one standard deviation or the one sigma level). Column 3 indicates the spatial uncertainty at the $k = 1$ level. Column 4 gives the level at which corrective action should be considered. This is determined at approximately the $k = 2$ level (approximately 2 SD or 2 sigma), although sometimes lower values are given. 'Approximate' is used in this context since the numbers are rounded to a near value that is considered reasonable in the context of corrective actions. While most of the data are derived from empirical published results, some input is also based on expert consensus, which is generally not evaluable by statistical means.

It should be emphasized that Recommendation 1 has priority, i.e. the AAARA principle should be invoked in every radiotherapy institution. It is extremely difficult to include every treatment scenario in a single table with precise quantitative data. However, Table 15 on page 244 does provide a sample that could be considered in every institution and a local version should be developed that includes typical accuracies that are possible along with action levels. Target definition is perhaps the extreme example of these types of variations. An action level cannot be stated without a description of the specific site based approach and technique. Furthermore, an institutional review of target definition needs to be performed by a peer review process, perhaps in the context of QA rounds.

RECOMMENDATION 4: DOSIMETRY AUDITS

An independent dosimetry audit should be performed for every new installation that is about to embark on radiation treatments. In addition, regular (e.g. annual) audits should be performed using remote services or on-site visits (or equivalent).

The term 'new installation' in this recommendation is intended to include new treatment devices such as ^{60}Co teletherapy machines, linacs, HDR

brachytherapy afterloading units or other speciality treatment machines such as helical tomotherapy and CyberKnife, new TPSs and possibly new dose calculation algorithms. In addition, the introduction of any major new technique such as IMRT, or a major software change, can also benefit from an independent audit. Such an audit not only minimizes the risk of major errors, but also aids in improving the accuracy of radiation treatments.

A more comprehensive clinical audit as recommended in the 97/43/EURATOM Directive [24] and provided, for instance, by the IAEA QUATRO audits, are advisable as well since these cover much more than dosimetry audit aspects. Such audits can be performed on a less frequent basis, depending on the outcome of the report of the audit.

RECOMMENDATION 5: COMPREHENSIVE QUALITY ASSURANCE (QA)

A comprehensive QA programme should be in place in every radiotherapy department. Routine QC procedures should be implemented according to published recommendations and local regulatory requirements.

Comprehensive QA programmes are recommended by the IAEA [563] through its basic safety standards and by European law through EURATOM 97/43 [24]. The AAPM and ESTRO have produced many reports advising on QA activities of different techniques and technologies. Many of these have been referenced in earlier parts of this publication.

A comprehensive QA programme includes a QA committee with representation from the three major professional groups in radiotherapy [509]. The function of this committee is to provide a review of the QA activities in place and a reporting process to provide accountability that the QA and QC procedures are being carried out at the recommended frequencies. Furthermore, the QA committee should also develop a reporting process in which any incidents and near misses should be reported to this committee and reviewed on a regular basis.

RECOMMENDATION 6: EDUCATION AND TRAINING

Professional staff should have appropriate education and training. Staffing levels should be adequate to ensure safe and accurate delivery of the radiation doses. The radiotherapy staff should also have the support of the institution's administrative leadership.

Staffing guidelines have been suggested by various organizations, e.g. Refs [513, 633–635]. Appropriate increases in staffing should be considered

as new and more complex technologies (e.g. IMRT, IGRT, respiration correlated imaging and delivery) are being implemented. Appropriate training for any technology, including upgrades and enhancements, is a prerequisite before that technology is put into clinical practice. All national and regional regulations regarding staffing levels, education, credentialling and continuing professional development need to be implemented. The IAEA report on Setting Up a Radiotherapy Programme [513] defines the minimum staffing levels for a basic radiotherapy facility. Support by the institution's administrative leadership is essential to allowing the radiotherapy team to accomplish all of the necessary tasks and obtain the appropriate tools required to ensure the accurate and safe delivery of radiation doses.

RECOMMENDATION 7: CLINICAL TRIALS AND REPORTING UNCERTAINTIES

"For reporting purposes, as part of clinical trials, publications, etc., the uncertainties associated with the relevant quantities and parameters should be estimated and presented. Such an estimate could be stated as follows: "Doses are judged to be accurate to *x* percentage of the prescription dose, or to be within *y* mm of the true location (at the *z* percentage CL [confidence level])." The uncertainty estimate might be based on generic analyses of the particular class of treatment, in which case it should be so-noted." (This recommendation is quoted from ICRU Report 83 [21] and is repeated here as it is very relevant to the context of this publication.)

RECOMMENDATION 8: APPLICATIONS TRAINING ON RADIOTHERAPY EQUIPMENT

Manufacturers of radiotherapy equipment should provide detailed operating and application training for all equipment, recognizing that the final responsibility associated with clinical implementation lies with the professionals in the clinical departments.

Advances and changes in the technology of radiotherapy evolve continuously. Novel ideas and their associated marketing strategies should not distract from clinical judgement and standard practice and should be subjected to adequate peer reviewed evaluation.

RECOMMENDATION 9: RESEARCH

A number of areas of research should be pursued to aid with improvements in providing accurate and safe radiotherapy with reduced uncertainties. Examples of these are summarized below in no particular order of priority.

(a) Display of uncertainties as part of the treatment planning process

Section 7.5 described some options for the display of treatment uncertainties as part of the treatment planning process. However, to date, none of these methods have found their way into commercial TPSs. Further research is required into practical methods of displaying and using treatment uncertainties as an aid to decision making and as a means of developing robust treatment plans that minimize the impact of uncertainties and provide the maximum therapeutic benefit for the patient.

(b) Probabilistic definition of CTV

Section 5.2.2 discussed the definition of the CTV and made it clear that it would be advantageous to introduce a probabilistic definition, e.g. to choose the CTV based on a defined probability of that region needing to be treated.

(c) Clarifying the PTV concept for brachytherapy

In brachytherapy, the determination of the PTV is more complex than it is for EBRT. As indicated in Section 5.3.2, the application of margins should be based on a systematic evaluation of uncertainties. So far, only a few studies have been published on uncertainties in 3-D image guided intracavitary brachytherapy. Further work on this is clearly warranted. Specifically, it would be of great interest to analyse the stability of different applicators and fixation techniques [171].

(d) The application of radiobiological models in the treatment planning process

As indicated in Section 7.5, radiobiological models that calculate TCP and NTCP are now available in a number of commercial TPSs. The quantification of accuracy and uncertainties in radiobiological model predictions is very complex. Generally, it is agreed that these models are probably not very accurate in their capability of predicting outcomes in an absolute sense. More research and more results from clinical studies are required to assess the capabilities of radiobiological models to predict clinical outcome and to define their role within the clinical treatment planning process.

(e) Cost–benefit analyses

The issue of how much time, energy and cost should be invested in improving accuracy and reducing uncertainties was raised in Sections 7.2 and 7.3. With ever increasing complexity and a consequent increasing workload and increasing QA requirements, there is the risk that the cost will outweigh the benefits. However, so far there have been relatively few studies that have performed quantitative analyses to determine at what point the extra costs are no longer of significant value. Clearly, this is another area requiring further research.

(f) Contribution to small field dosimetry

There is a need to provide a standard methodology, in the form of a dosimetry code of practice, for the reference and relative dosimetry of small static fields used in MV photon beams, in particular in stereotactic treatments and in IMRT. A code of practice for small field dosimetry currently being prepared by the IAEA is intended for use by clinical medical physicists for the determination of absorbed dose to water in this type of narrow beam under configurations where existing dosimetry protocols do not apply. The recommendations given in the code of practice, especially those relating to the type of dosimeters to be used and correction factors to be applied for the determination of relative beam factors, are given for specific clinical machines that use small fields. The data are extracted from the literature. There is a need for more data to ensure the robustness of the recommendations given in the code of practice. In addition, more work is needed for the development of absorbed dose to water standards in small fields.

Guidelines for the dosimetry of uniform and non-uniform fields that are composed of small subfields, such as those used in IMRT, are not included in this code of practice. More research is needed in this area to collect additional data for the purpose of preparing harmonized and consistent international recommendations in this area.

(g) Consistent description of inter- and intraclinician variability in defining target volumes

As indicated in Section 5.1, no consistent terminology has yet been developed to measure and report inter- and intraclinician variability. A wide variety of qualitative and quantitative descriptors have been used [110–121]. There is a need for a consensus on terminology and methods in this area.

(h) Guidelines for ART

The availability of IGRT and daily image guidance can provide information on changes to the set-up and target volume that would otherwise not be detectable. This may result in the need to re-optimize the treatment plan. However, the criteria and guidelines for determining when to adapt remain elusive. More studies with various groups of tumour sites are needed to determine criteria for repeat CT imaging and replanning for patients undergoing radiotherapy.

(i) IVD in brachytherapy

As indicated in Section 6.5.9, the use of IVD in brachytherapy is not widespread and therefore its impact on safety, quality and accuracy is largely unknown compared with the equivalent methodologies used in EBRT.

(j) Use of heterogeneity corrected dose calculations in brachytherapy

The current methodology used for treatment planning and dose calculations for brachytherapy are far behind what is employed for EBRT. It is crucial that more CT based imaging be used for brachytherapy and that dose distributions are calculated accounting for the different tissue heterogeneities near or within the target.

TABLE 15. ESTIMATES OF EXTERNAL BEAM RADIOTHERAPY RELATED UNCERTAINTIES

Quantity	Dose uncertainty ($k = 1$)	Spatial uncertainty or CT number uncertainty ($k = 1$)	Action level* ($\sim k = 2$)
Ionization chamber reference dosimetry			
Co-60 (SSDL)	0.75%		1.5%
Co-60 (clinic)	0.9%		1.8%
High energy photons (clinic)	1.5%		3.0%
Electrons (clinic)	1.4–2.1%		5.0%
Combined uncertainty	1.6–2.6%		

for footnotes see p. 248

TABLE 15. ESTIMATES OF EXTERNAL BEAM RADIOTHERAPY RELATED UNCERTAINTIES (cont.)

Quantity	Dose uncertainty ($k = 1$)	Spatial uncertainty or CT number uncertainty ($k = 1$)	Action level* ($\sim k = 2$)
TLD audits			
RPC — photons	1.7%		5.0%
RPC — electrons	1.7%		5.0%
IAEA — MV photons	2.0%		5.0%
IAEA — + Co-60	2.4%		5.0%
Treatment machine related uncertainties			
Lasers (non-IMRT/SRS/SBRT units)		1–2 mm	2 mm
Relative dose ratios (on axis and off axis)	2%		3%
Beam monitor stability (output constancy)	2%		3%
Machine jaw positioning		<1 mm	2 mm
Wedges	2%	2 mm	3%/3 mm
MLC static position		≤1 mm	2 mm
MLC dynamic position		≤1 mm	≤1 mm
MLC transmission	Several%		—
Table top/couch position		Variable	—
Table top/couch attenuation	Up to 20%		—
Patient positioning		< 1–15 mm	+
In vivo dosimetry	2–5%		7%
Imaging related uncertainties for treatment planning			
CT			
Image geometry		< 2 mm	3 mm

for footnotes see p. 248

TABLE 15. ESTIMATES OF EXTERNAL BEAM RADIOTHERAPY RELATED UNCERTAINTIES (cont.)

Quantity	Dose uncertainty ($k = 1$)	Spatial uncertainty or CT number uncertainty ($k = 1$)	Action level* ($\sim k = 2$)
Image resolution		< 1 mm	2 mm
CT number accuracy		20 HU	30 HU
Imaging dose	1–4 cGy		—
MR			
Image geometry		<1–15 mm	2 mm
Image resolution		<1 mm	1.5 mm
Imaging dose	0 (no dose)		
PET			
Image geometry		<2 mm	3 mm
Image resolution		4–7 mm	—
Imaging dose	15–25 mSv		—
Ultrasound			
Image geometry		<1 mm	1.5 mm
Image resolution		0.3–3 mm	1 mm
Imaging dose	0 (no dose)		—
Imaging related uncertainties for image guidance			
Port films			
Image geometry		~5 mm	7 mm
Imaging resolution		Poor	
Imaging dose (double exposure for localization)	~4 cGy		—
EPIDs			
Image geometry		1–2 mm	2 mm
Imaging resolution		<1 mm	2 mm
Imaging dose (double exposure for localization)	~2 cGy		—

for footnotes see p. 248

TABLE 15. ESTIMATES OF EXTERNAL BEAM RADIOTHERAPY RELATED UNCERTAINTIES (cont.)

Quantity	Dose uncertainty ($k = 1$)	Spatial uncertainty or CT number uncertainty ($k = 1$)	Action level* ($\sim k = 2$)
MV CT — helical tomotherapy			
Image geometry		1–2 mm	2 mm
Imaging resolution		1.6 mm	2 mm
CT number accuracy		30 HU	40 HU
Imaging dose (organ dose)	1–3 cGy		3 cGy
kV CBCT			
Image geometry		1 mm	2 mm
Imaging resolution		<1 mm	1 mm
CT number accuracy		20–100 HU	—
Imaging dose (organ dose)	5–25 cGy		—
MV CBCT			
Image geometry		1 mm	2 mm
Imaging resolution		2 mm	2 mm
CT number accuracy		80 HU	—
Imaging dose (organ dose)	5–10 cGy		—
Target definition (site dependent)		5–50 mm	—
Normal tissue definition		5–20 mm	—
TPS uncertainties			
Central axis data	2%		3%
Off-axis, high dose, low dose gradient	2%		3%
High dose gradient		2–4 mm	3 mm
Low dose, low dose gradient	3–5%		5%

for footnotes see p. 248

TABLE 15. ESTIMATES OF EXTERNAL BEAM RADIOTHERAPY RELATED UNCERTAINTIES (cont.)

Quantity	Dose uncertainty ($k = 1$)	Spatial uncertainty or CT number uncertainty ($k = 1$)	Action level* ($\sim k = 2$)
Build-up	50% ++		20%
Non unit density tissues	2–20%		4%
Patient (re)positioning			
Intracranial		1–2 mm	+
Head and neck		2–8 mm	+
Spine		1–4 mm	+
Thorax		10–20 mm	+
Lung — SBRT		2–5 mm	+
Breast		2–10 mm	+
Abdomen		5–15 mm	+
Prostate		3–15 mm	+
Pelvis		7–15 mm	+
Extremities**		3–5 mm	+
EBRT end to end in phantom	3–10%	2 mm	5–15%/3 mm
EBRT end to end in patient**	5–10%	5 mm	5%/4 mm

* Action level = maximum permissible error, dash (—) indicates no data available or it is not possible to take any action on this parameter

** Expert consensus

\+ Action levels should be determined in individual clinics dependent on the type of immobilization used.

++ Older TPS algorithms handled build-up calculations poorly. Newer algorithms can perform better than 50% uncertainty.

TABLE 16. ESTIMATES OF BRACHYTHERAPY RELATED UNCERTAINTIES

Quantity	Dose uncertainty ($k = 1$)	Spatial uncertainty ($k = 1$)	Action level* ($k = 2$)
Dose at a reference point in water			
Air kerma strength in clinic	1.3%		2.6%
Dose calculation			
In water, compared with published data (all sources)	1.6–3.6%		3.6–7.2%
Inhomogeneities (estimated including inter-seed attenuation, shielded applicators and lack of full scatter)	10%**		20%**
Dose delivery			
HDR			
Source calibration	1.5%		3.0%
Source position		1 mm	2 mm
Temporal accuracy	<0.5%		1%
Dose delivery (including registration of applicator geometry to anatomy)	4–7%		8–14%
Inter- and intra-fraction changes (estimated including contouring uncertainties)	5–11%		10–22%
LDR/MDR			
Source calibration	1.3%		2.6%
Linear uniformity	<5%		<10%
Source position		2 mm	4 mm
Temporal accuracy	1 s		2 s
Dose delivery (estimated including contouring uncertainties and anatomy changes during delivery)	<7.5%		15%

* Action level = maximum permissible error

** For high energy photon emitting sources, these values are likely to be much smaller.

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ABBREVIATIONS

2-D	two dimensional
3-D	three dimensional
4-D	four dimensional
AAARA	as accurate as reasonably achievable
AAPM	American Association of Physicists in Medicine
ART	adaptive radiotherapy
BIPM	International Bureau of Weights and Measures (Bureau International des Poids et Mesures)
CBCT	cone beam computerized tomography
CRT	conformal radiotherapy
CT	computerized tomography
CTV	clinical target volume
DICOM	Digital Imaging and Communications in Medicine
DRR	digitally reconstructed radiograph
DTA	distance-to-agreement
DVH	dose–volume histogram
EBRT	external beam radiotherapy
EORTC	European Organisation for Research and Treatment of Cancer
EPID	electronic portal imaging device
ESTRO	European Society for Radiotherapy and Oncology
EUD	equivalent uniform dose
EURATOM	European Atomic Energy Community
FMEA	failure modes and effects analysis
fMRI	functional MRI
GEC	Groupe Européen de Curiethérapie
GTV	gross tumour volume
HDR	high dose rate
HU	Hounsfield Unit
ICRP	International Commission on Radiation Protection
ICRU	International Commission on Radiation Units and Measurements
IGRT	image guided radiotherapy
IMRT	intensity modulated radiotherapy
IR	infrared
ISO	International Organization for Standardization
ITV	internal target volume
IVD	in vivo dosimetry

LDR	low dose rate
LED	light emitting diode
MBDCA	model based dose calculation algorithm
MLC	multileaf collimator
MOSFET	metal oxide semiconductor field effect transistor
MR	magnetic resonance
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NICE	National Institute for Health and Clinical Excellence
NTCP	normal tissue complication probability
OAR	organ at risk
OSLD	optically stimulated luminescence dosimetry
PDR	pulsed dose rate
PET	positron emission tomography
PRV	planning organ at risk volume
PSDL	primary standards dosimetry laboratory
PTV	planning target volume
QA	quality assurance
QALY	quality adjusted life years
QC	quality control
QM	quality management
QUATRO	Quality Assurance Team for Radiation Oncology
RAKR	reference air kerma rate
RC-CT	respiration correlated CT
RC-PET	respiration correlated PET
ROI	region of interest
ROSIS	Radiation Oncology Safety Information System
IROC Houston	Radiation Oncology Core Houston Quality Assurance Cente
RTOG	Radiation Therapy Oncology Group
RTT	radiotherapy technologist
RVR	remaining volume at risk
RVS	record and verify system
SBRT	stereotactic body radiotherapy
SD	standard deviation
SPECT	single photon emission tomography
SRS	stereotactic radiosurgery
SSD	source-surface distance
SSDL	secondary standards dosimetry laboratory
SUV	standardized uptake value
TCP	tumour control probability
TG	task group

TLD	thermoluminescent dosimetry
TNM	tumour-node-metastasis cancer staging system
TPS	treatment planning system
TV	treated volume
VMAT	volumetric modulated arc therapy
WHO	World Health Organization

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In recent years, there have been major developments in external beam radiotherapy, moving from simple two dimensional techniques to three dimensional image based conformal radiotherapy, intensity modulated radiotherapy, image guided radiation therapy and respiratory correlated four dimensional techniques. Similarly, brachytherapy has also seen an increase in the use of three dimensional image guided adaptive approaches. The underlying principle of these advances is an attempt to improve patient outcome while maintaining an acceptably low level of normal tissue complications and morbidity. While multiple reports have defined accuracy needs in radiation oncology, most of these reports were developed in an earlier era with different radiation technologies. In the meantime, the uncertainties in radiation dosimetry reference standards have improved and more detailed patient outcome data are available. In addition, no comprehensive report on accuracy and uncertainties in radiotherapy has been published. The IAEA has therefore developed this publication, based on international expert consensus, to promote safer and more effective patient treatment. It addresses accuracy and uncertainty issues applicable to the vast majority of radiotherapy departments including both external beam radiotherapy and brachytherapy, and considers clinical, radiobiological, dosimetric, technical and physical aspects.

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ISSN 2075–3772