

Accuracy required and achievable in radiotherapy dosimetry: have modern technology and techniques changed our views?

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Abstract. In this review of the accuracy required and achievable in radiotherapy dosimetry, older approaches and evidence-based estimates for 3DCRT have been reprised, summarising and drawing together the author's earlier evaluations where still relevant. Available evidence for IMRT uncertainties has been reviewed, selecting information from tolerances, QA, verification measurements, in vivo dosimetry and dose delivery audits, to consider whether achievable uncertainties increase or decrease for current advanced treatments and practice. Overall there is some evidence that they tend to increase, but that similar levels should be achievable. Thus it is concluded that those earlier estimates of achievable dosimetric accuracy are still applicable, despite the changes and advances in technology and techniques. The one exception is where there is significant lung involvement, where it is likely that uncertainties have now improved due to widespread use of more accurate heterogeneity models. Geometric uncertainties have improved with the wide availability of IGRT.

1. Introduction

There have been a range of published estimates of the accuracy required and achievable in radiotherapy dosimetry over at least the last 30+ years since ICRU report 24 [1] provided a summary in 1976. However most of these [see reviews in 2,3] have related to 3D CRT methods and hence before IMRT and the other rapidly advancing technologies and techniques in place today. Thus we are currently confronted with the critical need for accurate, practical dosimetry for commissioning, development, QA and both pre-treatment and in vivo verification for these technologies, for clinical practice and also for research; indeed dosimetry measurements, methods and resource requirements are recognized as a potential limiting step in the widespread clinical application of some technologies. The need has moved from 'simple' 1D and 2D dosimetry to requirements at all levels from 1D to 4D for IMRT, IGRT, ART, and 4D motion-managed RT [4]. The objective of all this development is to improve the balance of tumour control versus normal tissue complication incidence for curative treatments and to improve quality of life for patients receiving palliative treatments. However, these outcomes will not be safely achieved unless there are also matched improvements in accuracy in treatment delivery systems and appropriate dose measurement and modelling systems to support this [5]. There is considerable interest in this topic currently; with a forthcoming book from an IAEA expert group on accuracy and uncertainties in radiation therapy due to appear in 2013, lead by J. van Dyk.

This review is an update of the current author's series of evaluations of dosimetric accuracy for radiation therapy over the last 25 years [2,6-12] and repeats some text from those, where still relevant. It is limited to external beam megavoltage x-ray therapy and considers conventional and complex



treatment methods, but essentially those that are applicable in the majority of departments. In general it considers curative treatments, as the treatment processes must be set up with the greatest accuracy to deliver those. In general, too, it considers best practice based on having comprehensive quality systems in place, including relevant QA for all steps and parts of the radiotherapy process [13-16]. This recognises that poor practice, in the extreme as evidenced in widely reported accident and error situations [17-18], can considerably worsen the accuracy achieved. Many of the estimates of accuracy have involved uncertainty analyses with best guesstimates of values. However, wherever possible here values are based on evidence, using optimum values as then representative of 'achievable' values and hence as the levels to be aimed for.

2. What is accuracy in radiotherapy dosimetry?

The term *accuracy* in radiotherapy is often used loosely. Firstly, absolute accuracy must be distinguished from precision or reproducibility. Overall uncertainty is a combination of type A uncertainties, assessable by statistical means (often loosely referred to in practice as random) and type B uncertainties, which must be assessed by other means (often loosely referred to in practice as systematic). Thus random uncertainties can be estimated from repeated independent observations and can be expressed as a standard deviation (sd), assuming a normal distribution. Systematic uncertainties on the other hand can only be estimated by an analysis of the process under consideration, assigning reasonable variations to parameters where the uncertainties are by definition not exactly quantifiable. They can be expressed as an effective sd, being taken as the estimate of the limits within which the correct value is expected to occur in around 70% of cases. Uncertainties of both types (sd or effective sd) can be combined in quadrature to provide an estimate of overall uncertainty [19-21]. As is well recognised, systematic errors contribute to absolute deviations from the 'correct' value in any situation whilst random errors are associated with precision. However the distinction can become blurred in certain circumstances. In radiotherapy, within one centre and one radiation modality, it is reproducibility of dosimetry that is critical. However in transferring experience from one centre to another or in intercomparing results between centres or between modalities, for example in clinical trials, some systematic uncertainties also become significant. In intercomparisons between a number of centres, some systematic uncertainties are effectively randomly distributed (eg beam calibration). On the other hand some systematic uncertainties are common to all participants and can be omitted from routine consideration eg. those associated with a given dosimetry protocol if all participants follow the same protocol, or those associated with basic physical data if the protocols involved are all based on the same consistent set. Such factors only require consideration when estimating absolute accuracy but play no part in estimations of dosimetric consistency, except where different modalities may be being compared. Thus a clear understanding is required of which uncertainties require inclusion in any given situation. However in practice it is often difficult to separate the two types [22].

As a further point, it should be noted that any stated values should also have their meaning defined. All values stated in the following, whether for individual parameters or for cumulative values where all involved uncertainties are combined in quadrature, are given as one standard uncertainty (or the sd for normal distributions, or effective sd for combined type A and type B uncertainties where normal distributions are assumed). To express the uncertainties in terms of confidence intervals, the standard uncertainty, u_c , is multiplied by the coverage factor, k . Where a normal distribution applies, $k=2$ provides a confidence interval of approximately 95% and $k=3$, of approximately 99%. Further information on uncertainties and confidence intervals can be obtained from a range of sources, eg [20-21]. It may be noted that various uncertainties in radiation treatment are not well represented by Gaussian distributions, but by one of a range of other possibilities, which can make analysis more problematic. In addition, for geometric uncertainties in radiation treatment, the combination of the two types of uncertainties is generally dealt with via margin recipes, assigning different importance to each type to reflect their impact [23]. Lastly, it may be noted that combination in quadrature ($u_{\text{total}}^2 =$

$u_a^2 + u_b^2 + \dots$) generally results in the larger uncertainties dominating the overall uncertainty, with consequences for consideration of where effort should best be applied to reduce uncertainties.

In summary, then, accuracy is a measure of how close a result is to the 'true value', whilst precision is a measure of the spread of independent determinations of the result where the latter is generally determined as the sd of the distribution of results.

3. Required accuracy in radiotherapy dose delivery based on the clinical evidence

3.1. Dosimetry

The clinical requirements on accuracy are based on evidence from dose response (dose effect) curves for tumour control probability (TCP) and for normal tissue complication probability (NTCP). These typically have sigmoidal shapes, with a threshold dose, relatively steep rises and saturation (100% effect) at high enough doses. Generally, in practical clinical situations the two relevant curves overlap along the dose axis [eg see 2], such that the dose to the tumour is limited by what can be tolerated by the most at-risk normal tissues. Radiotherapy optimisation and many advances in technology and techniques are aimed at improving this balance, ie maximising tumour control while maintaining tissue complications at an acceptable level. The steepness of the given TCP or NTCP curve versus dose defines the change in response expected for a given change in delivered dose. Thus uncertainties in delivered dose translate into either reductions in TCP from the optimised expected value, or increases in NTCP from the optimised expected value, both of which worsen the clinical outcome. The accuracy requirements are defined by the most critical (steepest) curves, observed for normal tissues or steeply responding tumours. Steepness data of clinically derived TCP and NTCP is reviewed in a number of publications, eg. [1,2,10,19,24] indicating wide variations in the slopes of the curves depending on tissue, effect, uncertainties in clinical dosimetry and in assessing outcomes, radiobiological variability, technique used, dose per fraction, etc. At the steepest parts of the dose-response curves, and for the steepest curves, 5% changes in dose can produce 10-20% changes in TCP and 20-30% changes in NTCP. Brahme [25-26] and others expressed these steepnesses in terms of the normalised dose gradient, γ , the percentage change in TCP or NTCP per 1% change in dose. This parameter will typically be greatest (curve steepest) in the 50% effect region, γ_{50} , but will vary depending on which part of the curve is of interest (generally lower than 50% for NTCP and hopefully greater than 50% for TCP; however it is often the value at 50% effect that is compared). The steepest clinical curves are for normal tissue effects, with γ_{50} values of up to 6 or 7% per 1% change in dose [26-27] and as a general requirement, it is necessary to base accuracy recommendations on the steeper dose-effect relationships encountered in routine clinical situations, as overall process accuracy must be established to meet these more demanding situations. It may be noted that whilst there have been new clinical data and many other studies of such information over recent years, including reviews such as the QUANTEC report/s for normal tissue effects (QUantitative Analysis of Normal Tissue Effects in the Clinic) [28], these general values are still applicable.

ICRU Report 24 [1] reviewed the more limited information available up to that time and considered that $\pm 5\%$ accuracy was required in the delivery of absorbed dose to the target volume, but that in critical situations $\pm 2\%$ may be required. However it was recognised that the latter figure was not generally realisable in then current practice. It was not made clear what uncertainty value the figures represented. Mijnheer et al [19] obtained a figure for required accuracy by considering normal tissue complications. They considered the steepness of dose-effect curves in terms of the percentage increase in absorbed dose to produce a change in the probability of normal tissue complications from 25% to 50%. A representative value of 7% was taken for this relative gradient and it was concluded that any transfer of clinical information from one centre to another will involve unacceptable risks of complications if overall uncertainty in absorbed dose is larger than this value. This was then assigned to the 2 sd level, resulting in a value of 3.5%, as one relative sd, as the general accuracy requirement on absorbed dose delivery. Brahme et al [26] considered the effects of variations in dose on tumour control for typical values, showing that the most critical loss in tumour control

introduced by dosimetric inaccuracy is found at the highest level of tumour control probability. A general figure of 3% (relative sd) on the delivered absorbed dose to the patient was recommended as the tolerance level on accuracy in dose delivery, in order to keep variations in the probability of tumour control within acceptable limits. Thus overall a figure of 3% sd can be taken as a currently recommended general accuracy requirement, being considered as one relative sd, on the value of the dose delivered to the patient at the dose specification point. This implies there is a 95% probability that changes will be clinically observable for dose changes at twice this level, in situations described by the steeper dose-effect relationships. This is also consistent with more anecdotal evidence on clinical observations following inadvertent dose changes due to dosimetric errors [22].

Considering the different effects of systematic and random dose uncertainties on TCP and NTCP may give a further perspective. Overall, systematic uncertainties in the dose delivered will translate directly into changes in TCP and NTCP for the population of patients involved (or also as expected for an individual patient, but likely to be complicated by the effect of individual radio-sensitivity). For random uncertainties the effect is much more variable and depends on the steepness of the curve, the point of interest on the curve (where effects will now be greatest where the curvature of the curves is greatest), the level of uncertainty, etc. Generally, random uncertainties will smear effects and will reduce TCP and increase NTCP but in a less immediately clear way. It must be remembered too that some things randomly distributed between patients may be systematic for an individual patient. These considerations might indicate that tighter requirements are necessary on systematic uncertainties, of say better than 1 or 2%, with requirements still of around 3% on random uncertainties, to keep the changes in TCP and NTCP within acceptable tolerances (eg also within around 3-5%). Together these also imply that the overall required accuracy in absorbed dose distributions should be in the region of 3-5%. This may change for high-dose per fraction hypofractionated treatments, which would be significantly less forgiving of random uncertainties. Interestingly, these two sets of figures tie up with the levels of tolerance we typically set for pre-treatment or in-vivo verification of IMRT dose and dose distribution, yet we set these for typically 95% (of points or pixels) agreement, whether in phantom, 2D or 3D, or in vivo [29].

3.2. Geometry

In radiotherapy, geometric uncertainties translate to dosimetric uncertainties. Geometric uncertainties arise for a variety of reasons, including treatment machine specifications and tolerances, simulation and treatment set-up, patient or organ movement during treatment and changes of patient shape between fractions. Clinical information is limited concerning the effects of such variations on treatment outcome. Geometric miss of tumour/target will obviously decrease tumour control probability, whilst overlap of fields with adjacent normal structures, particularly critical organs, will be detrimental in terms of normal tissue complications. In general appropriate margins are defined around the target volume to allow for these uncertainties so it is difficult to find definitive data on the effect of inaccuracies. Conventional approaches to this have been to model the effects of overlap onto organs at risk or reduced coverage of target volume [e.g. 26], or to consider the various sources of uncertainty, combine them to give an overall value and then use the best practically achievable figures as the level to be recommended. On this basis the AAPM [30] arrived at a figure corresponding to 5 mm, one effective sd. Mijnheer et al [19] considered a wider set of data and recommended an accuracy of positioning of field edges and shielding edges of 4 mm, one sd, relative to expected anatomy. Even with this conventional approach, the requirements will be clearly more restrictive for stereotactic radiotherapy approaches, where geometric accuracy of around 1mm is required and again hypofractionated single or small number of fraction treatments are less forgiving of random geometric uncertainties.

However this approach no longer holds so clearly for newer technology and techniques, for at least three reasons; one is that geometric uncertainties now affect dose distribution within the target volume for IMRT and not just at the volume edges or interfaces to organs at risk; also IGRT, adaptive techniques and motion management techniques have provided the facility to reduce the uncertainties

significantly as compared to conventional approaches; and lastly the desire to dose-escalate based on these techniques demands greater attention be paid to reducing margins on the boundary between PTV and OaR (PRV concepts), but also taking care not to compromise on TCP. Uncertainties now must also consider imaging system geometric calibration, QA and tolerances, and the performance of overall IGRT systems including image registration and corrective actions [31]. The BIR in a 2003 report [32] provides a useful summary and detailed discussion of geometric uncertainties in general and also for particular treatment sites, whilst a more recent UK multidisciplinary report covers in detail how to ensure geometric accuracy [33]. The evidence points to anatomical variations of the order of a few mm in conventional head and neck treatments to up to a few cm in pelvic and thoracic regions. This gives rise to typical uncertainties for conventional treatments [34], for example, of the order of 1-2, 4 and 4 mm systematic (Σ) for head and neck, pelvic and thoracic treatments respectively and 1-2, 4 and 6 mm for random (σ). Van Herk [34] considers these also for IGRT treatments and suggests uncertainties of the order of 1, 2.5 and 3 mm systematic for head and neck, pelvic and thoracic treatment respectively and <1, 1 and 6 mm for random. Applying his widely-used margin recipe ($m = 2.5\Sigma + 0.7\sigma$), intended to provide coverage of the CTV with the 95% isodose for 90% of patients) he suggests that margins reduce by factors between around 0.55 and 0.65 using IGRT, depending on treatment site and hence on likely motion, but this is likely to be very dependent on local implementation, treatment techniques and correction protocols and requires careful assessment in the local situation. He stressed the danger of over-confidence in the process and of reducing margins too much [35] and the potential loss of coverage of sub-microscopic spread that we probably fortuitously achieved before. In addition, of course, none of this addresses the biggest geometric uncertainty, ie. that of variations in the target volume delineation at the beginning of the process.

3.3. Summary

In summarising the currently available evidence, general recommendations on accuracy in radiotherapy are still the same as previously reviewed and concluded, ie. for $\pm 3\%$ (sd) on the absorbed dose delivered at the specification point (but expanded to include a tighter requirement on systematic uncertainty of ideally $\leq 1-2\%$); for $\pm 3-5\%$ (sd) on the dose at all other points in the target volume; and for 'a few' mm (sd) on geometric uncertainties. The latter figure for evidence-based geometric precision requirements ranges from sub-mm (sd) for the most critical stereotactic cranial treatments to between 2-4mm (sd) for other treatments, where the latter is dependent on the site and whether IGRT-based methods are being used. For geometric effects on dosimetry within target volumes for IMRT, the recommended tolerances may be considered to be those given for MLC performance in recommendations for IMRT system QA and verification, ie typically 1 mm or less (see section 4.2). Other than the IGRT-linked change, the overall recommendations are still quite closely in line with the previous analysis. All these are given as one sd and are general requirements for routine clinical practice. In certain cases, eg. palliative, higher values may be acceptable. However, it is usually impractical to have different standards of accuracy for different treatment systems, techniques and processes and so the general values must be widely applied. In some special cases smaller uncertainties may be demanded if very steep complication curves are involved or tight geometric tolerances are required, as in stereotactic treatments, and these will require additional resource, implementation, QA and verification. It must be appreciated that these figures are on final delivered dose to the patient at the end of all the contributing stages involved in the radiotherapy process. The dosimetry chain begins with primary dosimetry standards and the required basic physical data. It leads through dosimeter calibration, treatment beam calibration in reference conditions, relative dosimetry in all other conditions and the treatment planning process, including acquisition of patient data, modelling and specification of treatment volume and dose. It ends with the delivery of the prescribed, planned and accepted treatment to the patient under day-to-day conditions over the course of the treatment, as verified beforehand and/or during treatment by further imaging and dosimetry. The accuracy requirement on each part of the whole process must be significantly less than the overall

recommendations to achieve the final values recommended. In general individual uncertainties are required to be of the order of 1% or 1 mm or less to achieve this.

4. Review of accuracy achievable in radiotherapy dosimetry

4.1. Estimates of overall dosimetric accuracy achievable from QA, in vivo dosimetry, audits and uncertainty analysis: conventional 3DCRT

Various attempts have been made to analyse the radiotherapy process to obtain cumulative uncertainties on delivered dose [6,7,18,19,22,25,26, 30]. Each major step, eg. absorbed dose to a reference point in water, measurement of relative doses and set up of the treatment planning systems, treatment planning of the individual patient and treatment delivery to the patient, has been broken down into sub-steps and best estimates of uncertainty have been assigned at each level for each contributing factor. The overall estimated cumulative uncertainties obtained have ranged from 2.5-8.5%, as one effective standard deviation (sd) [3]. This range in part reflects the judgements used by different authors, the number of separate sub-steps and parameters included and whether an optimal or a conservative approach was taken. A figure of 5% (sd) might be representative of these types of estimates, with smaller uncertainties for simpler treatments and larger for more complex.

More recently, uncertainty estimates based on harder evidence from intercomparisons, audits and *in vivo* dosimetry have been made from the author's own experience and programs [e.g. 2,9,11]. Table 1 reproduces a slightly modified summary [2] of these evaluations for external beam megavoltage x-ray treatments, following UK procedures and dosimetry protocols and utilising consistent results from

- the UK dosimetry intercomparisons and audits [36-37]
- the Scottish+ audit group of the UK radiotherapy dosimetry audit network [38], which includes intercomparisons in a number of phantoms simulating treatment sites and also some inter-centre *in vivo* intercomparisons
- analysis of QC records and specific experimental evaluation of uncertainties at many levels in the radiotherapy process in one department with a detailed quality system in place [9]
- systematic *in vivo* (diode) dosimetry in one department over more than 10 years [39,40].

The uncertainties are all given as effective sd values; therefore 95% confidence levels can be taken to be approximately twice these figures. It may be noted that the final cumulative patient values for a single centre are not very different to those for multi-centre intercomparisons. Line 1.2, multi-centre, based on ion chamber intercomparisons around the UK, can be compared to TLD intercomparisons, eg as reported by the Radiological Physics Center (RPC) largely for N American centres, where the distribution of output calibration audit results for megavoltage photon beams has a standard deviation of 1.7% [41-42], which of course includes some contribution from the relative uncertainties of the TLD measurements themselves. Alternatively, the IAEA/WHO TLD programme has verified calibrations of beams in a wide range of centres, largely in hospitals in low and middle income countries. Overall the standard deviation of the whole set of results is 6.3%, but these are weighted by some rather large deviations. The percentage of results within the 5% acceptance limit is reported to be 96% after corrective actions. In general participants using consistent modern dosimetry protocols (eg TRS-398 [43] or similar) showed sd of less than 3% [44-45]. Thwaites and Williams [46] and ESTRO booklet 9 [47] summarise a range of dose intercomparisons for megavoltage photon beams in reference conditions and indicate generally that means are close to the expected value and sd are generally less than around 2% in developed countries following modern protocols. The initial results from the recently established Australian Clinical Dosimetry Service (ACDS) are in line with this, with the sd of the distribution of mailed dosimeter audit results being around 2% and ion chamber audit results around half that [48]. The two publications mentioned that summarise audits [46-47] also do so for audits in anthropomorphic or semi-anthropomorphic phantoms and show sd in the range of 1.3-3.5%, which can be compared to line 2 multi-centre uncertainty values.

Table 1: Optimal uncertainties (1 effective sd) in radiotherapy dosimetry based on experimental determinations. Beam calibration methods follow the UK system and dosimetry protocol (based on direct absorbed dose to water calibration factors for the whole beam quality range at the standards laboratory). It is assumed that uncertainties can be combined or separated in quadrature.

<i>Source/step</i>	<i>Single centre (different beams/times)</i>	<i>Multi-centre</i>
1. Dose at reference point in water phantom		
1.1. uncertainties quoted on calibration factors by the UK standards lab (NPL) are 0.7% (1 effective sd)	0.7%	0.7 %
1.2. variation in reference dose determination between beams and through time	0.5%	0.7-1%
1.3. combined	0.9%	1.0- 1.2%
2. Dose to phantoms representing various treatment sites (at a range of points within target volumes; given relative to reference dose)	0.8-1.8%	1.1-2.3%
3. Patient dose at specification point (based on estimates from <i>in vivo</i> dosimetry; for a wide range of treatment sites and techniques, given relative to reference dose) + where lung is significantly involved*	1.5-3% (5%)*	1.6 – 3.2 % (5.1%)*
4. Estimated overall cumulative uncertainty on delivered patient dose at the specification point, including standards lab uncertainty	1.7 – 3.1%	1.9 – 3.4%
(+ where lung is significantly involved*	(5.1%)*	(5.2%)*

- see text for discussion of lung values

The overall cumulative uncertainties (Table 1) at the specification point are within, or close to, the recommended required values of 3% (1 sd), ie the clinical evidence-based requirements can be met on the experimental evidence available. The figures given are likely to be representative of fairly optimal situations in normal clinical practice. However overall uncertainties will be larger if any steps or sub-steps have larger uncertainties, whereas if special attention is given to minimising uncertainties for some special situations or treatments, values may be less. The only exception to the general values are those where there is significant involvement of lung. Here the *in vivo* measurements indicate that uncertainties increase, due both to motion and to the ability of planning systems to cope with such situations. This will depend on many factors, including the exact site, the beam directions, the planning algorithms, the lung correction approach, the amount of lung involved etc. However the lung-involved estimates were when advanced algorithms were not in such wide-spread use. It is likely now that these estimates would be reduced (better accuracy) if those measurements were re-done for clinical practice using advanced algorithms. There are a wide range of papers investigating the accuracy of older pencil-beam based models with simpler inhomogeneity corrections as compared to more modern convolution/superposition models using kernels to account for both photon and electron transport, or recently Monte Carlo-based approaches [49-51]. Generally the older algorithms can show deviations in situations involving significant lung tissue of up to 20%, whereas more modern

algorithms show deviations of a few % maximum [49-51]. Thus this alone is likely to reduce the overall lung-involved uncertainty values to be much closer to those for other treatment sites.

The overall cumulative uncertainties were estimated then for patient delivered dose at the specification point. For other points within the target volume, additional uncertainties are present, which can be estimated by folding in uncertainties from multi-point measurements in phantom or from 2-D (or 3D) verification of fields and treatments (here for example, experience is rapidly growing from the development and implementation of IMRT verification methods). Optimal uncertainties in these points are likely to be similar to those at level 2 in the table, relative to the specification point, giving estimated cumulative uncertainties (1 sd) on the dose at other points in the target volume in the range of approximately 2 - 4.5%.

It may be noted that other realistic phantom intercomparisons have shown uncertainties which are in general agreement with Table 1, e.g. the START trial audit [52] had sd of 1.2 and 1.3 % in the results of multi-centre measurements at the specification point for 2D and 3D breast plans respectively. The RTO1 trial audit [53] showed a sd of 1.3% for multi-centre measurements at the specification point in a prostate phantom, comparing to locally planned values and an sd of 2% for measurements within the CTV and of 4% for all measurements, including some outside the target volumes.

4.2 Estimates of overall dosimetric accuracy achievable for IMRT and more complex treatments

There have been a range of recent publications and recommendations recognising the need for tighter tolerances and accuracy for IMRT, eg AAPM Task Group 106 [54] on beam data commissioning, Low et al [55] on dosimetry for IMRT, IPEM report 96's guidance for clinical implementation [56] and ESTRO booklet 9 [47] on verification. The presentations at the AAPM 2011 summer school on uncertainties in external beam radiation therapy [57] provide useful comprehensive data, eg Moran and Ritter re treatment delivery systems [58]. In general the recommendations are around 1mm, 1° and 1% for specific linear, angular and dosimetric parameters, but others [eg. 59] recommend tighter tolerances for IMRT for accurate dosimetry, eg on MLC leaf positioning. In addition, small field situations, which are more or less similar for small sub-fields in IMRT or VMAT, also have special considerations [60-61]. Comprehensive requirements for TPSs are discussed in a number of publications, notably IAEA [50], where performance is heavily dependent on the algorithm employed as well as imaging system/s accuracy as input and the range of other relevant parameters that can affect dose calculation accuracy, eg slice thickness, CT number accuracy, dose calculation grid, etc. It may be noted that ICRU 83 [62] recommends generic values of 3.5% for dose agreement between planned and measured (delivered) doses in low dose gradient areas and 3.5 mm for DTA in high dose gradient areas and that they change the prescription and reporting requirements for more complex 3D treatments to be dose-volume based, rather than point based.. There is also a growing set of literature around robust planning, able to cope with changes and uncertainties and also uncertainty-included planning and analysis, eg Jin *et al*'s. [63-64] suggested dose uncertainty model for IMRT delivery. Their analysis for a series of prostate cases with varying inter- and intra-fractional motion indicated that consequent dose uncertainties for 95% of the CTV volume were from 1.3% to 2.9% and that prostate IMRT plans meeting similar plan objectives could have different dose uncertainties.

Therefore, it is unclear whether the increased complexity of IMRT will increase uncertainties, or the tighter tolerances on relevant parts of the process and greater effort put into QA and verification will decrease uncertainties and this may be a complex interplay of effects that might have different answers in different situations. Thus this short section considers a selection of the publications on QA, audit and in vivo dosimetry for IMRT to see whether the overall estimates of accuracy achievable may change when this is taken into account.

4.2.1. Phantom and pre-treatment verification measurements for IMRT

There is a wide range of recommendations on phantom measurements for departmental IMRT QA and verification processes [47, 54-57] and a large number of individual IMRT patients have had measurements made providing a wide body of information. These have generally used point dose measurements, often with 2-3% tolerance, to assess absolute dose delivery accuracy and also used 2D systems for verification of dose/fluence distributions [65-66]. In general, treatments are re-calculated onto a phantom, the treatment plan delivered and gamma index evaluation [67-68] carried out on a comparison between the expected dose distribution to be delivered (planning) and the measured actually-delivered dose distribution. The evaluation usually applies tolerances at the 3%/3mm level, for dose/distance-to-agreement, (usually in the range of 2%/2mm to 4%/4mm) and generally looks for 95-98% or so of points/pixels to lie within these tolerances, generally for the region lying at doses above some isodose level threshold, often the 20% isodose. These techniques have been extended into pseudo-3D tests of combined fields using appropriate 2D dosimeters in a phantom, or using one of the 3D systems or semi-3D systems [65-66, 69] now available, and delivering the whole treatment. A lot of effort has gone into this worldwide and has produced some feeling of confidence in local processes and procedures. However it is unclear exactly what statement these tolerances make on levels of accuracy achieved and there are papers which question the validity in particular of using the 2D verification approaches and whether in fact they do achieve what they intend [66,70]. Nevertheless if simplistically taken at face value, these are in-phantom measurements of the accuracy of delivery of IMRT and can be taken in the extreme to indicate that delivery is expected to be, and demonstrated to be, generally within 2-3% of absolute dose at a representative point and to within 3% and 3mm across the dose distribution, implying sd of 1-1.5% on dose to the representative point and at other dose points relative to this point and an overall sd in the range of 1.5-1.8%. This is well in line with the data given for single institutions in line 2 of Table 1. However, in fact it is not as simple as that and the results are highly dependent on differences in system, measurement resolution, analysis calculation and parameters, threshold, normalisation (global or local), tolerances set (in percentage pass rate, as well as dose or DTA values), actions taken, etc. [66-68,69]. In general it is too simplistic to reduce to a single gamma value and there should be at least an appreciation of where the differences lie and hence what their clinical significance is. Typically the 3 mm criterion on DTA may well imply that geometric uncertainties are within 1-1.8 mm, one sd (for pass rates of 100% to 90%), but linking overall dose uncertainties directly to the dose tolerance figure is a gross over-simplification and results in too low values of sd. This can be illustrated by considering the pass/fail rates if pushing the tolerances, eg 3%/3mm, 3%/2mm, 3%/1mm, etc.; and/or by considering the dose and DTA information separately before combination. For example, by examining a range of 'passing' IMRT and VMAT deliveries using the Delta-4 3D verification system, it has been observed by the author that 97-100 % gamma index pass rates using tolerances of 3%/3mm have shown dose sd of 1.5% to 2.3% and geometric sd of 1-1.3 mm. Similarly 95% pass rates have shown 1.5-2.5% sd on dose and 1-1.5 mm sd on geometry, whilst 90% pass rates have shown 2-3% sd on dose and up to 1.9mm sd on geometry. It may be noted that these are using a 20% threshold and global normalisation.

A general warning must also be given that these numbers might not be directly exactly applicable to other systems and usage, but they do at least give an indication of the involved uncertainties and their ranges that may be linked to often applied tolerance levels and pass/fail values. Typically 95-100% pass rates are expected/observed using 3%/3mm, implying 1-1.5% uncertainty at a representative dose specification point and uncertainties at other points in the range of 1.8-2.9%. These can be compared to Table 1 (lines 1.3 and 2 combined) of 1.2-2.0 %. This analysis also raises questions of how robust are the tolerances used in gamma analysis at picking up the levels of errors expected [66-68, 70] and whether the two numerical tolerance values for dose and DTA should be the same; in fact it implies that the DTA value should be numerically less than the dose value (eg 3%/2mm)

4.2.2 *In vivo dosimetry for IMRT*

There are a range of approaches to in vivo dosimetry for IMRT, including modification of conventional 3DCRT methods using point dose measurements coupled with other information on the distribution delivery, 2D transmission systems (eg DAVID), 2D field-by-field transit dosimetry using EPIDs and with back-projection to a representative patient plane [29, 69, 71], and full 3D dose reconstruction for all fields using EPIDs [29, 72]. Here the latter will be considered, as the full 3D equivalent of isocentre dose reconstruction from entrance and exit dose measurements employed to obtain the uncertainty values in line 3 of Table 2. The NKI [29, 72] approach is one of the longest running systems of this type. For this, Mans et al have reported experience on over 4000 patients [29]. The report is primarily about the efficacy of the system at identifying gross errors (17/4333 patients verified over four years, ie 0.4%). However the tolerances for isocentre dose and for numbers of points within the 3%/3mm distribution gamma index requirements, coupled with the referenced preceding papers leading up to this, can also be used to indicate sd of dosimetric parameters, using a similar simplistic and extremes argument as employed above for results for delivered dose distributions in phantom. In addition some of these papers give specific dosimetric distribution sd data and there are also other similar sets of results and data from similar long-running systems, eg that of MAASTRO [73]. Overall this implies that the sd of differences between expected dose and delivered dose to the isocentre is in the range 1-1.6% from these studies and the overall sd for other points in the in vivo delivered dose distribution verifications are between around 2.5% and 3.3%, however now specifically for delivery of IMRT to patients. This can be compared with the values from Table 1 (lines 1.3 and 3 combined) of 1.7-3.2%, again reasonably well in line with the tabulated 3DCRT data. NKI has more recently extended this to VMAT verification with similar results, eg the mean difference between measured and planned isocentre dose is 0.2%, sd = 1.6% and with a spread of values from -3% to +5% [72]. Of course, such 3D in vivo dosimetry provides as near as practically possible a total end-to-end test of the overall process.

4.2.3 *IMRT Audits and intercomparisons*

A number of IMRT-related dose delivery audits have been carried out in Europe, some of which are summarised in ESTRO Booklet 9 [47], including the ESTRO-QUASIMODO audit simulating a prostate PTV and OaR optimized treatment [74]. These all show mean dose differences between delivered and expected doses to be close to 0 and sd to be between 1.5 and 3.9%. More recently, the UK IPEM QA group has carried out a relatively simple mailed audit of IMRT fields [75], using alanine for absolute dose and film for dose distribution, involving 57/62 of the centres in the country and evaluating distributions against 2%/2mm to 4%/4mm criteria. This showed point doses to have sd for phantom delivery between 1.5 and 2.5% and effective sd of distributions of 1-1.5%, ie overall cumulative uncertainties of between 1.8 and 3.4%. A more ambitious audit of rotational IMRT techniques has been piloted in 10 centres by the national Clinical Trials QA Group [76], following on from the successful PARSPORT clinical trial and QA audits [77], also showing results in line with the other IMRT audits. The pilot rotational audit demonstrated sd of 2% for points in the PTV and 2.9% when all points measured are taken into account.

The widest set of IMRT audits has been those conducted by the RPC to support advanced technology clinical trials, beginning in 2001. The RPC has six different phantoms representing different areas of the body and designed for end-to-end test audits of IMRT treatments of the head and neck, prostate and lung and stereotactic treatments to the brain, lung, spine, and liver [78-79]. They contain simulated targets and OaRs and can take point dosimeters and radiochromic film for distribution measurements in appropriate planes. RPC-measured doses are evaluated against centre-expected doses, using rather wide tolerances of +/- 7% for absolute PTV doses and +/- 4mm in higher dose gradient areas, eg between PTV and OaR, for head and neck, prostate and liver, and rather tighter tolerances for spine and lung audits (5%, 3-5 mm). For the head and neck audits, 70% of centres met the criteria on the first round, rising to around 80% on repeats. For the other audits the pass rates reported were in the range 50-85%, but some of these were for small numbers of centres. The largest

group is for head and neck where over 750 institutions were audited. The distribution of differences between measured and expected doses to the PTVs showed means within 1-2 percent of zero and sd of around 5%. There was some evidence that smaller departments with poorer staff resources did worse. Summarising, Ibbott *et al.* [80] indicate that the studies suggest that the uncertainty in dose delivered to an anthropomorphic phantom with IMRT techniques is approximately 5% (sd).

Overall the results and indicated uncertainties from the European IMRT audits are in line with those for the multi-institution audits for 3DCRT, albeit showing a tendency to shift to rather higher sd. For the US studies, the uncertainties are significantly greater; this may partly reflect the stringency of the tests, but the tendency to correlate with the levels of staff resources in a given centre may say something about variable levels of QA in implementation of IMRT or in carrying out the audit irradiations.

4.3 Summary

Taking all this evidence into account, much of the information for IMRT as it pertains to uncertainties of dose delivery at the various levels to phantoms and patients is very similar to the evidence from 3DCRT, taking like-for-like situations. There is some evidence that the size of uncertainties achievable may shift upwards in more complex situations, but the range observed implies that similar uncertainties can be achieved. The widespread audits and in vivo reports on 3DCRT indicate that the levels of uncertainties reported here are representative of what it should be possible to generally achieve and the growing evidence from IMRT studies and the growing experience and expertise indicate that almost exactly the same levels of uncertainties ought to be achievable for IMRT.

5. Conclusion and observations

In this review of the accuracy required and achievable in radiotherapy dosimetry, the older approaches and evidence-based estimates for 3DCRT have been reprised, summarising and drawing together the author's earlier evaluations and repeating parts, where still relevant. Clinically-based accuracy requirements have not significantly changed, although a greater emphasis on high-precision delivery methods, including stereotactic radiotherapy, and on IMRT has focussed attention on reducing geometric uncertainties. At the same time the growing use of high-dose-per-fraction hypofractionated treatments, with steeper effective dose-response curves [81] may imply stricter dose and geometry requirements in these situations.

Available evidence for IMRT uncertainties has been reviewed, selecting information from tolerances, QA, verification measurements, in vivo dosimetry and dose delivery audits, to consider whether achievable uncertainties increase or decrease. Overall there is some evidence that they tend to increase, but that similar levels should be achievable (as evidenced by the lower uncertainty values in any of the spreads of values presented). Thus it is concluded that those earlier estimates of achievable dosimetric accuracy are still applicable, despite the advances in technology and techniques. The one exception is where significant amounts of lung are involved, where it is likely that uncertainties have now improved due to widespread implementation of more accurate heterogeneity modelling algorithms and are now likely to be more in line with the values presented for other treatment sites. The widespread availability of integrated IGRT systems has encouraged attention to geometric uncertainties and hence had a positive effect on what is achievable, which may further improve as motion management methods roll out more widely; all the evidence points to delivery to phantoms with sd of 1-1.5mm or so and delivery to patients in line with the figures in section 3.3, ie with sd of 'a few mm', depending on site and technique.

The accuracies and uncertainties presented here should be achievable, but require optimal approaches throughout, including comprehensive quality systems; attention to detail; safety, quality and accuracy cultures in radiotherapy departments [16]; and continuing vigilance. Practical, accurate, precise dosimeters and dosimetry systems are required to keep pace with the evolving complexity of technology and radiotherapy methods, for IMRT, small fields, 4D applications, etc. [82]. Increasingly,

biological imaging and biologically-based adaptive radiotherapy (BART) [83] will support individualised personal medicine in radiation oncology, where knowledge of individual radiosensitivity will support individualised prescription and dose escalation. This will tend to stratify dose-response curves, leading to increased steepness of the relevant curves for specific patient sub-groups and hence fuelling the demands for even greater accuracy. Low dose effects are becoming more important requiring more accurate measurement and modelling of those. Dose escalation will require better quantitatively-supported decision criteria and the basis for trade-off, considerations, with uncertainty modelling included. Adaptive and 4D radiotherapy will require better more robust methods, not only of 3D and 4D dosimetry and deformable image registration, but also of deformable dose accumulation [84]. These techniques would be expected to improve dosimetric uncertainties in situations where changes and intra-fraction motion respectively are significant. Dose distribution evaluation criteria must evolve and be robust themselves; noting too that the measurement uncertainties are folded into the comparison of measurement versus expected doses, thereby affecting the tolerances themselves [68]. Similar considerations apply to clinical trial dosimetry [85-86], noting that greater uncertainties in dosimetry can detrimentally affect the outcome and conclusions of a trial, or mean that a greater number of patients are needed to give it the required statistical power.

Some final issues: are our QA tools fast enough, efficient enough, and integrated enough into delivery systems and processes to cost-effectively cope with the expansion of complexity of technology and techniques? It will become the norm for EPIDs to be used as dosimeters as well as imagers, maybe in combination with other integrated dosimetry systems, to routinely manage verification on-line in real time and hence time-and-cost-efficiently. Further effort is required by the manufacturers to provide usable practical tools to support this. The available informatics will also need development to further efficiently support increases in complexity.. Maintaining and improving dosimetric and geometric accuracy is the key to gaining improvements from advancing technology and techniques; outcomes may well be better from high-quality simpler techniques than poorly-controlled poor-accuracy advanced techniques; the optimum is to implement the newer techniques in a high quality, safety and accuracy environment to achieve both high precision and high accuracy for all patients. The more complex the treatments the greater the potential for problems, of course, so radiotherapy must be conducted within a consistent and sustainable quality framework. There is clear evidence that poor quality radiotherapy produces poorer outcomes [87] and lastly, both generally and as shown by that study [87], the community needs to address the inconsistencies in target volume delineation as one of the major remaining grey uncertainty areas in the radiotherapy process.

6. References

- [1] International Commission on Radiation Units and Measurements 1976 Determination of absorbed dose in a patient irradiated by beams of x or gamma rays in radiotherapy procedures *International Commission on Radiation Units and Measurements* ICRU Report 24 Bethesda, Maryland
- [2] Mayles P, Thwaites DI (with Rosenwald J-C) 2007 Rationale and management of the quality system Chapter 37 *Handbook of Radiotherapy Physics: Theory and Practice* (eds. Mayles P, Nahum A and Rosenwald J-C) Taylor and Francis: London ISBN-13:978-0-7503-0860-1, 2007
- [3] van Dyk J (Ed) 1999 The Modern Technology of Radiation Oncology: A Compendium for Medical Physicists and Radiation Oncologists *Medical Physics Publishing* Madison WI
- [4] Thwaites DI and Malicki J 2011 Physics and technology in ESTRO and in Radiotherapy and Oncology: past, present and into the 4th dimension *Radiother. Oncol.* **100** 327-332
- [5] Nystrom H and Thwaites D 2008 Physics and high-technology advances in radiotherapy: are they still worth it? *Radiother. Oncol.* **86** 1-3
- [6] Thwaites DI 1989 Review and analysis of accuracy required and achievable in radiotherapy Accuracy in Radiotherapy *Phys. Med. Biol.* **34** 639

- [7] Thwaites DI 1993 Accuracy requirements in radiotherapy Chapter 11, *A Practical Course in Radiotherapy Physics* Vol 2 (ed: Mayles, P, and Nahum, A E), The Institute of Cancer Research/The Royal Marsden Hospital, London
- [8] Thwaites DI 1994 Uncertainties at the end point of the basic dosimetry chain *Measurement Assurance in Dosimetry* (ed: Svensson,H,) IAEA-SM-330 (IAEA, Vienna) 239-255
- [9] Allahverdi M and Thwaites DI 1998 Achievable accuracy in radiotherapy dosimetry ESTRO 17 (Edinburgh, Sept 1998) *Radioth. Oncol.* **48** (suppl 1) S187
- [10] Dobbs J and Thwaites DI 1998 Quality assurance and its conceptual framework Chapter 1 of *Physics Aspects of Quality Control in Radiotherapy* (eds: Mayles, P, et al) IPEM Report **81** (IPEM,York)
- [11] Thwaites DI 2003 Verification and external audit of dose for conventional radiotherapy and the new technology: how well can we deliver radiotherapy doses? Current achievements in oncology Rep *Pract. Oncol. Radiother.* **8** (2) 225
- [12] Thwaites DI 2006 Clinical dosimetry and QA for radiotherapy: developments in methods, applications and accuracy *Proc. Int. Conf. on quality assurance and new techniques in radiation medicine* IAEA: Vienna IAEA-CN-146 482-483
- [13] Kutcher GJ, Coia L, Gillin M, Hanson WF, Leibel S, Morton RJ, Palta JR, Purdy JA, Reinstien LE and Svensson GK 1994 Comprehensive QA for radiation oncology: report of AAPM Radiation Therapy Committee Task Group 40 *Med. Phys.* **21** 581-618
- [14] Thwaites DI, Scalliet P, Leer JWH and Overgaard J 1995 Quality assurance in radiotherapy (ESTRO report to the Commission of the European Union for the 'Europe against Cancer' programme) *Radioth. Oncol.* **35** 61-74
- [15] Leer JWH, McKenzie AL, Scalliet P and Thwaites DI 1998 Practical Guidelines for the Implementation of a Quality System in Radiotherapy ESTRO Series *Clinical Physics for Radiotherapy* (ESTRO- Garant, Leuven)
- [16] The Royal College of Radiologists, Society and College of Radiographers, Institute of Physics and Engineering in Medicine, National Patient Safety Agency, British Institute of Radiology 2008 Towards Safer Radiotherapy *The Royal College of Radiologists* London
- [17] International Atomic Energy Agency 2000 Lessons Learned from Accidental Exposures in Radiotherapy IAEA Vienna
- [18] International Commission on Radiological Protection (ICRP) 2000 Prevention of Accidental Exposures to Patients undergoing Radiation Therapy ICRP Publication **86** Pergamon
- [19] Mijnheer BJ, Batterman JJ and Wambersie A 1987 What degree of accuracy is required and can be achieved in photon and neutron therapy? *Radiother.Oncol.* **8** 237-252
- [20] International Organisation for Standardisation 1995 Guide to the Expression of Uncertainty in Measurement *International Organization for Standardization* Geneva
- [21] Comite International des Poids et Mesures 2008 Evaluation of measurement data Guide to the expression of uncertainty in measurement *BIPM* Paris
- [22] Dutreix A 1984 When and how can we improve precision in radiotherapy? *Radiother.Oncol.* **2** 275-292
- [23] van Herk M 2004 Errors and margins in radiotherapy *Semin. Radiat. Oncol.* **14** 52-64
- [24] International Commission on Radiation Units and Measurements 2006 ICRU Report 76 Measurement Quality Assurance for Ionizing Radiation Dosimetry Bethesda, Maryland, International Commission on Radiation Units and Measurements
- [25] Brahme A 1984 Dosimetric precision requirements in radiation therapy *Acta. Radiol.Oncol.* **23** 379-391
- [26] Brahme A, Ed. 1988 Accuracy requirements and quality assurance of external beam therapy with photons and electrons *Acta. Oncol.* (suppl 1) 5-76
- [27] Bentzen SM 2005 Steepness of the radiation dose-response curve for dose-per-fraction escalation keeping the number of fractions fixed *Acta. Oncol.* **44** 825-828

- [28] Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, Ten Haken RK and Yorke ED 2010 Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues *Int. J. Radiat. Oncol. Biol. Phys.* **76** S3-S9
- [29] Mans A, Wedling M, McDermott LN, Sonke JJ, Tielenburg R, Vijlbrief R, Mijnheer B, van Herk M, Stroom JC 2010 Catching errors with in vivo EPID dosimetry *Med. Phys.* **37** 2638-2644
- [30] American Association of Physicists in Medicine 1984 Physical aspects of quality assurance in radiation therapy *AAPM TG Report* **24**
- [31] Korreman S, Rasch C, McNair H, Verellen D, Oelfke U, Maingon P, Mijnheer B and Khoo V 2010 The European Society of Therapeutic Radiology and Oncology-European Institute of Radiotherapy (ESTRO-EIR) report on 3D CT-based in-room image guidance systems: a practical and technical review and guide *Radiother. Oncol.* **94** 129-144
- [32] British Institute of Radiology 2003 Geometric uncertainties in radiotherapy *BIR* London
- [33] The Royal College of Radiologists, Society and College of Radiographers, Institute of Physics and Engineering in Medicine, National Patient Safety Agency, British Institute of Radiology 2008 On target: ensuring geometric accuracy in radiotherapy *The Royal College of Radiologists* London
- [34] van Herk M 2011 Margins and Margin Recipes Chapter 8 (Palta J.R., Mackie T.R. Eds) *Uncertainties in External Beam Radiation Therapy Medical Physics Publishing* Madison WI
- [35] Engels B, Soete G, Verellen D and Storme G 2009 Conformal arc radiotherapy for prostate cancer: increased biochemical failure in patients with distended rectum on the planning computed tomogram despite image guidance by implanted marker *Int. J. Radiat. Oncol. Biol. Phys.* **74** 388-91
- [36] Thwaites DI, Williams JR, Aird EG, Klevenhagen SC, and Williams PC 1992 A dosimetric intercomparison of megavoltage photon beams in UK radiotherapy centres *Phys. Med. Biol.* **37** 445-461
- [37] Nisbet A, Thwaites DI and Sheridan ME 1998 A dosimetric intercomparison of kilovoltage X-rays, megavoltage photons and electrons in the Republic of Ireland *Radiother. Oncol.* **48** 95-101
- [38] Thwaites, DI 1996 External audit in radiotherapy dosimetry *Radiation Incidents* eds Faulkner K and Harrison RM (BIR, London 21-28; and, Thwaites, DI, Powley, S, Nisbet, A and Allahverdi, M, The United Kingdom's radiotherapy dosimetry audit network, in Standards and Codes of Practice for Medical Radiation Dosimetry, IAEA:Vienna (2003), IAEA-STI-PUB-1153, vol 2, 183-190
- [39] Thwaites DI, Blyth C, Carruthers L, Elliott PA, Kidane G, McLeod A, Paolucci M and Stacey C 2003 Experience with in vivo diode dosimetry for verifying radiotherapy dose delivery: Practical implementation of cost-effective approaches, Standards and Codes of Practice for Medical Radiation Dosimetry *IAEA Vienna IAEA-STI-PUB-1153* **2** 415-423
- [40] Huyskens DP, Bogaert R, Verstraete J, Loof M, Nystrom H, Fiorino C, Broggi S, Jornet N, Ribas M, and Thwaites DI 2001 Practical Guidelines for the Implementation of in vivo Dosimetry with Diodes in External Radiotherapy with Photon Beams (Entrance Dose) *ESTRO Booklet 5 ESTRO* Brussels Belgium
- [41] Aguirre JF, Alvarez P, Ibbott GS and Followill MD 2011 Testing, commissioning and validating an optically stimulated luminescence (OSL) dosimetry system for mailed dosimetry at the Radiological Physics Center *International Symposium on Standards, Applications and Quality Assurance in Medical Radiation Dosimetry (IDOS)* IAEA STI/PUB/1514 ISBN 978-92-0-116210-6 (IAEA: Vienna) **2** 411-421
- [42] Aguirre JF, Tailor R, Ibbott G, Stovall M and Hanson W 2002 Thermoluminescence dosimetry as a tool for the remote verification of output for radiotherapy beams: 25 years of experience *Proceedings of the International Symposium on Standards and Codes of Practice in Medical*

- Radiation Dosimetry* IAEA-CN-96/82, International Atomic Energy Agency (IAEA) Vienna, Austria
- [43] International Atomic Energy Agency 2000 Absorbed Dose Determination in External Beam Radiotherapy: An International Code of Practice for Dosimetry Based on Standards of Absorbed Dose to Water IAEA TRS-398 *International Atomic Energy Agency* Vienna
 - [44] Izewska J, Andreo P, Vatnitsky S, Shortt KR 2003 The IAEA/WHO TLD postal dose quality audits for radiotherapy: a perspective of dosimetry practices at hospitals in developing countries *Radiother. Oncol.* **69** 91-97
 - [45] Izewska J and Thwaites D 2002 IAEA Supported National Thermoluminescence Dosimetry Audit Networks for Radiotherapy Dosimetry *Proceedings of the International Symposium on Standards and Codes of Practice in Medical Radiation Dosimetry* IAEA-CN-96/137 International Atomic Energy Agency (IAEA) Vienna, Austria
 - [46] Thwaites DI and Williams JR 1994 Radiotherapy dosimetry intercomparisons in *Radiation Dose in Radiotherapy from Prescription to Delivery* (ed: Svensson H and Dutreix A) IAEA TECDOC 734 (IAEA, Vienna) 131-141
 - [47] Mijnheer B, Georg D (Eds.) ESTRO Booklet No. 9: Guidelines for the Verification of IMRT *ESTRO* Brussels, Belgium
 - [48] Williams I personal communication
 - [49] Morgan A, Knoos T, McNee S, Evans C and Thwaites DI Clinical implications of the implementation of advanced treatment planning algorithms for thoracic treatment *Radiother. Oncol.* **86** 48-54
 - [50] International Atomic Energy Agency 2004 Commissioning and quality assurance of computerized planning systems for radiation treatment of cancer IAEA TRS-430 *International Atomic Energy Agency*, Vienna
 - [51] Gershkevitch E, Schmidt R, Velez G, Miller D, Korf E, Yip F, Wanwilairat S and Vatnitsky YS 2008 Dosimetric verification of radiotherapy treatment planning systems: results of IAEA pilot study *Radiother. Oncol.* **89** 338-346
 - [52] Venables K, Winfield EA, Aird EG and Hoskin PJ 2003 Three-dimensional distribution of radiation within the breast: an intercomparison of departments participating in the START trial of breast radiotherapy fractionation *Int. J. Radiat. Oncol. Biol. Phys.* **55** 271-279
 - [53] Moore R, Stanley S, Bidmead AM, Dearnaley DP, Mayles WPM and Warrington AP 2003 Quality assurance of dosimetry in UK MRC RTO1 trial of dose escalation using conformal radiotherapy in prostate cancer *Clin. Oncol.* **15** 58-59
 - [54] Das IJ, Cheng CW, Wats RJ, Ahnesjö A, Gibbons J, Li XA, Lowenstien J, Mitra RK, Simon WE and Zhu TC 2008 Accelerator beam data commissioning equipment and procedures: report of the TG-106 of the Therapy Physics Committee of the AAPM *Med. Phys.* **35** 4186-4215
 - [55] Low DA, Moran JM, Dempsey JF, Dong L and Oldham M 2011 Dosimetry tools and techniques for IMRT *Med. Phys.* **38** 1313-1338
 - [56] Institute of Physics and Engineering in Medicine 2008 Guidance for the clinical implementation of intensity modulated radiation therapy *IPEM* report 96 IPEM, York
 - [57] Palta JR and Mackie TR (Eds) 2011 Uncertainties in External Beam Radiation Therapy *Medical Physics Publishing* Madison WI
 - [58] Moran JM and Riter T 2011 Limits of precision and accuracy of radiation delivery systems Uncertainties in External Beam Radiation Therapy Chapter 10 (Palta JR and Mackie TR (Eds)) *Medical Physics Publishing* Madison WI
 - [59] Li JS, Lin T, Chen L, Price RA and Ma CM 2010 Uncertainties in IMRT dosimetry *Med. Phys.* **37** 2491-2500
 - [60] Alfonso R, Andreo P, Capote R, Huq MS, Kilby W, Kjall P, Mackie TR, Palmans H, Rosser K, Seuntjens J, Ullrich W and Vatnitsky S 2008 A new formalism for reference dosimetry of small and nonstandard fields *Med. Phys.* **35** 5179-5186

- [61] Aspradakis MM, Byrne JP, Palmans H, Rosser K and Warrington AP 2010 Small Field MV Photon Dosimetry IPEM Report Number 103 *Institute of Physics and Engineering in Medicine* York UK
- [62] International Commission on Radiation Units and Measurements 2010 ICRU Report 83: Prescribing, Recording, and Reporting Photon-Beam Intensity-Modulated Radiation Therapy (IMRT) Bethesda, Maryland *International Commission On Radiation Units and Measurements*
- [63] Jin H, Palta JR, Kim YH and Kim S 2010 Application of a novel dose-uncertainty model for dose-uncertainty analysis in prostate intensity-modulated radiotherapy *Int. J. Radiat. Oncol. Biol. Phys.* **78** 920-928
- [64] Jin H, Palta J, Suh HTS and Kim S 2008 A generalized a priori dose uncertainty model of IMRT delivery *Med. Phys.* **35** 982-996
- [65] Korreman S 2013 Semi and virtual 3D dosimetry in clinical practice *7th Int. Conf. 3D Radiation Dosimetry* this issue
- [66] Feygelman V and Nelms B 2013 Dosimetric quality assurance of highly conformal external beam treatments: from 2D phantom comparisons to 4D patient dose reconstructions *7th Int. Conf. 3D Radiation Dosimetry* this issue
- [67] Low DA, Harms WB, Mutic S and Purdy JA 1998 A technique for the quantitative evaluation of dose distributions *Med. Phys.* **25** 656-661
- [68] Schreiner LJ, Holmes O and Salomans G 2013 Analysis and evaluation of planned and delivered dose distributions: practical concerns with gamma and chi evaluations *7th Int. Conf. 3D Radiation Dosimetry* this issue
- [69] McCurdy B 2013 Dosimetry in radiotherapy using a-Si EPIDs: systems, methods and applications, focussing on 3D patient dose estimation *7th Int. Conf. 3D Radiation Dosimetry* this issue
- [70] Nelms BE, Zhen H and Tome WA 2011 Per-beam, planar IMRT QA passing rates do not predict clinically relevant patient dose errors *Med. Phys.* **38** 1037-44
- [71] Greer P 2013 3D EPID-based dosimetry for pre-treatment verification of VMAT: methods and challenges *7th Int. Conf. 3D Radiation Dosimetry* this issue
- [72] Mijnheer B, Olaciregui-Ruiz I, Rozendaal R, Sonke J-J, Spreeuw H, Tielenburg R, van Herk M, Vijlbrief R and Mans A 2013 3D EPID-based in vivo dosimetry for IMRT and VMAT *7th Int. Conf. 3D Radiation Dosimetry* this issue
- [73] van Elmpt, W, McDermott, L, Nijsten, S, Wendling M, Lambin P, . Mijnheer, B 2008, "A literature review of electronic portal imaging for radiotherapy dosimetry," *Radiother. Oncol.* **88**, 289–309
- [74] Gillis S, de Wagter C, Bohsung J, Perrin B, Williams P, Mijnheer BJ 2005 An inter-centre quality assurance network for IMRT verification: results of the ESTRO QUASIMODO project *Radiother. Oncol.* **76** 340-353
- [75] Budgell G, Berresford J, Trainer M, Bradshaw E, Sharpe P and Williams P 2011 A national dosimetric audit of IMRT *Radiother. Oncol.* **99** 246–252
- [76] Hussein M, Tsang Y, Thomas R, Gouldstone C, Maughan D, Snaith J, Bolton S and Clark CH 2012 Rotational radiotherapy in the UK - a pilot audit ESTRO 31 *Radiother. Oncol.* **103** (suppl 1) S30-31
- [77] Clark CH, Hansen VN, Chantler H, Edward C, James HV, Webster G, Miles EA, Guerrero Urbano MT, Bhide SA, Bidmead AM and Nutting CM 2009 Dosimetry audit for a multi-centre IMRT head and neck trial *Radiother. Oncol. Ireland* **93** 102-8
- [78] Molineu A, Followill DS, Balter PA, Hanson WF, Gillin MT, Huq MS, Eisbruch A and Ibbott GS 2005 Design and implementation of an anthropomorphic quality assurance phantom for intensity-modulated radiation therapy for the Radiation Therapy Oncology Group *Int. J. Radiat. Oncol. Biol. Phys.* **63** 577-583

- [79] Followill DS, Evans DR, Cherry C, Molineu A, Fisher G, Hanson WF and Ibbott GS 2007 Design, development, and implementation of the radiological physics center's pelvis and thorax anthropomorphic quality assurance phantoms *Med. Phys.* **34** 2070-2076
- [80] Ibbott GS, Followill DS, Molineu HA, Lowenstein JR, Alvarez PE, Roll JE 2008 Challenges in credentialing institutions and participants in advanced technology multi-institutional clinical trials *Int. J. Radiat. Oncol. Biol. Phys.* **71** S71-S75
- [81] Yorke E D, 2011 Dosimetric uncertainties and normal tissue tolerance, Ch.1, (Palta J.R., Mackie T.R., eds), *Uncertainties in External Beam Radiation Therapy*, *Medical Physics Publishing, Madison, WI*
- [82] Andreo P 2011 Accuracy Requirements in Medical Radiation Dosimetry International Symposium on Standards, Applications and Quality Assurance in Medical Radiation Dosimetry 1-23 IAEA, Vienna.
- [83] Simpson B personal communication
- [84] Keall PJ, Mageras GS, Balter JM, Emery RS, Forster KM, Jiang SB, Kapatoes JM, Low DA, Murphy MJ, Murray BR, Ramsey CR, van Herk MB, Vedam SS, Wong JW and Yorke E 2006 The management of respiratory motion in radiation oncology report of AAPM Task Group 76 *Med. Phys.* **33** 3874-3900
- [85] Pettersen MN, Aird E and Olsen DR 2008 Quality assurance of dosimetry and the impact on sample size in randomized clinical trials *Radiother. Oncol.* **86** 195-199
- [86] Kron T, Haworth A and Williams I 2013 Dosimetry for audits and clinical trials: challenges and requirements 7th *Int. Conf. 3D Radiation Dosimetry* this issue
- [87] Peters L, O'Sullivan B, Giralt J, Fitzgerald TJ, Trotti A, Bernier J, Bourhis J, Yuen K, Fisher R and Rischin D Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results from TROG 02.02. *J. Clin. Oncol.* **28** 2996-3001