Dosimetry for audit and clinical trials: challenges and requirements

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Abstract. Many important dosimetry audit networks for radiotherapy have their roots in clinical trial quality assurance (QA). In both scenarios it is essential to test two issues: does the treatment plan conform with the clinical requirements and is the plan a reasonable representation of what is actually delivered to a patient throughout their course of treatment. Part of a sound quality program would be an external audit of these issues with verification of the equivalence of plan and treatment typically referred to as a dosimetry audit. The increasing complexity of radiotherapy planning and delivery makes audits challenging. While verification of absolute dose delivered at a reference point was the standard of external dosimetry audits two decades ago this is often deemed inadequate for verification of treatment approaches such as Intensity Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT). As such, most dosimetry audit networks have successfully introduced more complex tests of dose delivery using anthropomorphic phantoms that can be imaged, planned and treated as a patient would. The new challenge is to adapt this approach to ever more diversified radiotherapy procedures with image guided/adaptive radiotherapy, motion management and brachytherapy being the focus of current research.

1. Introduction
Radiotherapy is a locoregional cancer treatment modality that relies on accurate delivery of very high doses of radiation to a target whilst minimising dose to surrounding healthy structures. The required accuracy for dose delivery is typically quoted as being within +/- 5% of the prescribed dose [1, 2] while the spatial accuracy depends on the part of the body that is irradiated. It can vary from a few mm in the pelvis to less than 1mm when delivered to lesions in the brain. The consequences of not meeting these requirements can be very severe for the patient and radiotherapy departments are generally highly aware of the need for excellent quality assurance in the treatment planning and delivery process.

Most quality systems include the need for an external audit and many radiotherapy departments participate regularly in these audits [3, 4]. The largest two dosimetric audit networks at present are operated by the International Atomic Energy Agency (IAEA) [5, 6] and the American Radiological Physics Centre (RPC) in Houston [7, 8]. These two organizations also reflect the two key motivations for dosimetric audits: the IAEA provides a relatively simple audit of beam calibration that reduces the risk of misadministration while the RPC primarily supports co-operative clinical trials groups that use...
radiotherapy as part of clinical research [9]. More recently several other countries have established this type of service, and Australia has recently started to operate the Australian Clinical Dosimetry Service (ACDS) [10].

The objective of this paper is to describe some dosimetric audit systems and discuss their link to clinical practice and research. The second half of the manuscript is concerned with three examples for particularly challenging situations for radiotherapy audits: Image guided and adaptive radiotherapy (IGRT), Motion management and Brachytherapy.

2. Classification of dosimetric audits

Depending on the objective a range of different audit types are performed and several classification systems are used to describe them [11, 12]. In general, audits are classified according to their complexity. Table 1 lists the system recently introduced by the ACDS.

Commonly, a check of absolute dosimetry under reference conditions is referred to as a level I dosimetric audit [11, 12]. Figure 1 shows two such systems. The advantage of this type of audit is that they can be performed remotely by sending the dosimeters to participating centres where they are irradiated to a specified dose under clearly defined conditions [5, 6]. The detectors used for this type of audit are nearly exclusively luminescence detectors with thermoluminescence dosimeters (TLDs) [6, 13] being increasingly replaced by optically stimulated luminescence dosimeters (OSLDs) [14, 15] due to their faster readout and easier handling.

However, a single dosimetric point dose measurements is not always sufficient to characterise a radiation beam adequately for radiotherapy. For example electron beams usually require verification of radiation quality and dose to interpret the readings appropriately. This is illustrated in figure 2 that shows the electron dosimetry module developed by the RPC. Two sets of three TLD capsules are placed at two depths in a Perspex phantom.

A tool for postal audits under non-reference conditions was recently introduced by the IAEA [12]. It is based on the jig shown in figure 1a and introduces a horizontal bar to allow placement of the TLD capsule off central axis. Also an extension of the vertical bar is available that places the reference depth at 10 cm which is more in line with recent calibration protocols [16, 17]. This would be a typical level II audit. An interesting future development may be level II audits based on two dimensional detector systems such as film [18] or detector arrays. The latter have mainly been developed for IMRT QA [19] but offer the advantage of acquiring large amounts of data in few exposures and as such, provide an easy means of characterising radiation beams.

Anthropomorphic phantoms are the primary tool used in level III dosimetric audits. Figure 3 shows an anthropomorphic phantom customised for dosimetric intercomparisons for clinical trials of prostate and rectal cancer radiotherapy [20, 21]. In a level III audit the whole chain of treatment from imaging to planning and delivery can be tested. While strictly speaking an anthropomorphic phantom is not required it makes the process as realistic as possible and typically motivates staff in participating centres.
Table 1: Dosimetric services offered by the Australian Clinical Dosimetry Service

<table>
<thead>
<tr>
<th>Dosimetry level</th>
<th>ACDS</th>
<th>Detector type</th>
<th>Mode</th>
<th>System checked</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level I</td>
<td>Output under reference conditions</td>
<td>TLD, OSL</td>
<td>Remote</td>
<td>Every radiation beam</td>
<td>Identical to RPC audit</td>
</tr>
<tr>
<td>Level IB</td>
<td>Output under reference conditions</td>
<td>Ionisation chamber</td>
<td>On-site</td>
<td>Every radiation beam</td>
<td>Offered for new centres prior to opening</td>
</tr>
<tr>
<td>Level II</td>
<td>Dose distribution in physical phantoms</td>
<td>Detector array</td>
<td>Remote</td>
<td>Planning system</td>
<td>Can include inhomogeneity and allows clarification of level III findings</td>
</tr>
<tr>
<td>Level III</td>
<td>Anthropomorphic phantom end to end</td>
<td>Ion chamber, radiochromic film</td>
<td>On-site</td>
<td>Entire treatment chain</td>
<td>Treatment specific – most relevant for clinical trials</td>
</tr>
</tbody>
</table>

Due to their weight and complexity, anthropomorphic phantom based audits are often part of a site visit as was in the case of the phantom shown in figure 3. However, in principle anthropomorphic phantoms can also be mailed to users. The RPC has developed a suite of phantoms for this purpose [7, 8]. Most of them are plastic shells that can be filled with water after being sent to participating centres. The shells also contain dosimetric inserts with TLDs, OSLDs and/or radiochromic film that are shipped as integral part of the phantom or as separate module that must be inserted into the phantom prior to use [7, 8].

A variety of dosimeters have been used for dosimetric audits. While TLDs and OSLs are ideal for mailed dosimetry [5, 22], audits involving anthropomorphic phantoms typically also employ a two-dimensional dosimetry system such as radiochromic film [23, 24]. Ideally, one would like to take this one step further to three-dimensional systems such as gels [25] or presage [26]. Despite considerable interest, to date these systems are still largely experimental.

Finally, also in vivo dosimetry has been suggested as a tool for radiotherapy audits of various complexity [27, 28]. While possible in principle there are many additional uncertainties to account for, documentation and ethics need to be considered and many modern delivery techniques such as VMAT or IMRT would be difficult to assess. As such audits based on in vivo dosimetry are likely to stay more common in radiology where entrance dose is an important parameter in radiologic exposures that can be used for the establishment of diagnostic reference levels [29].

3. Auditing of modern radiotherapy delivery

As radiation delivery becomes more complex, auditing must test more aspects of the delivery to provide a reasonable assurance that a centre performs a particular treatment as per best practice. Anthropomorphic phantoms are well suited for this purpose and the RPC is performing a large number of audits using a variety of phantoms every year [7, 8, 24]. The results, which showed that a significant number of centres did not perform within tolerance, demonstrated in themselves that the audits are fulfilling an important role in identifying problems. To quote from Ibbott et al (2006): “The...
experience obtained through the irradiation of the phantoms by a number of institutions demonstrates that institutions vary significantly in their ability to deliver doses and dose distributions that agree with their own treatment plans” [8]. Repeat audits show in general that the results improve, a fact that has also been shown for the IAEA level I dosimetric audits [6].

An additional feature of complex audits is the need to be able to compare measured dose distributions with the ones planned for delivery. In the case of an audit it is not necessary to evaluate the quality of the dose distribution itself; the key point is if the dose predicted is identical to the dose given. In order to facilitate this, a clinical audit centre must have access to treatment planning or trials review software [30] that can display dose distributions from a variety of different planning systems.

In Australia, several audits of complex radiotherapy delivery have been performed. Figure 3c shows the dose distribution for a prostate cancer trial as assessed using radiochromic film [23]. The coronal sectioning of the phantom allows for easy film placement and provides a picture of the dose distribution. An ion chamber measurement in the centre of the phantom’s prostate complements this dose distribution. To date, these have been typically part of clinical trials [23, 31]; however, the establishment of the ACDS is likely to lead to such services also being offered to any centre wishing to have an independent check of complex procedures.

4. Auditing for clinical trials

In the context of clinical trials an audit must not only support patient safety but also minimise the risk of not being able to answer the trial question. There have been several trials that have demonstrated that protocol compliance and quality assurance are very important for trial outcomes [32]. In the worst case, this can mask a significant difference between arms in a clinical trial. Conversely, good quality assurance can reduce the number of patients required in a clinical trial to answer the trial question [33]. The level and complexity of the dosimetric audit therefore will vary depending on the importance of dosimetry for the trial question. If radiation is not part of the trial question (e.g., radiotherapy with or without administration of specific systemic treatment) possibly no external audit is required. However, if for example mucosal toxicity is a primary endpoint, it may be important to verify that the dose prediction by the planning system (or whatever other means is used to determine dose). In general though, audits for clinical trials need to go further than dosimetric audits as one needs to verify contouring and protocol compliance not just that what you see is what you get.

It has long been recognised that multicenter clinical trials not only test a new treatment approach but can also help to introduce new approaches and particularly technology safely [34-36]. This is something which is likely to be of increasing importance for advanced radiotherapy techniques and poses particular challenges as discussed in the next section.
5. Challenges for dosimetric audits

The increasing variety and complexity of radiotherapy makes audits increasingly challenging. In particular imaging plays an increasing role in the delivery and it is no longer sufficient to simply verify that the dose distribution is consistent with the planned distribution, additionally, an audit needs to assess that this dose distribution can be delivered to the correct part of the patient’s anatomy. As such, comprehensive dosimetric audits need to consider the tools that allow determining how the dose delivery is optimised for each individual patient on every day of the treatment course.

In order to optimise resources many audit and clinical trials groups have commenced a risk management approach to auditing [31, 37]. One of the risk management approaches is failure mode and effect analysis (FMEA). The fundamental idea is not to perform activities such as audits according to a predetermined schedule but to analyse processes and give priority to a particular audit item depending on the likelihood of something going wrong and the severity of the consequences [38].

5.1. Image guided and adaptive radiotherapy

Image guided radiotherapy refers to the use of high quality imaging equipment in the treatment room prior or during the delivery of radiotherapy with the aim to ensure optimal treatment delivery [39, 40]. This can range from ultrasound to planar X-rays with or without fiducial markers, to cone beam CT and possibly even MRI [41, 42]. It is this wide variety of approaches and the need for decision making that make an audit of IGRT difficult. A few attempts have been made [43] and the American Radiation Therapy and Oncology Group (RTOG) has issues guidelines for the inclusion of IGRT into clinical trials (available from the RPC webpage: http://rpc.mdanderson.org/).

Even more complex is the assessment of adaptive radiotherapy where IGRT is used not only to position the patient but also to select or adjust a treatment plan. A recent multicenter clinical trial on adaptive radiotherapy of bladder cancer [44] has a program for credentialing of participating centres that specifically tests the ability of centres to perform the tasks required for treatment according to protocol. Figure 4 shows a Perspex body phantom used for credentialing of centres for adaptive radiotherapy which involves selection of a plan of the day selected based on volumetric imaging. The credentialing process tests the image guidance and decision making chain and involves inserting a target volume in a cylinder into the phantom the size and location of which is unknown to the operator. The task consists of imaging the phantom, identifying the cylinder and positioning it in the correct location based on reference images that are provided to participating centres [31].

5.2. Motion management

A different task for modern radiotherapy is motion management [45], be it in treatment planning or delivery. A number of groups have developed phantoms that have moveable parts and can be used for auditing. Of particular interest is the work of the RPC that has developed a lung and a liver phantom for auditing of stereotactic extracranial procedures. Like in other complex radiotherapy delivery techniques two-dimensional detector systems such as radiochromic film prove to be particularly useful [46].
5.3. Brachytherapy
The ICRP publication 97 reported on more than 500 brachytherapy events [47], including one death, that could have been prevented through rigorous quality assurance exercises, including independent audits. Many of the reported incidents were a result of human error and therefore brachytherapy audits ideally should include site visits that not only check dosimetry, but also check internal processes that may lead to random (patient specific) errors, or systematic errors that may affect all patients.

A small number of brachytherapy dosimetry audits have been conducted [48-52]. These audits vary in complexity, ranging from simple verification of the calibration of the local well chamber used to determine the reference air kerma rate of the $^{192}$Ir source, to Level III audits involving measurement of dose in a phantom where the dwell positions and dwell times were calculated using the treatment planning computer. A small pilot study looking at the feasibility of conducting a brachytherapy audit was conducted in Australia. This study was based on the European audit described by Roue et al [52]. The Australian study was carried out in 7 centres using a small water phantom to confirm the dose predicted by the treatment planning system was consistent with measured dose using TLDs and 6-dwell positions. The study proved that such audits are feasible, and did detect one error at one treatment site. Recommendations for future studies, however, include the use of a phantom that more closely mimics a clinical situation, as this is more likely to detect errors that could occur in the clinic.

6. Outlook and conclusion
Audits are an essential part of quality radiotherapy. The complexity of modern radiotherapy makes a risk management approach essential as not all relevant aspects of a treatment delivery can be verified. By identifying the events that have the worst consequence and estimating how likely they are, it is possible to prioritise activities for dosimetric audits. It is likely that auditing in radiotherapy will go further along this road and include cost effectiveness, societal priorities and the desired outcome when deciding on new audits. It is also likely that dosimetric audits will not suffice to characterise practice and a more comprehensive audit is required. The IAEA has recently introduced such an audit specifically for radiotherapy [53-55]. However, whatever happens, given the high doses given in radiotherapy, there always will be an emphasis on safety: Primum non nocere.

7. References
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