Recommendation for the Frequency of Calibration Audits by a Quality Assurance Center Supporting NCI sponsored Clinical Trials.

This document represents work in progress within the Advanced Technology QA Consortium (ATC). Comments are welcome and should be directed to Marcia Urie, PhD or David Followill, PhD, co-chairs of the ATC Credentialing and QA Committee.

Executive Summary

The focus of this report is to provide data from the Radiological Physics Center (RPC) and the literature from which a consensus opinion could be developed regarding annual reference dosimetry TLD audits. Such audits would be conducted by a recognized quality assurance organization and would be performed by NCI cooperative group members, or their affiliates and collaborators. These institutions are primarily located in the USA and Canada.

After an extensive literature search, this committee was unable to find any peer-reviewed published data assessing the possible resulting impact on clinical trial outcome from a change in frequency (increase or decrease) of reference dosimetry audits. The following report analyzing data from the RPC, however, does provide data that indicate that a reduction in the frequency of TLD audits would likely lead to an increase in the number of institutions with an undetected calibration error. The data provided also indicate that in any given year, photon beam audits failed to meet the 5% agreement criteria at 7-14% of the institutions (3-5% of the photon beams) that enroll the majority of clinical trial patients. Including the impact of the number of patients enrolled onto clinical trials from institutions with TLD discrepancies, the percent of total patients per year potentially affected by photon beams with a TLD audit outside of the 5% criterion range from 5 to 12%.

Published data indicate that dose errors as small as 3% can affect the quality and outcome of a trial unless this is anticipated and the trial is powered appropriately. [3-5] As indicated in the World Health Organization report[1] the majority of radiotherapy errors originate from human error which is the probable cause for the majority of the beam calibration errors since it is the one dosimetry parameter most likely to change with time and subject to human interpretation of the calibration protocols. A reduction in the audit frequency and a corresponding increase in the number of undetected calibration errors may increase the uncertainty in tumor dose of patients entered onto trials. It is the consensus of this committee that uncertainties in the doses delivered to clinical trial patients should be kept small to avoid increasing patient accrual goals. The following recommendations are made:

1. The frequency of the reference dosimetry TLD audit should remain annual for participating instituions within the USA and Canada as is currently the parctice.

2. International institutions (outside the USA and Canada) wishing to participate in NCI sponsored clinical trials will have all of their photon beam calibrations verified using a TLD audit prior to enrolling patients onto the trial. Any new machine put into clinical service at the facility will

also have all of its photon beams audited as well. These audits should be performed at a minimal interval of every two years.

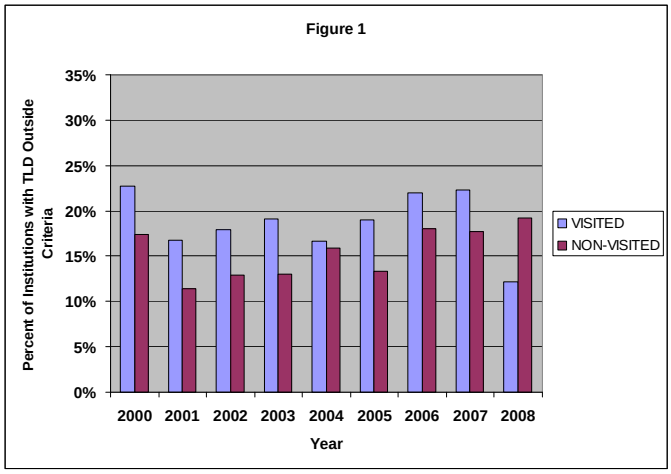
3. The RPC and EORTC will jointly conduct a study to determine the consequences and impact on clinical trial dosimetry of varying the frequency of the TLD audit.

Report

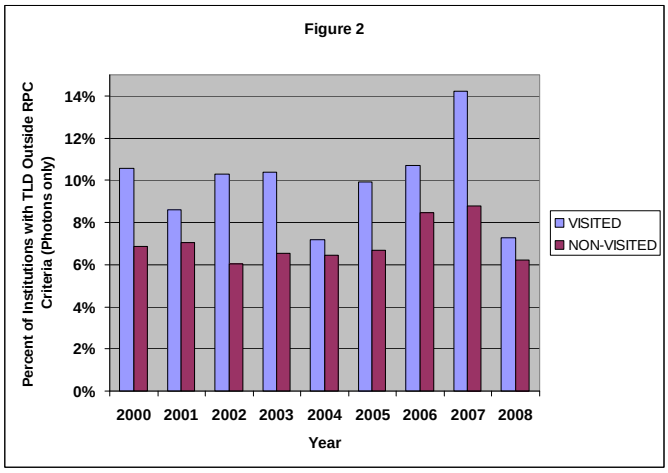
Currently, there are four quality assurance centers throughout the world that have large TLD audit programs to monitor the machine output of megavoltage radiotherapy machines. These groups include the Radiological Physics Center (RPC), International Atomic Energy Agency (IAEA), Radiation Dosimetry Services (RDS) and European Quality Assurance Laboratory/European Society for Therapeutic Radiology and Oncology (EQUAL-ESTRO). Of these four centers, the RPC has the largest TLD program and monitors all of the institutions (1669 institutions) that participate in NCI sponsored clinical trials, both within the USA and internationally. The RPC initiated its TLD program for photon beams in 1977. In 1982 electron beams were included, and in 2007, measurements of proton beams were initiated. (It is noted that the IAEA monitors about the same number of institutions as the RPC, about 1600. However, the IAEA measures far fewer beams per year, and reported measuring only 828 beams in 2006-2007 whereas the RPC measures approximately 13,000 beams annually.)

The aim of the RPC, as funded by the NCI, is to assure NCI of the correctness and consistency of the physical data for radiotherapy patients entered onto clinical trials. A secondary aim is to provide feedback to the participating institutions to correct any errors discovered by the RPC. These aims serve to help minimize the uncertainty in the radiotherapy doses delivered to clinical trial patients. The TLD audit of the machine output has been and continues to be an integral part of the RPC QA program. It is the only QA process that reaches every participating institution on an annual basis and as such is the one audit tool that provides continued assurance that the basic output of each machine used to calculate the tumor dose for each patient is accurate and consistent. In addition to the machine output audit, the TLD audit also serves as a mechanism to gather demographic data from each of the participating institutions such as personnel, therapy machines, treatment planning systems, etc. A third benefit of the TLD audit is that it raises the awareness of the institution to the need for accuracy in their machine calibration and extra attention is given to this need when the TLD are sent. New megavoltage machines of the same make, model, and energy used to treat patients these days are fairly similar in terms of their dosimetry properties; however, the one dosimetric quantity that is unique to each machine and highly dependent on personnel and human intervention is the machine output calibration. Numerous explanations for the initial TLD discrepancies in beam output calibrations have been identified, including errors made during calibration of machines by young or inexperienced personnel, errors in spreadsheets used to calculate the output, allowing the beam output to drift beyond the limits set forth by the institution, setup errors with the TLD, incorrect calibration parameters used, incorrect transfer of the reference calibration to the monthly output check system, problems with machine function, etc. A recent publication[1] by the World Health Organization titled “Radiotherapy Risk Profile” states that based on data from the Nuclear Regulatory Commission, 60% or more of radiotherapy incidents are due to human error. Whatever the reason for the discrepancy, the TLD audit provides a mechanism to identify potential calibration problems, enabling the institution to resolve any discrepancies and ensure that their output is correct and consistent with the other clinical trial participating institutions.

Over the past 8 years approximately 5% of all of the megavoltage beams audited with TLD have fallen outside of the RPC's ±5% dose criteria requiring some action and followup by the RPC staff. Today this would represent approximately ~140 photon and ~550 electron beams from nearly 3200 machines used to treat clinical trial patients. Of the approximately 770 institutions the RPC physicists have visited since its inception to conduct an on-site dosimetry review visit and who contribute ~85% of all clinical trial patients that receive radiotherapy, approximately 15 - 20% of these institutions per year (~150 institutions) (figure 1) have one or more photon or electron beams outside of the RPC's criteria requiring an investigation by the RPC. Of the remaining smaller institutions which contribute very few patients ~15% have a beam outside of the RPC's criteria each year. Very few institutions (≤ 50 out of 150 per year) have unacceptable TLD results in two consecutive years. This is because the RPC investigates the discrepancies and follows up with the institution to make sure the errors have been resolved. Performing less frequent audits will result in more institutions with undiscovered calibration errors for longer periods of time.



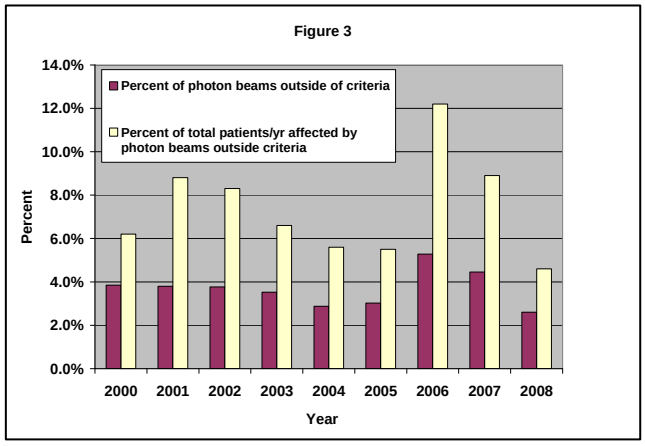
Because the majority of the NCI sponsored clinical trials employ only photon beams, figure 2 illustrates the percent of institutions with TLD results, over the past 8 years, from photons beams only, whereas figure 1 showed the percent of institutions for TLD results from both photon and electron beams. Figure 2 indicates that when only photon beams are considered, the percentage of institutions having a beam outside of the RPC's criteria is reduced from 15–20% to 6–14 %. A further breakdown of these data in terms of photon beams only, and not institutions, show that the percent of photon beams that have the initial TLD outside of the RPC's 5% criterion range from 3 to 5% as seen in figure 3. The larger trial contributors, i.e., the visited institutions that contribute the majority of clinical trial patients, are more likely to have one or more TLD problems. A further breakdown of the TLD results shown in Figures 1 and 2, isolating USA institutions, Canadian institutions and the rest of the international facilities can be seen in the Appendix A of this report in Figures A1-A6. One should note that when considering the percentages for the non-USA institutions in all figures, these values represent small numbers of institutions, but we believe that they are a representative sampling of the international radiation oncology sites that contribute patients to clinical trials.



It is difficult to discern the actual dosimetry errors from the simple mistakes such as setup errors. To the best of our knowledge, the data presented in this report do not include the results from common known irradiation mistakes based on information provided by the institutions. The RPC TLD results

represent potential calibration errors at participating institutions as supported by the fact that the frequency of reference calibration errors detected during the RPC's on-site dosimetry reviews using an ion chamber is 3% for photon beams only as compared to an average of 4% from the TLD audits. The percent of institutions with confirmed machine output calibration errors using an ion chamber is 13% which is close to the percentages (7-11%) from the TLD results (figure 2) over the same time period (2000-2008).

If one takes a closer look at the TLD results for institutions in terms of their patient contributions and limiting the data to photon beams, the percent of total patients per year affected, on average, by the photon beams outside the RPC's TLD criterion ranges from 5 to 12% as seen in Figure 3. These data were derived from knowing the numbers of patients put onto clinical trials by each institution, the number of photon beams at each institution and the fraction of the photon beams outside of the RPC's 5% criterion for the TLD audit. A more detailed description of this analysis can be found in Appendix B. A statistical analysis would be needed to determine whether 5-12% of the patients having dosimetry errors of ≥5% would have an impact on a trial outcome. In addition it is not known how reducing or increasing the frequency of the audit would impact on the outcome of a trial due to the uncertainty in patient dosimetry. Tom Pajak, an RTOG statistician, has stated that if a study involving RT is ever questioned as to the outcome, without proper radiation therapy QA, the results of the study would be less likely to be accepted, or additional patients might be required to improve the power of the study. Studies that include radiation therapy have the luxury of being able to quantify the delivered doses and have a high degree of certainty that the dose delivered is correct because of the QA programs currently in place. The purpose of these QA programs (including the annual TLD audit) is to provide the NCI with the highest quality data for its clinical trial research programs.



Is a TLD audit of the machine output necessary? It is the consensus of this committee that the TLD audit serves to provide assurance that the basic radiotherapy dosimetry at participating institutions is correct, helping to reduce the uncertainty in the delivered tumor doses to patients entered onto clinical trials and allowing the QA centers to focus their efforts on more specific QA or protocol issues. As such, the committee recommends that the annual TLD audit be continued for all clinical trial participants in the USA and Canada as is currently the practice. Numerous errors have been detected at the institutions monitored by the RPC, demonstrating the risk that such errors could go undetected without the regular oversight of the TLD program. An example of this occurred at the Moffit Cancer Center where 77 patients were overdosed by 50% with photons, due to an error in the beam calibration, over a 10 month period.[2] RPC data show that, despite the emphasis on board certification and licensure of medical physicists (in some states), a number of calibration errors continue to occur at institutions participating in clinical trials.

Should the TLD audit be administered annually, biennally or even less frequent? There exists no data to suggest the optimum frequency of the TLD audit in terms of its impact on clinical trial dosimetry. The precedent for performing the TLD audit annually was established by the RPC many years ago and all

current trial data and results are based on having this level of QA. Published data by Bentzen et al[3] reviewing EORTC trial results indicate that, based on their TLD audit program, in cases where the beam calibration was low or high there were decreases in tumor control probability or increases in normal tissue morbidity, respectively, when looking at the clinical dose response data. Bentzen et al[3] also indicated that sequential TLD audits improved the uniformity of the clinical outcome and that small deviations in beam output might lead to clinically important variations in outcome. These same conclusions were reached by Pettersen et al[4] when they discussed the impact of dosimetry quality assurance and its impact on sample size in randomized clinical trials as well as by Boyer and Schultheiss[5] who looked at the effect of dosimetry uncertainty on complication-free local tumor control. It is further recommended by this committee that a study to determine an appropriate frequency of the TLD audit should be conducted. The RPC and EORTC QA office have consulted statisticians and have designed a study to examine the frequency and errors detected by the TLD audit. The proposed study can be found in Appendix C.

It is the consensus of this committee that, until the study to determine the optimum frequency of the TLD audit is completed, international participants such as those in the EORTC, shall perform an initial independent beam calibration TLD audit of all photon energies at the institution prior to enrolling patients onto NCI sponsored clinical trials. In addition any new machine installed at the international participating institution will also have all of its photon beams similarly audited with TLD or similar dosimeter. This audit for international institutions should be conducted every two years as a minimum.

Mailed TLD audits have been and continue to be an integral part of quality assurance for clinical trials. The RPC's annual TLD audit of the machine calibration gives the NCI assurance that clinical trial patient radiation doses are accurate and consistent, reducing the risk that the outcome of a study was influenced by uncertainty in radiation doses as noted by Bentzen et al[3]. When conducting clinical trials it is important to have periodic documentation showing that the participants are qualified to perform their assigned tasks such as delivering the therapeutic dose to the patient in an accurate manner according to the specifications of the protocol.

References

[1] "Radiotherapy Risk Profile", World Health Organization, Geneva, Switzerland, 2008.

[2] http://www.usatoday.com/news/health/2005-04-02-radiation-overdoses_x.htm, accessed March 18, 2009.

[3] Bentzen et al, Clinical impact of dosimetry quality assurance programmes assessed by radiobiological modeling of data from the thermoluminescent dosimetry study of the European Organization for Research and Treatment of Cancer., European J. Cancer (36), 615-620, 2000.

[4] Pettersen et al, Quality assurance of dosimetry and the impact on sample size in randomized clinical trials., Radiotherapy and Oncology (86), 195-199, 2008.

[5] Boyer, A. and Schultheiss, T., Effects of dosimetric and clinical uncertainty on complication-free local tumor control., Radiotherapy and Oncology (11), 65-71, 1988.