International Journal of
Radiation Oncology
biology • physics

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EDITORIAL

Independent Phantom Irradiation Is Both Necessary and Cost Effective for Clinical Trial Credentialing

The Science Council and Therapy Physics Committee of the American Association of Physicists in Medicine

Received Dec 23, 2014, and in revised form Jan 12, 2015. Accepted for publication Jan 13, 2015.

The Science Council and Therapy Physics Committee (TPC) of the American Association of Physicists in Medicine (AAPM) applaud the report by Bekelman et al (1) and support the overarching goal of examining "challenges and opportunities for optimizing radiotherapy quality assurance (QA) in clinical trial design." The AAPM TPC includes an ad hoc committee, which provides scientific oversight of the activities of the Imaging and Radiation Oncology Core-Houston (IROC-Houston), which was formerly the Radiological Physics Center. From the AAPM perspective, several statements made by Bekelman et al regarding the possibility of eliminating independent credentialing of various treatment techniques for clinical trials led to an investigation of the value of measurement-based independent credentialing. Since the publication of the Bekelman report in 2012, the National Clinical Trials Network of the National Cancer Institute (NCI) has been restructured, but the issues we deal with in this editorial remain relevant.

As noted by Bekelman et al, several publications have shown that treatment outcomes are critically dependent on compliance with clinical trial requirements. Although no data are or likely will become available on the impact of clinical trial outcomes for institutions who fail an independent benchmark test (yet are allowed to enter patients on study), we think it is safe to assume that assurance of treatment delivery accuracy is important. For NCI-sponsored clinical trials involving advanced technologies, independent phantom irradiations have provided assurance that radiation dose delivery follows the guidelines stipulated in the protocols across all participating centers. This has been immensely beneficial to improving the quality of clinical trials and to participating institutions that were initially unable to pass the credentialing test (2).

The current credentialing process for radiation trials involving advanced technologies requires irradiation of an appropriate phantom provided and analyzed by IROC-Houston (the current names of the centers will be used for clarity). An anthropomorphic phantom is sent to the institution's physicist, who should work with the protocol team to treat the phantom as a patient following the guidelines from IROC-Houston. The credentialing process involves performing a computed tomographic simulation, generating a treatment plan, and delivering the plan in a single fraction. The irradiated dosimeters in the phantom are analyzed by the IROC-Houston and compared with the institution's treatment plan. This constitutes an independent analysis of the delivered dose distribution. The yearly pass rate for intensity modulated radiation therapy (IMRT) irradiations of an anthropomorphic head and neck (H&N) phantom have improved from 64% in 2003 to 88% in 2012 (2). This improvement is partially attributed to what the IROC-Houston has learned through its program and disseminated to the community.

We are concerned about how the statement on page 7 regarding the tier 2 trial-specific credentialing may be interpreted:

> "Considerable thought should be given to replacing physical phantom dosimetry tests with digital phantom dosimetry, such that an image data set is provided on which a treatment plan is generated by the participating institution. The actual irradiation is then performed on the institution's own phantom. The

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 92, No. 3, pp. 501–503, 2015
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2015.01.021

American Association of Physicists in Medicine Task Group 119 has proved the feasibility of this approach."

Earlier in the report, Bekelman et al state that no peer-reviewed analysis of the benefits of the IROC-Houston phantom test versus the IMRT benchmark of IROC-Rhode Island (formerly known as the Quality Assurance Review Center) has been reported (1). Another consideration for recommending changes to the current paradigm of independent IMRT dose analysis may be cost. We believe that independent review of institutional IMRT dose delivery is important to continue and is cost effective, as we discuss here.

The Need for Independent Measurements

The IMRT benchmark, used by IROC-Rhode Island, requires the institution to create an IMRT plan for a specific target and organ-at-risk geometry and beam arrangement (3). The institution's personnel perform their patient-specific QA measurements for the plan and then upload plan data and QA results to IROC-Rhode Island. These benchmarks pass the IROC-Rhode Island criteria if the submitted plans meet the planning guidelines and if the measurement results are reported as reasonable. However, each institution sets its own passing criteria. This type of benchmark credentialing ensures that the credentialed site is capable of creating a plan that meets certain specifications set by them, but it does not independently assess the institution's ability to accurately deliver that plan. A group of 113 institutions completed the IROC-Rhode Island IMRT benchmark and irradiated the independently evaluated IROC-Houston IMRT H&N phantom. All of the institutions passed the IROC-Rhode Island IMRT benchmark (planning study and self-reported measurements); however, 20 of these institutions failed the independently analyzed H&N phantom irradiation (4). The benchmark, with its lack of independent assessment, is unable to detect deliverability problems that the IMRT H&N phantom is able to detect.

The inability of institutions to accurately detect the failures of their IMRT delivery is further seen by an analysis of the failing H&N phantom irradiations. Along with returning the irradiated phantom for analysis, most institutions submitted their treatment plan and QA results for the phantom plan, following their clinic's patient-specific QA process. We analyzed the patient-specific QA results of those institutions that failed the H&N phantom irradiation between 2010 and present. All of those institutions either explicitly reported that they passed their own criteria or submitted results that were presumed to have passed. These institutions reported QA results for their H&N phantom irradiation pretreatment QA of 90% or more pixels passing, yet their phantom irradiations failed to meet the IROC-Houston's 7%/4 mm criteria. The institutions' gamma calculations were based on 2% to 5% dose agreement (relative or absolute) and 2- to 5-mm distance to agreement. Thus, for the H&N phantom irradiations, these institutions were rarely able to detect a delivery failure when using their own QA systems. Kruse (5) and Nelms et al (6) have highlighted some limitations of IMRT QA techniques for detecting poor-quality treatment plans, such as detector spacing, irradiation geometry, and generous passing criteria. Errors or inaccuracies in either the detector system or measurement method are generally not apparent and may be unknowingly compensated for by the institution during the evaluation of its own QA results. A dosimetry system irradiated by the institution but evaluated by IROC-Houston can reveal these errors (5, 6). With respect to virtual tests, it is important to note that AAPM Task Group 119 stated that all participants in that work had previously passed the IROC-Houston phantom for the IMRT H&N benchmark.

These data demonstrate that the digital benchmark with institutional QA, although feasible for multicenter trials, is inadequate at detecting failures when compared with an independent phantom irradiation. The data and analysis provided by the IROC-Houston and IROC-Rhode Island just presented dispute the proposal by Bekelman et al that digital benchmarks can replace independent phantom benchmarks. In addition, independent phantom benchmarks allow an institution to verify the entire planning, setup, and delivery process as an end-to-end test.

What Is the Cost Burden of Independent Measurement-Based Credentialing?

Because of the additional costs of shipping the IROC-Houston phantom, analyzing the dosimeters, and other IROC-Houston overhead associated with the independent phantom irradiation compared with the IROC-Rhode Island benchmark, we reviewed the benefits and quantify the costs of the H&N phantom irradiation program. We analyzed the costs of the phantom irradiation program by the number of patient cases. IROC-St. Louis (formerly known as the Image-Guided Therapy QA Center) and IROC-Rhode Island processed data for more than 5000 advanced technology patient cases for NCI-sponsored clinical trials from 2007 to 2011. The IROC-Houston phantom costs (preparation, dosimeters, personnel, analysis) were estimated as $130 per patient when averaged over these patients. The institutional cost to irradiate the phantom should be consistent with the cost for patient simulation, planning, and 1 treatment delivery. In relation to the total cost of conducting an advanced technology clinical trial, this price is considered reasonable, given the increased assurance of dosimetric consistency for a given clinical trial and the critical dependency of clinical trial outcomes on dosimetric consistencies across institutions.

Bekelman et al raised important considerations regarding the design of clinical trials and the distribution of effort and funds in support of cost-effective trials. However,

in light of the relatively low cost and high capacity to detect errors, physical phantom irradiations analyzed by an independent group like IROC-Houston are well worth the incremental cost and effort on everyone's part.

We propose further investigation into the appropriate use of benchmarks based on the degree of treatment delivery variation across institutions. There may be situations in which a technology is deemed to be too variable for routine use in national clinical trials, another level in which benchmarks are a part of credentialing, and a third situation wherein benchmarks are eliminated when the variation among institutions is minimal (7, 8).

From the experience with the IMRT H&N phantom, it has taken 10 years to achieve an 88% passing rate (2). Without independent phantom irradiations, the lack of delivery consistency across institutions will likely be unknown, degrading the quality of clinical trial data and potentially leading to more clinical trials in which violations of QA, protocol, or both (mostly unidentified when the credentialing is not done) will cause incorrect or less statistically valid trial results. We strongly argue that careful, independent clinical trial credentialing continues to have a role for effective and cost-efficient clinical trials involving radiation therapy.

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