Brief Report

The role of Imaging and Radiation Oncology Core for precision medicine era of clinical trial

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Abstract: Imaging and Radiation Oncology Core (IROC) services have been established for the quality assurance (QA) of imaging and radiotherapy (RT) for NCI's Clinical Trial Network (NCTN) for any trials that contain imaging or RT. The randomized clinical trial is the gold standard for evidence-based medicine. QA ensures data quality, preventing noise from inferior treatments obscuring clinical trial outcome. QA is also found to be cost-effective. IROC has made great progress in multi-institution standardization and is expected to lead QA standardization, QA science in imaging and RT and to advance quality data analysis with big data in the future. The QA in the era of precision medicine is of paramount importance, when individualized decision making may depend on the quality and accuracy of RT and imaging.

Keywords: Radiotherapy (RT); imaging; quality assurance (QA)

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Introduction

Healthcare has evolved into precision and personalized medicine with medical decisions, practices, and interventions basing upon the individualized information. Evidence based decision making is the cornerstone of modern medicine. Randomized clinical trials produce level one evidence for potential improvement of practice. NCI's Clinical Trial Network (NCTN) has supported practice changing randomized clinical trials for over fifty years. One of the key components of this clinical trial network is the rigorous quality assurance (QA) requirement, in particular, for radiation therapy and imaging. This rigor in quality is essential for a successful conduct of clinical trials involving radiotherapy (RT) and imaging.

Studies have shown that noncompliance with RT protocol guidelines has been linked to inferior clinical outcomes, including an increased rate of toxicity, increased treatment failure and overall mortality from multi-institutional clinical trials (1-4). Deviations from RT guidelines identified through central review included inadequate definition and treatment of target volumes, overdose administered to normal structures to be avoided and prolonged RT treatments exceeding guideline. The frequency of RT QA deviations was found to be significant, ranging from 8% to 71%, a quality issue that needs to be addressed.

QA in clinical studies is found to be cost-effective. Reduced uncertainties in RT dose can lead to a significant reduction in the number of patients required in a randomized clinical trial when the expected difference between the experimental and conventional arm is small (5). Measurement precision and the sensitivity of imaging measures to true change affect sample size in studies involving evaluation of response to therapy. Sample size can increase 15 folds when PET precision worsens from 10% to 40% at full measurement sensitivity to true change (6).

Technological advances in RT and imaging have enhanced the ability to identify and target tumors while protecting normal structures during cancer therapy interventions (7). Innovative technology in radiation oncology and imaging are being developed and translated into clinical practice to meet with current and future challenges. Technologies in functional imaging, treatment devices, nanotechnology, as well as information technology have been advancing rapidly. The quality and safety

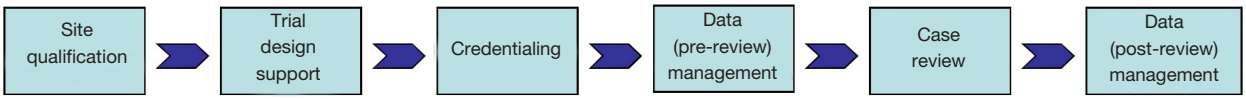

Figure 1 IROC's five core functions.

performance of these technologies are of paramount importance when introduced into clinical trials, either as primary objectives or as secondary aims. The need for a QA program for a clinical trial, adaptive to these ever-changing needs, is essential for evidence generation of efficacy and effectiveness for the advancement of medicine.

Imaging and Radiation Oncology Core (IROC) infrastructure

In the development of NCTN program (8), a QA IROC group was established to ensure the standardized and consistency of assessments and treatments. This core is tasked to provide RT and imaging quality, data management services to enforce consistent qualities of innovative technical developments in imaging and new therapeutic modalities for multi-institutional clinical trials. This core service organization provides scientific and technical expertise in both imaging and RT QA to the entire network. A number of QA centers in the past NCI Cooperative Group Program have joined their collective strengths to form the new IROC group. The mission of IROC is to provide integrated RT and imaging quality control programs in support of the NCI's NCTN program, thereby assuring high-quality data for clinical trials designed to improve the clinical outcome of cancer patients worldwide. IROC provides five QA core functions that include site qualification, protocol development support, credentialing, data management (pre- and post-review), and case review (see *Figure 1*).

The IROC QA centers include IROC Houston, IROC Ohio, IROC Rhode Island, IROC Philadelphia (RT), IROC Philadelphia (Imaging) and IROC St. Louis. Work flows, QA processes, informatics platforms, and tools are developed within IROC so that the multiple locations of the QA centers are transparent to the participating sites. The inter-dependencies between imaging and RT is synergized. The IT infrastructure of IROC allows easy transmission of imaging and RT datasets for receipt, assessment, validation, and archiving. The IROC network utilizes the American College of Radiology's TRIAD© (Transmission of Imaging and Data) system as the epicenter of the workflow for IROC QA centers, providing a common portal for data transfer from NCTN sites to the imaging network in IROC. Sharing and access of imaging and RT planning datasets with NCTN groups and NCTN investigators are implemented within the cloud via TRIAD, promoting rapid QA and implementation of centralized data analyses.

RT and imaging

Diagnostic imaging and radiation oncology have strong interdependency. With the advent of advanced imaging and RT technologies, they become ever more closely integrated. Within the clinical trial environment, there are ample opportunities for the integrated programs to develop between the disciplines.

Imaging has become a crucial biomarker for disease identification and response to therapy assessment. The advent of functional imaging has altered the definition of disease response (9), creating opportunities and challenges in standardizing the imaging and image evaluation. As such, ensuring the accuracy in imaging and image diagnostics has become the crucial core service required for successful execution and completion of the modern clinical trial. Imaging is also playing an increasingly essential role in modern RT, as image guided adaptive RT, utilizing advanced imaging modalities, is applied to multiple time points during treatments and is implemented in institutions globally (10). Multiple image data sets including advanced imaging technologies are used to define target volumes of interest and are applied to ensure consistent target coverage with daily uncertainty and with motion in real time during therapy delivery. These images can be used assess response to systemic and local therapy. In clinical trials, these images are submitted, archived and reviewed in an integrated format. They are used for multiple tasks including outcome analysis. This integration facilitates efficient and precise review from both RT and imaging perspective.

IROC Philadelphia RT and imaging

We have devoted a tremendous amount of effort in standardization for QA and established automated processes

in some of the peer reviews, including dose volume histogram review. Other review processes with few human interventions are being developed, such as target and critical structure segmentation quality evaluation.

Standardizing RT guidance in the protocol is crucial to the uniform practice and for the quality of data acquired for clinical trials. Different planning protocols may define varying planning target volume (PTV) dose criteria, resulting in differences in organ-at-risk (OAR) sparing (11). This could influence rates of toxicity and could influence how we compare clinical studies. IROC has been working in tandem with NRG Center of Innovation in Radiation Oncology (CIRO) in publishing templates for the guidance of radiation therapy for various disease sites aiming for such a standardization (12).

For the IROC QA process to be successful, RT structure names must be used consistently among all clinical trial sites. This QA process to ensure uniformity in structure naming is performed in the TRIAD submission process with automated validation profiles developed and implemented for each trial. A uniform radiation therapy structure name library is used for all NRG protocols (13). This structure name library is fully compliant with AAPM TG 263 and is published on NRG CIRO website (12).

TRIAD currently supports different layers of filters and rules and allows the definition of one layer or multiple layers depending on the complexity of the trial. Upon submission of digital data in TRIAD, the user can be prompted to select the layer that applies to the data being submitted. Users are able to see which structure(s) is (are) missing from within the TRIAD submission window before sending the data for QA. TRIAD allows the administrator to apply "hard" or "soft stop" to the validation. If a hard stop is applied, the user cannot proceed with submission if any of the list structures or validation parameters are missing, misspelled, or do not meet the defined protocol criteria (14). Similarly, in trials for which specialized imaging (PET, MRI) is required for tumor staging and target definition, TRIAD validation modules are implemented to ensure that the correct imaging sequences and parameters are obtained.

The case review process includes TRIAD validation profile for structure name standardizations, harmonized MIM software review with the built-in script and automated DVA form population following review with MiM. All the automatic processes are validated with a sufficient number of cases to ensure the accuracy. The dose volume analysis (DVA) form is compliant with a standard file format protocol that enables automated upload to Medidata Rave for accuracy and efficiency of clinical trial data collection.

MIM scripts, DVA form and related templates from these processes for all applicable NRG trials are published.

To ensure consistent segmentation of critical structures, we have built a number of structure atlases for automated contouring of these structures. We have evaluated and established the feasibility of automated QA of cardiac structures based on Atlas contours created from RTOG 0617 (15).

The quality of RT treatment plans varies across institutions and depends on the experience of the planner. For intra- and inter-institutional standardization of treatment plan quality, we use knowledge-engineering approach and build models that learn the OARs sparing patterns from submitted quality plans. Thereafter, the model predicts the dose that similar organs will receive in RT plans on the basis of the anatomies of the organs for newly submitted cases. These models can also be used to predict the feasibility of planning objectives, in addition to objective assessment of the quality of RT plans (16-18). Our predictive models cover multiple disease sites, including head and neck, brain, lung, and prostate.

IROC Philadelphia RT and imaging future directions

There are tremendous opportunities looking into the future for a close integration of QA in RT and imaging, as more advanced imaging modalities are frequently utilized in diagnosis, guiding treatment and treatment response assessments. Advanced RT technologies incorporate imaging as an integral component, such as online adaptive RT treatments with real time imaging. For example, the current RTOG 1106/ACRIN 6697 trial utilizes mid-treatment FDG-PET to allow for adaptive radiation panning in lung cancer. This trial illustrates the unique synergies between QA processes in RT and advanced diagnostic imaging modalities. In future trials, RT target definitions will become increasingly based on not only anatomical imaging but functional, molecular and other methods for biological guidance. RT standardizations will be complemented by standards from Imaging communities, such as those developed from the Quantitative Imaging Biomarker Alliance (QIBA), with tools developed from the Quantitative Imaging Network (QIN) implemented for QA needs of the clinical trial community.

IROC centers have the responsibility for the acquisition of quality data from clinical trials, and in making the data

sharable in that they have the properties of being findable, accessible, interoperable and re-usable. The data should be used to derive QA criteria, enabling evidence-driven QA processes. Methodologies in machine learning, i.e., deep learning, and/or artificial intelligence can be utilized in the evidence-generating efforts.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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