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PROCESSES FOR QUALITY IMPROVEMENTS IN RADIATION ONCOLOGY CLINICAL TRIALS

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Abstract

Quality assurance in radiation therapy has been an integral aspect of cooperative group clinical trials since 1970. In early clinical trials data acquisition was non-uniform and inconsistent; computational models for radiation dose calculation varied significantly. Process improvements developed for data acquisition, credentialing, and data management have provided the necessary infrastructure for uniform data. With continued improvement in the technology and delivery of radiation therapy, evaluation processes for target definition, radiation therapy treatment planning and therapy execution undergo constant review. As we move to multi-modality image-based definitions of target volumes for protocols, future clinical trials will require near-real time image analysis and feedback to field investigators. The ability of quality assurance centers to meet these real time challenges with robust electronic interaction platforms for imaging acquisition, review, archiving and quantitative review of volumetric radiation therapy plans will be the primary challenge for future successful clinical trials.

Keywords

clinical trials; quality assurance

Introduction

Quality assurance has played an integral role in cooperative group clinical trials for more than thirty years. Improvements in the process of quality assurance have supported compliance with the guidelines established for each study. This has increased the eligibility and treatment uniformity of the study population, which helps validate the study conclusions. Protocols have matured with increasing complexity over the past twenty years. The modern study has multiple imaging and biological correlates in addition to the primary therapeutic treatment endpoints. The quality assurance processes in each trial have to reflect the increasing complexity of both the protocol questions and the therapeutic technology used to care for patients on the study. The process of analysis and self-critique enables both investigators and quality assurance centers to develop improved guidelines and review processes for the next iteration of clinical trials. This process of self-renewal is an on-going aspect of education, which benefits regulatory

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agencies, the National Cancer Institute, study/site investigators, and the patient population we care for.

QARC began as part of the radiation oncology committee for the original ALGB in 1972. At that time radiation guidelines and protocol compliance were non-uniform and data, including films and radiation treatment plans, were not routinely collected for review. Within a short period of time a data collection process was developed by QARC and study investigators began reviewing protocol cases. During these reviews the diversity of treatment strategies was identified, including, for example, using full midline spinal shields in patients with lung cancer. Once identified as problems, changes in the guidelines were made to achieve uniformity of treatment execution. The primary area of non-compliance at that time was computational in nature and QARC recalculated each beam. Guidelines were established for computational methods and compliance became remarkably uniform as planning systems became commercially available from a limited number of vendors and methods became standardized. QARC evolved in workscope and stopped calculating each field in the early 1990's. Rather, the technique of benchmarks was developed to evaluate an institution's ability to participate in specific trials. Today these benchmarks are evolving to include imaging interpretation and target volume definition as well as treatment planning processes.

Credentialing Institutions for Protocol Activity

QARC developed a process of credentialing institutions via benchmark cases as one method for ensuring treatment uniformity and protocol compliance. Initially a specific benchmark appropriate to the treatment in the protocol was assigned to each protocol. For example, for protocols requiring treatment to the entire neuro-axis of the central nervous system, a benchmark was developed for cranio-spinal irradiation. The benchmark evaluated each institution with respect to computation, match techniques between the brain and spine fields, collimator/couch rotations, and dose to the spinal cord. For protocols developed to treat patients with Hodgkin's disease, a benchmark was established to evaluate computations for irregular blocking schema and dose to off-axis points.

As treatment planning and delivery technology have become more complex, benchmarks have been developed to address new technologies. When 3D CT-based planning systems were becoming commercially available, a benchmark was designed to assess the ability of an institution to use the three dimensional planning tools. Institutions used their own CT scans to define an anatomic target volume, develop a treatment plan that included a vertex field, and complete the benchmark. More than 450 institutions have been credentialed with this benchmark. The benchmark for intensity modulated radiation therapy follows a similar paradigm. Institutions are required to develop a treatment strategy for a hemi-annulus target 3mm from a central organ at risk, which they could define on one of their CT data sets. The treatment plan must provide coverage of the target with $\leq 60\%$ dose to the organ at risk. Acceptability criteria for the plan were developed in collaboration with members of the ATC. Additionally, dose verification data are required to be measured and submitted. Over 190 have been approved, approximately 70% on first submission.

QARC currently houses more than 2500 benchmark cases from institutions around the world; some of the results have been published (1-3). Benchmarks have been designed to ask appropriate questions without being overly burdensome (~3 hours to complete) so as not to discourage institutional participation in clinical trials.

Moving forward, imaging and image registration of various modalities will be an important aspect of protocols. For a recently opened COG trial for low grade glioma, target volume definition is driven by MR; registration of MR with the planning CT is mandatory. QARC initiated a benchmark that evaluates image registration performed at each institution. Two

image sets are provided: a planning CT, (obtained in a stereotactic head frame), which does not show the lesion of interest, and a MR, which reveals a small lesion in the left occipital region. Institutions register the image sets using whatever tools they normally do, define the target on the MR, and report the X, Y, and Z coordinates of the center of the lesion on the CT scan. QARC has credentialed more than 50 institutions using this benchmark; approximately 80% have been successful on the first submission. This benchmark has established a standard for clinical trials for protocols requiring image registration for target volume definition, showing the need for a 3 mm increase in planning target volume definition for uncertainties in image registration between MR and CT. The image registration benchmark also reflected the advancement of technologies. Prior QARC benchmarks asked institutions to use CT scans from their own database. For this benchmark QARC distributed the same DICOM image sets to each institution. Nearly all institutions were able to download these image sets from the web and load them into their planning systems without major problems.

Most benchmarks have tested treatment planning capability. For one head and neck trial, the majority of deviations were due to the inability of investigators to define accurately the target volumes according to the protocol. For a follow-up study, QARC initiated a benchmark that required physicians to draw the target volumes for a right tonsil tumor mass directly invading a level 2 lymph node over the parallax of the spinal cord, and then to develop a protocol compliant treatment plan. Treatment planning could be standard, 3D conformal, or IMRT. The benchmarks were assessed both for the ability of the physician to draw the target volumes and for the compliance of the treatment plan to protocol dose specifications. Institutions from around the world participated in this trial and the benchmark was a key process improvement. The study deviation rate was limited to less than 5%, which can be attributed largely to critique of both the target volume definitions and treatment planning during benchmark review. In the future most benchmarks will include in the credentialing process the drawing of appropriate target volumes as well as the development of dose compliant treatment plans.

Images Become a Point of Validation

The pediatric oncology group (POG) conducted a study (8725) of advanced Hodgkin's disease (Stages IIB, IIIA2, IIIB, IV) that evaluated the use of chemotherapy with radiation therapy for sites of original disease with radiation therapy as the randomization point of the study. Imaging of original disease and of response were collected by QARC. The published study (4) demonstrated no benefit to the addition of radiation therapy. A retrospective subset analysis found a statistically significant benefit in relapse free survival to those patients treated in a study compliant fashion (Table 1). These analyses imply that compliance to study guidelines may influence study outcome. Other publications (5-10) support the same conclusion.

With this information, the next iteration of Hodgkin's trials for advanced (9425) and early stage (9426) disease required pre-treatment review of the intended radiation therapy treatment fields and dosimetry. More than 95% of the imaging (pre-study, during, and after chemotherapy) and radiation therapy treatment objects were received at QARC for pre-treatment review and possible intervention. With this pre-review, the deviation rate was decreased to less than 10%, a marked improvement compared to previous Hodgkin's studies. A retrospective review by protocol radiologists to assess response to chemotherapy did not agree with the institutional judgment 50% of the time (11). This analysis identified the next generation of process improvement. As treatment strategies for Hodgkin's disease become increasingly determined by chemotherapy response, standards for assessing treatment response are crucial.

COG intermediate risk Hodgkin's disease study AHOD0031 has become the prototype for future cooperative group studies. The study is unique as response to chemotherapy, documented by anatomic and functional imaging studies, triggers multiple secondary

randomization points, including a no radiation therapy randomization. To date QARC has agreed at pre-treatment review with 78% of institutional assessments of response. The study deviation rate with respect to radiation oncology is less than 3%. This is a remarkable achievement for such a diverse group of study investigators located in many parts of the world.

Pre-treatment review of diagnostic imaging and radiation therapy treatment plans has played an important role in reducing protocol deviations in adult protocols as well. For example, CALGB non-small cell lung cancer study 30105 had a study deviation rate of 4% using pre-treatment interventional review of the planned radiation therapy. CALGB pancreas study 80003, which demonstrated an improvement in disease free survival with chemotherapy and radiation therapy, had only one deviation using this process of interventional review.

Future Considerations for Clinical Trials

Future clinical trials will become increasingly complex in both design and execution. Biologic correlative studies validated by both tissue and imaging will increasingly be imbedded into clinical trials. Images will be used for staging, eligibility, response, and outcome. Multiple imaging sets will be required on each patient, likely including metabolic and molecular imaging as well as CT and MR. These will likely be used for target volume definition for radiation therapy. Providing validation of registration will become an increasingly important aspect of clinical trials quality assurance.

Timely interactions between study investigators and quality assurance centers at the time of the study concept sheet will become increasingly important in future trials. By providing standardized templates for the imaging and radiation therapy sections of the protocol, quality assurance centers will expedite this process and make protocols more uniform across all cooperative groups, which may increase study compliance.

For the quality assurance centers, it will become increasingly important to function on a near-real time basis. Both in house and web based processes will be required. The database of each quality assurance center needs to facilitate data sharing with cooperative groups and industry sponsors, be compliant with national initiatives, and format information in a uniform manner for review.

Quality assurance centers need to establish facile pathways for image and data transfer. Efforts will be made to move to international participation for protocol enrollment in order to complete trials in a timely manner. Therefore quality assurance centers must be prepared to receive data from diverse imaging platforms and planning systems and to collate data into a uniform file set (or database) for review. It will be important for images and RT objects to be easily accessible for review using either in house or web based tools. As institutions mature in their informatics capabilities, they can be expected to submit data in a uniform format following the very successful strategy developed by the ATC for the RTOG (12). In turn, the quality assurance centers will need to place considerable emphasis on developing strategies for caBIG compliance and uploading objects to the national archive for research initiatives. This will require significant cooperation and strategic analysis of process by quality assurance centers and caBIG.

International cooperation and the ability to perform real time review will make the future of clinical trials very exciting. Processes are currently being developed to permit this expansion and the informatics tools required for success of this program are currently at our fingertips. This will greatly facilitate the validation of targeted therapies in clinical practice and ultimately improve the care of the patients we serve.

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Table 1

Relapse free survival indicating significantly better results when the radiation therapy was in accordance with protocol specifications.

Deviation Adjustment	
Survival According to Treatment* (POG 8725)	
Treatment	5 year Relapse Free Survival (%)
Arm 1: Chemotherapy Alone	85
Arm 2: Chemotherapy + RT:	
Appropriate volume	96
Major & Minor Deviations	86
* Only patients who were in complete remission at the end of chemotherapy	