Quality Assurance for Radiotherapy: A Priority for Clinical Trials

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Assessing quality of cancer care has become a national priority, particularly in the field of radiation oncology, where there have been rapid changes in practice over the past decade with the introduction of novel technologies and treatment paradigms. Professional organizations have been charged with the development of best practice guidelines as well as quality indicators to monitor the national quality of radiotherapy (RT) practice and to guide the use of new treatment approaches. Wide variations exist in RT techniques and practice patterns in the United States. Deviations from accepted standards of care can lead to disparities in the quality of care delivered. Moreover, in the realm of clinical trials, these deviations in RT quality can have direct implications on the clinical outcomes of patients enrolled in these studies, potentially confounding the study question at hand.

Lack of RT quality assurance (QA) in national and international cooperative group studies has lead to skepticism about study outcomes. One such example is the European Study Group for Pancreatic Cancer 1 Trial (ESPAC-1), which has been the subject of much criticism based on the poor RT quality control (1). This phase III, randomized trial of adjuvant chemotherapy or chemoradiotherapy for resected pancreatic cancer, which was reported in the New England Journal of Medicine, concluded that adjuvant chemoradiotherapy resulted in deleterious effects on survival (2). The concerns raised by the lack of quality control highlight the need for strict RT QA in prospective, cooperative group trials involving a specific RT question. A review process must be in place to document that the RT quality, including anatomic volume irradiated, fraction size, and dose delivered, meets protocol guidelines and to verify uniformity of the treatment to ensure that the outcome data are useful. Although it would appear to be clearly beneficial to standardize the RT quality in cooperative group trials by requiring rigorous RT QA, there is limited evidence supporting the value of QA programs (4).

In this issue of the Journal, Ohri and colleagues report the results of their systematic review and meta-analysis of cooperative group trials that report RT QA deviations to determine the impact of these deviations on patient outcomes (5). Based on their analysis of eight cooperative group studies, there was a clear association between RT deviations and inferior overall survival. The impact of RT protocol deviations can be so significant that in one trial included in the Ohri et al. meta-analysis, the Radiation Therapy Oncology Group (RTOG) 97-04 study, the “per protocol” vs “less than per protocol” RT QA score correlated more strongly with median survival than assigned treatment arm of adjuvant 5-fluorouracil vs gemcitabine before and after chemoradiation for resected pancreas cancer (6,7).

Ohri et al. included several pediatric studies, for which there has been a long-standing history of incorporating RT QA into trial designs. Much of this emphasis on QA stems back to the Pediatric Oncology Group protocol 8725 (not included in the meta-analysis), which randomized patients with intermediate-/advanced-stage Hodgkin lymphoma after eight cycles of chemotherapy to involved-field RT or no RT. The initial publication showed no benefit for RT; however, retrospective review of the data found a 10% survival advantage for patients receiving protocol-compliant RT (8–10).

These studies, and others, have lead to the integration of pretreatment rapid RT review for some studies. RTOG 0848, a large, international, phase III, randomized trial of adjuvant therapy of pancreatic cancer is evaluating the benefit of adjuvant chemoradiotherapy for patients with resected head of pancreas cancer (11). Prospective radiation quality control is mandated, with all treatment plans reviewed centrally before treatment, including evaluation of preoperative imaging, operative and pathology reports, treatment-planning computed tomography (CT) scans, all contours including regions of interest, normal structures, clinical target volumes (CTV), planning target volume, and dosimetric data before initiating RT. These data are reviewed by the radiation oncology principal investigators, and feedback is given to the treating sites, if necessary, in an attempt to achieve closer to 100% adherence to protocol RT guidelines.

QA in cooperative group trials is not a new phenomenon; in fact, the Quality Assurance Review Center has performed RT QA for cooperative group trials since its inception in 1972, when it was formed as part of the Radiation Oncology Committee for the original Cancer and Leukemia Group B (6). The original goal was to standardize protocol RT guidelines and to recalculate radiation doses that were calculated at local institutions using vastly different computational methods. With the increasing sophistication of RT planning and the use of commercial treatment-planning systems
with standardized computational algorithms, recalculating each treatment plan is no longer necessary or feasible. Technical aspects of RT can be measured by setting specific standards or benchmarks that can be met at the institutional level. The Quality Assurance Review Center and other QA centers now credential institutional sites for participation in clinical trials by having them submit representative cases or questionnaires that demonstrate the ability to meet protocol standards (6). Pretreatment rapid review of target volumes and normal tissue contours as well as treatment plans is also possible with the use of digitized formats for both imaging studies and RT planning data. This allows study investigators to provide real-time feedback to practitioners in the field and has substantially improved RT compliance rates.

One of the potential benefits of requiring RT QA in clinical trials is the impact this educational process has on overall quality of care as a result of training personnel who participate in trials on the best practices and safe implementation of RT practices for nonprotocol patients. The past decade has seen the introduction of new technologies such as intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy. More sophisticated treatment planning using computed tomography–based tumor and normal tissue delineation and IMRT treatment planning has the potential to improve local regional tumor control while reducing toxicity. However, successful locoregional tumor control depends on the accuracy of both the RT plan and its delivery. Conversely, poorly implemented RT field design, treatment planning, and delivery result in poor outcomes, both in terms of inferior cure rates and increased treatment-related toxicity. Radiation oncologists are benefiting significantly from the rapid proliferation of contouring atlases that have been developed to aid in defining computed tomography–based CTVs and organs at risk, which are required in many clinical studies. Normal tissue atlases are also in development to standardize the contouring for critical normal structures. This will help to standardize the calculation of dose-volume histograms for organs at risk and allow better assessment of any deviations from protocol-specified dose constraints.

The recent RTOG 0529 study (a phase II evaluation of dose-painted IMRT in combination with 5-fluorouracil and mitomycin-C) was designed to incorporate real-time RT QA (12). Critical to the implementation of IMRT for anal cancer is an understanding of the pelvic nodal anatomy; however, most practicing radiation oncologists were not familiar with the nodal drainage patterns. This educational need was identified and led to the development of a contouring atlas to identify the appropriate elective nodal volumes (13). This RTOG rectal and anal atlas helped to improve the compliance with protocol RT contouring guidelines and has also served to educate the radiation oncology community on the appropriate CTV and normal tissue contours for conformal RT for rectal and anal cancers.

The advantage of capitalizing on the expertise of the study investigators in the determination of the RT guidelines and the dissemination of these uniform, high-quality practice strategies cannot be underestimated. This is particularly important in the anatomic delineation of both target volumes and organs at risk and may require more intensive RT QA with real-time rapid review of contours and treatment plans. However, this is neither feasible nor essential for many clinical trials, and the development of a tiered system of RT QA, as recommended by the National Cancer Institute's working group on RT QA, is a valid approach (4). By having the rigor of RT QA tailored to the needs of the trial design, the process of QA for many studies can be streamlined by using either basic questionnaires to obtain general credentialing or trial-specific data submission requirements to gain trial-specific credentialing and reserving individual case review for studies that are specifically asking an RT-related question. Ultimately, as Ohri and colleagues (5) conclude, the benefits of improved clinical trial QA processes and adherence to protocol directed-RT guidelines may extend beyond the study participants and improve the overall quality of oncology care for our patients.

References


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