White Paper

Radiation Therapy Quality Assurance in Clinical Trials

Radialogica / IQVIA White Paper

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Table of contents

Introduction

Radiation therapy (RT) is a cornerstone treatment for cancer and frequently employed in clinical trials to explore novel systemic therapy agents in both curative and non-curative settings. The sophistication of RT provides patients with access to treatments with high levels of accuracy and precision as well as reduced toxicity, if employed correctly. However, the inherent complexity of RT planning and delivery requires rigorous quality assurance to reduce practice variability, minimize suboptimal treatments, and ensure safe and effective patient care.

Clinical trials use highly prescriptive treatment guidelines to standardize practice, isolate treatment effects, and minimize sources of variability that could potentially skew study results. Like other therapies, the impact of RT is often significantly modulated by investigator-related, patient-specific, and technological factors that influence the course of treatment. This introduces variability that can have direct consequences on overall treatment outcomes and trial endpoints.

Extensive research has demonstrated the importance of radiation therapy quality assurance (RTQA) on primary study outcomes in clinical trials. A meta-analysis of prospective clinical trials found that 32% of patients had RT treatment plans that were not-per-protocol and associated with an almost two-fold increase in risk of tumor recurrence and death compared to per-protocol plans.[1] Due to this potential interaction, RT quality must be rigorously controlled as any other study variable to ensure the quality of trial results.

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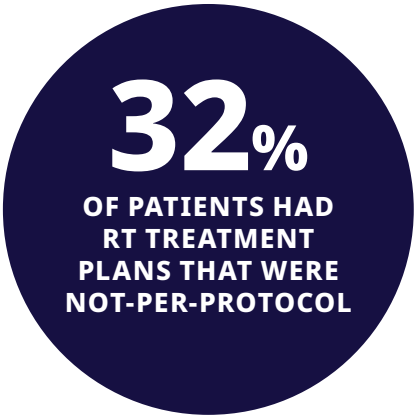
Numerous studies have demonstrated that surgical quality, training, and volume are directly correlated with cancer survival rates. RT, like surgery, is a local definitive therapy that requires an intimate understanding of anatomy and how to best deliver a treatment course with the same level of precision and expertise. However, RT offers an advantage over surgery in that quality assurance can be performed prior to the initiation of therapy. This presents a unique opportunity for prospective quality assessment and potential intervention that could mitigate sole dependence on training and volume, ensuring patients receive the safest and most effective treatment possible.

The purpose of this white paper is to highlight the fundamental role that RT plays in cancer treatment and its growing importance in the context of oncology clinical trials. This will include a review of the major sources of variability in RT, which can result in suboptimal treatment with a potential to adversely impact patient outcomes and study results. Finally, this white paper defines the key elements of a radiation therapy quality management program along with a guideline for practical prospective implementation into pharmaceutical clinical trials.



Radiation therapy in cancer treatment

RT is a proven and effective form of treatment for many types of cancer. According to the American Society for Radiation Oncology (ASTRO), nearly two-thirds of cancer patients in the United States, or more than one million new patients annually, will undergo RT during their treatment. This high rate of utilization is due in part to new technologies that deliver more accurate and precise treatment with fewer side effects compared to traditional RT methods.

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RT is a localized treatment that may be used alone or in combination with surgery and/or chemotherapy. The primary form of RT used for cancer treatment is external beam radiation therapy (EBRT), which is most commonly delivered by a linear accelerator. During EBRT, one or multiple beams of radiation are directed at the cancer from outside the body. EBRT typically involves multiple, or fractionated, treatments that are delivered over a number of days or weeks. Brachytherapy involves the insertion of radioactive sources directly into a tumor or into a body cavity close to the cancerous area. In certain situations, it enables clinicians to deliver high doses of radiation with less normal tissue exposure over a short period of time.

The anticipated growth in the number of cancer cases, combined with continued scientific and technological advancements, has fueled the need for more efficient and effective treatment delivery methods that can be readily integrated into clinical practice.

Such advancements have led to greater accuracy and precision of RT. These include:

- **Intensity-Modulated Radiation Therapy (IMRT):** IMRT is an advanced form of EBRT in which the intensity and angle of the radiation beams are varied, or modulated, to shape dose distribution. This conforms the radiation dose more closely to the shape of the tumor and allows delivery of higher doses of radiation to target volumes and lower doses to adjacent normal tissues when compared to historical methods (e.g., 3D conformal RT).
- **Volumetric Modulated Arc Therapy (VMAT):** VMAT is a form of IMRT that involves dynamic rotational delivery of radiation using a conventional linear accelerator to create a finely shaped dose distribution that more closely conforms to the tumor volume. VMAT can improve treatment precision, enhance normal tissue sparing, and shorten overall treatment times.
- **Image-Guided Radiation Therapy (IGRT):** IGRT entails the use of two-dimensional or three-dimensional imaging at the time of treatment to properly position the patient for daily delivery, ensuring greater accuracy in dose delivery.
- **Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT):** SRS and SBRT utilize IMRT and IGRT technologies to deliver extremely concentrated doses of radiation in one or a small number of fractions. SRS is used to target small lesions in the brain and SBRT uses the same concepts to treat small lesions throughout the body.
- **Proton Beam Therapy (PBT):** PBT is a form of EBRT that employs beams of protons generated by a cyclotron or synchrotron as opposed to x-ray beams from a linear accelerator. The principal advantage of proton therapy is the beam's signature energy distribution curve, known as the Bragg peak, which allows for depth-specific dose deposition that leads to better sparing of adjacent normal tissue.

Radiation therapy workflow

RT involves a multi-disciplinary care team that includes: radiation oncologists, who determine indications for RT, what volumes need to be treated, and the dose of radiation that will be prescribed; medical dosimetrists, who create computerized treatment plans; and radiation therapists, who position the patient and delivery device for treatment. In addition, physicists perform quality checks of the treatment delivery devices.

Once it has been determined that a patient will receive RT, the treatment planning process is initiated. This planning process involves multiple steps, which typically include:

- **Simulation:** Imaging the patient in the treatment position on a computed tomography (CT) scanner that is customized for RT.
- **Motion assessment and motion management:** Measuring the extent of tumor motion based on patient imaging and selection of appropriate techniques for managing tumor motion.
- **Image fusion:** Registering multiple image sets (e.g., MRI, PET) into a common spatial coordinate system.
- **Contouring:** Defining the outlines of the tumor, regions at risk for microscopic extension/spread, and adjacent critical structures to create a three-dimensional model of the patient's anatomy and target volumes.
- **Dose prescription:** Establishing dose objectives for target volumes and dose constraints for critical structures.
- **Optimization and dose calculation:** Determining optimal beam arrangements to achieve treatment objectives and quantifying the resulting dose distribution.
- **Plan review:** Analyzing qualitative and quantitative aspects of the treatment plan and performing a risk/benefit analysis of trade-offs between dose delivered to the target and adjacent critical structures.

Radiation therapy in pharmaceutical clinical trials

Since novel systemic agents are often first tested in the patients with metastatic disease, integration of RT is being increasingly considered in trials examining new pharmaceuticals.

The introduction of immunotherapy has also had a direct impact on RT in clinical trials. Robust pre-clinical and early clinical data have shown that RT can induce anti-tumor T cell activation in conjunction with immunotherapy, even in patients already shown to have tumors not responsive to immunotherapy alone.[2] Furthermore, randomized studies have shown that adding RT to immunotherapy leads to increased response rates outside of the radiated area, and improved outcomes.[3] Given the prevalence and expansion of indications for immunotherapy, there naturally will be a growth in utilization of RT in future clinical trials exploring this modality.

Radiation therapy and quality

Despite the high degree of computerization and automation that has come to define modern radiation oncology, there continues to exist significant variability in the quality of radiation treatment planning. Between physicians (or institutions), there can be dramatic differences in target/anatomic contour quality and definition, prescribed dose, balance between target coverage and normal tissue exposure, and plan optimization techniques. This variability in treatment quality can have direct consequences in terms of tumor control and toxicity.

Amongst many examples, a paper demonstrated that head and neck cancer patients treated at higher-volume centers achieve better survival rates given more expertise and higher-quality treatment plans. The authors succinctly stated, "In a manner analogous to surgery, radiation therapy is a local modality with a high degree of user dependence." [4]

Radiation therapy quality and clinical trials

Growing evidence and awareness of variability in RT and its impact on patient outcomes has led to efforts to standardize treatment and improve quality control. Protocol guidelines for RT are now standard in cooperative group studies, yet the implementation and usage of these guidelines can still vary. In the context of pharmaceutical clinical trials, the development and application of such guidelines remain limited to date, increasing concerns regarding the impact of RT on primary study outcomes.

In a larger study examining this issue, a meta-analysis from eight RT cooperative group studies across a range of anatomical disease sites found the frequency of RT protocol deviations ranged from 8% to 71% (median 32%). Furthermore, protocol deviations were associated with a nearly two-fold increase in cancer recurrence and mortality.[1] The authors concluded that "the magnitude of these effect sizes suggest that the delivery of high-quality RT is critical for the successful execution of clinical trials and for effective treatment of cancer patients."

In addition to the impact on cancer control, it is particularly important to control RT quality in pharmaceutical clinical trials given its potential interaction with systemic therapy. A prime example of this was a large randomized controlled trial for resected pancreatic cancer comparing adjuvant RT with either gemcitabine versus 5-FU. The primary analysis found no difference in survival between the different chemotherapy arms. However, in a post hoc analysis, 48% of radiation treatment plans were scored less-than-per-protocol and associated with significantly worse survival. Importantly, when RT quality was accounted for in the primary analysis, gemcitabine was found to result in superior survival. [5] Thus, the variability of RT delivery potentially eroded the ability to discern which systemic therapy agent was most efficacious.

In short, sponsors must avoid poor-quality RT skewing overall study results in a way that potentially puts approval at risk. For these reasons, RT quality assurance (RTQA) is routinely employed by cooperative groups with significant RT experience (e.g., RTOG and NRG Oncology).

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Implementation of RTQA in clinical trials

Robust management of RT quality is an essential component of study design irrespective of whether it is delivered as neoadjuvant, concurrent, or adjuvant therapy. In light of the association of suboptimal RT quality with inferior outcomes (e.g., toxicity, local control, and survival), RTQA must be a critical component to ensure optimal results are achieved.

The foundation of an RTQA program involves:

1. Defining and documenting standards of care and quality metrics for RT.
2. Monitoring compliance with treatment guidelines and evaluating conformance with radiation-specific quality metrics on a case-by-case basis.
3. Providing performance feedback that can be used to improve the treatment provided to a given subject and/or inform the treatment of future subjects.

This feedback loop is particularly relevant and consequential in RT, as treatment quality can be assessed — and treatments potentially modified and improved — prior to the initiation of therapy. The "actionable" component of the RTQA process offers the potential to have a direct and measurable impact on quality.

Treatment guidelines

The guidelines for RT in a clinical trial should include specific requirements for treatment planning and delivery, designed to ensure study subjects receive consistent, high-quality care. Treatment guidelines will typically encompass:

4. Permitted or required treatment modalities and treatment techniques.
5. Prescription guidelines for total dose and fractionation.

6. Contouring guidelines to specify target volumes and adjacent normal tissues with guidance on how such structures should be delineated.
7. Dose objectives for target volumes and adjacent normal tissues that reflect quantifiable values that will be extracted from the treatment plan and evaluated in a consistent manner. Automated data processing allows for rapid review and standardized assessments on a large scale.
8. Prescribed motion assessment and motion management strategies.
9. Descriptions of allowable image guidance practices.

Delivery requirements may be mandatory, optional, or conditional. Treatment guidelines frequently include some level of discretion to accommodate local practice guidelines. In such cases, the trade-offs between flexibility and consistency must be carefully considered.

Site qualification

Once treatment guidelines have been established, site qualification surveys are used to confirm that participating institutions have the necessary equipment, technical resources and clinical capabilities to satisfy the study requirements. In certain cases, sites may need to acquire necessary tools or training, or modify their standard workflows or practice patterns, in order to comply with relevant study requirements.

Case review

Once patient enrollment begins, robust plan evaluation and case reviews are performed to assess compliance with RT guidelines. Case submissions for study subjects are typically comprised of clinical and treatment-related information captured through an online case report form (CRF) and contained in the radiation treatment plan (DICOM) files that are submitted. Dynamic data filtering, conditional logic and consistency checking embedded within the online CRF can help streamline the submission process, reduce the potential for data entry errors, and facilitate automated evaluation and scoring based on intelligent rule sets.

Conformance with treatment planning guidelines, including contouring and dosimetry requirements, can be assessed in an automated manner based on information contained in the radiation treatment plan. Automated processing can be utilized to check for the presence of required contours and to extract and analyze pre-defined dosimetric quality measures for target volumes and organs at risk. Computerized plan evaluation can be complemented by a qualitative case review, typically performed by a Certified Medical Dosimetrist. Case reviews are utilized to verify data integrity and completeness, assess contour quality, confirm which contours may be conditionally required based on tumor location, and consider other subjective elements of plan quality.

Cases that demonstrate variations from the treatment guidelines may be escalated for review by a board-certified radiation oncologist. Expert reviews can be used to: determine the appropriateness of, or justification for, identified deviations; express judgment as to whether the variations from guidelines could have been avoided through better treatment planning; determine whether the deviations could be considered to adversely impact overall treatment quality and expected outcomes; and provide clinical recommendations that can be implemented as part of the plan modification process. The results of the case review include detailed performance feedback and recommendations for improvement documented in a case review report that is made available to sites.

For studies that include real-time, prospective case review, plan modifications may be performed by the site based on the results and recommendations of the case. While it may not be practical or feasible for sponsors to require such modifications, sites can certainly be encouraged to incorporate expert feedback when appropriate in support of delivering high-quality care. Our experience suggests that sites welcome and encourage such feedback, and plan modifications very frequently eliminate or mitigate variations from guidelines.

While the use of real-time, prospective case review and the incorporation of a formal feedback loop enhance the possibility of plan modifications and the potential to positively influence treatment quality, it may not be appropriate or justified for all studies. As an alternative, retrospective review can be implemented as a means of providing case-specific performance assessment and feedback on a more flexible timescale. Under this model, case review results might not directly support plan modifications, however feedback can be used to inform and enhance future treatments.

There may also be instances where case review reporting and feedback may not be feasible, for example in studies where subjects receive radiation prior to enrollment in the clinical trial. In such cases, the protocol may not include specific prescriptive requirements for RT. Nonetheless, information regarding the RT treatment, including elements of both planning and delivery, can still be collected and evaluated in order to properly characterize the treatment and utilize such information for secondary analysis.

Conclusion

Integration of RT in clinical trials is increasingly prevalent given the ability of radiation to augment systemic therapy efficacy. However, RT is highly user-dependent, and cannot be viewed as a uniform platform for pharmaceutical studies without robust RTQA. Clinical trials run by groups well-versed in RT have long integrated robust RTQA, but pharmaceutical-funded trials have often overlooked this important source of variance in their study treatments. Failure to adequately incorporate RTQA may seriously erode the power of a trial to demonstrate a significant impact of a pharmaceutical agent, and waste important opportunities to advance our therapeutic armamentarium for a bevy of oncologic indications.

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