Demystifying radiation oncology clinical trial concerns for protocol scientific review and institutional review board committee members

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A R T I C L E I N F O

A B S T R A C T

Clinical trials are essential for evaluating advanced technologies and treatment approaches involving radiation therapy to improve outcomes for cancer patients. Clinical trials at cancer centers with designation from the National Cancer Institute must undergo scientific review in additional to Institutional Review Board approval. Given the highly specialized nature and rapidly advancing technologies of radiation therapy, and the small number of radiation oncology investigators at some centers, a lack of radiation oncology expertise among reviewers may present challenges at some cancer centers. This commentary aims to provide an overview of radiation therapy and special considerations for radiation oncology research that will serve as a helpful resource in the scientific review of clinical trials involving cancer patients.

Radiation therapy (RT) is an essential modality in curative treatment approaches for cancer, with approximately 50% of cancer patients receiving RT as a component of their care [1,2]. The complexity of RT planning and delivery has increased considerably over the past several decades in parallel with advances in RT technologies [3]. Presently, there are a broad spectrum of investigative and emerging fields within radiation oncology, including combination therapy with cytotoxic and targeted therapies, stereotactic body radiation, and the use of novel approaches to mitigate RT-related normal tissue toxicity [2]. While the field of radiation oncology has expanded the implementation of image-guidance and advanced treatment delivery techniques, recent studies have highlighted gaps in awareness of RT and misperceptions of radiation oncology among medical students and physicians without specific training in radiation oncology [4,5] (see Fig. 1).

Within the field of radiation oncology, clinical trials are vital for the evaluation of advanced technologies and novel approaches designed to improve patient outcomes [2]. The development of clinical trial protocols in radiation oncology requires not only understanding of good clinical practice (GCP) and regulatory requirements, but also technical knowledge of radiation oncology and an understanding of clinical considerations specific to RT, such as available procedures, standard work flow, and expected toxicities [6]. Clinical trial protocol documents must be developed and written in a manner understandable to non-radiation oncologists involved in the review or conduct of the trial protocol [6]. Ensuring that non-radiation oncologists understand the basis motivating the research questions in RT clinical trials, as well as the significance of the study question, represents a unique challenge given limited knowledge of RT among non-radiation oncologists [4,5].

Protocol development specialists, clinical research staff, and Institutional Review Board (IRB) members charged with review of clinical trial protocols for RT may face special challenges in understanding aspects of RT clinical trials, as many of these individuals have not received formal training in radiation oncology. At National Cancer Institute (NCI)-designated cancer centers, an additional level of scientific review is required for all cancer-related clinical trials through the Protocol Review and Monitoring System (PRMS) [7]. Particularly at centers with a small number of radiation oncology faculty, there may be a lack of RT knowledge and expertise available within these review committees to

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support timely and effective review.

Our collective experiences as protocol developers, reviewers, investigators and radiation oncologists have identified an unmet need to provide an overview of radiation oncology clinical trials for non-radiation oncologists involved in the conduct or review of clinical trials. In this short primer, we provide a brief overview of radiation oncology, summarize clinical trial considerations unique to radiation oncology and present answers to questions encountered during IRB and scientific reviews of RT clinical trials at the University of Virginia over the past 5 years.

1. Overview of radiation oncology workflow

The workflow of radiation oncology starts with an initial clinical consultation. This includes a detailed oncologic history, a physical exam, and review of the patient's medical record for any pertinent laboratory, pathology or imaging findings. The radiation oncologist then determines if radiation therapy is indicated and, if indicated, will decide which radiation type and delivery modalities are best suited to the patient. For example, the radiation oncologist may recommend advanced treatment planning like intensity-modulated radiation therapy (IMRT) to minimize the volume of tissue receiving a high dose of radiation therapy when sensitive structures are located near the tumor. The radiation oncologist may also recommend daily image-guidance with computed tomography (CT) to ensure maximal accuracy and allow smaller treatment margins. The patient and radiation oncologists discuss these options, outlining the procedures, potential risks and benefits. Jointly, the patient and radiation oncologist determine how to proceed.

The next step is the simulation, or mapping, session. The purpose of the simulation is to place patients in a reproducible treatment position and obtain imaging to create a treatment plan. A CT scan is typically obtained in this setting. Immobilization techniques, which can vary depending on the site of disease, are employed to ensure consistent patient positioning. For example, prostate cancer patients are often immobilized during radiation treatment in a foam cradle that is custom fit to surround the pelvis by shaping a bag containing foam beads while applying vacuum suction. Additionally, an isocenter, a point in three-dimensional space around which the radiation source will rotate, is set during simulation [8,9]. Once the isocenter is selected, skin marks are placed, with either temporary ink and stickers or permanent tattoos, to help with alignment during the course of radiation therapy.

After successful simulation, the radiation oncologist must contour, or segment, the treatment sites and organs at risk (OARs). Contours are volumes delineated on the simulation CT scan, and contouring involves tracing along the border of a structure within a treatment planning software program. These include, from smallest to largest size, gross tumor (gross tumor volume or GTV), areas of possible microscopic disease (clinical tumor volume or CTV), and margins that account for patient motion (internal target volume or ITV) and set-up variability (planning target volume or PTV). A treatment plan may have multiple versions of the aforementioned volumes. The organs-at-risk (OARs) are the uninvolved organs close enough in proximity to the treatment site to receive potentially harmful doses of radiation [8,9].

Next, dosimetrists and physicists generate a preliminary treatment plan using the contours and any dose constraints provided by the physician. Several aspects of the plan are reviewed by the physician before treatment. These include beam placement, coverage of the target volumes, and dose to the OARs [8,9]. For each treatment plan, radiation dose, measured in Gray (Gy), is prescribed to a volume of tissue. Radiation plans are evaluated by looking at how much dose a given volume receives and how large a volume receives a given dose. Dose-volume histograms (DVHs) provide a graphical summary of the volume of each organ that receives a given dose. DVH review is therefore a criticial step in plan evaluation. For example, the volume of healthy lung receiving more than 20 Gy should be less than 37% when treating lung cancer. Additionally, radiation doses are not uniform and the dose distribution is therefore examined on each axial CT slice to look for volumes receiving more than 100% of the prescribed dose. In general, these 'hotspots' should not occur in OARs and should be kept below 110–115% of the prescribed dose [8].

After the physician approves the plan, quality assurance (QA) checks are completed to verify that the plan is free of significant errors and can be delivered as planned [10,11]. QA often involves delivering the treatment plan to a device that measures the accuracy of the delivered radiation dose compared to radiation treatment plan. The plan is transferred to the treatment unit, and the patient may then start the RT course. Conventional RT treatment schedules involve daily RT for several weeks, while stereotactic body radiation therapy (SBRT) is
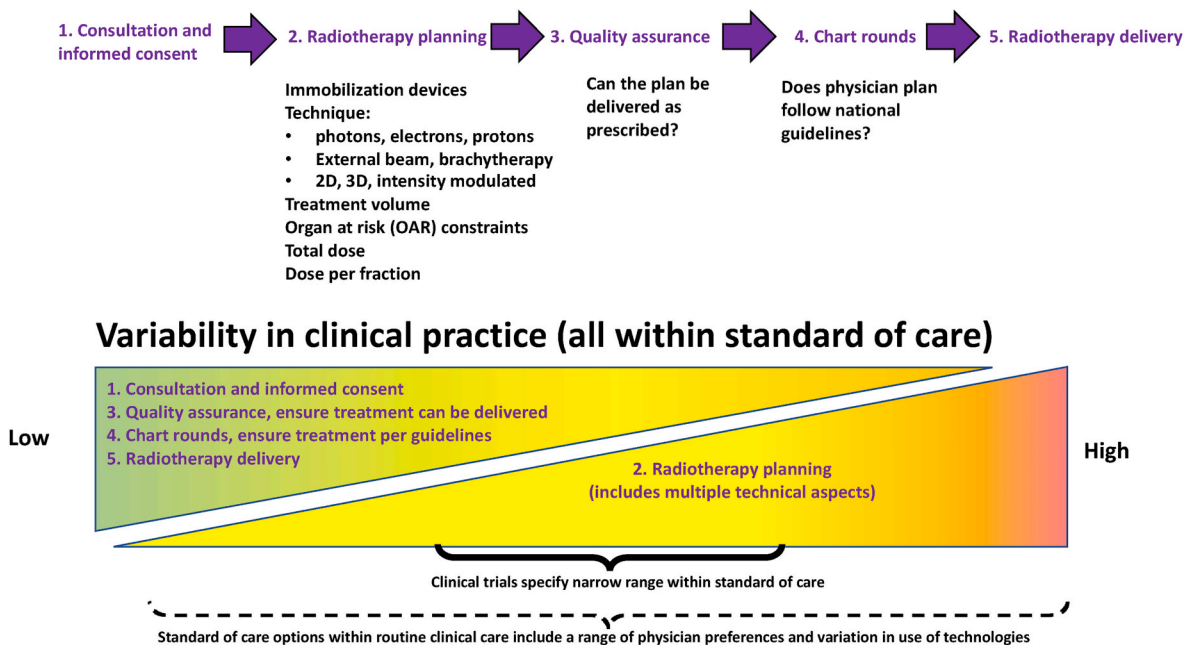

Fig. 1. An overview of the workflow for radiation therapy planning and delivery, with illustration of the broad range of variability in routine clinical practice as well as the tighter control of technical variables in clinical trials.

usually limited to 5 total treatments or less and may be delivered daily or less frequently. While on treatment, patients are monitored, at least weekly, for acute toxicities. Radiation oncology toxicities can also occur late, presenting months or years after treatment, which leads many radiation oncologists to follow patients at regular intervals indefinitely [2, 8,12].

Toxicities may develop in OARs located within the irradiated volume, and the probability and severity of toxicity events are a function of RT dose and volume [12,13]. Modern radiotherapy techniques deliver a range of radiation doses to non-target tissues. While the acute toxicities of radiation therapy are often unavoidable, they are largely temporary and reversible. Much of the late toxicity risks stems from the dose delivered to the OARs. The dose-volume constraints used for any given OAR are empirically determined and are an active area of research. Certain organs, like the spinal cord, have absolute maximum point dose constraints (e.g., maximum dose of 45 Gy), while others, like the bladder, have a range of dose-volume constraints (e.g., no more than 25% of the bladder receives 70 Gy). When determining whether dose-volume constraints will be exceeded for OARS, past radiation dose must be considered, as threshold toxicity doses to normal tissues are cumulative [2,8]. Much of the research and technology development in radiation oncology is aimed at optimizing dose distributions in order to effectively treat tumor while minimizing dose to the OARs in an effort to reduce late toxicity [13].

2. Radiation therapy techniques

There are two main methods by which radiation is delivered: external beam and brachytherapy. In external beam radiation therapy (EBRT), radiation is delivered from an external source to the patient and different technologies are utilized [14]. Typically, linear accelerators are used to generate beams of photons (X-rays) [14]. The shapes of the beams and photon intensity are modulated by collimators, which are machine-driven metal leaflets, inside the head of the linear accelerator unit. Historically, treatments were planned in 2-dimensional planar approaches. Modern radiotherapy utilizes three-dimensional (3D) planning techniques with CT-based planning. 3D conformal radiotherapy (3DCRT) uses multiple beams in chosen spatial directions to create a desired dose distribution. IMRT further improves upon 3DCRT involving modulation of the intensity of multiple small radiation beams to add another degree of control over the dose distribution. Arc based therapies, such as volumetric modulated arc radiotherapy (VMAT) and Tomotherapy™ helical delivery (Accuray, Sunnyvale, CA), use IMRT technology with a dynamic delivery pattern to deliver modulated radiation from 360° in different planes [14]. These techniques generate a conformal dose distribution at the expense of a larger volume receiving low-dose radiation exposure [15]. Proton beam therapy is a form of EBRT with theoretical advantages over photon-based therapies based upon physical characteristics that may provide more conformal dose distributions with reduced exit dose. The evidence basis for proton beam therapy continues to evolve to evaluate potential clinical benefits for specific indications [16]. Regardless of the form of EBRT, daily image-guidance can be performed using either planar or volumetric imaging to ensure precise treatment delivery with accurate patient positioning for each fraction [14].

RT courses are delivered in individual fractions, which are separate treatment sessions. For example, a 50 Gy total RT course can be delivered in 25 daily fractions of 2Gy each. Fractionated treatment provides normal tissues some time to heal without compromising therapeutic dose to cancerous cells [2,8]. Hypofractionated regimens, using higher doses per fraction and fewer treatments, can be very effective. In some cancers (e.g. breast cancer and prostate cancer), hypofractionation has been demonstrated in clinical trials to be equally effective as longer treatment courses [17–19]. SBRT is the shortest-course version of hypofractionation [14,20]. SBRT involves very focused delivery of radiation therapy, using image-guidance to allow tight treatment margins

and a high level of accuracy, and requires advanced treatment planning with 3DCRT and IMRT using multiple beam angles and customized beam shaping.

In brachytherapy (brachy means "short" in Greek), the radiation sources are much closer to the target area of treatment, either placed within a cavity, on a surface, or directly into the organ with needles or catheters [14]. As such, the radiation delivered is more localized and does not have to pass through the same structures as an external beam, thus increasing dose to the target and minimizing dose to normal surrounding tissues. Brachytherapy treatment courses are typically shorter, delivered in one to several days versus weeks for EBRT. Brachytherapy can be subdivided into high dose rate (HDR) therapy and low dose rate (LDR) therapy. A higher dose rate allows for more Gy to be delivered per unit time, and HDR brachytherapy can often be delivered over several minutes per fraction on an outpatient basis. HDR brachytherapy is temporary and delivered with a robotic after-loader device that avoids radiation exposure to health care personnel. The HDR source is removed prior to the end of the procedure. Multiple HDR brachytherapy procedures are often necessary to achieve the desired dose. Typically, LDR sources, such as seed implants for prostate cancer, are permanently placed inside a patient and deliver radiation dose over weeks or months. Brachytherapy can be used a monotherapy or in combination with EBRT as to 'boost' dose to the treatment site in a localized fashion [21].

3. RT technology assessment

The Food and Drug Administration (FDA) regulatory process requires new pharmacological therapies to undergo rigorous evaluation in clinical trials before use in clinical care. However, novel medical technologies do not face the same level of scrutiny. New medical technologies often replace the old based on theoretical advantages and empiricism [22,23]. This is rationalized by the stark time-scale differences between the rapid speed of technological development and the lengthy duration of prospective clinical trials [24–26]. The clinical equipoise among radiation oncologists that would be necessary to substantiate and complete a clinical trial may be undermined with highly promising new technologies that have a compelling technical performance. As such, many new technologies are incorporated into cancer care based on modest evidence of superior clinical efficacy [25,26]. IMRT and many applications of SBRT, for example, were widely adopted in the absence of prospective evidence from randomized controlled trials demonstrating superior outcomes compared to older technologies. However, some have argued that randomized trials comparing newer technologies to deliver radiation (which demonstrate reduced radiation doses to OARs) to older technologies may not be ethical. This is further discussed below.

Due to a lack of randomized controlled trials to establish the superiority of one RT method over another, there are often a broad range of techniques that are concordant with national guidelines and routine clinical practice. For example, consider the National Comprehensive Cancer Network guidelines for prostate cancer [27]. In unfavorable intermediate risk disease, there is a wide range of viable treatment options for a patient. One treatment pathway involves a radical prostatectomy with adjuvant therapy. That adjuvant therapy could be EBRT alone, androgen deprivation therapy (ADT), or both. Alternatively, the disease could be treated primarily with EBRT ± ADT ± brachytherapy [27]. Ideally, advances in EBRT or brachytherapy technology would require clinical trials to validate the advancement in any one of these treatment pathway permutations; however, considering the rapid pace of technological development, completing necessary clinical trials to validate these technologies is very challenging.

4. Radiation oncology clinical trials

To acquire meaningful information that can impact clinical decision-making, radiation oncology clinical trials must be prospective and often

examine two primary endpoints: the rates of tumor control and the incidence of late toxicity. This can require 10 years, or more, of follow up to ensure robust estimates for either of these endpoints [14,28]. Unfortunately, the need for prolonged observation to evaluate toxicity is poorly understood and has a low priority among current research funders [28]. Often, secular trends in diagnostic or therapeutic management may limit the external validity of RT clinical trial findings by the time the long-term results are evaluated and published [14]. Although acute toxicities are very common and largely unavoidable due to the nature of RT, the vast majority of acute toxicities are self-limited. Late toxicities, which occur on a time-scale of months to years, can disrupt function and quality of life permanently and are the principal focus of advanced RT technologies. As such, there is limited value in early toxicity evaluation during the observation window for acute adverse events.

Consider the standard three patients per dose paradigm of phase I dose escalation trials. These trials open and close to accrual relatively quickly, which often does not allow sufficient time to observe for delayed dose-limiting late toxicity events before moving to the subsequent dose level. The minimum reasonable time to observe for RT-related toxicity events, which can range from months to years, means that a 3 + 3 design for could require months to years of observation. Other trial design approaches, like the time to event continual reassessment method (TITE-CRM), have been developed for RT trials in response to these issues. TITE-CRM trials are continually open to accrual, and as the trial progresses and subjects experience late toxicity events, estimates of toxicity probability are recalculated for each dose level using a Bayesian design. Subsequent subjects are then assigned to doses based on continual assessment of toxicity event rates. TITE-CRM trials, and other novel trial algorithm strategies, have been shown to produce more accurate dose and toxicity estimates with better safety profiles than traditional designs. However, it can be burdensome on researchers to convince oversight committees that these new approaches are safe and worthwhile. Detailed and lengthy discussions are often necessary for oversight approval. It is our hope that increasing familiarity with such trial designs among review boards decrease some of the burden on clinical researchers to prove the trial design's validity [29].

Quality assurance (QA) is an important component of any RT clinical trial, as it is essential to verify that the RT is delivered according to protocol specifications in order to interpret clinical trial results [6,10]. In order to draw conclusions from an overall body of research, the RT technical details must be consistent between studies. To ensure consistent treatment on clinical trials, QA protocols have been established for clinical trials of radiation therapy, often including submission of technical RT data (i.e., imaging studies, contours, and treatment plan) for centralized peer review prior to initiation of protocol treatment. Analysis of results from multicenter cooperative group protocols has demonstrated the importance of QA, with inferior outcomes shown for RT plans that violate protocol specifications [10,30]. For early phase studies involving RT, it is important to ensure adherence to study QA details and to consider dose-volume parameters when interpreting toxicity events and even biomarker analyses due to the strong influence of RT dose-volume on outcomes [12,13,31].

Given the wide spectrum of guideline-concordant alternatives for RT dose-fractionation schedules and technologies, radiation oncology clinical trials often focus on comparison of two or more standard-of-care RT options. Although multiple options may be standard of care, there may still be a need to evaluate the comparative effectiveness of the different treatment approaches due to potential underlying advantages (e.g., cost and convenience) for a particular RT regimen. For example, both photon and proton RT techniques are considered standard of care in non-metastatic breast cancer. Proton therapy often generates more conformal treatment plans because a proton beam delivers little to no dose beyond the target volume (the "exit dose") in contract to photon beam therapy. For example, proton beam therapy reduces incidental radiation dose to the heart during thoracic radiation therapy and reduces the volume of tissue irradiated in pediatric patients. However, uncertainty remains regarding the biological effect of protons at the end of their physical range in tissue. Additionally, there may be differences in the ways protons and photons affect normal tissue. The RadComp trial is a multicenter pragmatic randomized trial that evaluated the differences in major cardiac events between photon and proton radiation therapy. It will enroll a total of 1278 patients to receive either therapy and investigators will conduct centralized, blinded review of these primary outcome events [32]. The need to complete such a large trial of two standard therapies may be surprising to investigators who focus exclusively on drug development trials.

5. Informed consent in RT trials

As in all medical research, the four principles of bioethics play an essential role in radiation oncology clinical trials. These principles are autonomy, beneficence, non-maleficence, and justice. One of the most ethically complex facets of clinical trial research is the process for obtaining informed consent. Obtaining informed consent is how researchers satisfy the principle of autonomy. The Department of Health and Human Services regulations at 45 CFR 46.116 outline the general requirements for informed consent and nine basic elements that must be contained within (Table 1). In order to obtain informed consent for a clinical trial, the relevant benefits and risks of the trial to the individual and to society must be explained, the potential subject must understand this information, and they must make an informed decision regarding participation. However, obtaining adequate informed consent in the radiation oncology setting can be very challenging [33].

The primary challenge in informed consent is ensuring adequate understanding of the clinical trial. RT is not well understood among the general public and the nuances of different treatments are very complex. Additionally, trials often involve multimodality combination therapy and multiple arms, which creates complicated trial structures. As such, informed consent documents and their associated explanations are often overly long and technical. This leads to poor participant understanding which undermines patient autonomy. Studies have shown that at least 75% of cancer patients cannot correctly answer questions regarding the efficacy of their therapy, the risks relative to other therapies, or the experimental nature of their treatments. Developing strategies to improve the informed consent process is an ongoing area of research within the field [33].

A related ethical concern arises from clinical equipoise and the rapid pace of technology development. Clinical equipoise is a state of genuine uncertainty regarding the efficacy of the experimental intervention compared to the control. However, in radiation oncology, technological advancements are made much more rapidly than the scientific community's ability to comparatively study these new tools. As such, the

Table 1
Requirements for appropriate informed consent for subjects participating in clinical trials.

1	Purpose, expected duration of participation, description of research procedures, and identification of procedures that are experimental.
2	A description of potential risks.
3	A description of potential benefits to the subject or society.
4	A description of alternatives to participation that may convey advantages to the subject.
5	A statement regarding how confidentiality will be maintained.
6	A description of any compensation, whether medical treatments are available should injury occur during the study, what those medical treatments may consist of, and where further information may be obtained.
7	A statement of who to contact if a research-related injury occurs, for additional questions, and for questions related to the rights of research subjects.
8	A statement indicating that participation is voluntary, there will be no penalty or loss of benefits should a potential subject choose not to participate, and that a subject may stop his/her participation at any time without repercussion.
9	Appropriate statements regarding identifiable private information or biospecimens.

adoption of novel technology into clinical practice often occurs without robust randomized controlled trials. It is unclear whether not studying these developments in randomized clinical trials constitutes an ethical violation [34]. For example, proton therapy in pediatric brain tumors is highly conformal, much more so than traditional photon modalities. This means that less of the normal pediatric brain is exposed to radiation. Is it then ethical to enroll pediatric patients in a phase 3 randomized controlled trial of proton versus photon therapy when the dosimetry of proton therapy is superior? It appears that there might not be a satisfactory level of clinical equipoise to establish such a trial. This highlights the need for other research methods to expand the scientific literature surrounding these technologies, especially methods that can better match the pace of their development [33].

Radiation safety considerations must also be incorporated into the clinical trial review and approval process, and the informed consent form must clearly describe any investigational radiation exposures to human subjects. The protocol and informed consent form must characterize additional study-related exposure to ionizing radiation therapy from diagnostic or treatment planning imaging studies, scans obtained for image-guidance, and investigational radiation therapy. A center's Radiation Safety Committee, Human Investigational Radiation Exposure, or other committee with similar expertise, should evaluate and approve the radiation safety aspects of each study prior to IRB approval and study activation. Further, an Investigational Device Exemption (IDE) may be required when radiation therapy devices are use outside the scope of their FDA-cleared indications for use. For example, IDEs are required for current clinical trials investigating the use of high-dose radiosurgery as a cardiac radioablation strategy to treat ventricular arrythmias.

In summary, the technical details, prolonged timeline to observe late events, broad range of options, and complexity of RT clinical trial design present challenges to reviewers of RT clinical trials who have limited expertise in radiation oncology. With the summary above, we hope to demystify RT for non-radiation oncologist members of IRBs and protocol review committees. We conclude with the presentation of common questions and answers encountered at the University of Virginia during the review of RT clinical trials.

6. Frequently asked questions during scientific and IRB reviews

6.1. How does this trial differ from standard of care?

There is a broad range of radiation therapy options for this clinical indication (see appropriate NCCN guidelines), including variation in technologies, treatment planning details, and radiation dose and number of fractions. Radiation dose or number of visits may be different than if subject does not participate. This clinical trial commits the subject and physician to adhering to a specified set of RT dose constraints. The trial protocol will also specify the follow up intervals and assessments, with the follow up schedule designed to adhere to standard of care expectations. Anonymized technical data, including image files and the radiation plan, may be shared with the lead organization for quality assurance and analysis. It is important to note that although an RT protocol may call for the use of a dose and modality acceptable per NCCN guidelines, the requirement to use a protocol specified dose and modality, which may be something different than what would be used if the subject were not participating, is what makes the RT a research procedure (**Figure**).

6.2. What are other choices if the patient does not join this study?

If the patient chooses not to participate in a trial, the patient is eligible for standard of care radiation therapy at the physician's discretion based on routine practice, physician preference, institutional policies, and other considerations. The standard of care RT may indeed be the same as what is called for in the study protocol. Clinical trials adhere to pre-specified treatment protocols to permit comparisons of outcomes.

6.3. It's not clear whether this is generalizable to other devices and isotopes. This study will take years to complete, what if a new isotope becomes available?

Regardless of the particular isotope or treatment unit, the concept of absorbed radiation dose would still apply. Iridium-192 is the primary radioactive isotope used for high dose-rate brachytherapy in the United States, which is not likely to change in the immediate future based on regulatory and economic factors.

6.4. There is no study visit planned with the patients 10 days after radiation therapy. Is this safe?

After a course of radiation therapy, it is standard to see patients for first follow up between 1 and 3 months after treatment to monitor for resolution of acute toxicity and evaluate for tumor response. Acute toxicities are expected to occur and resolve during and after radiation therapy, but treatment regimens and clinical trials focus on avoiding late toxicity. The observation period for late toxicity events starts 90 days after treatment. In cooperative group trials of radiation therapy, a 3-month follow up visit is frequently the first post-treatment assessment visit for this reason.

6.5. Is there value in continuing to collect adverse events and medications so far into follow up?

Late toxicity is the primary objective and focus of dose-volume constraints, advanced technologies, and RT clinical trials. Late toxicity events can occur years after radiation therapy, with no expiration date. As such, both routine clinical practice and research protocols involve follow up over the course of several years. By radiation oncologists to evaluate for and manage late toxicities. In contrast, acute toxicity is expected and often a secondary concern.

6.6. Do you need an IND from the FDA?

When a new drug or medical device is tested in clinical trials to support an application to the United States Food & Drug Administration (FDA) for a premarket regulatory decision, an investigational new drug application (IND, for drugs) or investigational device exemption (IDE, for devices) may be required. An IDE is required for a radiation-emitting device that has not yet been cleared for marketing [35]. However, once a radiation treatment unit is cleared for commercial use, the specific details of a radiation therapy course or clinical application are outside of the FDA's approval process. Therefore, it is rare for clinical trials of radiation therapy alone to require an IDE. On the other hand, an IND may be required for combination of RT with a novel drug on a clinical trial.

6.7. Is there a good way to assess effects during radiation therapy without extra visits for the patients?

Patients are seen weekly by the nurse and physician for on-treatment visits (OTVs), which includes a focused history and a physical examination. During this time, clinical trial subjects may be asked to complete quality of life questionnaires or other surveys required by clinical trial protocols.

6.8. If differing radiotherapy fractionation options are listed in a trial, would you expect different efficacy or toxicity of the treatment?

For many disease sites, the use of hypofractionated radiation therapy (i.e., using >2 Gy per fraction up to doses of 30–50 Gy) has been shown to have similar efficacy and toxicity as standard fractionation (i.e., using 1.8–2 Gy per fraction, up to doses of 50–80 Gy). In some cases, there is physician discretion of using a certain regimen to meet dose constraints for OARs and also provide treatment in a timely manner; nonetheless. Unless the clinical trial is evaluating one dose fractionation regimen vs another, efficacy and toxicity are likely similar, and allowing the use of multiple fractionation options is acceptable.

6.9. If a patient receiving radiation therapy has a break in their treatment or is admitted to the hospital, is this automatically an adverse event related to treatment?

Not necessarily. Certain patients receiving radiation therapy are at high risk for treatment breaks or hospital admission. First, some patients are malnourished in part because of their cancer (e.g., those with head and neck, pancreatic cancers), and it is expected that they may need IV fluids or percutaneous endoscopic gastrostomy (PEG) feeding tube during their treatment course. Radiation therapy is routinely held and restarted per the discretion of the treatment team. The treating radiation oncologist should be able to list the likely and unlikely events during radiation therapy for particular disease sites, and this may be specified in a consent or protocol.

6.10. Why are routine labs (eg, CBC, CMP) not being checked prior to starting radiation therapy or during treatment?

For many cancer patients, checking labs prior to starting is not necessary during radiation therapy, as radiation therapy does not often impact lab values.

The above questions and answers provide a foundation of content that can be used to support the sharing of radiation oncology information with reviewers of clinical trials that involve radiation therapy. This list is not comprehensive but includes topics that have come up during IRB and scientific review committee reviews of radiation therapy trials at the authors' institutions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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