Clinical trial challenges for new technology in radiation oncology

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Stephen Kry, Professor from the University of Texas MD Anderson Cancer Center, explores clinical trial challenges for new technology in radiation oncology, including the radiotherapy treatment technique, proton therapy

While novel drugs must show efficacy before they are approved for clinical use, there is no such requirement for the new technologies that drive development in radiation oncology. As long as the technology is shown to be safe, it can be implemented. One advantage of this is that it allows new treatments to be implemented very quickly into clinical practice as there are relatively few scientific and regulatory requirements.

On the other hand, there is little data to demonstrate which patients stand to benefit or the degree of benefit received by the patient. Expensive new therapies are, therefore, often implemented with little more than a theoretical justification. Despite not being required, clinical trials comparing novel treatments to traditional ones are the most clear and robust method for establishing the value and efficacy of these advancements.

However, clinical trials evaluating novel technologies have unique challenges compared to traditional trials of novel drugs. While the technical administration of drugs is not generally in question, the lack of clinical experience and familiarity with novel technologies create real and substantial challenges to optimal care delivery. Additionally, any significant change in technique or technology is invariably associated with iterative refinement, as the initial release will invariably leave room for advancement.

Because of these two issues, it takes years, or often decades, for the community to optimally understand how to use novel technologies and for novel technologies to evolve enough to start meeting their potential. This is a substantial problem for trial design; conducting a trial with a novel technology that isn't being used to its potential sets it up for failure, even when it may have excellent long-term capabilities.

Radiotherapy treatment technique – proton therapy

A contemporary example of this issue is found with the relatively new radiotherapy treatment technique of proton therapy. Since the 1930s, radiation therapy has been conducted using large doses of x-rays to treat solid tumors. Naturally, there has been a dramatic evolution of x-ray treatments during this time. A major change in technology over the past decade is the increasingly mainstream use of highly accelerated protons, instead of x-rays, to kill tumor cells.

Proton therapy has substantial theoretical advantages compared to x-rays, but is also a much more expensive modality. It is ultimately unknown when proton therapy is worthwhile and for which types of patients. What is clear is that with ten years of experience delivering proton therapy, we are much less skilled at using this tool than we are at using x-rays, with which we have 90 years of experience. X-rays are undoubtedly an inferior tool, but we are exceptionally good at using them.

Clinical trials comparing proton therapy to x-ray therapy are being undertaken to evaluate the advantage of protons in treating lung, esophageal, prostate, and other tumors. Despite the clear theoretical benefit of protons, trial results show, at most, a modest benefit. However, the outcomes from proton therapy are based on a relatively crude use of this novel technology.

Even in the past ten years, there has been substantial clinical practice growth and familiarization with delivering proton therapy, along with simultaneous evolution in the technical aspects. For example, the three-dimensional shaping of the dose distribution has already become far superior (leading to more sparing of healthy tissue and less toxicity), and treatments are more robust to patient movement or changes in the patient's internal anatomy. The proton clinical trial results that are just being reported are already bordering on being obsolete, are often not representative of current practice, and are far from capturing the full potential of this novel technology.

This is a systemic challenge when running clinical trials for novel technologies. As the technologies are constantly evolving and refining to enhance patient outcomes, and as practitioners gain increasing familiarity with these refinements, it is impossible to compare two different approaches cleanly. We can only compare two different approaches with different histories. Any evaluation is not simply x-ray versus proton therapy, but rather highly honed x-rays therapy versus nascent efforts with proton therapy. Importantly, it is critical that the nascent nature of novel technology does not undermine its performance in clinical trials. Several guiding principles should be met to minimize this risk.

Clinical trials for new radiation oncology technology

First, novel technology should be evaluated to ensure it is being optimally used (at least as well as current standards allow). This is often done by clinical trial quality assurance bodies, such as the Imaging and Radiation Oncology Core, which supports several-hundred clinical trials from the National Cancer Institute in the United States. Several active trials are comparing (or allowing as a radiotherapy modality) proton therapy.

Before any proton therapy facility can enroll patients in trials, they must undergo extensive evaluation by the Imaging and Radiation Oncology Core (as described under the proton approval process at https://irochouston.mdanderson.org). This evaluation includes verifying that accurate radiotherapy doses are correctly delivered under various clinically relevant scenarios (e.g., through surrogate patient irradiation test) and verifying that the facility employs up-to-date and best clinical practices. Importantly, this process is iterative so that institutions have a chance to improve their practice, and it is done in a scientific context (not a regulatory one) to promote a collaborative move to treatment optimization.

Second, as technological evolution and clinical practice standards often develop and change most rapidly immediately following their clinical introduction, trials comparing new technologies should not be immediately compared to clinical standards. There must be some time for the basic evolution of technology and basic familiarization of techniques before efficacy can be meaningfully examined. How long a wait is required depends on how complicated the novel practice elements are, but an appropriate interval should be implemented while never losing sight of the critical need for a high-quality evaluation based on a clinical trial.

The Imaging and Radiation Oncology Core has historically not allowed institutions to even be evaluated for potential participation in proton clinical trials until they have six months of clinical practice to become familiar with this technology. But this is after more than a decade of broader technical refinement of this technology by the community and manufacturers as a whole.

In working with proton institutions, the Imaging and Radiation Oncology Core has identified numerous qualitative and quantitative areas for improvement at individual proton centers (Taylor 2016; Taylor 2022). These issues have included incorrect calibration of imaging and treatment equipment, and deficiencies in clinical practice. The Imaging and Radiation Oncology Core has also identified systematic problems with early features of proton therapy technology, including major inadequacies in the way the intended dose was calculated (Taylor 2017). These sorts of findings have made critical progress in raising the technological bar of this novel technology, raising and standardizing the clinical practice of this novel technology, and setting the stage for the best currently possible clinical trials to evaluate this novel technology.

Positively impacting patient care & clinical trials

While there are clearly challenges in conducting trials with novel technology, a rigorous, robust, and appropriately timed evaluation of institutions using novel technology, such as that implemented by the Imaging and Radiation Oncology Core, is a well-proven approach that positively impacts patient care and clinical trials.

References

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