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At the very start of their clinical training, radiation oncologists tend to embrace technology. The specialty draws a preponderance of technophiles to it, and those few who are not at first passionate about technology quickly become so. This has been especially true over the past 2 decades with the introduction of innovative therapies such as three-dimensional conformal radiation therapy (3DCRT), intensity-modulated radiation therapy (IMRT), stereotactic radiosurgery (SRS), stereotactic body radiation therapy (SBRT), image-guided radiation therapy (IGRT), and proton therapy. These new treatments promise more accurate and precise delivery of radiation dose to the patient, with the expectation of improved outcomes with respect to both tumor control and toxicity reduction.

The National Cancer Institute sponsored a workshop at the end of 2006 to discuss issues regarding radiation oncology technology and identify opportunities for research. Vikram et al summarize the discussions from this workshop, providing a “state of the science” around these and other technologies commonly used in radiation oncology practices. As they point out, there is much to learn and discover about these technologies, particularly with respect to their clinical effectiveness.

Evidence or Incentive
Unlike pharmaceuticals, the US Food and Drug Administration (FDA) review process for medical devices does not require proof of clinical benefit. For the most part, the FDA actually does not “approve” medical devices—rather, they “clear” them as being medically or technically similar to existing, or predicate, technologies. Safety is a critical component of the review process, but proof that a device can actually achieve its clinical goals is not a requirement. Once available to the practicing radiation oncologist, the use of a device is often determined by indirect or surrogate measures of clinical benefit. For example, an improved radiation dose distribution is commonly accepted as indirect evidence of an improved clinical outcome.

Regrettably, another important factor in the adoption of a new technology is the status of its reimbursement. We are not so cynical as to suspect that a majority of early adopters of new technology put payment above clinical benefit; however, the ability to get paid for the use of a device helps build the business case for its acquisition. Sadly, support for a device (or lack thereof) becomes driven more by reimbursement than by high-quality clinical data. Health-care payers become the de facto gate keeper for new technology—a process that is an ineffective, inefficient, and unjust.

We concur with Vikram et al that high-quality clinical trials are often necessary to establish clinical benefit from new technologies. Unfortunately, the list of cancer sites that lack class I evidence to support the widespread adoption of technologies like 3DCRT or IMRT is long (including brain, head and neck, lung, esophagus, pancreas, rectum, and gynecologic cancers). Good data in prostate cancer show an improvement in biochemical (prostate-specific antigen) control with radiation dose escalation that could not be achieved without conformal therapy modalities.[1-4] Two of these trials also suggest a clinical disease-free survival benefit to dose escalation, but none show an overall survival benefit. We will need to await the results of the recently closed randomized dose-escalation trial, Radiation Therapy Oncology Group (RTOG) 0126, to determine whether the dose escalation in prostate cancer that is made feasible with 3DCRT leads to an improvement in overall survival. For most other disease sites, unlike prostate cancer, no phase III trials support technology use, and for many there are no ongoing phase III trials.

We disagree with the belief that all technologies in all clinical sites require randomized clinical trials (RCTs) to justify their use. Indeed, several of the techniques and methods that are commonly used in clinical practice today were introduced through incremental changes based on failure analysis. For example, nerve-sparing prostatectomy was not evaluated in an RCT to prove its superiority to older surgical techniques. Abdominoperineal resection for anal cancer was abandoned in favor of an
organ-sparing method with chemoradiation therapy in the absence of an RCT. Other examples support the adoption of new therapies in the absence of class I evidence. Black proposed that RCTs would be unnecessary when (1) the magnitude of benefit is large, (2) the affected population is small or the benefit may not be realized early, (3) the randomization itself poses ethical concerns, or (4) when there is low external validity and the result is not likely to be applicable to actual clinical practice.[5] In situations where RCTs are not feasible, investigators should strive to collect high-quality prospective data for observational studies as an alternative to the RCT.

In addition to the criteria mentioned above, substantial hurdles limit our ability to conduct phase III trials that compare technologies. Clinical dogma and economic reasons are often reasons to use new technologies before compelling data are available. Many physicians believe that a surrogate metric such as comparative dosimetry is adequate evidence for offering new treatments. Furthermore, the investment in a technology can convince even a skeptic that there is an advantage to the new acquisition.

An Infrastructure for Technology Assessment

Recognizing that an RCT cannot and need not be carried out for every new technology and every clinical scenario, it is essential that when these trials are required they are conducted with the appropriate level of quality control to ensure the results can be interpreted meaningfully. Determining the level of quality control is nontrivial, but clearly should be based on published scientific data.

The RTOG has established an Advanced Technology Integration Committee that works closely with disease site committees to incorporate new technologies into clinical trials. Many of the studies directly evaluate new technologies, such as several phase II dose escalation studies in lung, brain, and prostate cancer. Several ongoing phase III trials in prostate and lung cancers are comparing traditional to escalated radiation doses that could only be safely administered with 3DCRT or IMRT. While these studies are not a direct comparison of an older vs a new technology, they will indirectly measure their value.

Other trials have tested the feasibility of evaluating new technologies in the cooperative group setting. As Vikram et al have explained, multicenter studies have shown significant variability in IMRT dose distributions. The RTOG, working with the Advanced Technology Consortium (ATC), has defined strict guidelines for clinical trial participation when using these modern therapies. A critical element of these RTOG studies has been the electronic submission of full volumetric data sets of participants’ CT scans along with segmented anatomy, 3D dose distributions, and dose-volume histograms. Participating institutions and investigators need to demonstrate a thorough understanding of the protocol, target definition, dosimetry, and verification methods prior to enrolling their first patient.

RTOG investigators who wish to introduce or evaluate new technologies in a clinical trial work with the group’s Advanced Technology Integration Committee to establish participation criteria. With input from the members of the ATC, including the Radiological Physics Center, the Image Guided Therapy Quality Assurance Center, RTOG headquarters, and quality assurance staff review the technical requirements for each study. Compatibility across different technology platforms is emphasized to both maximize participation and deemphasize vendor-specific technology evaluations. For example, an investigator proposing an SBRT trial may have familiarity with a robotic delivery method, but success of the clinical trial depends on investigating the clinical question on a variety of SBRT platforms including different treatment planning, delivery, and verification systems.

International Harmonization of Clinical Trials

The ATC and RTOG are working closely together to develop collaborations with international partners and to harmonize credentialing and quality assurance requirements. The ATC has successfully supported an SBRT lung cancer trial with the Japanese Cooperative Oncology Group using digital treatment plan data exchange as well as a Web-based remote review for quality assurance. Collaborative trial development is ongoing with the European Organisation for Research and Treatment of Cancer (EORTC), Groupe d’Oncologie Radiothérapie Tte Et Cou (GORTEC), and partner institutions in South America and Asia. These alliances require a careful review of existing credentialing/quality assurance standards and will challenge the status quo in North America and abroad. They are placing an emphasis on data-driven quality standards and not “business as usual.”

Conclusion

Just as new drugs require clinical proof to support their use, the application of new technologies will benefit greatly if they are supported by high-quality evidence from carefully designed clinical studies. Ideally, direct comparisons of a new technology to one that it is replacing are desirable. It is
recognized, however, that in some situations an RCT cannot be accomplished. Regardless, as a minimum, prospective collection of high-quality data (similar to the support ATC has provided for RTOG protocols) is necessary to allow valid comparisons of results. It is vitally important that all stakeholders support high-quality clinical research of new technology, including equipment manufacturers, clinicians, patients, hospitals, and payers. Without support for clinical evidence development, the benefits of new technologies will be slow to arrive and disseminate to those in need.

**References:**

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