Randomized Trials and Technology Assessment

Despite a major increase in the development of new technologies in medicine, there is relatively little consensus as to how to best evaluate new medical technology for clinical use. Terasawa and colleagues’ comparative effectiveness review about proton radiation therapy for cancer in this issue exemplifies this problem (1).

The standard approach for therapeutic pharmaceuticals in oncology is to identify a target, develop drugs to attack that target, and test the most promising drugs first in phase 1 studies before progressing to phase 3 randomized clinical trials. Approval of drugs by the U.S. Food and Drug Administration relies on this process. Because third-party payers require approval as a condition of reimbursement, pharmaceutical companies have no option but to adhere to this clinical evaluation process. Although the basic science foundation for drug development often comes from academia (supported by government funding), financial support for drug development comes largely from pharmaceutical companies. Academic medicine can benefit financially from the clinical research enterprise, and the financial rewards to the pharmaceutical companies can be enormous, with best-selling drugs bringing in revenues of billions of dollars per year.

The approaches used to develop new technologies are inherently different from those used to develop drugs. To start with, the definition of a medical technology or device is unclear. A scalpel, a word processor, and a calculator may be essential for the delivery of medical care, but it is not clear that they are medical devices that should require approval. It is also unclear what defines a device as “new.” These definitions are not simple, and regulatory agencies have made few attempts to clarify them.

Relatively few medical devices differ dramatically from their predecessors. Surgical devices are often variants of scalpels and retractors, and new radiation devices are usually variants of treatment delivery machines. In these situations, the biology of the intervention remains the same. Some devices, such as intensity-modulated radiation therapy and proton radiation therapy, differ substantially from their predecessors, but the biological basis of these technologies is essentially unchanged from the conventional intervention. New radiation delivery systems produce the same type of radiation beam as older systems, but they differ from the older systems in that the accuracy of radiation delivery may be enhanced, and the dose to normal tissues may be decreased, thereby theoretically improving the likelihood of local tumor control without complications. One might view these new delivery systems as similar to the development of infusion pumps for cancer drug delivery. For these devices, regulatory agencies demand that the device does what it is supposed to do and that it can perform that task safely. They generally do not view a new radiation delivery machine in a manner very different from that of a new drug infusion pump. Consequently, randomized trials of radiation therapy modalities are scarce.

Randomized trials are ethically necessary to evaluate experimental interventions with uncertain risk–benefit profiles, which present potential risks to patients. Although newer technologies may be inherently different from previous versions, the dividing lines are much less clear than they are for drugs. When is a new technology experimental? We perform randomized trials in oncology to protect patients, but are trials necessary when new technologies involve the same biology as their predecessors, when risks to the patient are very low, or if observational studies demonstrate their appropriateness?

Protons are charged particles with a biology very similar to that of x-rays (2). They have been used clinically for more than 30 years in thousands of patients, with minimal unexpected adverse events (3). Although the technology of proton therapy delivery differs from that of x-rays, it is very well defined. The major potential benefit of proton therapy is minimization of irradiation of and toxicity to normal tissues, which may allow higher doses to be delivered to the tumor and thereby increase tumor control. The major problem with proton therapy is that it is far more expensive than conventional radiation therapy.

As the systematic review by Terasawa and colleagues (1) shows nicely, few randomized studies have compared protons with the best conventional radiation therapy. Why? First, constructing a new proton facility costs $100 million to $150 million. Technology companies do not usually have the resources to construct multiple facilities for testing purposes alone, because the potential financial rewards are much less than for those of oncology drugs. There is no patent protection on protons, only on specific techniques of generating those beams. If an institution invests more than $100 million to construct such a facility, can it afford a negative result from a randomized trial? In addition, many patients are hesitant to accept randomization when they perceive no increased risk, but do perceive potential benefit, from the use of protons. However, current knowledge about how radiation interacts with tumor and normal tissue is imperfect. Randomized trials are important to be sure that we have not overlooked important confounding factors and unintended consequences when implementing new radiation technologies.

As physicians, we have an ethical responsibility to deliver the best medical management to our patients while minimizing costs to society. To do this, we need at least some clinical evidence of incremental value of a new, more expensive therapy. For many diseases, randomized trials cannot, and should not, be performed: The diseases are too rare, the risks of the new therapy are too low, and the potential benefits are substantial enough that the use of protons, for example, may be appropriate on the basis of...
technical issues alone. However, in other situations, we believe that randomized trials can and should be done. Trials can help us assess the value of new technologies compared with existing treatments and help us understand unexpected effects that arise that even the best modeling cannot predict. Diseases in which randomized trials should be done include common types of cancer, such as lung and prostate cancer, with endpoints of either improved cancer outcome or decreased toxicity and improved quality of life. We require evidence to understand the risks and benefits of new radiation therapy technologies, and randomized trials are a critical part of that evidence.

Terasawa and colleagues have performed a valuable service by demonstrating the lack of good phase 3 studies evaluating proton-beam therapies. However, much work needs to be done to establish general guidelines on technology assessment. We must address important definitional, financial, and technical issues if the evaluation of radiation therapy and the general field of technology assessment are to move forward.

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