Stereotactic Radiation Takes Root in Cancer Therapy

By Susan Jenks

A decade after gaining approval from the U.S. Food and Drug Administration to treat cancer, the CyberKnife is emerging as a potent tool for killing small, localized tumors with stereotactic radiosurgery, especially in the lungs.

Now in progress are the first randomized clinical trials, comparing the CyberKnife with conventional surgery for early lung cancers. Besides its robotic arm, which enables the CyberKnife to deliver bursts of high-dose radiation from multiple angles, the radiation device features real-time tracking to continually adjust or correct for tumor movements during treatment.

But whether these capabilities make the CyberKnife, made by Accuray, superior to a half-dozen or so other technologies that
perform stereotactic body radiation therapy (SBRT) or to other methods of radiation therapy delivery is still unknown.

Nor do radiation oncologists consider head-to-head comparisons of existing machines as important to patient care as better defining the treatment’s overall promise—a finding shared by a recent technology review commissioned by the Agency for Healthcare Research and Quality (AHRQ), which called for more comparative studies with other radiation therapies.

“Every machine has its pros and cons,” said Robert Timmerman, M.D., professor of radiation oncology and neurosurgery at the University of Texas Southwestern Medical Center in Dallas, who uses the CyberKnife and likes it.

Although there’s little debate about advances seen with stereotactic radiosurgery in treating inoperable lung cancers, he said, “What if you could use these therapies to push cancer into a chronic form?”

By treating small tumor metastases, “you could reduce the tumor burden and stave off the threat of imminent death,” speculates Timmerman, adding that this approach would effectively mop up microscopic disease and allow patients to receive systemic therapy when it works best.

A 5-year-old ongoing study has already yielded “provocative, though by no means definitive, results” as a proof of principle, according to Timmerman. The 25 advanced lung cancer patients, all receiving erlotinib (Tarceva) and CyberKnife treatments simultaneously, have a mean survival time of more than 20 months, compared with 2.3 months typically seen in patients on erlotinib alone. (However, without a concurrent randomized comparison group, determining how much of a role patient selection plays in these favorable results is difficult.)

**Other Radiation Technologies**

Other experts also emphasized the collective potential of the different radiation technologies, including the CyberKnife, which require linear accelerators to deliver high-energy particles to treat patients’ malignancies.

“In some areas of cancer, stereotactic radiation is well established as an alternative therapy,” said Walter Curran, M.D., executive director of the Winship Cancer Institute of Emory University in Atlanta and chair of the Radiation Therapy Oncology Group (RTOG).

For example, a 2004 RTOG-sponsored phase III trial of 333 patients with brain metastases, led by Thomas Jefferson University Hospital in Philadelphia, found that adding stereotactic radio surgery to whole-brain radiation conferred an overall survival advantage to patients with a single unresectable brain metastasis and improved functional autonomy for patients with two or three brain metastases.

“It may seem modest,” Curran said, “but it was the first trial ever where a difference was shown.”

These technologies also work well in patients with vascular abnormalities deep within the brain, which are inoperable, such as trigeminal neuralgia and acoustic neuroma. But the greatest area of growth in recent years has been in treating lung cancers. However, if these cancers are still operable, surgery is still the first choice, Curran said.

Whether that will change depends on the outcome of several clinical trials, now under way, comparing CyberKnife and stereotactic radiosurgery with conventional surgery. RTOG and the American College of Surgical Oncology are conducting a randomized study in patients with early lung cancer and pulmonary compromise, while Accuray has partnered with the University of Texas M.D. Anderson Cancer Center in Houston and 20–25 global centers, including some in China, to test conventional surgery against its radiation device in stage I, non–small-cell lung cancer.

“These are difficult studies to do,” said Omar Dawood, M.D., vice president of global clinical development at Accuray. “Accrual doesn’t come without challenges,” such as persuading patients to undergo surgery when less-invasive radiation therapy is an option—or, in lung cancer, finding patients diagnosed at the earliest stages of the disease. “As a physician, it can be frustrating,” Dawood said.

The company has not publicly disclosed how many patients have so far enrolled in the study, known as the STARS trial. But the primary endpoint is improved overall survival and disease-specific survival at 3, 4, and 5 years, Dawood said.

**More Studies Needed**

In a May *Annals of Internal Medicine* report, based in part on the technology brief commissioned by AHRQ, investigators cited the STARS trial as one of the few studies that may provide answers about stereotactic radiosurgery’s effectiveness and safety, compared with surgery—at least in early lung cancer.

More such studies are needed, they said, as well as studies offering “convincing evidence that the theoretical advantages of SBRT over other radiation therapies actually occur in the clinical setting.”

The *Annals* review, performed by investigators at the ECRI Institute Evidence-Based Practice Center in Plymouth Meeting and Temple University Hospital in Philadelphia, looked at 124 relevant prospective and retrospective single-group studies in databases from January 2000 to December 2010. The studies involved as few as three patients to as many as 398, with patient inclusion criteria of inoperable tumors, patients refusing surgery, no prior radiation therapy, and biopsy-proven disease.

“It’s not so much one machine versus another,” said Elise Berliner, Ph.D., director of the technology assessment program at AHRQ, who oversaw the project. “More important are the technical parameters,” she said, such as radiation dose, the number of treatments involved, the positioning system used as radiation is delivered, and the patterns of radiation.

“Even the published studies” with this type of information “leave a lot of blanks,” she said.

In SBRT, “the whole assumption is you’re irradiating the precise part of a tumor,” Berliner said. “But the big [safety] issue is what if you miss the tumor? Right now, we don’t know.”

Another theoretical issue involves what’s happening on the margins of tumors during these therapies. “There are no good long-term studies,” Berliner said, adding that the FDA is setting up a system of monitoring that would track situations where radiation therapies may cause harm.

The most frequently reported adverse events in the literature review were pain, fatigue, nausea, bleeding, and diarrhea.
Challenges to Future Studies
David Palma, M.D., a radiation oncologist at the London Regional Cancer Program, took issue with the review’s call for more randomized trials or prospective studies with concurrent control subjects, noting the difficulty of evidence-based evaluations of new medical technologies.

“New technologies are often the sum of numerous small innovations, and demonstrating clinical benefit for each incremental innovation is virtually impossible,” he wrote in a letter to the *Annals*. Also, he said, generating the type of data requested for stereotactic body radiation “may now be exceedingly difficult, as many patients and physicians would not agree to a randomization against older techniques.”

Patients and investigators also resist clinical trials with disparate choices, one involving surgery, the other a less invasive option, such as radiation, said Jeanette Linder, M.D., chief of radiation oncology at Sinai Hospital of Baltimore, part of LifeBridge Health.

Some patients with multiple lung metastases occurring months to years apart, who in the past would undergo more surgery, today might have SBRT instead. Similarly, in ovarian cancers, despite some controversy, Linder said, this can be a good option for reducing tumor burden and treating one or two persistent spots, when patients are “clean elsewhere” for cancer.

“That, to me, is a paradigm shift” in the use of these therapies, Linder said. As for which technology tool is best or better, she too hesitated.

Although Linder described the CyberKnife’s adaptive treatment capability as “fantastic” and a clear advance, “no one machine can do everything.” For large tumors, she prefers Varian’s TrueBeam, because of faster beam output and larger field size, greatly shortening the time patients spend on the table.

But, biologically, whether treating over an hour versus treating over minutes matters is uncertain.

“Not every question has an answer,” Linder stressed.