Early Breast Cancer: Single Dose of Radiation During Surgery Gains Support

By Charlie Schmidt

Localized lumpectomy, followed by weeks of external-beam radiation, is a well-established standard treatment for early breast cancer. But now, results from a phase III clinical trial, published in The Lancet on June 5, suggest that some patients might do just as well with only a single dose of radiation during surgery. Lead author Jayant Vaidya, M.D., Ph.D., from University College London, said this intraoperative approach offers comparable clinical benefits at lower cost to both patients and their health care systems.

The single-dose approach, dubbed targeted intraoperative radiotherapy (TARGIT), was given to 1,113 women from 28 participating treatment centers in nine countries. Treatment results were compared to those obtained from 1,119 matched control subjects given postsurgical, whole-breast external-beam radiation for 3–6 weeks. Eligible patients were at least 45 years old, with invasive ductal breast carcinoma and no evidence of lobular carcinoma. According to the Lancet report, the study detected no statistically significant differences between the treated group and control subjects after 4 years of follow-up.

Some researchers take a cautious view of the data, claiming that the study wasn’t long enough to justify changes to routine clinical
practice. “We need more time to get a better handle on long-term outcomes,” said Bruce Haffty, M.D., chair of radiation oncology at the Robert Wood Johnson Medical School in New Brunswick, N.J., and a member of the American Society for Therapeutic Radiation and Oncology’s task force on partial-breast irradiation. “Still, the results are interesting, and the single-dose intraoperative approach merits investigation.”

The study’s authors have a more bullish perspective. Vaidya said that “for patients who match the selection criteria we used in our study, it’s ethically, morally, and clinically hard to deny them this alternative.” And coauthor Laura Esserman, M.D., from the University of California, San Francisco, described the TARGIT approach as “absolutely ready for prime time.” She added, “For patients who can get the single treatment, it’s a wonderful thing; they wake up from surgery and they’re done.”

**Partial- vs. Whole Breast RT**

TARGIT is not the first study to challenge the current standard, which is lumpectomy followed by whole-breast irradiation at a total dose of 40–56 grays (Gy), fractionated into daily doses over 5–7 weeks. Other studies have shown that accelerated dosing schedules and partial-breast irradiation in postsurgical patients can yield clinical benefits comparable to those of the current standard. For instance, in February in the *New England Journal of Medicine*, a team led by Timothy Whelan, M.D., from McMaster University in Ontario, reported 10-year data showing that an accelerated 3-week schedule is “not inferior” to 5 weeks of radiation after lumpectomy for invasive breast cancer.

TARGIT provides the first phase III data showing that whole- and partial-breast treatments are also equivalent, according to Frank Vicini, M.D., chief of oncology services at Beaumont Hospital in Royal Oak, Mich. “So, in other words, TARGIT represents an accelerated, partial-breast treatment approach,” he said.

Partial-breast irradiation is becoming increasingly common among older women who meet specific criteria—lymph node-negative tumors, smaller than 2 cm, with limited margins. “Five years ago, it was very rare, but now perhaps 10% of women get partial-breast treatments,” Haffty said. Driving the trend is mounting evidence that if cancer does return after treatment, it almost always does so near the lumpectomy cavity, even among women who received whole-breast irradiation. This has led to speculation that irradiating the entire breast might not be necessary, Haffty said.

Earlier, Vaidya had found that even widespread cancers in other parts of the breast could remain dormant for decades without producing clinical tumors. In the mid-1990s, he theorized that a single intraoperative dose to the tumor bed itself would ward off recurrence. Working with Photoclectron Corp., he developed the technology used in the TARGIT trial: a system that delivers low-energy X-rays (maximum, 50 kV) through a 3.2-mm-diameter tube. Given over 20–25 minutes, the highest doses that this “Intrabeam system” delivers occur at the tumor bed surface (typically 20 Gy) and drop to 5–7 Gy at a depth of 1 cm.

The Intrabeam system is only one among several radiation technologies used in partial-breast treatment. The Mammmocyte Radiation Therapy system delivers targeted radiation doses through a single catheter, whereas an alternative approach, interstitial brachytherapy, relies on multiple catheters. Both approaches are invasive, however, and most patients reject them in favor of a type of partial-breast, external-beam radiation called 3D conformal radiotherapy, said Vicini.

A phase III clinical trial comparing all three methods to conventional whole-breast irradiation (NSABP B-39/RTOG 0413) is now under way, with Vicini as principal investigator.

**Dosing Levels**

Some experts question whether the Intrabeam system’s dosing levels are high enough. Abram Recht, M.D., professor of radiation oncology at Harvard Medical School in Boston, said the system’s peak delivery differs little from that of conventional X-rays. “Mammograms are only 40 kV,” he said. “The biggest concern with the TARGIT trial is that they might have underdosed tumor cells that aren’t within a few millimeters of the applicator.”

Recht points out that not much is known about the distribution of tumor cells in relation to the excision cavity or how much radiation is necessary. “This is an empirical question,” he said. “Does the machine have what it takes to do the job?”

An ongoing Italian study, headed by Umberto Veronesi, M.D., director of the National Institute of Cancer in Milan, uses a different partial-breast technique—full-dose intraoperative therapy with electrons—that delivers much higher doses penetrating deeper into breast tissue. The ELIOT trial, as this study is known, closed in 2007, and results are expected later this year, Vicini said.

Vaidya’s response is that the Intrabeam system increases “relative biological effectiveness,” such that biological effects from the radiation are actually higher than what one would predict from the physical dose. What’s more, the relative biological effectiveness increases with depth, he added. “The radiobiological effects are more like 70 Gy even though the physical dose is just 20 Gy,” Vaidya said.

Whether physicians should commit to partial-breast irradiation during surgery also is debated. Haffty points out that some physicians won’t decide until they get the final pathology reports. “And then when you know the tumor margins, and you know that the nodes are negative, you can proceed with irradiation,” he said. “But when you’re doing it intraoperatively, you don’t have all that information.”

Anticipating this point of contention, Vaidya and his colleagues gave themselves a safety valve: If pathology reports revealed extensive lymphovascular involvement, node positivity, unexpected lobular carcinoma, or...
other complicating features, they offered whole-breast radiotherapy. The researchers expected that 15% of patients would require postoperative, whole-breast treatments, and in fact, 14% of the treatment cohort received both the TARGIT intervention and external beam, Vaidya said.

Finally, the issue of the duration of follow-up in the TARGIT trial remains. Recht’s view is that breast cancer is notoriously slow and that TARGIT might turn out to delay relapse among some individuals but not prevent it.

Vaidya countered that differences between the two groups are so small that even if relapses double in the treatment group during the next 5 years, the differences would still not be statistically significant. If patients meet the TARGIT criteria, he said—older than 45 years and having small (<3–3.5 cm) unifocal, invasive, ductal carcinoma—TARGIT is an acceptable alternative to whole-breast radiotherapy.

“There are times when you need to be cautious, and there are times when you should feel confident about treating patients in a different way,” Esserman said. “We’re going to offer this as standard therapy at UCSF, and we’re going to continue to test the technology in higher-risk patients.”

Cost Savings
Esserman is the only American on a report with 24 authors from Europe, the UK, and Australia—which raises questions about whether TARGIT, a less costly option that limits radiation treatment to a single dose, finds a more receptive audience in countries with nationalized health care, where fee-for-service concerns don’t apply. Vaidya said that in the UK, TARGIT could generate savings on the order of $23 million per year. “And that’s only in terms of manpower costs otherwise paid to the radiation therapist,” he said. “So it’s a substantial underestimate that doesn’t account for the health care system having to plan for and deliver radiation treatments or the productivity savings that would come from patients who don’t have to leave work to come to the clinic every day.”

Recht thinks that different opinions about TARGIT might not fall along international lines so much as medical
Specialties. Surgeons devised TARGIT, he said, including Vaidya and Michael Baum, M.D., professor emeritus of surgery at University College London. Surgeons are intuitively more at ease with intraoperative radiotherapy, Baum suggested. “It’s more akin to what they do all the time,” he said. “They don’t feel as comfortable with external beam.” But Vaidya disagreed, saying the TARGIT team also had substantial representation from radiation oncologists.

Meanwhile, disagreements over whether TARGIT may be ready for prime time occur in the shadow of another, somewhat ironic question: whether patients need any type of radiation after lumpectomy. Vaidya’s view is that intraoperative radiation changes the tumor cavity’s microenvironment, making it less prone to cancer recurrence. Intraoperative dosing may trigger immune reactions that deter tumor growth, according to Esserman. But Vicini said that some patients have such a low risk of recurrence that they might not need any radiation therapy.

“There’s no question that there is a subset of patients who can get by without it because the magnitude of the benefit is so small,” he said. “We’re still looking into this, but the reality is that at this point in time it remains very hard to clearly identify who needs it and who doesn’t.”

Dr. Vaidya received support from Photoelectron Corp. and later received honoraria. He also receives support from Carl Zeiss, which distributes the Intrabeam system, for travel and accommodation at meetings and conferences.