site, the cell has to reprogram, going through the mesenchymal–epithelial transition again.

Weinberg acknowledges that the field is currently ignorant of what enables certain cells to go through these transitions—the cell’s microenvironment may be only part of the story—but he believes that only specific cells, the CSCs, can go through the epithelial–mesenchymal transition.

**Agreeing To Disagree**

No short-term end to the CSC debate is in sight, but proponents welcome the dispute. “The field has become much more developed, more complex, and nuanced. This is very good because there are certain things that are becoming clearer that have been controversial,” said Wicha.

Hayes agreed. “What the stem cell theory does is help us identify targets that in theory are driving the tumor and that we [can’t eliminate] right now. You can call them CSCs if you like,” said Hayes. “There are cells that have stem cell characteristics and cells that don’t. Those are the two ends of the continuum, and there are a bunch of things in between. I think that the people who want this to be black and white are being naïve. This is science, and there is a continuum.”

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**Intraoperative Radiotherapy Makes Uncertain Headway in the U.S.**

**By Judy Peres**

When the for-profit Cancer Treatment Centers of America began advertising that breast cancer patients could get their full dose of radiotherapy at the same time as their lumpectomy—potentially avoiding 5–7 weeks of conventional radiation—the disapproval of the academic medical establishment was nearly audible.

“There is some confusion about new technologies being associated with better outcomes. At M.D. Anderson, we have decided on the basis of scientific evidence that we are not yet ready to adopt this [intraoperative therapy] as a standard of care.”

—Thomas Buchholz, M.D.

Uncertain Efficacy

Several recent studies have found that these technologies—known generically as accelerated partial breast irradiation (APBI)—are becoming increasingly popular, including among patients not considered appropriate under the guidelines of the American Society for Therapeutic Radiation and Oncology. The authors of the most recent study (Hattangadi et al., “Accelerated Partial Breast Irradiation Using Brachytherapy for Breast Cancer: Patterns in Utilization and Guideline Concordance,” JNCI, December 2011) expressed concern that financial incentives, rather than proven effectiveness, might be driving the trend. They pointed out that the dramatic increase in use of APBI corresponded with U.S. Food and Drug Administration clearance of the first balloon catheter–based brachytherapy device in 2002 and Medicare’s approval of reimbursement for the procedure in 2004.

APBI using brachytherapy is more lucrative for providers than conventional external-beam radiation. Medicare pays hospitals
approximately $17,000 for a 1-week post-operative course of high-dose-rate brachytherapy (such as MammoSite), compared with less than $10,000 for 33 fractions of standard radiation. And 1 week of APBI is more attractive to many patients than 6 1/2 weeks of daily radiation treatments, which may help providers increase market share. At the same time, population-based cohort studies or randomized trials offer no evidence that brachytherapy is better than, or even as good as, traditional whole-breast irradiation (WBI) for breast cancer. A study presented last December at the San Antonio Breast Cancer Symposium by researchers from M. D. Anderson found that Medicare patients treated with APBI brachytherapy had twice as many local recurrences as those who received WBI. Examining Medicare billing claims for more than 130,000 women who underwent lumpectomies for invasive breast cancer, the researchers also found that the brachytherapy group had more acute and late toxic effects (including hospitalization and infection) than the WBI group.

But IORT, whether with high-energy electrons or low-energy photons, may be different. At least for now, Medicare does not pay for the procedure: The agency established a code last fall but has yet to determine a reimbursement amount.

“There’s no financial incentive for providers to do IORT,” said James Hugh of American Medical Accounting and Consulting, a reimbursement consultant who specializes in radiation oncology. Even when the Centers for Medicare and Medicaid Services do determine a reimbursement amount for IORT, he said, it’s almost certain to be less than the reimbursement for conventional radiotherapy “because it all happens in one day.”

Donald Goer, Ph.D., chief scientist at IntraOp Medical Corp., maker of the Mobetron linear accelerator, agreed. (Goer said 15 of the electron IORT devices in the U.S. are Mobetrions.)

“In the U.S., most hospitals that use the Mobetron get very low reimbursement that would never pay for the machine,” he said. “They’re doing IORT because they really believe in it.”

Pablo Lavagnini, M.D., worked with Umberto Veronesi, M.D., who pioneered IORT at the European Institute of Oncology in Milan. Lavagnini says he tried to introduce it in the U.S. 4 years ago and ultimately went to work for Cancer Treatment Centers of America “because they were the only ones who agreed to accept this technology.” (His centers use Novac7 linear accelerators made in Italy.)

**Reimbursement on the Way**

All that could change in the coming months. Medicare will establish a reimbursement rate for IORT by the end of the year, said Hugh. And this summer, the results of a large randomized trial of IORT versus standard WBI are expected. That trial, known as ELIOT (for intraoperative radiotherapy with electrons), is being conducted by the European Institute of Oncology, which began using the technique in 1999. According to unpublished data presented at a February 2012 meeting in Riyadh, Saudi Arabia, patients considered suitable for APBI by the American Society for Therapeutic Radiation and Oncology have a 5-year local recurrence rate of 1.5% with IORT—equivalent to the recurrence rate among patients who received standard WBI.

“In a year or two,” Goer predicted, “U.S. hospitals will be rapidly adopting IORT technology. By the end of the decade, I believe IORT will become the standard of care and will reduce breast cancer health care costs by $1 billion a year while improving treatment for the patient.”

Hospitals are already buying Intrabeam machines—the low-energy X-ray devices made by Carl Zeiss Meditec of Germany and used in the TARGIT trial. Michael Alvarado, M.D., a surgeon at the University of California, San Francisco, Comprehensive Cancer Center and a principal investigator of the phase IV trial in the U.S., said he believes at least 25 Intrabeam devices are in the U.S., and others are probably on order, because “we’ve gotten inquiries from 35 institutions interested in taking part in the trial.” (Zeiss declined to say how many devices it had sold in the U.S. and at what price. Other sources said the Intrabeam device costs around $450,000, compared with Mobetron’s $1.4 million price.) The phase IV study will enroll 750 patients for a single-arm trial to look at efficacy, cosmetic effects, and patient satisfaction.

The TARGIT trial found that IORT was not inferior to WBI with external beams on the basis of a local recurrence rate in the conserved breast of 1.2% in the Intrabeam arm versus 0.95% in the external-beam radiation arm. However, critics complain that the median follow-up in the TARGIT trial was too short to be clinically meaningful.

Alvarado, whose institution participated in TARGIT-A, pointed out that the trial had a group of 585 patients with a median follow-up of 54 months. “We feel the data are strong at 4 years,” he said. “The chance they will change significantly over the next 6 years—that’s almost impossible.”

**Dealing With Patient Demand**

While they wait for existing data to mature and for new data to be reported, breast centers are coming up with different responses to the demand for quicker radiotherapy—a demand they expect will intensify as more women hear about IORT.

Some centers use IORT to replace the boost portion of standard radiotherapy, shortening treatment by about 1 week. That approach is common in Europe. But Catherine Park, M.D., associate professor of radiation oncology at UCSF, said Americans are having trouble adapting to that. “If you don’t put the boost and the external-beam radiation together,” she said, “people fear you might lose some efficacy. How to interdigitate with chemotherapy is another issue.”

The Cleveland Clinic has a Mobetron, which they use only for advanced and recurrent tumors. St. Joseph Hospital in Orange, Calif., which also has a Mobetron, offers patients the option to replace the boost portion of standard radiotherapy with IORT. Radiation oncologist Afsinh Forouzannia, M.D., said they also do one-shot treatment, but only in patients who are being monitored as part of a protocol.

Nora Hansen, M.D., director of the Lynn Sage Comprehensive Breast Center at Northwestern Memorial Hospital in...
Chicago, said her center has been doing IORT with an Intrabeam for nearly a year and has treated about 50 patients so far. “We don’t have a strict protocol,” she said, “but we tend to use it on women in their 60s who have relatively small, invasive [ductal] cancers.”

“Patients love it,” said Hansen. But it’s frustrating for those who find out later, from the final pathology report, that they have a positive node or involved margins. In such cases the patient undergoes WBI, and the IORT is treated as a boost.

Memorial Sloan–Kettering Cancer Center has its own IORT protocol using a high-dose-rate afterloader that technicians wheel into a special shielded operating room. Beryl McCormick, M.D., chief of external-beam radiotherapy, said the center has 60 patients in a phase I/II feasibility study. Although the study has completed enrollment, she said, the center continues to offer the technology to older women with low-risk breast cancer. “But we do only a few cases a year,” she said, because getting time in the operating room is so difficult.

### Tentative Uptake

Mc Cormick does not see IORT becoming widespread in the U.S. because the technology is expensive and the difficult logistics of having a radiation oncologist on call to the operating room.

Alphonse Taghian, M.D., chief of breast radiation oncology at Massachusetts General Hospital, has the same concern. He agrees that patients will demand shorter treatments, but he does not believe IORT is the answer.

Although the Intrabeam device is not expensive, he said, “operating room time is expensive, and it takes a long time [about half an hour] to get the dose delivered.” Another problem he sees with IORT in general is that, to be eligible, patients need to have clean margins, negative lymph nodes, and no high-risk markers. “We need to wait for the final pathology report to say we’re comfortable that [a given patient] is a good candidate,” he said.

Taghian said the TARGIT trial “proved the principle that partial-breast irradiation is equivalent to WBI in the short term.” What remains to be seen is which of the 10 or more APBI techniques will become dominant.

“It’s like a horse race,” said Taghian, and he, like McCormick, is betting on a type of external-beam radiation called 3D conformal that can be given in 10 sessions over 1–2 weeks. “It’s simple,” he said. “It’s not invasive, it can be taught in community hospitals, and it’s at least 30% cheaper than 6 weeks of radiation.”

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### The Plight of Childhood Cancers for Families

By Kurt Ullman

They are among the most frightening words a parent can hear: “Your child has cancer.” Those words are repeated 12,000 times every year in the U.S. Even though around 75% of children go into remission with treatment, the diagnosis is traumatic for children and parents alike.

Vickie Sardi-Brown recalls the trauma of learning about her son’s diagnosis in July 2008. “It is important to understand that one day our son Matthew was an active 6-year-old going to day camp,” she said. “One day he came home complaining of arm pain. Two weeks later he couldn’t move the arm, and soon after that we got the diagnosis of osteosarcoma.”

Unlike treatments for other childhood illnesses, cancer treatment moves quickly. It is not unusual for a child to be diagnosed one day, hospitalized for surgery the next, and getting chemotherapy soon thereafter.

“The speed can be incredibly disorienting,” said Kenneth Mitten, a social worker in the department of patient care at St. Jude Children’s Hospital in Memphis, Tenn. “Within 24–36 hours, [parents] are wading through information on treatment protocols, learning the definition of new terms, and still trying to come to grips with the fact that their child has cancer.”

Because they often involve intrusive, painful procedures, the treatments themselves usually add to parents’ stress. To cope, the child may exhibit behaviors and emotions unfamiliar to the parent.

“When the child gets angry with them during the course of treatment, parents feel they are doing something wrong,” said Bernadette Mazurek Melnyk, Ph.D., R.N., dean of the College of Nursing at Ohio State University in Columbus. “They were used to parenting