Less Radiation After Lumpectomy in Breast Cancer: New Results Stir Debate

By Caroline McNeil

Recent findings from two large trials support the idea that early breast cancer patients who have a lumpectomy may not need as much radiation therapy as they would normally receive. The 5-year results from the Standardization of Breast Radiotherapy trials (START A and B) suggest that the total amount of radiation can be safely reduced from the commonly used dose of 50 Gy and that it can be delivered in fewer sessions, or fractions, at a higher dose per fraction.

The less arduous and less costly approach, known as hypofractionation, “seems to offer rates of local-regional tumor recurrence and late adverse effects at least as favorable as [those obtained using] the standard schedule,” concluded the START investigators, led by John Yarnold, M.D., of Royal Marsden Hospital in Sutton, England. Reported in *The Lancet* and *Lancet Oncology* in March, the findings came out soon after similar 10-year results from a large Canadian trial were presented at the San Antonio Breast Cancer Symposium last December.

Taken together, the studies could influence practice in clinics around the world. Nonetheless, some experts warn that more follow-up is needed and that questions remain about the long-term adverse effects of hypofractionation.

“Potentially we can learn a lot from these trials. But in applying the results we need to be cautious … we need to know which patients could benefit.”

### The Studies

When lumpectomy plus whole-breast irradiation became a standard treatment for early breast cancer in the 1990s, the dose of radiation was generally 50 Gy, given in 25 fractions of 2 Gy per fraction over 5 weeks. This schedule evolved pragmatically, according to *The Lancet* report by the START Trialists’ Group, based on the assumption that a high total dose delivered in small fractions provided good tumor control while minimizing adverse effects on normal tissue.

Early attempts to modify this schedule, using fewer but larger fractions, resulted in greater toxicity and higher recurrence rates. But in these early hypofractionation trials, the total dose of radiation was not reduced.

The current studies, in contrast, lowered the total dose by about 10 Gy. In START A, which included more than 2,000 lumpectomy patients, the standard 50-Gy, 25-fraction schedule was compared with either 41.6 Gy given in 13 fractions of 3.2 Gy per fraction or 39 Gy given in 13 fractions of 3.0 Gy. Treatments were given over a 5-week period. After a median of 5 years of follow-up, local recurrence rates were similar in the 50-Gy and 41.6-Gy arms, as were adverse effects, such as breast hardness and changes in appearance. Heart disease, lung fibrosis, and rib fractures were also uniformly low, as expected. (These side effects of radiation to the breast area typically occur later.) The patients in the third, lowest-dose arm had slightly higher recurrence rates and fewer late tissue effects.

In an editorial accompanying the studies, Harry Bartelink, M.D., Ph.D., of The Netherlands Cancer Institute in Amsterdam and Rodrigo Arriagada, M.D., Ph.D., of the Institut Gustave Roussy in Villejuif, France, emphasized the need for more follow-up. They pointed out that late adverse effects often don’t show up for 10 years or more. And local recurrence rates could also change over the next 5 years, Bartelink said in an interview. He noted that there was a statistically significant difference between 10-year rates and 5-year rates in at least one large study—a trial by the European Organisation for Research and Treatment of Cancer (EORTC) that showed that a boost of radiation reduced recurrence rates. That boost, or extra round of radiation, which follows whole-breast irradiation and is targeted to the area of the tumor, has become common practice.

Yarnold agreed that the START results must be considered preliminary but said he does not expect that continued follow-up will alter the relationship between the arms. On the basis of other studies, the UK researchers expect an eventual 30% increase in adverse effects and tumor relapse rates in both arms. “Follow-up will make the data more precise, but we don’t expect it to alter the results,” he said.

That view is supported by 10-year results from the large Canadian trial of hypofractionation led by Timothy Whelan, M.D., of the Hamilton Regional Cancer Center in Ontario. With more than 1,000 patients, that trial compared a 3-week schedule of 42.5 Gy in 16 fractions with the standard 5-week, 50-Gy, 25-fraction
schedule. After 10 years, there was no statistically significant difference between the arms in local recurrence or adverse effects, Whelan reported at the San Antonio conference.

In Practice
Whether the 5-year START and 10-year Canadian results will affect practice patterns is unknown. Hypofractionation is already common in the UK and Canada, according to Yarnold and Whelan. In the UK, three-quarters of early breast cancer patients have a hypofractionated schedule, a practice that has been common for several decades.

“But that is definitely not the case in the rest of Europe,” said Bartelink, who led the EORTC trial that established a boost of radiation as beneficial. Likewise, in the United States, the longer schedule is more common. Until this year, the National Comprehensive Cancer Network, an alliance of 21 large cancer centers that issues cancer care guidelines, recommended only the 45- to 50-Gy, 5-week schedule followed by a boost to the tumor bed in higher risk patients, said the University of Michigan’s Pierce, who is a member of the network’s breast cancer committee. At its last meeting, the committee agreed to include a 3-week, 16-fraction, hypofractionated schedule as an alternative to the standard dose and schedule after lumpectomy. That decision was based on the updated Canadian results, Pierce said. The START results will probably be discussed at this year’s meeting, she said.

But even with guidelines changing, both Pierce and Bartelink urge caution for several reasons. One is the universally acknowledged need for more follow-up. “I think the 10-year data [from Canada] make us all feel a lot better,” Pierce said. But she noted that there is still more to know, especially about the cardiovascular effects of hypofractionation. “The window of time for heart damage generally starts at 10 years,” she said.

Another worrisome issue, they say, is the changes in practice that have emerged since these trials began in the late 1990s. For example, the boost of radiation to the tumor bed immediately after the standard schedule has become common, especially in younger women, since 2002, when the results of the EORTC trial were published. But it is not clear whether or how the boost will affect outcomes on a hypofractionated schedule. About a third of patients in START had a boost, so further follow-up and analysis may help answer this question.

The difference in the use of chemotherapy in the trials and in current practice, especially in the U.S., is also a concern. “We tend to be aggressive in terms of use and type of chemotherapy,” Pierce said. “Most patients diagnosed with invasive breast cancer, including some node-negative patients, now get chemo after lumpectomy and then radiation.” Only a minority of patients in the Canadian and START trials had chemotherapy. So whether hypofractionated schedules will interact differently with chemotherapy and result in more frequent or severe side effects remains unknown.

Pierce also noted that the Canadian trial did not include node-positive patients, nor did it accept patients with large breast sizes (defined as a maximum width of the breast of more than 25 cm), who are less likely to receive a homogeneous dose of radiation in all tissues. “I think physicians will be discussing these results with patients, but in counseling patients, we need to know which ones are appropriate candidates,” she said.

More Research
Help with that question may eventually come from another direction. In The Netherlands, Bartelink and his colleagues are looking for biomarkers to show which patients will benefit, in terms of local tumor control, from radiation therapy. Using different genetic profiles based on MammaPrint, a DNA microarray analysis tool, the researchers are conducting a prospective study to see whether a profile can predict recurrence with different radiation schedules.

Other new research is focusing on biological questions about hypofractionation, such as why it appears to work in early breast cancer though not in head and neck cancer. The UK group is hoping to answer this question using tissue from the START trials. Their hypothesis, Yarnold said, is that the rapidly proliferating squamous cells affected in head and neck cancers respond differently to radiation than the more slowly proliferating cells in breast tissue. At the DNA level, there may be a difference in how the tissues handle the double-strand breaks caused by radiation. “We are actively pursuing this idea,” he said.

Yarnold and his colleagues are also conducting the FAST trial, which is comparing extremely hypofractionated schedules—5.7 Gy or 6.0 Gy per fraction once a week for 5 weeks—with the standard 25-fraction schedule. The primary endpoint in this trial, which enrolled 900 patients and is now in follow-up, is the schedule’s adverse effects on healthy tissue, Yarnold said. But the findings could lead to a larger phase III trial that would test this level of hypofractionation in terms of both adverse effects and tumor control, he said.

Although the larger trial is in the proposal stage, it does suggest that the START and Canadian trial results, even after further follow-up, may not be the last word on radiation therapy after breast-conserving therapy. “We think there is reason to believe that 13 or 15 fractions are probably not the limits of hypofractionation,” Yarnold said.

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