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EDITORIAL

A Trial of Two Questions

THE NATIONAL Surgical Adjuvant Breast and Bowel Project (NSABP) B-21 trial addresses two important questions for women with node-negative, less than 1 cm breast cancer who have undergone breast-conserving surgery (BCS): (1) Is breast irradiation really necessary if adjuvant tamoxifen alone is administered? And (2) do such women who are treated with breast irradiation gain additional benefit from adjuvant tamoxifen? On the surface, the answer would seem to be yes to both questions. But as is often the case in medical decision making, the answer is "It depends."

There are now six published randomized trials evaluating the role of breast irradiation after BCS.[1-6] All of these studies have demonstrated that breast irradiation substantially reduces the risk of recurrence of cancer in the breast, thereby increasing the likelihood of breast conservation. Since the publication of the first of these trials,[1,2] there has been interest in identifying patients in whom the risk of local recurrence is so low that breast irradiation is not required. Trials have evaluated the need for breast irradiation when surgery is more extensive,[3,4] when tumors are small (< 2 cm),[3,4,6] and when adjuvant systemic therapy is used.[5] Despite some early positive results,[7,8] with longer follow-up investigators were unable to identify a group of patients in whom radiation could be avoided.[3,4]

Fisher et al[9] have now evaluated the need for breast irradiation when the tumor is small (≤ 1 cm) and the patient receives long-term endocrine therapy. After lumpectomy, 1,009 patients were randomly assigned either to tamoxifen alone, breast irradiation plus placebo, or breast irradiation plus tamoxifen. The risk of local recurrence at 8 years was 16.5% for patients treated with tamoxifen alone compared with 9.3% for breast irradiation alone. Given that tamoxifen is unlikely to have any effect on local recurrence in estrogen receptor (ER)–negative patients, when the analysis is limited to patients with ER-positive tumors, there is still a significantly lower rate of local recurrence with breast irradiation. In this population, the rate of local recurrence was 12.6% with tamoxifen alone compared with 5.4% with breast irradiation alone at 8 years (approximate event rates as determined from the yearly risk estimates assuming a constant hazard). These results suggest that the risk of local recurrence with tamoxifen alone is substantial and that radiation is more effective than tamoxifen in preventing local recurrence.

When this trial was developed, available data suggested that size was a major determinant of local recurrence. Thus, investigators selected the smallest tumors to study the group at lowest risk for local failure. Other studies have examined different factors that are predictive of a decreased risk for local recurrence after BCS, such as age more than 50 years,[2-4] low or moderate grade,[2,10] wide margin of excision,[11] absence of lymphatic/vascular vessel invasion[10,11] and favorable histopathology.[3,10,11] These studies have been unable to identify a low-risk group of patients who would not benefit from breast irradiation. These results are consistent with those of NSABP B-21 and support breast irradiation as standard treatment after BCS.

At the time this trial was conceived, practice guidelines did not advocate adjuvant systemic therapy for women with node-negative tumors ≤ 1 cm.[12,13] Systemic therapy for small tumors has been hotly debated recently, reminiscent of the discussions of treatment for node-negative breast cancer in the early 1990s.[14-16] The discussion has centered on the lack of data from randomized trials about the efficacy of adjuvant therapy for small tumors and the modest absolute benefits that are likely to be achieved. Evidence from randomized trials plays an important part in determining the value of treatment in women at low risk of recurrence. NSABP B-21 is the first randomized trial of systemic therapy restricted to women with node-negative breast cancer and tumors ≤ 1 cm in diameter. The results demonstrate—perhaps not surprisingly—that the *relative* benefit of tamoxifen in reducing local recurrence compared with no hormonal therapy is similar to that for women at

higher risk of recurrence.[17] Interestingly, the risk of distant recurrence in such patients is very low. The risk of local recurrence at 8 years for women treated with breast irradiation alone was 9.3%, which was reduced to 2.8% with the addition of tamoxifen. Again, if we look at only ER-positive patients, the risk of local recurrence at 8 years is estimated to be 5.4% reduced to 1.7%. Some might consider an absolute benefit of this magnitude relatively modest.

Should a woman with node-negative breast cancer and a tumor ≤ 1 cm who has undergone BCS be treated with breast irradiation and tamoxifen? "It depends." It depends on a number of important factors: a careful assessment for an individual patient of the underlying risk of recurrence, and the absolute benefits and risks associated with the proposed treatment(s); good communication between physician and patient about these benefits and risks, including quality of life; and an effort to incorporate the patient's values or preferences in the final decision. This process of shared physician-patient decision making is not an easy task. Studies have documented problems at each of these steps: inaccurate estimates of the benefits and risks of adjuvant therapy by clinicians[18,19]; problems with information transfer between oncologists and patients regarding treatment options[20,21]; and lack of desired involvement by patients in treatment decision making.[22] Recognizing these issues, health researchers have developed decision aids to facilitate shared decision making for patients and physicians.[23-26] A variety of instruments have been developed for the use of adjuvant therapy[23,24] and breast irradiation after BCS.[27] These instruments have been shown to improve patients' understanding and involvement in decision making without increasing the length of the medical consultation.[28,29]

The NSABP has done its part. With a number of landmark studies over the last 20 years, including B-21, the NSABP has provided accurate estimates of the benefits and risks of both breast irradiation[1] and adjuvant tamoxifen.[30-33] Because of the inclusion of many centers and physicians in these studies, these data are likely to be generalizable to patients who are seen every day in our clinics. The information from the NSABP trials can be used as a basis for communicating with women the various treatment options that are available. For breast irradiation, patients should be informed not only about the benefits of reduction in local recurrence but also the side effects of therapy, such as fatigue, skin irritation, breast discomfort, poor cosmetic outcome, and the need to attend daily treatments for up to 5 to 6 weeks.[34] Given the benefits observed in the B-21 trial, previous research suggests the majority of women are likely to choose breast irradiation, even without measurable survival benefits.[27] The choice of adjuvant tamoxifen in addition to breast irradiation is more complex. Women and their physicians will need to consider not only the reduction in local recurrence but the additional benefits of reduction of distant recurrence, contralateral breast cancer, and fractures, weighed against the risks of thromboembolic events, uterine cancer, and the other side effects of tamoxifen.[30-33] Given that a significant proportion of women with breast cancer will want to avoid recurrence, a number are likely to choose adjuvant therapy.[21,35,36]

Until now, treatment decision making from the perspective of individual patients and their physicians has been discussed. As women at lower risk are offered new therapies, we will, in some instances based on health insurance groups and publicly funded health care, have to decide as a society if we can afford to offer such treatments. These decisions are likely to be more difficult, but approaches similar to decision aids performed on a wide representative sample can help inform such decisions.[37]

Is this the final word on the role of breast irradiation and adjuvant therapy in "low-risk" patients? Probably not. It is possible that eventually a group of patients with a relatively low absolute benefit from breast irradiation will be identified such that some of these patients may choose not to receive radiation. Indeed, two trials were recently completed in which the need for breast irradiation in addition to tamoxifen was evaluated in women with node-negative breast cancer who were more than 50 years old[38] and ≥ 70 years with primary tumors ≤ 2 cm.[39] The results of such studies are preliminary and require longer follow-up. Other systemic therapies, such as chemotherapy[40] and the newer endocrine therapies (aromatase inhibitors[41] and gonadotrophin-releasing hormone analogs[42]), are currently being evaluated and may afford such patients additional benefits and possibly reduced risks. As we have seen with the results of NSABP B-21, these studies will provide important information but not all the answers. The information will have to be communicated with our patients and their preferences will have to be incorporated through a balanced process of shared physician-patient decision making.

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