We thank Drs. Sartor and Tepper for their editorial on our randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. They conclude that the use of the shorter approach can produce excellent local control with acceptable cosmesis in carefully selected patients (1). This conclusion is based on questions about the generalizability of the trial results and the possibility of physician bias in the selection of patients for the study. We feel that the methodologic points they have raised are open to question.

GENERALIZABILITY

Patients who fit the inclusion criteria for a trial are screened, and those who satisfy the exclusion criteria are then excluded. The remaining eligible patients are approached for consent. The results of our study are most easily generalized to the population of patients represented by these eligible patients. Data are rarely reported from oncology trials that pertain to the generalizability of trial results. In our trial, the numbers of patients screened, excluded, and randomly assigned to treatment groups were reported. A total of 3732 patients were screened and met the inclusion criteria; 1303 were then excluded (2). The most common reasons for ineligibility were primarily technical or administrative, including an axillary lymph node dissection not performed (29%), the presence of invasive cancer or intraductal cancer at the margin of excision (18%), enrollment in another clinical trial (17%), breast deemed too large for satisfactory radiation (6%), or the inability to commence radiation in a timely fashion (5%).

We agree with the authors that the results of this trial do not apply to patients with positive margins of excision or very large breast size. These patients were ineligible for the study. We disagree, however, that the results do not apply to patients with close margins of excision, lobular carcinoma, or estrogen receptor-negative tumors. These patients were included in the trial, and there is no evidence in any of these subgroups that the rapid fractionation schedule was less effective than the longer traditional schedule. The randomized trials that have demonstrated the efficacy of breast irradiation in women who have had breast-conserving surgery dictated that margins had to be free of tumor as an inclusion criterion (3,4). The notion that close margins increase local recurrence is based on small retrospective studies. With respect to ductal carcinoma in situ, we agree that these patients were not included in our trial; hence the results...
may not directly apply to them. However, it is likely that the shorter radiation schedule would work in a less aggressive stage of disease.

Drs. Sartor and Tepper further suggest that one of the reasons for success of the rapid fractionation schedule may be dependent on careful selection of patients with a low likelihood of substantial burden of residual malignant cells in the breast after breast-conserving surgery. With regard to this speculation, women at high risk for local recurrence, who were younger than 50 years and whose tumor was greater than 2 cm in diameter, were eligible for this trial. There was no evidence to suggest that the rapid fractionation schedule was any less effective in any of these subsets, as seen in Table 2 of our article (2).

**PHYSICIAN BIAS**

The authors also suggest that, because nearly half of the patients refused randomization, physician bias may have influenced the selection of patients for the trial. It should be pointed out that a consent rate of 50% is typical for most randomized trials and is considered respectable. The main reason for non-consent of eligible patients in this study was patient choice, not physician choice. Potential for selection bias, therefore, is not likely, in our opinion.

Drs. Sartor and Tepper point out the potential advantages of accelerated partial breast irradiation techniques, which have not been evaluated in randomized trials. We agree that currently such techniques must be considered experimental. In contrast, the rapid fractionation schedule for whole breast irradiation has already been evaluated in a large randomized trial and shown to provide results similar to standard approaches. It represents an important advance in breast-conserving therapy, providing an effective treatment that is more convenient and less costly. For the reasons stated above, we believe the results of this study are generalizable and should be shared with all women with lymph node-negative breast cancer who fit the eligibility criteria of the trial. It has been estimated that, after breast-conserving surgery, as many as 14%–18% of women per year in the United States may not receive radiation therapy (5,6). The reasons for this are unclear but appear to be related to older age (and as described by the editorialists), health insurance, income, and distance from treatment centers. In such situations, the shorter radiation schedule may improve access and increase the number of women able to receive breast irradiation.

**REFERENCES**


**NOTES**

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**RESPONSE**

We would like to take this opportunity to again congratulate Drs. Whelan et al. for their very well-designed and -conducted study. Our comments did not imply that the study’s results should not be widely applied to many breast cancer patients, as defined by the disease characteristics of those treated on the trial. Rather, as is true for interpretation of any clinical trial, one must use caution in extrapolating the results obtained from treatment of a defined patient population to a broader population in which the treatment was untested. In this respect, we believe that the authors’ suggested extension of shorter fractionation schedules to patients who were ineligible for participation in the trial is premature.

The results of any clinical trial predict the efficacy of the tested intervention in a future cohort of patients represented by those who were actually treated, not necessarily those who met the eligibility criteria. By their thorough (and highly commendable) reporting of the proportion of patients deemed eligible versus those actually enrolled, the authors illustrate that a substantial proportion of patients who met all eligibility criteria were not enrolled, raising the possibility that unmeasured, or unmeasurable, factors may contribute to selection of patients enrolled in the trial. We strongly agree that the degree of non-enrollment in this trial compares favorably with other studies. The problem of applying study results to patients with disease characteristics that would have made them eligible for a trial, but on which they were not in fact well-represented, is not unique to this study but is an issue frequently encountered in the medical literature. Thus, we urge caution in applying study results as the standard of care based solely on eligibility, when patients actually treated represent a more select group.

We believe that this important study will and should have a substantial impact on treatment patterns of patients with early-stage breast cancer. We hope that the use of shorter courses of radiotherapy will improve convenience of radiotherapy to the patient and reduce logistic barriers to receipt of appropriate care.

**NOTES**

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