With the advent of screening, an increasing proportion of newly diagnosed breast cancers are 1 cm or less in size (stages T1a and b), and an emerging dilemma is addressed in the article by Fisher et al. (1). As pointed out by Lippman and Hayes (2) in their accompanying editorial, there is no biologic rationale for expecting any qualitative difference in efficacy of adjuvant systemic therapies between smaller tumors and larger/lymph node-positive tumors. A tumor requires a blood supply to grow beyond the size of a few millimeters (about 1 million cells) (3). Neovascularization generates endothelium, which is fragile and leaky, and cancer cells can readily break away from a tumor bolus to enter the circulation via highly permeable new blood vessels. The potential to metastasize, therefore, exists from the nascent phase of tumor development and provides mechanistic support for Fisher’s hypothesis that breast cancer is a systemic disease at the outset for many patients. Adjuvant therapy is ostensibly indicated whenever micrometastases are present. Patients without micrometastases do not require adjuvant treatment by definition and are cured by locoregional treatment alone. Of those patients with micrometastases, there is an implicit gradation in prognosis and response to adjuvant therapy dependent on the micrometastatic load. Fisher et al. have highlighted the nuances of pathologic size determination. Although maximum tumor diameter is a prognostic factor, grade (histologic and nuclear) and lymphovascular invasion are strong predictors of outcome, and neither of these variables were analyzed independently by the authors. Of interest, stratification of patients according to estrogen receptor (ER) status revealed no statistically significant benefit for chemotherapy with respect to disease-free, event-free, or overall survival, with a hazard ratio of 1.28. A type II error may have occurred in this analysis, which was based on small numbers of ER-negative patients, although even with ER-positive tumors, statistically significant benefit for chemotherapy was confined to overall survival (hazard ratio = 0.40).

Approximately equal numbers of patients analyzed underwent mastectomy or breast conservation. It would have been interesting to analyze the relapse-free survival (RFS), event-free survival (EFS), and overall mortality for these two surgical groups and to have incorporated this subdivision into analysis of benefits of systemic treatment; historically, mastectomy was rejected as standard treatment of breast cancer because of its lack of impact on mortality rather than influence on local recurrence rates. Mastectomy has never been evaluated for tumors of 10 mm or less, but improvement in DFS or EFS per se would not justify mastectomy for this group. Similarly, recommendations for systemic therapy should not be based on the inappropriate end points of RFS and EFS.

Patients must make individual decisions about systemic chemotherapy once fully informed about the likely benefits and side effects of treatment. According to the paradigm of biologic predetermination, all patients should receive some form of systemic therapy. Models of logarithmic cell kill indicate that this will be more effective when directed at smaller micrometastatic foci. Potential risks and morbidity have hitherto restricted use of chemotherapy among lymph node-negative patients, and the data cited therein do not appear prima facie to justify expansion of current recommendations to tumors of 1 cm or less. Identification of those patients with micrometastatic disease will help rationalize systemic therapy, but absolute gains may remain modest and selection criteria imperfect. Nonetheless, some patients may be denied the chance of elimination of micrometastatic disease if systemic therapy is withheld at the time of presentation.

Detection of occult bone marrow metastases may represent a promising method for identifying patients who will relapse and hence benefit most in absolute terms from systemic chemotherapy. A clinical trial to investigate the prognostic significance of bone marrow micrometastases in patients with T1 lymph node-negative tumors would be useful; limited data suggest that up to 85% of patients with occult micrometastases eventually relapse (4).

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Fisher et al. (1) recommend adjuvant chemohormonal therapy for all patients with small breast cancers. The editorial by Lippman and Hayes (2) emphasizes the need for definitive clinical trials before routine acceptance of adjuvant chemotherapy. Our letter extends the discussion on risks and benefits to adjuvant hormonal treatment, in relation to age and ethnicity.

Of the 1024 estrogen receptor-positive patients evaluated in this article (1), 7% of the tumors were T1a and 93% were T1b, and 60% of all tumors were measured as 10 mm (where T1a is ≤0.5 cm in greatest dimension and T1b is larger than 0.5 but not larger than 1 cm in greatest dimension). Most patients were younger than 70 years, and 37% were younger than 50 years. Although adjuvant tamoxifen improved relapse-free survival (P = .01), overall survival was not statistically significantly im-
proved ($P = .41$). Recurrences in younger patients were 1.7 times more common than in patients over 50 years of age. Moreover, it should be noted that conditions other than breast cancer accounted for half the mortality at 8 years. In a study of more than 300,000 breast cancer patients, Diab et al. (3) found an association between increasing age at diagnosis and favorable biologic features. Thus the impact of breast cancer recurrence is comparatively smaller in older patients. These findings indicate the need for including the age of the patient and the risk of morbidity and mortality from side effects in decisions regarding adjuvant interventions, including tamoxifen.

In the Early Breast Cancer Trials’ (EBCTG) overview of tamoxifen for early breast cancer (4), the only statistically significant increase in deaths attributable to tamoxifen was from endometrial cancer. However, older women, African-American women, and patients with small breast cancers were underrepresented. In the Breast Cancer Chemoprevention Trial of the National Surgical Adjuvant Breast and Bowel Project (NSABP) (5), 36% of the participants were older than 59 years. In women older than 50 years of age, tamoxifen was also associated with an increase in relative risks for pulmonary emboli of 3.01 (95% confidence interval [CI] = 1.15 to 9.27) and stroke of 1.59 (95% CI = 0.93 to 2.77). Furthermore, the National Center for Health Statistics Database reports a twofold increased incidence of and mortality from pulmonary embolism in African-American women (6). A twofold increase in relative risk for hospitalized strokes and a relative risk for ischemic strokes of 1.38 (95% CI = 1.01 to 1.89)—even after adjusting for hypertension, diabetes mellitus, educational status, smoking, and coronary artery disease—have been reported for African-American women (7). Moreover, these risks start a decade earlier than for Caucasian women. Hence, one must consider the effects of hormonal interventions on these complications in relation to age and ethnicity.

In summary, several factors must be considered in advising hormonal therapy to patients with T1a/lymph node-negative hormone-receptor-positive breast cancers. With increasing detection of small breast tumors, trials addressing the overall benefit from adjuvant hormonal interventions should be designed. Such trials should ensure adequate representation of women older than 70 years of age and African-American women older than 60 years of age, who have an increased predisposition to and morbidity and mortality from thromboembolic events. As noted by Fisher et al., the NSABP trials represent a start for discussing these issues, but only through additional prospective trials may questions concerning the risk/benefit ratios of adjuvant hormonal interventions be answered.

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RESPONSE

We concur with Benson and della Rovere’s statement that “an emerging dilemma is addressed in the article by Fisher et al.” (1). We believe, however, that their perspective with regard to our findings is too narrow. So, too, is the view of others, including that of Mirchandani and Muggia, involved in the dialectic that has ensued with regard to our article on the prognosis and treatment of patients with tumors of 1 cm or less. Along with the findings reported from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Prevention Study (P-1) (2) and from our trials aimed at preventing invasive cancer in women with ductal carcinoma in situ (3,4), our article must be viewed as part of an overall effort that is aimed at eradicating breast cancer closer to its phenotypic expression. All of those studies have, paradoxically, demonstrated benefits from therapies that have resulted in controversy with regard to the clinical application of the findings, not with the data itself. It is evident that we have embarked on an era of medicine in which success results in the genesis of difficult problems. When a group of breast cancer patients with an increasingly better prognosis is defined and when evidence of a therapeutic benefit among the few in the group who are likely to have a tumor recurrence is demonstrated, treatment decisions become more difficult. When there is no discriminant to indicate with precision who is likely to have a treatment failure, the question arises as to what risk of recurrence may be deemed low enough to preclude treating the entire group.

We have never stated that all patients with a “good prognosis” should receive chemotherapy, tamoxifen, or radiation therapy after lumpectomy for invasive or noninvasive breast cancer. We do contend, however, that, because the odds of another breast cancer event in patients with tumors 1 cm or less can be altered by systemic therapy, the use of therapeutic agents of proven benefit should receive consideration in that group. Patients and physicians should consider the merits of using such therapy on the basis of data rather than on personal bias. Our studies have provided such data. Although we support the need for “cost-benefit” consideration when therapeutic decisions are made, in patients such as those who participated in our studies, such estimates attain credibility only when they are made after a long follow-up period; e.g., the
conclusions from such estimates made after 5 years might be invalid after more prolonged follow-up time, during which more breast cancer events could occur.

In their letter, Benson and della Rovere have expressed concern about several aspects of our article. Although they indicate that no significant differences in the outcomes examined were noted in most comparisons, Fig. 1 of our paper does demonstrate a benefit with respect to recurrence-free survival for both estrogen receptor (ER)-negative and ER-positive patients who received systemic adjuvant therapy, i.e., chemotherapy in the case of ER-negative patients and tamoxifen alone or tamoxifen and chemotherapy in the case of ER-positive patients. Although relative risk estimates were consistent with those observed among patients with larger tumors, results did not achieve conventional statistical significance, since statistical power was inadequate to do so. For survival (Fig. 4), the essentially overlaid curves among ER-negative patients suggest no survival difference, whereas, among ER-positive patients, a survival advantage is apparent, although the absolute magnitude of this difference is small.

We did not examine results for patients who underwent mastectomy and breast-conserving surgery separately, as Benson and della Rovere would have desired, mainly because of the size of the patient cohort. We did, however, note the percentages of breast cancer recurrence events by site, and, in all treatment groups, at least 50% of such events were tumors at sites other than in the ipsilateral breast. All patients who underwent breast conservation received radiotherapy; thus, as was expected, local recurrence was low.

Because they were not uniformly available for all patients, tumor grade and lymphovascular invasion were not reported. Tumor nuclear grade was examined but did not emerge as a significant prognostic factor. However, tumor type was a significant prognostic factor: tumors other than invasive ductal or lobular carcinoma indicated lower failure risk. Consequently, this characteristic might be used to make decisions with regard to selection of systemic adjuvant therapy.

Another point raised by Benson and della Rovere is the potential for metastatic disease to provide information about tumor cell dissemination and, thus, aid in determining whether or not systemic adjuvant therapy should be used. They suggest that there is an increased risk of failure for those patients with localized disease who exhibit bone marrow micrometastases. The most reliable information about the potential clinical implications of both lymph node (LN) and bone marrow (BM) micrometastases will come from ongoing prospective studies that evaluate sentinel lymph node biopsy, in particular, the ancillary studies associated with randomized trials of the American College of Surgeons Oncology Group (LN and BM) and the NSABP (LN).

Finally, with regard to the establishment of risk gradients for patients with tumors under 1 cm, referred to in the editorial by Lippman and Hayes (5), it is unlikely that a determination of risk on a millimeter-by-millimeter basis could satisfactorily be evaluated in existing databases. Except in large, carefully defined cohorts, of which we are not aware, there would be inadequate statistical power to discern between a linear risk extending from 10 mm to zero versus another functional form, such as some threshold, e.g., 5 mm, below which risk might be even lower. While risk differentials between T1a and T1b tumors are plausible, our study was unable to provide such information.

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