Postoperative radiotherapy for breast cancer is known to substantially reduce the risk of locoregional recurrence, both when given after mastectomy and after breast-conserving surgery. Recent reports [cited below] suggest that radiotherapy following mastectomy may also have a beneficial impact on survival, and the article by Vinh-Hung et al. (1), published in this issue of the Journal, further suggests that radiotherapy given after breast-conserving surgery improves survival.

Three randomized clinical trials (2–4) of postmastectomy radiotherapy, conducted in Canada and Denmark, have shown a 9%–10% improvement in overall survival at 10 years for patients that received radiotherapy compared with patients who did not receive radiotherapy. These results contrast with those of a patient-based meta-analysis of randomized clinical trials (5) in which radiotherapy was shown to be associated with a reduced risk of dying of breast cancer; however, this reduced risk was offset by increased mortality from vascular causes. There are several possible explanations for this apparent discrepancy. Many of the trials included in the patient-based meta-analysis (5) were initiated a long time ago, and these trials were often small and involved radiotherapy techniques and fractionation schedules that resulted in higher doses to the heart than are obtained with modern radiotherapy techniques. In a reanalysis of data from these trials, a substantial reduction was found in the risk of mortality associated with radiotherapy of 12.4% ($P<.001$) when only recent trials were included (6). In addition, patients treated in the Canadian and Danish trials (2–4) received adjuvant chemotherapy and/or tamoxifen (i.e., systemic therapy) in conjunction with radiotherapy. Hence, if the burden of distant micrometastases can be reduced by systemic therapy, then radiotherapy given to locoregional sites might prevent secondary dissemination, thus being potentially curative. This hypothesis is supported by the results of a meta-analysis of randomized clinical trials of adjuvant radiotherapy (7) in which patients also received systemic therapy. In these trials, adjuvant radiotherapy statistically significantly reduced the risk of mortality (odds ratio = 0.83, 95% confidence interval [CI] = 0.74 to 0.94; $P = .04$). These results have led to the general acceptance that radiotherapy given after mastectomy to patients at moderate or high risk of dying from breast cancer has favorable effects on survival.

Radiotherapy is given to most patients who undergo breast-conserving surgery because multiple trials [reviewed in (1)] have shown a substantial risk of local recurrence if this technique is omitted. Given the evidence in favor of an association of radiotherapy after mastectomy with an impact on survival, similar benefits might be expected for radiotherapy after breast-conserving surgery. However, multiple individual trials (and previous meta-analyses that have included some of those trials) have not found a statistically significant association of radiotherapy after breast-conserving surgery with survival [reviewed in (1)]. Vinh-Hung et al. (1) now present a literature-based meta-analysis of all clinical trials of breast-conserving surgery with and without radiotherapy; 15 such trials, which were initiated between 1976 and 1994, were identified. The combined data from 13 trials for which mortality results were available indicated a relative risk of mortality of 1.086 (95% CI = 1.003 to 1.175) in patients not receiving radiotherapy after breast-conserving surgery.

In view of the increasing evidence for substantial gains in survival when radiotherapy is administered after mastectomy and the higher rate of recurrence if radiotherapy is omitted after breast-conserving surgery, it is surprising that improvements in survival resulting from the use of radiotherapy after breast-conserving surgery are not larger. A relative risk of mortality of 1.086 resulting from omission of radiotherapy after breast-conserving surgery implies an absolute increase in 10-year survival due to administration of radiotherapy after breast-conserving surgery of approximately 3% and 1.5% for groups of patients with prognostic features that lead to expected 10-year survivals of 50% and 80%, respectively. These expected increases in 10-year survival values are much lower than those found in the Danish and Canadian trials (2–4) for administration of radiotherapy after mastectomy in patients who also received adjuvant systemic therapy. However, there are differences between patients in these types of trials. For example, patients undergoing mastectomy tend to have poorer prognostic factors, and radiotherapy is usually administered to the regional lymph nodes and chest wall, whereas radiotherapy is often only given to the residual breast in patients undergoing breast-conserving surgery.

The most likely explanation for improved survival from use of radiotherapy after breast-conserving surgery is that local failure may result in secondary dissemination of disease. Local failure is known to predict for poorer survival compared with non-failure, both after mastectomy and breast-conserving surgery. For example, in a group of more than 2000 women treated with breast-conserving surgery followed by radiotherapy, patients who experienced local failure had poorer survival at 10 years than those with local control (55% versus 75%, respectively; $P<.001$) (8). In addition, for patients who experienced local failure, the peak time for development of distant metastases was 5–6 years after diagnosis, whereas for patients with local control (with a lower overall incidence of metastases), it was only 2 years after diagnosis, consistent with metastatic spread from recurrent lesions. However, these types of studies do not establish a cause–effect relationship, because initial prognostic factors might predict for both local recurrence and survival. If
there is a cause–effect relationship between local recurrence and survival, the smaller association of radiotherapy after breast-conserving surgery with improved survival compared with radiotherapy after mastectomy might be due to a more profound impact of local recurrence in the chest wall after mastectomy than in the residual breast after breast-conserving surgery, as suggested by Vinh-Hung et al. (1).

Given that none of the individual trials of breast-conserving surgery with or without radiotherapy has shown a statistically significant association between survival and radiotherapy, then how reliable are the results of the current meta-analysis? All but two of the trials included in the meta-analysis by Vinh-Hung et al. (1) showed a trend in favor of a survival benefit from radiotherapy; hence, the meta-analysis is internally consistent. One weakness in the current meta-analysis is that it was based on published data and not on survival data for individual patients included in the trials. Stewart and Parmar (9) have reported that meta-analyses of randomized clinical trials that are based on published data may overestimate the effects of treatment to improve survival (by as much as threefold) compared with meta-analyses that are based on survival data for individual patients.

In contrast to the results of individual trials and the relatively small benefit in survival with radiotherapy demonstrated in the meta-analysis by Vinh-Hung et al. (1), it is intriguing that analysis of registry data by the same authors (1,10,11) and by others (reviewed in (1)) suggests a large survival benefit from use of radiotherapy after breast-conserving surgery. Guidelines for evidence-based medicine assign highest priority to large, randomized clinical trials and meta-analyses of these trials. Randomized clinical trials have the advantage of ensuring a balance of prognostic factors between the groups that are compared but suffer from the disadvantage of a selected patient population. Population-based studies suffer from potential imbalances in prognostic factors between patients that do and do not receive an intervention; however, they do have the advantage of a large size and the inclusion of a less selected patient/subject population. These two different types of studies should be regarded as complementary, and the results of the registry analyses lend credence to the current meta-analysis (1) by supporting a role for radiotherapy in improving survival after breast-conserving surgery.

In conclusion, what are the implications of the meta-analysis by Vinh-Hung et al. (1) for oncologic practice? Because most patients already receive radiotherapy after breast-conserving surgery, the results of their study will largely reinforce current practice. Radiotherapy to the conserved breast (using modern techniques) probably carries a minimal risk for cardiac toxicity (12). In addition, the emergence of high-precision radiotherapy techniques, such as intensity-modulated radiotherapy and partial-breast irradiation, will help avoid irradiation of the heart, with further improvement in the risk–benefit ratio of using radiotherapy. There are probably groups of patients with good prognostic factors such that radiotherapy might not be necessary for reducing the rate of disease recurrence after breast-conserving surgery. Moreover, these same patients are also likely to have high rates of survival, and any gains in absolute survival from radiotherapy would probably be small. In general, however, the meta-analysis presented by Vinh-Hung et al. (1) reinforces the view that the large majority of patients undergoing breast-conserving surgery should also receive radiotherapy.

References

(9) Stewart LA, Parmar MK. Meta-analysis of the literature or of individual patient data: is there a difference? Lancet 1993;341:418–22.