
DILEMMAS IN BREAST DISEASE

This section of the journal addresses special aspects of breast disease management that presents a challenge to practicing clinicians, generally for which there is no clear answer or consensus. Invited consultants who are authorities in the field summarize available data in order to clarify the issue and facilitate rational decisions.

Is Breast Irradiation Routinely Necessary Following Conservation Therapy of Breast Cancer?

INTRODUCTION The gradual acceptance of Fisher's "Alternative Hypothesis" of the biology of breast cancer, as confirmed by numerous prospective trials of the past twenty years, has served to support the validity of breast conservation therapy. Appropriate questions are being raised as to whether irradiation is always necessary, especially in view of current evidence that local recurrence of breast cancer does not appear to adversely affect survival rates. We need to investigate the costs/benefit of accepting a higher rate of local breast cancer occurrence in order to avoid the expense, morbidity, and inconvenience of adjuvant radiation therapy following conservation surgery. Is there a subset of women with a specific group of tumors in whom the omission of radiation would be acceptable? There is no clear answer at present, but the following essays by Drs. Pierce, Lichter, and Nemoto strive to summarize the available data and add clarity to the issue.

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Treatment policies that direct our management decisions are often based upon clinical observations in the absence of data. The importance of radiotherapy in the

maintenance of local (breast) control following breast-preserving surgery is clearly, however, an exception to this rule. Every randomized trial to date comparing limited breast surgery with or without breast radiotherapy has shown a highly statistically significant reduction of in-breast failures by the addition of radiotherapy for both invasive and non-invasive (intraductal) disease (1-6).

Therefore, deviation from this standard of care can only be considered when omission of breast radiotherapy is not expected to significantly affect patient outcome. Can we select patients with clinical factors that predict for such a low risk for breast recurrence following limited surgery that omitting breast radiotherapy represents no hazard to them?

It is first important to emphasize the magnitude of benefit with respect to local control when radiotherapy is administered following conservative surgery. Four trials have randomized women with invasive disease following local excision to observation versus breast radiotherapy only. In the Milan trial, women with small breast cancers (less than 2.5 cm in diameter) were randomized following quadrantectomy to radiotherapy (RT) or no additional therapy (1). With a median follow-up of only 39 months, 8.8% of women who did not undergo radiotherapy experienced a local recurrence compared to only 0.3% of those who had radiotherapy. In a similar trial sponsored by the Uppsala-Örebro Breast Cancer Group, lesions 2 cm or less treated with excisional biopsy and negative margins were followed with and without RT (2). Recurrence rates were 2.3% with RT versus 18.4% without RT with 63 month median follow-up. A third study was reported by the Ontario Cancer Institute and Princess Margaret Hospital (3). Node-negative women with tumors 4 cm or less randomized to receive RT experienced a 5.5% local breast failure rate compared to 25.7% in the control group at 43 months median follow-up. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 study reported a cumulative incidence of breast recurrence of 12% with RT versus 53% without RT at 10 years (4). Thus, despite variation in selection criteria, radiotherapy has been needed to consistently reduce breast failure.

These trials are of additional benefit in highlighting clinical and pathologic factors that might predict for a favorable outcome with conservative surgery only. Factors that appear to predict for decreased risk of breast failure in the absence of radiotherapy include a wide surgical resection with attention to margins such as quadrantectomy, tumor size less than or equal to 2 cm, unifocal disease, the absence of an extensive intraductal component (EIC), and increasing age.

Using these and other restrictive criteria, studies have examined the outcome of conservative surgery only in highly selected populations. At the University of Miami, patients with primary tumors less than or equal to 2.5 cm, clear resection margins, no vascular, lymphatic, or perineural invasion, and minimal to no in situ disease are offered breast-conserving therapy with and without RT

(7). With 80 month median follow-up, the five year local recurrence rate was 6% for surgery only and 0% for patients choosing to receive radiotherapy. The Cleveland Clinic published their retrospective experience with partial mastectomy with or without radiotherapy for patients with stage 0, I, or II disease (8). With a mean follow-up of 8.5 years, there was a significant increase in local recurrence in the absence of RT at eight years after surgery. Local control rates at 12 years of follow-up were reportedly similar, however, for women treated with or without radiotherapy. When breast recurrence rates were compared by stage, radiotherapy did not appear to significantly benefit women with stage 0 or I disease. However, in-breast failure was significantly reduced using adjuvant radiotherapy in patients with stage II disease, with five and ten year reported local recurrence rates of 4 and 10 percent with RT versus 11 and 22 percent without RT, respectively. In a study at the Joint Center for Radiation Therapy in Boston of a group of node-negative women with infiltrating ductal carcinoma no greater than 2 cm in size, no evidence of lymphatic vessel invasion or EIC, and clear margins of at least 1 cm, omission of RT resulted in a three year crude local recurrence rate of 7.3% (9). This compares to a 2% rate of recurrence at three years using radiotherapy for women with less favorable criteria (margin uncertainty, younger age, and larger tumors). Analysis of these results led to the premature closure of this trial. The authors concluded that even in a highly selected group of breast cancer patients, there is a substantial risk of early local recurrence for those treated with wide excision alone. Therefore, even with highly favorable characteristics, in-breast recurrence rates appear to be greater in the absence of radiotherapy.

Alternative strategies to observation and standard radiotherapy include the use of tamoxifen following limited breast surgery. A Scottish Adjuvant Breast Cancer Trial demonstrated a 7% rate of breast recurrence for estrogen receptor positive tumors treated with tamoxifen in the absence of radiotherapy compared to 0% failures with radiotherapy and Tamoxifen (10). Further local therapy following recurrence (mastectomy or local excision with or without radiotherapy) among patients not randomized to receive RT has reportedly resulted in comparable rates of ultimate local control as patients randomized to RT. Based upon this and other series suggesting a local benefit with the use of tamoxifen, a NSABP trial is currently randomizing patients with tumors less than or equal to 1 cm to RT, tamoxifen only, or RT and tamoxifen.

Although local control is the obvious endpoint when considering surgery in the absence of RT, thought must

also be given to the possible more subtle effects of increased breast failure upon survival. To suggest distant dissemination is affected by local recurrence implies Halstedian thinking, where en bloc therapy was deemed necessary for cure. Although women with earlier stages of disease were cured by ablative surgery, the propensity for distant failure in the majority of women with breast cancer engendered an alternative hypothesis, proposed by Fisher, which suggested that breast cancer is a systemic disease at inception with little, if any, local influence upon survival. NSABP trials have shown that while limited surgical procedures result in significantly higher rates of breast failure, this has not resulted in significantly higher rates of distant dissemination (4–6). Conversely, durability of local control has not translated into improved survival. Although these conclusions are statistically sound, clinical observations question the comprehensiveness of this hypothesis. It is unquestionable that poorly controlled local disease can provide a nidus for tumor dissemination once a critical size is reached. The risk for development of metastatic disease increases with tumor size, therefore undoubtedly the risk must also increase with time in patients with inadequately controlled local disease. This rationale argues strongly against local therapy having no impact upon survival. Since breast cancer represents a heterogeneous disease, it is reasonable that no one hypothesis is appropriate in every case or that the explanations proposed by Halsted and Fisher are mutually exclusive. As suggested by Hellman, a third hypothesis can be proposed in which development of metastases are a function of tumor growth and progression (11). Therefore, persistent local disease could in fact give rise to metastatic disease.

The argument for a causal relationship between local control and survival is most compelling for patients with pure intraductal disease. Data from a randomized trial of patients with ductal carcinoma in situ (DCIS) are available from the NSABP B-06 study (6). Although the trial was intended for women with invasive stage I or II disease, 76 cases were retrieved of pure DCIS only. With a median follow-up of 83 months, 43% of patients treated with lumpectomy only have experienced a breast failure compared to only 7% treated with lumpectomy and RT. Of the nine patients failing after lumpectomy only, two patients with an invasive recurrence have died of disease. By comparison, there have been no deaths secondary to recurrent disease among patients treated with RT. Although these results are not significantly different, the approximate 50% risk of an invasive recurrence following treatment failure in DCIS suggests the potential for decreased survival with inadequate local control. A subse-

quent NSABP trial for DCIS (B-17) demonstrated a significant event-free survival advantage for patients receiving breast radiotherapy due to reduction of ipsilateral breast cancers, most notably invasive cancers (5). No survival difference was found, but longer follow-up is needed.

The importance of maximal local control is also evident in node-positive stage II disease. In every trial randomizing women to post-mastectomy radiotherapy, a reduction in chest wall and/or regional failure has been demonstrated. Only recently has this translated into improvement in survival. With maturation of data from the Stockholm trial, a significant reduction in distant metastases and deaths due to breast cancer is seen for patients receiving post-mastectomy RT (12). Results of a recent meta-analysis of post-mastectomy trials also demonstrate a trend toward improved survival for patients receiving radiotherapy (13). Studies of women treated with mastectomy and chemotherapy and randomized to receive radiotherapy have also shown a significant benefit in disease-free (14, 15) and overall survival (14). Realization of a similar benefit in women with early stage disease will require significantly larger cohorts of women and long-term evaluation.

In summary, there have yet to be subgroups of women identified with invasive or non-invasive disease for whom breast-conserving surgery without irradiation has led to comparable local control and survival as with adjuvant radiotherapy. Additional clinical trials with well-defined criteria randomizing women to radiotherapy or observation are needed to identify low-risk patients whose increase in breast failure without irradiation is considered acceptable. As in prior studies comparing radical mastectomy to modified radical mastectomy (MRM), and MRM to lumpectomy and radiotherapy, establishing a new standard of care can only be achieved through a stepwise methodical approach. Since recurrent disease and loss of a breast often result in severe psychological distress to a woman, it will be important to study local failure as well as success of salvage therapy among patients randomized to observation to determine ultimate control while preserving the breast.

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