Breast-conserving therapy with lumpectomy and breast irradiation is an accepted standard treatment for patients with early-stage invasive breast cancer or ductal carcinoma in situ (DCIS). For both diseases, investigators have tried to identify subgroups of patients who can be "safely" treated with lumpectomy without radiation. Some data suggest that it may be reasonable to omit radiation therapy in patients with small, low-grade invasive or noninvasive tumors and/or in "elderly" patients. Additional studies are needed to better identify criteria to prospectively select appropriate patients for treatment with lumpectomy alone. [ONCOLOGY 11(9):1361-1374, 1997]

**Introduction**

Breast-conservation therapy with lumpectomy and breast irradiation is a widely accepted, preferred treatment option for both patients with early-stage invasive breast cancer and those with ductal carcinoma in situ (DCIS). Numerous randomized trials demonstrate that, in women with invasive cancer, such breast-conserving therapy provides survival outcomes equivalent to those achievable with mastectomy.[2-6] The same appears to be true for DCIS,[7-9] although no randomized comparative data are available. Due to the cost, inconvenience, and potential toxicity of breast irradiation, there is continued interest in identifying subsets of patients who may be "adequately" treated with lumpectomy alone. This article reviews the results of clinical studies assessing lumpectomy without radiation therapy for early-stage invasive cancer and DCIS. The studies reviewed have varying follow-up periods. Thus, to facilitate comparisons between the studies, the annual breast failure rate will be the primary outcome reported. If not reported in the study, the annual failure rate was estimated by dividing the overall failure rate by the average duration of follow-up.

**Ductal Carcinoma In Situ**

**Randomized Data**

One randomized study comparing lumpectomy alone to lumpectomy plus radiation therapy—the National Surgical Adjuvant Project for Breast Cancer (NSABP) B-17 trial[10-12]—has been published (Table 1). Overall, in this trial, the addition of radiation reduced the annual breast failure rate from approximately 5% to 2%. In a retrospective subset analysis, the addition of radiation decreased the annual breast recurrence rate in all subgroups, regardless of margin status and the presence or absence of moderate/marked comedo necrosis. In the subgroup of patients with the most favorable risk profile, ie, those with clear margins and absent/minimal comedo necrosis, the absolute reduction in the annual breast failure rate was less than 1%. In the "highest-risk" group, ie, those with positive margins and prominent necrosis, the addition of radiation reduced the absolute annual breast failure rate by 7% (from 10% to 3%).[11]

Additional randomized data are available from NSABP B-06.[7,8] This study was intended to include only patients with invasive cancer. However, on histologic review, a small subset of patients were judged to have DCIS. In NSABP B-06, as in the larger NSABP B-17 study, the addition of radiation reduced the breast failure rate from approximately 6% to 1%. Following breast-conserving therapy for DCIS, recurrent lesions may be either invasive or noninvasive. In the NSABP B-17 trial, the addition of breast irradiation reduced the fraction of recurrences that were invasive. Among the group treated with local incision alone, 50% of the recurrences were invasive, whereas in the irradiated group, only 29% of the recurrences were invasive. Thus, the addition of radiation reduced both the incidence of a breast recurrence and the fraction of recurrences that were invasive.
Looking at the data another way, the annual rate of an invasive breast cancer recurrence was reduced from approximately 2.6% to 0.6% (a 76% relative risk reduction \( P < .001 \)). Since patients with DCIS who develop an invasive recurrence are likely to be at a higher risk of death from distant metastases than those who have a recurrence of DCIS, this is an interesting observation. No differences in overall survival were reported in the NSABP B-17 trial.

**Nonrandomized Data**

The data from multiple nonrandomized series using lumpectomy without radiation therapy are summarized in Table 2.[13-26] The annual breast failure rate ranges from 2% to 6%, with a weighted mean of ~4%.

In the first six studies listed in Table 2, most or all of the patients had small mammographically detected lesions and negative resection margins. In this subgroup of studies, the breast failure rate ranged from 2% to 4.6%, with a weighted mean of 3.2%. In all of these studies, the observed annual breast failure rate exceeds that generally reported following lumpectomy plus radiation therapy.[9,10]

**Prognostic Factors**—In several of the studies listed in Table 2, various prognostic factors were identified that are related to the breast failure rate. Although the particular factors identified in the individual studies vary, a low-grade, noncomedo subtype appears to have the most favorable prognosis (Table 3).[14-20, 25, 26] The annual breast recurrence rate among patients with these "favorable" factors ranged from 0% to 3.8%.

Dr. Silverstein and colleagues at the Breast Center in Van Nuys, California, recently described a prognostic index based on tumor size, margin width, and histologic appearance.[20] In their retrospective analysis, patients with the most favorable prognosis, ie, those with the lowest index score (small tumor, wide excision margin, and less aggressive pathology), appeared to have a very low breast recurrence rate following lumpectomy without radiation therapy. These patients did not benefit from breast irradiation.

In contrast, patients with a moderate index score (5 to 7) had a higher relapse rate following lumpectomy alone and did derive benefit from breast irradiation. Patients with the least favorable tumors (index score 8 or 9) also derived a modest benefit from radiation therapy, although the breast relapse rate in these patients was unacceptably high with or without radiation.[20] These results conflict with those of the randomized NSABP B-17 trial.[11] The number of patients in these nonrandomized reports is small. Also, duration of follow-up in both the randomized and nonrandomized studies is short. Additional follow-up data from all of these studies will be interesting.

**Invasive Cancer**

**Randomized Data**

The data from five randomized studies comparing outcomes after lumpectomy alone to those after lumpectomy plus radiation therapy are summarized in Table 4.[2-5,27-33] Only patients with negative resection margins and relatively small (≤ 2 to 4 cm) tumors were included in these studies. In each study, the addition of radiation reduced the annual breast recurrence rate from approximately 5% to 1%. No survival differences were reported (discussed below).

**Nonrandomized Data**

Table 5 outlines the results from several nonrandomized series in which radiation therapy was omitted following lumpectomy.[29, 30, 34-42] It is likely that patients in these series were selected for treatment without irradiation because they were perceived to have more "favorable" characteristics (eg, most of the studies included only patients with small tumors). Despite this, the observed annual breast failure rate was generally greater than the 1% typically seen with lumpectomy plus radiation therapy.

The study by Schnitt et al represents the "cleanest" group of women prospectively selected for lumpectomy without irradiation.[35] This study enrolled 86 patients with a solitary T1 infiltrating cancer, without lymphatic vascular invasion or an extensive intraductal component, who had microscopically negative margins by at least 1 cm (all but two of the patients had negative reexcisions). All 87 patients had pathologically negative axillary nodes. Approximately 75% of the lesions were detected mammographically, and the median age of the patients was 67 years (range, 27 to 84 years).

With a median follow-up of 56 months, the annual breast failure rate was 3.6%. This is a remarkably high breast recurrence rate, in light of the favorable nature of the tumors treated. In a subset analysis, no recurrences were seen in 42 of the patients with the "most favorable" histologic findings (26 grade 1 infiltrating, 9 mucinous, and 7 tubular tumors). It is difficult to know
how to interpret this type of retrospective identification of a most-favorable subgroup, since all of the enrolled patients were initially considered to have a favorable prognosis. Indeed, if all 14 recurrences are assigned to the remaining 45 "less-favorable" patients, the annual recurrence rate in this group is 6.6%.

**Results in Elderly Patients**—Some investigators have selected women for treatment without irradiation based on their age. Table 6 outlines the results reported in "elderly" women treated with lumpectomy without radiation therapy.[41-49] As there is no uniform definition of "elderly" in these studies, the range of patient age is included. The lowest failure rates (0% to 2.75%) were noted in the study populations of Nemoto et al and von Rueden et al, in whom margins were usually negative and tumor sizes were less than 2 to 5 cm.[42,43] However, the studies by Lee et al and Reed and Morrison reported an ~5% annual failure rate in similarly selected patients.[47,49] Higher recurrence rates were generally reported in series that did not specify margin status.[46] The average follow-up in most of these studies was short (less than 4 years), and the patient numbers were small.

**Discussion**

**Impact of Radiation on Breast Recurrence**

For both invasive cancer and DCIS, the addition of radiation following a lumpectomy reduces the annual breast failure rate. For DCIS, the randomized data demonstrate that radiation therapy decreases the failure rate for all patient subgroups. For the favorable subgroup of patients with noncomedo disease and negative margins, the absolute magnitude of this benefit is small. A similar theme is illustrated by the nonrandomized series discussed. As shown in Table 2 and Table 3, in some well-selected subgroups, the annual breast failure rate following lumpectomy without radiation therapy may be low enough (eg, ≤2%) to be "clinically acceptable."[50,51] One of the difficulties in applying this approach to large populations of patients, however, is that there is no consensus on how best to classify and define these low-risk categories.[12,52,53] Nevertheless, lumpectomy without radiation therapy does appear to be a viable treatment option for some "favorable"-prognosis patients with DCIS.

It should be emphasized that these favorable subgroups have been far easier to identify in a retrospective than in a prospective fashion. Additional clinical studies are necessary to determine whether these favorable subsets can be accurately defined prospectively.[53] For patients with invasive cancer, it has been difficult to prospectively identify patient subgroups in whom irradiation can be routinely omitted. Some data suggest that older patients and/or those with small low-grade lesions can be "safely" treated without radiation therapy (Table 5 and Table 6). However, the number of patients in these studies is small and follow-up is limited.

Many older women wish to undergo breast-conserving therapy[54] and, for the most part, can tolerate radiation therapy well.[46,55-59] Additional clinical experience is necessary to better define which, if any, patients should be treated with lumpectomy alone.[54,55]

For elderly patients, the annual breast failure rates without radiation need to be considered relative to the woman's life expectancy. Compared to young women, the elderly will experience a lower overall breast failure rate since they have a higher intercurrent death rate and are therefore "at risk" for a recurrence for a shorter time. In other words, patients must survive in order to experience a breast recurrence. This concept is illustrated in Figure 1. Mortality (from all causes) at 10 years is shown in the dotted line as a function of the patient's age (x-axis).[60,61] The "corrected" 10-year breast failure rate is calculated by multiplying the estimated ~50% 10-year failure rate (5% per year) by the 10-year survival rate (100 minus the mortality shown).

Additional randomized data are forthcoming. The Cancer and Leukemia Group B (CALGB) is conducting a trial (CALBG #9343) to assess the impact of breast irradiation in elderly women treated with lumpectomy and tamoxifen (Nolvadex). Similarly, the NSABP is conducting a study in which women with ≤1-cm, node-negative cancers are being randomized to one of three treatments following lumpectomy: breast irradiation, tamoxifen, or both. Although women of all ages will be included in this study, they will be stratified by age.

**Impact of Radiation on Survival**

It can be argued that the addition of radiation reduces the breast failure rate but has no impact on survival. However, the available clinical studies did not have sufficient statistical power to detect small differences in survival.[62] Figure 2 shows the total number of patients needed in both arms of a randomized trial to detect a 5% difference in overall survival as a function of the survival rate of the control group (with a P value of .05 and power of 80%). Each of the dots on the graph
corresponds to one of the randomized studies shown in Table 4. Since each of the data points lies below the line, none of these studies had the power to detect a 5% improvement in overall survival. For example, the number of patients treated in the studies shown in Table 4 varied from 381 to 1,265, but the number of patients needed to detect an improvement in survival from 80% to 85% is approximately 2,000.[53]

Furthermore, the length of follow-up in these studies is somewhat short in a disease such as breast cancer for which the natural history may be quite prolonged. Theoretically, having a recurrence in the breast probably does have a detrimental impact on survival since having an uncontrolled growing local tumor is likely to be a continued source of systemic dissemination and death.[63-67] A recent meta-analysis suggested that the addition of radiation therapy reduced the death rate from 21.1% to 19.9%—a 1.2% absolute improvement in survival.[68] No survival differences were reported in NSABP B-17. The follow-up in that study was short (average, 3.6 years), however.

**Morbidity and Cost of Radiation**

The benefits of radiation therapy, with respect to local control and perhaps survival, need to be balanced against its morbidity and cost. The morbidity of carefully performed, modern breast irradiation is low. Patients generally experience mild fatigue and skin irritation during radiation treatments. The incidence of long-term toxicities, including radiation pneumonitis, rib fracture, and cardiac injury, is generally less than 1%. Radiation-induced tumors are also possible, but are very uncommon (less than 1%), especially when systemic chemotherapy is not used.

Due to the uncertain survival impact of breast irradiation following lumpectomy for invasive and noninvasive breast cancer, it is incumbent on the treating radiation oncologist to minimize the risks of radiation-induced complications. This is especially true in young women, who are likely to live for many decades, and thus be at risk for experiencing long-term complications. In particular, care should be taken to minimize incidental radiation to the heart during treatment for left-sided lesions. Three-dimensional imaging tools such as CT are very helpful in this regard.

**Summary**

Lumpectomy plus radiation remains the standard treatment approach for patients with invasive and noninvasive cancer who wish to preserve their breast. The addition of radiation following lumpectomy reduces the breast failure rate in all subgroups of patients that have been prospectively studied. The magnitude of benefit is extremely small in well-selected patients with small, noncomedo DCIS lesions, and in these women, the omission of radiation therapy may be reasonable. Additional clinical studies are necessary to determine which patient subgroups, if any, may be routinely "safely" treated without breast irradiation. To date, no survival detriment has been associated with the omission of breast irradiation. However, the clinical studies were not large enough to detect clinically significant reductions in survival that might be associated with a higher breast failure rate.

**References:**


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