Eighteen-Year Results in the Treatment of Early Breast Carcinoma with Mastectomy versus Breast Conservation Therapy

The National Cancer Institute Randomized Trial

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BACKGROUND. Between 1979–1987, the National Cancer Institute conducted a randomized, prospective study of mastectomy (MT) versus breast conservation therapy (BCT) in the treatment of patients with early-stage breast carcinoma. After a median potential follow-up of 18.4 years, the authors present the updated results.
METHODS. After informed consent was obtained from each patient, 237 evaluable women with clinical AJCC Stage I and Stage II breast carcinoma were enrolled on an institutionally reviewed protocol and randomly assigned to undergo modified radical MT (116 patients) or BCT (121 patients), which was comprised of lumpectomy, axillary lymph node dissection, and radiation therapy. Negative surgical margins in the lumpectomy arm were not required. The 237 randomized patients were followed for a median potential follow-up of 18.4 years. The primary endpoints were overall survival and disease-free survival.
RESULTS. At a median follow-up of 18.4 years, there was no detectable difference with regard to overall survival between patients treated with MT and those treated with BCT (58% vs. 54%; $P = 0.67$ overall). Twenty-seven women in the BCT arm (22%) experienced an in-breast event. After censoring in-breast events in the BCT arm that were salvaged successfully by MT, disease-free survival also was found to be statistically similar (67% in the MT arm vs. 63% in the BCT arm; $P = 0.64$ overall). There was no statistically significant difference with regard to contralateral breast carcinoma between the two treatment arms ($P = 0.70$).
CONCLUSIONS. After nearly 20 years of follow-up, there was no detectable difference in overall survival or disease-free survival in patients with early-stage breast carcinoma who were treated with MT compared with those treated with BCT. For BCT patients, long-term in-breast failures continued to occur throughout the duration of follow-up. There was no statistically significant difference in the incidence of contralateral breast carcinoma between the two treatment groups. ***Cancer* 2003;98:697–702.** *Published 2003 by the American Cancer Society.**

KEYWORDS: breast carcinoma, conservation, radiation therapy, mastectomy.

Breast conservation therapy (BCT) (comprised of lumpectomy, axillary lymph node evaluation, and adjuvant radiation therapy) is a well defined alternative to mastectomy (MT) for appropriate candidates with early-stage breast carcinoma. Several randomized studies worldwide have demonstrated that BCT and MT offer comparable survival.[1–4] Recently, 2 groups published their 20-year results, which support this assertion.[5,6] In general, the goals of BCT are twofold: 1) to reduce the risk of cancer recurrence in a reasonable manner and, ultimately, cancer or treatment-related death, and 2) to preserve the

breast anatomy as best as possible. Although there still are regional and age-related biases,[7,8] BCT is increasingly gaining acceptance in the medical and lay population. Nevertheless, long-term randomized data remain relatively scarce.

In 1979, the National Cancer Institute (NCI) opened a randomized, prospective study comparing MT with BCT in the treatment of patients with clinical AJCC Stage I and Stage II breast carcinoma. The current study updates previous reports with a median potential follow-up of 18.4 years.[9,10] With long-term patient follow-up, which in individual cases has exceeded 22.7 years, the updated results of our single-institution randomized trial continue to demonstrate no detectable difference between MT and BCT with regard to overall and disease-free survival. Subsequent contralateral, ipsilateral, or other secondary cancer events also are reported in this update.

MATERIALS AND METHODS

Patients

A detailed description of the study design, eligibility requirements, radiation and surgical techniques, and statistical methods, as well as a comparison of patient characteristics in each group, have been published in previous reports of this study.[9,10] Two hundred forty-seven patients with clinically diagnosed Stage I or Stage II (T1 or T2; N0 or N1; M0) invasive carcinoma of the breast were enrolled between July 1979 and December 1987. Patients had a single invasive unilateral breast lesion without any other palpable or mammographically suspicious areas, no history of prior cancer or Paget disease, and no evidence of metastatic disease and were not pregnant or breastfeeding. Patients with in situ lesions were not eligible. Patients were stratified by age (age $<$ 50 years vs. age $\geq$ 50 years) and clinical lymph node status (positive vs. negative). After fully informed consent was obtained, patients were assigned randomly to undergo MT and axillary lymph node dissection or BCT including excisional biopsy, axillary lymph node dissection, and adjuvant radiation therapy. Negative surgical margins on pathologic examination were not required. Six patients assigned to undergo MT and four patients assigned to the BCT treatment arm declined to receive their randomized treatment assignment and were treated elsewhere and never followed, and therefore were omitted from the current study. Thus, 237 evaluable patients were treated in the study with 116 patients assigned to the MT group and 121 assigned to the BCT group. The data from these patients previously were analyzed in June 1989 after a median follow-up of 5.6 years and again in November 1993 after a median follow-up of 10.1 years. With data available through March 2002, the median follow-up for the current study was 18.4 years at the time of last follow-up (with a range of 14.3–22.7 years). Only two women, both from the BCT arm, were lost to follow-up (one in 1993 and the other in 1996). The data concerning these 2 patients were censored after 4.8 years and 13.3 years, respectively. They were both disease free at the time of last follow-up.

Techniques

The MT group underwent a Patey modified mastectomy with a complete (Level I –III) axillary lymph node dissection on campus at the NCI.[11] No postmastectomy chest wall or lymph node irradiation was performed. The BCT group underwent excisional biopsy (at the NCI or elsewhere after an NCI review of pathology) with the removal of all macroscopic tumor but these patients were not required to have microscopically negative surgical margins. In the case of an incomplete excision, a second excision was permitted. One patient underwent a second excision but was believed to have macroscopic tumor remaining and underwent a mastectomy. Based on intention to treat, she was analyzed in the BCT group. A complete (Level I–III) axillary lymph node excision was performed through a separate incision.

All adjuvant radiation was performed at the NCI and was comprised of 4500–5040 centigrays (cGy) of radiation delivered via 4 megavoltage photons in noncoplanar tangent fields to the whole breast in 180-cGy fractions 5 days per week over a period of 5–5.5 weeks. Patients with pathologically positive lymph nodes also received 4500–5040 cGy to an anterior supraclavicular field prescribed to a depth of 3 cm. In patients with either a positive axilla or a medially located primary lesion, the internal mammary lymph nodes were included in the treatment by extending the tangent fields across midline. The internal mammary lymph nodes were assumed to be included when the pleurosternal junction (located by either ultrasound or computed tomography during treatment planning) was covered by the radiation portal.[12] Lung inhomogeneity correction factors were applied to dose calculations after 1981.[13] The axilla was not specifically treated unless there was extracapsular lymph node extension. A radiation boost of 1500–2000 cGy to the tumor bed was delivered to all patients with either iridium-192 temporary implants (81%) or en face electron beam irradiation (19%).

Patients with positive axillary lymph nodes received adjuvant chemotherapy comprised of cyclophosphamide (Cytoxan®;Bristol-Myers Squibb Oncology, Princeton, NJ) and doxorubicin (Adriamycin®; Pharmacia, Kalamazoo, MI). At the initiation of the

study, chemotherapy was administered for 1 year in 28-day cycles of doxorubicin intravenously at a dose of 30 mg/m^2 on Day 1 and cyclophosphamide orally at a dose of 150 mg/m^2 on Days 3–6.[14] In 1983, the dose of cyclophosphamide was increased to 200 mg/m^2. In 1985, the dose of doxorubicin was increased to 40 mg/m^2; the cycle length decreased to 21 days and the total duration of chemotherapy was decreased to 6 months (9 cycles). After 1985, lymph node-positive, postmenopausal patients were given tamoxifen (Nolvadex®; Novartis Pharmaceuticals, East Hanover, NJ) at a dose of 20 mg orally twice per day for 5 years. Tamoxifen also was prescribed frequently after 1985 to women with ipsilateral tumor recurrences or new contralateral breast tumors.

Statistical Analysis

Using the Kaplan–Meier method, the probabilities of overall survival and disease-free survival were calculated.[15] Overall survival was determined from the date of randomization until death or last follow-up contact. Disease-free survival, which included local, regional, and distant failure or any combination thereof, was measured from the date of randomization until documented failure or last follow-up contact. The study was designed to have 80% power to detect a 15% difference in disease-free survival at 5 years using a 2-sided significance level of 0.05. Patients in the BCT group with an isolated, ipsilateral in-breast event occurring at any time who were salvaged successfully by MT were not considered failures. Unless they subsequently developed a disease recurrence at another site, these salvaged patients were counted as free of disease as of the date of last follow-up contact. The differences between pairs of actuarial curves were analyzed using the Mantel–Haenszel test, with two-tailed P values reported.[16] Estimates reported at 5-year intervals up to 20 years were calculated using the Kaplan–Meier method.

All second cancer events were recorded. A second cancer event was defined as: 1) any recurrence of the index breast carcinoma or 2) a second primary tumor. Because of the long duration of follow-up, the definition of a second primary tumor was limited to include either an isolated, contralateral breast carcinoma, without evidence of regional or distant disease, or the development of a nonbreast cancer. Recurrences of the index breast tumor were characterized further as local, regional, or distant. A local event had to be confined to the chest wall or ipsilateral breast. A regional event could include the ipsilateral supraclavicular, infraclavicular, or axillary lymph node regions or the ipsilateral internal mammary lymph nodes. A distant event included all other sites. A locoregional or distant event after the treatment of any isolated contralateral breast carcinoma was assigned to the initial breast tumor. Data regarding two patients were excluded from analyses involving the development of second primary tumors because the dates of these new tumors were not able to be determined.

TABLE 1
Patient Characteristics

Characteristics	Mastectomy (n = 116)	BCT (n = 121)
Age, (median yrs)	50	50
< 40	19%	23%
40–59	56%	51%
> 60	25%	26%
Histology		
Infiltrating ductal	95%	93%
Infiltrating lobular	3%	2%
Other	2%	5%
Positive LNs		
0	58%	61%
1–3	28%	28%
4–9	8%	4%
> 10	6%	7%
Tumor size (cm)		
0–2	48%	43%
2.1–4	43%	50%
4.1–5	9%	7%
Estrogen receptor		
Negative	11%	15%
Positive	46%	43%
Unknown	43	42%

BCT: breast conservation therapy; LNs: lymph nodes.

RESULTS

Primary Endpoints

There were no apparent significant differences in patient characteristics between the two groups (Table 1).[10] After a median follow-up of 18.4 years, there was no statistically detectable difference in overall survival or disease-free survival between the MT and BCT arms of the trial (Figs. 1,2). and The estimated overall survival at 20 years was 58% for the MT group and 54% for the BCT group (P = 0.67 overall). With respect to disease-free survival, the estimated 20-year disease-free survival was 67% for the MT group and 63% for BCT group (P = 0.64 overall). Both the overall survival and disease-free survival demonstrated similar probabilities over time (Table 2).

Second Events

Table 3 outlines the second cancer event profile at a median of 18.4 years of follow-up. Patients in the MT arm experienced 55 second cancer events and patients

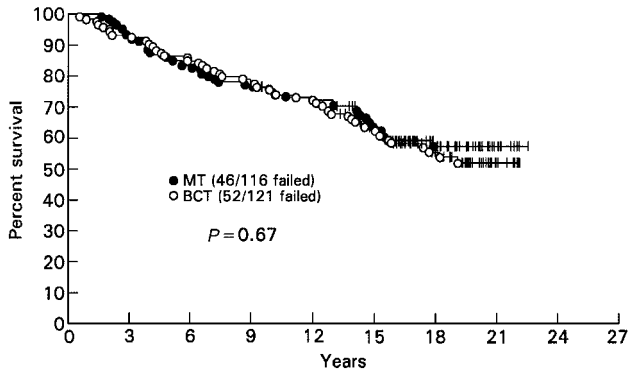

FIGURE 1. Comparison of overall survival between the mastectomy (MT) and breast conservation therapy (BCT) treatment arms in patients with early-stage breast carcinoma after a median follow-up of 18.4 years. No statistically significant difference was reported ($P = 0.67$).

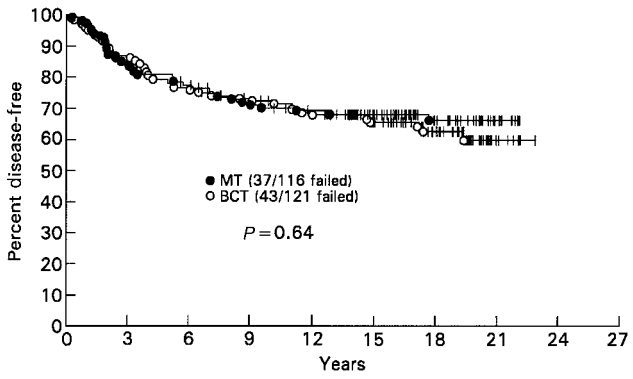

FIGURE 2. Comparison of disease-free survival between the mastectomy (MT) and breast conservation therapy (BCT) treatment arms in patients with early-stage breast carcinoma after a median follow-up of 18.4 years. No statistically significant difference was reported ($P = 0.64$).

in the BCT arm experienced 49 second cancer events after isolated, ipsilateral in-breast tumors were removed, with a total of 4 patients experiencing > 1 second tumor. In the MT group, there were no isolated chest wall events, 3 regional events, 27 distant events, and 8 local and regional and/or distant events. In the BCT group, there were the 27 isolated, ipsilateral in-breast events; no regional-only events; 30 distant events; and 4 local and regional and/or distant events. There were seven contralateral breast carcinomas in the MT group and five in the BCT group. Patients in the MT arm had 10 nonbreast cancer events, which included 2 sarcoma cases; 2 ovarian carcinoma cases; 2 lung carcinoma cases; 1 case each of melanoma, renal cell carcinoma, and colon carcinoma; and 1 unknown, second nonbreast cancer. Patients in the BCT arm also had 10 nonbreast cancer events, which included 3 lung carcinoma cases and 1 case each of non-Hodgkin lymphoma, sarcoma (of the ipsilateral breast that was successfully treated with mastectomy), colon carcinoma, melanoma, ovarian carcinoma, cervical carcinoma, and endometrial carcinoma.

Of the 121 patients in the BCT arm, 27 (22%) experienced isolated, ipsilateral in-breast events after their primary BCT at a median of 18.4 years of follow-up. Sixteen of these events were salvaged successfully (59%), rendering the patients free of disease. However, 11 patients ultimately failed regionally or distantly and were not rendered free of disease (41%). Isolated, ipsilateral in-breast events continued to occur throughout the entire duration of follow-up. However, information regarding the location of these in-breast events was inconsistent and unavailable for meaningful analysis.

The development of distant disease as all or part of a second event was observed in nearly equal numbers between the two arms. The MT group experienced 8 local and regional and/or distant events and 27 purely distant events. The BCT group had 4 local and regional and/or distant events and 30 purely distant events. There was no statistically significant difference in distant disease-free survival between the two groups ($P = 0.82$).

There was no apparent statistically significant difference in isolated, contralateral breast carcinomas between the two arms. After a median follow-up of 18.4 years, the MT group had 7 contralateral breast carcinoma cases whereas the BCT group had 5 cases of contralateral breast carcinoma ($P = 0.70$ for the overall difference in probability of isolated contralateral breast carcinoma).

There also was no apparent difference in the occurrence of nonbreast cancers between the MT and BCT groups. The MT group had 10 such cancers, including 2 sarcoma cases; 2 ovarian carcinoma cases; 2 lung carcinoma cases; and 1 case each of melanoma, renal cell carcinoma, and colon carcinoma. There were 10 nonbreast cancers in the BCT group: 3 lung carcinoma; 1 case each of non-Hodgkin lymphoma, sarcoma, colon carcinoma, ovarian carcinoma, cervical carcinoma, and endometrial carcinoma; and 1 unknown nonbreast cancer event. In a manner similar to the incidence of in-breast events, nonbreast cancers continued to be observed throughout the entire duration of follow-up, nearly equally between the MT and BCT arms.

DISCUSSION

After a median potential follow-up of 18.4 years, the updated results of this trial continue to demonstrate no statistically significant difference in overall survival or disease-free survival in patients with early breast carcinoma who are treated with MT or BCT. These

TABLE 2
Overall and Disease-Free Survival Probabilities over 20 Years

Endpoint	5 years[a]	10 years[a]	15 years	20 years[b]
Overall survival				
Mastectomy	86%	75%	65%	58%
BCT	87%	76%	64%	53%
Disease-free survival				
Mastectomy	81%	70%	68%	67%
BCT	78%	73%	66%	60%

BCT: breast conservation therapy.
[a] Denotes follow-up period with published results.
[b] Denotes estimated rate using the Kaplan–Meier method.

TABLE 3
Incidence of Cancer Events in the Two Treatment Arms

	Mastectomy (n = 116)	BCT (n = 121)
Site		
Local (isolated chest wall or in-breast)	0	27
Regional only	3	0
Local and regional/distant	8	4
Distant only	27	30
Contralateral breast tumors	7	5
Nonbreast histology tumors	10	10

BCT: breast conservation therapy.

results support the findings of two recently published randomized trials, which arrived at similar conclusions.[5,6] In those studies, there was no statistically significant difference in overall survival, disease-free survival, or distant disease-free survival. In addition, three previously published randomized trials found no difference in long-term outcome between MT and BCT, which included radiation therapy.[1,2,4] Furthermore, two meta-analyses, published in 1995 and in 2000 by the Early Breast Cancer Trialists' Collaborative Group, failed to find any difference in survival between patients undergoing MT and those receiving BCT with radiation therapy[17] and, in fact, revealed a cause-specific advantage in patients who received radiation therapy,[18] although this advantage has been called into question by a reported increase in nonbreast cancer deaths.

A major difference between the NCI study and the other randomized trials is the rate of ipsilateral in-breast failure reported in the BCT group. Patients treated with lumpectomy and radiation therapy were found to have a cumulative 22% in-breast event probability after a median follow-up of 18.4 years. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) trial, the overall rate of ipsilateral failure with tumor-free margins was 14.3%, and that in the Milan trial was only 8.8%. However, the inclusion criteria and the methods used between trials differed and may explain the higher rate of local failure in the NCI trial. The NCI trial allowed for all cT1 and T2 tumors (according to the 1988 American Joint Committee on Cancer [AJCC] staging manual), which included those measuring up to 5 cm in size, whereas the NSABP excluded tumors measuring > 4 cm and the Milan trial excluded those tumors measuring > 2 cm. Nearly 10% of the tumors treated in the NCI study were > 4 cm in greatest dimension. Although the NCI trial required macroscopic removal of tumor and even permitted a second excision to meet this goal, negative surgical margins on pathologic examination were not required and frequently were not obtained. Unfortunately, it was not possible to ascertain accurate margin status on the 121 evaluable patients because of referring patterns and inaccessibility to complete pathology specimens. Because positive, or even close, margin status generally is agreed to be one of the more significant predictors of local failure after breast-conserving surgery and radiation therapy,[19,20] with unknown or possibly positive surgical margins it would be reasonable to expect a higher in-breast event rate in the BCT arm of the NCI trial than in other trials in which surgical margin status was reported to be negative. Indeed, long-term surveillance performed by the NCI demonstrated that in-breast events occurred throughout the entire duration of follow-up, even as late as 20 years after the initial BCT. The NSABP, which to our knowledge is the only other group conducting a randomized trial from North America, also observed late-occurring events and advocated the need for long-term follow-up in clinical trials.[5]

With a longer follow-up, the theoretical possibility of radiation-induced carcinogenesis becomes more probable. In the NCI study, there was no apparent statistically significant difference in the probability of the development of an isolated contralateral breast carcinoma between the two treatment arms. In fact, nominally there were two fewer contralateral breast tumors reported in the BCT arm compared with the MT arm. The NSABP and Milan study updates also did not appear to detect any increase in the incidence of contralateral breast tumors.

Because scatter radiation to the contralateral breast may not represent the only source of radiation-induced malignancy, all second nonbreast cancer cases in the NCI study, both inside and outside the radiation fields, were recorded. The survival curves for second nonbreast tumors in the two treatment arms were found to overlap (data not shown). Although

other data, which may have implicated postoperative radiation exposure in nonbreast cancer mortality (such as severe cardiac or pulmonary toxicity) could not be analyzed meaningfully, the current study data regarding contralateral breast carcinoma and nonbreast cancer events are useful. In this context, the inclusion of radiation therapy as part of BCT did not incur any increased risk to this group compared with the MT group. However, the current study was not intended to answer questions regarding radiation-induced malignancy. It was not powered as such and inherent patient factors such as BRCA1 and BRACA 2 are unknown. Lastly, 20 years of follow-up may not be sufficient to account for the entire latency period of radiation-induced carcinogenesis.

The findings of the current NCI trial of MT versus BCT in the treatment of patients with early-stage breast carcinoma are consistent with those of other published, long-term randomized trials comparing these two treatment modalities. With nearly 20 years of follow-up, there was no detectable difference with regard to overall survival or disease-free survival between the MT and BCT arms. Perhaps because of differing inclusion criteria and methods, most notably surgical margin status, the NCI in-breast event rate was found to be higher than that reported in the two other trials with comparable follow-up. In-breast events were observed throughout the entire period of follow-up. Finally, in the BCT arm in the current study, similar to the BCT arms of the other randomized trials, long-term, inbreast events continued to be observed throughout the entire follow-up period. Therefore, we believe that diligent surveillance is warranted.

REFERENCES

1. Blichert-Toft M, Rose C, Andersen JA, et al. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. *J Natl Cancer Inst Monogr*. 1992;11:19–25.
2. Van Dongen JA, Voogd AC, Fentiman SI, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 Trial. *J Natl Cancer Inst*. 2000;92:1143–1150.
3. Jacobson JA, Danforth DN Jr., Cowan KH, et al. Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *N Engl J Med*. 1995;332:907–911.
4. Arriagada R, Le MG, Rochard F, et al. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. *J Clin Oncol*. 1996; 14:1558–1564
5. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347:1233–1241.
6. Veronsei U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347:1227–1232.
7. Albain KS, Green SR, Lichter AS, et al. Influence of patient characteristics, socioeconomic factors, geography, and systemic risk on the use of breast-sparing treatment in women enrolled in adjuvant breast cancer studies: an analysis of two intergroup trials. *J Clin Oncol*. 1996;14:3009–3017.
8. Madan AK, Aliabadi-Wahle S, Beech DJ. Age bias: a cause of underutilization of breast conservation treatment. *J Cancer Educ*. 2001;16:29–32.
9. Straus K, Lichter A. Lippman M, et al. Results of the National Cancer Institute early breast cancer trial. *J Natl Cancer Inst Monogr*. 1992;11:27–32.
10. Lichter AS, Lippman ME, Danforth DN Jr., et al. Mastectomy versus breast-conserving therapy in the treatment of stage I and II carcinoma of the breast: a randomized trial at the National Cancer Institute. *J Clin Oncol*. 1992;11:27–32.
11. Danforth DN Jr., Findlay PA, McDonald HD, et al. Complete axillary lymph node dissection for stage I-II carcinoma of the breast. *J Clin Oncol*. 1986;4:655–662.
12. Lichter AS, Fraas BA, Fredrickson HA, et al. Computed tomography in treatment planning: primary breast cancer. In: Ling CC, Rogers CC, Morton RJ, editors. Computed tomography in radiation therapy. New York: Raven Press, 1983:99–107.
13. Fraas BA, Lichter AS, Fredrickson HA, et al. The influence of lung density corrections on treatment planning for primary breast cancer. *Int J Radiat Oncol Biol Phys*. 1988; 14:179–190.
14. Lippman ME, Edwards BK, Findlay P, et al. Influence of definitive radiation therapy for primary breast cancer on ability to deliver adjuvant chemotherapy. *NCI Monogr*. 1986; 1:99–104.
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observation. *J Am Stat Assoc*. 1958;53:457–481.
16. Mantel N. Chi-square tests with one degree of freedom: extensions of the Mantel–Haensel procedure. *J Am Stat Assoc*. 1963;58:690–700.
17. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: an overview of the randomized trials. *N Engl J Med*. 1995;333:1444–1455.
18. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomized trials. *Lancet*. 2000;355:1757–1770.
19. Freedman GM, Hanlon AL, Fowble BL, Anderson PR, Nicoloau N. Recursive partitioning identifies patients at high and low risk for ipsilateral tumor recurrence after breast-conserving surgery and radiation. *J Clin Oncol*. 2002;20: 4015–4021.
20. Park CC, Mitsumori M, Nixon A, et al. Outcome at 8 years after breast-conserving surgery and radiation therapy for invasive breast cancer: influence of margin status and systemic therapy on local recurrence. *J Clin Oncol*. 2000;18: 1668–1675.