Int. J. Radiation Oncology Biol. Phys., Vol. 66, No. 2, pp. 352–357, 2006

0360-3016/06/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2006.04.046

CLINICAL INVESTIGATION **Breast**

COMPARISON OF RISK OF LOCAL-REGIONAL RECURRENCE AFTER MASTECTOMY OR BREAST CONSERVATION THERAPY FOR PATIENTS TREATED WITH NEOADJUVANT CHEMOTHERAPY AND RADIATION STRATIFIED ACCORDING TO A PROGNOSTIC INDEX SCORE

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Purpose: We previously developed a prognostic index that stratified patients treated with breast conservation therapy (BCT) after neoadjuvant chemotherapy into groups with different risks for local-regional recurrence (LRR). The purpose of this study was to compare the rates of LRR as a function of prognostic index score for patients treated with BCT or mastectomy plus radiation after neoadjuvant chemotherapy.

Methods: We retrospectively analyzed 815 patients treated with neoadjuvant chemotherapy, surgery, and radiation. Patients were assigned an index score from 0 to 4 and given 1 point for the presence of each factor: clinical N2 to N3 disease, lymphovascular invasion, pathologic size >2 cm, and multifocal residual disease.

Results: The 10-year LRR rates were very low and similar between the mastectomy and BCT groups for patients with an index score of 0 or 1. For patients with a score of 2, LRR trended lower for those treated with mastectomy vs. BCT (12% vs. 28%, $p = 0.28$). For patients with a score of 3 to 4, LRR was significantly lower for those treated with mastectomy vs. BCT (19% vs. 61%, $p = 0.009$).

Conclusion: This analysis suggests that BCT can provide excellent local-regional treatment for the vast majority of patients after neoadjuvant chemotherapy. For the few patients with a score of 3 to 4, LRR was >60% after BCT and was <20% with mastectomy. If these findings are confirmed in larger randomized studies, the prognostic index may be useful in helping to select the type of surgical treatment for patients treated with neoadjuvant chemotherapy, surgery, and radiation. © 2006 Elsevier Inc.

Breast conservation, Prognostic index, Mastectomy.

INTRODUCTION

Randomized prospective clinical trials have demonstrated that neoadjuvant chemotherapy can increase the percentage of patients treated with breast conservation therapy (BCT) (1–3). However, there is a concern that patients with advanced disease who are treated with BCT after first responding to neoadjuvant chemotherapy may have higher rates of local-regional recurrence (LRR) compared with patients with early-stage disease who are treated with breast-conserving surgery up-front. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial, patients who were considered to be mastectomy candidates at initial diagnosis but became eligible for BCT after neoadjuvant chemotherapy had an ipsilateral breast recurrence rate of 15.9%, compared with a rate of 9.9% among neoadjuvant chemotherapy patients in whom BCT was originally planned (2). In addition, some series investigating BCT after neoadjuvant chemotherapy have reported LRR rates in excess of 20% (4, 5), whereas others, including a series from our institution, have reported LRR rates for such patients of less than 10% (6–8).

These differences in clinical outcome across series emphasize the importance of applying appropriate selection criteria to determine which patients are suitable candidates for BCT after neoadjuvant chemotherapy. To clarify further this issue, we recently reviewed our institutional experience of using BCT after neoadjuvant chemotherapy and deter-

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Presented at the Forty Seventh Annual Meeting of the American Society of Therapeutic Radiology and Oncology (ASTRO), October 16–20, 2005, Denver, CO.

Supported in part by the Nellie B. Connally Breast Cancer Research Fund and the Arlette and William Coleman Foundation.

Received Dec 21, 2005, and in revised form April 19, 2006. Accepted for publication April 24, 2006.

mined 4 factors that were independently associated with developing LRR. Using the presence or absence of each of these 4 factors, we then developed a prognostic index on a scale of 0 to 4 (8, 9). This prognostic index identified subgroups of patients with significantly different rates of LRR at 10 years: patients with a prognostic index score of 0 to 1 had a low LRR risk of only 7%; patients with a score of 2 had an intermediate LRR risk of 28%; and patients with a score of 3 to 4 had a high LRR risk of 61%.

How this prognostic index should affect decisions regarding the type of surgical treatment remains unclear. This is because some of the factors that were used in the prognostic index score may also increase the risk of LRR after neoadjuvant chemotherapy, mastectomy, and postmastectomy radiation (10). Our purpose in this study was to investigate this issue further by applying the prognostic index to a relatively large cohort of patients treated with neoadjuvant chemotherapy, mastectomy, and radiation, and then to compare the LRR rates between the mastectomy and BCT groups stratified according to the prognostic index score.

METHODS AND MATERIALS

Multimodality treatment

We retrospectively analyzed the outcomes of 815 patients with unicentric breast cancer treated with neoadjuvant chemotherapy, surgery, and postoperative radiation at The University of Texas M. D. Anderson Cancer Center (Houston, TX) between 1974 and 2000. Of these patients, 331 were treated with BCT, previously reported by Chen *et al.* (8, 9), and 484 were treated with mastectomy. We only considered patients who had data available for each of the 4 elements used in the prognostic index. The institutional review board approved this retrospective study, and informed consent was waived. Compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations was strict.

All patients were clinically staged according to the 2002 American Joint Committee on Cancer guidelines (11). Patients were assessed at presentation using physical examination, mammography, ultrasonography of the breast and regional nodal basins, and staging studies to exclude metastatic disease. The neoadjuvant chemotherapy regimens followed those used in prospective institutional trials during the study period and the details concerning these regimens have been described in previous reports (8, 12–14). Briefly, patients received one of the following combinations of chemotherapy: 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC); vincristine, doxorubicin, cyclophosphamide, and prednisone (VACP); or doxorubicin and docetaxel (AT).

Most of the patients were evaluated in a multidisciplinary setting before and after completion of neoadjuvant chemotherapy. Patients deemed eligible for BCT were carefully selected not to have diffuse calcifications, residual skin involvement after chemotherapy, or significant residual disease after chemotherapy that would preclude obtaining clear surgical margins. BCT typically involved excision of the residual primary tumor with a margin of normal tissue without an attempt to resect the prechemotherapy tumor volume. The decision to treat with BCT or mastectomy was determined on an individual case basis according to our institutional selection criteria and the biases of the patient and her care providers.

All patients in this series received external beam radiation therapy as a component of their treatment. Typically, 50 Gy was delivered in 25 fractions to the breast or chest wall using tangential fields, followed by a 10-Gy boost to the tumor bed or chest wall scar using an appositional electron field. Patients treated with mastectomy received comprehensive regional nodal radiation consisting of supraclavicular and internal mammary chain fields in addition to the fields used to treat the chest wall. For BCT patients, regional nodal radiation was delivered at the discretion of the radiation oncologist.

Adjuvant chemotherapy was given after surgery and before radiation in 254 (77%) of the BCT patients and 460 (95%) of the mastectomy patients. Indications for chemotherapy varied depending on the protocol open at the time of treatment, as well as patient and physician preferences. Tamoxifen was used by 129 (39%) of the BCT patients and 154 (32%) of the mastectomy patients. In general, before 1995 tamoxifen was recommended to postmenopausal patients with estrogen receptor–positive tumors; after 1995 tamoxifen was recommended to all patients with estrogen receptor–positive tumors. Tamoxifen was the only hormone therapy used during the period of this study.

Prognostic index and statistical analysis

The 331 BCT patients were previously analyzed to develop the prognostic index (8, 9). In this prior analysis, 4 independent risk factors were identified on multivariate analysis using forward stepwise Cox logistic regression analysis that predicted for significantly higher rates of LRR (Table 1), clinical N2 to N3 disease (detected by palpation or imaging), lymphovascular invasion (LVI), residual pathologic primary tumor size >2 cm after neoadjuvant chemotherapy, and pathologically multifocal pattern of residual disease after neoadjuvant chemotherapy. The prognostic index scored each patient on a scale from 0 to 4 according to the presence of each risk factor (1 point for each factor). For the present analysis, each of the 484 mastectomy patients was also scored from 0 to 4 using this prognostic index.

The distributions of patient characteristics between the 2 groups were compared using the two-sided Pearson Chi-square test. Actuarial rates of LRR were calculated according to the Kaplan-Meier method from the date of histologic diagnosis of the initial biopsy (15). Hazard ratios for LRR were calculated using a Cox regression model (15). LRR was defined as disease recurrence in the ipsilateral breast or chest wall, or in the ipsilateral axillary, supraclavicular, infraclavicular, or internal mammary nodes. All LRR were counted as events, regardless of whether they were at the first site of failure or occurred after distant metastasis. Differences in LRR outcome between groups (BCT vs. mastectomy) were compared for each prognostic index score using the two-sided log-rank test (15).

RESULTS

The median follow-up of the BCT and mastectomy patients was 60 months (range, 10–180 months) and 76 months (range, 8–288 months). The distribution of patients accord-

Table 1. Prognostic index*

Clinical N2–N3 disease
Lymphovascular invasion
Residual pathologic primary size >2 cm
Pathologically multifocal residual disease

* The prognostic index ranges from 0 to 4, assigning one point for the presence of each factor.

Table 2. Distribution of prognostic index

	Breast conservation $n = 331$ No. (%)	Mastectomy $n = 484$ No. (%)
Prognostic index score		
0	157 (47)	83 (17)
1	119 (36)	196 (41)
2	43 (13)	137 (28)
3	12 (4)	64 (13)
4	0 (0)	4 (1)
Prognostic index factors*		
Clinical N2–N3 disease	77 (23)	205 (42)
Lymphovascular invasion	51 (15)	152 (31)
Pathological size >2 cm	45 (14)	252 (52)
Pathologically multifocal disease	76 (23)	69 (14)

* Percentages do not add up to 100% because several patients had multiple factors or no factors.

ing to their prognostic index score is shown in Table 2. The distribution of other patient characteristics is shown in Table 3. When compared with the BCT patients, a greater percentage of mastectomy patients had more advanced clinical stage, larger residual tumor sizes after neoadjuvant chemotherapy, higher numbers of pathologically positive nodes, and negative margins (>2 mm margin). The 10-year actuarial rates of overall survival for patients treated with BCT and mastectomy were 86% and 59%, respectively.

Overall, the 10-year actuarial rate of LRR for patients who had BCT was similar to those who had mastectomy: 12% vs. 9%, respectively ($p = 0.98$). Of the 27 BCT patients who had a LRR, 15 had ipsilateral breast tumor recurrences (10-year actuarial rate, 7%), and 12 had recurrences involving the regional nodes (10-year actuarial rate, 5%). Of the 41 mastectomy patients who had a LRR, 27 had ipsilateral chest wall recurrences (10-year actuarial rate, 6%), and 14 had recurrences involving the regional nodes (10-year actuarial rate, 3%). Similar to the BCT cohort, the prognostic index score segregated the mastectomy patients into subgroups with significantly different 10-year rates of LRR (0–4%, 1–7%, 2–12%, and 3 or 4–19%; $p = 0.007$) (Figs. 1a, 1b).

When LRR was analyzed as a function of the type of surgery according to the prognostic index score, the 10-year

Table 3. Distribution of patient characteristics

	Breast conservation $n = 331$ No. (%)	Mastectomy $n = 484$ No. (%)	p value
Stage			<0.001
I	13 (4)	0 (0)	
IIA	79 (24)	7 (1)	
IIB	113 (34)	77 (16)	
IIIA	80 (24)	152 (32)	
IIIB	23 (7)	203 (42)	
IIIC	23 (7)	45 (9)	
Age (y)			0.041
<40	96 (29)	103 (21)	
40–60	189 (57)	309 (64)	
>60	46 (14)	72 (15)	
Adjuvant tamoxifen			0.110
Yes	129 (39)	154 (32)	
No	195 (59)	317 (65)	
Unknown	7 (2)	13 (3)	
Adjuvant chemotherapy			<0.001
Yes	254 (77)	460 (95)	
No	77 (23)	24 (5)	
Residual tumor size (cm)			<0.001
0	79 (24)	75 (16)	
0–2	202 (61)	157 (32)	
>2	50 (15)	252 (52)	
Margin status			<0.001
Negative	258 (78)	430 (89)	
Close (<0.2 cm)	53 (16)	36 (7)	
Positive	13 (4)	14 (3)	
Unknown	7 (2)	4 (1)	
Positive nodes			<0.001
0	169 (51)	137 (28)	
1–3	93 (28)	170 (35)	
4–10	33 (10)	131 (27)	
>10	13 (4)	41 (9)	
Unknown	23 (7)	5 (1)	

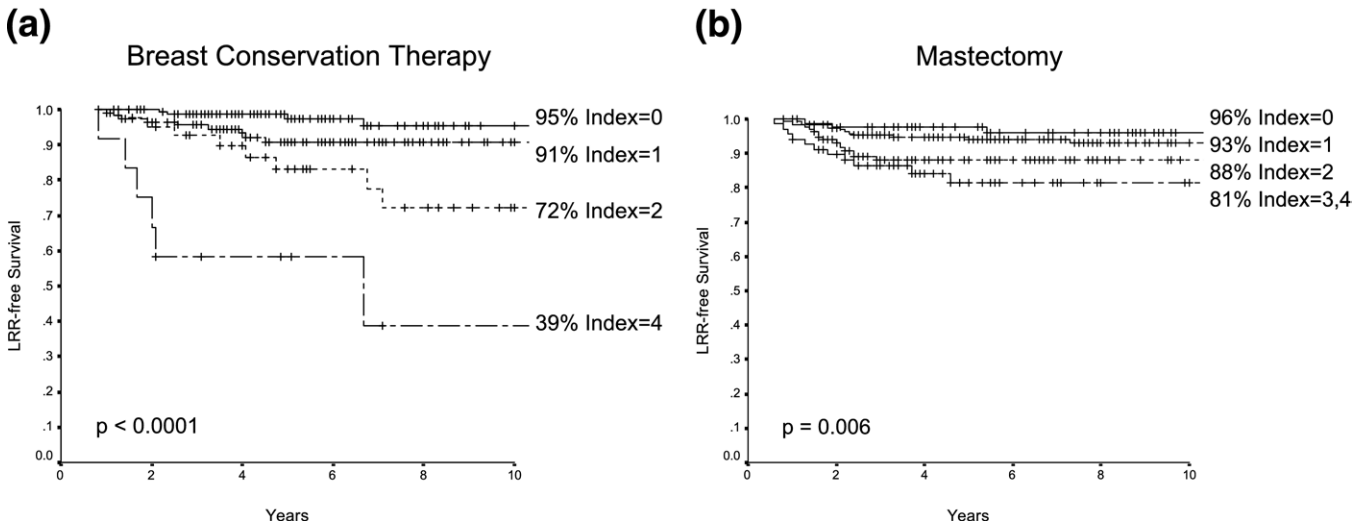

Fig. 1. (a) Ten-year rates of local-regional recurrence (LRR)-free survival of 331 breast conservation therapy patients stratified according to prognostic index score. (b) Ten-year rates of LRR-free survival of 484 mastectomy patients stratified according to prognostic index score.

LRR rates were similar between patients who had a score of 0 (4% for mastectomy vs. 5% for BCT, $p = 0.95$) or 1 (7% for mastectomy vs. 9% for BCT, $p = 0.51$) (Figs. 2a, 2b). For patients with a score of 2, the 10-year LRR rate trended lower for those treated with mastectomy compared with those treated with BCT, but this was not statistically significant (12% vs. 28%, $p = 0.28$) (Fig. 2c). However, for patients with a score of 3 or 4, the 10-year LRR rate was significantly lower for those treated with mastectomy compared with those treated with BCT (19% vs. 61%, $p = 0.009$), (Fig. 2d).

We further analyzed the difference in outcome between the groups treated with mastectomy and BCT in the patients with a score of 3 to 4. In this cohort, the use of adjuvant chemotherapy was similar (92% in the BCT patients vs. 88% in the mastectomy patients, $p = 0.73$). In a Cox regression analysis specific to the patients in this cohort, the use of adjuvant chemotherapy was not a significant factor with respect to LRR ($p = 0.73$), whereas the type of surgical procedure was significant (hazard ratio, 0.29; 95% CI = 0.11 to 0.77, $p = 0.014$).

DISCUSSION

This study applied a prognostic index previously developed on patients treated with neoadjuvant chemotherapy and BCT to a cohort of patients treated with neoadjuvant chemotherapy, mastectomy, and radiation. For both cohorts, the prognostic index identified subgroups of patients with significantly different risks of LRR. By comparing the 2 cohorts stratified according to the index score, we found that for patients with a score of 0 or 1, BCT provided effective local-regional treatment and having a mastectomy did not provide any significant reduction in LRR. However, for the small group of patients with an index score of 3 or 4, the rate of LRR was 61% after BCT, which was significantly higher than the 19% LRR rate after mastectomy.

The value of this prognostic index is that in addition to standard selection criteria it helps to define further which patients are appropriate candidates for BCT. Standard criteria outside of this index include nonmulticentric tumors, no diffuse calcifications, ability to achieve negative margins with acceptable cosmesis, and the ability to undergo radiation treatment (16, 17). It is important to note that all of the patients in our analysis met these criteria, and the prognostic index is valid and applicable only after these standard criteria have been satisfied. For patients who are candidates for BCT after neoadjuvant chemotherapy, the prognostic index may be useful in helping to select the type of surgical treatment.

For the vast majority of patients who met the standard BCT criteria, BCT after neoadjuvant chemotherapy provided excellent local-regional treatment. In this study, more than 80% of BCT patients had a prognostic index score of 0 or 1 with corresponding 10-year LRR rates of 5% and 9%. These excellent outcomes in part are attributable to appropriate patient selection but also reflect the importance of well-coordinated multidisciplinary care. Specifically, within our institution, patients whose tumors demonstrate a favorable response to neoadjuvant chemotherapy have the tumor bed localized with metallic markers after 1 or 2 cycles (17). In addition, we believe that the interactions between the surgeon and pathologist are critically important to ensure proper specimen orientation, radiographs of serially sectioned specimens, and careful pathologic assessment that specifically addresses margin status, disease multifocality, and degree of chemotherapy-induced fibrosis (17).

For the small subset of patients who undergo BCT after neoadjuvant therapy and are found to have higher index scores, the information provided by the prognostic index can be useful in estimating the risk of LRR and deciding whether a completion mastectomy may help to decrease this risk. Patients with an index score of 2 and 3 to 4 had 10-year

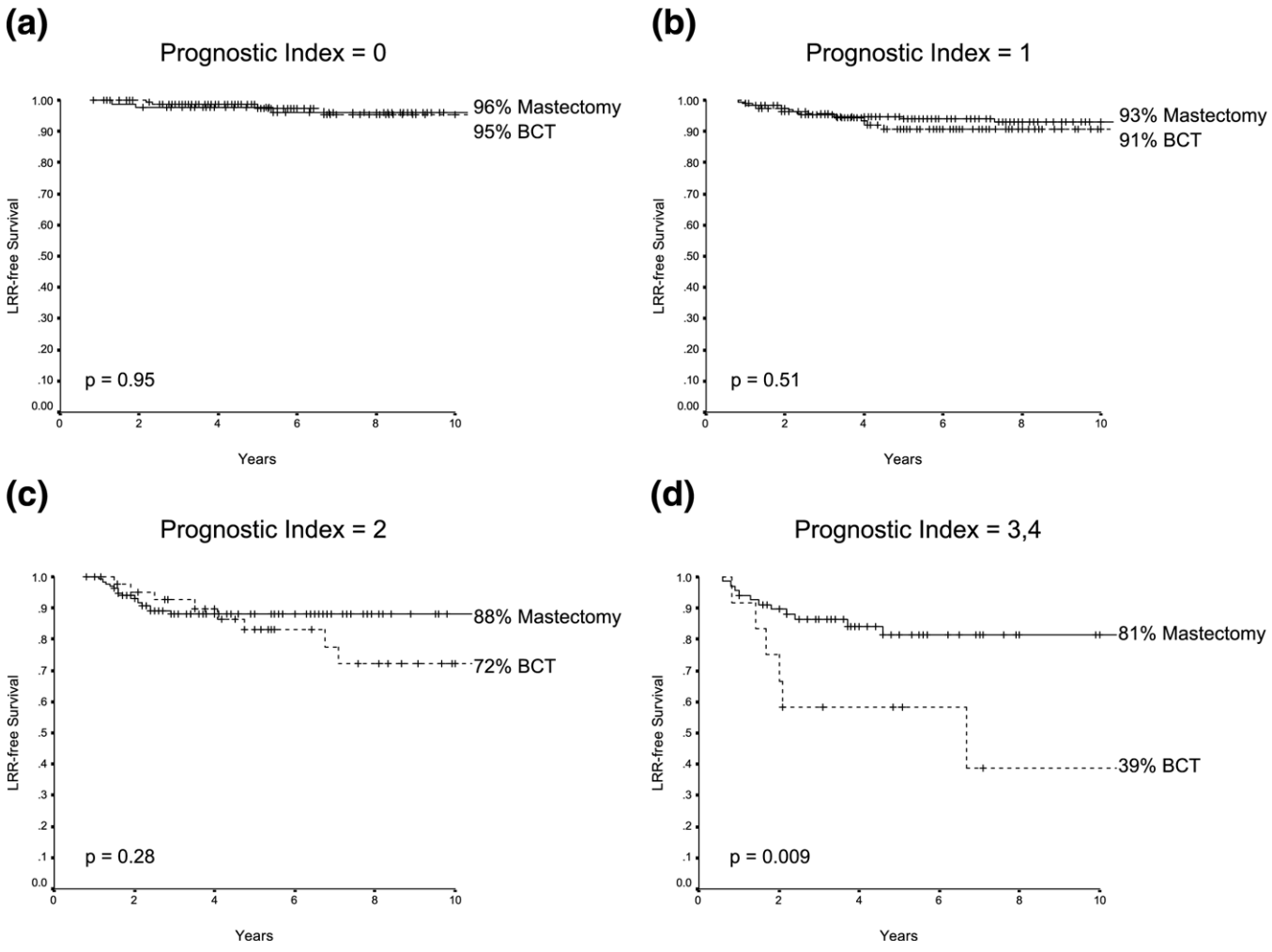

Fig. 2. (a) Ten-year rates of local-regional recurrence (LRR)-free survival of the breast conservation therapy (BCT) ($n = 157$) and mastectomy ($n = 83$) patients with a prognostic index score of 0. (b) Ten-year rates of LRR-free survival of the BCT ($n = 119$) and mastectomy ($n = 196$) patients with a prognostic index score of 1. (c) Ten-year rates of LRR-free survival of the BCT ($n = 43$) and mastectomy ($n = 137$) patients with a prognostic index score of 2. (d) Ten-year rates of LRR-free survival of the BCT ($n = 12$) and mastectomy ($n = 68$) patients with a prognostic index score of 3 or 4.

LRR rates of 28% and 61%, respectively. For patients with a score of 2, our data did not demonstrate a significantly lower risk of LRR with mastectomy; however, our sample size within this cohort did not provide adequate statistical power to address this question (10-year rates, 12% for mastectomy vs. 28% for BCT, $p = 0.28$). For patients with a score of 3 to 4, mastectomy was associated with a significantly lower rate of LRR (10-year rates, 19% for mastectomy vs. 61% for BCT, $p = 0.009$). Before this study, it was unclear whether having a completion mastectomy could have improved the outcome for patients with these disease features because many of the risk factors incorporated into the prognostic index also affect LRR after neoadjuvant chemotherapy, mastectomy, and radiation. In a previous report of 542 patients treated with neoadjuvant chemotherapy, mastectomy, and radiation, we demonstrated that clinical N-stage, multifocal disease, and LVI were all associated with higher rates of LRR (10).

It is important to recognize the limitations of this review. Foremost, this is a retrospective analysis in which the type of surgical treatment was not a randomized variable and subject to selection biases. We identified several factors in Table 3 that might have biased the mastectomy patients to have a worse expected outcome. The prognostic index and the results of this analysis should be validated on an independent set of data. In addition, because BCT candidates at our institution are carefully selected in a multidisciplinary setting, the cohort of BCT patients with a prognostic index score of 3 or 4 was relatively small ($n = 12$). Finally, it should be emphasized that all of the mastectomy patients in this review received postoperative radiation. Without radiation treatment, it could be possible that the mastectomy patients with an index score of 2, 3, or 4 may have had higher LRR rates than did the BCT patients of similar index score. Under different circumstances, it is certainly conceivable that some mastectomy patients with an index score of

3 or 4 may not be routinely treated with radiation. At our institution, we generally offer postmastectomy radiation after neoadjuvant chemotherapy to patients with 4 or more positive axillary lymph nodes, and to patients who present with clinical T3 tumors or clinical Stage III disease (14).

CONCLUSION

In conclusion, the prognostic index is a tool that can help identify subgroups of patients with higher rates of LRR and further refine the selection criteria for BCT candidates after neoadjuvant chemotherapy. Although this analysis was retrospective and should be validated in a prospective trial, it suggests that BCT can provide excellent local-regional treatment for the vast majority of patients who fulfill generally accepted selection criteria after neoadjuvant chemotherapy. For the few patients with a prognostic index score of 3 or 4, the rate of LRR was greater than 60% after BCT, and our findings suggest that having a completion mastectomy may reduce this recurrence rate to less than 20%.

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