Classifying Local Disease Recurrences after Breast Conservation Therapy Based on Location and Histology

New Primary Tumors Have More Favorable Outcomes than True Local Disease Recurrences

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Supported in part by the Department of Health and Human Services National Cancer Institute (Grants CA16672 and T32CA77050 to Dr. Buchholz) and by USAMRMC Breast Cancer Research Program Career Development Awards (Grants BC980154 and BC961478 to Dr. Hunt).

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Received February 28, 2002; revision received May 14, 2002; accepted June 20, 2002.

BACKGROUND. To distinguish true local recurrences (TR) from new primary tumors (NP) and to assess whether this distinction has prognostic value in patients who develop ipsilateral breast tumor recurrences (IBTR) after breast-conserving surgery and radiotherapy.

METHODS. Between 1970 and 1994, 1339 patients underwent breast-conserving surgery at The University of Texas M. D. Anderson Cancer Center for ductal carcinoma in situ or invasive carcinoma. Of these patients, 139 (10.4%) had an IBTR as the first site of failure. For the 126 patients with clinical data available for retrospective review, we classified the IBTR as a TR if it was located within 3 cm of the primary tumor bed and was of the same histologic subtype. All other IBTRs were designated NP.

RESULTS. Of the 126 patients, 48 (38%) patients were classified as NP and 78 (62%) as TR. Mean time to disease recurrence was 7.3 years for NP versus 5.6 years for TR ($P = 0.0669$). The patients with NP had improved 10-year rates of overall survival (NP 77% vs. TR 46%, $P = 0.0002$), cause-specific survival (NP 83% vs. TR 49%, $P = 0.0001$), and distant disease-free survival (NP 77% vs. TR 26%, $P < 0.0001$). Patients with NP more often developed contralateral breast carcinoma (10-year rate: NP 29% vs. TR 8%, $P = 0.0043$), but were less likely to develop a second local recurrence after salvage treatment of the first IBTR (NP 2% vs. TR 18%, $P = 0.008$).

CONCLUSIONS. Patients with NP had significantly better survival rates than those with TR, but were more likely to develop contralateral breast carcinoma. Distinguishing new breast carcinomas from local disease recurrences may have importance in therapeutic decisions and chemoprevention strategies. This is because patients with new carcinomas had significantly lower rates of metastasis than those with local disease recurrence, but were more likely to develop contralateral breast carcinomas. ***Cancer* 2002;95:2059–67.**
DOI 10.1002/cncr.10952

KEYWORDS: breast conservation therapy, local disease recurrence, new primary tumor, histology.

The optimal management of patients with ipsilateral breast tumor recurrences (IBTR) after breast-conserving surgery and radiation therapy (BCT) is not well defined. Specifically, should all subsets of these patients receive systemic therapy? Numerous reports indicate that IBTR after BCT is an independent predictor of the risk of developing distant metastatic disease. An analysis of the results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06

trial found that the risk of distant failure for patients with IBTR after BCT is at least threefold greater compared with those without IBTR.[1] Other studies have also shown a poor prognosis for these patients, with 5-year overall and distant disease-free survival rates of approximately 60–70% and 45–65%, respectively.[2–4]

Despite information from these studies, it is not clear that all IBTR are equal in terms of predicting a poor prognosis. Other studies have suggested that there are subgroups of patients who have a relatively favorable prognosis after an IBTR. Older age, small tumors, noninvasive or focally invasive histology, negative axillary lymph nodes, low histologic grade, and location remote from the primary tumor site have all been identified as factors of an IBTR that indicate a more favorable distant disease-free survival period.[2–7] The most important prognostic indicator that has been identified so far, however, is the time interval to IBTR. Studies have demonstrated repeatedly that patients with an IBTR less than 1–5 years after the primary tumor have reduced overall and distant disease-free survival periods compared with those with IBTR occurring more than 5 years after the primary tumor.[2,4–11]

One hypothesis is that some subgroups of patients have a favorable prognosis because IBTR consists of two distinct types of disease: true local recurrences (TR) and new ipsilateral primary tumors (NP). This distinction was first articulated by Veronesi et al.[5] who described TR as "cases consistent with the regrowth of malignant cells not removed by surgery or not killed by radiotherapy," (page 20) whereas NP were described as "de novo cases of malignancies arising from mammary epithelial cells of the residual breast tissue" (ibid). Theoretically, an NP IBTR is independent of the primary breast carcinoma and the prognosis of these patients may be more favorable than those with a TR. Another hypothesis that may distinguish NP from TR is that the development of an NP may indicate an underlying genetic predisposition for breast carcinoma and thereby be associated with higher rates of carcinoma in the contralateral breast. If these hypotheses are true, the clinical management and chemoprevention strategies for patients with IBTR should reflect this distinction.

In this study, we classified IBTR as either NP or TR based on tumor location and histology and assessed whether this distinction has prognostic value for patients with IBTR after BCT. We recognized that using only clinical and pathologic features to distinguish NP from TR is likely to be less precise than molecular methods, but chose this methodology because these criteria are readily available to every clinician.

MATERIALS AND METHODS

Between 1970 and 1994, 1339 breast carcinoma patients were treated at the University of Texas M. D. Anderson Cancer Center by breast-conserving surgery, 139 (10.4%) of whom had an IBTR as the first site of failure. An IBTR was defined as a histologically confirmed recurrence of disease within the previously treated breast. We excluded 13 of the 139 patients because their records lacked information regarding their IBTR. The remaining 126 patients formed the study population.

For their primary therapy, all patients underwent breast-conserving surgery for primary breast neoplasms and 86 (68%) patients also underwent axillary lymph node dissection. All patients were treated with postoperative radiotherapy delivered to the entire ipsilateral breast with medial and lateral tangential fields using photon beams (median dose, 50 Gy), with or without regional lymph node irradiation as clinically indicated. Seventy-eight (62%) patients also received a boost to the primary tumor bed delivered by electron beams (median dose, 10 Gy) and 16 (13%) patients received a brachytherapy boost. Of the primary tumors, 112 (89%) were invasive carcinomas and 14 (11%) were ductal carcinoma in situ (DCIS). The decision to use systemic therapy was made by the patient and the treating medical oncologist according to the prognostic variables of each case. For treatment of the primary tumor, 25 (20%) patients were treated with chemotherapy, 3 (2%) patients received tamoxifen, in addition to chemotherapy, and 1 (1%) received tamoxifen alone.

After evaluating hospital records, operative reports, pathology reports, mammography reports, and radiotherapy records of the 126 patients, we classified each IBTR as either an NP or TR based on its location and histology. For the purposes of this study, an IBTR was designated as a TR if it was located within 3 cm of the primary tumor bed and if the histologic subtype was consistent with the primary tumor (i.e., infiltrating ductal carcinoma [IDC], lobular carcinoma, medullary carcainoma, tubular carcinoma). If the IBTR failed to meet either of these two criteria, it was designated as an NP. In most cases, the hospital records documented the specific location of the tumors and whether the IBTR recurred at or near the vicinity of the primary tumor site. When the location or histology of the tumors was unclear, mammograms and pathology slides were obtained and reevaluated.

Two patients in which there was a change in histology from DCIS to IDC were considered histologically characteristic of TR because this change is consistent with a natural progression of breast carcinoma.

TABLE 1
Treatment of Patients with IBTR

Treatment	All Patients (n = 126) (%)	NP (n = 48) (%)	TR (n = 78) (%)	P value
Surgery				
Local reexcision	8	6	10	0.439
Salvage mastectomy	82	94	75	0.006
None	10	0	15	0.004
Systemic therapy				
Chemotherapy	26	20	31	0.222
Hormonal therapy	14	10	17	0.330
Both	17	13	19	0.325

IBTR: ipsilateral breast tumor recurrence; NP: new primary tumor; TR: true local disease recurrence.

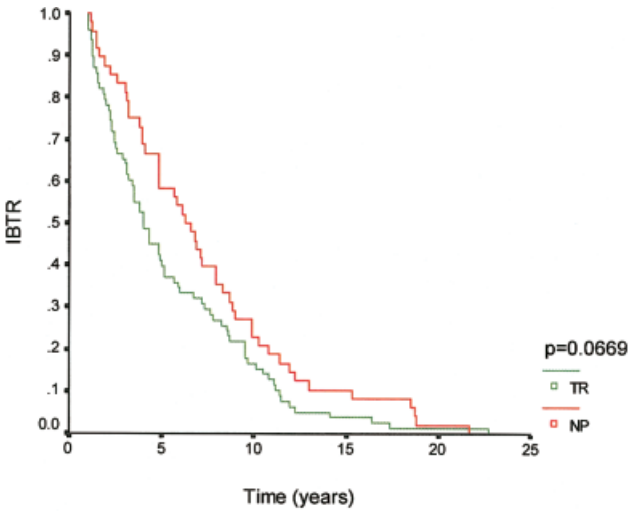

FIGURE 1. Actuarial curves showing the time interval from the primary tumor to development of ipsilateral breast tumor recurrences (IBTR). In patients with true local disease recurrnce, IBTR developed earlier than in patients with new primary tumors.

However, three patients in which there was a change from an IDC to DCIS were considered histologically characteristic of NP. Only one of these three patients had DCIS as a component of her primary tumor. The time to disease recurrence for the three patients were 4.1, 9.9, and 10.8 years, respectively. In three patients, the location of the IBTR could not be delineated because the tumor mass encompassed the entire breast at the time of disease recurrence. Because the histology was consistent with the original primary tumor, we classified these three patients as TR.

The therapeutic management of patients with IBTR depended on the clinical circumstances of each patient. The decision to treat with completion mastectomy and/or systemic therapy was made by the patient and her treating physician. Table 1 shows the treatment of the IBTR according to classification of NP versus TR. There were no significant differences between the two groups with respect to systemic therapy. However, a greater percentage of patients with NP were treated with completion mastectomy. Of the 12 (15%) patients with TR who did not receive surgery for their IBTR, 10 had tumor masses larger than 3 cm (3 of whom had carcinomas encompassing the entire residual breast tissue), 1 had lymph node involvement at the time of IBTR diagnosis, and 1 developed distant disease within 1 month after diagnosis. Eleven of these patients received chemotherapy with or without tamoxifen and one patient refused any treatment because of the development of distant disease.

All patients were classified as having either an NP or TR before any analysis of the outcome data. The Kaplan–Meier method[12] was used to calculate actuarial statistics for the time interval to IBTR and the rates of overall survival, cause-specific survival, distant disease-free survival, and contralateral breast carcinoma-free survival. For survival statistics, all event and follow-up times were measured from the date of IBTR diagnosis. Comparisons of survival between patients with NP versus TR were made using the log rank test.[13] To reduce any bias introduced by the more favorable survival of patients without invasive disease, we also calculated survival statistics for the 114 patients with invasive IBTR, excluding 12 patients whose IBTR consisted entirely of DCIS. Of these 12 patients, 7 had disease classified as NP and 5 as TR. Univariate analyses comparing various clinical and pathologic characteristics between patients with NP versus TR were performed. Proportions and means were compared using the chi-square two-sided test and the Student t test, respectively. Cases with unknown values were excluded from the univariate analysis.

After this analysis was completed, we further divided the NP patients into three subgroups on the basis of their IBTR classification criteria: different location, different histology, or both. Outcomes and time to disease recurrence for each subgroup were calculated using Kaplan–Meier survival curves and compared with one another using the log rank test. This additional analysis ensured that these subgroups were similar to one another, allowing their collective grouping into the category "NP."

RESULTS

For the 126 patients studied, the median follow-up period for the surviving patients was 12.4 and 7.0 years after diagnosis of the primary tumor and IBTR, respectively. The length of follow-up was similar between the patients with NP versus TR (12.3 and 7.2 years vs. 12.8 and 7.0 years, respectively). Figure 1 shows that the

TABLE 2
Comparison of Location and Histology between Patients with NP and TR

	All patients (n = 126) (%)		NP (n = 48) (%)		TR (n = 78) (%)		P value	
	Primary	IBTR	Primary	IBTR	Primary	IBTR	Primary NP vs. TR	IBTR NP vs. TR
Location								
Central	10	12	10	13	10	10	.977	0.697
UOQ	42	41	36	36	48	45	.186	0.295
UIQ	28	24	31	19	26	27	.495	0.296
LOQ	10	15	8	19	10	13	.721	0.366
LIQ	10	8	15	13	6	5	.129	0.137
Histology								
Invasive ductal	72	77	68	69	76	81	.397	0.124
Invasive lobular	5	6	4	7	5	5	.806	0.790
Both invasive ductal and lobular	6	4	4	4	6	4	.593	0.806
DCIS only	11	10	11	16	12	7	.846	0.066
Other	6	3	13	4	1	3	.008	0.618

NP: new primary tumor; TR: true local disease recurrence; IBTR: ipsilateral breast tumor recurrence; DCIS: ductal carcinoma in situ.

patients with TR developed their IBTR after a shorter interval from their initial treatment than patients with NP (mean time interval: TR 5.6 vs. NP 7.3 years; log rank comparison of curves, $P = 0.0669$).

Forty-eight (38%) had their disease recurrence classified as an NP and 78 (62%) as a TR. Table 2 shows the characteristics of the patients according to the classification criteria used to distinguish NP from TR. Thirty-three percent of the IBTR were located at a site different from the primary and 17% were composed of a different histologic subtype. Of the patients classified as having NP disease, 88% had different location, 44% had different histology, and 48% differed in both respects. It is noteworthy that 10% of the tumors designated as NP were classified solely on the basis of histology because the IBTR occurred at or near the primary tumor bed.

Actuarial survival rates showed that patients with IBTR classified as NP had more favorable outcomes, regardless of whether the analysis included the 12 patients whose IBTR consisted entirely of DCIS. Figure 2A shows that the 10-year overall survival rate of all patients classified as having NP was 77%, which was better than the 46% rate of patients with TR ($P = 0.0002$). In addition, patients with NP also had better 10-year rates of cause-specific survival (NP 83% vs. TR 49%, $P = 0.0001$) and distant disease-free survival (NP 77% vs. TR 26%, $P < 0.0001$; Fig. 3A). When the 12 patients with DCIS were excluded from the analysis, patients with NP still had significantly better 10-year overall survival (NP 71% vs. TR 44%, $P = 0.0012$), cause-specific survival (NP 80% vs. TR 46%, $P = 0.0005$), and distant disease-free survival rates (NP 77% vs. TR 23%, $P < 0.0001$; Figs. 2B, 3B). The overall survival ($P = 0.0029$), cause-specific survival ($P = 0.0016$), and distant disease-free survival rates ($P < 0.0001$) also remained significant when the 12 patients who did not have surgery for their IBTR were excluded from the analysis. In addition to poor survival rates, patients with TR showed a higher rate of developing a second or third local recurrence after salvage treatment of the first IBTR (TR 18% vs. NP 2%, $P = 0.008$).

Patients with NP had a significantly higher rate of contralateral breast carcinoma. Figure 4 displays the contralateral breast carcinoma-free 10-year survival rate for all patients studied (NP 71% vs. TR 92%, $P = 0.0043$; Fig. 4A) and for patients with invasive disease only (NP 68% vs. TR 92%, $P = 0.0035$; Fig.4b).

Table 3 displays a comparison of clinical characteristics for patients with NP versus TR. No significant differences were found between the two groups with respect to patient age, history of primary carcinomas other than breast carcinoma, and treatment with tamoxifen, chemotherapy, or radiation boost to the primary tumor bed ($P > 0.1$ for all comparisons). However, only four patients in this study were treated with tamoxifen, so its value in preventing NP IBTR could not be assessed. Patients with NP had a higher rate of having a first-degree relative with breast carcinoma, but this difference was not statistically significant (NP 19% vs. TR 13%, $P = 0.366$).

Table 4 summarizes the pathologic characteristics that were compared between patients with NP versus TR. No significant differences were found between the NP and TR patients with respect to primary tumor stage, primary tumor size, axillary lymph node in-

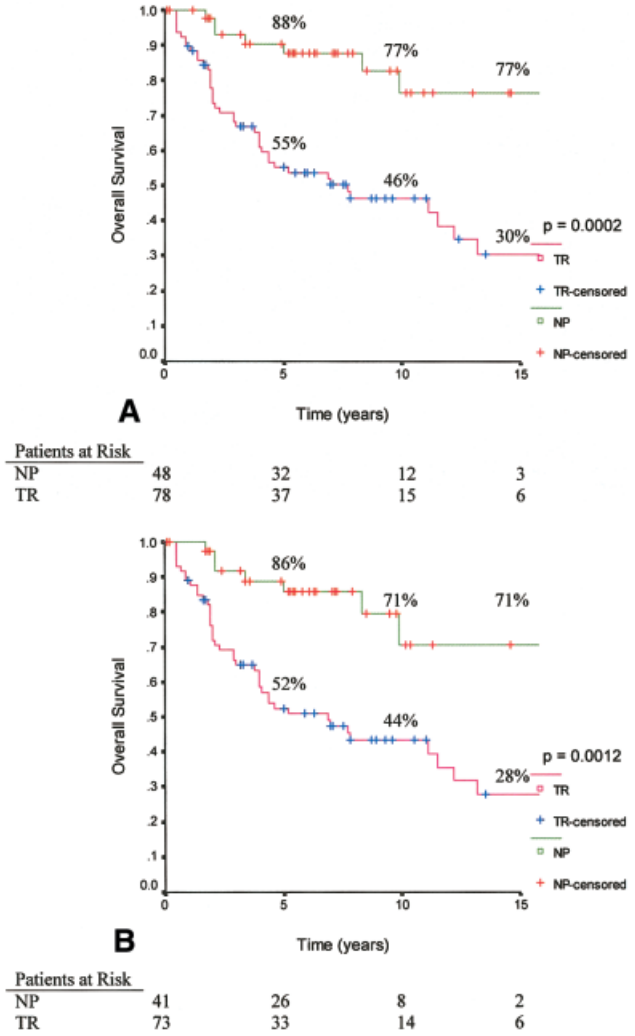

FIGURE 2. Actuarial curves showing improved overall survival for patients classified as having a new primary tumor compared with patients with true local disease recurrence in (A) all 126 patients studied and (B) the 114 patients with invasive carcinoma only.

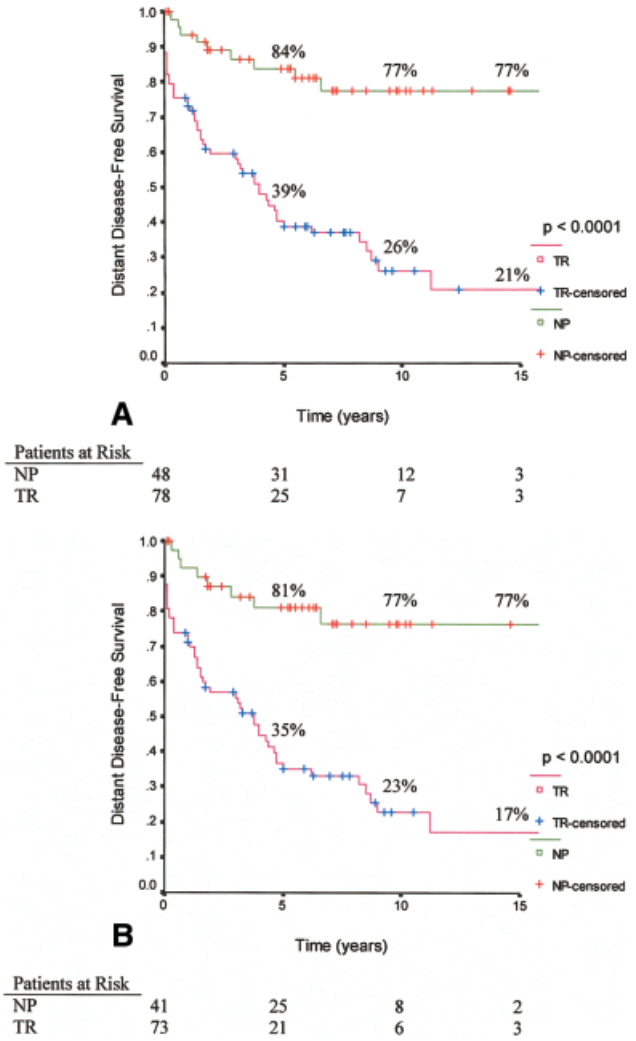

FIGURE 3. Actuarial curves showing improved distant disease-free survival for patients classified as having a new primary tumor compared with patients with true local disease recurrence in (A) all 126 patients studied and (B) the 114 patients with invasive carcinoma only.

volvement, positive margins, extensive intraductal component, nuclear grade, lymph node involvement at IBTR, and estrogen/progesterone receptor status of the IBTR ($P > 0.1$ for all comparisons). Patients designated as having NP disease had a higher rate of primary tumors with positive estrogen receptor status (NP 77% vs. TR 53%, $P = 0.049$) and positive progesterone receptor status (NP 75% vs. TR 42%, $P = 0.014$). Patients with TR had a higher rate of skin involvement by the IBTR (TR 28% vs. NP 2%, $P = 0.003$).

Among the three subgroups of NP patients according to classification criteria (different location, different histology, or both), no differences were found in rates of overall survival, cause-specific survival, and distant disease-free survival, and time interval to disease recurrence ($P = 0.5672$, 0.3490, 0.7487, and 0.6385, respectively).

DISCUSSION

In this study, we used location and histology to classify IBTR as either NP or TR. Using these criteria, 38% of patients with IBTR after long follow-up had clinical findings compatible with NP. Despite the relatively imprecise method used to distinguish NP and TR, our classification had significant prognostic value. Patients classified as having NP had more favorable overall, cause-specific, and distant disease-free survival rates than those with TR. Our findings support data from other studies that have attempted to define indicators of prognosis following IBTR. Specifically, the

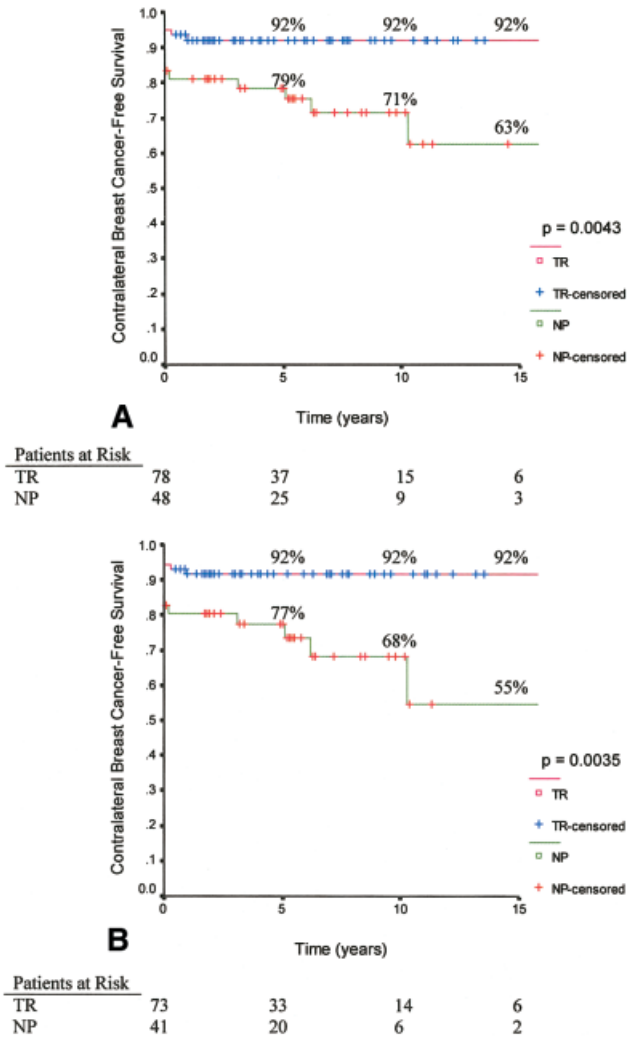

FIGURE 4. Actuarial curves showing a higher rate of contralateral breast carcinoma in patients classified as having a new primary tumor compared with patients with true local disease recurrence in (A) all 126 patients studied and (B) the 114 patients with invasive carcinoma only.

features of NP tumors have been correlated with better outcomes, including longer time interval to IBTR and location remote from the primary tumor site.[2–4,10,11] Conversely, the TR tumors shared traits that have been correlated with poor outcomes such as early onset of IBTR, location near the primary tumor site, and pathologic evidence of skin involvement.[2,4–7,14]

Our data also support the hypothesis that an NP tumor is a disease entity independent from the primary breast carcinoma. The subgroup of patients with NP had a much better outcome than patients with IBTR.[1–4] Specifically, the 5-year overall and distant disease-free survival rates for our patients with NP were 88% and 84%, respectively, compared with previously reported 5-year rates of 60–70% and 45–65%, respectively.[2–4] The overall and distant disease-free survival rates for our patients with NP (10-year rate: 77% and 77%) are more comparable to the survival rates reported for women treated with BCT for a primary carcinoma who did not experience an IBTR (10-year rate: 70–80% and 60–70%).[1,15,16] This observation makes intuitive sense because NP patients should have a prognosis similar to patients with de novo early-stage primary breast carcinomas. In addition, our findings suggest that previous studies reporting a poor prognosis for patients with IBTR following BCT[1–4,7] may actually underestimate the mortality rate of a TR, which was approximately 50–60% at 10 years in our study. Those studies may have overestimated the rates of survival because they included a subgroup of patients with NP in the overall statistical analysis.

In addition to assessing outcomes, we attempted to identify clinical and pathologic risk factors that may be predictive for developing NP versus TR. Theoretically, TR develop from residual surviving tumor clonogens. Therefore, the risk factors for developing TR should be related to issues regarding the local treatment of the primary tumor (e.g., surgical margin status, radiotherapy technique). However, we did not find positive margins or the use of a radiation tumor bed boost to be associated significantly with the development of either TR or NP disease. Conversely, because NP are believed to be de novo occurrences of breast carcinoma, the risk factors for developing NP should not be related to issues surrounding the surgical and radiation treatment of the primary tumor. Rather, they are more likely related to issues reflecting genetic predisposition and susceptibility to breast carcinoma such as family history and young age at diagnosis.[17–19] Our finding that patients with NP have significantly higher rates of carcinoma in the contralateral breast adds some support to this hypothesis because previous studies have shown a correlation between family history and the development of contralateral breast carcinoma.[20,21] However, we did not find family history or patient age to be associated significantly with IBTR classified as NP.

This distinction between NP and TR has important implications in the clinical management of IBTR. Currently, the decision to use systemic therapy for the treatment of IBTR is controversial. We have shown that patients with NP generally have a favorable long-term prognosis. Therapeutic decisions concerning systemic therapy for these patients should be similar to those used for patients with equivalent stage first primary breast carcinomas. However, the risk of developing contralateral breast carcinomas, coupled with the possibility of a genetic predisposition, highlights the need for better chemoprevention strategies

TABLE 3
Comparison of Clinical Characteristics between Patients with NP and TR

Characteristic	All patients (n = 126) (%)	NP (n = 48) (%)	TR (n = 78) (%)	P value
Age				
At primary (mean ± SE)	44.7 ± 1.4	43.9 ± 1.6	45.3 ± 1.3	0.497
Younger than 40 yrs at primary (%)	36	42	32	0.274
At IBTR (mean ± SE)	51.0 ± 1.5	51.2 ± 1.7	50.8 ± 1.4	0.852
Younger than 40 yrs at IBTR (%)	22	21	22	0.898
Time to IBTR in yrs (mean ± SE)	6.2 ± 0.6	7.3 ± 0.7	5.6 ± 0.5	0.0669
Two or more local disease recurrences	12	2	18	0.008
Family history (First-degree relative)	15	19	13	0.366
Carcinomas other than breast	14	13	15	0.654
Radiation boost for primary	74	79	71	0.283
Hormonal therapy for primary	3	0	5	0.111
Chemotherapy for primary	20	19	21	0.810

NP: new primary tumor; TR: true local disease recurrence; SE: standard error; IBTR: ipsilateral breast tumor recurrence.

TABLE 4
Comparison of Pathologic Characteristics between Patients with NP and TR

Characteristics	All patients (n = 126) (%)	NP (n = 48) (%)	TR (n = 78) (%)	P value
Stage of primary tumor				
0	11	10	12	0.846
1	46	46	46	0.972
2	43	44	42	0.874
Tumor size of primary (n = 111)				
Tumor size in cm (mean ± SE)	1.7 ± 0.1	1.8 ± 0.1	1.7 ± 0.1	0.804
Larger than 2 cm (%)	41	45	39	0.369
Positive axillary lymph nodes at primary (n = 86)	30	27	32	0.598
Positive margins versus close/negative margins (n = 81)	14	10	16	0.471
Extensive intraductal component in primary (n = 124)	26	22	28	0.427
Modified Black's nuclear Grade 3				
Primary (n = 69)	33	29	35	0.579
IBTR (n = 87)	40	33	43	0.307
Lymph node involvement at IBTR	9	4	12	0.155
Skin involvement at IBTR (n = 113)	19	2	28	0.003
Positive estrogen receptor status				
Primary (n = 64)	63	77	53	0.049
IBTR (n = 53)	68	75	65	0.468
Positive progesterone receptor status				
Primary (n = 55)	56	75	42	0.014
IBTR (n = 45)	47	46	47	0.965

NP: new primary tumor; TR: true local disease recurrence; SE: standard error; IBTR: ipsilateral breast tumor recurrence.

in these patients. One strategy would be to recommend tamoxifen for patients with NP, as randomized trials have demonstrated its benefit in reducing contralateral and ipsilateral disease recurrences with minimal side effects.[22–24] The NSABP P-1 trial showed that 5 years of tamoxifen reduced the 5-year risk of developing breast carcinoma by as much as 50% in all age groups.[24] The beneficial effects of tamoxifen in decreasing rates of NP could not be studied adequately in this population due to its infrequent use. However, Buchholz et al.[25] reported that tamoxifen use significantly decreased the rate of IBTR after BCT. In that study, the 8-year rate of IBTR was only 3% for lymph node-negative breast carcinoma patients treated with BCT and tamoxifen. It is noteworthy to speculate to what degree the reduction in IBTR with tamoxifen use is reflective of the therapeutic versus chemopreventive effects of this agent.

In contrast to patients with NP, patients with IBTR classified as TR have a poor prognosis in terms of both

survival rates and the development of a second or third local disease recurrence. These data highlight the need for adjuvant systemic therapy for this category of patients. In addition, the 18% rate of second local disease recurrences suggests that aggressive surgery is warranted.

The main limitation of this study is that the IBTR were classified using clinical and pathologic criteria without molecular confirmation. In the future, more precise molecular studies will likely be able to identify the clonal relatedness of the IBTR and the primary tumor. However, our methodology has greater clinical applicability than molecular techniques that require sophisticated analyses. Our criteria are based on readily available information and our results demonstrate that these criteria can identify subgroups of patients with significantly different outcomes after IBTR.

Smith et al.[26] also classified IBTR as NP or TR based on clinical and pathologic criteria and investigated the outcomes of these patients in light of this distinction. Similar to our findings, they reported that NP patients had a longer time to disease recurrence and significantly more favorable overall, cause-specific, and distant disease-free survival rates. In addition, they found that patients whose tumors were classified as NP were younger than those with TR (mean age: 49 vs. 55 years). They noted that all eight patients who tested positive for BRCA 1/2 mutations developed NP. This finding adds support to the hypothesis that patients who are genetically predisposed to developing breast carcinoma are more likely to have NP recurrences.

In conclusion, based on differences in location and/or histology between the primary tumor and the IBTR, we classified more than one-third of patients as having NP rather than TR. These patients have outcomes that are similar to those for patients treated for early-stage primary breast carcinoma and significantly better than those for patients with TR. Accordingly, this distinction between NP and TR should be incorporated into the therapeutic management of IBTR. Our data support the use of systemic therapy and aggressive local management for patients with TR and the need to investigate chemoprevention strategies for patients with NP.

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