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ORIGINAL REPORT

Predictors of Locoregional Recurrence After Neoadjuvant Chemotherapy: Results From Combined Analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27

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ABSTRACT

Purpose
The limited information on predictors of locoregional recurrence (LRR) after neoadjuvant chemotherapy (NC) has resulted in controversy about the optimal use of adjuvant radiotherapy and the timing of sentinel lymph node biopsy.

Patients and Methods
We examined patterns and predictors of LRR as first event in combined analysis of two National Surgical Adjuvant Breast and Bowel Project (NSABP) neoadjuvant trials. NC was either doxorubicin/cyclophosphamide (AC) alone or AC followed by neoadjuvant/adjuvant docetaxel. Lumpectomy patients received breast radiotherapy alone; mastectomy patients received no radiotherapy. Pathologic complete response was defined as the absence of invasive tumor in the breast. Multivariate analyses were used to identify independent predictors of LRR. The primary end point was time to LRR as first event.

Results
In 3,088 patients, 335 LRR events had occurred after 10 years of follow-up. The 10-year cumulative incidence of LRR was 12.3% for mastectomy patients (8.9% local; 3.4% regional) and 10.3% for lumpectomy plus breast radiotherapy patients (8.1% local; 2.2% regional). Independent predictors of LRR in lumpectomy patients were age, clinical nodal status (before NC), and pathologic nodal status/breast tumor response; in mastectomy patients, they were clinical tumor size (before NC), clinical nodal status (before NC), and pathologic nodal status/breast tumor response. By using these independent predictors, groups at low, intermediate, and high risk of LRR could be identified. Nomograms that incorporate these independent predictors were created.

Conclusion
In patients treated with NC, age, clinical tumor characteristics before NC, and pathologic nodal status/breast tumor response after NC can be used to predict risk for LRR and to optimize the use of adjuvant radiotherapy.

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INTRODUCTION

For patients with early-stage breast cancer who receive surgery as their initial treatment, there is abundant information on rates and predictors of locoregional recurrence (LRR), with or without adjuvant systemic therapy.[1-4] This information has been used for decisions about the use of locoregional external radiotherapy (XRT) after mastectomy or the addition of regional nodal XRT after breast-conserving surgery (BCS). In contrast, there is limited information on rates and predictors of LRR for patients who receive neoadjuvant chemotherapy. The reason for this paucity of data is twofold. First, considerably fewer patients with operable breast cancer are being treated with neoadjuvant versus adjuvant chemotherapy. Second, by the time neoadjuvant chemotherapy became established as an alternative to adjuvant chemotherapy, the role of locoregional XRT in patients with positive nodes was well established. Thus, most available databases of patients treated with neoadjuvant chemotherapy include patients who, at the discretion of the treating physician, were treated with postoperative XRT

(because they had pathologically positive nodes at surgery or because their tumors were presumed to be node positive before neoadjuvant chemotherapy).

Until the late 1990s, National Surgical Adjuvant Breast and Bowel Project (NSABP) adjuvant and neoadjuvant breast cancer clinical trials did not allow chest wall/regional nodal XRT after mastectomy or regional nodal XRT after BCS. This was because up until that time, there was no convincing evidence that XRT to those areas significantly improved overall survival, although it did increase morbidity.[5,6] Only after a significant overall survival benefit with the addition of postmastectomy XRT was demonstrated in the late 1990s for patients with positive nodes receiving adjuvant chemotherapy[7-9] was the addition of chest wall and regional nodal XRT after mastectomy and regional nodal XRT after breast-conserving therapy allowed in subsequent NSABP trials. Before this change, the NSABP conducted two trials of neoadjuvant chemotherapy (NSABP B-18 and NSABP B-27). Data from these two trials provided us with the opportunity to examine the rates and patterns of LRR in patients treated with neoadjuvant chemotherapy and to identify independent predictors of LRR in this setting.

PATIENTS AND METHODS

In NSABP B-18, between October 1988 and April 1993, 1,523 patients were randomly assigned to receive either four cycles of neoadjuvant doxorubicin and cyclophosphamide (AC) or the same chemotherapy given after surgery (Fig 1). Eligible patients had operable, palpable breast cancer (T1-3N0-1M0) diagnosed by fine-needle aspiration (FNA) or core needle biopsy. Results from the study, including details on enrollment, eligibility, treatment, tumor response, and outcome have been reported previously on several occasions.[10-13] The protocol was closed to follow-up on June 8, 2007.

In NSABP B-27, between December 1995 and December 2000, 2,411 patients were randomly assigned to receive either four cycles of neoadjuvant AC or four cycles of neoadjuvant AC followed by four cycles of either neoadjuvant or adjuvant docetaxel (Fig 1). Eligible women had primary operable breast cancer (T1c-3N0M0 or T1-3N1M0) diagnosed by core needle biopsy or FNA. Results from the study, including details on enrollment, eligibility, treatment, response, and outcome have been previously reported through 6.5 years[14,15] and 8.5 years of follow-up.[13] B-27 was closed to follow-up on December 31, 2009.

Stratification variables for both studies were age, clinical tumor size, and clinical nodal status (cN). FNA results were used to establish eligibility; hormone receptor status was not available at random assignment and was not used for stratification. Both protocols were approved by the local human investigations committee or institutional review board at NSABP sites, with assurances filed with and approved by the US Department of Health and Human Services. Patients were required to give written consent before entering these studies.

Treatment Regimens

In NSABP B-18, patients were assigned to receive four cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC) on day 1 of every 21-day cycle either before or after surgery. Patients age $\geq$ 50 years received tamoxifen (10 mg orally twice per day for 5 years) starting after chemotherapy, regardless of hormone receptor status.

In NSABP B-27, patients were assigned to receive four cycles of neoadjuvant AC as in B-18 either alone (group 1) or followed by four cycles of neoadjuvant docetaxel at 100 mg/m^2 on day 1 of every 21-day cycle (group 2) or followed by the same docetaxel regimen postoperatively (group 3). All patients received tamoxifen (20 mg per day for 5 years) starting on the first day of chemotherapy, regardless of hormone receptor status. In both studies, patients undergoing lumpectomy received breast XRT. Mastectomy patients received no XRT.

Statistical Methodology

The combined data set includes all eligible patients with follow-up from the neoadjuvant AC arm of NSABP B-18 and from all three arms of NSABP B-27. To avoid bias due to varying length of follow-up in the two studies, follow-up data for the analyses were administratively censored at 10 years. Cumulative incidence curves, point estimates, and confidence intervals for

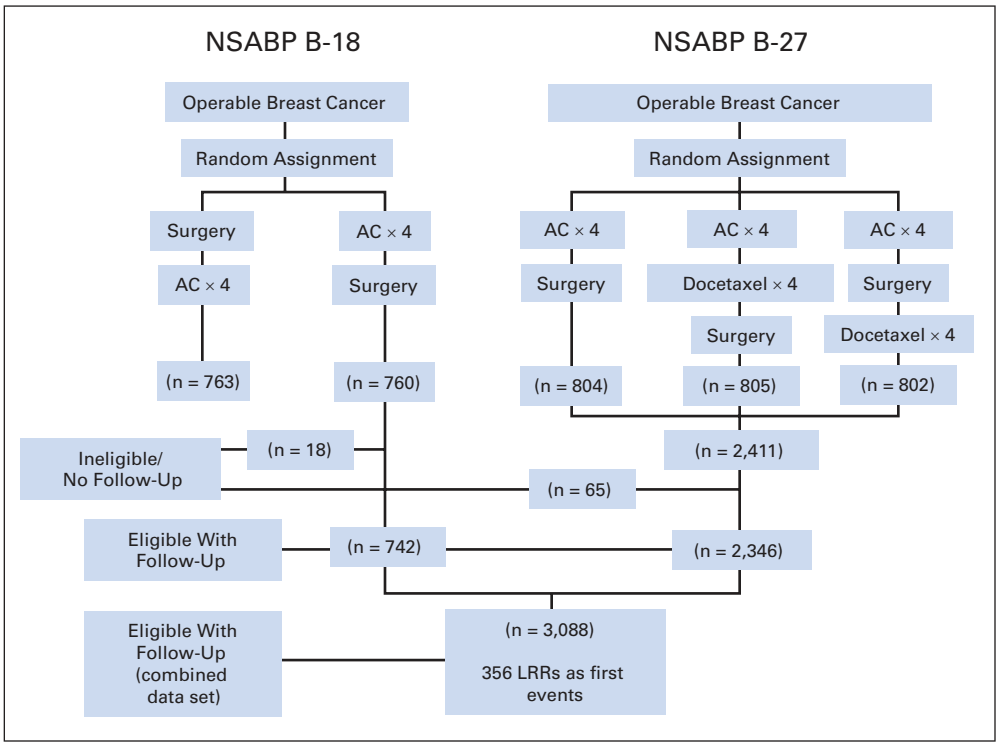

Fig 1. CONSORT diagram for National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 and B-27 trials. AC, doxorubicin/cyclophosphamide; LLR, locoregional recurrence.

LRR were calculated according to the methods outlined in Gray.[16] Univariate and multivariate analyses were used to identify independent predictors of LRR by using Cox proportional hazards methodology[17] in the combined data set. Although an alternate competing risks regression model was considered,[18] the cause-specific hazard model was used for comparability with other risk modeling reports in the literature,[2,3,19] and because the model coefficients specifically reflect the influence of covariates on the hazard of failure for the event of interest.[20,21] Covariate effect estimates for the two models were examined and found to be similar; however, the cause-specific hazard model will produce larger cumulative risk estimates, representing an upper bound on the actual risk. Factors evaluated in these analyses included patient and tumor baseline characteristics before neoadjuvant chemotherapy (age at random assignment, clinical tumor size, and clinical nodal status) as well as pathologic tumor characteristics after neoadjuvant chemotherapy (pathologic nodal status [ypN] and presence or absence of pathologic complete response [pCR] in the breast). In addition, multivariate analyses were performed separately in patients treated with mastectomy and in those treated with lumpectomy plus breast XRT. Tests of proportionality were performed for all final models,[22] and all yielded nonsignificant results. pCR was defined as absence of invasive tumor in the breast. The primary end point was time to first LRR defined as the occurrence of LRR in the absence of any prior recurrence, second primary cancer, or concomitant diagnosis of distant recurrence.

RESULTS

Characteristics of the Patient Population

A total of 742 and 2,346 eligible patients with follow-up were included in the neoadjuvant AC arm of NSABP B-18 and in the three arms of NSABP B-27, respectively. Table 1 describes the distribution of patient and tumor characteristics used as stratification variables (age, clinical tumor size, clinical nodal status, and combined clinical staging). Patients in NSABP B-27 were slightly younger than those in NSABP B-18 (57% *v* 51% younger than age 50 years; $P = .01$) and presented more frequently with tumors more than 5 cm (29% *v* 13%) and less frequently with tumors ≤ 2 cm (14% *v* 28%; overall $P < .001$). At surgery, the median number of removed axillary nodes was 13 in B-18 patients (mean, 13.8 ± 6.5) and 13 in B-27 patients (mean, 14.1 ± 6.5). Median follow-up at study closures was 15.4 years in B-18 and 10.7 years in B-27. Median follow-up in the combined data set was 11.75 years.

Table 1. Distribution of Selected Patient and Tumor Characteristics in NSABP B-18 and B-27 at Random Assignment (before neoadjuvant chemotherapy)

Characteristic	NSABP Trial (%)	
	B-18 (neoadjuvant AC arm) (n = 742)	B-27 (all three arms) (n = 2,346)
Patient age at random assignment, years		
< 50	51	57
≥ 50	49	43
Clinical tumor size at random assignment, cm		
cT1 (≤ 2.0)	28	14
cT2 (2.1-5.0)	59	57
cT3 (> 5)	13	29
Clinical nodal status at random assignment		
cN0	73	70
cN1	27	30
Combined clinical stage at random assignment		
cT1-2N0	65	51
cT1-2N1	22	20
cT3N0	8	19
cT3N1	5	10

Abbreviations: AC, doxorubicin/cyclophosphamide; NSABP, National Surgical Adjuvant Breast and Bowel Project.

Incidence of LRR by Protocol Arm and in the Combined Data Set

The 10-year cumulative incidence of LRR was 14.3% and 12.2% in the neoadjuvant AC arms of B-18 and B-27, respectively ($P = .05$). There was a significant reduction in the 10-year cumulative incidence of LRR with the addition of neoadjuvant docetaxel (8.5%; $P = .02$ *v* the AC-alone arm of B-27) and a nearly significant reduction with adjuvant docetaxel (9.5%; $P = .08$ *v* the AC-alone arm of B-27).

In the combined data set, there have been 356 LRRs reported as first events among 3,088 eligible patients with follow-up. Of those, 335 occurred in the first 10 years of follow-up. The 10-year cumulative incidence of LRR was 11.1% for the entire cohort of patients (8.4% local; 2.7% regional). LRR incidence was 12.6% among 1,947 patients treated with mastectomy (9.0% local; 3.6% regional) and 10.3% among 1,100 patients treated with lumpectomy plus breast XRT (8.1% local; 2.2% regional). Thus, local recurrences accounted for 71% of 10-year LRRs in mastectomy patients and for 79% of 10-year LRRs in patients receiving lumpectomy plus breast XRT.

Univariate and Multivariate Analyses of Predictors of LRR in the Combined Data Set

Of the 3,088 eligible patients with follow-up in the combined data set, information on surgery type and all covariates was available for 2,961 patients. In this cohort, age at random assignment, clinical tumor size before neoadjuvant chemotherapy, clinical nodal status before neoadjuvant chemotherapy, and pathologic nodal status/pCR in the breast after neoadjuvant chemotherapy and surgery were significant predictors of LRR by univariate analysis. All these factors remained significant independent predictors of LRR in multivariate analysis: age at random assignment (≥ 50 years *v* < 50 years; hazard ratio [HR], 0.78; 95% CI, 0.63 to 0.98; $P = .03$), clinical tumor size before neoadjuvant chemotherapy (> 5 cm *v* ≤ 5 cm; HR, 1.51; 95% CI, 1.19 to 1.91; $P < .001$), clinical nodal status before neoadjuvant chemotherapy (cN-positive *v* cN-negative; HR, 1.61; 95% CI, 1.28 to 2.02; $P < .001$), and pathologic nodal status/pathologic breast tumor response (ypN negative/no breast pCR *v* ypN negative/breast pCR; HR, 1.55; 95% CI, 1.01 to 2.39 and ypN positive *v* ypN negative/breast pCR; HR, 2.71; 95% CI, 1.79 to 4.09; $P < .001$; Table 2).

Independent predictors of LRR were also evaluated separately for patients treated with mastectomy and for those treated with lumpectomy plus breast XRT. In the multivariate Cox proportional hazards model for patients treated with mastectomy, age was not a significant independent predictor of LRR, but clinical tumor size (HR, 1.58; 95% CI, 1.12 to 2.23; $P = .0095$), clinical nodal status (HR, 1.53; 95% CI, 1.08 to 2.18; $P = .017$), and pathologic nodal status/pathologic breast tumor response (HR, 2.21; 95% CI, 0.77 to 6.30 for ypN negative/no breast pCR *v* ypN negative/breast pCR and HR, 4.48; 95% CI, 1.64 to 12.21 for ypN positive *v* ypN negative/breast pCR; $P < .001$) were significant predictors (Table 3). In the multivariate Cox proportional

Table 2. Multivariate Analysis of Independent Predictors of 10-Year LRR in the Combined Data Set*

Variable	HR	95% CI	P
Age ≥ 50 *v* < 50 years†	0.78	0.63 to 0.98	.03
Clinical tumor size > 5 *v* ≤ 5 cm†	1.51	1.19 to 1.91	< .001
Clinical nodal status cN(+) *v* cN(−)†	1.61	1.28 to 2.02	< .001
Nodal/breast pathologic status			< .001
ypN(−)/no breast pCR *v* ypN(−)/breast pCR†	1.55	1.01 to 2.39	
ypN(+) *v* ypN(−)/breast pCR†	2.71	1.79 to 4.09	

NOTE. The total No. of patients was 2,961, with 320 locoregional recurrence (LRR) events.
Abbreviations: HR, hazard ratio; pCR, pathologic complete response.
*Includes only patients for whom surgery type and all covariates are known.
†Category used as baseline for comparison of risk.

hazards model for patients treated with lumpectomy plus breast XRT, clinical tumor size was not a significant independent predictor of LRR, but age (HR, 0.71; 95% CI, 0.53 to 0.96; $P = .025$), clinical nodal status (HR, 1.70; 95% CI, 1.26 to 2.31; $P < .001$), and pathologic nodal status/pathologic breast tumor response (HR, 1.44; 95% CI, 0.90 to 2.33 for ypN negative/no breast pCR *v* ypN negative/breast pCR and HR, 2.25; 95% CI, 1.41 to 3.59 for ypN positive *v* ypN negative/breast pCR; $P < .001$) were significant independent predictors (Table 3).

Incidence of Local and Regional Recurrence According to Independent Predictors

We examined the incidence of local, regional, and LRR separately in patients treated with BCS plus breast XRT and in those treated with mastectomy, according to the independent predictors of LRR (Figs 2A and 2B and Figs 3A and 3B).

Patients Treated With Lumpectomy Plus Breast XRT

Ipsilateral breast tumor recurrence. For patients treated with lumpectomy plus breast XRT, the majority of LRRs were ipsilateral breast tumor recurrences (IBTRs) with rates ranging from 5.2% to 8.7% in those age ≥ 50 years and from 6.9% to 13.6% in those younger than age 50 years (Figs 2A and 2B). In patients age ≥ 50 years, IBTR rates did not appear to be influenced by pathologic nodal status/pathologic breast tumor response or initial clinical nodal status (Fig 2A). However, in patients younger than age 50 years, there was a trend toward increasing IBTR rates with decreasing pathologic breast tumor response and positive pathologic nodal status (Fig 2B). For clinically node-negative patients, IBTR rates were 6.9%, 8%, and 10.5% for those with ypN negative/breast pCR, ypN negative/no breast pCR, and ypN positive, respectively. For clinically node-positive patients, the respective IBTR rates were 7%, 10%, and 13.6% (Fig 2B).

Regional nodal recurrence. Rates of regional nodal recurrence in patients treated with lumpectomy plus breast XRT were low for patients with clinically negative nodes (0.5% to 2.3%) and for those with clinically positive nodes but pathologically negative nodes at surgery (0% to 2.4%; Figs 2A and 2B). Pathologic nodal status/pathologic breast tumor response did not seem to influence rates of regional nodal recurrence in clinically node-negative patients, but in clinically node-positive patients, the rates of regional recurrence were higher in those who remained pathologically node positive after neoadjuvant chemotherapy (7.5% to 8.7%; Figs 2A and 2B).

Patients Treated With Mastectomy

Chest wall recurrence. Rates of chest wall recurrence generally increased with decreasing pathologic breast tumor response and positive pathologic nodal status; this increase was more pronounced in patients with tumors more than 5 cm compared with patients who had tumors ≤ 5 cm and in patients with clinically positive nodes compared with patients who had clinically negative nodes (Figs 3A and 3B). Although the number of patients is low, chest wall recurrences after mastectomy were infrequent in patients who achieved breast pCR with pathologic negative nodes irrespective of tumor size and clinical nodal status (one local recurrence in 94 patients; Figs 3A and 3B).

Regional nodal recurrence. Regional nodal recurrence rates were generally low in clinically node-negative patients, irrespective of clinical tumor size (2.3% to 4.3% in patients with tumors ≤ 5 cm and 2.3% to 6.2% in those with tumors > 5 cm). Rates were higher for clinically node-positive patients, particularly if they remained pathologically node positive at surgery (Figs 3A and 3B).

Table 3. Multivariate Analysis of Independent Predictors of 10-Year LRR According to Type of Surgery

Variable	No. of Patients	LRR Events	HR	95% CI	P
Patients treated with mastectomy*	1,071	131			
Clinical tumor size > 5 *v* ≤ 5 cm†			1.58	1.12 to 2.23	.0095
Clinical nodal status cN(+) *v* cN(−)†			1.53	1.08 to 2.18	.017
Nodal/breast pathologic status					< .001
ypN(−)/no breast pCR *v* ypN(−)/breast pCR†			2.21	0.77 to 6.30	
ypN(+) *v* ypN(−)/breast pCR†			4.48	1.64 to 12.21	
Patients treated with lumpectomy plus breast XRT*	1,890	189			
Age ≥ 50 *v* < 50 years†			0.71	0.53 to 0.96	.025
Clinical nodal status cN(+) *v* cN(−)†			1.70	1.26 to 2.31	< .001
Nodal/breast pathologic status					< .001
ypN(−)/no breast pCR *v* ypN(−)/breast pCR†			1.44	0.90 to 2.33	
ypN(+) *v* ypN(−)/breast pCR†			2.25	1.41 to 3.59	

Abbreviations: HR, hazard ratio; LRR, locoregional recurrence; pCR, pathologic complete response; XRT, external radiation therapy.
*Includes only patients for whom all covariates are known.
†Category used as baseline for comparison of risk.

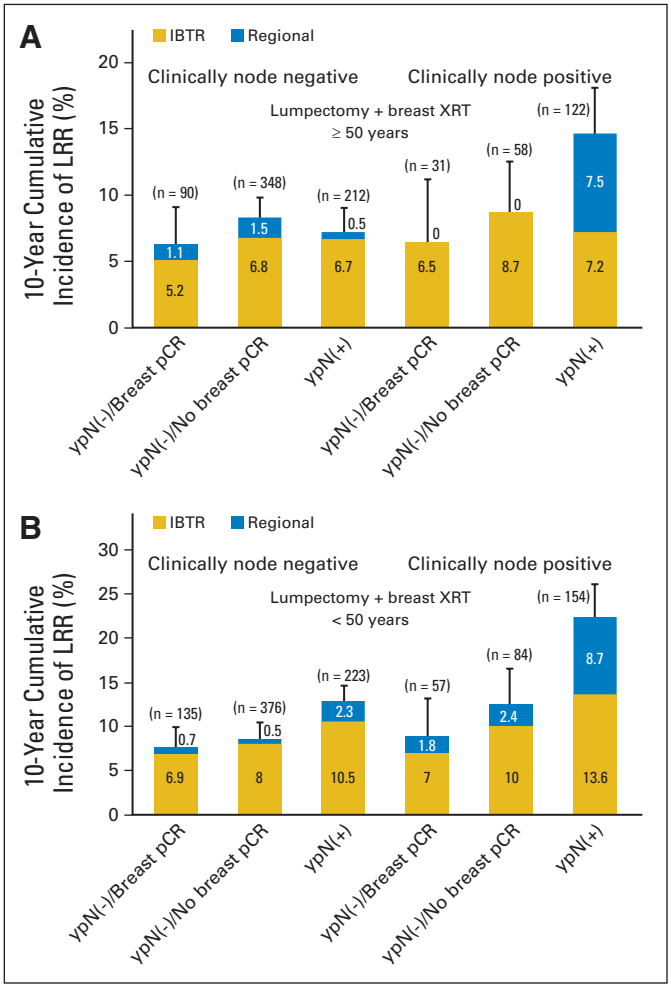

Fig 2. Ten-year cumulative incidence of locoregional recurrence (LRR) in patients (A) age ≥ 50 years treated with lumpectomy plus breast external radiotherapy (XRT) and (B) younger than age 50 years treated with lumpectomy plus breast XRT. IBTR, ipsilateral breast tumor recurrence; pCR, pathologic complete response [after neoadjuvant chemotherapy]; ypN, pathologic nodal status [after neoadjuvant chemotherapy].

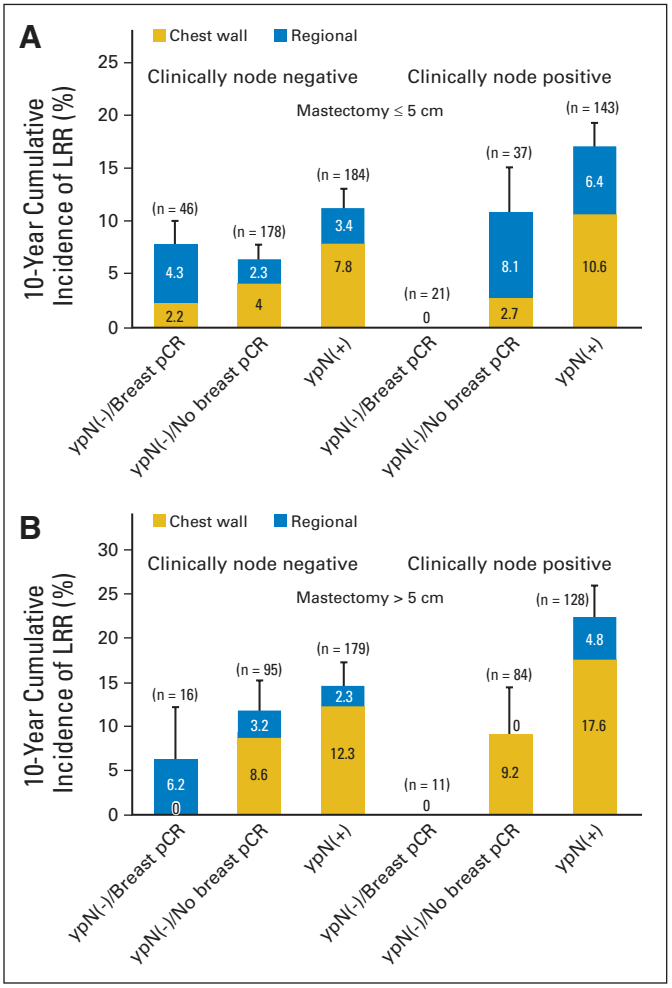

Fig 3. Ten-year cumulative incidence of locoregional recurrence (LRR) in patients with (A) ≤ 5-cm tumors treated with mastectomy and (B) > 5-cm tumors treated with mastectomy. pCR, pathologic complete response [after neoadjuvant chemotherapy]; ypN, pathologic nodal status [after neoadjuvant chemotherapy].

Rates of LRR According to Number of Pathologically Positive Nodes at Surgery

When rates of LRR for patients with pathologically positive nodes at surgery were examined according to the number of positive nodes (one to three *v* at least four), the rates were generally higher for those with at least four positive nodes versus those with one to three positive nodes. However, based on the independent predictors of LRR, the rates of LRR were consistently above 10% for all subsets of patients with one to three positive nodes (with the exception of clinically node-negative patients age ≥ 50 years treated with BCS plus XRT; Appendix Figs A1A-A1D, online only).

Development of Risk Prediction Nomograms to Predict LRR After Neoadjuvant Chemotherapy

Results of multivariate analyses in which age and tumor size were used as continuous variables were similar to those in which age and tumor size were used as discrete variables. These independent predictors of LRR were then incorporated into two separate risk prediction nomograms: one for patients treated with lumpectomy plus breast XRT (Fig 4A) and one for patients treated with mastectomy (Fig 4B). Ten-year predicted locoregional event rates from fitted Cox proportional hazard models were plotted according to variables of interest (age, tumor size, clinical nodal status, and pathologic nodal status/pathologic breast tumor response).

DISCUSSION

We described the largest prospectively collected cohort of patients with operable breast cancer treated with neoadjuvant chemotherapy for whom information on rates and patterns of LRR is available. Patients met predefined eligibility criteria and were monitored uniformly as part of each protocol. The major strength of the data, however, is that use of XRT was legislated by protocol and not left to the discretion of the treating physician. Thus, mastectomy patients were not permitted to receive chest wall or regional nodal XRT, and lumpectomy patients were required to receive breast XRT but were not permitted to receive additional regional nodal XRT, irrespective of the number of residual positive nodes at surgery or the original clinical nodal status or clinical

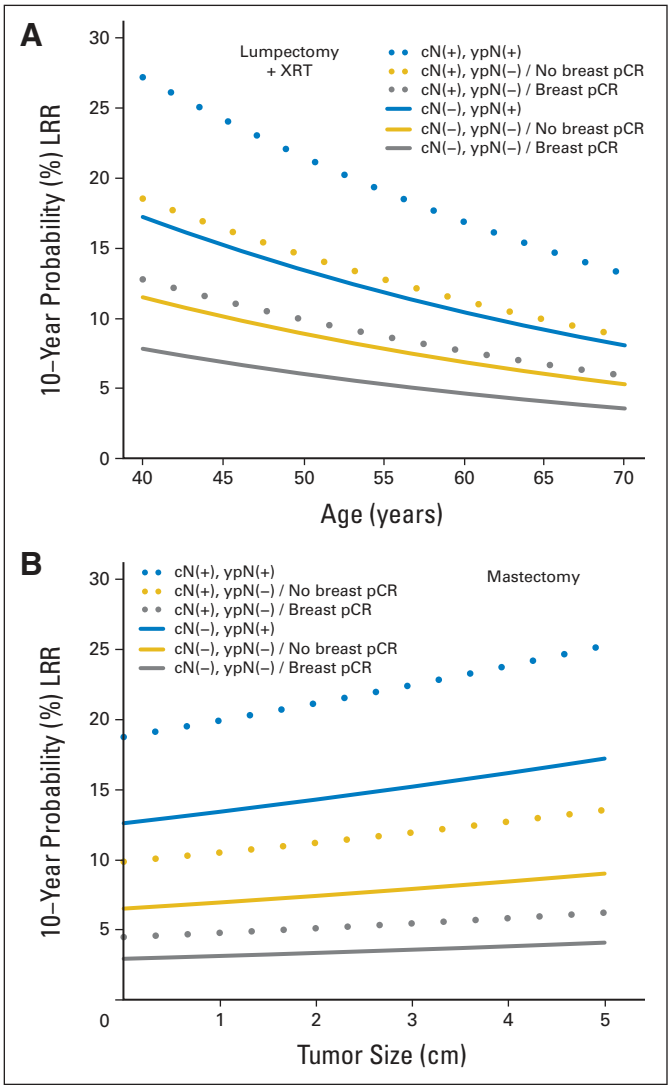

Fig 4. Nomogram to predict 10-year risk of locoregional recurrence (LRR) in patients treated with (A) lumpectomy plus breast external radiotherapy (XRT) after neoadjuvant chemotherapy or (B) mastectomy after neoadjuvant chemotherapy. cN, clinical nodal status [before neoadjuvant chemotherapy]; pCR, pathologic complete response [after neoadjuvant chemotherapy]; ypN, pathologic nodal status [after neoadjuvant chemotherapy].

tumor size before neoadjuvant chemotherapy. To that extent, the two trials provide us with a large cohort of patients for whom the natural history of LRR can be assessed without the confounding effects of nonuniform postmastectomy chest wall radiation or radiation to regional nodal basins.

One significant limitation of the study is the lack of information on estrogen receptor (ER), progesterone receptor, and human epidermal growth factor receptor 2 *neu* (HER2/*neu*) status. More than 85% of patients in B-18 and 41% of patients in B-27 were diagnosed by FNA. When B-18 was conducted, tamoxifen was given on the basis of a patient's age and not by ER status. In B-27, the decision was made to give tamoxifen to all patients concurrently with chemotherapy (the trial was conducted before Southwestern Oncology Group [SWOG] 8814 showed superiority for the sequential administration of chemotherapy and endocrine therapy).[23] Because both trials were conducted before the era of adjuvant trastuzumab, there was no need for HER2/*neu* status assessment. Although there is information on ER, progesterone receptor, and HER2/*neu* status (as well as grade and lymphovascular invasion) on the residual tumor at the time of surgery, using this information introduces selection bias, because only tumors that did not achieve breast pCR would be included. Another potential limitation is that two different neoadjuvant chemotherapy regimens were used (AC and AC→docetaxel), and in one group of B-27, docetaxel was added as adjuvant therapy. However, when we assessed the multivariate models without including the docetaxel-treated cohorts, the findings were similar.[24]

Our results clearly demonstrate that, in addition to age and clinical tumor characteristics available before neoadjuvant chemotherapy, pathologic response in the breast and pathologic axillary nodal status have a major impact on the rates and patterns of LRR. The results further suggest that the impact of age, clinical tumor size, and clinical nodal status on the absolute LRR rates are low if a patient achieves a pCR in the breast with pathologically negative axillary nodes. However, this observation must be interpreted with caution, because the number of patients who achieved pCR in the breast with negative nodes is relatively small in some categories (eg, mastectomy patients). In addition, it should be reiterated that the results of this study apply only to patients with operable breast cancer at presentation, because patients with T4 or N2 disease at presentation were not eligible for these two trials. In fact, data on LRR rates in patients with locally advanced breast cancer reported from the MD Anderson Cancer Center suggest higher rates of LRR, even with pCR to neoadjuvant chemotherapy.[19]

Our results on the rates of LRR according to number of positive nodes after neoadjuvant chemotherapy are also of interest. Although they suggest that the risk of LRR is increased with an increasing number of residual positive nodes, they also indicate that the risk of LRR is considerable ($>$ 10%) for most subsets of patients with one to three positive nodes.

Finally, our nomogram could be a useful tool for predicting risk of LRR and the optimal use of XRT in patients treated with neoadjuvant chemotherapy. However, before it can be adopted clinically, it needs to be validated in other independent data sets. Furthermore, information on the effect of hormone receptor status, HER2/*neu* status, and the therapeutic effect of adding trastuzumab to chemotherapy in patients with HER2-positive disease are additional factors that will have to be incorporated in future iterations of such nomograms.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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