Predictors of Locoregional Recurrence After Failure to Achieve Pathologic Complete Response to Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer

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ABSTRACT

Background: This study evaluated factors predictive of locoregional recurrence (LRR) in women with triple-negative breast cancer (TNBC) treated with neoadjuvant chemotherapy who do not experience pathologic complete response (pCR). **Methods:** This is a single-institution retrospective review of women with TNBC treated with neoadjuvant chemotherapy, surgery, and radiation therapy in 2000 through 2013. LRR was estimated between patients with and without pCR using the Kaplan-Meier method. Patient-, tumor-, and treatment-specific factors in patients without pCR were analyzed using the Cox proportional hazards method to evaluate factors predictive of LRR. Log-rank statistics were then used to compare LRR among these risk factors. **Results:** A total of 153 patients with a median follow-up of 48.6 months were included. The 4-year overall survival and LRR were 70% and 15%, respectively, and the 4-year LRR in patients with pCR was 0% versus 22.0% in those without ($P < .001$). In patients without pCR, lymphovascular space invasion (LVSI; hazard ratio, 3.92; 95% CI, 1.64–9.38; $P = .002$) and extranodal extension (ENE; hazard ratio, 3.32; 95% CI, 1.35–8.15; $P = .009$) were significant predictors of LRR in multivariable analysis. In these patients, the 4-year LRR with LVSI was 39.8% versus 15.0% without ($P < .001$). Similarly, the 4-year LRR was 48.1% with ENE versus 16.1% without ($P = .002$). In patients without pCR, the presence of both LVSI and ENE were associated with an even further increased risk of LRR compared with patients with either LVSI or ENE alone and those with neither LVSI nor ENE in the residual tumor ($P < .001$). **Conclusions:** In patients without pCR, the presence of LVSI and ENE increases the risk of LRR in TNBC. The risk of LRR is compounded when both LVSI and ENE are present in the same patient. Future clinical trials are warranted to lower the risk of LRR in these high-risk patients.

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Background

Breast cancer is a heterogeneous group of diseases and encompasses a variety of molecular and morphologic subtypes. Triple-negative breast cancer (TNBC) represents approximately 15% to 20% of all breast cancers.¹ Compared with hormone receptor-positive breast cancer, TNBC follows an aggressive clinical course with a shorter disease-free interval and overall survival.^{1,2} In addition, a higher rate of locoregional recurrence (LRR) has been reported for TNBC.^{3–5}

Patients with locally advanced TNBC typically receive chemotherapy, surgery, and radiation therapy (RT). More recently, the concept of neoadjuvant chemotherapy (NAC) followed by surgery and RT has been introduced in women with locally advanced or palpable TNBC,⁶ because TNBC has been shown to have greater chemosensitivity than other breast cancer subtypes.^{1,5} Patients who achieve a pathologic complete response (pCR) after NAC have been reported to have significantly improved survival outcomes and locoregional control compared with those with residual disease.^{7,8} However, in those receiving NAC, the predictive value of other pathologic or treatment-related factors for local control is unclear because data are lacking.

Patients with residual disease after NAC have a 2- to 3-fold higher relative risk of developing LRR⁸; however, most remain free of LRR.⁸ For that reason, identifying patients with residual disease after NAC who are at high risk for LRR is clinically meaningful because it allows close monitoring for recurrence and early incorporation of salvage treatments.^{9,10} Therefore, this study aimed to evaluate factors predictive of LRR in patients with TNBC who have residual disease and therefore do not experience pCR after NAC.

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Methods

An Institutional Review Board–approved institutional database was used as a source for this analysis. All consecutive patients with TNBC who were treated with NAC, surgery, and RT in 2000 through 2013 were identified. TNBC was defined by the lack of estrogen and progesterone receptor expression and lack of HER2 expression or gene amplification. Patients with metastatic disease at diagnosis and those who developed progressive disease during treatment were excluded.

Patient-, tumor-, and treatment-specific factors were analyzed, including age, race, smoking history; tumor stage, histology, and grade; and type of NAC used. Before NAC, all patients were staged clinically by physical examination along with incorporation of diagnostic imaging. After NAC, all patients were staged surgically. Downstaging was defined as a decrease in T stage, N stage, or both after NAC (eg, clinical T3 disease treated with NAC and subsequently staged as $\leq$ T2 based on final pathology). pCR was defined as no evidence of invasive disease in the breast or regional lymph nodes after NAC. LRR was defined as reappearance of cancer in the ipsilateral breast, chest wall, or regional lymph nodes. The presence or absence of lymphovascular space invasion (LVSI), extranodal extension (ENE), or pathologically positive lymph nodes was determined during surgery. All patients in this database were treated with whole-breast or chest wall RT with or without regional nodal irradiation (RNI). RNI was delivered to 81% of patients. RNI at our institution includes treating levels I, II, and III of the axilla, interpectoral, supraclavicular, and internal mammary lymph nodes. It is our institutional practice to use 3D tangents for whole-breast RT and (infrequently) the deep inspiration breath hold technique. Before 2007, RNI was delivered using 3D tangents with or without internal mammary field, with supraclavicular field. This practice shifted to using intensity-modulated RT after 2007.

Time intervals for the analysis were calculated from date of diagnosis. Overall survival and LRR were estimated using the Kaplan-Meier method. Rates of LRR for patients who achieved pCR and those who did not were compared using log-rank statistics. Univariable and multivariable Cox proportional hazards methods were used to evaluate factors predictive of LRR in patients who did not experience pCR (ie, those with residual disease) after NAC. Stepwise regression, a modification of the forward selection method with selection criterion $P < .05$ based on Cox regression models, was applied to obtain the final multivariable model. In patients who did not experience pCR, the Kaplan-Meier method was used to estimate whether those with multiple risk factors had an increased risk of LRR compared with those with a single risk factor. Statistical analysis was performed using SPSS

Statistics, version 25 (IBM Corporation), and $P < .05$ was considered statistically significant.

Results

A total of 153 patients were included in the analysis; baseline characteristics are shown in Table 1. Median age at diagnosis was 49.5 years (range, 28.8–77.3 years). The most common NAC regimen was doxorubicin/cyclophosphamide/paclitaxel (AC-T; $n=62$; 40.5%). Patients receiving epirubicin/paclitaxel (ET) were part of an institutional phase II trial.¹¹ Adjuvant chemotherapy was also administered in 46 patients (30.1%). A total of 73 patients (47.7%) underwent breast-conserving surgery, and 118 (77.1%) underwent axillary lymph node dissection. The rate of pCR was 29.4% ($n=45$). Most patients (81.0%) received comprehensive RT, including treatment of the whole breast or chest wall along with regional nodes. The median RT dose was 50.4 Gy, and a sequential boost was delivered in 101 patients (66.0%).

Median follow-up was 48.6 months (range, 6.1–167.6 months). At the time of analysis, 49 patients had died. The 4-year overall survival was 70% for the whole cohort (Figure 1A), and the 4-year progression-free survival was 67.9% (see supplemental eFigure 1, available with this article at JNCCN.org). A total of 21 patients developed LRR, including 5 in-breast recurrences, 11 nodal recurrences, and 11 chest wall recurrences. Of the 11 nodal recurrences, failure occurred in the axilla in 8 patients and in the axilla and other nodal regions in 3 patients. There were no isolated internal mammary failures. The 4-year locoregional control for the whole cohort was 85% (Figure 1B). Among the 45 patients who experienced pCR, none had LRRs. Conversely, in the 108 patients without pCR, 21 (19.4%) had LRRs. The 4-year rate of locoregional control in patients who achieved pCR was 100% versus 78% in those who did not achieve pCR after NAC (Figure 2A) ($P < .001$).

To identify factors predictive of LRR, univariable and multivariable analyses were performed on patients who had residual disease after NAC (summarized in Table 2). On univariable analysis, LVSI and ENE were associated with LRR. On multivariable analysis, LVSI (hazard ratio, 3.92; 95% CI, 1.64–9.38) and ENE (hazard ratio, 3.32; 95% CI, 1.35–8.15) both remained as independent factors predictive of LRR. The rate of locoregional control at 4 years was 61.2% for patients with LVSI versus 85.0% in patients without LVSI after NAC (Figure 2B) ($P < .001$). The rate of locoregional control at 4 years was 51.9% in patients with ENE versus 83.9% in patients without ENE after NAC (Figure 2C) ($P = .002$).

Only 10 patients had both LVSI and ENE present in their residual disease. Of these, 5 (50%) developed LRR. There were 35 patients who had either LVSI or ENE, but not both. Of these, 10 (28.6%) developed LRR. There were

Table 1. Baseline Patient Characteristics

Characteristic	n (%)
All patients	153 (100)
Age at diagnosis, y	
<50	78 (51.0)
≥50	75 (49.0)
Race	
White	86 (56.2)
Black	67 (43.8)
Menopausal status	
Premenopausal	78 (51.0)
Postmenopausal	75 (49.0)
Clinical T stage	
T1	12 (7.8)
T2	66 (43.1)
T3	44 (28.8)
T4	31 (20.3)
Clinical N stage	
N0–1	120 (78.4)
N2–3	33 (21.6)
Multifocal	
No	133 (86.9)
Yes	20 (13.1)
Histology	
Ductal	135 (88.2)
Other	18 (11.8)
Grade	
I or II	25 (16.3)
III	128 (83.7)
Pathologic complete response	
No	108 (70.6)
Yes	45 (29.4)
Pathologic T stage	
T0	57 (37.3)
T1	44 (28.8)
T2	28 (18.3)
T3	13 (8.5)
T4	11 (7.2)
Pathologic N stage	
N0	93 (60.8)
N1	32 (20.9)
N2	15 (9.8)
N3	13 (8.5)
LVSI	
Absent	119 (77.8)
Present	34 (22.2)

(continued)

Table 1. Baseline Patient Characteristics (cont.)

Characteristic	n (%)
Margins	
Negative	143 (93.5)
Positive	10 (6.5)
Lymph node assessment	
Sentinel lymph node	35 (22.9)
ALND	118 (77.1)
Pathologic lymph node status	
Negative	91 (59.5)
Positive	62 (40.5)
Extranodal extension	
Absent	132 (86.3)
Present	21 (13.7)
Downstage after NAC	
No	52 (34.0)
Yes	101 (66.0)
Surgery type	
Breast-conserving surgery	73 (47.7)
Mastectomy	80 (52.3)
NAC type	
AC-T	62 (40.5)
FEC-T	27 (17.6)
ET	32 (20.9)
Other	32 (20.9)
Adjuvant chemotherapy	
No	107 (69.9)
Yes	46 (30.1)
RT boost	
No	52 (34.0)
Yes	101 (66.0)
RT volume	
Regional nodal irradiation	124 (81.0)
Whole-breast	29 (19.0)
RT dose, Gy	
Median (range)	50.4 (46.0–54.0)
RT boost dose, Gy	
Median (range)	10.0 (4.0–20.0)
Failures	
In-breast	5 (3.3)
Chest wall	11 (7.2)
Regional node	11 (7.2)

Abbreviations: AC-T, doxorubicin/cyclophosphamide/paclitaxel; ALND, axillary lymph node dissection; ET, epirubicin/paclitaxel; FEC-T, fluorouracil/epirubicin/cyclophosphamide/docetaxel; LVSI, lymphovascular space invasion; NAC, neoadjuvant chemotherapy; RT, radiation therapy.

Figure 1. (A) Overall survival and (B) locoregional control in patients with triple-negative breast cancer treated with neoadjuvant chemotherapy.

63 patients who did not have either LVSI or ENE, and of these, only 6 (9.5%) developed LRR. At 4-year follow-up, patients who had both LVSI and ENE had a lower rate of locoregional control than those with either LVSI or ENE alone, those with neither LVSI nor ENE, and those with pCR (Figure 2D) ($P < .001$).

Discussion

This is a large retrospective study evaluating factors predictive of LRR in women with TNBC who do not experience pCR after NAC. We found that in these women, ENE and LVSI are independent predictors of LRR. Patients with both of these risk factors have an especially high rate of LRR. In this cohort, 50% of patients who had both risk factors developed LRR. If confirmed in other studies, these factors should be considered when recommending adjuvant therapy for patients with TNBC. Therefore, future clinical trials are warranted in this patient population to lower the risk of LRR.

It is well-known that patients who achieve pCR after NAC have favorable outcomes with lower rates of LRR.^{6,7} Analysis of the NSABP B-18 and B-27 trials showed the critical impact of pathologic response to NAC in the breast and axillary lymph nodes on LRR.⁷ In this analysis, patients who did not experience pCR in both breast/chest wall and lymph nodes were twice as likely to develop LRR as those who did. However, this analysis encompassed all subtypes of breast cancers. In a TNBC-specific cohort of patients receiving NAC, surgery, and RT, Chen et al¹² reported that at 2-year follow-up, patients who experienced pCR had a 0% rate of LRR versus 27.5% in those who did not. This is similar to our findings, wherein patients who experienced pCR had a 0% rate of LRR versus 22% in those who did not. However, these other studies failed to describe features in the residual tumor that are more likely to result in an increased risk of

LRR. Our study went a step further to show that patients with residual disease after NAC who have ENE and/or LVSI have significantly higher rates of LRR than those with residual disease who do not have these pathologic features.

The presence of upfront LVSI is a well-known predictor of LRR in breast cancer,^{13–16} but it is not well evaluated in the post-NAC setting. Post-NAC LVSI was also recently shown by Hamy et al¹⁵ to be an independent predictor of disease-free and overall survival in a subgroup of 330 patients with TNBC. Our results are in accordance with this finding, showing that even in patients receiving adjuvant RT, post-NAC LVSI confers a high risk of LRR. Hamy et al¹⁵ reported a higher incidence of post-NAC LVSI in patients with low-grade histology, luminal tumors, and a larger number of involved lymph nodes, similar to characteristics of chemoresistant tumors. These findings and ours establish the additional independent risk afforded by LVSI over the simple presence of invasive cancer after NAC. It is theorized that cells that develop the ability to penetrate the vascular endothelium, survive within the intravascular space, and persist through chemotherapy are both biologically aggressive and poised to metastasize regionally and distally, helping to explain the close association between LVSI and LRR.¹⁶ Therefore, we propose that post-NAC LVSI status should be evaluated in future analyses. If our findings are independently validated in additional prospective analyses, then post-NAC LVSI could be incorporated into future post-NAC prognostic indices to help clinicians make appropriate patient recommendations.

In addition, ENE is known to confer an increased risk of recurrence in those with breast cancer.^{17,18} Even though NAC has been shown to decrease the incidence of ENE found at the time of surgery,¹⁹ there are few existing data on the prognostic implications of persistent ENE

Figure 2. Locoregional control in patients with triple-negative breast cancer treated with neoadjuvant chemotherapy (A) among those who experienced pCR versus no pCR; in patients without pCR, those with (B) LVSI versus no LVSI and (C) ENE versus no ENE; and (D) comparison of all subgroups.

Abbreviations: ENE, extranodal extension; LVSI, lymphovascular space invasion; pCR, pathologic complete response.

after NAC. This is of particular importance in the TNBC population, because a higher rate of ENE than in estrogen/progesterone receptor-positive subtypes is reported.²⁰ Our study thus reports novel data showing that patients with ENE after NAC have 3 times the increased risk of LRR compared with those with residual disease not extending through the nodal capsule. Multiple potential explanations for this correlation exist. It is possible that occult microscopic tumor persists more commonly in patients with ENE. In addition, tumors with ENE that persist after NAC may simply be more aggressive, radiation-resistant, and likely to recur. As such, we propose that post-NAC ENE also be evaluated and independently verified in prospective studies, similarly to LVSI.

Various strategies of treatment intensification have been evaluated in patients with TNBC to improve outcomes. The addition of carboplatin to standard NAC has produced improved rates of pCR but have an unknown effect on survival.^{21,22} In addition, a recent meta-analysis of 9 randomized clinical trials showed that platinum-based NAC is associated with significantly increased rates of pCR but also with higher rates of hematologic toxicities.²³ Our analysis raises the interesting question whether the addition of platinum agents to NAC regimens would result in a lower rate of residual LVSI and ENE and corresponding improvements in LRR. This has yet to be evaluated in subset analyses of these studies. A recent trial evaluating the use of PARP inhibitor veliparib in

Table 2. Factors Predictive of Locoregional Recurrence in Patients With No Pathologic Complete Response

Characteristic	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age, y				
<50	Ref		Ref	
≥50	2.10 (0.87–5.09)	.1	NS	
Race				
White	Ref		Ref	
Black	1.29 (0.55–3.05)	.56	NS	
Menopausal status				
Postmenopausal	Ref		Ref	
Premenopausal	0.47 (0.19–1.13)	.09	NS	
Clinical T stage				
T1–2	Ref		Ref	
T3–4	1.88 (0.76–4.67)	.17	NS	
Clinical N stage				
N0–1	Ref		Ref	
N2–3	1.90 (0.76–4.70)	.17	NS	
Multifocal				
No	Ref		Ref	
Yes	2.38 (0.91–6.23)	.08	NS	
Histology				
Ductal	Ref		Ref	
Other	0.74 (0.17–3.19)	.69	NS	
Grade				
I or II	Ref		Ref	
III	0.78 (0.28–2.12)	.62	NS	
Pathologic T stage				
T0–2	Ref		Ref	
T3–4	1.39 (0.51–3.83)	.52	NS	
Pathologic N stage				
N0–1	Ref		Ref	
N2–3	1.95 (0.75–5.12)	.17	NS	
Margins				
Negative	Ref		Ref	
Positive	0.91 (0.21–3.90)	.9	NS	
Lymph node assessment				
Sentinel lymph node	Ref		Ref	
ALND	1.08 (0.36–3.23)	.89	NS	
Pathologic lymph status				
Negative	Ref		Ref	
Positive	2.48 (0.96–6.40)	.06	NS	
LVSI				
Absent	Ref		Ref	
Present	4.18 (1.76–9.96)	.001	3.92 (1.64–9.38)	.002

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Abbreviations: AC-T, doxorubicin/cyclophosphamide/paclitaxel; ALND, axillary lymph node dissection; ET, epirubicin/paclitaxel; FEC-T, fluorouracil/epirubicin/cyclophosphamide/docetaxel; HR, hazard ratio; LVSI, lymphovascular space invasion; NAC, neoadjuvant chemotherapy; NS, not significant; RT, radiation therapy.

Table 2. Factors Predictive of Locoregional Recurrence in Patients With No Pathologic Complete Response (cont.)

Characteristic	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Extranodal extension				
Absent	Ref		Ref	
Present	3.64 (1.50–8.85)	.004	3.32 (1.35–8.15)	.009
Downstage after NAC				
No	Ref		Ref	
Yes	0.49 (0.20–1.18)	.11	NS	
Surgery type				
Breast-conserving surgery	Ref		Ref	
Mastectomy	1.18 (0.49–2.85)	.71	NS	
NAC type				
AC-T	Ref		Ref	
FEC-T	0.70 (0.19–2.56)	.59	NS	
ET	0.63 (0.20–2.04)	.45	NS	
Other	0.67 (0.21–2.14)	.5	NS	
Adjuvant chemotherapy				
No	Ref		Ref	
Yes	0.54 (0.21–1.38)	.2	NS	
RT boost				
No	Ref		Ref	
Yes	1.21 (0.49–3.00)	.68	NS	
RT volume				
Regional nodal irradiation	Ref		Ref	
Whole-breast	0.74 (0.22–2.52)	.63	NS	

Abbreviations: AC-T, doxorubicin/cyclophosphamide/paclitaxel; ALND, axillary lymph node dissection; ET, epirubicin/paclitaxel; FEC-T, fluorouracil/epirubicin/cyclophosphamide/docetaxel; HR, hazard ratio; LVSI, lymphovascular space invasion; NAC, neoadjuvant chemotherapy; NS, not significant; RT, radiation therapy.

combination with carboplatin and paclitaxel in the neoadjuvant setting showed that pCR rates were driven mainly by carboplatin and not by the PARP inhibitor.²⁴ Trials studying immunotherapeutic agents in the neoadjuvant setting are also underway.

The question whether the addition of platinum in the adjuvant setting improves outcomes in patients with residual disease after NAC has yet to be evaluated in a prospective trial. Recently published data from the CREATE-X trial showed a survival benefit with adjuvant capecitabine in HER2-negative patients with residual disease after NAC.²⁵ Subanalysis of this trial suggests that this benefit was driven primarily by the benefit of capecitabine in the TNBC cohort. However, the practice of administering capecitabine in the adjuvant setting for TNBC remains controversial, as evidenced by the recommendation in the NCCN Clinical Practice Guidelines in Oncology for Breast Cancer to “consider adjuvant capecitabine in patients with TNBC” who received

standard neoadjuvant treatment.²⁶ Patients in our study were treated before publication of the CREATE-X results, and a minority received adjuvant chemotherapy; however, none received capecitabine in the adjuvant setting. In our study, the presence of LVSI and ENE at the time of surgery was associated with absolute increases in LRR rates of 25% and 32%, respectively. Based on these data, we propose that the presence of LVSI and/or ENE in residual disease be further studied. If these findings are prospectively validated, then LVSI and ENE can be considered when discussing recommendations with patients regarding adjuvant chemotherapy such as capecitabine.

Use of sentinel lymph node biopsy with NAC is controversial.²⁷ The ACOSOG Z1071 trial showed a slightly higher false-negative rate of sentinel lymph nodes after NAC; however, it was <10% if ≥2 sentinel nodes were removed.²⁸ In this analysis, 22.9% of patients underwent sentinel lymph node biopsy. Notably, LRR in our study occurred despite all patients receiving adjuvant

RT. Relative radioresistance of the TNBC subtype compared with other breast cancer subtypes has previously been reported.⁵ Therefore, the addition of concurrent radiosensitizing agents may be the preferred method of enhancing locoregional control in patients with residual disease after NAC, particularly when LVSI or ENE is present. Concurrent radiosensitizing chemotherapy and RT have demonstrated favorable local disease response in locally advanced breast cancer in the upfront setting and in patients whose disease is resistant to first-line chemotherapy.^{29–31} Likewise, hyperthermia is a well-known radiosensitizer, and its combination with RT has demonstrated improved local control compared with RT alone in randomized studies,^{32,33} with acceptable toxicity profiles.³⁴ Therefore, treatment with concurrent radiosensitizing chemotherapy or hyperthermia should also be considered in future prospective trials for patients with TNBC who have residual LVSI and/or ENE after NAC.

Given the retrospective nature of this series, our study has several inherent limitations. Our data represent patients from a single institution, and treatment regimens at other institutions may differ and result in different outcomes. Therefore, our results should be interpreted with caution, and future larger prospective trials should be considered to validate our findings. In addition, our analysis of only 153 patients may limit the power to detect other meaningful predictors of LRR.

Conclusions

Our study results show that ENE and LVSI in residual breast cancer after NAC predict increased risk of LRR in patients with TNBC. On prospective validation, these factors can be used by clinicians to counsel their patients and make appropriate recommendations for adjuvant treatment or surveillance. For these patients, additional adjuvant chemotherapy, and the addition of radiosensitizing agents concurrently with RT, may be warranted to lower the risk of LRR in future prospective clinical trials.

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