Predictors of Distant Metastases in Triple-Negative Breast Cancer Without Pathologic Complete Response After Neoadjuvant Chemotherapy

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ABSTRACT

Background: Pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) for triple-negative breast cancer (TNBC) predicts decreased distant metastasis. However, most patients do not experience pCR, and other risk factors for distant metastasis after NAC are poorly characterized. This study investigated factors predictive of distant metastasis in TNBC without pCR after NAC.

Methods: Women with TNBC treated with NAC, surgery, and radiation therapy in 2000 through 2013 were reviewed. Freedom from distant metastasis (FFDM) was compared between patients with and without pCR using the Kaplan-Meier method. In patients without pCR, univariate and multivariable Cox analyses were used to determine factors predictive of distant metastasis. **Results:** We identified 153 patients with median follow-up of 4.0 years (range, 0.5–14.0 years). After NAC, 108 had residual disease (pCR, 29%). Five-year FFDM was 98% and 55% in patients with and without pCR, respectively ($P<.001$). Factors independently predicting FFDM in patients without pCR were pathologic nodal positivity (hazard ratio, 3.08; 95% CI, 1.54–6.14; $P=.001$) and lymphovascular space invasion (hazard ratio, 1.91; 95% CI, 1.07–3.43; $P=.030$). Patients with a greater number of factors had worse FFDM; 5-year FFDM was 76.5% for patients with no factors ($n=38$) versus 54.9% and 27.5% for patients with 1 ($n=44$) and 2 factors ($n=26$), respectively ($P<.001$).

Conclusions: Lack of pCR after NAC resulted in worse overall survival and FFDM, despite trimodality therapy. In patients with residual disease after NAC, pathologic lymph node positivity and lymphovascular space invasion predicted worse FFDM.

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Background

Triple-negative breast cancer (TNBC) is an often-used surrogate for the basal subtype of breast cancer defined by the lack of estrogen receptor (ER) and progesterone receptor (PR) expression and *HER2* gene amplification. As a group, patients with this subtype of breast cancer have a relatively worse prognosis than women with non-TNBC.¹ This is driven primarily by an increased propensity for distant failure compared with other subtypes of breast cancer, particularly within the first 5 years of diagnosis.^{2,3} Distant failure is a seminal event in the natural history of TNBC, with a 5-year overall survival (OS) rate of approximately 25% and median survival of 24 months in women with metastatic disease.⁴

With the advent of next-generation sequencing and other technologies, a highly diverse and heterogeneous molecular landscape underlying TNBC has been revealed, and multiple molecular subclassifications have been established.⁵ This heterogeneity is also manifested clinically because TNBC does not respond universally or predictably to current therapies. There is a sharp decrease in breast cancer-specific survival during the first 3 to 5 years after diagnosis with TNBC as opposed to other types of breast cancer, which show a more consistent decline in survival over time.⁶ This is mirrored in their pattern of distant recurrence, in which distant failure is much more common during the first 5 years after diagnosis but then decreases and becomes less common than distant relapse in non-TNBC cancers by 10 years after diagnosis.³ Together, this suggests that, although as a whole TNBC is biologically aggressive, there is a subset of patients with curable disease that is sensitive to standard therapy.

Despite the known heterogeneity within TNBC, management has changed little because TNBC is typically still treated as a single disease entity. With the increasing use of neoadjuvant chemotherapy (NAC), one factor that has emerged as an indicator of responsiveness to standard therapy has been the occurrence of a pathologic complete response (pCR) after NAC. There has been some variation in how pCR has been defined in

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the literature,⁷ but is generally defined as a lack of all signs of invasive carcinoma in tissue removed by surgery after treatment with chemotherapy. Patients who exhibit pCR have improved long-term outcomes² with improved disease-free survival (DFS) compared with those who have residual disease.^{4,8,9} However, most women treated with standard anthracycline- and taxane-based NAC do not experience pCR,^{8,9} and data are scarce regarding clinically identifiable prognostic risk factors in this cohort of patients who have residual disease after NAC. We recently identified risk factors for locoregional recurrence (LRR) in patients with TNBC without pCR after NAC.¹⁰ The present study aimed to identify factors predictive of distant metastasis in patients with TNBC without pCR after NAC.

Methods

Data Source and Study Population

An Institutional Review Board–approved database was used as the source for this analysis. All consecutive patients with TNBC treated between 2000 and 2013 with NAC, surgery, and adjuvant radiation therapy (RT) were identified. TNBC was defined by <1% ER and PR expression and lack of *HER2* expression or gene amplification. Patients with distant metastatic disease at diagnosis or whose disease progressed during NAC were excluded, and no patients with metaplastic breast cancers were included. TNBC was not routinely further subtyped. Patients who did not receive NAC or who experienced disease progression during the course of treatment were also excluded. For the 23 patients (15%) treated during the 2000 to 2003 period, the specialized breast pathologists at Washington University began testing for *HER2* during this time, before approval of adjuvant trastuzumab. Patients who were not classified as having TNBC by virtue of *HER2* testing at the time of diagnosis were also excluded.

Patient-, tumor-, and treatment-specific factors were analyzed, including age, race, menopausal status, tumor and node stage, histology, tumor grade, and type of NAC used. Before treatment, all patients were staged clinically with physical examination and diagnostic breast imaging, including mammography and ultrasound. MRI was performed at the discretion of the breast surgeon. PET was not routinely used to clinically stage patients. After NAC, all patients were staged surgically. All surgery was performed at a single institution by specialized breast surgeons, and all specimens were centrally examined at a single institution by a small group of specialized breast pathologists. Standardized protocol for finding the surgical clip was that the clip was grossly searched for by the prosector, and if initial gross examination did not reveal the clip, the specimen was radiographically scanned to locate the clip and examine the tissue accordingly.

The tumor bed was extensively sampled, and in cases with “no residual tumor,” the entire tumor bed area was examined before this diagnosis was made. Pathologic downstaging was defined as a decrease in pathologic T and/or N stage after surgery compared with clinical stage before NAC. pCR was defined as no evidence of invasive disease in the breast or regional lymph nodes (LNs) after NAC, based on hematoxylin-eosin staining routinely. Keratin staining was used occasionally if needed (13.7% of cases). Residual cancer burden scoring was not routinely performed. Multifocal disease was defined as more than one focus of tumor in the same breast at the time of surgery, independent of quadrant or distance. The presence or absence of lymphovascular space invasion (LVSI), extranodal extension, or pathologically positive LNs was determined by a pathologist at the time of surgery. Distant failure was diagnosed clinically, radiographically, and/or pathologically.

Statistical Analysis

Time intervals were calculated from diagnosis until death or last follow-up. Patients were censored at the date of last clinical contact. OS and freedom from distant metastasis (FFDM) were estimated using the Kaplan-Meier method. The rates of FFDM for patients who experienced pCR and those who did not were compared using log-rank statistics. Univariate and multivariable analyses were performed using the Cox proportional hazards model to evaluate factors associated with distant failure in patients without pCR (ie, those with residual disease) after NAC. To confirm appropriate selection of predictive variables entered into multivariable analysis, a backward logistic regression method (with selection criterion $P < .10$) was applied to obtain the final multivariate model. Significance was considered at $P < .05$, and all significance levels were 2-sided. SPSS Statistics, version 25 (IBM Corp) was applied for all statistical analyses.

Results

Patients and Treatment Characteristics

A total of 153 patients with a median follow-up of 4.04 years (range, 0.51–13.97 years) were included in the study cohort. Patient characteristics and treatment strategies are summarized in Table 1. Clinical stage T3 or T4 disease was found in 49% of patients at diagnosis. Only 25% of patients were clinically LN-negative at diagnosis, with the remaining 75% being LN-positive. The most common NAC regimen was AC-T (doxorubicin/cyclophosphamide followed by paclitaxel) ($n = 62$; 40.5%). Among all patients, 52.3% had a mastectomy and 47.7% underwent partial mastectomy. All patients received adjuvant RT, with most patients ($n = 124$; 81%) receiving comprehensive RT to any residual breast tissue, the underlying chest wall, axilla,

Table 1. Patient- and Treatment-Related Characteristics

Characteristic	n (%)
Total, N	153
Age at diagnosis	
<50 y	78 (51)
≥50 y	75 (49)
Race	
White	86 (56.2)
Black or other	67 (43.8)
Menopausal status	
Premenopausal	78 (51)
Postmenopausal	75 (49)
Clinical T stage	
T1	12 (7.8)
T2	66 (43.1)
T3	44 (28.8)
T4	31 (20.3)
Clinical N stage	
N0	38 (24.8)
N1	82 (53.6)
N2–3	33 (21.6)
Multifocal disease	
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	
N0–1	125 (81.7)
N2–3	28 (18.3)
Lymphovascular space invasion	
Absent	119 (77.8)
Present	34 (22.2)

(continued)

Table 1. Patient- and Treatment-Related Characteristics (cont.)

Characteristic	n (%)
Margins	
Negative	143 (93.5)
Positive	10 (6.5)
LN assessment	
SLNB	35 (22.9)
ALND	118 (77.1)
Pathologic LN status	
Negative	91 (63.4)
Positive	62 (40.5)
Extranodal extension	
Absent	42 (66.6)
Present	21 (33.3)
Downstaging after NAC	
No	52 (34.0)
Yes	101 (66.0)
Surgery type	
Partial mastectomy	73 (47.7)
Mastectomy	80 (52.3)
NAC type	
AC-T	62 (40.5)
FEC-T	27 (17.6)
ET	32 (20.9)
Platinum-based	10 (6.5)
TC	1 (0.7)
Other	21 (13.7)
Adjuvant chemotherapy	
No	107 (69.9)
Yes	46 (30.1)
Adjuvant chemotherapy type	
ET	22 (47.8)
Platinum-based	9 (19.6)
AC-T	4 (8.7)
Other	11 (23.9)
RT boost	
No	52 (34.0)
Yes	101 (66.0)
RT volume	
RNI	124 (81.0)
Whole breast	29 (19.0)
Treatment era	
2000–2008	101 (66.0)
2009–2013	52 (34.0)

Abbreviations: AC-T, doxorubicin/cyclophosphamide/paclitaxel; ALND, axillary lymph node dissection; ET, epirubicin/paclitaxel; FEC-T, fluorouracil/epirubicin/cyclophosphamide/paclitaxel; LN, lymph node; NAC, neoadjuvant chemotherapy; RNI, regional nodal irradiation; RT, radiation therapy; SLNB, sentinel lymph node biopsy; TC, docetaxel/cyclophosphamide.

and supraclavicular and internal mammary LNs. The remaining patients received whole-breast RT alone ($n=29$; 19.0%); partial breast RT was not used. The median RT dose was 50.4 Gy (range, 46–60 Gy). A boost was used in 66.0% of patients, with a median dose of 10 Gy (range, 4–20 Gy). Of patients receiving a boost, 64% were treated with whole-breast irradiation, and the remaining 36% received a boost as part of post-mastectomy RT. Adjuvant chemotherapy was used in 46 patients (30.1%), with ET (epirubicin/docetaxel) being the most common ($n=22$; 47.8%), as part of an institutional protocol evaluating 4 cycles neoadjuvant ET followed by 2 cycles of adjuvant ET.¹¹ Adjuvant carboplatin was used in 2 patients, and adjuvant capecitabine was used in 1 patient. The most common adjuvant regimen used in patients who received neoadjuvant AC-T was platinum-based (5 of 14 patients; 35.7%).

Outcomes

Median OS for the entire cohort was 4.1 years, and the 5-year OS rate was 67%. For all patients, the overall distant recurrence rate was 31.3%, with a 5-year FFDM of 67%. After NAC, 45 patients (29.4%) in our cohort experienced pCR, whereas 108 (70.6%) had residual disease. A larger percentage were at least pathologically downstaged after NAC ($n=101$; 66%). The 5-year OS rates were 98% versus 54% in patients with and without pCR, respectively ($P<.001$) (Figure 1A). Distant metastasis occurred in only 1 patient with pCR and 47 patients without pCR. The 5-year FFDM rates were 98% versus 55% in patients with pCR and without pCR, respectively ($P<.001$) (Figure 1B). Among all patients with documented

distant metastasis, median time to distant metastasis was 1.25 years (range, 0.34–8.54 years), and only 5 of 48 patients (10.4%) had positive margins. Among the 45 patients who experienced pCR, none had an LRR. Among the 108 patients with residual disease after NAC, 21 developed LRR, including 5 in-breast recurrences, 11 nodal recurrences, and 11 chest wall recurrences. Of the nodal recurrences, 8 failed in the axilla, 3 failed in both the axilla and other nodal regions, and no patients had isolated failures in the internal mammary nodes.

Univariate and Multivariable Analyses

In univariate analysis, factors associated with distant metastasis in the cohort of patients with residual disease after NAC ($n=108$) included increasing clinical T stage, increasing clinical N stage, positive pathologic LN status, multifocality, LVSI, extranodal extension, and failure of downstaging after NAC. On multivariable analysis, only positive pathologic LNs (hazard ratio, 3.08; 95% CI, 1.54–6.14; $P=.001$) and LVSI (hazard ratio, 1.91; 95% CI, 1.07–3.43; $P=.030$) remained significant independent predictors of distant metastasis (Table 2). Figure 2 presents FFDM for patients not experiencing pCR with and without positive pathologic LNs and LVSI. Furthermore, patients with multiple factors had worse FFDM, with a 5-year FFDM of 76.5% in patients with 0 of these 2 factors ($n=38$) versus FFDM rates of 54.9% and 27.5% for patients with 1 ($n=44$) and 2 factors ($n=26$), respectively ($P<.001$) (Figure 3).

Discussion

This study identified risk factors predicting distant metastatic disease in patients who do not experience

Figure 1. (A) OS and (B) FFDM by pCR ($P<.001$ for both).

Abbreviations: FFDM, freedom from distant metastasis; OS, overall survival; pCR, pathologic complete response.

Table 2. Univariate and Multivariable Analyses of FFDM in Patients Not Achieving Pathologic Complete Response

Characteristic	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age, y				
<50	Ref		Ref	
≥50	1.69 (0.95–3.02)	.07	NS	
Race				
White	Ref		Ref	
Black or other	1.13 (0.64–1.99)	.67	NS	
Menopausal status				
Postmenopausal	Ref		Ref	
Premenopausal	0.70 (0.40–1.24)	.22	NS	
Clinical T stage				
T1–2	Ref		Ref	
T3–4	2.49 (1.36–4.54)	.003	NS	
Clinical N stage				
N0–1	Ref		Ref	
N2–3	2.06 (1.13–3.76)	.02	NS	
Multifocal disease				
No	Ref		Ref	
Yes	2.85 (1.48–5.51)	.002	NS	
Histology				
Ductal	Ref		Ref	
Other	1.51 (0.71–3.23)	.29	NS	
Grade				
I or II	Ref		Ref	
III	0.61 (0.31–1.20)	.15	NS	
Pathologic T stage				
T0–2	Ref		Ref	
T3–4	3.36 (1.81–6.22)	<.001	NS	
Margins				
Negative	Ref		Ref	
Positive	1.63 (0.65–4.12)	.30	NS	
LN assessment				
SLNB	Ref		Ref	
ALND	2.28 (0.97–5.36)	.06	NS	
Pathologic LN status				
Negative	Ref		Ref	
Positive	6.39 (3.32–12.33)	<.001	3.08 (1.54–6.14)	.001
LVI				
Absent	Ref		Ref	
Present	4.03 (2.28–7.12)	<.001	1.91 (1.07–3.43)	.030
Extranodal extension				
Absent	Ref		Ref	
Present	5.37 (2.97–9.70)	<.001	NS	

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Table 2. Univariate and Multivariable Analyses of FFDM in Patients Not Achieving Pathologic Complete Response (cont.)

Characteristic	Univariate Analysis		Multivariable Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Downstaging after NAC				
No	Ref		Ref	
Yes	0.29 (0.16–0.51)	<.001	NS	
Surgery type				
Partial mastectomy	Ref		Ref	
Mastectomy	1.59 (0.89–2.83)	.12	NS	
NAC type				
AC-T	Ref		Ref	
FEC-T	1.69 (0.77–3.70)	.19	NS	
ET	1.20 (0.56–2.57)	.64	NS	
Other	1.22 (0.56–2.66)	.62	NS	
Adjuvant chemotherapy				
No	Ref		Ref	
Yes	0.82 (0.44–1.52)	.52	NS	
Adjuvant chemotherapy type				
Other	Ref		Ref	
Anthracycline-based	0.69 (0.32–1.49)	.33	NS	
RT boost				
No	Ref		Ref	
Yes	1.12 (0.61–2.06)	.72	NS	
Treatment era				
2000–2008	Ref		Ref	
2009–2013	0.70 (0.35–1.38)	.30	NS	

Abbreviations: AC-T, doxorubicin/cyclophosphamide/paclitaxel; ALND, axillary lymph node dissection; ET, epirubicin/paclitaxel; FEC-T, fluorouracil/epirubicin/cyclophosphamide/paclitaxel; FFDM, freedom from distant metastasis; HR, hazard ratio; LN, lymph node; LVSI, lymphovascular space invasion; NAC, neoadjuvant chemotherapy; NS, not significant; RT, radiation therapy; SLNB, sentinel lymph node biopsy.

pCR: pathologic nodal positivity, increasing nodal stage, multifocal disease, and LVSI. Importantly, there was an additive detriment to exhibiting multiple factors, with a 5-year FFDM rate of 76% with 0 factors compared with 0% with all 4 factors. With the aim of identifying appropriate candidates for treatment intensification, our study provides practical foundational work for further risk stratification in patients with TNBC treated with trimodality therapy. Given that these factors are readily available in surgical pathology reports and that they are predictive in patients without pCR, which represents most TNBC cases after NAC, it is our belief that these findings are clinically relevant and applicable in the care of patients with TNBC.

In our cohort, the overall distant recurrence rate was 31.3%, translating to a 5-year FFDM of 67% for all patients. This is consistent with rates reported in the literature, in which approximately one-third of patients with TNBC experienced a distant recurrence, significantly worse

than in non-TNBCs, with distant metastasis rates of approximately 20%.³ Similarly, Haffty et al¹² showed a comparable distant metastasis rate of 29% at 5 years in their analysis of 117 patients with TNBC compared with 12% among patients without TNBC. In addition, the pCR rate after NAC in our cohort was 29.4%, which is also consistent with data in the TNBC literature that typically range from 30% to 40%.⁸

Despite the known heterogeneity underlying TNBC, rates of distant metastasis reported in the literature are relatively consistent. In contrast, the rate of isolated LRR in TNBC has varied in the literature from 4.6% to 22%.^{12,13} Taken together, this supports the notion that there may be a regularly occurring and potentially definable subset of TNBC with resistance to standard chemotherapies. This subset may be responsible for lack of pCR and, ultimately, the consistently observed frequency of distant relapse across populations and treatment modalities.

Figure 2. FFDM by (A) pathologic LN status ($P<.001$) and (B) LVSI ($P=.002$) in patients without pathologic complete response after neoadjuvant chemotherapy.

Abbreviations: FFDM, freedom from distant metastasis; LN, lymph node; LVSI, lymphovascular space invasion.

It has been reported that the risk of distant recurrence in patients with TNBC is highest within the first 3 to 5 years after diagnosis and treatment, as opposed to in those without TNBC, who show more consistent distant relapse rates over time.^{1,3} These findings are corroborated by our results, which showed a median time to distant metastasis of 1.25 years, with 94% of the distant recurrences

occurring by 5 years, further supporting the idea that although biologically aggressive as a group, many TNBCs are potentially curable. Our multivariable analysis revealed that positive LNs and increasing pathologic N stage (defined as pN2–3 disease) were both associated with distant metastasis. This result is consistent with other analyses showing that nodal positivity and increasing pathologic N stage are associated with worse OS and FFDM.^{14–17} This may be explained by the hypothesis that patients with early LN involvement may already have radiographically occult distant metastasis, which is a subsequent driver of mortality in TNBC.¹⁸

LVSI is more commonly observed in patients with TNBC than in those without TNBC.¹⁹ Ahn et al²⁰ also found LVSI to be a poor prognostic factor for both DFS and OS in both univariate and multivariate analyses. However, not all studies have shown LVSI to influence survival. Urru et al²¹ found that LVSI was not significantly associated with survival in multivariate analysis. Regardless of the implications for survival, several groups have shown that the presence of LVSI predicts the development of distant metastatic disease.^{21–23} Therefore, our results showing LVSI to be independently predictive of distant metastasis in patients without pCR are in accordance with the literature.

Multifocality is defined as ≥ 2 tumors in the same quadrant of the breast. Complex literature has been published on this topic, although to date multifocality has been primarily examined indiscriminately in the

Figure 3. FFDM in patients without pathologic complete response, stratified by number of factors significant in multivariable analysis, including pathologic node positivity and lymphovascular space invasion ($P<.001$).

Abbreviation: FFDM, freedom from distant metastasis.

context of all breast cancers, with most studies not reporting subgroup data for patients with TNBC. Some groups have reported a greater probability of nodal metastases and relapse and worse survival in multifocal tumors, but these associations have been inconsistent, with other groups showing that multifocality is not an independent predictor of prognosis in multivariate analysis.^{24–26} Although significant in univariate analysis, multifocality did not remain independently predictive of distant metastasis in our study. Of particular interest to the study of TNBC, between 4.4% and 15.9% of foci have been noted to be discordant in their receptor expression.²⁷ A recent meta-analysis showed that multifocality is associated with significantly worse OS and strong trends toward worse DFS compared with unifocal tumors.²⁸ Furthermore, adverse outcomes have been observed in patients with multifocal tumors specifically after NAC.^{25,29} Despite this, the true impact of multifocality is still somewhat controversial because of the heterogeneity of studies and the presence of other confounding factors, including the observations that multifocal tumors are more likely to receive aggressive therapy and that multicentric tumors are often included in the group of multifocal tumors in some studies. It is our institutional practice to define multifocal tumors as those with >1 focus in the same breast, regardless of whether they are in the same quadrant or of the distance between foci. Multicentric tumors are defined, both traditionally and at our institution, as those with multiple foci of disease in separate quadrants. This more comprehensive criterion used in our study therefore includes what are traditionally defined as both multifocal and multicentric tumors.

The challenge remains to identify new treatment paradigms for the 60% to 70% of patients who do not experience pCR after NAC. Although improvements in adjuvant therapy, such as capecitabine, have improved outcomes in these patients, those with TNBC still have inferior OS and DFS compared with their non-TNBC counterparts.³⁰ Next-generation sequencing and RNA expression analysis have identified targetable alterations in pathways, with agents currently under investigation in as many as 90% of patients with TNBC who do not experience pCR after NAC according to sampling of the residual chemoresistant portion of the tumor.³¹ As the cost of next-generation sequencing technologies continues to decrease, patients not experiencing pCR, and in particular those with high-risk features such as nodal status and LVSI, will be prime candidates for further sequencing studies and use of more targeted systemic therapies.³² Intuitively, targeting of the pathways in the residual tumor persistent after NAC may also treat micrometastatic disease ultimately

responsible for distant metastasis, because these pathways would be derived from this pool of persistent chemoresistant tumor cells.³¹

Further challenges also remain because of the issue of clonal evolution among these tumors. Genomic analyses have revealed that many TNBCs show substantial clonality and intratumoral heterogeneity, consistent with their association with homologous recombination (HR) deficiency and intrinsic genomic instability. On average, there are approximately 60 somatic coding mutations per tumor, with some harboring as many as 160 per tumor.⁵ This has important clinical implications for the development of resistance to therapies and lack of response to targeted therapies. For example, if there is an initiating mutation in the HR pathway, this would confer sensitivity to standard DNA-damaging therapy, as described earlier; however, there could be development of a mutation in a subclone that reverses HR deficiency and reverses the sensitivity to DNA-damaging agents, which could then survive treatment and cause relapse. As an example, preclinical data show that loss of *PTEN* can reverse HR deficiency in *BRCA1*-deficient cells and reverse the added sensitivity to DNA-damaging agents. This is relevant because loss of *PTEN* is recurrently mutated in up to 9.6% of TNBCs, and mutations of *BRCA1* and *PTEN* are frequent.³³ This highlights the need to develop effective strategies for assessing intratumoral heterogeneity and clonal evolution in this particularly genetically unstable group of tumors.

Our study had several limitations. We included patients with TNBC who were diagnosed based on standard biomarker analysis of ER, PR, and *HER2* via immunohistochemistry. Gene expression profiling has resulted in the classification of breast cancer into 5 intrinsic subtypes, of which basal-like breast cancer most closely overlaps with TNBC. Approximately 80% of TNBCs as identified by immunohistochemistry are basal-like breast cancers by gene expression profiling; however, these categories are not synonymous, and gene expression profiling remains the gold standard for identification of this clinical entity.^{1,30} Thus, differences in intrinsic TNBC subtypes may affect these observed differences. As a retrospective study, our analysis was also limited by selection bias. The study cohort was derived from a single institution with a tertiary referral pattern, and our patient population may not accurately represent the patterns of care at other institutions. The adjustment variables used in our multivariable analysis may have been incomplete, and some variables for which data were not collected include LN positivity ratio, Ki67, tumor-infiltrating lymphocytes, p53 status, and necrosis, the absence of which could affect our results.

Conclusions

Our study highlights the established poor prognosis of patients with TNBC who do not experience pCR after NAC. Furthermore, our findings show that among this cohort of women, there is still significant heterogeneity in outcomes. We have identified positive LNs and LVSI as significant risk factors predicting distant metastatic disease among patients without pCR. These data can be used to stratify patients in relation to their prognoses and potentially inform treatment decisions among these high-risk patients. Prospectively designed trials are warranted to investigate novel therapeutic approaches

aimed at improving the high rates of distant failure and relatively poor survival in this high-risk cohort.

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