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Low Rates of Local-Regional Recurrence Among Inflammatory Breast Cancer Patients After Contemporary Trimodal Therapy

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ABSTRACT

Background. Inflammatory breast cancer (IBC) represents a rare (2–3 %) but aggressive subset of breast cancer with a historically reported 5-year overall survival rate of 50 % and a 3-year local-regional recurrence (LRR) rate of 20 %. This study aimed to evaluate long-term LRR in a contemporary cohort of non-metastatic IBC patients undergoing trimodal therapy at a single institution and identify factors associated with local and distant failure.

Methods. The study identified 262 patients with non-metastatic IBC who received trimodal therapy (neoadjuvant chemotherapy, modified radical mastectomy, adjuvant radiation) from an institutional prospective database (2007–2019). Long-term outcomes of local-regional and distant metastasis were reported. Survival outcomes were analyzed using the Cox proportional hazards regression model.

Results. The median age at diagnosis was 52 years, and the median follow-up period was 5.1 years. In this cohort, 82 (31.3 %) patients achieved a pathologic complete response (pCR) in the breast and axilla. Local-regional recurrence was observed in 18 (6.9 %) patients (11 isolated to the chest wall, 4 isolated to regional nodes, and 3 involving chest wall and ipsilateral axillary nodes). Distant metastasis was observed in 92 (35.1 %) patients. During the follow-up period, 90 deaths occurred. In the multivariate analysis, pCR was associated with improved disease-free survival (hazard ratio [HR], 0.26; 95 % confidence interval [CI], 0.13–0.51; $p = 0.001$) and overall survival (HR, 0.31; 95 % CI, 0.15–0.65; $p = 002$).

Conclusions. During a median follow-up period longer than 5 years, the local-regional relapse rate for the IBC patients treated with contemporary trimodal therapy was 6.9%, similar to that for the non-IBC patients. After chemotherapy, surgical resection with modified radical mastectomy to negative margins and postmastectomy radiation therapy resulted in excellent long-term local-regional control.

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Inflammatory breast cancer (IBC) is an aggressive and rare breast malignancy accounting for 2–5 % of cases but responsible for up to 10 % of breast cancer-related deaths in the United States.[1,2] Clinical presentation is characterized by progressive erythema, edema, and skin thickening with peau d'orange changes in at least one third of the breast. Tumor emboli in the dermal lymphatics is a pathognomic histopathologic finding, although not required for diagnosis.[3] Guidelines recommend trimodal therapy to include neoadjuvant systemic therapy followed by modified radical mastectomy, with removal of all initially involved skin to negative margins and radiation therapy to the chest wall with comprehensive regional nodal irradiation to the undissected regional nodal basins.[4]

With modern systemic therapy, contemporary survival rates have improved significantly and currently approach 74% at 5 years for patients treated with anti-human epidermal

growth factor receptor 2 (HER2)-targeted therapy.[5] Given the extensive skin involvement, local-regional control in IBC remains a significant clinical priority. Historical local-regional recurrence (LRR) rates for IBC are reported to be as high as 35.7% without trimodal therapy.[6] In current practice with trimodal therapy, LRR rates remain high versus non-IBC, with varying rates reported in the literature ranging from 21 % at 3 years to 17 % at 5 years.[7,8] Furthermore, improved local control has been associated with improved disease-free and overall survival.[9,10]

Improved survival outcomes with modern therapy highlight attention to survivorship concerns including significant comorbidity related to surgery, most notably lymphedema, which is reported to have an impact on approximately half of IBC patients treated with trimodal therapy.[11] Among non-IBC patients, an evolving clinical landscape exists, with increasing focus on de-escalation of surgery in the breast and axilla, thereby decreasing morbidity without sacrificing oncologic outcomes.

To understand whether strategies to deescalate surgical therapy should be considered in IBC, it is critically important to define the long-term local-regional outcomes in this unique patient population. Previous analysis from our institutional multidisciplinary practice showed a 4-year LRR probability of 5.65 % (95 % confidence interval [CI], 2.76–14.7 %) among 114 non-metastatic IBC patients.[12] This study aimed to update results of long-term LRR in a larger contemporary cohort of non-metastatic IBC patients undergoing trimodal therapy and to identify factors associated with local and distant failure.

METHODS

Patient Selection

Using the prospectively maintained multidisciplinary IBC clinical database at the University of Texas MD Anderson Cancer Center, we identified patients who received trimodal therapy and had surgical resection performed at our institution between 2007 and 2019. The institutional review board approved a retrospective review of this database.

The clinical diagnosis of IBC, made by an experienced IBC multidisciplinary team, was defined as rapid onset of breast erythema or swelling with or without an underlying breast mass on imaging. Invasive disease was confirmed pathologically, and suspicious nodes identified on ultrasound imaging underwent fine-needle aspiration (FNA) or core biopsy according to institutional practice. Clinical, pathologic, treatment, and survival information was collected via medical record review.

Tumor-node-metastasis (TNM) staging was defined by the American Joint Committee on Cancer (AJCC) seventh edition.[1] Trimodal therapy was defined as receipt of neoadjuvant systemic therapy (NAST) including anti-HER2-targeted therapy for patients with HER2-positive disease, modified radical mastectomy (MRM), and adjuvant radiation therapy (RT) to the chest wall and regional nodes. All the patients underwent surgery at our institution including standard axillary dissection, with resection of levels 1 and 2 lymph nodes. When preoperative imaging demonstrated abnormal level 3 axillary nodes or when suspicious level 3 nodes were identified during the operation, a level 3 dissection was included. Pathologic complete response (pCR) was defined as no residual invasive carcinoma in the breast or axillary lymph node specimens (despite the presence of *in situ* carcinoma). Radiographic response to NAST was classified as complete response in the breast/axilla, partial response, and stable or progressive disease.

The majority of the patients received radiation treatment at MD Anderson (92.4 %, $n = 242$). According to institutional practice, the patients received radiation therapy to the chest wall with comprehensive regional nodal irradiation to the undissected regional nodal basins including the supraclavicular, infraclavicular, and internal mammary nodal basins. Radiation therapy was tailored to clinical risk factors. Patients typically received 50 Gy in 25 fractions once daily with a chest wall boost. Accelerated hyperfractionated radiation therapy in BID fractions of 51 Gy in 34 fractions was recommended for high-risk patients (patients < 45 years old; those with positive, close, or unknown margin status; and those who had less than a partial response to neoadjuvant systemic therapy). The treatment planning goal was for the 90% isodose line to cover all nodal target volumes with extended dose coverage as needed.

Statistical Analysis

Demographics, clinicopathologic features, and treatment received were analyzed. Patient characteristics are summarized as number (%) for categorical variables and as median (interquartile range [IQR]) for continuous variables. Recurrence and survival outcomes were evaluated. Local-regional recurrence was defined as histologically confirmed breast cancer recurrence in the ipsilateral chest wall and/or ipsilateral regional lymph nodes including the ipsilateral axilla, internal mammary, and infra- and supraclavicular lymph nodes. Distant metastasis was defined as the presence of radiographically and/or histologically confirmed breast cancer other than at local-regional sites. Local recurrence-free survival was defined as the time from surgery until LRR. Overall survival (OS) was defined as the time from diagnosis to death or last follow-up evaluation, and disease-free survival (DFS) was defined as the time from surgery until LRR, distant metastasis, or death.

Both OS and DFS were estimated using the Kaplan-Meier method, and Kaplan-Meier curves show OS and DFS

stratified by tumor subtype and pCR status. A uni- and multivariate Cox proportional hazards model was performed to identify factors associated with OS and DFS. To account for death as a competing risk, we used competing risk regression models to evaluate factors associated with DFS (local or distant disease), with death considered a competing event and subdistribution HR (sHR) with 95% CI was reported.[13]

All tests were two-sided. A *p* value lower than 0.05 was considered statistically significant. Analyses were conducted using STATA version 17 (StataCorp LP, College Station, TX, USA).

RESULTS

Patient Demographics and Clinicopathologic Features

During the study period, 262 patients were treated. The median age at diagnosis was 52 years (range, 22–81 years), and the median follow-up period was 5.1 years (range, 0.5–15.5 years). The majority of the patients were white and post-menopausal, with a BMI of 30 kg/m^2 or higher. Ductal carcinoma was the most common histologic subtype (88.9 %), and the majority of the patients had grade 3 (75.2 %), hormone receptor (HR)-positive HER2-negative (HR+/HER2–) (40.1 %) tumors. At presentation, nodal involvement with one to three nodes was present on the pretreatment imaging of 77 (29.4 %) patients, and 165 (63.2 %) patients had four or more nodes involved (Table 1)

Surgical Pathology, Treatment Patterns, and Response

The surgical margins were negative in all the patients. One patient had a positive inferior margin and underwent re-excision to negative margins. At the time of surgery, six (2.3 %) patients underwent flap closure with the plastic surgery team due to extensive skin excision. Autologous reconstruction with flap closure was performed in a delayed fashion for 73 (27.9 %) patients and included a deep inferior epigastric artery perforator (DIEP) flap (10.7 %), a transverse rectus abdominis myocutaneous (TRAM) flap (7.3 %), a latissimus dorsi flap (5.7 %), or other type of closure (1.5 %). Wound complication was seen in six patients (4 hematomas requiring operative intervention, 1 abscess requiring antibiotic therapy with drain placement, and 1 latissimus dorsi flap revision) (Table 1).

On post-treatment imaging and clinical evaluation, 40 (15.3 %) patients had a complete response in the breast, 85 (32.4 %) had a complete response in the axilla, and 23 (8.8 %) had a complete response in both the breast and axilla. A partial response was observed in 208 (79.4 %) patients, and 20 (7.6 %) patients had stable disease or progression. Surgical pathology showed that 88 (33.6 %) patients had achieved

TABLE 1 Patient, disease and treatment characteristics of patients with a diagnosis of stage III inflammatory breast cancer

Characteristic	Total ($n=262$) n (%)
Age (years)	
≤40	51 (19.5)
41–50	71 (27.1)
51–60	82 (31.3)
61–70	47 (17.9)
>70	11 (4.2)
Race/ethnicity	
White, non-Hispanic	212 (80.9)
Hispanic	22 (8.4)
Black	19 (7.3)
Native American	2 (0.8)
Other	7 (2.7)
BMI (kg/m^2)	
<18.5	2 (0.8)
18.5–24.9	47 (17.9)
25–29.9	74 (28.2)
≥30	138 (52.7)
Unknown	1 (0.4)
Menopause status	
Pre-menopausal	100 (38.2)
Peri-menopausal	26 (9.9)
Post-menopausal	136 (51.9)
Tumor histology	
Ductal	233 (88.9)
Lobular	6 (2.3)
Other/unknown	23 (8.8)
Tumor Subtype	
HR+/HER2–	105 (40.1)
HR–/HER2–	62 (23.7)
HR–/HER2+	44 (16.8)
HR+/HER2+	51 (19.5)
Histologic grade	
2	60 (22.9)
3	197 (75.2)
Unknown	5 (1.9)
Clinical N stage	
N0	9 (3.4)
N1	112 (42.7)
N2	17 (6.5)
N3	124 (47.3)
Radiologic response to NAST (breast and axilla)	
Complete response	23 (8.8)
Partial response	208 (79.4)
Stable/disease progression	20 (7.6)
Unknown	11 (4.2)
pCR (breast and axilla)	
No	180 (68.7)
Yes	82 (31.3)

Table 1 (continued)

Characteristic	Total (*n* = 262) *n* (%)
Lymphovascular invasion	
No	124 (47.3)
Yes	122 (46.6)
Unknown	16 (6.1)
Reconstruction	
None	190 (72.5)
Immediate	6 (2.3)
DIEP	28 (10.7)
TRAM	19 (7.3)
Latissimus dorsi	15 (5.7)
Other	4 (1.5)

BMI, body mass index; *HR*, hormone receptor; *HER2*, human epidermal growth factor receptor 2; *NAST*, neoadjuvant systemic therapy; *pCR*, pathologic complete response; *DIEP*, deep inferior epigastric artery perforator, *TRAM* transverse rectus abdominis myocutaneous

pCR in the breast, 106 (40.5 %) had achieved pCR in the axilla, and 82 (31.3 %) had achieved pCR in both the breast and axilla. The majority of the patients with breast and axillary pCR (*n* = 82) were HR–/HER2+ (40.2 %, *n* = 33) followed by HR–/HER2– subtype (24.4 %, *n* = 20). Of 85 patients with a complete radiologic response in the axilla, only 45 (52.9 %) had axillary pCR. The median number of nodes removed was 22 (IQR, 4–52), and the median number of positive nodes was 7 (IQR, 1–31). Lymphovascular invasion (LVI) was noted in 122 (46.6 %) patients (Table 1).

Local-Regional Recurrence

Local-regional recurrence was observed in 18 (6.9 %) patients, and the median time to recurrence was 18.3 months (IQR, 9.7–36.4 months). The Kaplan Meier estimated 5-year probability of LRR was 7.6 % (95 % CI, 4.6–12.2 %). Among the patients with LRR, eight (44 %) had HR–/HER2– disease, and 5 (27.8 %) had HR+/HER2– disease. Positive margins were present in one patient who underwent re-excision to negative margins. All the patients with recurrence were found to have residual disease on pathology after MRM. Recurrence was isolated to the chest wall in 11 (64.7 %) patients and to regional nodes in 4 (23.5 %) patients (1 in the ipsilateral axilla, 3 in the ipsilateral supraclavicular basin). Three patients had recurrence in both the chest wall and the ipsilateral axillary nodes. Only two patients who experienced recurrence had wound complications at time of surgery.

Disease-Free Survival

Distant metastasis was observed in 92 (35.1 %) patients, and the median time to distant metastasis was 11 months
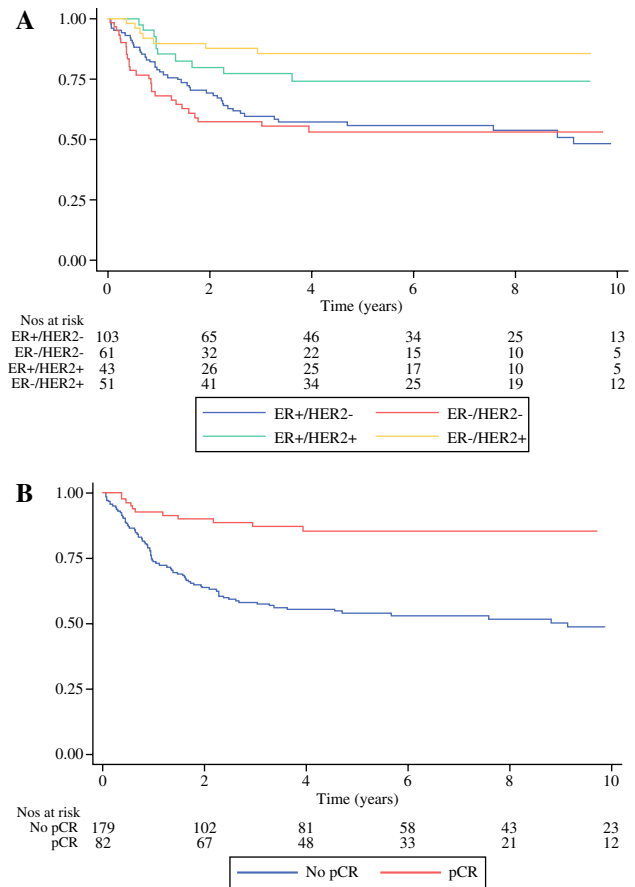

FIG. 1 Kaplan-Meier curves of disease-free survival by **A** tumor subtype and by **B** pathologic complete response among stage III inflammatory breast cancer (IBC) patients. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2

(IQR, 5.4–26.3 months). An event of local recurrence or distant metastasis was observed in 96 (36.6 %) patients, and 80 of these patients had distant metastases alone, whereas 12 patients had both local recurrence and distant metastasis, and 4 patients had local recurrences alone.

The median time to any recurrence was 11.2 months (IQR, 5.5–24.9 months). Of the patients who experienced an event, 77 (80 %) died. Death was a competing risk for 13 patients who died without experiencing recurrence or distant metastasis. The 5-year probability of local recurrence or distant metastasis was 35 % (95 % CI, 29.3–41.5 %), whereas the 5-year probability of local recurrence, distant metastasis, or death was 39.8 % (95 % CI, 33.9–46.2 %).

Kaplan-Meier analysis of DFS demonstrated significantly better survival among the patients with HR–/HER2+ disease than among those with other tumor subtypes (*p* = 0.0001; Fig. 1A). The patients who achieved pCR in the breast and axilla also had better survival than those who did not (*p* = 0.0001; Fig. 1B).

The univariate Cox proportional hazard model for DFS demonstrated that lobular histology, tumor subtype, radiologic response to NAST, LVI, and pCR are predictors of DFS. In the multivariate analysis, DFS was better for the patients who achieved pCR than for those who did not (HR, 0.26; 95 % CI, 0.13–0.51; $p = 0.001$). Worse DFS was noted for the patients with perimenopausal status (HR, 2.39; 95 % CI, 1.09–5.22; $p = 0.029$), HR–/HER– tumor subtype (HR, 1.76; 95 % CI, 1.01–3.09; $p = 0.048$), clinical N3 status (HR, 2.19; 95 % CI, 1.34–3.57; $p = 0.002$), or LVI (HR, 1.61; 95 % CI, 1.07–2.57; $p = 0.048$) (Table 2). The univariate competing risk analysis demonstrated that age BMI, histology, clinical stage, imaging response, LVI, and pCR were predictors of survival. In the multivariable analysis, pCR was the strongest predictor of DFS (eTable1).

Overall Survival

During the follow-up period, 90 (34.4 %) deaths were observed, and the 5-year overall survival was 70.4 % (95 % CI, 64.1–75.7 %). Kaplan-Meier analysis demonstrated significantly better survival among the patients with HR–/HER2+ disease than among the patients who had other tumor disease subtypes ($p = 0.0001$; Fig. 2A). The patients who achieved pCR in the breast and axilla also had better survival than those who did not ($p = 0.0001$; Fig. 2B).

In a univariate Cox proportional hazard model, age, histology, tumor subtype, clinical stage, radiologic response, LVI, and pCR were significantly associated with survival (Table 3) In a multivariable analysis, the patients with perimenopausal status had worse survival than those with premenopausal status (HR, 2.61; 95 % CI, 1.11–6.16; $p = 0.028$), and similarly, the patients with clinical N3 disease had worse survival than those with N1 disease (HR, 2.42; 95 % CI, 1.41–4.15; $p = 0.001$). The patients with HR+HER2+ disease had better survival than those who had HR+HER2– disease (HR, 0.18; 95 % CI, 0.05–0.63; $p = 0.007$), and the patients with pCR had better survival than those without pCR. (HR, 0.31; 95 % CI, 0.15–0.65; $p = 0.02$; Table 3).

DISCUSSION

We previously demonstrated a LRR rate of 3.5 % after a median follow-up period of 3.6 years among IBC patients who received trimodal therapy. In this study, we demonstrated persistently low rates of LRR after a longer follow-up period for a larger cohort of patients who received contemporary trimodal therapy, including aggressive surgical management to negative margins combined with comprehensive adjuvant radiation. The patients with LRR were more likely to have HR–/HER2– disease, and no patient who had

recurrence achieved pCR. In this study, pCR was significantly associated with improved DFS and OS.

Inflammatory breast cancer patients have historically experienced worse outcomes than non-IBC patients, and trimodal therapy with surgical management to negative margins has been a cornerstone of therapy. We examined long-term LRR rates for IBC patients and found that the 5-year LRR rate was low (6.9 %). Historical LRR rates for IBC were as high as 67 % among the patients with a minimal response to neoadjuvant chemotherapy.[14]

Similar to non-IBC, LRR risk varies by subtype, and patients with HER2+ disease have the lowest recurrence risk and longest survival.[7,15,16] We found that 44 % of the patients who experienced recurrence had HR–/HER2– tumor subtype. The low LRR rates observed in our study reflect more contemporary systemic therapy regimens, including targeted therapies for HER2+ disease, and importantly, aggressive local-regional treatment with surgery and radiation in a multidisciplinary setting. Importantly, negative surgical margins were achieved in all but one patient who underwent re-excision to negative margins. As such, the LRR observed in this study was lower than in other contemporary reports.[7,8] Local-regional recurrence in IBC is associated with a poor prognosis, and treatment is challenging, with often limited response.

Furthermore, underutilization of guideline-concordant care is associated with suboptimal oncologic outcomes, as demonstrated in several retrospective studies.[17,18] Liu et al.[17] analyzed data from the National Cancer Database (NCDB) from 2010 to 2011 and reported that only 77 % of IBC patients received neoadjuvant chemotherapy and surgical therapy, and that not all received recommended radiation therapy.

The pCR rate in the breast and axilla after standard NAST was 31.3 %, similar to that in prior studies,[8,16] including a pCR rate of 35 % observed in an institutional database of 57 non-metastatic IBC patients.[16] Furthermore, pCR varied with biologic subtype, with the highest rates observed in HR–/HER2+ (40.2 %) followed by HR–/HER2– subtype (24.4 %). In an analysis of more than 4000 non-metastatic IBC patients in the NCDB with a diagnosis between 2010 and 2015, 38.8 % of the patients with HER2+ disease achieved pCR, whereas 19.1 % of the HR+/HER– patients achieved pCR.[5] Inability to achieve pCR strongly predicted OS, with 5-year OS approaching 82 % among those who achieved pCR.

Another trial conducted at Memorial Sloan Kettering Cancer Center evaluated 117 IBC patients, and the patients who achieved pCR had an LRR of 0 %, in contrast to 15 % of the patients who did not achieve pCR.[7] In the NOAH trial evaluating trastuzumab therapy in HER2+ breast cancer that included IBC patients, a pCR rate of 38 % was reported for those randomized to treatment with trastuzumab/

TABLE 2 Cox proportional hazards model (uni- and multivariable) of factors associated with disease-free survival of stage III inflammatory breast cancer patients

Variable	Univariate				Multivariate			
	Hazard ratio 95 % CI				Hazard ratio 95 % CI			
	HR	Upper	Lower	p Value	HR	Upper	Lower	p Value
Age (years)								
<40	1 (Ref)				1 (Ref)			
41–50	1.04	0.60	1.80	0.901	0.60	0.29	1.26	0.179
51–60	0.89	0.51	1.56	0.685	0.52	0.22	1.23	0.137
61–70	1.33	0.73	2.41	0.355	1.33	0.51	3.43	0.561
>70	1.30	0.49	3.44	0.602	0.64	0.16	2.50	0.519
Race/ethnicity								
White, non-Hispanic	1 (Ref)				1 (Ref)			
Other	0.81	0.49	1.34	0.403	0.99	0.53	1.86	0.978
BMI (kg/m^2)								
18.5–24.9	1 (Ref)				1 (Ref)			
25–29.9	1.46	0.91	2.32	0.114	1.02	0.57	1.81	0.953
>30	0.78	0.48	1.24	0.289	0.64	0.38	1.08	0.094
Unknown	3.96	0.54	28.82	0.174	3.75	0.43	33.04	0.233
Menopause status								
Pre-menopausal	1 (Ref)				1 (Ref)			
Peri-menopausal	1.61	0.86	3.01	0.133	2.39	1.09	5.22	**0.029**
Post-menopausal	0.96	0.64	1.43	0.823	1.17	0.59	2.33	0.646
Tumor histology								
Ductal	1 (Ref)				1 (Ref)			
Lobular	3.27	1.20	8.91	**0.021**	2.36	0.63	8.83	0.204
Other/unknown	1.38	0.76	2.52	0.294	1.88	0.93	3.80	0.077
Tumor subtype								
HR+/HER2–	1 (Ref)				1 (Ref)			
HR–/HER2–	1.18	0.77	1.83	0.446	1.76	1.01	3.09	**0.048**
HR–/HER2+	0.51	0.28	0.93	**0.029**	0.72	0.36	1.43	0.343
HR+/HER2+	0.30	0.15	0.59	**0.000**	0.61	0.28	1.32	0.210
Histologic grade								
2	1 (Ref)				1 (Ref)			
3	1.05	0.67	1.66	0.829	0.86	0.50	1.47	0.579
Clinical N stage								
N0	1.96	0.83	4.63	0.125	1.58	0.58	4.31	0.368
N1	1 (Ref)				1 (Ref)			
N2	0.65	0.23	1.81	0.409	1.17	0.38	3.59	0.788
N3	1.44	0.96	2.15	0.076	2.19	1.34	3.57	**0.002**
Radiologic response to NAST (breast and axilla)								
Complete response	0.26	0.08	0.83	**0.023**	0.44	0.13	1.47	0.184
Partial response	1 (Ref)				1 (Ref)			
Stable/disease progression	1.84	1.05	3.24	**0.034**	1.76	0.89	3.48	0.107
Unknown	0.53	0.17	1.69	0.285	0.73	0.22	2.48	0.617
Lymphovascular invasion								
No	1 (Ref)				1 (Ref)			
Yes	1.86	1.25	2.77	**0.002**	1.61	1.01	2.57	**0.048**
Unknown	1.52	0.64	3.59	0.344	1.89	0.63	5.67	0.258
pCR (breast and axilla)								
No	1 (Ref)				1 (Ref)			
Yes	0.22	0.12	0.41	**0.0001**	0.26	0.13	0.51	**0.0001**

Significant p values given in bold ($p < 0.05$)

CI, confidence interval; BMI, body mass index; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; pCR, pathologic complete response
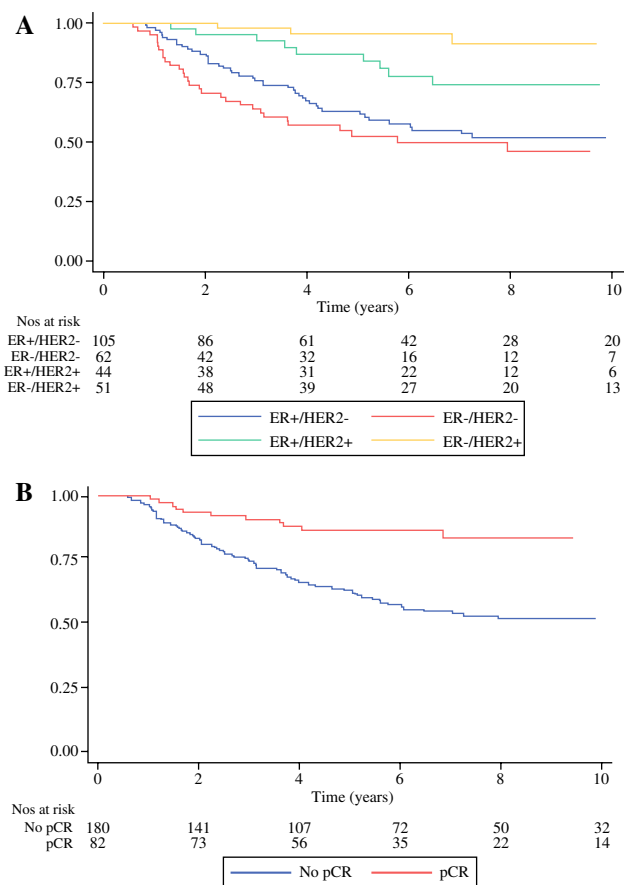
FIG. 2 Kaplan-Meier curves of overall survival by **A** tumor subtype and by **B** pathologic complete response among stage III inflammatory breast cancer (IBC) patients. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2

chemotherapy compared with 19 % for the patients who received chemotherapy alone. Receipt of trastuzumab was associated with better OS for HER2+ IBC patients than chemotherapy alone.[19]

Although guideline-concordant surgical management includes total mastectomy to negative margins and levels 1 and 2 axillary lymph node dissection, there is considerable interest in deescalating surgery in the breast and axilla. In non-IBC patients, exceptional response to NAST may facilitate breast-conservation surgery (BCS), but data are sparse regarding the oncologic safety of breast conservation in IBC. In addition, available studies are small and retrospective in nature, and the certainty of IBC diagnosis is unclear.[20–23] A Surveillance, Epidemiology, and End Results (SEER) study evaluating outcomes of 3374 women with non-metastatic IBC (2001–2013) demonstrated no difference in breast cancer-specific survival or OS for patients receiving BCS.[20] However, selection bias was inevitable in the absence of statistical analyses that sufficiently adjusted for imbalances in baseline characteristics among different surgical groups.

Furthermore, the patients who received BCS alone constituted only 4.4 % of the study population, which would have made it challenging to make any valid comparisons between these groups.

A review by Brzezinska et al.[21] reported unusually high 5-year OS (70.3 %) and local regional recurrence-free survival (87.5 %) before the use of targeted therapies (1999–2013), suggesting that these patients were unlikely to have an IBC diagnosis. In addition, all 35 patients presented with a localized mass, which is not a consistent presentation in IBC. In line with other reports, this study found that completion axillary surgery showed axillary pCR in 40.5 % of the patients, and notably, the cohort had a high nodal burden of disease at presentation.[23,24]

The excellent response to NAST has engendered discussions of less extensive axillary surgery for IBC patients, similar to what has been accomplished in cN0 and cN1 non-IBC, wherein prospective trials have established the feasibility of sentinel lymph node biopsy for patients who achieve axillary pCR.[25,26] Patients with IBC were not included in these studies, prohibiting extrapolation of these data.

In IBC, DeSnyder et al.[27] demonstrated an identification rate of only 25 % among 16 patients who underwent dual-tracer sentinel lymph node mapping. Other studies also have shown unacceptably high false-negative rates. Thus additional studies are necessary to reliably identify select patients who may potentially benefit from de-escalating axillary surgery. Increasing pCR rates with more novel therapies such as seen with immunotherapy in Keynote 522 may present some more opportunities within the context of a clinical trial.[28] However, IBC has been traditionally excluded from clinical trials that examine novel systemic therapies, and caution should be exercised when these results are extrapolated to the IBC population.

This study had several limitations. It was retrospective in nature with a limited sample size. However, this is not unusual given that IBC is a rare disease. In addition, patients were treated before the approval of pembrolizumab for triple-negative breast cancer, which may improve pCR rates in this population. Additionally, the clinical landscape continues to expand with therapeutic opportunities to improve outcomes for patients treated with neoadjuvant chemotherapy and found to have residual disease at surgery. It is possible that with improved adjuvant systemic therapies, clinical outcomes, including local-regional outcomes, will continue to improve.

We demonstrated persistently low LRR rates with adherence to guideline-concordant trimodal care for patients with IBC when surgical resection involving total mastectomy to negative margins (with extensive skin resection if required) including levels 1 and 2 axillary lymph node dissection is performed. Although low LRR rates are promising, they are predicated on aggressive local-regional therapy with

TABLE 3 Cox proportional hazards model (uni- and multivariable) of factors associated with overall survival of stage III inflammatory breast cancer patients

Variable	Univariate				Multivariate			
	Hazard ratio 95 % CI				Hazard ratio 95 % CI			
	HR	Upper	Lower	p Value	HR	Upper	Lower	p Value
Age (years)								
<40	1 (Ref)				1 (Ref)			
41–50	1.48	0.76	2.88	0.251	0.86	0.37	2.01	0.728
51–60	1.27	0.65	2.47	0.483	0.66	0.25	1.76	0.411
61–70	2.07	1.03	4.17	**0.041**	1.84	0.65	5.25	0.254
>70	2.34	0.83	6.56	0.107	1.35	0.31	5.83	0.684
Race/ethnicity								
White, non-Hispanic	1 (Ref)				1 (Ref)			
Other	0.82	0.47	1.42	0.473	1.10	0.55	2.19	0.786
BMI (kg/m^2)								
18.5–24.9	1 (Ref)				1 (Ref)			
25–29.9	1.09	0.63	1.87	0.763	0.66	0.34	1.31	0.239
>30	0.82	0.50	1.36	0.449	0.76	0.42	1.35	0.345
Unknown	4.33	0.59	31.62	0.149	4.87	0.52	45.23	0.164
Menopause status								
Pre-menopausal	1 (Ref)				1 (Ref)			
Peri-menopausal	1.92	0.94	3.92	0.073	2.61	1.11	6.16	**0.028**
Post-menopausal	1.22	0.78	1.92	0.377	1.36	0.65	2.85	0.411
Tumor histology								
Ductal	1 (Ref)				1 (Ref)			
Lobular	3.42	1.38	8.47	**0.008**	2.43	0.69	8.59	0.172
Other/unknown	1.44	0.74	2.79	0.281	1.64	0.75	8.63	0.215
Tumor subtype								
HR+/HER2−	1 (Ref)				1 (Ref)			
HR−/HER2−	1.24	0.79	1.96	0.348	1.50	0.83	2.72	0.180
HR−/HER2+	0.40	0.19	0.81	**0.011**	0.49	0.22	1.09	0.079
HR+/HER2+	0.11	0.03	0.34	**0.0001**	0.18	0.05	0.63	**0.007**
Histologic grade								
2	1 (Ref)				1 (Ref)			
3	0.99	0.60	1.61	0.96	0.98	0.54	1.79	0.958
Clinical N stage								
N0	2.62	1.10	6.26	**0.03**	2.60	0.92	7.31	0.070
N1	1 (Ref)				1 (Ref)			
N2	0.81	0.29	2.28	0.686	1.45	0.46	4.57	0.526
N3	1.37	0.88	2.13	0.167	2.42	1.41	4.15	**0.001**
Radiologic response to NAST (breast and axilla)								
Complete response	0.34	0.11	1.07	0.065	0.70	0.21	2.36	0.567
Partial response	1 (Ref)				1 (Ref)			
Stable/disease progression	2.10	1.14	3.87	**0.018**	1.45	0.67	3.15	0.344
Unknown	0.41	0.10	1.69	0.219	0.55	0.13	2.39	0.426
Lymphovascular invasion								
No	1 (Ref)				1 (Ref)			
Yes	1.75	1.14	2.69	**0.011**	1.42	0.85	2.38	0.182
Unknown	0.67	0.16	2.81	0.588	0.72	0.09	5.52	0.754
pCR (breast and axilla)								
No	1 (Ref)				1 (Ref)			
Yes	0.25	0.13	0.49	**0.00001**	0.31	0.15	0.65	**0.002**

Significant p values given in bold ($p < 0.05$)

CI, confidence interval; *BMI*, body mass index; *HR*, hormone receptor; *HER2*, human epidermal growth factor receptor 2; *NAST*, neoadjuvant systemic therapy; *pCR*, pathologic complete response

modified radical mastectomy and comprehensive adjuvant radiation therapy after neoadjuvant systemic therapy. This remains the standard of care in the absence of evidence that de-escalation of surgery is an oncologically safe strategy for this population with aggressive disease.

REFERENCES

1. Hance KW, Anderson WF, Devesa SS, Young HA, Levine PH. Trends in inflammatory breast carcinoma incidence and survival: the Surveillance, Epidemiology, and End Results Program at the National Cancer Institute. *JNCI J Natl Cancer Institute*. 2005;97:966–75.
2. Dawood S. Biology and management of inflammatory breast cancer. *Expert Rev Anticancer Ther*. 2010;10:209–20.
3. Lim B, Woodward WA, Wang X, Reuben JM, Ueno NT. Inflammatory breast cancer biology: the tumour microenvironment is key. *Nature Rev Cancer*. 2018;18:485–99.
4. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology (version 4.2023). Retrieved 19 April 2023 at https://www.nccn.org/.
5. Kupstas AR, Hoskin TL, Day CN, Boughey JC, Habermann EB, Hieken TJ. Biological subtype, treatment response, and outcomes in inflammatory breast cancer using data from the National Cancer Database. *Br J Surg*. 2020;107:1033–41.
6. Fleming RY, Asmar L, Buzdar AU, et al. Effectiveness of mastectomy by response to induction chemotherapy for control in inflammatory breast carcinoma. *Ann Surg Oncol*. 1997;4:452–61.
7. Romanoff A, Zabor EC, Petruolo O, et al. Does nonmetastatic inflammatory breast cancer have a worse prognosis than other nonmetastatic T4 cancers? *Cancer*. 2018;124:4314–21.
8. Nakhlis F, Regan MM, Warren LE, et al. The impact of residual disease after preoperative systemic therapy on clinical outcomes in patients with inflammatory breast cancer. *Ann Surg Oncol*. 2017;24:2563–9.
9. Liauw SL, Benda RK, Morris CG, Mendenhall NP. Inflammatory breast carcinoma: outcomes with trimodality therapy for nonmetastatic disease. *Cancer*. 2004;100:920–8.
10. Liao Z, Strom EA, Buzdar AU, et al. Locoregional irradiation for inflammatory breast cancer: effectiveness of dose escalation in decreasing recurrence. *Int J Radiat Oncol Biol Phys*. 2000;47:1191–200.
11. Farley CR, Irwin S, Adesoye T, et al. ASO visual abstract: lymphedema in inflammatory breast cancer patients following trimodal treatment. *Ann Surg Oncol*. 2022;29:6379–80.
12. Rosso KJ, Tadros AB, Weiss A, et al. Improved locoregional control in a contemporary cohort of nonmetastatic inflammatory breast cancer patients undergoing surgery. *Ann Surg Oncol*. 2017;24:2981–8.
13. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.
14. Thoms WW Jr, McNeese MD, Fletcher GH, Buzdar AU, Singletary SE, Oswald MJ. Multimodal treatment for inflammatory breast cancer. *Int J Radiat Oncol Biol Phys*. 1989;17:739–45.
15. van Uden DJP, van Maaren MC, Bult P, et al. Pathologic complete response and overall survival in breast cancer subtypes in stage III inflammatory breast cancer. *Breast Cancer Res Treat*. 2019;176:217–26.
16. Hieken TJ, Murphy BL, Boughey JC, Degnim AC, Glazebrook KN, Hoskin TL. Influence of biologic subtype of inflammatory breast cancer on response to neoadjuvant therapy and cancer outcomes. *Clin Breast Cancer*. 2018;18:e501–6.
17. Liu J, Chen K, Jiang W, et al. Chemotherapy response and survival of inflammatory breast cancer by hormone receptor- and HER2-defined molecular subtypes approximation: an analysis from the National Cancer Database. *J Cancer Res Clin Oncol*. 2017;143:161–8.
18. Rueth NM, Lin HY, Bedrosian I, et al. Underuse of trimodality treatment affects survival for patients with inflammatory breast cancer: an analysis of treatment and survival trends from the National Cancer Database. *J Clin Oncol*. 2014;32:2018–24.
19. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet*. 2010;375:377–84.
20. Chen H, Wu K, Wang M, Wang F, Zhang M, Zhang P. A standard mastectomy should not be the only recommended breast surgical treatment for non-metastatic inflammatory breast cancer: a large population-based study in the Surveillance, Epidemiology, and End Results database 18. *Breast*. 2017;35:48–54.
21. Brzezinska M, Williams LJ, Thomas J, Michael Dixon J. Outcomes of patients with inflammatory breast cancer treated by breast-conserving surgery. *Breast Cancer Res Treat*. 2016;160:387–91.
22. Bonev V, Evangelista M, Chen JH, et al. Long-term follow-up of breast-conserving therapy in patients with inflammatory breast cancer treated with neoadjuvant chemotherapy. *Am Surg*. 2014;80:940–3.
23. Imeokparia FO, Hughes TM, Dossett LA, Jeruss JS, Chang AE, Sabel MS. Axillary pathologic complete response in inflammatory breast cancer patients: implications for SLNB? *Ann Surg Oncol*. 2019;26:3374–9.
24. Fayanju OM, Ren Y, Greenup RA, et al. Extent of axillary surgery in inflammatory breast cancer: a survival analysis of 3500 patients. *Breast Cancer Res Treat*. 2020;180:207–17.
25. Hunt KK, Yi M, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy is accurate and reduces the need for axillary dissection in breast cancer patients. *Ann Surg*. 2009;250:558–66.
26. Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA*. 2013;310:1455–61.
27. DeSnyder SM, Mittendorf EA, Le-Petross C, et al. Prospective feasibility trial of sentinel lymph node biopsy in the setting of inflammatory breast cancer. *Clin Breast Cancer*. 2018;18:e73–7.
28. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med*. 2020;382:810–21.