The Prognostic Value of Skin Involvement in Breast Cancer Patients With Chest Wall Recurrence

Danyang Zhou
Sun Yat-Sen University Cancer Center Department of Medical Oncology https://orcid.org/0000-0002-1932-8554
Mei Li
Sun Yat-sen University Cancer Center
Fei Xu
Sun Yat-sen University Cancer Center
Qiufan Zheng
Sun Yat-sen University Cancer Center
Qianyi Lu
Sun Yat-sen University Cancer Center
Ruoxi Hong
Sun Yat-sen University Cancer Center
Shusen Wang (wangshs@sysucc.org.cn)
Sun Yat-sen University Cancer Center https://orcid.org/0000-0003-3752-8506

Research article

Keywords: skin involvement, chest wall recurrence, persistent chest wall progression, breast cancer

Posted Date: May 17th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-512385/v1

Abstract

Background: To assess the prognosis of skin involvement in female breast cancer patients with chest wall recurrence (CWR).

Methods: We retrospectively analyzed the clinical-pathological data of breast cancer patients with CWR who were diagnosed pathologically between January 2000 and April 2020. Progression free survival (PFS) was defined as time from diagnosis of CWR to the first disease progression. Persistent chest wall progression was three consecutive chest wall progression without distant organ involvement.

Results: A total of 476 patients with CWR were included in this study. Among them, skin involvement or not was queried and confirmed in 345 patients. Skin involvement was significantly correlated to tumor size (P=0.003) and initial nodal status (P<0.001). By Kaplan-Meier analysis, skin involvement predicted a shorter PFS (P<0.001), especially local disease progression (P<0.001). Skin involvement was an independent biomarker for PFS by the multivariate analysis (P=0.034). Patients with skin involvement were more likely to experience persistent chest wall progression (P=0.040). After eliminating the potential deviation caused by insufficient follow-up time, persistent chest wall progression was more likely to be associated with positive lymph nodal status (P=0.046), negative PR (P=0.001) and positive HER2 (P=0.046) of the primary site, negative ER (P=0.027) and PR (P=0.013) of chest wall lesion and skin involvement (P=0.020).

Conclusion: Skin involvement predicted poor local disease control in female breast cancer patients with CWR and it was more likely to be related to persistent chest wall progression. We improved the stratification of prognosis and provided new insights for biological behaviors of the disease and further individualized treatment in breast cancer patients with CWR.

Introduction

Breast cancer is the leading cause of cancer morbidity and mortality among women worldwide in 2020, accounting for 24.5% and 15.5%, respectively [1]. Recurrent breast cancer after optimal therapy is a thorny clinical problem [2, 3]. Chest wall recurrence (CWR) can occur in 5–40% of breast cancer patients [4–7] and this disease is traditionally viewed as a harbinger of systemic disease and poor prognosis [8]. However, two-thirds of patients with recurrences involving the chest wall have no other sites of metastases and can therefore achieve favorable outcomes [9–11]. Several studies have illustrated that patients with CWR represent a heterogeneous population [12]. The disease occurs with varying frequency depending on initial tumor stage, tumor grade, lymphovascular invasion and therapy strategy [5, 13–15]. Survival after CWR is also influenced by a multitude of factors, such as initial nodal status, status of hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2), the length of disease-free interval (DFI) and the use of radiation for chest wall lesion [6, 16, 17].

A proportion of patients with CWR suffer persistent and stubborn chest wall progression without distant metastasis for a long time in clinical practice. Although these patients do not have fatal visceral

metastases, compression, ulceration, and pain from the chest wall disease are also painful. Unfortunately, little attention has been paid to persistent chest wall progression. The clear definition of persistent chest wall progression and biomarkers for subsequent recurrence or disease progression were not consistent.

Chest wall diseases typically present as one or more asymptomatic nodules in or near the mastectomy or lumpectomy scar. Skin, as the largest organ of the body, plays an important role in several vital processes, including the growth and progression of tumors. Skin involvement originates most commonly from melanoma and female breast cancer and other common sources included the lung and gastrointestinal tract. The pattern of skin infiltration is different in different types of tumors. Skin involvement from lung cancer usually occurred early, whereas invasion from the breast may occur several years after tumor excision [18]. Compared with most tumors, the relationship of skin involvement and visceral metastases is relatively weak in breast cancer. Skin involvement is known to frequently occur in anatomical areas close to the primary tumor [19]. However, little is known about the impact of skin involvement on prognosis in breast cancer patients with CWR. In this study, we aimed to identify the relationship between skin involvement and clinicopathological features and survival outcome of breast cancer patients with CWR, especially those with persistent chest wall progression, and provide suggestions to the management of recurrent breast cancer.

Methods

Patients

We reviewed female breast cancer patients with recurrence of chest wall diagnosed pathologically at Sun Yat-sen University Cancer Center between January 2000 and April 2020. Only patients meeting all of the following criteria were included: (1) non-IV stage at initial diagnosis, (2) having received curative surgery for primary disease, (3) women with histologically confirmed CWR, (4) chest wall as the only site of disease progression after curative therapy for primary disease. Patients were excluded from the study if they were male, had serious systemic disorder, had second primary malignancy, and had simultaneous distant metastasis (presence of distant metastasis was defined as any metastasis in internal organs, bones, soft tissue and non-regional lymph nodes). For all included patients, clinical-pathological data, including age at initial diagnosis, TNM stage, skin involvement, as well as the pathological parameters and treatment strategy of primary site and recurrent site were recorded and analyzed for this study. Progression free survival (PFS) was defined as time from diagnosis of CWR to the first disease progression. And overall survival (OS) was time from diagnosis of CWR to death (all causes). Patients who were still alive and who had not had progressive disease were censored at the date of their last clinical visit. Persistent chest wall progression was defined as three consecutive chest wall progression without new distant organ involvement. All patients included were followed-up regularly until death or study data cutoff (31 December 2020). This retrospective study was approved by the Ethical Committees of Sun Yat-sen University Cancer Center.

Statistics

Clinical-pathological paraments of patients included were shown using descriptive statistics. Patient characteristics was compared by Chi-squared test. Survival analyses were conducted using the Kaplan-Meier method and Cox-proportional hazards model. *P* values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 25.0 and all *P* values were two-sided.

Results

Patient characteristics

A total of 25272 female breast cancer patients visited Sun Yat-sen University Cancer Center between January 2000 and April 2020, and 476 (1.9%) of them met the inclusion criteria and were collected in this retrospective study (Fig. 1). The clinical-pathological characteristics of 476 patients were summarized in Table 1. Invasive ductal carcinoma (IDC) was the main pathological subtype of primary site in these patients. Almost half of the patients were T1-2 or N positive according to the TNM stage. Compared with the primary lesion, the proportion of Ki-67 > = 15% increased significantly in recurrent lesions, while the positive proportion of estrogen receptor (ER), progesterone receptor (PR) and HER2 did not change significantly. The median PFS and OS were 19.41 and 103.76 months after recurrence of chest wall, respectively. The median follow-up time after the initial diagnosis of breast cancer was 63.7 months, and the median follow-up time after diagnosis of CWR was 37.4 months.

Table 1
Clinical-pathological characteristics of 476 patients with recurrence of chest wall.

Factor	Median (range) / number (frequency)
Age (year)	46 (24–83)
Pathology subtype (IDC / others)	385 (80.9%) / 91 (19.1%)
T stage (1–2 / 3–4 / unknown)	252 (52.9%) / 71 (14.9%) / 153 (32.1%)
N stage (positive / negative / unknown)	237 (49.8%) / 158 (33.2%) / 81 (17.0%)
Pathology of primary site	
ER (< 1% / >=1% / unknown)	163 (34.2%) / 251 (52.7%) / 62 (13.0%)
PR (< 1% / >=1% / unknown)	186 (39.1%) / 230 (48.3%) / 60 (12.6%)
HER2 (positive / negative / unknown)	116 (24.4%) / 258 (54.2%) / 102 (21.4%)
Ki-67 (< 15% / >=15% / unknown)	62 (13.0%) / 236 (49.6%) / 178 (37.4%)
Pathology of chest wall	
ER (< 1% / >=1% / unknown)	170 (35.7%) / 259 (54.4%) / 47 (9.9%)
PR (< 1% / >=1% / unknown)	233 (48.9%) / 196 (41.2%) / 47 (9.9%)
HER2 (positive / negative / unknown)	122 (25.6%) / 277 (58.2%) / 77 (16.2%)
Ki-67 (< 15% / >=15% / unknown)	61 (12.8%) / 314 (66.0%) / 101 (21.2%)
Skin involvement (yes / no / unknown)	198 (41.6%) / 147 (30.9%) / 131 (27.5%)
PFS (months)	19.41 (0.6-157.3)
OS (months)	103.76 (0.6-255.9)

Prognostic value of skin involvement

We further interrogated the impact of skin involvement on the clinical outcome of chest wall recurrent breast cancer. Of these 476 patients, skin involvement or not was queried and histologically confirmed in 345 patients. Tissue biopsy was obtained by local lesion excision in all these patients. The patho-clinical characteristics of these 345 patients were shown in Table 2. There were 198 patients with skin involvement and 147 without skin involvement. Skin invasion in CWR was significantly correlated with T3-4 ($P = 0.003$) and N positive ($P < 0.001$) of the primary breast cancer in these patients. None of the 345 patients received extended resection for recurrent sites. In addition, there was no significant bias in systematic therapy and radiotherapy between skin involvement and non-skin involvement cohorts.

Table 2
Clinical-pathological characteristics of 345 patients with/without skin involvement.

Factor	Skin involvement (n = 198)	Non-skin involvement (n = 147)	*P*
Age (year)			0.596
< 46	98	77	
>=46	100	70	
Pathology subtype			0.676
IDC	169	88	
Others	29	13	
T stage			**0.003**
T1-2	99	88	
T3-4	40	13	
N stage			**< 0.001**
Positive	119	59	
Negative	49	66	
Pathology of primary site			
ER			0.726
< 1%	75	56	
>=1%	95	77	
PR			0.694
< 1%	78	65	
>=1%	92	70	
HER2			0.498

Note: 105 patients were unknown in Factor T (59 were skin involvement and 46 were non-skin involvement), 52 patients were unknown in Factor N (30 were skin involvement and 22 were non-skin involvement), 42 patients were unknown in Factor ER of primary site (28 were skin involvement and 14 were non-skin involvement), 40 patients were unknown in Factor PR of primary site (28 were skin involvement and 12 were non-skin involvement), 68 patients were unknown in Factor HER2 of primary site (46 were skin involvement and 22 were non-skin involvement), 118 patients were unknown in Factor Ki-67 of primary site (66 were skin involvement and 52 were non-skin involvement), 29 patients were unknown in Factor ER of chest wall (19 were skin involvement and 10 were non-skin involvement), 29 patients were unknown in Factor PR of chest wall (19 were skin involvement and 10 were non-skin involvement), 53 patients were unknown in Factor HER2 of chest wall (36 were skin involvement and 17 were non-skin involvement), 64 patients were unknown in Factor Ki-67 of chest wall (34 were skin involvement and 30 were non-skin involvement).

Factor	Skin involvement (n = 198)	Non-skin involvement (n = 147)	*P*
Positive	47	34	
Negative	105	91	
Ki-67			0.239
< 15%	26	25	
>=15%	106	70	
Pathology of chest wall			
ER			0.659
< 1%	71	51	
>=1%	108	86	
PR			0.226
< 1%	87	76	
>=1%	92	61	
HER2			0.527
Positive	48	43	
Negative	114	87	
Ki-67			0.237
< 15%	26	25	
>=15%	138	92	
Systemic treatment			0.519
Yes	183	133	
No	15	14	
Radiotherapy			0.360

Note: 105 patients were unknown in Factor T (59 were skin involvement and 46 were non-skin involvement), 52 patients were unknown in Factor N (30 were skin involvement and 22 were non-skin involvement), 42 patients were unknown in Factor ER of primary site (28 were skin involvement and 14 were non-skin involvement), 40 patients were unknown in Factor PR of primary site (28 were skin involvement and 12 were non-skin involvement), 68 patients were unknown in Factor HER2 of primary site (46 were skin involvement and 22 were non-skin involvement), 118 patients were unknown in Factor Ki-67 of primary site (66 were skin involvement and 52 were non-skin involvement), 29 patients were unknown in Factor ER of chest wall (19 were skin involvement and 10 were non-skin involvement), 29 patients were unknown in Factor PR of chest wall (19 were skin involvement and 10 were non-skin involvement), 53 patients were unknown in Factor HER2 of chest wall (36 were skin involvement and 17 were non-skin involvement), 64 patients were unknown in Factor Ki-67 of chest wall (34 were skin involvement and 30 were non-skin involvement).

Factor	Skin involvement (n = 198)	Non-skin involvement (n = 147)	*P*
Yes	66	56	
No	132	91	

Note: 105 patients were unknown in Factor T (59 were skin involvement and 46 were non-skin involvement), 52 patients were unknown in Factor N (30 were skin involvement and 22 were non-skin involvement), 42 patients were unknown in Factor ER of primary site (28 were skin involvement and 14 were non-skin involvement), 40 patients were unknown in Factor PR of primary site (28 were skin involvement and 12 were non-skin involvement), 68 patients were unknown in Factor HER2 of primary site (46 were skin involvement and 22 were non-skin involvement), 118 patients were unknown in Factor Ki-67 of primary site (66 were skin involvement and 52 were non-skin involvement), 29 patients were unknown in Factor ER of chest wall (19 were skin involvement and 10 were non-skin involvement), 29 patients were unknown in Factor PR of chest wall (19 were skin involvement and 10 were non-skin involvement), 53 patients were unknown in Factor HER2 of chest wall (36 were skin involvement and 17 were non-skin involvement), 64 patients were unknown in Factor Ki-67 of chest wall (34 were skin involvement and 30 were non-skin involvement).

By Kaplan-Meier analysis, skin involvement predicted a shorter PFS after CWR ($P < 0.001$), but it had no significant prognostic value for OS (Fig. 2). Factors with significance on univariate analysis, including pathology subtype (hazard ratio (HR) = 0.490, 95% confidence interval (CI) 0.329–0.729, $P < 0.001$), T stage of the primary (HR = 1.731, 95% CI 1.198–2.501, $P = 0.003$), N stage of the primary (HR = 2.081, 95% CI 1.522–2.845, $P < 0.001$), ER (HR = 0.550, 95% CI 0.416–0.727, $P < 0.001$), PR (HR = 0.554, 95% CI 0.417–0.734, $P < 0.001$), Ki-67 (HR = 1.769, 95% CI 1.149–2.725, $P = 0.010$) and skin involvement (HR = 1.837, 95% CI 1.387–2.433, $P < 0.001$) were subjected to multivariate analysis. N stage of the primary (HR = 1.821, 95% CI 1.181–2.809, $P = 0.007$) and skin involvement (HR = 1.535, 95% CI 1.034–2.278, $P = 0.034$) were independent impact factors for PFS by multivariate analyses (Table 3).

Table 3
Cox proportional hazard regression analysis of progression free survival in 345 breast cancer patients.

Faction	Univariable		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (< 46 vs > = 46)	1.123 (0.859–1.469)	0.396		
Pathology subtype (IDC vs others)	0.490 (0.329–0.729)	**< 0.001**	0.570 (0.280–1.158)	0.120
T (1–2 vs 3–4)	1.731 (1.198–2.501)	**0.003**	1.153 (0.743–1.788)	0.526
N (< 1 vs > = 1)	2.081 (1.522–2.845)	**< 0.001**	1.821 (1.181–2.809)	**0.007**
ER (< 1% vs > = 1%)	0.550 (0.416–0.727)	**< 0.001**	0.663 (0.414–1.061)	0.086
PR (< 1% vs > = 1%)	0.554 (0.417–0.734)	**< 0.001**	0.694 (0.428–1.127)	0.140
HER2 (negative vs positive)	0.861 (0.627–1.181)	0.353		
Ki-67 (< 15% vs > = 15%)	1.769 (1.149–2.725)	**0.010**	1.300 (0.726–2.327)	0.377
Skin involvement (no vs yes)	1.837 (1.387–2.433)	**< 0.001**	1.535 (1.034–2.278)	**0.034**
Note: ER, PR, HER2 and Ki-67 are all from pathology of chest wall.				

As we have observed the significant predictive value of skin involvement for PFS, we further divided disease progression patterns into local disease progression and distant disease progression. Patients with skin involvement are more likely to suffer from local disease progression events ($P < 0.001$), while skin involvement had no significant association with distant disease progression ($P = 0.113$) (Fig. 3).

Skin involvement and persistent chest wall progression

A total of 40 out of 345 (11.6%) patients experienced persistent chest wall progression. Of the 40 patients, 29 were from the skin involvement group and the remaining 11 were from the non-skin involvement group, accounting for 14.6% and 7.5% ($P = 0.040$), respectively. To eliminate the potential bias caused by insufficient follow-up time, 114 patients with follow-up time less than 24 months after CWR were excluded from this analysis. Table 4 showed the comparison of characteristics between patients who experiencing persistent CWR or not. The following variables were significantly correlated with persistent CWR: N stage ($P = 0.046$), PR ($P = 0.001$) and HER2 ($P = 0.046$) of primary site, ER ($P = 0.027$) and PR ($P = 0.013$) of chest wall and skin involvement ($P = 0.020$).

Table 4
Comparation of clinical-pathological characteristics in patients with/without persistent chest wall progression.

Factor	Persistent chest wall progression (n = 40)	Non-persistent chest wall progression (n = 191)	*P*
Age (year)			0.987
< 46	21	100	
>=46	19	91	
Pathology			0.431
IDC	34	152	
Others	6	39	
T stage			0.403
1–2	20	104	
3–4	7	21	
N stage			**0.046**
Positive	26	82	
Negative	10	70	
Pathology of primary site			
ER			0.061
< 1%	19	59	
>=1%	17	105	
PR			**0.001**
< 1%	24	59	
>=1%	13	106	
HER2			**0.046**
Positive	15	41	
Negative	18	107	
Ki-67			0.052
< 15%	4	34	
>=15%	25	72	

Factor	Persistent chest wall progression (n = 40)	Non-persistent chest wall progression (n = 191)	*P*
Pathology of chest wall			
ER			**0.027**
< 1%	19	57	
>=1%	18	120	
PR			**0.013**
< 1%	24	75	
>=1%	13	102	
HER2			0.586
Positive	14	53	
Negative	23	107	
Ki-67			0.817
< 15%	7	32	
>=15%	29	119	
Skin involvement			**0.020**
Yes	29	100	
No	11	91	

Note: Continues chest wall recurrence is defined as three consecutive chest wall progression without new distant organ involvement. 79 patients were unknown in Factor T (13 were repeated local progression and 66 were non- repeated local progression), 43 patients were unknown in Factor N (4 were repeated local progression and 39 were non-repeated local progression), 31 patients were unknown in Factor ER of primary site (4 were repeated local progression and 27 were non-repeated local progression), 29 patients were unknown in Factor PR of primary site (3 were repeated local progression and 26 were non-repeated local progression), 50 patients were unknown in Factor HER2 of primary site (7 were repeated local progression and 43 were non-repeated local progression), 96 patients were unknown in Factor Ki-67 of primary site (11 were repeated local progression and 85 were non-repeated local progression), 17 patients were unknown in Factor ER of chest wall (3 were repeated local progression and 14 were non-repeated local progression), 17 patients were unknown in Factor PR of chest wall (3 were repeated local progression and 14 were non-repeated local progression), 34 patients were unknown in Factor HER2 of chest wall (3 were repeated local progression and 31 were non-repeated local progression), 44 patients were unknown in Factor Ki-67 of chest wall (4 were repeated local progression and 40 were non-repeated local progression).

Discussion

The unpleasant symptoms from CWR, such as lymphoedema, ulceration, pain, fungal infection and persistent disease progression pose challenges in the clinical practice. However, these patients represent

a heterogeneous population, and some of them may achieve a long-term survival after CWR. Here we hope to summarize the characteristics of breast cancer patients with CWR and provide novel insights for patient stratification and further individualized treatment. In the present study, we found that skin involvement predicted poor local disease control in breast cancer patients with CWR, especially local disease progression events. In addition, patients with skin involvement tended to experience persistent chest wall progression after CWR than those without skin involvement.

The mechanisms that predispose certain internal malignancies to invade the skin have rarely been discussed in the previous literature. Skin can be divided into epidermis and dermis in anatomic structure. A complex network of multitude of cell types and the flexibility of dermal vessels and the lymph nodes in skin maintain several vital processes such as inflammation, immune response, wound healing, and angiogenesis [20–24]. The levels of tumor-infiltrating lymphocytes (TILs) in skin metastases are the lowest and the composition of TILs presents a higher FOXP3 and a lower CD8/FOXP3 ratio, compared to other metastatic lesions from primary breast cancer [25]. This suggests that cutaneous tissue may harbor a more permissive immune microenvironment for tumor growth. A physiological mitigation of the cytotoxic immune activity in skin tissue through different immunosuppressive mechanisms, a process known as “immune privilege”, has been described [26, 27]. In addition, the interaction between tumor cells and certain factors secreted from the dermis or epidermis participate in the skin homing mechanism of metastatic cells. Chemokines and their receptors are involved in tumorigenesis and metastasis. The chemokine receptor CCR10 has been demonstrated to be involved in cutaneous metastases of melanomas and may mediate melanoma survival in the skin [28, 29]. Breast cancer, which has a similar metastatic pattern as malignant melanoma but also a high incidence of skin metastases, shows high expression levels of CXCR4 and CCR7 rather than CCR10 [30]. Structurally, skin involvement from breast cancer of female occurs mainly by hematogenous and lymphatic routes [18, 31]. Regional distribution of dermal lymph vessels, from the perspective of tumor invasion, constitutes a functional unit [32]. Joan et al. finds that more superficially located tumors may be more likely than are deeper tumors to metastasize via lymphatics to axillary nodes due to the rich lymphatic system in the breast dermis, although the size of primary site is less than 5 cm [33]. In addition, cutaneous deposits from breast adenocarcinomas with distinct angiogenic profiles in skin have different growth patterns [34]. The suppressive immune microenvironment in the skin lacks supervision and killing of tumors, and the abundant vascular and lymphatic system in the dermis provides nutrition and spreading channels, which contribute to the growth, invasion and metastasis of tumors. This may partly explain why skin involvement is an independent prognostic factor for disease progression in breast cancer patients with CWR, especially local disease progression.

The treatment of recurrent chest wall disease is complex, particularly when radiotherapy has been previously conducted for chest wall. Full thickness chest wall resection, as one of the most common therapeutic approaches, is not curative, is disfiguring, and is associated with significant morbidity. Previous studies suggested that multiple sites or large areas of skin involvement are not suitable for local surgical treatment, although systemic chemotherapy is also difficult. Second-and third-line salvage chemotherapy results in overall response rates of 20–30%, at best [35–38]. In our study, skin involvement

predicted poorer local disease control in patients with CWR, while similar overall survival was observed between these patients with skin involvement or not. Our results suggested that skin involvement should not be considered as a contraindication for local therapy in breast cancer patients with chest wall recurrent diseases. On the contrary, more effective treatment strategies and more clinical studies are needed to improve clinical outcomes and quality of life for these patients, especially in the relatively early stage of skin invasion.

A certain proportion of patients with CWR after local or systemic treatment have second recurrence or disease progression in a shorter time. However, biomarkers for subsequent recurrence or disease progression were not consistent. Anees et al. finds that primary tumor characteristics and treatment factors, time to recurrence, characteristics and treatment of recurrent chest wall were not significantly predictive for an additional CWR in their study [16]. The study from Carmen et al. shows that disease free interval between primary lesion and CWR remain highly correlated with disease progression after chest wall chest [14]. Bruce G et al. demonstrates that PR status is a significant factor for distant metastasis and HER-2/neu status is related to local-regional disease progression after local recurrence [6]. The varying lengths of follow-up, different patient selection criteria, and a variety of treatment strategies can be an explanation for the difference among varied studies. Although some studies explore the second CWR after CWR, that is, re-recurrence, there are few studies on persistent chest wall progression. To our knowledge, this is the first study on the characteristics of patients with persistent chest wall progression and the prognosis of skin involvement in these patients. In our study, initial nodal status, status of ER, PR and HER2 and skin involvement are significantly different between patients with persistent chest wall progression and non-persistent chest wall progression. Persistent chest wall progression was likely more to be associated with positive lymph node status, negative PR and positive HER2 in primary lesion, negative ER and PR in chest wall lesion and skin involvement of chest wall. Positive lymph node status, negative HR status and positive HER2 status were generally markers of poor prognosis in breast cancer. KI67, as a nuclear protein expressed in proliferating cells, is associated with poor prognosis of breast cancer. Consistent with our results, KI67 expression was also elevated in recurrent chest wall lesions and was associated with higher aggressiveness.

The current study had several limitations. Studies involving multiple institutions would add more power to the study. Like any retrospective analysis of this nature, the population was accrued over 2 decades, during which treatment for breast cancer as well as treatment for recurrences changed based on new guideline. Not all patients received the same treatment, even if there was no significant bias between basic therapy, such as systemic therapy and local treatment. Acknowledging the limitations of such an analysis, however, we believe the results can help individualize treatment decisions and provide a strong incentive for future investigations. Certainly, patients with CWR without skin involvement will enjoy a relatively high rate of local disease control and a long-term progression free survival.

Conclusions

Increasing attention has been paid to recurrent chest wall in breast cancer due to the clinical commonness and the complexity of treatment. We stratified these patients into different prognosis by skin involvement and found that skin involvement was markedly related to the local disease progression. In addition, we described the pattern of persistent chest wall progression for the first time and demonstrated that skin involvement was a predictor for persistent chest wall progression in breast cancer CWR. We hope that the biological behavior and prognostic stratification factors revealed by this study might shed light on individualized therapies for these patients.

Abbreviations

CWR	chest wall recurrence
HR	hormone receptor
HER2	human epidermal growth factor receptor 2
DFI	disease-free interval
PFS	progression free survival
OS	overall survival
IDC	invasive ductal carcinoma
ER	estrogen receptor
PR	progesterone receptor
HR	hazard ratio
CI	confidence interval
TILs	tumor-infiltrating lymphocytes

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Committees of Sun Yat-sen University Cancer Center. Informed consent was obtained from all patients for being included in the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

National Natural Science Foundation of China U1601224

National Natural Science Foundation of China 81272896

National Natural Science Foundation of China 81602313

Authors' contributions

DY Z: Conceptualization, formal analysis, data curation, data interpretation, manuscript drafting, and manuscript editing.

M L: Conceptualization, formal analysis, data curation, data interpretation, manuscript drafting, and manuscript editing.

F X: Formal analysis, data interpretation, and manuscript editing.

QF Z: Formal analysis, data interpretation, and manuscript editing.

QY L: Formal analysis, data interpretation, and manuscript editing.

RX H: Conceptualization, data interpretation, and manuscript editing.

SS W: Conceptualization, data interpretation, and manuscript editing.

All authors read and approved the final manuscript.

Acknowledgements

Not applicable

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2021.
2. Brackstone M, Fletcher GG, Dayes IS, Madarnas Y, SenGupta SK, Verma S. Locoregional therapy of locally advanced breast cancer: a clinical practice guideline. Curr Oncol. 2015;22(Suppl 1):S54-S66.

3. Wakeam E, Acuna SA, Keshavjee S. Chest Wall Resection for Recurrent Breast Cancer in the Modern Era: A Systematic Review and Meta-analysis. Annals of surgery. 2018;267(4):646-55.
4. Elder EE, Kennedy CW, Gluch L, Carmalt HL, Janu NC, Joseph MG, et al. Patterns of breast cancer relapse. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2006;32(9):922-7.
5. Maishman T, Cutress RI, Hernandez A, Gerty S, Copson ER, Durcan L, et al. Local Recurrence and Breast Oncological Surgery in Young Women With Breast Cancer: The POSH Observational Cohort Study. Annals of surgery. 2017;266(1):165-72.
6. Haffty BG, Hauser A, Choi DH, Parisot N, Rimm D, King B, et al. Molecular markers for prognosis after isolated postmastectomy chest wall recurrence. Cancer. 2004;100(2):252-63.
7. Hsi RA, Antell A, Schultz DJ, Solin LJ. Radiation therapy for chest wall recurrence of breast cancer after mastectomy in a favorable subgroup of patients. International journal of radiation oncology, biology, physics. 1998;42(3):495-9.
8. D'Aiuto M, Cicalese M, D'Aiuto G, Rocco G. Surgery of the chest wall for involvement by breast cancer. Thorac Surg Clin. 2010;20(4):509-17.
9. van Tienhoven G, Voogd AC, Peterse JL, Nielsen M, Andersen KW, Mignolet F, et al. Prognosis after treatment for loco-regional recurrence after mastectomy or breast conserving therapy in two randomised trials (EORTC 10801 and DBCG-82TM). EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group. European journal of cancer (Oxford, England : 1990). 1999;35(1):32-8.
10. Recht A, Silen W, Schnitt SJ, Connolly JL, Gelman RS, Rose MA, et al. Time-course of local recurrence following conservative surgery and radiotherapy for early stage breast cancer. International journal of radiation oncology, biology, physics. 1988;15(2):255-61.
11. Elfgen C, Schmid SM, Tausch CJ, Montagna G, Güth U. Radiological Staging for Distant Metastases in Breast Cancer Patients with Confirmed Local and/or Locoregional Recurrence: How Useful are Current Guideline Recommendations? Annals of surgical oncology. 2019;26(11):3455-61.
12. Chagpar A, Langstein HN, Kronowitz SJ, Singletary SE, Ross MI, Buchholz TA, et al. Treatment and outcome of patients with chest wall recurrence after mastectomy and breast reconstruction. American journal of surgery. 2004;187(2):164-9.
13. Nielsen HM, Overgaard M, Grau C, Jensen AR, Overgaard J. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2006;24(15):2268-75.
14. van der Pol CC, van Geel AN, Menke-Pluymers MBE, Schmitz PIM, Lans TE. Prognostic factors in 77 curative chest wall resections for isolated breast cancer recurrence. Annals of surgical oncology. 2009;16(12):3414-21.

15. Ragaz J, Olivotto IA, Spinelli JJ, Phillips N, Jackson SM, Wilson KS, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. Journal of the National Cancer Institute. 2005;97(2):116-26.
16. Chagpar A, Meric-Bernstam F, Hunt KK, Ross MI, Cristofanilli M, Singletary SE, et al. Chest wall recurrence after mastectomy does not always portend a dismal outcome. Annals of surgical oncology. 2003;10(6):628-34.
17. Miyauchi K, Koyama H, Noguchi S, Inaji H, Yamamoto H, Kodama K, et al. Surgical treatment for chest wall recurrence of breast cancer. European journal of cancer (Oxford, England : 1990). 1992;28A(6-7):1059-62.
18. Hu SCS, Chen GS, Lu YW, Wu CS, Lan CCE. Cutaneous metastases from different internal malignancies: a clinical and prognostic appraisal. Journal of the European Academy of Dermatology and Venereology : JEADV. 2008;22(6):735-40.
19. Saeed S, Keehn CA, Morgan MB. Cutaneous metastasis: a clinical, pathological, and immunohistochemical appraisal. Journal of cutaneous pathology. 2004;31(6):419-30.
20. Matejuk A. Skin Immunity. Archivum immunologiae et therapiae experimentalis. 2018;66(1):45-54. doi: 10.1007/s00005-017-0477-3.
21. Agius E, Lacy KE, Vukmanovic-Stejic M, Jagger AL, Papageorgiou A-P, Hall S, et al. Decreased TNF-alpha synthesis by macrophages restricts cutaneous immunosurveillance by memory CD4+ T cells during aging. The Journal of experimental medicine. 2009;206(9):1929-40.
22. Auffray C, Sieweke MH, Geissmann F. Blood monocytes: development, heterogeneity, and relationship with dendritic cells. Annual review of immunology. 2009;27:669-92.
23. Bedoui S, Whitney PG, Waithman J, Eidsmo L, Wakim L, Caminschi I, et al. Cross-presentation of viral and self antigens by skin-derived CD103+ dendritic cells. Nature immunology. 2009;10(5):488-95.
24. Ginhoux F, Collin MP, Bogunovic M, Abel M, Leboeuf M, Helft J, et al. Blood-derived dermal langerin+ dendritic cells survey the skin in the steady state. The Journal of experimental medicine. 2007;204(13):3133-46.
25. Dieci MV, Tsvetkova V, Orvieto E, Piacentini F, Ficarra G, Griguolo G, et al. Immune characterization of breast cancer metastases: prognostic implications. Breast cancer research : BCR. 2018;20(1):62.
26. Gilhar A, Paus R, Kalish RS. Lymphocytes, neuropeptides, and genes involved in alopecia areata. The Journal of clinical investigation. 2007;117(8):2019-27.
27. Wang X, Marr AK, Breitkopf T, Leung G, Hao J, Wang E, et al. Hair follicle mesenchyme-associated PD-L1 regulates T-cell activation induced apoptosis: a potential mechanism of immune privilege. The Journal of investigative dermatology. 2014;134(3):736-45.
28. Murakami T, Cardones AR, Hwang ST. Chemokine receptors and melanoma metastasis. Journal of dermatological science. 2004;36(2):71-8.
29. Kakinuma T, Hwang ST. Chemokines, chemokine receptors, and cancer metastasis. J Leukoc Biol. 2006;79(4):639-51.

30. Müller A, Homey B, Soto H, Ge N, Catron D, Buchanan ME, et al. Involvement of chemokine receptors in breast cancer metastasis. Nature. 2001;410(6824):50-6.
31. Marneros AG, Blanco F, Husain S, Silvers DN, Grossman ME. Classification of cutaneous intravascular breast cancer metastases based on immunolabeling for blood and lymph vessels. J Am Acad Dermatol. 2009;60(4):633-8.
32. Güth U, Wight E, Schötzau A, Langer I, Dieterich H, Rochlitz C, et al. Correlation and significance of histopathological and clinical features in breast cancer with skin involvement (T4b). Human pathology. 2006;37(3):264-71.
33. Cunningham JE, Jurj AL, Oman L, Stonerock AE, Nitcheva DK, Cupples TE. Is risk of axillary lymph node metastasis associated with proximity of breast cancer to the skin? Breast cancer research and treatment. 2006;100(3):319-28.
34. Colpaert CG, Vermeulen PB, Van Beest P, Soubry A, Goovaerts G, Dirix LY, et al. Cutaneous breast cancer deposits show distinct growth patterns with different degrees of angiogenesis, hypoxia and fibrin deposition. Histopathology. 2003;42(6):530-40.
35. Ibrahim N, Samuels B, Page R, Doval D, Patel K, Rao S, et al. Multicenter phase II trial of ABI-007, an albumin-bound paclitaxel, in women with metastatic breast cancer. 2005;23(25):6019-26.
36. Martín M, Ruiz A, Muñoz M, Balil A, García-Mata J, Calvo L, et al. Gemcitabine plus vinorelbine versus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. 2007;8(3):219-25.
37. Saunders Y, Stebbing J, Broadley K, Johnston SJCo. Recurrent locally advanced breast cancer: the treatment of chest wall disease with further chemotherapy. 2001;13(3):195-9.
38. Vassilomanolakis M, Koumakis G, Demiri M, Missitzis J, Barbounis V, Efremidis AJCi. Vinorelbine and cisplatin for metastatic breast cancer: a salvage regimen in patients progressing after docetaxel and anthracycline treatment. 2003;21(4):497-504.

Figures

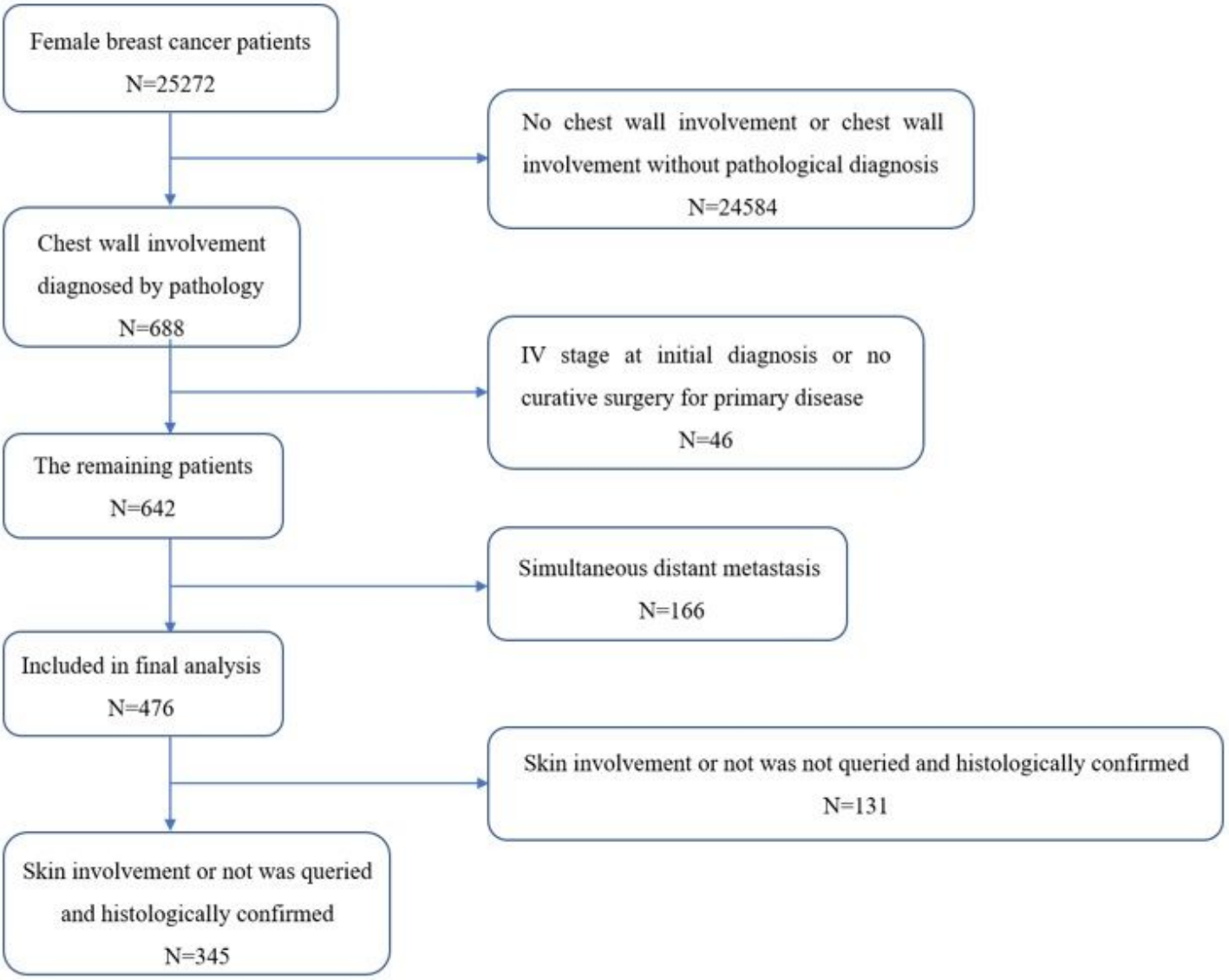

Figure 1

A flow chart outlining patients' selection.

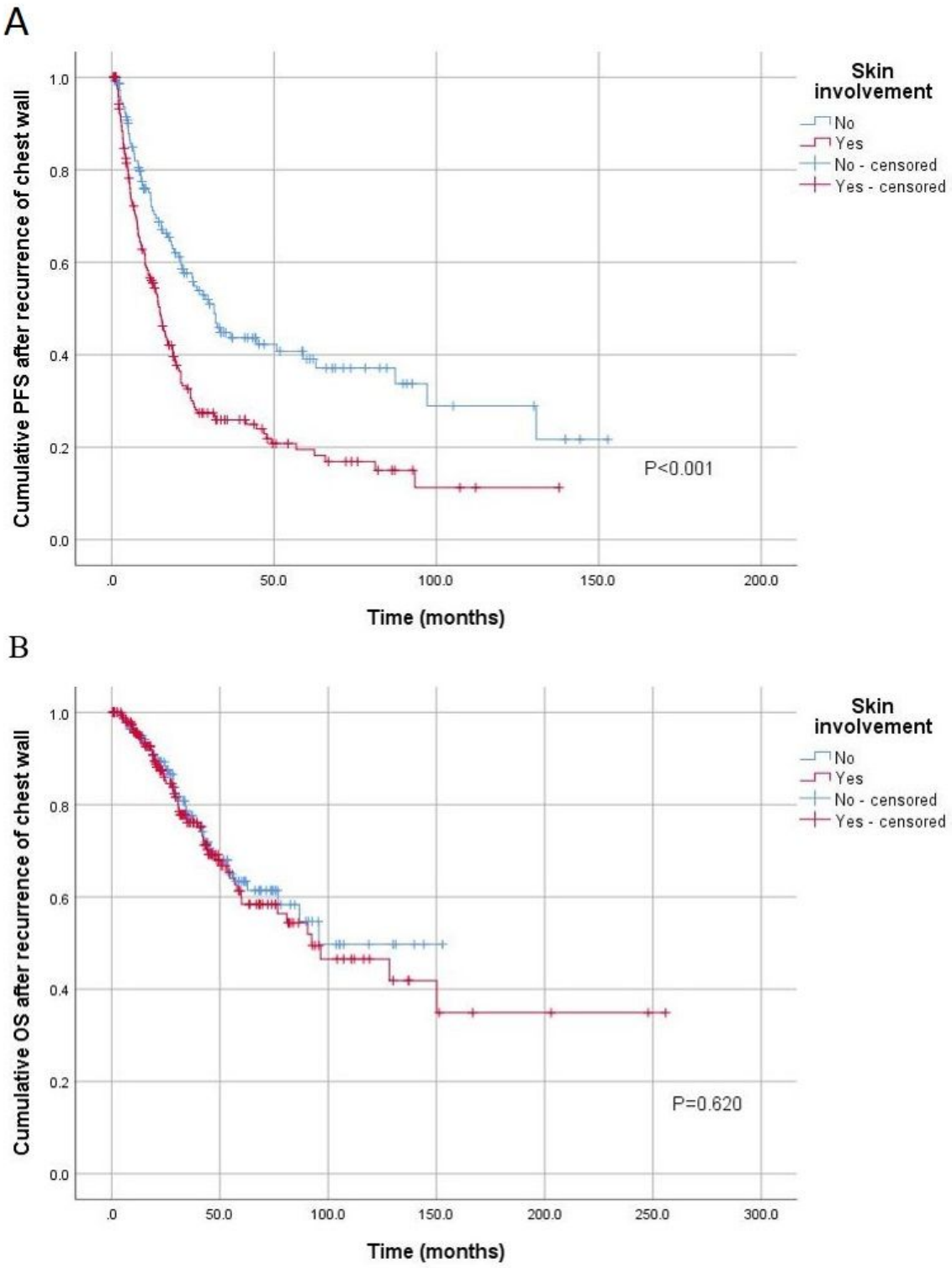

Figure 2

Kaplan–Meier curve for PFS and OS of 345 breast cancer patients stratified by skin involvement. A. Kaplan–Meier curve for PFS stratified by skin involvement in 345 breast cancer patients. B. Kaplan–Meier curve for OS stratified by skin involvement in these patients.

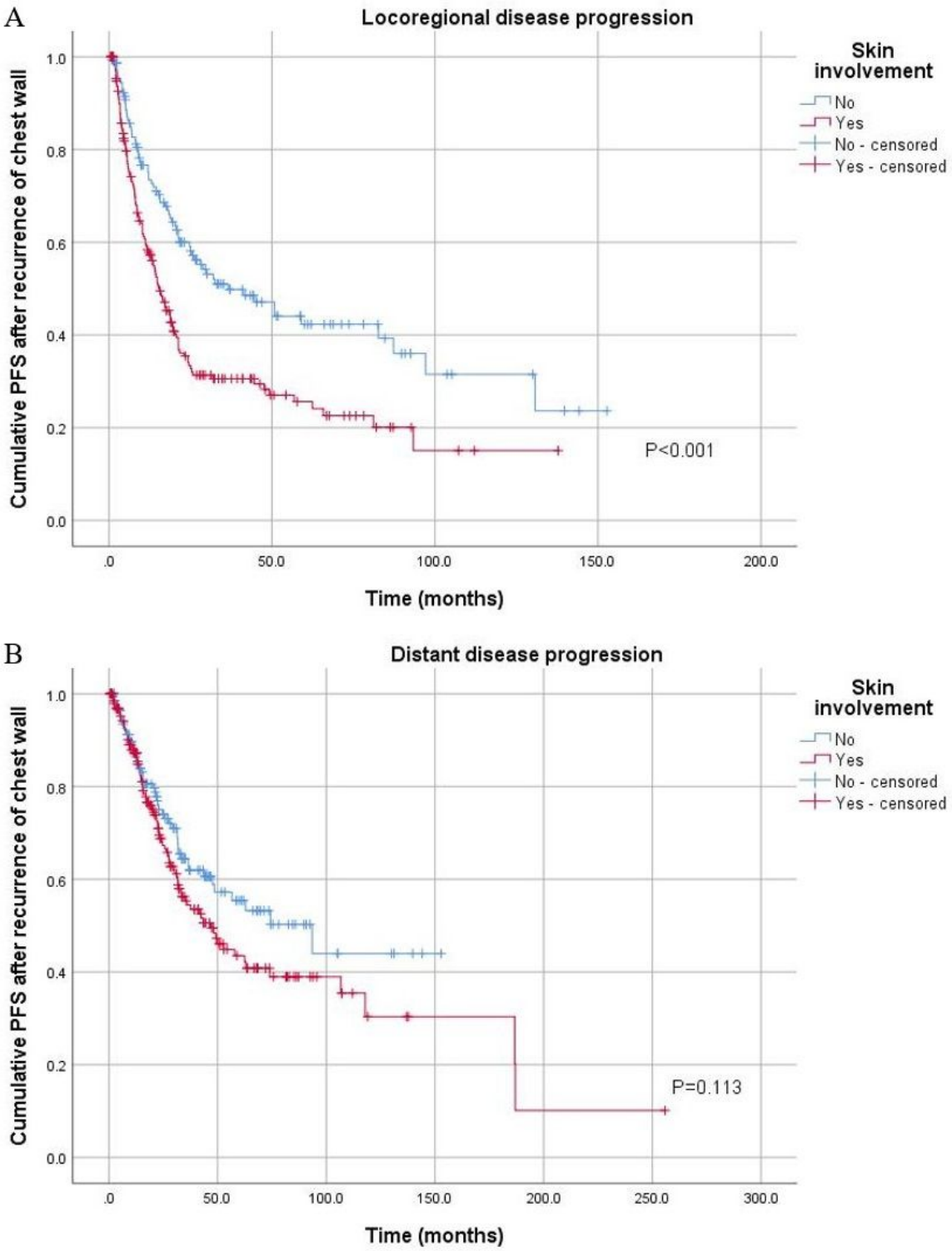

Figure 3

Kaplan–Meier curve for local and distant disease progression of 345 breast cancer patients stratified by skin involvement. A. Kaplan–Meier curve for local PFS stratified by skin involvement in 345 breast cancer patients. B. Kaplan–Meier curve for distant PFS stratified by skin involvement in these patients.