

Original Article

Clinical characteristics and prognostic analysis of ipsilateral supraclavicular lymph node metastases in breast cancer patients: a retrospective study

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Received April 7, 2019; Accepted July 25, 2019; Epub September 1, 2019; Published September 15, 2019

Abstract: Background: To investigate the clinical characteristics and prognosis of different subtype breast cancer patients with pathologically proven ipsilateral supraclavicular lymph node metastasis (ISCLM). Methods: We performed a retrospective analysis of clinical data for total 156 patients who diagnosed with ISCLM, among 3,133 breast cancer patients. Breast cancer subtypes were classified as hormone receptor (HR) positive (+)/human epidermal growth factor receptor 2 (HER2) negative (-), HR+/HER2+, HR-/HER2+ and triple-negative breast cancer (TNBC) subtypes using immunohistochemical staining. We subsequently analyzed matched cohorts, evaluating clinical features and survival in different subtypes. Results: The patients in this study accounted for 5% of all breast cancer patients treated during the same period. Breast cancer subtypes were confirmed in all 156 patients (39.7% with HR+/HER2-, 23.7% with HR+/HER2+, 14.7% with HR-/HER2+, and 21.8% with TNBC). The median overall survival after ISCLM was 47 months (95% confidence interval (CI), 3-94 months), and the overall 1-, 3- and 5-year survival rates were 92.3, 73.7 and 48.1%, respectively. We found that the survival rate is impacted by breast cancer subtypes ($P = 0.001$), and patients with TNBC had the shortest survival. Time to ISCLM less than 24 months and ISCLM size > 3 cm were independent predictors of poor survival in patients with ISCLM ($P = 0.007$ and 0.001 , respectively). Conclusions: Clinical breast cancer subtypes were still independent prognostic predictors among breast cancer patients with ISCLM. ISCLM arising from TNBC has the worst prognosis. Multidisciplinary therapy is beneficial for breast cancer patients with ISCLM.

Keywords: Breast cancer, ISCLM, subtype, prognosis

Introduction

Breast cancer is one of the most frequent-occurring cancers in China and is the fourth leading cause of cancer-related death in Chinese women [1]. The incidence of ipsilateral supraclavicular lymph node metastasis (ISCLM) in breast cancer patients claims only a small proportion, about 1-4% of all cases of breast cancer [2]. However, according to the latest (7th) edition of the American Joint Committee on Cancer - Tumor Node Metastasis (AJCC-TNM), synchronous ISCLM is defined as the occurrence of supraclavicular lymph node metastases at the primary diagnosis (N3c) of br-

east cancer. ISCLM can also occur months to years after initial diagnosis and after treatment of the primary tumor, which is considered as regional relapse. In clinical practice we are seeing an increased number of ISCLM breast cancer patients. The presence of ISCLM is usually indicative of poor prognosis.

Breast cancer patients in early stages can be cured by local and systemic treatment [3, 4]. However, 20% to 30% of patients with early stage breast cancer will relapse with regional advanced recurrence or distant metastasis [5]. The supraclavicular region is one of the most common metastatic locations [6, 7]. ISCLM is a

difficult clinical issue that negatively impacts patients with advanced breast cancer. Combined modality therapy is currently considered essential for treating breast cancer patients with ISCLM.

Nowadays, researchers do not consider breast cancer as a homogeneous disease process, but rather as a compilation of reproducibly identified intrinsic subtypes as defined by microarray (luminal A, luminal B, basal-like and human epidermal growth factor receptor 2 (HER2)-enriched subtypes). The characteristics are determined by unique clinicopathologic features and a distinct prognosis [6, 8]. Although most studies of molecular subtypes in breast cancer report differences in survival, to our knowledge, there are few reports about prognostic analysis of ISCLM in different subtype breast cancer patients.

In our single-institution cohort study, we examined the clinicopathologic characteristics and outcome of breast cancer patients diagnosed with ISCLM after the treatment. We analyzed the clinical features and survival outcomes of both primary breast cancer and ISCLM. The aim of our study is to elucidate the contribution of breast cancer subtype to outcomes, particularly after ISCLM.

Patients and methods

Patient selection

Between 1994 and 2008, 231 patients were diagnosed with breast cancer with ISCLM at Tianjin Medical University Cancer Hospital and institute (TMUCH). We retrospectively analyzed breast cancer patients with ISCLM who underwent an operation. The primary breast cancer was totally resected, and there was ISCLM but without evidence of distant metastases. The investigation contained complete clinical and follow-up data. The ISCLM was diagnosed by ultrasonography-guided Fine needle aspiration (FNA) or surgical biopsy after confirmation of primary breast cancer [9]. Ultimately, 156 patients met the criteria and were enrolled in our study.

Primary breast cancer characteristics

The participants of the study were 156 female patients, who received radical mastectomy or

modified radical mastectomy at primary breast cancer with synchronous or metachronous ISCLM between 1994 and 2008 at TMUCH. All 156 patients had a histologic confirmation of invasive breast cancer by breast pathologists. In these cases, clinical and pathology data were extracted from medical record. These variables included patient age, primary tumor size, lymph node stage, stage of primary breast cancer, primary tumor histology, including estrogen receptor (ER) status, progesterone receptor (PR) status and HER2 status, and treatment including local and systemic therapies. ER and PR status reported by clinical breast cancer pathological database was determined by immunohistochemistry (IHC) [10, 11]. ER and PR stains were assessed using Allred scores, with positive scores ranging from 2 to 8 [12]. HER2 status was determined by IHC or fluorescence in situ hybridization (FISH). HER2 was reported negative if classified as either 0 or 1+ by IHC or non-amplified FISH. HER2 was reported positive if classified as 3+ by IHC or amplified FISH.

ISCLM-specific data

All patients included in the analysis were diagnosed with ISCLM arising from breast cancer. There was no evidence of distant metastases at diagnosis of ISCLM. ISCLM-specific data extracted from the database contained the size of ISCLM and local/systemic therapies, including surgical resection, chemotherapy, endocrine therapy, trastuzumab, and radiotherapy. Distant metastases to lymph node were also recorded.

Assignment of breast cancer subtype

Breast cancer subtypes were assigned as previously described: HR+ (ER+ and/or PR+)/HER2-, HR+/HER2+, HR-/HER2+ and triple-negative (ER-/PR-/HER2-). The status of HR and HER2 were acquired from the medical data record as described above.

Statistical analysis

Statistical analysis was performed using SPSS software, version 22 (IBM, Armonk, NY). The Kaplan-Meier method and log-rank test were used to compare differences among survival curves. Overall survival (OS) was defined as the time from the date of mastectomy to death or

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Table 1. Characteristics of primary breast cancer

Variables	All patients (n = 156)	Triple-negative (n = 34; 21.8%)	HR-/HER2+ (n = 23; 14.7%)	HR+/HER2- (n = 37; 23.7%)	HR+/HER2+ (n = 62; 39.7%)
Age, years	45 (21-67)	41 (22-61)	44.1 (24-65)	48 (29-67)	48 (28-66)
Median (range)					
≥ 50	66 (42.3%)	14 (41.2%)	12 (52.2%)	13 (35.1%)	27 (43.5%)
< 50	90 (57.7%)	20 (58.8%)	11 (47.8%)	24 (64.9%)	35 (56.5%)
AJCC staging					
I	34 (21.8%)	8 (23.5%)	7 (30.4%)	10 (27.0%)	9 (14.5%)
II	69 (44.2%)	15 (44.1%)	8 (34.8%)	15 (40.5%)	31 (50.0%)
III	53 (34.0%)	11 (32.4%)	8 (34.8%)	12 (32.4%)	22 (35.5%)
Tumor grade					
I	18 (11.5%)	4 (11.7%)	2 (8.7%)	6 (16.2%)	6 (9.7%)
II	77 (49.4%)	19 (55.9%)	13 (56.5%)	18 (48.6%)	27 (43.5%)
III	61 (39.1%)	11 (32.4%)	8 (34.8%)	13 (35.1%)	29 (46.8%)

HR hormone receptor, - negative, HER2 human epidermal growth factor receptor 2, + positive, AJCC American Joint Committee on Cancer.

last follow-up. Time to ISCLM (TTISCLM) was defined as the time from the date of mastectomy to date of ISCLM. ISCLM-specific survival (ISCLMS) was defined as the time from the date of ISCLM to the date of death or last follow-up. Cox regression analysis was adopted for the multivariate analysis of prognostic factors. Categorical variables were compared using the Chi-squared test and continuous variables by rank-sum test. $P < 0.05$ was considered significant.

Results

Clinical characteristics of primary breast cancer

Table 1 summarizes the clinical characteristics of primary breast cancer. The median age at breast cancer diagnosis was 45 years (range, 21-67 years); 57.7% patients were aged < 50 years. Approximately 60% (93 of 156 patients) were premenopausal at diagnosis, and 40% (63 of 156 patients) were postmenopausal. Most patients had invasive ductal histology (86.5%). The majority of patients (44.2%) presented with stage II disease and no patients presented with stage IV disease. The median tumor size was 2.6 cm (range, 0.8-8 cm) and 65% of patients had primary tumors measuring ≥ 2 cm. The 62% (97 of 156 patients) of patients had positive axillary lymph nodes at diagnosis. There were no significant differences in primary tumor characteristics between the four breast cancer subtypes, including age, AJCC stage,

grade, tumor size, and axillary lymph node status ($P > 0.05$). 56% of primary breast tumors (87 of 156 patients) were ER- and 60% (93 of 156 patients) were PR-, whereas 62% (96 of 156 patients) were HER2-. All clinical breast cancer subtypes were represented: 39.7% were HR+/HER2-, 23.7% were HR+/HER2+, 14.7% were HR-/HER2+, and 21.8% were triple-negative (**Table 1**).

Local and systemic therapies for primary breast cancer

In this analysis, all 156 patients underwent either radical mastectomy or modified radical mastectomy at breast cancer diagnosis. 35% (55 of 156 cases) of patients received post-mastectomy irradiation. Approximately 74% (115 of 156 patients) received adjuvant chemotherapy, including 51% (59 of 115 patients) treated with chemotherapy of anthracycline-and/or taxane-contained regimens. Approximately 22% (34 of 156 patients) received trastuzumab in the adjuvant setting. 55% (86 of 156 patients) received endocrine therapy. As expected, a higher percentage of patients with HR+ breast tumors received endocrine therapy ($P < 0.001$), whereas a higher percentage of patients with HER2+ breast tumors received trastuzumab ($P < 0.001$).

Characteristics and treatment of ISCLM

58% of patients presented tumor size ≤ 3 cm supraclavicular metastasis whereas 42% pre-

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Table 2. ISCLM characteristics and therapies

Variables	All patients (n = 156)	Triple-negative (n = 34; 21.8%)	HR-/HER2+ (n = 23; 14.7%)	HR+/HER2- (n = 37; 23.7%)	HR+/HER2+ (n = 62; 39.7%)
Size of ISCLM lesions					
≤ 3 cm	90 (57.7%)	21 (61.8%)	14 (60.9%)	18 (48.6%)	37 (59.7%)
> 3 cm	66 (42.3%)	13 (38.2%)	9 (39.1%)	19 (51.4%)	25 (40.3%)
TTISCLM					
≤ 12 months	41 (26.3%)	20 (58.8%)	11 (47.8%)	1 (2.7%)	9 (14.5%)
12-24 months	28 (17.9%)	11 (32.4%)	10 (43.5%)	2 (5.4%)	5 (8.1%)
24-36 months	68 (43.6%)	2 (5.9%)	1 (4.3%)	23 (62.2%)	42 (67.7%)
> 36 months	19 (12.2%)	1 (2.9%)	1 (4.3%)	11 (29.7%)	6 (9.7%)
Bone metastases	44 (28.2%)	3 (8.8%)	9 (39.1%)	6 (16.2%)	26 (41.9%)
Liver metastases	23 (14.7%)	2 (5.9%)	6 (26.1%)	2 (5.4%)	13 (21.0%)
Lung metastases	16 (10.3%)	2 (5.9%)	5 (21.7%)	1 (2.7%)	8 (12.9%)
Endocrine therapy	31 (19.9%)	0 (0.0%)	0 (0.0%)	12 (38.7%)	19 (30.6%)
Trastuzumab	19 (12.2%)	0 (0.0%)	7 (30.4%)	0 (0.0%)	12 (19.4%)
Chemotherapy	91 (58.3%)	16 (47.1%)	15 (65.2%)	26 (70.2%)	32 (51.6%)
ISCLM irradiation	44 (28.2%)	14 (41.2%)	8 (34.8%)	9 (24.3%)	13 (21.0%)
ISCLM surgical resection	97 (62.2%)	14 (41.2%)	15 (65.2%)	20 (54.1%)	48 (77.4%)

HR hormone receptor, - negative, HER2 human epidermal growth factor receptor 2, + positive, TTISCLM time to ipsilateral supraclavicular lymph node metastases from the date of mastectomy.

sented with tumor size > 3 cm ISCLM lesions (**Table 2**). There were no significant subtype-specific differences with regard to the size of ISCLM ($P > 0.05$).

Clinical data regarding regional therapies for ISCLM for all 156 patients were available: 62% underwent surgical resection, and 28% received local irradiation. There were no significant differences between the four clinical subtypes with regard to regional therapies ($P > 0.05$).

In ISCLM, 58% (91 of 156) of patients received systemic chemotherapy (**Table 2**). 22% (19 of 85 HER2+ patients) received trastuzumab for ISCLM, whereas 31% (31 of 99 HR+ patients) received endocrine therapy. Subtype-specific differences were not found with regard to systemic chemotherapy. As expected, a higher percentage of patients with HR+ tumors received endocrine therapy ($P = 0.000$), whereas a higher percentage of patients with HER2+ received trastuzumab ($P = 0.000$).

OS and natural history of ISCLM

The median TTISCLM was 30 months (range, 0-94 months). The majority (44%) of ISCLM were diagnosed 24-36 months after mastectomy (**Table 2**). Significant differences in TTISCLM

by breast cancer subtype were found ($P < 0.05$). TTISCLM was found to be shorter for patients with TNBC and HR-/HER2+ tumors (11 and 16 months, respectively). In contrast, TTISCLM was 35 months for patients with HR+/HER2- tumors, and 32 months for HR+/HER2+ tumors.

The follow-up was ended in May 2013, and 93 of 156 (60%) patients had died. The median OS was 61 months (range, 6-113 months). The median survival differed significantly by breast cancer subtype ($P = 0.011$). Patients with TNBC tumors had a shorter median OS (48 months) than patients with other subtypes (HR-/HER2+, 55 months; HR+/HER2-, 87 months; HR+/HER2+, 79 months).

The median ISCLM-specific survival was 47 months (range, 3-94 months), and the 1-, 3- and 5-year survival rate was 92.3, 73.7 and 48.1%, respectively. ISCLMS differed significantly by subtype ($P = 0.001$) (**Figure 1**). The median ISCLM-specific survival was 31, 43, 58 and 49 months for the TNBC, HR-/HER2+, HR+/HER2- and HR+/HER2+ subtypes, respectively.

After the ISCLM, the distant metastatic sites were bone (37.8%), liver (21.2%), and lung (13.5%) (**Table 2**). As in previous reports, a higher percentage of ISCLM was found in

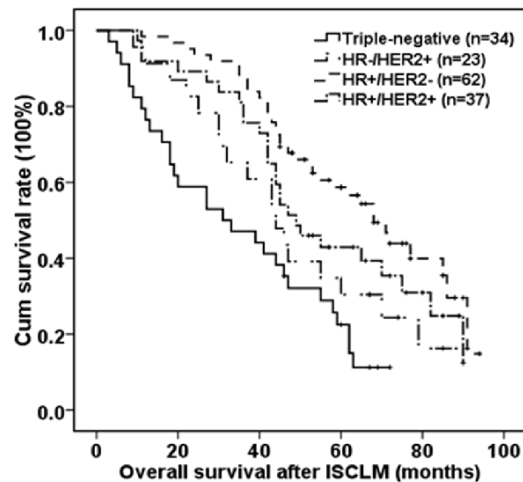


Figure 1. Survival from the time of ISCLM is shown by clinical breast subtype. Survival from the time of ISCLM is shown by clinical breast subtype ($P = 0.000$ by log-rank test). HR hormone receptor, - negative, HER2 human epidermal growth factor receptor 2, + positive.

patients with TNBC ($P < 0.05$), whereas mainly distant metastases were present in patients with HER2+ tumors ($P < 0.05$).

Prognostic analysis of ISCLM-specific survival

The triple-negative phenotype, the presence of tumor size > 3 cm ISCLM lesions, TTISCLM less than 24 months, absence of surgical resection, receipt of systemic chemotherapy, and high histologic grade of primary were found to predict worse survival after ISCLM in invariable analysis (**Table 3**). TNBC was independently associated with worse survival after ISCLM (hazard ratio (HR), 2.6; 95% confidence interval (CI), 2.22-4.67; $P = 0.0001$) when compared with non-TNBC in multivariable analysis. In addition, TTISCLM less than 24 months (HR, 2.3; 95% CI, 1.21-3.45; $P = 0.007$) and ISCLM tumor size > 3 cm (HR, 2.0; 95% CI, 1.67-2.54; $P = 0.001$) were both found to be important independent predictors of poor survival after ISCLM.

Discussion

To the best of our knowledge, this study represents the largest single-institution retrospective study on the rate of ISCLN. Regional lymph relapse of breast cancer is much more difficult to manage than local recurrence. It is also associated with a significantly greater morbidity.

Also there are no specific guidelines for the treatment of patients with ISLM, especially metachronous ISCLM. The majority of breast cancers usually develop lymph node metastases, and the most common metastatic sites are axillary and supraclavicular [7]. ISCLM of breast cancer is gaining attention for its important role in promoting tumor regional and distant metastases. Supraclavicular lymph node metastases were prognostic factors correlated with relatively poor survival [13]. In the past, it was classified as distant metastasis. However, after Brito et al. reported the clinical course and prognosis of breast cancer patients with ISCLM, there was no evidence of distant metastases with combined-modality treatments (chemotherapy, surgery and radiotherapy), which are similar to those of patients with stage IIIB locally advanced breast cancer [14]. Thus the revision of AJCC staging system reclassifies ISCLM as N3c stage IIIC stage [15]. The disease-free survival (DFS) rates of patients (at a median follow-up of 11.6 years) at 5 and 10 years were 34% and 32%, respectively. Overall survival (OS) rates at 5 and 10 years were 41% and 31%, respectively.

In this study from our single-institution, a retrospective study demonstrated that the 1-, 3- and 5-year survival rate was 92.3, 73.7 and 48.1%, respectively, with a median survival after ISCLM of 47 months. This is better than the findings of other published series [16, 17]. Clearly, our 156 patients were highly selected, with primary breast tumors totally resected, without distant metastasis, and also given aggressive treatment at diagnosis of ISCLM.

Molecular subtypes of breast cancer were introduced to reflect the biology of tumors and marked differences in patient prognosis. Nguyen et al. [18] reported that HER-2 enriched and TNBC tumors were associated with an increased risk of local recurrence in a cohort of 793 patients with breast cancer treated with breast-conserving surgery. Previous reports have indicated early-stage basal-like or triple-negative breast cancer patients experience reduced disease-free and overall survival relative, compared to other breast cancer subtypes [19, 20]. According to Kennecke et al. [19], the triple-negative subtype was an independent predictor of locoregional relapse and distant metastasis in patients with early-stage breast

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Table 3. Univariate and multivariate analysis of risk factors for ipsilateral supraclavicular lymph node metastasis-specific survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Triple negative (vs. non triple-negative)	2.73 (1.76-4.21)	0.0	2.59 (2.22-4.67)	0.0001
Age \geq 50 years (vs. < 50)	-	0.67	-	-
ISCLM lesions > 3 cm (vs. \leq 3 cm)	2.12 (1.21-3.11)	0.002	2.06 (1.67-2.54)	0.001
ISCLM surgical resection (vs. none)	1.31 (0.66-1.97)	0.003	-	0.27
Chemotherapy (vs. endocrine/trastuzumab)	1.43 (0.56-3.04)	0.04	-	0.09
TTISCLM \leq 2 years (vs. > 2 years)	2.10 (1.01-3.21)	0.004	2.31 (1.21-3.45)	0.007
AJCC stage of primary tumor II-III (vs. I)	-	0.6	-	-
Histology grade III of primary tumor (vs. I-II)	2.01 (0.86-3.47)	0.022	-	0.1
Presence of distant metastases (vs. none)	-	0.29	-	-

HR hazard ratio, CI confidence interval, TTISCLM time to ipsilateral supraclavicular lymph node metastases from the date of mastectomy, AJCC American Joint Committee on Cancer.

cancer. However, there are limited data regarding ISCLM and the clinical course over time of patients with triple-negative, regional advanced breast cancer. A single series by David et al. [6] reported that triple-negative breast cancer was associated with an increased risk of local and regional relapse. The median overall survival was only 2.4 years after the diagnosis of supraclavicular metastasis.

This cohort study showed that compared with non-triple-negative subtypes, TNBC has the worst survival after diagnosis of ISCLM. The prognostic contribution of clinical breast cancer subtypes still persisted among patients diagnosed with ISCLM. In this current series of patients treated at a single institution between 1994 and 2008, survival after ISCLM arising from TNBC was 31 months, compared with 43, 58, and 49 months for patients with the HR-/HER2+, HR+/HER2-, and HR+/HER2+ subtypes, respectively. The present study determined that the inferior outcome of TNBC with ISCLM is a reflection of a higher risk population. The results of the current study are consistent with several reports evaluating the prognostic implication of tumor subtype among patients with breast cancer [6, 19, 20].

Our analysis also indicated a relatively better prognosis after diagnosis of ISCLM arising from HR+/HER2- breast tumors; whereas the median time to ISCLM was 16, 22 and 32 months for patients with TNBC, HR-/HER2+, and HR+/HER2+ tumors. However, because of drug prices or noncompliance, some patients gave up

treatment. The current study showed that triple-negative breast tumors developed disease recurrence more rapidly after mastectomy with the supraclavicular lymph node than that of non-triple-negative breast tumors. Supraclavicular lymph node metastases are not a common follow-up finding in patients with breast cancer. A higher incidence of ISCLM had been found in triple-negative breast cancer patients [21], showing regional relapse specificity associated with specific genes [22-24]. Our study also confirmed the prognostic influence of ISCLM size of breast cancer and TTISCLM. TTISCLM less than 24 months and ISCLM lesions more than 3 cm were found to be important predictors of poor survival after ISCLM. Distant metastases were observed in 42% of patients secondary to ISCLM. The presence of distant metastases had the significant effect on the survival after ISCLM, suggesting that supraclavicular lymph node metastases are important in causing the patient's death [25].

There are no specific guidelines for the treatment of breast cancer patients with ISCLM, especially metachronous ISCLM. The report from Brito et al. [14] concluded that patients with ISCLM but no distant metastases warrant combined-modality treatments (chemotherapy, surgery and radiotherapy) and have similar prognosis to stage IIIB category. Chen et al. [17] published a series of 5409 cases of women with primary breast cancer who were treated surgically. Of these, 127 (2.3%) developed supraclavicular metastases defined as nodal recurrence at an isolated site, and 47 had a

neck dissection of level IV and part of levels III and V. There was a significant improvement in 5- and 10-year survival without distant metastases for those who had neck dissection (16.3%, 8.2%, respectively) compared with 8.5% and 3.8%, respectively, for those who did not. Also there is a tendency to treat supraclavicular nodal recurrence as locoregional disease and to treat the nodes with radiotherapy in conjunction with systemic treatment [26]. The role of neck dissection in such cases is not yet clear. We are currently collecting data from several units to give a large series of patients, which may provide some information in this area. Additionally, the value of radiotherapy in the treatment of ISCLM remains controversial.

There also has several limitations in this study. First, the patients included in this study all underwent mastectomy at breast cancer diagnosis and the ISCLMs are metachronous or synchronous. Thus, the results from this database maybe generalize across the entire breast cancer with ISCLM population, but we cannot distinguish them because these situations of metachronous and synchronous ISCLM are similar in clinicopathological aspects and survival [27]. Moreover, the database covers a long period (1994-2008), during which time new therapies have been used in clinical practice. Thus, the results of the current study may not be entirely applicable to the modern breast cancer patient population. In addition, this analysis was based on a single-center, retrospective study, and practice patterns (i.e., the routine use of adjuvant/neoadjuvant chemotherapy, referral base for surgical resection and local radiotherapy, etc.) may have introduced bias. Second, breast cancer subtype naming was based primarily on receptor status acquired through medical records from primary breast tumor. A mismatch in HR and HER2 status between primary and metastatic lesions may occur; however, a routine biopsy of ISCLM is not feasible in all cases, so we cannot rule out the possibility that some misclassification may have occurred. Finally, we should also pay attention to the inconsistency of chemotherapy regimens, and we did not analyze the effect of different treatments on ISCLM. The value of radiotherapy in treatment of ISCLM remains controversial.

Conclusion

In summary, this cohort study investigated the prognostic contribution of breast cancer subtypes among patients with ISCLM in a Chinese patient population. The results presented indicate that clinical breast cancer subtypes remain an independent predictor of prognosis and survival among breast cancer patients with ISCLM. Moreover, supraclavicular lymph node metastases arising from TNBC confer the worst prognosis, and more effective and novel agents capable of controlling supraclavicular lesion and distant metastases TNBC are needed.

Acknowledgements

This study was supported by the grant from National Natural Science Foundation of China (No. 81702698).

Disclosure of conflict of interest

None.

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