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Patterns of supraclavicular area failure after mastectomy in breast cancer patients: implications for target volume delineation

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Abstract

Purpose: To characterize the pattern of post-mastectomy supraclavicular lymph node (LN) metastases in patients with breast cancer (BC) and to provide insights for individualized clinical target volume delineation for radiotherapy.

Methods: We retrospectively analyzed 88 patients with BC who developed post-mastectomy regional LN metastases. The affected regional LNs were categorized as the ipsilateral medial supraclavicular LN area (IMSC-LN), ipsilateral lateral supraclavicular LN area (ILSC-LN), ipsilateral infraclavicular LN area (IIC-LN), and $\geq$2 groups in the ipsilateral clavicular LN area (MMIC-LN). Clinical characteristics were included in a multivariate analysis to identify risk factors for clavicular LN metastases.

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Results: The ILSC-LNs (68.2%) were the most common metastatic site. IMSC-LN metastases showed a significant association with estrogen-receptor (ER) negative status, left-sided BC, and positive axillary LNs. Tumor size $\geq$2.4 cm and Her2 type were predictors of ILSC-LN metastases. Additionally, tumor size $\geq$2.4 cm, and level I ipsilateral axillary metastases were associated with MMIC-LN metastasis.
Conclusion: ILSC-LN was the most frequently affected group of supraclavicular lymph nodes. ER-negative status, left-sided BC, tumor size, and positive ipsilateral axillary LNs are potentially associated with the pattern of supraclavicular LN metastatic involvement.

Keywords
Breast cancer, supraclavicular lymph nodes, metastasis, radiotherapy, target volume delineation, post-mastectomy

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Introduction

Lymphatic metastasis is the predominant breast cancer (BC) mode of metastasis. Approximately 20% of patients who undergo mastectomy for BC develop locoregional recurrence (LRR).[1–3] In patients with primary BC, the incidence of supraclavicular (SC) lymph node (LN) recurrence can be up to 4.3%.[4,5] Among women who experience LRR, recurrence in the SC fossa was shown to be associated with poorer prognosis compared with other factors (e.g. 5-year overall survival was shown to be 24%).[6] Radiotherapy (RT) plays a key role in the management of BC, and it has been shown to lower LRR and improve survival.[7–10] The isolated LRR-free survival rate of patients who received chemotherapy plus RT was shown to be 90% compared with 74% for patients who received chemotherapy alone.[9]

The consensus definitions for clinical target volume (CTV) in the BC atlas that was developed by the Radiation Therapy Oncology Group (RTOG) have been widely adopted in many countries. The anatomical boundaries of SC CTV extend from the medial edge excluding the thyroid and trachea to the lateral edge of the sternocleidomastoid muscle and the junction of the first rib and the clavicle.[11] However, a recent retrospective study revealed significant rates of SC LN recurrence outside the RTOG consensus volume.[12] Furthermore, Jing et al.[13] recommended extension of the SC CTV borders in high-risk patients to cover the LRR area. To improve the accuracy of RT CTV delineation, Dijkema et al.[14] classified the regional LNs into medial SCLNs, lateral SCLNs, and infraclavicular (IC) LNs. However, there is no clear consensus on the anatomical boundaries of the CTV in the SC area.[13,14] With the increasing impetus on reducing the adverse effects of RT and limiting the doses to at-risk organs, identification of the CTV definitions in the SC area is critical for BC patients.

In this study, we sought to characterize the pattern of SC LN metastases, which might provide new evidence for individualized delineation of SC LNs in patients with BC.

Materials and methods

Patients

A retrospective analysis was conducted using data from 88 BC patients who developed post-mastectomy SC and IC-LN

metastases, and these patients were identified at the Fujian Cancer Hospital between January 2011 and July 2017. Patients were included only if SC or IC-LN metastases were first detected by computer tomography (CT) imaging after modified radical mastectomy with axillary dissection. The exclusion criteria were as follows: (a) patients who did not undergo surgery; or (b) surgery was performed after primary SC or IC-LN metastases. This study was approved by the Ethics Committee of the Fujian Medical University Cancer Hospital, Fuzhou, China on 2 March 2018 (KT2018–007-01). Signed patient consent was not required because the data had been de-identified such that the identity of the patients could not be ascertained in any way.

Methods

Metastatic involvement of SC and IC-LN regions was categorized as follows: ipsilateral medial SC LN area (IMSC-LN), ipsilateral lateral SC LN area (ILSC-LN), ipsilateral IC LN area (IIC-LN), and involvement of $\geq$2 groups in the ipsilateral clavicular LN area (MMIC-LN). The following CT criteria were used to diagnose LN metastases: short-axis diameter >5 mm or LN size >5 mm with early enhancement, or the absence of internal fat in CT images.[15] The CT scan was the only diagnostic modality, and to reduce the number of false-negative metastasis results, two experienced radiologists who were blinded to the patients' clinical information independently identified the subgroup for each metastatic LN.

Delineation

The lateral SC LN (LSC-LN) transverse cervical nodal chain is delineated as described below. The medial margin of the LSC-LN is formed by the lateral border of the sternocleidomastoid and the scalenus anterior muscles. The lateral external LSC-LN extends from the clavicle to the trapezius muscles. The ventral external LSC-LNs are surrounded by clavicle or skin and the dorsal border is formed by the ventral surface of the omohyoid muscle, levator scapulae muscle, and the scalenus medius muscle. The cranial margins of the LSC-LN are the cranial CT-slice omohyoid muscles, and the caudal ISC-LN consists of the caudal CT-slice external jugular vein or transverse cervical vessels.

The medial SC LN (MSC-LN) medial edge lies at the medial edge of the internal carotid artery and the internal jugular vein. The lateral margin is formed by the lateral border of the sternocleidomastoid muscle and the scalenus anterior muscle. The ventral external MSC-LN lies on the dorsal surface of the sternocleidomastoid muscle, and the dorsal boundary is formed by the dorsal border of the internal carotid artery or the ventral border of the scalenus anterior muscle. The caudal CT-slice cricoid cartilage is the cranial external margin of the MSC-LNs, and the cranial CT-slice jugular–subclavian junction or caudal CT-slice external jugular vein are the caudal margins of the MSC-LNs.

For the IC-LN, the skin or the origin of the pectoralis major muscle on the clavicle forms the medial margin, and the medial border of the coracoid process, the pectoralis minor muscle, and the coracobrachialis muscle form the lateral margin. The pectoralis major muscle or skin forms the ventral margin, while the clavicle or the subclavius muscle form the dorsal margin and surround the IC-LN. The IC-LNs run along the caudal end of deltoid muscle to the caudal coracoid process.

Metastatic involvement of two or more groups in the ipsilateral clavicular LN area (MMIC-LN) referred to the involvement of two or more of the following: LSC-LN, MSC-LN, or IC-LN.

Statistics

Data pertaining to the following clinical characteristics were collected: age, menopausal status, tumor location, laterality of BC (left- or right-sided), tumor size, histological type, lymphatic vessel invasion, vascular invasion, estrogen receptor (ER) status, progestogen receptor (PR) status, Her2 status, Ki-67, chest wall radiation status, ipsilateral clavicular radiation status, and axillary metastasis status. The characteristic of ipsilateral axillary metastases was classified on the basis of the CT imaging results. Two experienced radiologists who were blinded to the clinical information independently identified the subgroup of each axillary metastatic LN.

The incidence of locoregional metastases was calculated and compared among subgroups. The cut-off tumor size that was associated with metastatic involvement of specific LN groups was assessed by receiver operating characteristic (ROC) curve analysis using Cutoff Finder software (http://molpath.charite.de/cutoff).[16] The subgroup characteristics were analyzed by univariate and multivariate logistic regression analysis. P values ≤ 0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

There were 88 patients with post-mastectomy SC or IC LN metastases who were eligible for the analysis. Among them, the number of patients with metastatic involvement of IMSC-LN, ILSC-LN, IIC-LN, and MMIC-LN was 48 (54.5%), 60 (68.2%), two (2.3%), and 19 (21.6%), respectively (Table 1). The mean age of the patients was 45 years (range, 25–70 years).

Table 1. Frequency of metastatic involvement of each group of supraclavicular lymph nodes in the study population (n = 88).

Regional LN metastases	N	(%)
IMSC-LN	48	54.5
ILSC-LN	60	68.2
IIC-LN	2	2.3
MMIC-LN	19	21.6

LN, lymph node; IMSC-LN, ipsilateral medial supraclavicular lymph node area; ILSC-LN, ipsilateral lateral supraclavicular lymph node area; IIC-LNL, ipsilateral infraclavicular lymph node area; MMIC-LN, ≥ 2 groups in the ipsilateral clavicular lymph node area.

The patient characteristics are summarized in Table 2.

ILSC-LN

The characteristics of the 60 patients with LRR in ILSC-LNs are presented in Table 3. The Cutoff Finder software indicated that the optimal tumor size in this group was 2.4 cm (Figure 1). On univariate binomial logistic analysis, tumor size ≥ 2.4 cm was associated with a significantly higher risk of ILSC-LN metastasis compared with other SC LNs (odds ratio [OR] = 3.020, 95% confidence interval [CI]: 1.282–7.117; P = 0.011). Subsequently, we adjusted for menopausal status, tumor location, left or right BC, tumor size, Her-2 status, axillary metastasis status, and carcinoma of the nipple status in the multivariate logistic analysis. The results showed that tumor size ≥ 2.4 cm (OR = 3.500; P = 0.020) was associated with a higher risk of metastases in ILSC-LN, while over expression of Her-2 (OR = 0.229; P = 0.025) was associated with a lower risk of metastases.

IMSC-LN

Triple-negative status (OR = 3.850; 95% CI: 1.143–12.965; P = 0.030), ER negative status (OR = 0.431, 95% CI: 0.204–0.911; P = 0.028), and left-sided BC (OR = 0.387,

Table 2. Baseline characteristics of patients with post-mastectomy regional lymph node metastases.

Characteristics	N (%)
Age (years, mean ± SD)	45 ± 9.9
Menopausal status (missing 1)	
Premenopausal	48 (55.2)
Postmenopausal	39 (44.8)
Tumor size (missing 22)	
(cm, median, Q25–Q75)	3.0, 2.3–5.0
Left/right breast cancer	
Left breast cancer	56 (63.6)
Right breast cancer	32 (36.4)
Lymphatic vessel invasion (missing 14)	
Negative	44 (59.5)
Positive	30 (40.5)
Vascular invasion (missing 14)	
Negative	47 (63.5)
Positive	27 (36.5)
Carcinoma of the nipple (missing 17)	
Negative	66 (93.0)
Positive	5 (7.0)
ER status (missing 4)	
Negative	50 (42.7)
Positive	67 (57.3)
PR status (missing 4)	
Negative	38 (45.2)
Positive	46 (54.8)
Her2 status (missing 6)	
Negative	24 (29.3)
Positive	58 (70.7)
Ki-67 status (missing 16)	
<14%	11 (15.3)
≥14%	61 (84.7)
Subtype (missing 8)	
Luminal A	2 (2.5)
Luminal B	48 (62.5)
Her2 type	19 (23.8)
Triple-negative	11 (13.8)
Chest wall radiation status	
No	53 (60.2)
Yes	35 (39.8)
Ipsilateral SC radiation status	
No	63 (71.6)
Yes	25 (28.4)
Ipsilateral axillary level I metastases	
Negative	63 (71.6)
Positive	25 (28.4)

ER, estrogen receptor; PR, progestogen receptor; SC, supraclavicular; SD, standard deviation.

95% CI: 0.189–0.834; P = 0.015) were associated with a higher risk of metastases to IMSC-LNs. After adjusting for menopausal status, tumor location, left or right BC, ER status, pathology results, radiation status, and axillary metastasis status, left BC (OR = 0.191; P = 0.020) and positive axillary LNs (OR = 4.175; P = 0.043) were associated with a higher risk of local failure. ER-positive status was associated with a significantly lower risk of metastasis to IMSC-LNs (OR = 0.232; P = 0.029; Table 4).

MMIC-LN

Nineteen (21.6%) patients were found to have regional metastases in MMIC-LN. The Cutoff Finder software indicated that the optimal tumor size in this group was 2.4 cm (Figure 2). In the univariate binomial logistic regression models, positive ipsilateral axillary level I LNs (OR = 2.574, 95% CI: 1.013–6.540; P = 0.047), triple-negative BC (OR = 3.905, 95% CI: 1.202–12.686; P = 0.023), tumor size ≥2.4 cm (OR = 4.706, 95% CI: 1.009–21.955; P = 0.049), absence of lymphatic invasion (OR = 0.150, 95% CI: 0.032–0.694; P = 0.015), and absence of vascular invasion (OR = 0.264, 95% CI: 0.071–0.984; P = 0.047) showed a significant association with MMIC-LN metastases. On multivariate logistic analysis, tumor size ≥2.4 cm (OR = 11.784; P = 0.037), and presence of level I ipsilateral axillary metastases (OR = 10.040; P = 0.007) showed a significant association with regional metastases (Table 5).

Discussion

To the best of our knowledge, this is the first study that characterized the postoperative recurrence patterns in SCLNs after BC surgery and identified the associated risk factors. In accordance with the RTOG guidelines, we identified the subgroups of patients who experience a high rate of metastases in the SCLNs. In this

Table 3. Results of univariate and multivariate analysis for ILSC-LN patients.

	Univariate analysis	Multivariate analysis	
Characteristics	P	P (95% CI)	OR
Tumor size	0.011	0.020 (1.222–10.022)	
≥2.4 cm			3.500
<2.4 cm			1
Subtype	0.108	0.025 (0.063–0.833)	
Her2 type			0.229
Other type			1
Menopausal status		0.875	
Tumor location		0.535	
Left/right breast cancer		0.748	
Axillary metastasis status		0.479	
Carcinoma of the nipple		0.462	

ILSC-LN, ipsilateral lateral supraclavicular lymph node area; OR, Odds ratio; CI, confidence interval.

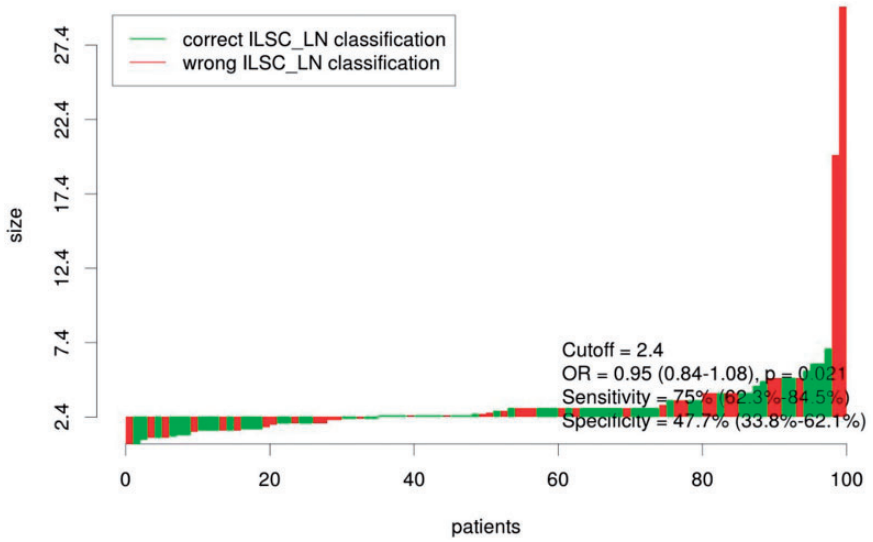

Figure 1. The cutoff value for tumor size in ILSC-LN using Cutoff Finder software.
ILSC-LN, ipsilateral lateral supraclavicular lymph node area.

study, among patients with regional LN metastases, the most common metastasis area was the ILSC-LN area (68.2%) followed by IMSC-LN area (54.5%). The least common metastasis area was IIC-LN area (2.3%). Tumor size ≥2.4 cm was associated with ILSC-LN metastases while left-sided BC, positive axillary LNs, and ER-status were associated with higher local failure rates in the IMSC-LNs. These findings may have implications for contouring the clinical target volume during RT.

Several recent studies have identified some SCLN metastases that were located outside the RTOG volume. In a study by Brown et al.,[12] approximately 39% LN

Table 4. Results of univariate and multivariate analysis for IMSC-LN patients.

	Univariate analysis	Multivariate analysis	
Characteristics	P	P (95% CI)	OR
Left/right breast cancer	0.015	0.020 (0.047–0.774)	
Left breast cancer			0.191
Right breast cancer			1
ER status	0.028	0.029 (0.063–0.862)	
Positive			0.043
Negative			1
Ipsilateral axillary level I metastases	0.578	0.043 (1.048–16.634)	
Positive			4.175
Negative			1
Menopausal status		0.056	
Tumor location		0.922	
Carcinoma of the nipple		0.466	
Chest wall radiation status		0.553	

IMSC-LN, ipsilateral medial supraclavicular lymph node area; ER, estrogen receptor; OR, Odds Ratio; CI, confidence interval.

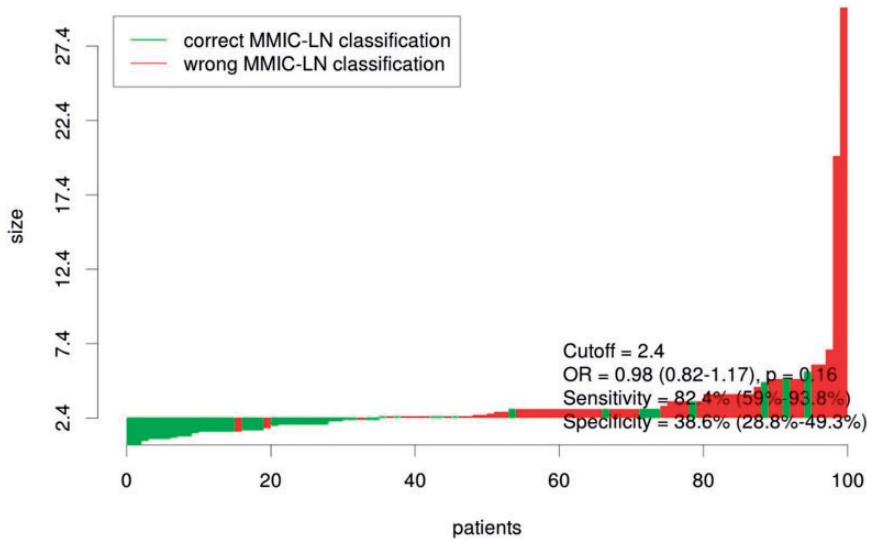

Figure 2. The cutoff value for tumor size in MMIC-LN using Cutoff Finder software.
MMIC-LN, metastatic involvement of ≥2 groups in the ipsilateral clavicular lymph node area.

metastases were outside the volume, and the posterolateral SC area (posterolateral to the RTOG volume) was among the highest at-risk areas for SCLN metastases. However, very few studies have focused on mapping the SC area. Jing et al.[13] showed that over 81% of patients had SC LN metastases in the lateral portion of the SC volume, and the authors recommended enlargement of the present atlas. Consistent with the previous study, we found that the ILSC-LNs (68.2%) were the most common metastatic

Table 5. Results of univariate and multivariate analysis for MMIC-LN patients.

	Univariate analysis	Multivariate analysis	
Characteristics	P	P (95% CI)	OR
Tumor size	0.049	0.037 (1.154–120.341)	
≥2.4 cm			11.784
<2.4 cm			1
Ipsilateral axillary level I metastases	0.047	0.007 (1.883–53.542)	
Positive			10.040
Negative			1
Menopausal status		0.403	
Tumor location		0.525	
Carcinoma of the nipple		0.411	
Left/right breast cancer		0.182	
Chest wall radiation status		0.153	

MMIC-LN, involvement of ≥2 groups in the ipsilateral clavicular lymph node area; OR, Odds ratio; CI, confidence interval.

site for patients with post-mastectomy SCLN metastases.

An increasing amount of evidence suggests that axillary LN metastasis is a strong prognostic factor.[17] In particular, several studies have investigated the incidence of SCV (0% to 20%) and axillary LN (ALN) (0% to 10%), and they also demonstrated that prognosis is better in isolated recurrence than with multiple sites.[6,18] However, few studies have found an association between SC and ALN. Yu et al.[19] reported a strong association between SCLN and ALN metastasis. Consistent with this result, we found that positive ALNs were associated with IMSC-LN ($P = 0.043$, $OR = 4.175$) and MMIC-LN ($P = 0.007$, $OR = 10.040$) metastases. On multivariate analysis, patients with positive ALN had a significantly higher risk of SCLN metastasis.

Her-2 is a member of epidermal growth factor receptor family and its positive expression is associated with a poor prognosis.[20–24] It regulates cell growth, differentiation, adhesion, and motility.[25] Moreover, Her-2 receptor expression was shown to be associated with aggressive characteristics of BC.[26,27] Li et al.[27] demonstrated high Her-2 expression in BC patients with ALN metastasis. In a recent retrospective cohort study, Her-2-positive status was associated with a higher risk of ALN metastasis.[28] Very few studies have investigated the relationship between Her-2 status and SCLN metastasis. Overexpression of Her-2 was associated with a lower risk of ILSC-LN metastasis; however, the underlying mechanism is not clear. On univariate and multivariate analysis, negative ER status was a risk factor for IMSC-LN metastasis. This result is consistent with several studies. In a previous study, ER-positive status was associated with a lower risk of LRR and metastasis; in addition, in accordance with an expert panel of the American Society of Clinical Oncology, ER negativity is associated with poor outcomes in patients with BC.[27,29] In another study by He et al.,[28] hormone receptor $(HR)^-/Her2^-$ was associated with a lower risk of LN metastasis.

On univariate analysis, negative lymphatic invasion and vascular invasion status showed a significant association with MMIC-LN metastasis; however, after controlling for menopausal status, left/right BC, PR status, carcinoma of the nipple, Her-2 status, location of the tumor, and

chest wall radiation status on multivariate logistic analysis, there was no significant association of negative lymphatic vessel invasion and vascular invasion status. Further studies should be designed to confirm whether RT may increase the risk of contralateral SC LN metastasis and incorporate a subgroup analysis that is disaggregated by disease stage to determine the relationship between staging and subgroups of SCLN metastasis.

There are several limitations in this study. First, this was a retrospective study with a relatively small sample size ($n = 88$). A larger sample size is required to clarify the role of irradiation of SCLNs in mastectomy patients. Second, not all pathological characteristics were included in the analysis. For example, clavicular regions as well as internal mammary regions were important. Further studies should be designed to confirm ipsilateral internal mammary nodes. Additionally, there may be anatomical variability with respect to the location of SCLNs, but two experienced radiologists (who were blinded to clinical information) independently identified the subgroups of LNs that were affected by metastases to minimize any errors. A further study on survival analysis in each group with SC radiation status will provide valuable insights.

Conclusion

The ILSC-LN area showed the highest risk of metastatic involvement among the SC LNs in BC patients. Tumor size ≥ 2.4 cm and $Her2^-$ subtype were associated with a higher risk of ILSC-LN metastases. Left-sided BC, positive axillary LNs, ER-negative status, and tumor size ≥ 2.4 cm exhibited an association with local failure rates post-mastectomy. Further study with a larger sample size is required to clarify the role of SCLNs in mastectomy patients.

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Author contributions

All authors participated in the conduct of the research, as follows: PCL, manuscript writing and performing procedures; XJL, manuscript writing and data analysis; JLL, FFL, and QYZ, contributed to draft conception and design; LRT, YXH, and XQZ, contributed to writing the manuscript; KXD and XYL, participated in data analysis; and JXW, contributed to writing the manuscript, draft conception, and design. All authors approved the final manuscript.

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