Clinical significance of extranodal extension in sentinel lymph node positive breast cancers

Xia Yang

Fudan University Shanghai Cancer Center

Xiaoxi Ma

Fudan university shanghai cancer center

Wentao Yang

Fudan university Shanghai Cancer Center

Ruohong Shui (✉ shuiruohong2014@163.com)

Fudan University Shanghai Cancer Center

Research

Keywords: Breast cancer, Sentinel lymph node, Extra-nodal extension

Posted Date: March 9th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-16356/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Scientific Reports on September 7th, 2020.
See the published version at <https://doi.org/10.1038/s41598-020-71594-7>.

Abstract

Background The precise stage of lymph node (LN) metastasis is a strong prognostic factor in breast cancer, and sentinel lymph node (SLN) is the first station of nodal metastasis, whereas the clinical value of extranodal extension (ENE) in SLN are still in exploration.

Objective Our study aimed to evaluate the predictive and prognostic values of ENE in SLN and to investigate the feasibility of ENE to predict non-SLN metastasis, disease free survival (DFS) and overall survival (OS) in clinical practice.

Methods 183 cases of primary invasive breast cancer (cT1-2N0 breast cancer with 1-2 positive SLNs) underwent SLN biopsy and axillary lymph node dissection (ALND) between 2008 and 2015 were extracted from the pathology database of Fudan University Shanghai Cancer Center. Sections were reviewed for the microscopic features of SLN, including the number and pattern of SLN metastasis, SLNs positive ratio, nodal vascular invasion (NVI), and ENE. The associations between tumor features including ENE and non-SLN metastasis, DFS and OS were analyzed. Moreover, ENE was subclassified into circumferential (CD-ENE) and perpendicular (PD-ENE) and set a threshold as 2mm or 3mm to evaluate the prognostic value of ENE.

Results 73/183 (39.9 %) cases were positive for ENE in SLN. Logistic regression analysis indicated that ENE, the number and pattern of SLN involvement, SLN positive ratio, and NVI were significantly associated with the presence of non-SLN metastasis in univariate analysis. ENE, higher number of SLN involvement, SLN macrometastasis, and NVI were significantly associated with a higher rate of non-SLN metastasis in multivariate analysis. Cox regression analysis showed ENE in SLN was associated with DFS and OS in univariable analysis, but not in multivariable analysis. Whereas the size of ENE (CD-ENE and PD-ENE) subdivided by 3mm (or 2mm) cutoff values were not found as strongly prognostic factors of DFS and OS as well.

Conclusions Our study indicated that ENE in SLN was a predictor for non-SLN metastasis in breast cancers, patients with ENE in SLN had a higher rate of non-SLN metastasis. ENE in SLN was associated with DFS and OS in univariable analysis, but not in multivariable analysis. The size of ENE (CD-ENE and PD-ENE) which was classified by a 3mm (or 2mm) cutoff value had no significant prognostic values in this study. The prognostic value of ENE in SLN and the cutoff values of ENE in SLN in breast cancers need further investigation.

Introduction

Sentinel lymph node (SLN) is the first station of nodal metastasis ^[1, 2]. SLN biopsy (SLNB) could accurately predict axillary lymph node status and has been established as standard treatment in patients with clinically negative lymph nodes (cN0) breast cancers ^[3-5]. In 2010, the results of American College of Surgeons Oncology Group (ACOSOG) Z0011 trial indicated that patients with limited disease burden on SLN (even 1-2 macrometastasis) without ALND could obtain excellent regional control, and SLNB may be

reasonable management for selected patients with early-stage (clinical T1N0 or T2N0) breast cancer treated with breast conserving surgery, radiotherapy and adjuvant systemic therapy^[6]. Based on these results, American Society of Clinical Oncology Clinical Practice Guideline and National Comprehensive Cancer Network (NCCN) recommends that women who meet the Z0011 criteria may not undergo ALND^[7, 8]. Thus, increasing number of patients are omitting ALND in favor of SLNB can avoid the underlying morbidity of ALND^[9-11]. However, a subset of patients with limited disease burden on SLN may have relatively high aggressive behavior and poor survival after SLNB. Thus, it is important to explore the poor prognostic factors in breast cancers with SLNs involvement.

Extranodal extension (ENE), which defined as extension of neoplastic cells through the lymph nodal capsule into the peri-nodal adipose tissue, has emerged as an important prognostic factor in several types of malignancies^[12-19]. Several studies suggested that the presence and extent of ENE in SLN were significantly correlated with non-SLN metastasis and the number of involved lymph nodes in breast cancers^[20-25]. However, few studies have focused on the prognosis value of ENE in SLN. The clinical significance of ENE in SLN in breast cancers is still in exploration.

The study aimed to establish the pathological assessment of ENE in positive SLN and to evaluate the clinical significance of ENE in SLN involved breast cancers, including its association with non-SLN metastasis, disease free survival (DFS) and overall survival (OS).

Methods

183 consecutive patients with primary invasive breast cancers (cT1-2N0 breast cancer with 1–2 positive SLNs) who underwent SLN biopsy and ALND at Fudan University Shanghai Cancer Center from 2008 to 2015 were analyzed. Patients with incomplete clinical information, recurrence /metastasis at diagnosis, previous axillary surgery, or received neoadjuvant chemotherapy were excluded. Informed consent was obtained from all patients. All cases were invasive ductal carcinoma (invasive carcinoma of no special type, NST). The SLN was identified using 1% isosulfan blue dye and 99mTc-labeled sulfur colloid. SLN biopsy was performed as lymph nodes that demonstrated blue dye uptake, radiotracer uptake, or both. Imprint cytology of SLN was performed during operation. Each SLN was serially cut to tissue blocks along the short axis at 2 mm intervals and imprint was performed on both sides of each tissue block. Those patients with metastatic tumor cells on imprint slice received additional ALND. Final diagnosis of SLN was performed on paraffin-embedded tissues. All tissue blocks of SLN were fixed in formalin, embedded in paraffin, and examined using hematoxylin and eosin (H&E) staining with serial section. The pattern of metastasis (micrometastasis or macrometastasis) was analyzed. If SLN macrometastasis was recognized on paraffin-embedded slices in patients with negative results of imprint cytology, these patients received additional ALND. Non-SLNs were evaluated using H&E staining.

Results

Clinicopathological features of patients

The clinicopathological characteristics of 183 primary invasive carcinomas were listed in Table 1. All patients were female. The median age was 49.4 years, ranging from 27 to 78 years. 51.9% of patients (95/183,) had a limited tumor size (no more than 2cm), and 62.3% (114/183) of the patients had one positive SLN. The majority of cases (74.9%) had macrometastasis in SLN. The median number of SLN biopsied was 2.7 (1-5) and the median SLN positive ratio was 0.56 (0.1-1). 73/183 (39.9 %) cases were positive for ENE in SLN. The size of ENE varied between ENE positive cases. The median of CD-ENE was 3mm (varied between 0.1–10 mm), while the median of PD-ENE was 2mm (ranged from 0.1 to 7.0 mm) (Fig 1). Among other nodal features, most patients (138/183, 75.4%) had no more than 3 total LN involvements, and 66.7% (122/183) of the patients had no NVI in SLN. Among the clinicopathological characteristics examined in this cohort, ENE in SLN was associated with higher N stage, the number of SLN biopsied, the number and pattern of SLN metastasis, SLN positive ratio and NVI (Table 1).

The associations between tumor characteristics including ENE in SLN and non-SLN metastasis

In the 73 patients with ENE in SLN, 59 (80.8%) had additional non-SLN metastasis, comparing with 23/110 (20.9 %) patients without ENE in SLN ($P < 0.001$). Univariate analysis indicated that ENE, the number and pattern of SLN involvement, SLN positive ratio, and NVI were significantly associated with the presence of non-SLN metastasis (Table 2). Multivariate analysis including predictive factors indicated that ENE, higher number of SLN involvement, SLN macrometastasis, and NVI were significantly associated with a higher rate of non-SLN metastasis (Table 2).

The associations between tumor characteristics including ENE in SLN and long-term survival

Survival data were available for all patients in this cohort. Over a median follow-up of 62.2 months (range 8–136), 32 patients (17.5%) had local and/or distant recurrence, and 12 patients (6.6%) died during this follow-up period. The DFS and OS of patients with SLN involvement classified according to the number of SLN biopsied (Figs. 2a, 3a), the number of SLN involvement (Figs. 2b, 3b), the pattern of SLN metastases (Figs. 2c, 3c), SLN positive ratio (Figs. 2d, 3d), ENE (Figs. 2e, 3e), CD-ENE (Figs. 2f, 3f), PD-ENE (Figs. 2g, 3g), NVI (Figs. 2h, 3h) were illustrated graphically.

Cox proportional hazards regression analyses were performed to evaluate the prognostic value of tumor features (Table 3). It showed that ENE, NVI, and histological grade were significantly associated with DFS in univariable analysis. Multivariable analysis including prognostic variables confirmed that histological grade and NVI had strongly prognostic values for DFS, while ENE in SLN was not an independent predictor of DFS. Similarly, ENE, tumor size, histological grade, N stage, and NVI were found significantly correlated with OS in univariable analysis, whereas ENE and other tumor features except tumor size and histological grade were not independent factors for OS in multivariable analysis. Moreover, survival analysis indicated that the size of ENE which subdivided as CD-ENE ($\leq 3\text{mm}$ vs $> 3\text{mm}$) and PD-ENE ($\leq 2\text{mm}$ vs $> 2\text{mm}$), were significantly associated with DFS and OS in univariable analysis, but were not found as strongly prognostic factors of DFS and OS in multivariable analysis as well (Table 4).

Discussion

Invasive breast cancer is the most common malignancy in women. The most common metastasis site of breast cancer is axillary lymph nodes, and SLN is the first station of nodal metastasis ^[1, 2]. Recently, a study about the relationship between Oncotype-DX recurrence score (RS) and lymph node burden in clinically node negative breast cancer patients found that RS couldn't predict nodal burden and wasn't useful to guide decisions regarding the extent of axillary surgery ^[27]. Therefore, it is necessary to find a useful histological marker that can identify those patients who have a high risk to non-SLN nodal metastasis and poor prognosis.

ENE has been recognized as a prognostic predictor in several types of malignancies^[16, 28-31], and has been included in the AJCC TNM staging system of head and neck cancers ^[32, 33]. ENE has been required to be described in routine pathological reports according to the College of American Pathologists (CAP) ^[34]. However, it has not yet been included in the eighth edition of AJCC Cancer staging system of breast cancers^[35]. Some studies have demonstrated that the presence of ENE in involved axillary nodes was associated with the total number of involved axillary nodes and poor prognosis in breast cancer ^[36-38]. However, the predictive and prognostic significance of ENE in SLN still needs further investigation.

In this retrospective analysis including 183 breast cancers with SLN involvement, we found 82 patients (38.6%) were ENE positive in SLN. The rate of ENE in SLN in this study was compatible with previous reports ^[25, 39, 40]. Previous studies have demonstrated the presence of ENE in SLN was associated with overall nodal burden ^[21, 22, 41, 42]. Some studies showed that ENE in SLN was associated with four or more metastatic axillary nodes ^[20, 25, 43]. ENE in the involved lymph node was regarded as a demonstration of tumor migration and invasion ability which recruit degradation factors that permit cancer cells to break through the lymph node capsule ^[22, 40, 44]. In our cohort, patients with ENE in SLN had a significantly higher frequency of non-SLN involvement, the presence of ENE in SLN was positively correlated with non-SLN metastasis in univariate and multivariate analysis. Our study indicated that the presence of ENE in SLN was a predictor for non-SLN metastasis, and such patients may benefit from further ALND.

The prognosis value of ENE in SLN is still in exploration. A meta-analysis including 624 patients (163 ENE+ and 461 ENE-) showed that ENE in SLN was associated with a higher risk of both mortality (RR = 2.51; 95% CI: 1.66-3.79, P < 0.0001) and recurrence of disease (RR = 2.07, 95% CI: 1.38-3.10, P < 0.0001) ^[45]. Schwentner L et al found that ENE in SLN was linked to worse overall survival in univariate analysis, while this correlation disappeared when adjusting for nodal status, age, and comorbidities in multivariate analysis ^[44]. Similar results have been found in a study that conducted by Choi et al ^[25]. Other studies with a relatively small population indicated that the presence of ENE in SLN was associated with poorer prognosis ^[40, 46]. Our results were consistent with previous study ^[47], Kaplan Meier curves and log-rank test showed that ENE in SLN was associated with lower DFS and OS. However, the presence of ENE in

SLN was not an independent predictor for DFS and OS in Cox multivariable regression analysis. Our study indicated that the prognostic value of ENE in SLN in breast cancers still need further investigation.

Methodologies for ENE size measurement is still not standardized [40, 44, 46]. Aziz et al evaluated the clinical significance of ENE which was divided into circumferential (CD-ENE) and perpendicular (PD-ENE) extra-nodal growth, and the results showed that PD-ENE (with 3mm as cut-off value) was an independent prognostic factor for disease-free survival of breast cancers [48]. Choi et al and Gooch et al's study showed that the extent of ENE was associated with greater axillary disease burden, and ENE >2mm was the strongest predictor of N2 disease ($p < 0.001$), and poorer DFS and OS [25, 39]. The 2017 AJCC TNM classification of head and neck cancer [32] classified ENE into ENEmi and ENema based on a 2-mm cutoff value for the extension distance of cancer cells from the lymph node capsule. In our study, we measured the extent of ENE by the widest (CD-ENE) or highest (PD-ENE) diameter of the invasive front. Our study showed that the size of ENE (CD-ENE and PD-ENE) subdivided by a 3mm (or 2mm) cutoff value was not an independent factor for DFS and OS. Our study indicated that the association between the size of ENE in SLN and prognosis in breast cancers still need further study, and the cutoff values of ENE in SLN still need further exploration.

Regarding other nodal features, our study indicated that NVI in SLN were a prognostic factor for DFS, which significantly predicted the risk of recurrence in early stage breast cancers. Meanwhile, our study had some limitations. It was a single-institution retrospective analysis including relatively small samples. Further large-scale prospective and retrospective studies still need to evaluate the clinical values of ENE in SLN in breast cancers.

Conclusions

Our study indicated that ENE in SLN was a predictor for non-SLN metastasis in early stage breast cancers, patients with ENE in SLN had a higher rate of non-SLN metastasis. ENE in SLN was associated with DFS and OS in univariable analysis, but not in multivariable analysis. The size of ENE (CD-ENE and PD-ENE) which was classified by a 3mm (or 2mm) cutoff value had no significant predictive and prognostic values in this study. The prognostic value of ENE in SLN and the cutoff values of ENE in SLN in breast cancers need further investigation.

Declarations

Acknowledgements

Not applicable

Authors' contributions

Work design (all authors). Pathological assessment (R.S and W.Y). ENE evaluation (X.Y and XX.M). Data Collection and Drafting the article (X.Y). Data statistics and analysis (X.Y). Revision of the article (R.S).

Ethics approval and consent to participate

The study was approved by Ethics Institutional Review Board of Fudan University Shanghai Cancer Center. All procedures performed involving human participants were in accordance with the ethical standards of Ethics Institutional Review Board of Fudan University Shanghai Cancer Center and with the 1964 Helsinki declaration and its later amendments. Written informed consent was obtained from all patients of the study, who signed the informed consent allowing the use of their biological material, donated for our Biobank, for scientific projects, and for data publication.

Consent for publication

Not applicable.

Competing interests

The authors have declared that no competing interest exists.

Funding

This work was supported by grants from Research Project of the Science and Technology Commission of Shanghai Municipality (Project No: 15411965100, for Ruohong Shui) and Shanghai Science and technology development fund (19MC1911000).

References

- [1] GIULIANO A E, KIRGAN D M, GUENTHER J M, et al. Lymphatic mapping and sentinel lymphadenectomy for breast cancer [J]. *Ann Surg*, 1994, 220(3): 391-8; discussion 8-401.
- [2] VERONESI U, PAGANELLI G, VIALE G, et al. Sentinel lymph node biopsy and axillary dissection in breast cancer: results in a large series [J]. *J Natl Cancer Inst*, 1999, 91(4): 368-73.
- [3] ALBERTINI J J, LYMAN G H, COX C, et al. Lymphatic mapping and sentinel node biopsy in the patient with breast cancer [J]. *JAMA*, 1996, 276(22): 1818-22.
- [4] VERONESI U, PAGANELLI G, GALIMBERTI V, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes [J]. *Lancet*, 1997, 349(9069): 1864-7.
- [5] KRAG D, WEAVER D, ASHIKAGA T, et al. The sentinel node in breast cancer—a multicenter validation study [J]. *N Engl J Med*, 1998, 339(14): 941-6.
- [6] GIULIANO A E, MCCALL L, BEITSCH P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial [J]. *Ann Surg*, 2010, 252(3): 426-32; discussion 32-3.

- [7] LYMAN G H, TEMIN S, EDGE S B, et al. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology clinical practice guideline update [J]. J Clin Oncol, 2014, 32(13): 1365-83.
- [8] GRADISHAR W J, ANDERSON B O, BLAIR S L, et al. Breast cancer version 3.2014 [J]. J Natl Compr Canc Netw, 2014, 12(4): 542-90.
- [9] CAUDLE A S, HUNT K K, TUCKER S L, et al. American College of Surgeons Oncology Group (ACOSOG) Z0011: impact on surgeon practice patterns [J]. Ann Surg Oncol, 2012, 19(10): 3144-51.
- [10] LOVELAND-JONES C E, RUTH K, SIGURDSON E R, et al. Patterns of nodal staging during breast conservation surgery in the medicare patient: will the ACOSOG Z0011 trial change the pattern of care? ECI [J]. Breast Cancer Res Treat, 2014, 143(3): 571-7.
- [11] LIU M, WANG S, CUI S, et al. The feasibility of the ACOSOG Z0011 Criteria to Chinese Breast Cancer Patients: A Multicenter Study [J]. Sci Rep, 2015, 5(15241).
- [12] LEE Y C, WU C T, KUO S W, et al. Significance of extranodal extension of regional lymph nodes in surgically resected non-small cell lung cancer [J]. Chest, 2007, 131(4): 993-9.
- [13] AN Y, PARK H S, KELLY J R, et al. The prognostic value of extranodal extension in human papillomavirus-associated oropharyngeal squamous cell carcinoma [J]. Cancer, 2017, 123(14): 2762-72.
- [14] KIM C W, KIM J, YEOM S S, et al. Extranodal extension status is a powerful prognostic factor in stage III colorectal cancer [J]. Oncotarget, 2017, 8(37): 61393-403.
- [15] JIANYONG L, JINJING Z, ZHIHUI L, et al. A Nomogram Based on the Characteristics of Metastatic Lymph Nodes to Predict Papillary Thyroid Carcinoma Recurrence [J]. Thyroid, 2018, 28(3): 301-10.
- [16] KIM C W, KIM J, PARK Y, et al. Prognostic Implications of Extranodal Extension in Relation to Colorectal Cancer Location [J]. Cancer Res Treat, 2018,
- [17] AI Q Y, KING A D, POON D M C, et al. Extranodal extension is a criterion for poor outcome in patients with metastatic nodes from cancer of the nasopharynx [J]. Oral Oncol, 2019, 88(124-30).
- [18] BILLFALK-KELLY A, YU E, SU J, et al. Radiologic Extranodal Extension Portends Worse Outcome in cN+ TNM8 Stage I Human Papillomavirus-Mediated Oropharyngeal Cancer [J]. Int J Radiat Oncol Biol Phys, 2019,
- [19] MARKS P, GILD P, SOAVE A, et al. The impact of variant histological differentiation on extranodal extension and survival in node positive bladder cancer treated with radical cystectomy [J]. Surg Oncol, 2019, 28(208-13).

- [20] RIVERS A K, GRIFFITH K A, HUNT K K, et al. Clinicopathologic features associated with having four or more metastatic axillary nodes in breast cancer patients with a positive sentinel lymph node [J]. *Ann Surg Oncol*, 2006, 13(1): 36-44.
- [21] CIL T, HAUSPY J, KAHN H, et al. Factors affecting axillary lymph node retrieval and assessment in breast cancer patients [J]. *Ann Surg Oncol*, 2008, 15(12): 3361-8.
- [22] FUJII T, YANAGITA Y, FUJISAWA T, et al. Implication of extracapsular invasion of sentinel lymph nodes in breast cancer: prediction of nonsentinel lymph node metastasis [J]. *World J Surg*, 2010, 34(3): 544-8.
- [23] KWON Y, RO J, KANG H S, et al. Clinicopathological parameters and biological markers predicting non-sentinel node metastasis in sentinel node-positive breast cancer patients [J]. *Oncol Rep*, 2011, 25(4): 1063-71.
- [24] MITTENDORF E A, HUNT K K, BOUGHEY J C, et al. Incorporation of sentinel lymph node metastasis size into a nomogram predicting nonsentinel lymph node involvement in breast cancer patients with a positive sentinel lymph node [J]. *Ann Surg*, 2012, 255(1): 109-15.
- [25] CHOI A H, BLOUNT S, PEREZ M N, et al. Size of Extranodal Extension on Sentinel Lymph Node Dissection in the American College of Surgeons Oncology Group Z0011 Trial Era [J]. *JAMA Surg*, 2015, 150(12): 1141-8.
- [26] EDGE S B, COMPTON C C. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM [J]. *Ann Surg Oncol*, 2010, 17(6): 1471-4.
- [27] TEVIS S E, BASSETT R, BEDROSIAN I, et al. OncotypeDX Recurrence Score Does Not Predict Nodal Burden in Clinically Node Negative Breast Cancer Patients [J]. *Ann Surg Oncol*, 2019, 26(3): 815-20.
- [28] FAJKOVIC H, CHA E K, JELDRES C, et al. Extranodal extension is a powerful prognostic factor in bladder cancer patients with lymph node metastasis [J]. *Eur Urol*, 2013, 64(5): 837-45.
- [29] LEE I S, PARK Y S, RYU M H, et al. Impact of extranodal extension on prognosis in lymph node-positive gastric cancer [J]. *Br J Surg*, 2014, 101(12): 1576-84.
- [30] WU M H, SHEN W T, GOSNELL J, et al. Prognostic significance of extranodal extension of regional lymph node metastasis in papillary thyroid cancer [J]. *Head Neck*, 2015, 37(9): 1336-43.
- [31] SAKAI M, SUZUKI S, SANO A, et al. Significance of lymph node capsular invasion in esophageal squamous cell carcinoma [J]. *Ann Surg Oncol*, 2012, 19(6): 1911-7.
- [32] AMIN M B, GREENE F L, EDGE S B, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging [J]. *CA Cancer J Clin*, 2017, 67(2): 93-9.

- [33] LYDIATT W M, PATEL S G, O'SULLIVAN B, et al. Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual [J]. CA Cancer J Clin, 2017, 67(2): 122-37.
- [34] WEAVER D L. Pathology evaluation of sentinel lymph nodes in breast cancer: protocol recommendations and rationale [J]. Mod Pathol, 2010, 23 Suppl 2(S26-32).
- [35] GIULIANO A E, EDGE S B, HORTOBAGYI G N. Eighth Edition of the AJCC Cancer Staging Manual: Breast Cancer [J]. Ann Surg Oncol, 2018, 25(7): 1783-5.
- [36] O'KEEFFE N A, O'NEILL C, ZAHARE A, et al. A quantitative analysis of tumour characteristics in breast cancer patients with extranodal extension in non-sentinel nodes [J]. Breast, 2018, 38(171-4).
- [37] SIVRIDIS E, GIATROMANOLAKI A, GALAZIOS G, et al. Node-related factors and survival in node-positive breast carcinomas [J]. Breast, 2006, 15(3): 382-9.
- [38] STRANZL H, OFNER P, PEINTINGER F. Postoperative irradiation in breast cancer patients with one to three positive axillary lymph nodes. Is there an impact of axillary extranodal tumor extension on locoregional and distant control? [J]. Strahlenther Onkol, 2006, 182(10): 583-8.
- [39] GOOCH J, KING T A, EATON A, et al. The extent of extracapsular extension may influence the need for axillary lymph node dissection in patients with T1-T2 breast cancer [J]. Ann Surg Oncol, 2014, 21(9): 2897-903.
- [40] SHIGEMATSU H, TAGUCHI K, KOUI H, et al. Clinical Significance of Extracapsular Invasion at Sentinel Lymph Nodes in Breast Cancer Patients with Sentinel Lymph Node Involvement [J]. Ann Surg Oncol, 2015, 22(7): 2365-71.
- [41] CHANGSRI C, PRAKASH S, SANDWEISS L, et al. Prediction of additional axillary metastasis of breast cancer following sentinel lymph node surgery [J]. Breast J, 2004, 10(5): 392-7.
- [42] JOSEPH K A, EL-TAMER M, KOMENAKA I, et al. Predictors of nonsentinel node metastasis in patients with breast cancer after sentinel node metastasis [J]. Arch Surg, 2004, 139(6): 648-51.
- [43] KATZ A, SMITH B L, GOLSHAN M, et al. Nomogram for the prediction of having four or more involved nodes for sentinel lymph node-positive breast cancer [J]. J Clin Oncol, 2008, 26(13): 2093-8.
- [44] SCHWENTNER L, DAYAN D, WOCKEL A, et al. Is extracapsular nodal extension in sentinel nodes a predictor for nonsentinel metastasis and is there an impact on survival parameters?-A retrospective single center cohort study with 324 patients [J]. Breast J, 2018, 24(4): 480-6.
- [45] NOTTEGAR A, VERONESE N, SENTHIL M, et al. Extra-nodal extension of sentinel lymph node metastasis is a marker of poor prognosis in breast cancer patients: A systematic review and an exploratory meta-analysis [J]. Eur J Surg Oncol, 2016, 42(7): 919-25.

[46] CHOI A H, SURRUSCO M, RODRIGUEZ S, et al. Extranodal extension on sentinel lymph node dissection: why should we treat it differently? [J]. Am Surg, 2014, 80(10): 932-5.

[47] VANE M L G, WILLEMSSEN M A, VAN ROOZENDAAL L M, et al. Extracapsular extension in the positive sentinel lymph node: a marker of poor prognosis in cT1-2N0 breast cancer patients? [J]. Breast Cancer Res Treat, 2019, 174(3): 711-8.

[48] AZIZ S, WIK E, KNUTSVIK G, et al. Extra-nodal extension is a significant prognostic factor in lymph node positive breast cancer [J]. PLoS One, 2017, 12(2): e0171853.

Tables

Table 1 Clinicopathological characteristics of patients

Variables		No. of patients	%	Extranodal extension		P-value
				Negative (n=110)	Positive (n=73)	
Age (Y)	< 50	103	56.3	61	42	0.781
	≥ 50	80	43.7	49	31	
Pathologic T stage	T1	95	51.9	59	36	0.567
	T2	88	48.1	51	37	
Histologic grade	I-II	109	59.6	63	46	0.438
	III	74	40.4	47	27	
N stage	1	138	75.4	103	35	<0.001
	2-3	45	24.6	7	38	
No. of SLNs	≤3	123	67.2	66	57	0.011
	≥3	60	32.8	44	16	
No. of SLNs metastasis	1	114	62.3	77	37	0.008
	2	69	37.7	33	36	
SLNs positive ratio	≤0.5	107	58.5	79	28	<0.001
	>0.5	76	41.5	31	45	
Pattern of SLNs metastasis	micrometastasis	46	25.1	41	5	<0.001
	macrometastasis	137	74.9	69	68	
NVI	No	122	66.7	102	20	<0.001
	Yes	61	33.3	8	53	

Abbreviations: ENE extranodal extension; SLN sentinel lymph node; NVI nodal vascular invasion.

Table 2 Correlations between tumor features in SLN and non-SLN metastasis

Variables		Univariable analysis			Multivariable analysis		
		OR	95% CI	P-value	OR	95% CI	P-value
Age (Y)	< 50	1	-	-			
	≥50	0.82	0.41-1.62	0.563			
Pathologic T stage	T1	1	-	-			
	T2	1.49	0.76-2.93	0.25			
Histologic grade	I-II	1	-	-			
	III	0.86	0.43-1.72	0.676			
No. of SLNs	≤3	1	-	-			
	≥3	0.5	0.23-1.10	0.086			
No. of SLNs metastasis	1	1	-	-	1	-	-
	2	3.43	1.71-6.89	0.001	3.72	1.40-9.93	0.009
SLNs positive ratio	≤0.5	1	-	-	1	-	-
	>0.5	3.09	1.54-6.20	0.002	0.65	0.32-1.83	0.414
Pattern of SLNs metastasis	micrometastasis	1	-	-	1	-	-
	macrometastasis	18.29	2.84-53.50	0.003	8.09	1.51-23.73	0.020
ENE	Negative	1	-	-	1	-	-
	Positive	10.98	6.54-29.01	<0.001	3.85	1.84-11.58	0.006
NVI	No	1	-	-	1	-	-
	Yes	10.8	4.95-23.57	<0.001	2.88	1.06-8.43	0.039

Abbreviations: ENE extranodal extension; SLN sentinel lymph node; NVI nodal vascular invasion.

Table 3 Correlations between tumor features and prognosis (DFS and OS) in whole cohort

Variables		Disease free survival				Overall survival			
		Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
		HR (95% CI)	P- value	HR (95% CI)	P- value	HR (95% CI)	P- value	HR (95% CI)	P- value
Age (Y)	< 50	1	-			1	-		
	≥ 50	0.63 (0.31- 1.30)	0.211			0.24 (0.05- 2.10)	0.115		
Phathologic T stage	T1	1	-			1	-	1	-
	T2	1.68 (0.80- 3.55)	0.17			12.71 (1.64- 28.50)	0.015	3.20 (1.76- 15.17)	0.039
Histologic grade	I-II	1	-	1	-	1	-	1	-
	III	1.93 (1.26- 4.87)	0.006	2.22 (1.09- 4.49)	0.027	8.04 (1.76- 36.70)	0.007	8.76 (1.12- 38.45)	0.007
N stage	1	1	-			1	-	1	-
	2-3	1.41 (0.65- 3.07)	0.385			4.98 (1.58- 15.70)	0.006	2.12 (0.57- 7.81)	0.265
No. of SLNs	≤3	1	-			1	-		
	≥3	0.67 (0.30- 1.50)	0.335			1.42 (0.45- 4.48)	0.547		
No. of SLNs metastasis	1	1	-			1	-		
	2	1.09 (0.54- 2.21)	0.812			0.85 (0.25- 2.81)	0.783		
SLNs positive ratio	≤0.5	1	-			1	-		
	>0.5	1.61 (0.80- 3.26)	0.184			1.04 (0.33- 3.28)	0.947		
Pattern of SLNs metastasis	micrometastasis	1	-			1	-		
	macrometastasis	0.83 (0.38- 1.80)	0.636			0.97 (0.26- 3.60)	0.968		
ENE	Negative	1	-	1	-	1	-		
	Positive	2.25 (1.11- 4.58)	0.025	1.31 (0.28- 4.25)	0.531	8.15 (1.78- 24.18)	0.007	3.75 (0.47- 20.18)	0.214
NVI	No	1	-	1	-	1	-		
	Yes	2.83 (1.39- 5.76)	0.004	2.25 (1.01- 7.13)	0.036	6.51 (1.76- 24.06)	0.005	2.10 (0.36- 12.17)	0.409

Abbreviations: ENE extranodal extension; SLN sentinel lymph node; NVI nodal vascular invasion.

Table 4 Correlations between the size of ENE and prognosis (DFS and OS)

Variables		Disease free survival				Overall survival			
		Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
		HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
CD-ENE	none	1	-	1	-	1	-	1	-
	≤3	1.78 (0.82-3.85)	0.145	0.51 (0.15-1.79)	0.293	6.14 (1.24-30.41)	0.026	3.06 (0.42-18.28)	0.327
	≥3	5.37 (1.98-14.53)	0.001	2.51 (0.74-8.53)	0.139	15.98 (2.92-57.27)	0.001	6.01 (0.83-22.30)	0.125
PD-ENE	none	1	-	1	-	1	-	1	-
	≤2	1.82 (0.75-4.39)	0.185	0.57 (0.17-2.64)	0.573	6.26 (1.15-34.18)	0.034	2.76 (0.28-21.75)	0.382
	≥2	2.74 (1.22-6.16)	0.015	1.14 (0.33-3.90)	0.837	10.19 (2.06-50.52)	0.004	4.22 (0.53-33.67)	0.173

Abbreviations: circumferential (CD-ENE); perpendicular (PD-ENE).

Figures

Figure 1

(a) Involved sentinel lymph node (SLN) without extranodal extension (ENE), (b) SLN with ENE, (c) the diameter of CD-ENE, (d) the diameter of PD-ENE. Original magnification: 200x.

Figure 2

Kaplan-Meier curves depicting the associations of risk factors in SLN with DFS in all cases, which were stratified according to (a) number of SLN (b) number of SLN involvement (c) pattern of SLN metastases (d) SLN positive ratio (e) ENE (f) CD-ENE (g) PD-ENE (h) NVI.

Figure 3

Kaplan-Meier curves depicting the associations of risk factors in SLN with OS in all cases, which were stratified according to (a) number of SLN (b) number of SLN involvement (c) pattern of SLN metastases (d) SLN positive ratio (e) ENE (f) CD-ENE (g) PD-ENE (h) NVI.