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Original article

Total tumor load assessed by one-step nucleic acid amplification assay as an intraoperative predictor for non-sentinel lymph node metastasis in breast cancer

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ABSTRACT

Background: This study aimed to determine the relationship between CK19 mRNA copy number in sentinel lymph nodes (SLN) assessed by one-step nucleic acid amplification (OSNA) technique, and non-sentinel lymph nodes (NSLN) metastization in invasive breast cancer. A model using total tumor load (TTL) obtained by OSNA technique was also constructed to evaluate its predictability.

Methods: We conducted an observational retrospective study including 598 patients with clinically T1-T3 and node negative invasive breast cancer. Of the 88 patients with positive SLN, 58 patients fulfill the inclusion criteria.

Results: In the analyzed group 25.86% had at least one positive NSLN in axillary lymph node dissection. Univariate analysis showed that tumor size, TTL and number of SLN macrometastases were predictive factors for NSLN metastases. In multivariate analysis just the TTL was predictive for positive NSLN (OR 2.67; 95% CI 1.06–6.70; P = 0.036). The ROC curve for the model using TTL alone was obtained and an AUC of 0.805 (95% CI 0.69–0.92) was achieved. For TTL >1.9 × 10^5 copies/μL we got 73.3% sensitivity, 74.4% specificity and 88.9% negative predictive value to predict NSLN metastases.

Conclusion: When using OSNA technique to evaluate SLN, NSLN metastases can be predicted intra-operatively. This prediction tool could help in decision for axillary lymph node dissection.

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1. Introduction

Sentinel lymph node (SLN) biopsy have become the standard technique for determining axillary nodal involvement in patients with early-stage breast cancer who are clinically negative.

Identifying the SLN as non-metastatic spares unnecessary axillary lymph node dissection (ALND) and therefore decreases the chances of significant co-morbidities [1].

Intraoperative diagnosis of positive SLN can allow ALND in the same surgical procedure when criteria are present, thus avoiding a second surgery to treat the axilla and decreasing the patient's associated discomfort and institutional costs [2,3].

The one-step nucleic acid amplification (OSNA, Sysmex, Kobe, Japan) assay is a molecular method that measures the quantity of cytokeratin (*CK*)-19 mRNA (a duct epithelial cell marker that is highly expressed in more than 95% of breast cancers) in axillary lymph nodes [4]. Cutoff values were defined to classify macrometastases (more than 5000 copies/μL), micrometastases (250–5000 copies/μL) and negative nodes (fewer than 250 copies/μL) [5].

Combined analysis of nine studies that compared OSNA with histopathology demonstrated high concordance between both methods (96%) and reported high sensitivity, specificity and negative predictive value for OSNA [2]. As the OSNA assay is essentially an automated procedure, it has clear advantages in standardization, reproducibility and objectivity.

There is so far no clear consensus on how to approach ALND. Several studies have identified predictors of metastases to non-sentinel lymph nodes (NSLNs), to select patients who can be spared ALND, and different nomograms have been proposed to select patients who would not benefit from ALND.

Recently, the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial defined a select cohort of patients with positive SLNs in whom a complete ALND may be safely omitted [6]. However, many patients still require prediction of non-SLN metastases.

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With the increasing use of OSNA, different groups have started to study the relationship between *CK19* mRNA copy number and the NSLN metastization.

Ohi et al. (2012) and Osako et al. (2013) demonstrated that the NSLN macrometastatic rate increased in proportion to *CK19* mRNA copy numbers [7,8]; Ohi et al. verified that the *CK19* mRNA copy number in SLN is the most important predictive factor of NSLN metastases, and that higher copy numbers are strongly associated with four or more axillary lymph node metastases [7].

Other groups also evaluated the correlation between the total tumor load (TTL) in SLN and additional NSLN metastases [9,10]. Banerjee et al. (2014), in a small subgroup of 45 women who had undergone ALND, found that using the *CK19* mRNA copy number alone resulted in an AUC of 0.828, which indicates that OSNA is more useful than nomograms in predicting the risk of NSLN metastasis [2].

This study aimed to determine the relationship between *CK19* mRNA copy numbers and subsequent NSLN metastization, and to determine the TTL intraoperatively as a threshold above which metastases are expected, to support surgeons' oncological decisions regarding the need to perform ALND.

2. Materials and methods

This observational retrospective study was conducted between October 2010 and December 2014, and initially enrolled 598 women with invasive breast cancers. Inclusion criteria were patients whose disease had been assessed clinically and ultrasonographically as node-negative and at tumor stage cT1–3, and who had undergone intraoperative SLN evaluation by OSNA. We excluded patients who had received neoadjuvant treatment, whose biopsies showed CK19-negative tumors, or those who did not undergo ALND. Of the 598 patients, 88 had positive SLNs. Of these 88, 61 had been analyzed by OSNA, three of whom were excluded because they had not undergone ALND. Finally, 58 valid patients were studied. Data collected included age, tumor size, grade, histological subtype, estrogen and progesterone receptor status, HER2 status, Ki67, lymphovascular invasion, multifocality, total number of SLNs and non-SLNs, type of surgery, the number of positive and negative non-SLNs, and *CK19* mRNA copies.

SLNs were detected using radioisotopes and blue dye, and sent for pathological analysis. When macrometastases were found during intraoperative evaluation, patients underwent level II ALNDs. Depending on patient and tumor characteristics, lumpectomies or mastectomies were also performed.

OSNA evaluations were completed for the isolated SLNs. The OSNA assay procedure has already been described in detail [4]. The analysis result included the number of *CK19* mRNA copies per μL. These copy numbers were used semi-quantitatively to characterize node involvement; those with <250 copies/μL were considered non-metastatic, 250–5000 copies/μL as having micrometastases, and >5000 copies/μL as having macrometastases.

NSLNs obtained from ALND were studied after being processed by histopathologic methods. Immunohistochemical staining was not used.

2.1. Statistical analysis

Data were evaluated descriptively, with frequencies used for categorical variables and medians for continuous variables. Chi-square and ANOVA tests were used to compare positive and negative NSLNs. We conducted univariate and multivariate analyses, from which non-significant variables ($P > 0.05$) were dropped. Logistic regression was used to assess the capacity of the studied variables to identify positive NSLNs.

The TTL variable was studied using area under the receiver operating characteristic (ROC) curve (AUC), after log transformation to avoid nonlinearities. The statistical analyses were carried out in SPSS 20.0 for Windows and MedCalc 15.8.

3. Results

3.1. Patients' characteristics

Of the 58 patients with positive SLNs who were analyzed by OSNA in this study, 15 (25.86%) were found to have positive nodes

Table 1
Patient's characteristics and comparison of negative versus positive NSLN.

	Negative NSLN (n = 43)	Positive NSLN (n = 15)	*P* value
Age – years (mean ± SD)	57.10 ± 11.09	57.77 ± 12.68	0.717
Histologic type			0.371
Invasive ductal carcinoma	35	12	
Invasive + ductal carcinoma in situ	3	1	
Invasive lobular carcinoma	5	1	
Invasive papillary carcinoma	0	1	
Tumor size (mean in mm ± SD)	20.65 ± 7.06	25.93 ± 10.79	0.035
Lymphovascular invasion			0.469
Yes	20	8	
No	20	5	
ER			0.440
Positive	36	14	
Negative	6	1	
PR			0.061
Positive	29	14	
Negative	13	1	
HER2			0.699
Positive	7	2	
Negative	30	12	
SLN number (mean ± SD)	2.23 ± 1.15	2.60 ± 1.06	0.282
SLN macrometastases (mean ± SD)	1.19 ± 0.55	1.80 ± 0.68	0.001
NSLN resected (mean ± SD)	11.86 ± 6.11	12.80 ± 5.36	0.599
TTL - log (mean ± SD)	4.65 ± 0.84	5.54 ± 0.71	0.000

ER: estrogen receptors; PR: progesterone receptors; HER2: human epidermal growth factor receptor 2; SLN: sentinel lymph nodes; NSLN: non-sentinel lymph nodes; TTL: total tumor load.

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