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Original Articles

Impact of the Sentinel Node Frozen Section Result on the Probability of Additional Nodal Metastases as Predicted by the MSKCC Nomogram in Breast Cancer

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Objective: Sentinel lymph node frozen section is used to obviate the need for a second operation in breast cancer patients with involved nodes. However, the overall sensitivity, specificity and accuracy of sentinel lymph node frozen section are debated, and the impact of sentinel lymph node frozen section positivity on the risk of additional nodal metastases is not known and was the focus of this investigation.
Methods: We used our hospital record system to identify 176 sentinel lymph node biopsies done out of 354 cases of Stage T1-3N0 breast cancers managed from 2005 to 2007 and evaluated the sentinel lymph node frozen section results against the predictions of additional nodal metastases based on the Memorial Sloan–Kettering Breast Cancer Nomogram which is a validated tool for this purpose.
Results: Sentinel lymph node metastases size was an independent predictor of sentinel lymph node frozen section sensitivity and those with macrometastases had 15 times the odds (odds ratio, 15.4; 95% confidence interval, 3.4–69.1) of having a true-positive frozen section when compared with those with micrometastases. The breast cancer nomogram predicted that the latter patients have a very low probability of additional nodal metastases with a median probability at 10% (inter-quartile range, 7–14%).
Conclusions: A negative sentinel lymph node frozen section is also associated with a low probability of additional nodal metastases. Additional prognostic factors in the breast cancer nomogram are of little clinical impact because the most predictive factor in the nomogram is the method of detection.

Key words: breast cancer – nomogram – additional nodal metastases – sentinel lymph node – frozen section – prognosis

INTRODUCTION

Lymph node status is one of the most clinically significant prognostic markers in the treatment of invasive carcinoma of the breast (1). Until 15 years ago, it was common practice in North America to perform a completion axillary lymph node dissection (CALND) on almost every breast carcinoma patient (2). This protocol changed with the widespread implementation of the sentinel lymph node biopsy (SLNB) as a highly accurate, less morbid method of avoiding conventional axillary lymph node dissection (3). More recently, the application of rapid pathological techniques to SLN biopsies has allowed for the intraoperative identification of metastatically involved SLNs via frozen section (SLNFS). The benefit of intraoperative analysis is clear: a positive

intraoperative SLNFS can allow for an immediate axillary lymph node dissection and prevents the need for a second surgical procedure on that patient.

However, the sensitivity of intraoperative SLNFS is reported to vary and can be as low as 33% in some series depending on intraoperative and gold standard pathological techniques (4). Some reports have shown correlations between the histological subtype (5), tumor size (6) or lymphovascular invasion (LVI) status (7) and SLNFS sensitivity. Nevertheless, these factors probably influence only the size of the nodal metastatic lesions, since SLNFS sensitivity approaches 100% with macrometastases (4,8).

In the present study, our institution's experience with intraoperative SLNFS over a period of 3 years was reviewed. In particular, factors that were potentially predictive of the protocol's sensitivity were assessed. In addition, using the Memorial Sloan–Kettering Breast Cancer Nomogram (MSKCC BCN), we determined the probability of additional nodal metastases (ANM) outside the SLN in our cohort and correlated it with the SLNFS results.

PATIENTS AND METHODS

Patient Selection and Data Collection

From 2005 to 2007, 354 patients underwent surgical resection of T1-3N0 stage, biopsy-proven invasive carcinoma of the breast at the McGill University Health Centre. One hundred seventy-six of those patients underwent an SLNFS. All 176 patients within this clinical stage range were included in the present study. A chart review of these patients was performed retrospectively in accordance with the ethics policy of our institution. All data are calculated on a per-patient (not per-node) basis.

Surgical Procedure

Radionucleotide ^{99}technicium injection was the routine method used for SLN identification, with blue dye only used for the cases of unsuccessful migration of the radioisotope. Peritumoral, subareolar or intradermal injections were performed, depending upon tumor localization and surgeon preference.

Intraoperative and Final Histopathological Analyses

Pathologic assessment was done as follows: at gross examination, the sentinel nodes were cut longitudinally in 2–3 mm-thick slices. For frozen section, a 4–5 μm-thick section was performed on each slice and stained with hematoxylin and eosin (H&E). If the sentinel node was negative at the intraoperative examination, a permanent paraffin section, 4 μm in thickness, was obtained on each slice. If still no metastasis was detected, a pancytokeratin immunohistochemical (IHC) stain (AE1/AE3) along with three H&E-stained deeper sections cut at 200 μm intervals was obtained. If on the permanent section, there was a metastatic tumor with <0.2 cm (micrometastasis), deeper sections were ordered to ensure that the metastasis remained in the micrometastatic range. The tumor stage was classified according to the American Joint Commission on Cancer (AJCC) classification.

Memorial Sloan–Kettering Cancer Center Breast Cancer Nomogram

This nomogram predicts the risk of ANM (9) and was calculated with the online version of the nomogram (http://www.mskcc.org/mskcc/html/15938.cfm). The following characteristics are needed in the nomogram: frozen section (Y/N), tumor size (cm), tumor type and grade (invasive ductal I, II, III or invasive lobular), number of positive SLNs, SLN detection method (frozen section, routine H&E, IHC, or serial H&E), number of negative SLNs, LVI (Y/N), multifocality (Y/N) and estrogen receptor positivity (Y/N). We contrasted the probability of ANM with SLNFS positivity.

Statistical Analysis

The sensitivity, specificity, accuracy and positive and negative predictive values of SLNFS results were calculated relative to 'final pathologic status' as follows: sensitivity = TP/(TP + FN); specificity = TN/(TN + FP); accuracy = (TP + TN)/(TP + FP + FN + TN), where TP, true-positive; TN, true-negative; FP, false-positive; and FN, false-negative. All these variables were determined on a per-patient basis and were not determined on a per-SLN basis. Continuous variables were summarized as median and inter-quartile range (IQR). The χ^2 statistic or Fisher's exact test was used to determine the significance in differences between groups for categorical variables. Multivariable analyses were conducted by the use of binomial logistic regression. Patient variables were used to identify the factors likely to predict SLN status. The analysis was carried out initially by inserting one variable in the model and then using forward stepwise regression to obtain a final model. The Wald statistic was used to test the significance of individual logistic regression coefficients for each independent variable. An overall test of model adequacy was obtained by the Hosmer and Lemeshow goodness-of-fit test. Odds ratios (ORs) and 95% confidence intervals (95% CIs) for all individual variables in the final model were estimated. All P values determined to be ≤ 0.05 were considered to be statistically significant. The software program SPSS 13.0 for Windows (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses.

RESULTS

Patient and Tumor Characteristics

One hundred seventy-six patients and 376 lymph nodes were analysed in the present study. The mean patient age was 56.8 years (range, 23–81) and each patient had on average 2.1

SLNs dissected (range, 1–6). The median primary tumor size was 1.5 cm (IQR, 0.9–2.2; range, 0.2–5.2). Other patient and tumor characteristics are presented in Table 1.

Overall Sensitivity of SLNFS

On final pathological analysis, 57 of 176 (32%) of SLNs were positive for metastatic carcinoma (Table 2). Of these 57 positive nodes, 33 were identified on intraoperative SLNFS, for an intraoperative protocol sensitivity of 57.9%. All (119/119) of the truly negative nodes were correctly identified on intraoperative SLNFS (100% specificity). Overall, frozen section analysis correctly identified the metastatic status of 152 of 176 nodes (86% accuracy).

Table 1. Patient characteristics

Number of patients	176
Total number of SLNs	376
Patient age, years (range)	56.8 (23–81)
Number of SLNs dissected/patient (range)	2.11 (1–6)
Primary tumor size, cm (median; IQR)	1.5 (0.9–2.2)
Primary tumor histological type	
Ductal (%)	133 (75.6)
Lobular (%)	12 (6.8)
Mixed (%)	21 (11.9)
Other (%)	9 (5.1)
Histological grade	
1 (%)	23 (13.1)
2 (%)	112 (63.6)
3 (%)	16 (9.1)
Primary tumor molecular marker status	
ER+ (%)	144 (81.8)
PR+ (%)	110 (62.5)
Her2+ (%)	16 (9.1)
Primary tumor characteristics	
LVI present (%)	37 (21.0)
Multifocality present (%)	46 (26.1)
DCIS present (%)	142 (80.7)
LCIS present (%)	21 (11.9)
Findings on axillary dissection	
Frozen section false-negative	$n = 24$
	7 had axillary LN dissection
	None had ANM
Frozen section true-positive	$n = 33$
	All had axillary LN dissection
	17 had ANM

SLNs, sentinel lymph node; IQR, inter-quartile range; ER, estrogen receptor; PR, progesterone; Her2, human epidermal growth factor 2; LVI, lymphovascular invasion; DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*; LN, lymph node; ANM, additional nodal metastases.

Factors Correlating with Intraoperative SLNFS Sensitivity

Out of the 57 final pathology reports showing nodal metastatic disease, 48 reported the size of the largest metastatic focus. Of those 48 nodes, 26 (54.2%) contained micrometastases ($\leq$2 mm) and 22 (45.8%) contained macrometastases. The TP nodes had significantly larger metastatic foci than the FN nodes (6.80 vs. 1.11 mm, respectively, $P < 0.001$). FN SLNFS patients had mostly micrometastasis in their final SLN pathology (86%). The nodes that contained macrometastases (>2 mm) had 15 times the odds of being TP when compared with those with metastatic lesions <2 mm [OR = 15.4 (3.4–69.1)]. Of the clinicopathological features examined in this study (Table 3), only one (nodal metastasis size) was 'independently' (in multivariate analysis) associated with altered intraoperative SLNFS sensitivity, suggesting that a positive intraoperative SLNFS is dependent on the presence of macrometastases. On univariate analysis

Table 2. Operating characteristics of intra-operative SLN pathology (compared with final SLN pathology)

		Final SLN pathology		Total
		−	+	
Intra-operative SLN pathology	−	119	24	143
	+	0	33	33
Total		119	57	176

Sensitivity = 58%; specificity = 100%. Intra-op, intraoperative.

Table 3. Intraoperative SLNB sensitivity in various clinicopathological subpopulations

	Intra-operative (+) (SLNFS+)	Final pathology (+)	Sensitivity	*P* value
Age < 50	8	16	50	0.42
Age ≥ 50	24	40	60	
Primary tumor ≤1.5 cm	6	15	40	0.05
Primary tumor >1.5 cm	26	41	63	
LVI+	20	26	77	<0.001
LVI−	10	27	37	
ER+	28	48	58	0.8
ER−	5	8	63	
Macro-mets	19	22	86	<0.001
Micro-mets	7	26	27	

SLNB, sentinel lymph node biopsy; macro-mets, macrometastases; micro-mets, micrometastases.

(Table 3), the presence of LVI was also predictive of SLNFS sensitivity [OR = 5.95 (1.8–19.7)]; however, multivariate analysis suggests that LVI was in fact simply predictive of macrometastatic disease. No other clinicopathological features analysed in the present study were independently predictive of an altered intraoperative SLNFS sensitivity.

Intraoperative SLN Status and MSKCC-BCN Probability

Receiver-operating curve (ROC) analysis (Fig. 1) demonstrates that based on the SLNFS result, we can already determine that a positive case will always have an MSKCC-BCN probability of ANM of >28.5%, whereas a negative case will always have an MSKCC-BCN prediction of ANM of <42%. The overlap area is thus between 28.5 and 42%. The interesting finding, however, is that 12 out of 14 subjects in the overlap area are TPs. Thus, the median probability of ANM (by the nomogram) in FN subjects was only 10% ($n = 24$; IQR, 7–14%). The median probability of non-sentinel lymph node spread in TP subjects was 49% ($n = 33$; IQR, 36–58%). ROC analysis suggests that 25% is the best threshold probability of ANM between a FN and a TP subject with majority (75%) of FN subjects having an ANM probability of <14%.

Correlation with ALND Results

Of the FN SLNFS subjects ($n = 24$), only seven patients underwent full ALND at a later date following a positive final SLN pathology. All seven patients had no disease in their axilla. Eleven patients had ITC (<0.2 mm), and therefore, ALND was not performed. Five patients decided not to undergo ALND. One patient was found to have a primary non-resectable lung cancer and a decision was made not to perform an ALND. In the 33 TP SLNFS subjects, all had ALND and 17 had ANM.

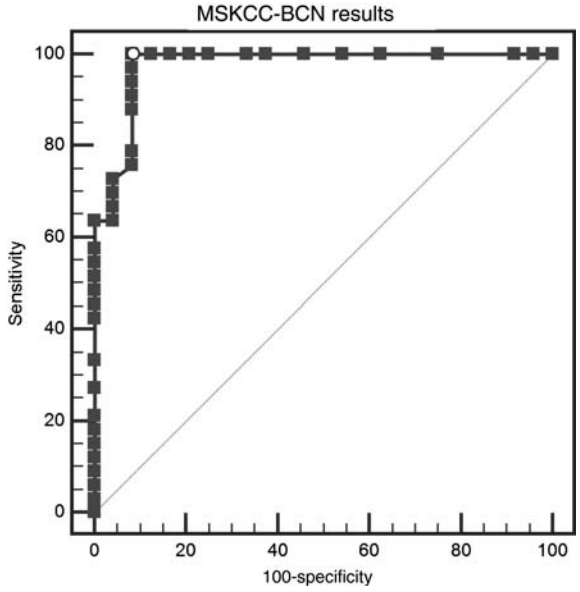

Figure 1. Receiver-operating curve (ROC) curve demonstrating the close relationship between the SLNFS result (classification variable) against the MSKCC-BCN probability. Area under the ROC curve = 0.974; standard error = 0.020; 95% confidence interval = 0.893–0.997; P (area = 0.5) < 0.0001. SLNFS, sentinel lymph node frozen section; MSKCC BCN, Memorial Sloan–Kettering Breast Cancer Nomogram.

DISCUSSION

The current study is a chart review of patients who underwent a SLNFS during surgery for biopsy-proven invasive carcinoma of the breast at the McGill University Health Centre between 2005 and 2007. We had an overall 58% sensitivity and thus a 42% FN rate for the detection of cancer in the SLN. When categorized by metastasis size, we had 27% sensitivity for micrometastases and 86% sensitivity for macrometastases. This is in keeping with reports in the literature where micrometastases have been shown to be the main association of negative SLNFS results (8). We have also demonstrated that only SLN metastases size was an independent predictor of increased SLNFS positivity. Our data thus are in keeping with the literature that suggests that in breast cancer patients having SLNB, the failure of routine intraoperative FS is largely the failure to detect micrometastatic disease (4).

It is known that additional nodal metastases outside the SLN correlate independently with macrometastatic disease in the SLN (OR, 13.9; 95% CI, 1.13–170.4; $P = 0.039$) (10). These results, taken together with the data presented in this study, suggest that an FN intraoperative result implies the presence of micrometastatic disease with a low likelihood of ANM. Weiser et al. (11) have also shown that the likelihood of ANM is inversely related to three clinicopathological variables: tumor size ≤1.0 cm; absence of LVI; and SLN micrometastases (≤2 mm). None of 24 patients with all three predictive factors had ANM, whereas 58% of the patients with none of the factors had ANM. After multivariate analysis, however, tumor size was retained in addition to SLN micrometastases (11), suggesting that tumor size may have some independent predictive value for ANM over macrometastases. We did not confirm this in this study. Overall, it is likely that macrometastases are a significant predictor of ANM. A negative frozen section (implying micrometastases) may help determine which patients are likely to have disease limited to the SLN and therefore are at low risk, for ANM even if the SLN is found to have disease in final pathology. Indeed, a prospective study, with the longest follow-up in the literature, reports that disease-free and overall survival in early-stage breast cancer without CALND was not different between SLN-negative subjects and those with micrometastases (12).

Although it is agreed that SLN micrometastases represent a lower risk group, such subjects have still been reported to have prognostically significant disease (compared with those with a negative SLN) in a study reporting data from the late

1970s (13). However, these data are not generalizable to the prognostic significance of SLN micrometastases in present-day patients who virtually all receive systemic adjuvant therapy. Indeed, later prospective follow-up studies have reported that after a median follow-up of 77 months (range, 24–106 months), neither loco-regional recurrences nor distant metastases occurred in any of 27 patients with SLN micrometastases who also did not have CALND (12). There were also no statistically significant differences for overall ($P = 0.656$), loco-regional ($P = 0.174$), and axillary and distant disease-free survival ($P = 0.15$) between patients with TN SLN and SLN micrometastases (12). More recently, an analysis of unselected patients provides evidence that a completion level I and II ALND may be safely omitted in early-stage breast cancer patients with SLN micrometastases (14). Others suggest that ALND might be avoided in these patients, providing that adjuvant systemic treatment equal to treatment provided to treat node-positive disease is administered (15,16). A recent meta-analysis also found no concrete evidence from the SLNB studies that micrometastases had a reduced recurrence-free survival rate compared with lymph node-negative patients (17).

The MSKCC BCN is a prediction model that identifies spread outside the SLN. There was clearly a higher probability of ANM for our TPs compared with FNs on frozen section. The nomogram includes a number of factors and we demonstrate that the method of detection is the most important, and indeed, others have demonstrated before us that the method of detection in the nomogram is a surrogate for SLN metastasis size (18). It is clear therefore that the predictions of the MSKCC BCN are primarily dependent on the size of SLN metastatic disease. Indeed, Alran et al. (19) report that if breast cancer cohorts are restricted to those with SLN micrometastases, then the MSKCC BCN can no longer accurately predict ANM. Although this has been refuted by Coutant et al. (20), our findings tend to agree with those of Alran et al. (19). This suggests that the relationship between the nomogram and ANM is mainly dependent on SLN metastases size and a complex nomogram can be simplified if this is taken into account. Indeed, such a simplification has been reported by Kohrt et al. (21) with no loss of discriminative capacity of the model.

We now take this further by documenting that SLNFS-negative patients (irrespective of other considerations such as tumor size and LVI) have a low predicted probability of ANM of about 10%. Our finding of 10% ANM in negative SLNFS is supported by results of both a recent retrospective study of SLN micrometastases and an earlier meta-analysis that puts ANM at between 10 and 15% (22,23). Even in the overlap group with probability of ANM between 28.5 and 42%, most (12 out of 14) are positive SLNFS results and this thus strengthens the association between negative results and a low probability of ANM. Confirmation that low risk of ANM also translates to a parallel low clinical risk has now been demonstrated in a trial that actually compared CALND on all subjects vs. CALND only on those with SLNFS positivity (24). In this trial, 10-year survival was closely similar in both groups of patients, confirming that the SLN policy of foregoing CALND when the SLNFS is negative is as effective as the once standard treatment of axillary dissection (24).

In summary, the majority of FN SLNFS are micrometastasis and are unlikely to have ANM and thus such negativity might in itself be an indicator of low probability of ANM. The MSKCC BCN, to a large extent, simply reflects the content of the SLN in terms of micro- or macrometastatic disease and thus would be expected to correlate with SLNFS results, which is clearly demonstrated here. We conclude that frozen section alone can be predictive of ANM and a negative SLNFS signals a median 10% probability of ANM, whereas a positive SLNFS signals a higher probability and a need for CALND. Although final pathology seems irrelevant in this decision process, examination of these findings in a larger series is required for confirmation of this conclusion.

Conflict of interest statement

None declared.

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