Is sentinel node biopsy reliable in large breast tumors?

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Summary

Purpose: The value of sentinel lymph node biopsy (SNB) in patients with larger breast tumors (diameter > 3 cm) has been questioned due to high false-negative rates reported from initial studies. The aim of this study was to analyze the safety and prognostic reliability of SNB in this group of patients. *Methods:* During a 6-year period (2001-2007), 84 women with mean age 51.7 ± 11.6 years diagnosed with a breast tumor larger than 3 cm in diameter on pathological analysis were retrospectively identified from the database of our institution. Sentinel node identification was performed after injection of blue dye subcutaneously at the subareolar area. The sentinel node specimen was sent for frozen section analysis. Regardless of the SNB results, all patients underwent completion axillary clearance. *Results:* Breast surgery consisted of mastectomy in 62 patients (73.8%) and partial mastectomy in 22 patients (26.2%). There were 69 invasive ductal cancers (82.1%), 14 lobular cancers (16.6%) and one case of anaplastic carcinoma (1.3%). Nine tumors (10.7%) were identified to be multifocal after the histopathological report. The mean number of sentinel nodes removed was 1.5 ± 0.7 (range 1-4) while SNB detection was not feasible in three patients (3.6%). Of 56 positive SNBs, seven (12.5%) were not identified by routine hematoxylin and eosin staining during frozen section analysis but were detected by subsequent immunohistochemistry on the final histopathological report. All patients with multifocal tumors presented nodal metastases on pathological analysis (100%), while the rate of nodal metastatic disease in patients with unifocal tumors was 16% (12 patients), although no statistical significance was documented. The overall false-negative rate, defined as the percentage of all node-positive tumors in which the SNB was negative, was 14.3%. The false-negative rate was significantly higher for the group of patients with multifocal tumors (55.5%) compared to the group with unifocal tumors (9.3%) ($p < 0.001$). Conclusions: The present study indicates that sentinel node biopsy is feasible in patients with larger breast tumors (max. diameter > 3 cm), with comparable false-negative and sentinel detection rates (14.3% and 96.4%, respectively). Larger tumor size seems to be associated with increased incidence of nodal metastases while multifocality appears to be related to increased false-negative rates; hence completion axillary clearance should be initially considered for these cases.

Key words: Breast cancer; Sentinel lymph node; Multifocality.

Introduction

Breast cancer is the commonest malignancy among the female population and one of the leading causes of mortality worldwide [1]. For women diagnosed with breast cancer, the assessment of axillary nodal status is a crucial parameter for staging the disease as well as a critical indicator of prognosis. Although axillary lymph node dissection is still the gold standard for evaluating nodal status in breast cancer, the long-term complications of this technique in breast cancer survivors, such as reduced shoulder mobility, shoulder weakness, sensory disturbance, neuralgia and permanent arm lymphoedema [2,3], lead to a wide acceptance of sentinel node biopsy in all cases of early breast cancer. Since Morton and colleagues introduced this technique in 1992 [4], it has been well established and validated in the surgical treatment of early breast cancer. A lot of studies have evaluated the role of the sentinel node in cases of early invasive breast cancer [5, 6] and despite concerns regarding false-negative rates, and variation and long-term implications of failing to identify axillary metastases, this technique has become widely applicable.

In cases of larger breast tumors, the value of SNB has been questioned. Initial studies resulted in high false-negative rates as to 18% for T2-T3 tumors [7] and the reliability of this technique has been doubted, while other studies have reported no statistically significant difference in false-negative rates when SLNB is applied in larger tumors compared to axillary lymph node dissection (8,9). Therefore, further validation trials for added assurance regarding the safety of SLNB in terms of axillary recurrence and survival are necessary.

In this study, the experience with sentinel node dissection for larger breast tumors (> 3 cm) with clinically negative axilla in a tertiary institution is reported, aiming to evaluate the safety of this technique and to define the major factors of false-negative results in this group of patients.

Materials and Methods

A retrospective review of the clinical records of patients diagnosed with breast cancer during a 6-year period was undertaken after approval by the ethics committee of our institution. All cases with a breast tumor larger than 3 cm in diameter on pathological analysis were included in the study. Neoadjuvant chemotherapy or radiotherapy, multifocal tumor diagnosed preoperatively, clinically suspected axillary node metastases and

Revised manuscript accepted for publication March 25, 2009

known allergy to the blue dye were exclusion criteria for the study. Eighty-four women were eligible for inclusion in the study. Sixty-two patients derived from the initial learning and validation phase of SNB when axillary lymph node dissection was routinely added while 22 patients were additionally included afterwards due to large sized tumors > 3 cm where axillary dissection was the optimal surgical approach independently of sentinel node results. All procedures were performed by two surgeons. Sentinel node identification was performed after injection of blue dye (Patent Blue V; Guerbet, Paris, France) subcutaneously at the subareolar area. No radioactive tracer was used in any case. After the excision of the specimen it was sent for frozen section analysis. At least three sections were prepared from the sentinel node or each part of bisected nodes, and examined by hematoxylin and eosin staining (HES). All patients underwent an additional axillary lymph node dissection including levels I and II, even if the frozen section analysis was negative.

The definitive assessment of fixed SLNs included serial sectioning with hematoxylin-eosin staining and anti-cytokeratin immunohistochemical (IHC) staining. The overall false-negative rate, which was the primary end-point, was defined as the percentage of all node-positive tumors in which the SNB was negative.

Statistical analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS 13.0, SPSS Inc, Chicago, Illinois, USA; $p < 0.05$ was considered statistically significant.

Results

A total of 84 women with breast cancer met the inclusion criteria and were enrolled in the study. The mean age of the patients was 51.7 ± 11.6 years. Breast surgery consisted of mastectomy in 62 patients (73.8%) and partial mastectomy in 22 patients (26.2%). Primary tumor diameter ranged from 30 to 59 mm (36 ± 0.6) including 60 T2 tumors (71.4 %) and 24 T3 tumors (28.6 %). There were 69 invasive ductal cancers (82.1%), 14 lobular cancers (16.6%) and one case of anaplastic carcinoma (1.3%). The mean number of sentinel nodes removed was 1.5 ± 0.7 (range 1-4) while SNB detection was not feasible in three patients (3.6 %).

Of 56 positive SNBs, seven (12.5%) were not identified by routine hematoxylin and eosin staining during frozen section analysis but were detected by subsequent immunohistochemistry on the final histopathological report. Twelve patients with a negative SNB were found to have positive axillary non-sentinel lymph nodes after the definitive histopathological assessment, resulting to an overall false-negative rate of 14.3%.

Among the 84 patients enrolled in the study, nine (10.7%) had a multifocal tumor at the final histopathological report. All these patients presented nodal metastatic disease on pathological analysis, while the rate of nodal metastases in patients with unifocal tumors was 16% (12 patients), but no statistical significance was documented. The false-negative rate was also significantly higher for the group of patients with multifocal tumors (5 of 9, 55.5%) compared to the group with unifocal tumors (7 of 75, 9.3%) ($p < 0.001$). Nevertheless, due to the small statistical sampling, these differences might not be meaningful.

All patient characteristics are summarized in Table.

Table 1. — *Patient characteristics*.

Patients	84	
Age (mean ± SD), years	51.7 ± 11.6	
Type of surgery		
Total mastectomy	62 (73.8%)	
Partial mastectomy	22 (26.2%)	
Staging/Histopathological analysis		
Primary tumor diameter (mm)	30-59, 36±0.6	
T2	60 (71.4%)	
T3	24 (28.6%)	
Invasive ductal cancer	69 (82.1%)	
Lobular cancer	14 (16.6%)	
Anaplastic cancer	1 (1.3%)	
Number of sentinel nodes removed	1.5 ± 0.7 (range 1-4)	
No *feas*ible detection	3 patients (3.6%)	
Focality		
Unifocal tumors	75 (89.3%)	
Multifocal tumors	9 (10.7%)	
Nodal metastatic disease	12 of 75 unifocal tumors (16%) 9 of 9 multifocal tumors (100%)	
	Nodal metastatic disease in patients with negative SNB	*False-negative rate*
Overall	12	14.3%
Unifocal tumors	7	9.3%
Multifocal tumors	5	55.5%

Discussion

Sentinel lymph node biopsy is today a well established technique for treating patients with early-stage breast carcinoma. It provides important prognostic information to direct adjuvant treatment and helps avoid the morbidity of unnecessary lymph node dissection. Several studies have demonstrated an increased rate of axillary metastases in patients with larger breast tumors [10,11] suggesting that fewer patients in this group have any benefit from this procedure. Nonetheless, the reliability and feasibility of this technique in multifocal or large unifocal tumors has been poorly investigated and even if some patients with a negative SNB do not require additional axillary lymph node dissection, this would be a major benefit.

Although an association between experience with this technique and the detection rate of the sentinel node has been reported [12], our detection rate of 96.4% is comparable to that of other early validation studies [13,14]. Therefore, although most of the patients enrolled in this study came from the learning curve of this technique, the results indicate that SNB is also feasible in larger breast tumors, in accordance with the results of Bergkvist *et al.* [15] who stated that the surgical experience is not a crucial parameter for higher false-negative results when performing sentinel node biopsy.

The accuracy of SNB in multicentric and multifocal invasive breast cancers has been evaluated by Tousimis *et al.* [16] and it resulted that there were three false-negative SNBs in a total of only four T3 breast tumors. In the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial [17], although patients were not excluded on the basis of large tumor size, only

three of 75 multifocal tumors were T3 and no information was given about the T stage of the three tumors found with a false-negative SNB.

A recent study by Schüle *et al.* [18], evaluated the sentinel node biopsy in patients with breast cancer larger than 3 cm in diameter and it resulted that this technique is reliable in cases of unifocal tumors although there was a statistically higher proportion of false-negative results in multifocal tumors.

In the present study, although multifocality was an exclusion criterion, nine patients were identified to have a multifocal breast tumor after the final histopathological report. The false-negative rate of SNB in this subgroup of patients was statistically higher compared to the subgroup of patients with unifocal tumors, thus proposing that SNB is not reliable in these tumors. In contrast, other studies propose that SNB results are comparable in unifocal and multifocal tumors and state that this technique is reliable even if multifocality is detected preoperatively [16,19]. Therefore, current recommendations for SNB in multifocal tumors might be re-evaluated.

Although larger breast tumor and multifocality have been reported to be independent risk factors for nodal metastatic disease [20], the results of this study support that SNB is also feasible and efficient in cases of T2 and T3 tumors, unless multifocality is detected. Larger multifocal tumors necessitate complete axillary lymph node dissection. A major impediment still remains the lack of an exact definition of a multifocal tumor as it varies considerably among several studies [15,21]. Therefore, an international consensus is essential along with more randomized control trials in order to derive strong recommendations for the optimal treatment of these patients.

Conclusion

Although the reliability of sentinel node dissection in larger breast tumors has been questioned in initial studies, the current study indicates that this technique is feasible in patients with larger breast tumors (max. diameter > 3 cm), with comparable false-negative and sentinel detection rates, unless multifocality is present.

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