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The accuracy of sentinel lymph-node biopsy in breast cancer after previous excisional biopsy

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Summary. *Aim:* Sentinel node biopsy (SLNB) is considered to be the standard of care for staging the axilla in clinically node-negative women with breast cancer. A previous breast excisional biopsy has been considered a contraindication to the use of SLNB. We examined the success rate of SLN localization and then the evaluation of the incidence of axillary relapse in patients with breast cancer undergoing excisional biopsy. *Patients and Methods:* 858 patients with breast carcinoma underwent a SLNB and only positive sentinel nodes were submitted to axillary dissection; 82 patients had undergone an excisional biopsy before. *Results:* The sentinel node was identified in 100% of cases, it was negative in 74.4% and positive in 23.1%. Complete axillary dissection was performed in all positive cases, and in 74% of cases no other positive nodes were found. The follow-up median was 63.5 months and no axillary recurrence was observed. *Conclusions:* SLNB accuracy in breast cancer patients who have previously undergone excisional biopsy is comparable with that in patients undergoing no excisional biopsy, so that it may be considered a standard procedure.

Key words: breast cancer, excisional biopsy, sentinel lymph-node biopsy, accuracy

«L'ACCURATEZZA DEL LINFONODO SENTINELLA DOPO BIOPSIA ESCISSIONALE DEL CARCINOMA DELLA MAMMELLA»

Riassunto. *Scopo:* La biopsia del linfonodo sentinella (BLS) nel carcinoma della mammella con linfonodi ascellari clinicamente negativi è considerato la migliore scelta per stadiare il cavo ascellare. Inizialmente una precedente biopsia escissionale del carcinoma era considerata una controindicazione. Esaminiamo il tasso di successo della BLS e la incidenza della recidiva a livello ascellare in pazienti con carcinoma della mammella precedentemente sottoposti a biopsia escissionale del tumore. *Pazienti e metodi:* 858 pazienti con carcinoma della mammella sono stati sottoposti a BLS e i pazienti con linfonodi sentinella metastatici a svuotamento del cavo ascellare; 82 pazienti erano stati sottoposti precedentemente a biopsia escissionale del tumore. *Risultati:* Il linfonodo sentinella è stato identificato nel 100% dei casi, è risultato indenne nel 74,4% e metastatico nel 23,1%. La dissezione del cavo ascellare è stata effettuata in tutti i casi con linfonodi sentinella metastatici e nel 74% dei casi non si sono ritrovati altri linfonodi ascellari metastatici. Il follow-up mediano è stato di 63,5 mesi e non si sono osservate recidive ascellari. *Conclusioni*: L'accuratezza del BLS in pazienti con carcinoma della mammella sottoposte precedentemente a biopsia escissionale è uguale a quella dei pazienti non sottoposti a biopsia.

Parole chiave: carcinoma della mammilla, biopsia escissionale, linfonodo sentinella, accuratezza

Introduction

Nowadays the sentinel lymph-node biopsy (SLNB) is the standard of care in women who have been confirmed by ultrasound as clinically node negative.

Particularly, if the SLNB is not metastatic, the patient will not need to undergo an axillary lymph-node dissection (ALND). We have the results of several trials and meta-analysis, in which the total survival, the disease-free survival and regional control were statistically equivalent between patients who were randomized to completion axillary dissection or no completion axillary dissection after a negative SLNB (1-3).

SLNB represents a significant advance in the staging of breast cancer, since it avoids the morbidity of axillary dissection in node-negative women. In fact SLNB is associated with reduced arm morbidity, moderated or severe lymphedema, and better quality of life than standard axillary treatment (4).

Initially to ensure and maintain the high accuracy and low false-negative rate of the SLNB procedure, several selection criteria and related contraindications for the procedure have been reported, the latter including a previous excisional biopsy. The reason for the contraindications for the previous excisional biopsy was the possibility of an altered anatomy of the lymphatic channels of the breast, thereby hindering the clear identification of the sentinel node.

This study is a retrospective analysis of the success rate, accuracy, and negative predictive value of SLN localization and also an evaluation of the incidence of axillary relapse in patients with breast cancer undergoing excisional biopsy.

Materials and methods

Between February 1999 and December 2008, 858 patients with breast carcinoma underwent a SLNB and only those who were sentinel node-positive were submitted for axillary dissection. Out of 858 patients, 82 patients had undergone an excisional biopsy before and 42 patients (51%) had been treated in other centres before coming to our institute. Out of these 82 patients, 17 showed SLN localization by both radio-colloid and blue dye, and 65 by radio- colloid only. All patients also received partial or total resection of the breast to obtain disease-free surgical margins. A detailed report of both methods used to identify the SLN is provided in a previous trial carried out by the authors (5).

Complete axillary dissection was performed when the sentinel nodes contained metastases.

Before 2003, histological examination of the sentinel node was performed on a few sections of the specimen, such as the lymph nodes of a typical axillary dissection. Starting from March 2003, the number of sections was increased so that a complete examination of the whole sentinel node to detect micrometastases was possible.

Here is described the technique used in our institution. First of all, the SLN is sliced at 2 mm intervals perpendicular to the long axis. One routine Haematoxylin-Eosin (H&E) stained section is examined; if negative, serial level slices are performed through each block (two sections for each level, with a spacing of 50 μ between the following levels). One segment for each level is stained with H&E while the other undergoes an additional immuno-histochemical analysis with keratins to compare clusters of histologically suspected cells. This approach offers a good sensitivity in order to detect any micrometastases and isolated tumoral cells, and with reasonable costs. All patients underwent a follow-up every 4-6 months, depending on the axillary status, during the first 5 years after surgery. Bilateral mammograms were annually repeated; breast and axillary ultrasound were repeated every 6 months. The staging of the disease was immediately performed before the surgery with bone scintigraphy; liver ultrasound X-rays of the chest had been pre-operatively performed.

We usually repeat the staging at time intervals that depend on the initial extension of the disease and the clinical observation during the follow-up.

Results

Between February 1999 and December 2008, 82 patients with invasive breast cancer, already treated

with excisional biopsy and clinically negative, were included in this study. Their characteristics are shown in Table 1. The median age at the time of entering the study was 49 (range 24-82). The average size of the primary carcinoma was 1.2 cm. In 11 patients (13.4%) it was under 0.5 cm, in 19 patients (23.2%) it was between 0.5-1 cm, in 26 patients (31.7%) it was between 1-1.5 cm, in 20 patients (24.4%) it was between 1.5-2 cm, and in 6 patients it was between 2-3 cm. The most common histological type was ductal carcinoma, in 60 patients (76.1%). Lobular carcinomas were observed in 10 patients (12.1%), mixed ductal and lobular carcinomas in 1 patient (1.2%), while 11 patients (13.3%) showed different types of carcinoma, mainly well-differentiated forms (cribriform, tubular, mucinous and papillary).

Most patients (75, 93.5%) were treated with breast conservative surgery followed by external-beam radiotherapy on the whole breast through two tangential fields (50 plus 10 Gy as a boost to the tumour bed) with a linear accelerator, while 7 patients (8.5%) were treated with total mastectomy. In 28 cases (34%) we found residual carcinoma, in 16 of them (19.5%) it was in situ and in the others (14.6%) it was invasive. The sentinel node was identified in 100% of cases and was negative in 61 patients (74.4%), while it was positive in 19 ones (23.1%); while in 2 patients only isolated tumoral cells were present (Table 2). Complete axillary dissection was performed in all 19 patients with sentinel node positive and in 14 cases (74%) no other positive nodes were found (Table 3).

None of the patients within this group experienced axillary recurrence at follow-up (median 63.5 months and range 37 to 146 months).

Table 1.

Characteristics	N.	%
Tumour grade		
G1	26	31.7
G2	20	24.3
G3	14	17.0
Unknown	22	26.8
Histological type		
Ductal	60	73.1
Lobular	10	12.1
Ductal+lobular	1	1.2
Tubular	2	2.4
Papillary	6	7.3
Other	3	3.6
Proliferative fraction (Ki67)		
<20%	38	46.3
>20%	26	40.8
Unknown	18	21.9
ER		
Absent	17	20.7
Present	53	64.6
Unknown	12	14.6
PgR		
Absent	18	21.9
Present	52	63.4
Unknown	12	14.6
HER2/neu overexpression		
0/1+	51	62.2
2+	12	14.6
3+	7	8.5
Unknown	12	14.6
Type of surgery		
Total mastectomy	7	8.5
Breast conserving surgery	75	91.5
Tumour size		
<0.5 cm	11	13.41
0.5-1 cm	19	23.17
1-1.5 cm	26	31.70
1.5–2 cm	20	24.39
2-3 cm	6	7.31
pT		
pT1a	11	13.41
pT1b	19	23.17
pT1c	46	56.09
pT2	6	7.31

Discussion

A previous breast excisional biopsy has been considered a contraindication to the use of SLNB as it was commonly supposed that the excisional biopsy resulted in subsequent disruption of the breast lymphatic drainage. Some authors have suggested that altered lymphatic drainage decreases the likelihood of successful lymphatic mapping, and indeed have suggested that any nodes removed after an excisional biopsy may not actually represent an accurate reflection of lymphatic drainage from the site of primary tumour (6-11).

In recent years, due to several studies on the sentinel node, we have come to better understand the anatomy involved in the lymphatic drainage of the breast. In the past we believed that different sentinel

Table 2. Characteristics of sentinel node

	N.	%
N 0	61	74.39
N+	19	23.17
Isolated tumoral cells	2	2.43

Table 3. Characteristics of axillary dissection in sentinel node positive

	N.	%
N 0	14	73.68
N+<3	1	5.26
N+>3	4	21.05

nodes existed in relationship to the different quadrants, while studies on multicentric cancer had shown that there is only one sentinel node. Multiple lymphatic trunks might drain to different sentinel lymph node(s) and may be overlooked. However, with the use of lymphatic mapping and the increased experience in SLNB, there is now increasing evidence-based support of the theory that the lymphatics of the mammary gland drain through a few common afferent lymphatic trunks to specific axillary sentinel lymph nodes, regardless of the tumour location (12, 13). Ferrari *et al.* demonstrated that intradermal radioisotope injections in two different quadrants of the breast give the same SLN visualization in most cases (14).

Kim *et al.* reported five patients with multicentric breast cancer who had undergone a sentinel node mapping and a biopsy procedure. Clinically each patient showed carcinoma in two different quadrants of the breast. One tumor was mapped with technetium-labeled sulfur colloid and the other was mapped with isosulfan blue dye. In each case at least one both hot and blue node was identified in the axilla (15).

The possibility of a high rate of false negative results in patients who had previously undergone an excisional biopsy for cancer was refuted by studies in which the sentinel node was isolated and simultaneously ALND was performed: in Maza *et al.* the sentinel node was identified in 100% of cases and it was positive in 22.2%, the false -negative rate was 0% (16). Wong *et al.* reported a rate of identification of 92.5% and a false-negative rate of 8%; the sentinel node was metastatic in 33.9% (17); Heuts *et al.* reported a rate of identification of 98% and a false-negative rate of 0% (18); Coskun *et al.* reported a rate of identification of 98% and a false-negative rate of 6.4% (19); Blanco *et al.* reported a rate of identification of 92.1% (20).

In our study the sentinel node was identified in 100% of cases, was positive in 23% and was the only positive node in 73.6% of cases with positive axillary node. In the entire population up to 2008 the sentinel node was positive in the 38% of cases and was the only positive node in 58.2% of cases.

The high percentage of negative sentinel nodes is related to the fact that the case-sample that previously underwent excision biopsy contained a higher proportion of small-sized tumours with respect to the total study population, indeed pT1a is 13.4% against 4.2%, pT1b is 23.1% against 13.7%; meanwhile the presence of cancers with a diameter larger than 2 cm is 7.3% against 25.8%. No lymph node recurrence was observed during a median follow-up time of 63.5 months.

Van der Ploeg and colleagues reported an identification rate of 96.5% in patients who underwent the excisional biopsy, and no lymph node recurrence was detected during follow-up (median 39 months) (21).

Ohtake *et al.* compared sentinel lymphoscintigrams in breast cancer patients who had previously undergone excisional biopsy with sentinel lymphoscintigrams in patients undergoing no excisional biopsy, and reported a rate of identification respectively of 98% and of 99% (22).

Luini *et al.* reported an identification rate of 99%, in the 29.6% of cases the SLN was positive, and was the only positive node in 61.5%; an axillary relapse in 0.8% of cases was observed (23).

The possibility that a breast carcinoma might be removed as a result of diagnostic error depends on the experience of the centre, but is higher in small-size tumours, in well-differentiated tumours and in young patients. In such cases the probability of negative axillary lymph nodes is high and for this reason avoiding axillary dissection is important in order to improve quality of life.

Conclusion

Our results and literature review confirm that, in patients who have previously undergone excisional biopsy, sentinel node biopsy may be used to identify those patients with a negative sentinel node, that are a higher percentage than the total case study, thus avoiding a complete axillary dissection.

References

1. Krag DN, Anderson SJ, Julian TB, *et al.* Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 2010; 11: 927-33.
2. Veronesi U, Viale G, Paganelli G, *et al.* Sentinel lymph node biopsy in breast cancer: ten-year results of a randomized controlled study. Ann Surg 2010; 251: 595-600.
3. Van der Ploeg IM, Nieweg OE, van Rijk MC, *et al.* Axillary recurrence after a tumour-negative sentinel node biopsy in breast cancer patients: a systematic review and meta-analysis of the literature. Eur J Surg Oncol 2008; 34: 1277-84.
4. Mansel RE, Fallowfield L, Kissin M, *et al.* Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: The ALMANAC Trial. J Natl Cancer Inst 2006; 98: 599-609.
5. Marrazzo A, Taormina P, Noto A, *et al.* Localization of the sentinel node in breast cancer: prospective comparison of vital staining and radioactive tracing methods. Chir Ital 2004; 56: 621-7.
6. Veronesi U, Paganelli G, Galimberti V, *et al.* Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. Lancet 1997; 349: 1864-7.
7. Albertini JJ, Lyman GH, Cox C, *et al.* Lymphatic mapping and sentinel node biopsy in the patient with breast cancer. JAMA 1996; 276: 1818-22.
8. Krag D, Weaver D, Ashikaga T, *et al.* The sentinel node in breast cancer: a multicenter validation study. N Engl J Med 1998; 339: 941-6.
9. Borgstein PJ, Pijpers R, Comans EF, *et al.* Sentinel lymph node biopsy in breast cancer: guidelines and pitfalls of lymphoscintigraphy and gamma probe detection. J Am Coll Surg 1998; 186: 275-83.
10. Feldman SM, Krag DN, McNally RK, *et al.* Limitation in gamma probe localization of the sentinel node in breast cancer patients with large excisional biopsy. J Am Coll Surg 1999; 188: 248-54.
11. Ollila DW, Guilano AE. Intraoperative lymphatic mapping and sentinel lymphadenectomy using isosulfan blue dye. Breast Dis 1998; 8: 248-54.
12. Tuttle TM, Colbert M, Christensen R, *et al.* Subareolar injection of ^{99m}TC facilitates sentinel lymph node identification. Ann Surg Oncol 2002; 9: 77-81.
13. Chao C, Wong SL, Woo C, *et al.* Reliable lymphatic drainage to axillary sentinel lymph nodes regardless of tumor location within the breast. Am J Surg 2001; 182: 307-1.
14. Ferrari A, Dionigi P, Rovera F, *et al.* Multifocal and multicentricity are not contraindications for sentinel lymph node biopsy in breast cancer surgery. World J Surg Oncol 2006; 4: 79-87.
15. Jin Kim H, Heerdt AS, Cody HS, *et al.* Sentinel lymph node drainage in multicentric breast cancers. Breast J 2002; 8: 356-61.
16. Maza S, Thomas A, Winzer KJ, *et al.* Subareolar injection of technetium-99m nanocolloid yield reliable data on the axillary lymph node tumour statusin breast cancer patients with previous manipulations on the primary tumour: a prospective study of 117 patients. Eur J Nucl Med Mol Imaging 2004, 31: 671-5.
17. Wong SL, Edwards MJ, Chao C, *et al.* The effect of prior breast biopsy method and concurrent definitive breast procedure on success and accuracy of sentinel lymph node biopsy. Ann Surg Oncol 2002; 9: 272-7.
18. Heuts EM, van der Ent FW, Kengen RA, *et al.* Results of sentinel node biopsy not affected by previous excisional biopsy. Eur J Surg Oncol 2006; 32: 278-81.
19. Coskun G, Dogan L, Karaman N, *et al.* Value of sentinel lymph node biopsy in breast cancer patients with previous excisional biopsy. J Breast Cancer 2012; 15: 87-90.
20. Blanco I, Diaz D, Moriyon C, *et al.* Sentinel node biopsy in patients with breast cancer and previous breast surgery. Rev Esp Med Nucl 2011; 30: 223-8.
21. Van der Ploeg IM, Oldenburg HS, Rutgers EJ, *et al.* Lymphatic drainage patterns from the Treated Breast. Ann Surg Oncol 2010; 17: 1069-75.
22. Ohtake E, Asaga T, Inaba M. Sentinel lymphoscintigraphy in patients with breast cancer undergoing excisional biopsy. Ann Intern Med 2005; 9: 671-5.
23. Luini A, Galimberti V, Gatti G, *et al.* The sentinel node biopsy after previous breast surgery: preliminary results on 543 patients treated at the European Institute of Oncology. Breast Cancer Res Treat 2005; 89: 159-63.

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