EUROPEAN JOURNAL OF CANCER 43 (2007) 2664–2668

available at www.sciencedirect.com

journal homepage: www.ejconline.com

Unnecessary axillary node dissections in the sentinel lymph node era

Mattia Intra[a,*], *Nicole Rotmensz*[b], *Denise Mattar*[a], *Oreste D. Gentilini*[a], *Annarita Vento*[a], *Paolo Veronesi*[a,c], *Marco Colleoni*[d], *Concetta De Cicco*[e], *Enrico Cassano*[f], *Alberto Luini*[a], *Umberto Veronesi*[a]

[a]*Division of Breast Surgery, European Institute of Oncology, Via Ripamonti, 435, 20141 Milan, Italy*
[b]*Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy*
[c]*University of Milan School of Medicine, Milan, Italy*
[d]*Division of Medical Oncology, European Institute of Oncology, Milan, Italy*
[e]*Division of Nuclear Medicine, European Institute of Oncology, Milan, Italy*
[f]*Unit of Diagnostic Senology, European Institute of Oncology, Milan, Italy*

ARTICLE INFO

Article history:
Received 10 February 2006
Received in revised form 23 August 2007
Accepted 3 September 2007
Available online 10 October 2007

Keywords:
Breast cancer
Sentinel lymph node biopsy
Complete axillary dissection
Unnecessary dissection
Uninvolved axillary nodes
Non-metastatic lymph nodes

ABSTRACT

In the sentinel lymph node era, axillary lymph node dissection (ALND) for uninvolved axillary lymph nodes should be considered unnecessary and inappropriate. Between January 2000 and August 2005, 3487 out of 10,031 invasive breast cancer patients consecutively operated at the European Institute of Oncology were considered not suitable for sentinel lymph node biopsy (SNB) and were directly submitted to ALND ('direct ALND'). In 2875 cases (82%) a variable grade of axillary involvement was shown, while in 612 patients (18%) no evidence of metastatic spreading was documented in the axilla. In particular, the presence of suspicious nodes at pre-operative clinical evaluation of the axilla (191 patients), neoadjuvant treatment (188 patients), large tumour >2 cm (88 patients), multifocality of disease (76 patients), previous excisional biopsy (49 patients), were considered the most frequent contraindications to SNB and led to an 'unnecessary ALND'. According to the wider extension of the indications for SNB over the time, the number of 'unnecessary ALNDs' progressively decreased from 26% (in 2000) to 9% of the 'direct ALNDs' (in 2005). As the clinical indications to SNB are progressively extending to encompass most breast cancer patients with non-metastatic disease who were previously excluded, great effort should be made to avoid 'unnecessary ALNDs'.

© 2007 Elsevier Ltd. All rights reserved.

1. Introduction

The disease status of the axillary lymph nodes is the most significant prognostic factor for patients with early-stage breast cancer.[1] Sentinel lymph node biopsy (SNB) is feasible and accurate, works well in a wide range of practice settings, is sufficiently robust to withstand variations in technique, increases staging accuracy by allowing enhanced pathologic analysis, has less morbidity than axillary lymph node dissection (ALND), and gives local control comparable to that of ALND.[2] In the American Society of Clinical Oncology (ASCO) guideline recommendations, the sensitivity of SNB for node involvement ranged from 71% to 100%, and the false-negative rate averaged 8.4%, across 69 studies (10,454 patients) analysed.[3]

* *Corresponding author*: Tel.: +39 2 57489839; fax: +39 2 57489780.
E-mail address: mattia.intra@ieo.it (M. Intra).
0959-8049/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2007.09.001

Since SNB has become a standard method for the axillary staging of operable breast cancer, ALND should be limited to patients with metastatic axillary nodes. Therefore, in the SNB era, ALNDs for uninvolved axillary lymph nodes should be considered inappropriate and unnecessary.

At the European Institute of Oncology (EIO) SNB has been routinely applied in clinical practice since 2000. The evolution over time of ALNDs for uninvolved axillary limph nodes ('unnecessary ALNDs') and the progressive contemporary change of the indications for SNB are described in the present study.

2. Patients and methods

Between January 2000 and August 2005, 10,031 primary invasive breast cancer patients were consecutively treated at EIO. SNB was performed in 6544 (65%) patients. In 3487 (35%) patients, SNB was considered not clinically suitable or contraindicated and ALND was directly performed ('direct ALND'). According to the data of the literature, the personal indications for SNB changed over the time period. In the first part of our experience only unifocal, small (⩽2 cm) invasive breast cancers with clinically uninvolved axillary nodes and no previous surgical or medical treatment were considered indications for SNB. In the second part, SNB was indicated for virtually all patients with clinically node-negative breast cancer.

Locally advanced disease, local recurrences, carcinoma *in situ* or those where axillary lymph nodal status would not define risk category or established adjuvant treatment (elderly, metastatic patients), were excluded from the current analysis.

2.1. *Lymphatic mapping procedure*

Lymphoscintigraphy was performed according to our standard technique described previously.[4] Briefly, all patients underwent lymphoscintigraphy after subdermal injection of radiolabelled colloids on the day or the day before surgery, with an activity of 10–12 MBq in a volume of 0.2 ml of isotonic sodium chloride solution, for all aliquot particles of human albumin size range <80 nm (Nanocoll; Nycomed Amersham-Sorin, Saluggia-VC, Italy) in the skin directly overlying the tumour. Lymphoscintigraphy images were obtained in anterior and oblique-anterior views at 15 and 30 min after injection. Delayed acquisition at 120 min was carried out only if sentinel nodes were not evident at first images. All nodes with radiotracer up-take were removed and sent for histopathology examination following our previously described standard protocol.[5]

2.2. *Data management*

Data were entered by surgeons into a database designed with Microsoft Access® once weekly on a mean number of 40 patients per week, and checked by a team of dedicated personnel. The re-codification of indications and contraindications for SNB was done blindly by an independent team of physicians, regardless of the year of surgery and the outcome of the disease.

3. Results

SNB was performed in 6544 patients, and 4194 (64%) resulted negative. ALND in these patients was avoided, and are currently in clinical follow up. In 2350 (36%) patients, the SNB was positive and this group of patients underwent an ALND, which showed a variable grade of metastatic involvement of the axilla. In 3487 patients (35%) SNB was considered not clinically suitable or contraindicated and ALND was directly performed ('direct ALND'). Table 1 shows the steadily increased use of SNB over time, from 46% to 77% of all the patients treated at EIO. Inversely, the 'direct ALND' progressively reduced. In the second part of the table the outcome is stable; eventually, the ratio negative/positive SNB is similar.

Of the 3487 'direct ALNDs', one or more metastatic axillary nodes were shown in 2875 (82%), while in 612 patients (18%) no evidence of metastatic spreading in the axilla at final histology, was documented ('unnecessary ALNDs'). The clinical contraindications to SNB of the 612 'unnecessary ALNDs' are shown in Table 2. The presence of suspicious nodes at pre-operative clinical evaluation of the axilla (191 patients), neoadjuvant treatment (188 patients), large tumour >2 cm (88 patients), multifocality of disease (76 patients), previous excisional biopsy (49 patients), were considered the most frequent contraindications to SNB and led to an 'unnecessary ALND'. Over the time period, the evolution of the surgeon's approach, along with the refinement of the technique, increased SNB practice and broadened the indications. Consequently, all the contraindications to SNB progressively decreased. Only neoadjuvant chemotherapy and/or hormo-

Table 1 – SNB and 'direct ALND' at EIO

	2000 (%)	2001 (%)	2002 (%)	2003 (%)	2004 (%)	2005[a] (%)	TOTAL (%)
Direct ALND	641 (54)	664 (43)	650 (36)	616 (32)	584 (27)	332 (23)	3487 (35)
SNB	544 (46)	894 (57)	1141 (64)	1328 (68)	1549 (73)	1088 (77)	6544 (65)
TOTAL	1185	1558	1791	1944	2133	1420	10031
SNB	2000 (%)	2001 (%)	2002 (%)	2003 (%)	2004 (%)	2005[a] (%)	TOTAL (%)
Negative	338 (62)	582 (65)	738 (65)	845 (64)	1002 (65)	689 (63)	4194 (64)
Positive	206 (38)	312 (35)	403 (35)	483 (36)	547 (35)	399 (37)	2350 (36)
TOTAL	544	894	1141	1328	1549	1088	6544

SNB: sentinel lymph node biopsy; direct ALND: direct axillary lymph node dissection; EIO: European Institute of Oncology.
a As of August 2005.

Table 2 – Clinical contraindications to SNB at EIO over the time period in the 612 patients submitted to direct ALND with no metastatic axillary nodes

Contraindication	2000	2001	2002	2003	2004	2005[a]	TOTAL
Clinically suspicious axillary nodes	51	46	47	30	15	2	191
Neoadjuvant chemotherapy	29	25	30	30	38	27	179
Neoadjuvant hormonotherapy	3	1	3	2			9
Large tumour (>2 cm)	28	20	21	12	6	1	88
Multifocality/ Multicentricity of disease	30	32	10	3	1		76
Previous breast surgery	15	20	8	4	2		49
Sentinel node not visualised at lymphoscintigraphy	2	2	1		1		6
Primary tumour localised in axillary extension	2	1		1			4
Primary tumour in central quadrant	2	1					3
Young age	3						3
Male breast cancer		1	1				2
Pregnancy			1				1
PET positivity						1	1
TOTAL patients with contraindication to SNB	165	149	122	82	63	31	612
TOTAL patients with indication to SNB	583	908	1173	1321	1582	1595	7162
RATIO contraindications/indication to SNB	28%	16%	10%	6%	4%	2%	

SNB: sentinel lymph node biopsy; EIO: European Institute of Oncology; ALND: axillary lymph node dissection; PET: positron emission tomography.
a As of August 2005.

Table 3 – Total, positive and negative (unnecessary) ALND, and SNB at EIO

	2000 (%)	2001 (%)	2002 (%)	2003 (%)	2004 (%)	2005[a] (%)	TOTAL (%)
TOTAL ALND	847	976	1053	1099	1131	731	5837
Positive ALND	682	827	931	1017	1068	700	5225
Direct ALND	641	664	650	616	584	332	3487
Negative (unnecessary) ALND	165	149	122	82	63	31	612
Ratio negative (unnec.) ALND/direct ALND[b]	165/641 (26)	149/664 (22)	122/650 (19)	82/616 (13)	63/584 (11)	31/332 (9)	612/3487 (17)
Ratio neg (unnec.) ALND/ALND TOT[c]	165/847 (19)	149/976 (15)	122/1053 (12)	82/1099 (7)	63/1131 (6)	31/731 (4)	612/5837 (10)

ALND: complete axillary lymph node dissection; SNB: sentinel lymph node biopsy; EIO: European Institute of Oncology. TOTAL ALND comprises Positive ALND + Negative (unnecessary) ALND.
a As of August 2005.
b Proportion of ALND resulting negative on all direct ALND.
c Proportion of ALND resulting negative on all ALND.

notherapy, remained a steady contraindication to SNB (Table 2). The number of 'unnecessary ALNDs' progressively decreased from 28% in 2000 to 2% in 2005 (Table 2). The proportion of 'direct ALNDs' that were unnecessary decreased from 26% (in 2000) to 9% (in 2005), and the proportion of all ALNDs that were unnecessary decreased from 19% (in 2000) to 4% (in 2005) (Table 3).

4. Discussion

Before SNB was universally accepted in the clinical practice, ALND was offered to all breast cancer patients without any distinction, and the complete removal of non metastatic axillary lymph nodes was accepted with great satisfaction by patients and physicians. The advent of SNB strongly modified the treatment of breast cancer, dramatically reducing the overall number of ALND and so, improving the quality of life of breast cancer patients.[2] So, today, in the SNB era, an ALND for uninvolved axillary lymph nodes is considered unnecessary and inappropriate.

We, as pioneers, started routinely applying SNB in the clinical practice from January 2000, after the first phase of a SNB validation study[6] and the conclusion in December 1999 of the clinical prospective randomised trial, comparing SNB and ALND.[7] Initially, in the attempt to ensure a high SNB accuracy and a low false-negative rate, we kept the same indications for SNB considered in this institutional randomised trial: patients more than 40 and less than 75 years old, with an invasive breast carcinoma less than 2 cm. Very young patients, large tumours (> 2 cm), multicentric carcinomas and patients submitted to previous neoadjuvant treatment and/or excisional biopsy were not considered eligible. Particular tumour sites were also considered at higher risk to false negative SNB (retroareolar or axillary tail tumours) and were submitted to 'direct ALND'. So, as SNB was prudentially and strictly limited to patients with small unique invasive tumours and clinically

negative axillary lymph nodes, the number of 'unnecessary ALNDs' was relatively high in the first years, resulting in 26% of all the 'direct ALNDs' and 20% of total ALNDs (Table 3).

In view of the gained experience and the increased data from the literature, the indications for SNB have been extended to encompass most of the patients with non-metastatic disease, previously excluded for technical or only theoretical reasons. Therefore, many of the historical contraindications for SNB progressively disappeared, and the initial restrictive selection of patients has been progressively enlarged.

The American Society of Clinical Oncology (ASCO) guideline recommendations[3] represented an important milestone in the SNB concept evolution. The main indications to SNB have been clarified. SNB is feasible and highly accurate (97–99%) in predicting the status of the axillary lymph nodes in several clinical situations, but SNB is still not recommended by ASCO for large or locally advanced invasive breast cancers (T3 and T4), inflammatory breast cancer, when breast-conserving surgery is to be done, pregnancy, in the setting of prior nononcologic breast surgery or axillary surgery, and in the presence of suspicious palpable axillary lymph nodes.

Since the ASCO guideline recommendations were published in 2005, new and wider data about SNB indications have been collected and are available, confirming several old indications to SNB and adding new ones. Today, the suitability of SNB is well established in most of the possible clinical scenarios and SNB is indicated for virtually all patients with clinically node-negative invasive breast cancer. Large tumours,[8] multifocal and multicentric tumours[9] and following neo-adjuvant chemotherapy[10] are no longer considered absolute contraindications to perform SNB. No particular tumour sites (central or axillary tail) are considered to be a technical obstacle to SNB. Early concerns about SNB performed after a surgical biopsy of the primary tumour have been proved unfounded, with equal success (and accuracy) after excisional or core-needle biopsy and after small or large volumes of resection.[11] SNB can also be considered in patients with clinically suspicious axillary nodes if preoperative palpation or ultrasonography-guided fine needle aspiration cytology (FNAC) is non-diagnostic.[12] SNB should also be considered in patients previously submitted to breast conserving surgery and SNB alone (with negative SNB), when an invasive local recurrence with non clinically suspicious axillary nodes occurs.[13,14] Recently, SNB has even been performed in mastectomised patients who developed, during the follow up, a unique invasive limited local subdermic recurrence amenable to surgical excision, with clinically negative axillary nodes.[15] No data support any contraindication to SNB in younger or older individuals.[7] Tumour biology, prognostic factors, and outcome have been reported to be equivalent in male and female breast cancer patients, providing a scientific basis for the extrapolation of treatment for males with breast cancer from treatment algorithms for females with this disease. Since there are no biological or anatomical issues which would alter the lymphatic drainage in men with respect to women, SNB can also be applied to male patients with breast cancer and a clinically negative axilla.[16] Finally, using particular technical precautions, SNB has also been demonstrated to be safe and sure in pregnancy.[17,18]

Enlarging the SNB indications, the number of 'unnecessary ALNDs' in our series drastically decreased up to 9% of the 'direct ALND' and to 4% of total ALND in 2005 (Table 3). The 'unnecessary ALND' reduction is equally distributed over the time period in all the previously considered contraindications, including clinically involved axillary nodes, with the only exception in patients submitted to neoadjuvant treatment. In the first 8 months of 2005, only 31 'unnecessary ALNDs' were performed (Table 2): one patient with a tumour more than 6 cm in size, one patient with positive positron emission tomography (PET) in the axilla (that means a falsely positive PET) and 27 patients submitted to neoadjuvant chemotherapy. SNB is sufficiently documented after neoadjuvant chemotherapy as demonstrated by a large multicentric evaluation on 428 patients of the National Surgical Adjuvant Breast and Bowel Project Protocol (B-27)[10] with results comparable to those obtained from multicentre studies evaluating SNB before systemic therapy, suggesting that the SNB concept is also applicable following neoadjuvant treatment. In a recent meta-analysis[19] of 21 studies (1273 patients) that examined the results of SNB after preoperative chemotherapy, SNB appears to be an accurate technique for determining the need for axillary treatment in patients who are clinically node-negative following preoperative chemotherapy. The number of 'unnecessary ALNDs' after neoadjuvant chemotherapy in our series still remains constantly high, probably due to a residual and unjustified fear of a possible false negative SNB. In particular, 110 patients submitted to 'unnecessary ALND' showed a local advanced disease (cT4 in 20 cases) or axillary nodes clinically metastatic (cT2–T3N1 in 90 cases) at presentation, but 78 cases (cT2–T3) did not have axillary nodes clinically palpable before the neoadjuvant treatment and, despite theoretical suitability to SNB, were submitted to 'unnecessary ALND'.

Despite the enlarged indications for SNB, some ALND for non-metastatic axillary nodes seem to be unavoidable. The main reason of 'unnecessary ALND' in our series was the presence of clinically suspicious, palpable axillary nodes. In 191 cases, the preoperative clinical evaluation of the axilla raised suspicion of metastatic involvement of the axilla, not confirmed by the successive ALND. It is well known that clinical examination of the axilla is falsely positive in as many as 30% of cases and is by itself insufficient justification for ALND.[12] To reduce 'unnecessary ALNDs' in our series, every time a suspicious axillary node was clinically detected, fine needle aspiration cytology (FNAC) (eventually ultrasonography-guided) was proposed, and only in case of positivity, was ALND performed. In patients with clinically suspicious axillary nodes, if FNAC resulted as negative or indeterminate, SNB was proposed, decreasing the number of 'unnecessary ALND' for clinically suspicious axillary nodes from 51 (in 2000) to 2 (in 2005). The use of PET is also under investigation, trying to predict the axillary lymph-nodal status. The sensitivity of PET compared with ALND and SNB is low, whereas PET scanning has high specificity and positive predictive values.[20,21] PET scanning cannot replace histologic staging in early stage breast cancer, but the low rate of false–positive findings suggests that PET can identify women who can forego SNB and require ALND. In case of positive axillary PET, 'direct' ALND can be reasonably proposed, while if PET is

negative, SNB must always be considered. In our series, only one patient had an axillary false positive PET and was submitted to 'unnecessary ALND'. Nevertheless, an evaluation of PET examination with SNB technique in case of PET negativity could be succinctly evoked and eventually deeply carried out in a subsequent study.

Since we started in 1996, the radioisotope technique, with 99Tecnectium, was adopted to identify sentinel node,[3] with a sentinel node identification rate of about 99%. In 25 cases, preoperative radiocolloid injection could not identify the sentinel node, and Blue Dye injection was intra-operatively performed. In 18 patients, the Blue Dye injection identified the sentinel node, but in seven cases, could not avoid 'direct ALND' which resulted unnecessarily in four cases.

In conclusion, as the clinical indications for SNB are progressively extending to encompass most breast cancer patients with non-metastatic disease previously excluded for technical or only theoretical reasons, great effort should be made to avoid 'unnecessary ALNDs'. The progressive decrease of 'unnecessary ALND" at EIO reflects the general change of indications in SNB.

Conflict of interest statement

None declared.

REFERENCES

1. Goldhirsch A, Glick JH, Gelber RD, et al. Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. *Ann Oncol* 2005;**16**:1569–83.
2. Cody III HS. Sentinel lymph node biopsy for breast cancer: does anybody not need one? *Ann Surg Oncol* 2003;**10**: 1131–2.
3. Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol* 2005;**23**:7703–20.
4. Mariani G, Erba P, Villa G, et al. Lymphoscintigraphic and intraoperative detection of the sentinel lymph node in breast cancer patients: the nuclear medicine perspective. *J Surg Oncol* 2004;**85**:112–22.
5. Viale G, Sonzogni A, Pruneri G, et al. Histopathologic examination of axillary sentinel lymph nodes in breast carcinoma patients. *J Surg Oncol* 2004;**85**:123–8.
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. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 2003;**349**:546–53.
8. Olson JA, Fey J, Winawer J, et al. Sentinel lymphadenectomy accurately predicts nodal status in T2 breast cancer. *J Am Coll Surg* 2000;**191**:593–9.
9. Tousimis E, Van Zee KJ, Fey JV, et al. The accuracy of sentinel lymph node biopsy in multicentric and multifocal invasive breast cancers. *J Am Coll Surg* 2003;**197**:529–35.
10. Mamounas EP, Brown A, Anderson S, et al. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 2005;**23**:2694–702.
11. Haigh PI, Hansen NM, Qi K, Giuliano AE. Biopsy method and excision volume do not affect success rate of subsequent sentinel lymph node dissection in breast cancer. *Ann Surg Oncol* 2000;**7**:21–7.
12. Specht MC, Fey JV, Borgen PI, Cody III HS. Is the clinically positive axilla in breast cancer really a contraindication to sentinel lymph node biopsy? *J Am Coll Surg* 2005;**200**:10–4.
13. Intra M, Trifiro G, Galimberti V, Veronesi P, Gentilini O, Luini A. Second axillary sentinel node biopsy for ipsilateral breast tumour recurrence. Br J Surg 2007; [Epub ahead of print].
14. Port ER, Garcia-Etienne CA, Park J, Fey J, Borgen PI, Cody III HS. Reoperative sentinel lymph node biopsy: a new frontier in the management of ipsilateral breast tumor recurrence. *Ann Surg Oncol* 2007;**14**:2209–14.
15. Intra M, Veronesi P, Gentilini OD, et al. Sentinel lymph node biopsy is feasible even after total mastectomy. *J Surg Oncol* 2007;**95**:175–9.
16. Gennari R, Renne G, Travaini L, Bassi F, Zurrida S. Sentinel node biopsy in male breast cancer: future standard treatment? *Eur J Surg* 2001;**167**:461–2.
17. Gentilini O, Cremonesi M, Trifiro G, et al. Safety of sentinel node biopsy in pregnant patients with breast cancer. *Ann Oncol* 2004;**15**:1348–51.
18. Cody III HS. Sentinel lymph node biopsy for breast cancer: indications, contraindications, and new directions. *J Surg Oncol* 2007;**95**:440–2.
19. Xing Y, Foy M, Cox DD, Kuerer HM, Hunt KK, Cormier JN. Meta-analysis of sentinel lymph node biopsy after preoperative chemotherapy in patients with breast cancer. *Br J Surg* 2004;**93**:539–46.
20. Lovrics PJ, Chen V, Coates G, et al. A prospective evaluation of positron emission tomography scanning, sentinel lymph node biopsy, and standard axillary dissection for axillary staging in patients with early stage breast cancer. *Ann Surg Oncol* 2004;**11**:846–53.
21. Veronesi U, De Cicco C, Galimberti VE, et al. A comparative study on the value of FDG-PET and sentinel node biopsy to identify occult axillary metastases. *Ann Oncol* 2007;**18**:473–8.