

Accuracy of frozen section of sentinel lymph nodes: a prospective analysis of 659 breast cancer patients of the Swiss multicenter study

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For the Swiss Multicenter Study Group Sentinel Lymph Node in Breast Cancer

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Abstract *Objective* To assess the accuracy of sentinel lymph node (SLN) frozen section in a prospective multicenter study of early-stage breast cancer patients. *Summary background data* The decision to perform an immediate completion axillary node dissection (ALND) is based on results of SLN frozen section. However, SLN frozen sections are not routinely performed in all centers. Moreover, the accuracy of SLN frozen section remains a matter of great debate. *Methods* Prospective multicenter trial analyzing 659 early stage breast cancer patients (pT1 and pT2 ≤ 3 cm, cN0) enrolled between January 2000 and December 2003. SLN were intraoperatively examined by frozen section.

Final histopathology consisted in performing step sectioning as well as staining with H&E and immunohistochemistry. *Results* SLN were identified in 98.3% (648/659) of all patients. The accuracy of frozen section was 90.1% (584/648), the sensitivity for SLN macro-metastases 98% (142/145), and the specificity 100%. A total of 47 patients with SLN micro-metastases ($n = 36$) or isolated tumor cells ($n = 11$) underwent a delayed completion ALND. In 96% (45/47) of these patients the ALND specimens were free of macro-metastases. *Conclusions* SLN frozen section provides highly accurate information regarding identification of SLN macro-metastases, a delayed completion ALND

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can be avoided in 98% of these patients. More importantly, in the present investigation the vast majority (96%) of patients with SLN micro-metastases or isolated tumor cells undergoing delayed completion ALND did not benefit from the second operation as ALND specimens were free of macro-metastases. We strongly recommend the routine use of SLN frozen section in early stage breast cancer patients.

Keywords Accuracy · Frozen section · Sentinel lymph node · Breast cancer · Micrometastases

Introduction

The sentinel lymph node (SLN) procedure accurately reflects the status of the axillary lymph nodes [1, 2] and has become the new standard of care in clinically node-negative breast cancer patients. The axillary lymph node status represents one of the most important prognostic factors in breast cancer patients and determines among other parameters the need for subsequent adjuvant treatment. In most published series the SLN procedure was found to be associated with a high identification rate and a very low false negative rate [1, 3]. Long-term follow-up studies showed that the axillary recurrence rate after SLN biopsy alone was not higher than after standard level I & II axillary lymph node dissection (ALND) [3, 4]. Conversely, morbidity after SLN biopsy alone proved to be significantly lower compared to the considerable rate of short- and intermediate-term sequelae after level I & II ALND [5, 6]. Due to improved screening and diagnosis, breast cancer is detected increasingly early, and consecutively the percentage of node positive patients is constantly decreasing. Therefore, a large fraction of breast cancer patients benefit from the less invasive SLN procedure and are spared the complications associated with ALND. First introduced in specialized, academic centres, the SLN biopsy has also become routine practice in the surgical therapy of breast cancer patients in non-academic clinics and community hospitals [6]. However, the value of the intraoperative frozen section of the SLN still remains controversial. Frozen section has the clear advantage to spare patients with a positive SLN from undergoing a second operation (delayed completion level I & II ALND). On the other hand, some physicians perceive this procedure to be time-consuming, costly, associated with a potential tissue loss and, finally, to be inaccurate in the detection of metastatic deposits [7, 8]. Furthermore, frozen section examination is not available in all institutions offering breast cancer surgery.

Therefore, the objective of the present prospective multicenter study was to test two different hypotheses: first, that frozen section is highly accurate in the detection of

SLN macro-metastases avoiding a delayed completion ALND, and second, that most patients with a negative frozen section result, but positive final histopathology due to micro-metastases or isolated tumor cells do not benefit from further axillary surgery.

Patients and methods

Between January 2000 and December 2003, a total of 698 patients with early-stage breast cancer were prospectively enrolled in this multicenter study. Inclusion criteria for the present study were: (1) presence of palpable breast cancer, (2) tumor size histologically equal to or less than 3 cm in diameter, (3) absence of clinically palpable axillary lymph nodes, (4) no prior history of breast cancer or other malignancies, (5) no neoadjuvant therapy, (6) no pregnancy. Patients with non-palpable breast cancer were considered ineligible for this study. Thirty-nine patients did not meet the inclusion criteria and were therefore excluded. Preoperative axillary ultrasound was not required in the study protocol and therefore not routinely performed. Written informed consent was obtained from all patients. The study was approved by the Local Ethic Committees. A total of 13 centres participated in this study, amongst them the Swiss University Hospitals in Basel, Berne, and Zurich, as well as different non-academic institutions (community hospitals and private practices).

Lymphatic mapping and operative technique

SLN mapping was performed by using a combination of a radiolabeled colloid and a vital blue dye as described previously. Briefly, ^{99m}Tc -labeled nanocolloid (Nanocoll[®], Nycomed AG, Wädenswil, Switzerland) at a dose of 70 MBq was injected, peritumorally at four places, whereas at the injection site closest to the axilla half of the dose was injected peritumorally and subdermally. Lymphoscintigraphy was performed preoperatively to identify lymphatic flow to axillary and/or parasternal lymph nodes. Hot spots were marked on the skin. The SLN were intraoperatively identified first by the use of a handheld gamma probe (Navigator[®], USSC, RMD Waterton, MA, USA, C-Trak[®], Care Wise Medical Products Corp., Morgan Hill, CA, USA, or Neoprobe[®], Ethicon Endo-Surgery, Johnson & Johnson, Cincinnati, OH, USA). Up to 5 mL of isosulfan blue (Lymphazurin[®], Ben Venue Labs Inc., Bedford, Ohio, USA and Hospital Pharmacy University Hospital Zurich) or 2 to 4 mL of patent blue V (Guerbet Group, Roissy, France) were injected in the same fashion as the radioactive tracer 5 to 10 min prior to incision. The choice of the blue dye was left to the institutions' preference. Hot and/or blue

lymph nodes were excised and labeled separately as SLN. Dissection was continued until all hot and blue nodes had been removed and the background count of the axilla was less than 10% of the hottest lymph node *ex vivo*.

Prior to participation to this study, the SLN procedure had to be validated at all institutions based on at least 20 breast cancer patients in whom both SLN and completion level I & II ALND were performed. A SLN identification rate and a sensitivity of at least 95% were requirements for participating to this trial. All participating centers were supervised by the principal investigators (GB, ORK, MZ) for their first 20 cases. The results of the validation period (20 patients) were critically reviewed by one of the principal investigators. Only after adequate performance had been proven, the hospitals were allowed to enroll patients to the present study. The principal investigators were instructed at large medical centers abroad in institutions with vast experience for SLN technique.

Pathologic examination of lymph nodes

Sentinel lymph nodes

Frozen sections were routinely performed intraoperatively. Lymph nodes larger than 5 mm in diameter were bisected, whereas lymph nodes less than or equal to 5 mm in diameter were not bisected but completely submitted for frozen section analysis. The SLN were intraoperatively examined at three levels with Hematoxylin & Eosin (H&E) stained sections at a cutting interval of 150 μm . The remaining tissue of the SLN was formalin-fixed and embedded in paraffin for histologic analysis. The residual tissue was then examined using step sectioning at a cutting interval of 250 μm . Step sections were stained with Hematoxylin & Eosin (H&E). If no carcinoma cells were detected, immunohistochemistry with cytokeratin antibody Lu-5 or CK 22 using a standard immunoperoxidase method (ABC Elite kit) was performed. Lu-5 (Bio Medicals, Augst, Switzerland) is a pan-cytokeratin monoclonal antibody that recognizes types I and II cytokeratin subfamilies of all epithelial and mesothelial cells. Micro-metastases are defined based on a size exceeding 0.2 mm and less than or equal to 2 mm in diameter according to the American Joint Committee of Cancer (AJCC) classification [9]. Hence, isolated tumor cells (ITC) or tumor cell clusters measuring less than or equal to 0.2 mm in diameter did not meet the definition of micro-metastases. Therefore, these patients were considered as node-negative.

Non-sentinel lymph nodes

Non-sentinel lymph nodes were all examined by standard histopathology. Lymph nodes larger than 5 mm were

bisected, whereas lymph nodes less than or equal to 5 mm in diameter were not bisected but completely embedded in paraffin. Therefore, two levels from each larger lymph node and one level from the smaller lymph nodes were stained with H&E only.

All patients with SLN macro-metastases in frozen sections underwent immediate completion level I & II ALND. If the SLN was negative in frozen section but was found to contain macro-metastases in final histopathology, patients underwent delayed completion level I & II ALND. Due to the lack of clear data in the literature regarding the prognostic impact of SLN micro-metastases and according to our protocol, the decision to perform a completion ALND in patients with SLN micro-metastases or isolated tumor cells was left to each hospital's directives. No completion ALND was performed in women with tumor-free SLN.

Statistical analyses

Accuracy is defined as the ratio of correct test results (true positive and true negative) divided by the total number of tests (true positive + true negative + false positive + false negative). Sensitivity is defined as the ratio of true positive test results divided by the sum of true positive + false negative. Specificity is defined as the ratio of true negative test results divided by the sum of true negative + false positive. For compilation of data Microsoft Access database Software (Microsoft Corporation, Redmond, WA, USA) was used. Statistical analyses were performed with GraphPad InStat software version 3.05 (GraphPad Software, San Diego, California, USA).

Results

Between January 2000 and December 2003, SLN biopsies were performed on 659 breast cancer patients meeting the inclusion criteria. The overall SLN identification rate was 98.3% (648/659). The characteristics of the patients with successful SLN mapping are listed in Table 1. The median age was 58.9 years (range 28–90). Over two third of the patients (458/648 = 70.7%) had a pT1 tumor (≤ 2 cm), 29.3% had a pT2 tumor (≤ 3 cm). The median tumor size was 17 mm (range 1–30). A median number of two SLN per patient were harvested.

On preoperative lymphoscintigraphy, a lymphatic flow was detected in 643 patients (643/659 = 97.6%). In 556 patients (556/643 = 86.5%) there was an axillary flow of the $^{99\text{m}}\text{Tc}$ -labeled nanocolloid without detection of an additional flow to the internal mammary nodes. In 85 patients (85/643 = 13.2%) an additional flow to the internal mammary nodes was observed. None of these

Table 1 Tumor characteristics of patients with successful SLN mapping ($n = 648$)

Parameters	No.	%
Age (years)		
Median	58.9	
Range	(28–90)	
Menopausal status		
Premenopausal	181	27.9
Postmenopausal	467	72.1
Tumor size in mm		
Median	17.0	
Range	(1–30)	
T stage		
T1a	18	2.8
T1b	73	11.3
T1c	367	56.6
T2	190	29.3
Histology		
Ductal	561	86.6
Lobular	72	11.1
Other	15	2.3
Histological grading		
G1	123	19.0
G2	385	59.4
G3	140	21.6
Primary tumor		
Tumorectomy	587	90.1
Mastectomy	61	9.9
Quadrant		
Upper outer	340	52.5
Upper inner	118	18.2
Lower outer	74	11.4
Lower inner	50	7.7
Areolar	66	10.2
Estrogen receptor status		
Positive	558	86.1
Negative	90	13.9
Progesteron receptor status		
Positive	500	77.2
Negative	148	22.8
No. of SLN per patient		
Median	2.0	
Range	(1–14)	

patients underwent additional biopsy of the internal mammary nodes. Only two patients ($2/643 = 0.3\%$) had a lymphatic drainage to the internal mammary nodes without any flow to the axillary lymph nodes. One of these patients underwent a biopsy of the extraaxillary lymph nodes which did not show evidence of malignancy.

SLN frozen sections were negative in 499 patients ($499/648 = 77.0\%$), whereas SLN macro-metastases were detected in 142 patients ($142/648 = 21.9\%$), and SLN micro-metastases in 7 patients ($7/648 = 1.1\%$) (Fig. 1). All 149 patients with macro- or micro-metastases in SLN frozen section underwent immediate completion level I & II ALND. In this subset, Non-SLN metastases were found in 63/142 patients (44.4%) with SLN macro-metastases, however, no Non-SLN metastases were detected in the 7 patients with SLN micro-metastases ($0/7 = 0\%$). In the subset of patients with negative frozen section, final histopathology with H&E step sections and immunohistochemistry detected three patients with SLN macro-metastases, 61 patients with SLN micro-metastases, and 19 patients with isolated tumor cells (Fig. 1).

Overall, 435 patients ($435/648 = 67.1\%$), including those with SLN isolated tumor cells (according to AJCC classification), were definitively node-negative, and 213 patients ($213/648 = 32.9\%$) were definitely classified as node-positive. The detection of three SLN macro- and 61 SLN micro-metastases in H&E step sections and immunohistochemistry led to an upstaging of 14.7% ($64/435$) from node-negative to node-positive patients.

All three patients in whom SLN macro-metastases were detected only in final histopathology underwent delayed completion level I & II ALND. In one of these three patients another Non-SLN macro-metastasis was found. Thirty-six of the 61 patients with SLN micro-metastases and 11 of the 19 patients with SLN isolated tumor cells in the final histopathology also underwent a delayed completion ALND according to the hospitals directives (Table 2). Only in two patients with SLN micro-metastases ($2/36 = 5.5\%$) and in none with SLN isolated tumor cells ($0/11 = 0\%$) the ALND specimen revealed further macro-metastases.

In summary, 84% ($42/50$) of the patients undergoing a delayed completion ALND had no benefit as the ALND specimens were completely tumor free. Most notably, only in 4% ($2/47$) of patients with SLN micro-metastases or SLN isolated tumor cells, macro-metastases were found in the final ALND specimens. After a median follow-up of 46 months (range: 16–72 months) none of the 33 patients with SLN micro-metastases or SLN isolated tumor cells who did not undergo further axillary surgery developed axillary recurrence. Only one patient died from distant metastases.

The accuracy of frozen section regarding the detection of macro-metastases was 99.5% ($645/648$). The accuracy of detection of macro- or micro-metastases (without ITC) was 90.1% ($584/648$). The specificity of SLN frozen section in our analysis was 100% as there were no false-positive results at all.

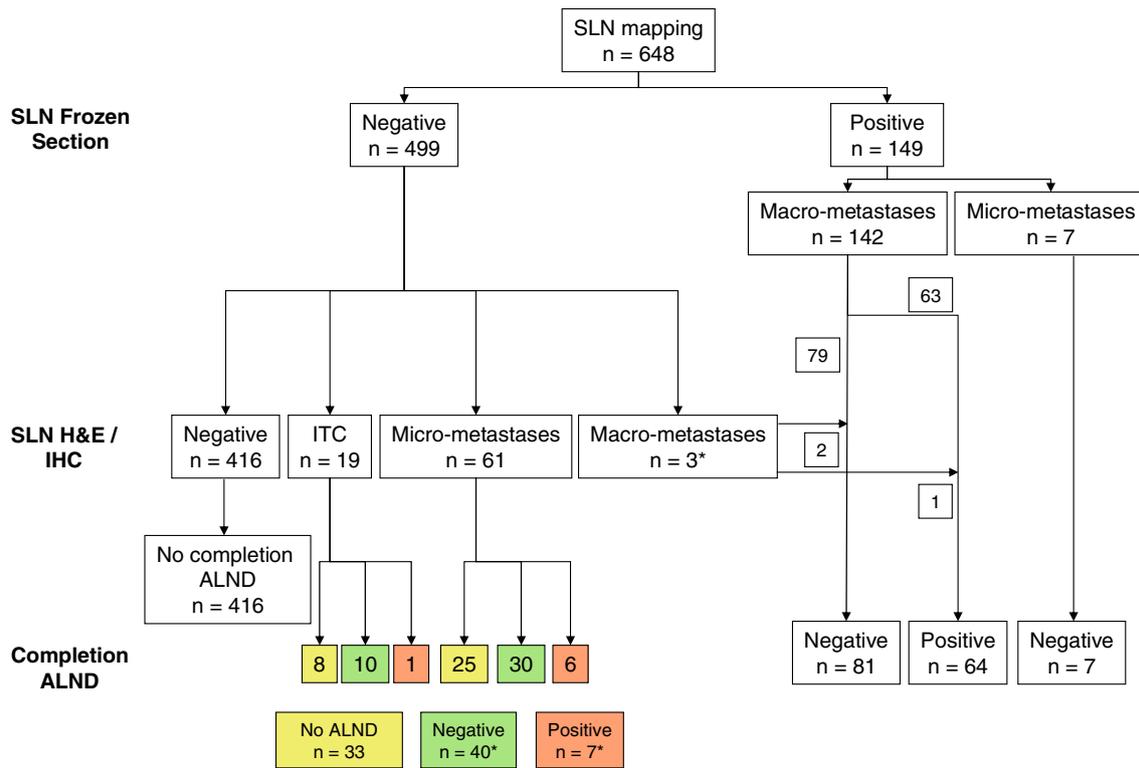


Fig. 1 Patients’ flow chart. * Patients undergoing delayed completion ALND

Table 2 Results of delayed completion ALND according to the final SLN histopathology in 50 patients with false-negative SLN frozen section results (compare Fig. 1)

Final results of delayed completion axillary lymph node dissection		Negative ALND specimen	Micro-metastases in ALND specimen	Macro-metastases in ALND specimen
False-negative SLN frozen section results <i>n</i> = 50	ITC in SLN, <i>n</i> = 11	10/11	1/11	0/11
	Micro-metastases in SLN, <i>n</i> = 36	30/36	4/36	2/36
	Macro-metastases in SLN, <i>n</i> = 3	2/3	0/3	1/3

ITC: isolated tumor cells; SLN: sentinel lymph node, ALND: axillary lymph node dissection

The sensitivity of SLN frozen section to detect any tumor deposits in the SLN (macro-metastases & micro-metastases & isolated tumor cells) was 64.2% (149/232). The sensitivity to detect positive sentinel nodes according to the 6th AJCC classification (macro- & micro-metastases but excluding isolated tumor cells) was 70.0% (149/213). The sensitivity of SLN frozen section to detect macro-metastases was 97.9% (142/145), whereas the sensitivity for the detection of micro-metastases was only 10.3% (7/68) (Table 3).

Discussion

The present prospective multicenter investigation based on a large sample of early stage breast cancer patients

provides compelling evidence that frozen section of the SLN provides highly accurate information regarding the identification of macro-metastases. Based on frozen section results a delayed completion ALND as a second intervention could be avoided in 98% in our investigation. Conversely, frozen section is not an accurate tool to detect SLN micro-metastases or isolated tumor cells. However, most patients (45/47 = 96%) with SLN micro-metastases or isolated tumor cells in frozen section or final histopathology did neither benefit from an immediate nor a delayed completion ALND as the ALND specimens did not contain macro-metastatic disease. Moreover, patients with SLN micro-metastases and SLN isolated tumor cells who did not undergo a delayed completion

Table 3 Review of the literature

Author	Year	No. of patients	Intraoperative examination	Sensitivity (%) macro-metastases	Sensitivity (%) micro-metastases	Overall accuracy	Specificity (%)	Final pathology stains
Turner ¹¹	1999	278	FS & IC	98	28	93	100	H&E/IHC
Weiser ¹²	2000	890	FS	92	17	89	99	H&E/IHC
Chao ¹⁴	2002	203	FS	96	28	92	99	H&E/IHC
Creager ¹⁶	2002	656	FS	100	52	84	98	H&E/IHC
Grabau ¹³	2005	272	FS	95	29	91	98	H&E/IHC
Brogi ¹⁵	2005	133	FS & IC	96	20	95	99	H&E/IHC
Langer	2008	648	FS	98	10	90	100	H&E/IHC

FS, frozen section; IC, imprint cytology; H&E, hematoxylin and eosin; IHC, immunohistochemistry

ALND developed no axillary recurrence after a median follow-up of 46 months.

Intraoperative SLN examination represents an appealing concept in the management of early stage breast cancer patients. It permits an immediate completion axillary lymph node dissection during the initial operation if the sentinel lymph node contains metastatic deposits which occurs in approximately 30% of early stage breast cancer patients [10]. A second surgical intervention is often perceived as very distressing for most patients. Of course, the sine qua non for the frozen section to be beneficial is a high sensitivity to detect at least macro-metastases combined with a high specificity (low rate of false positive results) to avoid performing an unnecessary ALND. Sensitivities between 92% and 100% to detect SLN macro-metastases are reported in the literature [11–16]. Other series which did not distinguish between macro- and micro-metastases reported sensitivities for SLN frozen section between 54% and 94% [17–26] (Table 3). These large variations reflect the different histopathological techniques used for frozen section analyses and final histopathology. These differences include variations in the cutting intervals, the number of sections, and the additional use of immunohistochemistry. The Veronesi group maximized the accuracy of intraoperative SLN examination [27] by performing a total of 60 sections per node. One section of each pair was stained with H&E, the other was immunostained for cytokeratin. Additional pairs were cut if residual lymph node tissue was left. The results were usually available after 40 to 50 min. Unfortunately, this method is expensive, very time consuming, prolongs the operation, and is impracticable for most institutions.

The specificity of frozen section approaches 100% in most series (Table 3). This finding is of utmost importance as it avoids unnecessary axillary surgery due to a false-positive intraoperative finding. Although a few false-positive results have been reported after frozen section analysis [22], they occur more often using the imprint cytology method. Imprint

cytologies are usually made by touching the cut surfaces of the SLN to a glass slide followed by immediate fixation. The interpretation of imprint cytology requires an experienced cytopathologist to decide whether or not tumor cells are present and explains why this method is more prone to false-positive results compared to regular frozen section.

Interestingly, some authors favor imprint cytology over frozen section for the intraoperative SLN analysis [25, 28]. Several groups have studied the use of intraoperative imprint cytology in the evaluation of SLN. The accuracy of these studies varies from 78 to 98%, sensitivity ranges from 29 to 94%, and specificity from 88 to 100% [16]. A few groups assessed the utility of combined frozen section and imprint cytology in the evaluation of SLN. However, the accuracy, sensitivity, and specificity of these studies were similar to frozen section or imprint cytology alone [16]. Using standardized methods and careful pathologic review, no differences in sensitivity between frozen section and imprint cytology were found. Moreover, all methods were highly effective to identify macro-metastases, but less effective in the detection of micro-metastases [15].

The reported sensitivity of frozen section for the detection of SLN micro-metastases ranges only between 10% and 52% [11–14, 16, 22]. Therefore, while intraoperative frozen section examination identifies almost all macro-metastases, most micro-metastatic deposits are missed. However, the prognostic and therapeutic implications of SLN micro-metastases continues to be a matter of great debate [29–36]. Unidentified micro-metastases have been held responsible for the occurrence of up to 30% of distant metastases of breast cancer patients with negative axillary lymph nodes after ALND [37, 38]. Various retrospective studies reported a significant disease-free and overall survival disadvantage in breast cancer patients with micro-metastases [39], others, however, failed to find any significant association [40]. In a previous prospective multicenter study, we analyzed 27 patients with SLN

micro-metastases, who did not undergo a completion ALND [3]. No evidence was found that the presence of SLN micro-metastases is associated with axillary recurrence or distant disease after a median follow-up of 42 months. This supports our theory that formal axillary dissection might be omitted in these patients. It is hoped that ongoing prospective trials from the American College of Surgeons Oncology Group (ACOSOG), National Surgical Adjuvant Breast and Bowel Project (NSABP), and International Breast Cancer Study Group (IBCSG) will provide a definite answer regarding prognostic and therapeutic implications of micro-metastases in early stage breast cancer patients.

Most interestingly, in the present investigation the vast majority of patients with SLN micro-metastases or isolated tumor cells did not benefit from delayed completion level I & II ALND as 96% (45/47) of these cases had no further macro-metastatic disease in the ALND specimens.

Furthermore, in patients with SLN micro-metastases and SLN isolated tumor cells who did not undergo further surgery, there were no axillary recurrences after a median follow-up of 46 months. New therapeutic computer-based algorithms such as the Memorial Sloan-Kettering Cancer Center nomogram to predict the likelihood of additional lymph node metastases may be helpful to identify patients who could potentially benefit from further surgery [41].

Some concerns were raised regarding the potential tissue loss during frozen section examination, which is an important issue in melanoma surgery [8]. However, the risks of tissue loss can be minimized by employing appropriate techniques and adequate pathological experience [42].

In summary, the present prospective multicenter study based on 659 breast cancer patients clearly shows that SLN frozen section identifies SLN macro-metastases with very high accuracy. Therefore, a delayed completion ALND can be avoided in 98% of these patients. Therefore, we strongly recommend the routine use of SLN frozen section in early stage breast cancer patients. Conversely, the detection rate of micro-metastases or isolated tumor cells in frozen section analysis is low. However, in the present investigation the vast majority (96%) of patients with SLN micro-metastases or isolated tumor cells did not benefit from a completion level I & II ALND as they had no further macro-metastatic disease in the ALND specimens.

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