



Intra-operative evaluation of the sentinel lymph node for T1-N0 breast-cancer patients: always or never? A risk/benefit and cost/benefit analysis

G. Canavese, P. Bruzzi, A. Catturich, C. Vecchio, D. Tomei, F. Carli, M. Truini, G.B. Andreoli, V. Priano, B. Dozin

► To cite this version:

G. Canavese, P. Bruzzi, A. Catturich, C. Vecchio, D. Tomei, et al.. Intra-operative evaluation of the sentinel lymph node for T1-N0 breast-cancer patients: always or never? A risk/benefit and cost/benefit analysis. *EJSO - European Journal of Surgical Oncology*, 2010, 36 (8), pp.737. 10.1016/j.ejso.2010.06.010 . hal-00608926

HAL Id: hal-00608926

<https://hal.science/hal-00608926>

Submitted on 16 Jul 2011

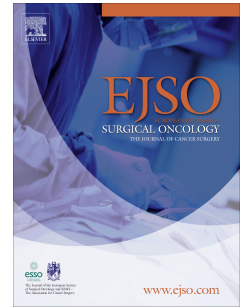
HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Accepted Manuscript

Title: Intra-operative evaluation of the sentinel lymph node for T1-N0 breast-cancer patients: always or never? A risk/benefit and cost/benefit analysis

Authors: G. Canavese, P. Bruzzi, A. Catturich, C. Vecchio, D. Tomei, F. Carli, M. Truini, G.B. Andreoli, V. Priano, B. Dozin



PII: S0748-7983(10)00186-1

DOI: [10.1016/j.ejso.2010.06.010](https://doi.org/10.1016/j.ejso.2010.06.010)

Reference: YEJSO 2998

To appear in: *European Journal of Surgical Oncology*

Received Date: 19 April 2010

Revised Date: 17 May 2010

Accepted Date: 7 June 2010

Please cite this article as: Canavese G, Bruzzi P, Catturich A, Vecchio C, Tomei D, Carli F, Truini M, Andreoli GB, Priano V, Dozin B. Intra-operative evaluation of the sentinel lymph node for T1-N0 breast-cancer patients: always or never? A risk/benefit and cost/benefit analysis, *European Journal of Surgical Oncology* (2010), doi: 10.1016/j.ejso.2010.06.010

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Intra-operative evaluation of the sentinel lymph node for T1-N0 breast-cancer patients : always or never?

A risk/benefit and cost/benefit analysis.

G. Canavese, MD^a, P. Bruzzi, MD^b, A. Catturich, MD^a, C. Vecchio, MD^a, D. Tomei, MD^a, F. Carli, MD^c, M. Truini, MD^c, G.B. Andreoli, MD^d, V. Priano, MD^a and B. Dozin, PhD.^b

^aAdvanced Surgical Senology Unit, ^bClinical Epidemiology Unit, ^cAnatomy and Cytohistology Unit and ^dInstitute Medical Direction.

National Cancer Research Institute, Genoa, Italy

Corresponding author : Beatrice Dozin, PhD

Clinical Epidemiology, National Cancer Research Institute,

Largo R. Benzi, 10, 16132 Genoa, Italy

Phone : 39 – 010 – 5737492

Fax : 39 – 010 – 354103

e-mail : beatrice.dozin@istge.it

Abstract

Aim : To investigate whether omitting intra-operative staging of the sentinel lymph node (SLN) in T1-N0 breast-cancer patients is feasible and convenient because it could allow a more efficient management of human and logistic resources without leading to an unacceptable increase in the rate of delayed axillary lymph node dissection (ALND).

Methods : According to the experimental procedure, T1a-T1b-patients were to not receive any intra-operative SLN evaluation on frozen sections (FS). In all T1c-patients, the SLN was macroscopically examined; if the node appeared clearly free of disease, no further intra-operative assessment was performed; if the node was clearly metastatic or presented a dubious aspect, the pathologist proceeded with analysis on FS. T2-patients, enrolled in the study as reference group, were treated according the institutional standard procedure; they all received SLN staging on FS.

Results : The study included 395 T1-N0 patients. Among the 118 T1a-T1b-patients whose SLN was not analyzed at surgery, 12 (10.2%) were recalled for ALND. In the group of 258 T1c-patients, 112 received SLN analysis on FS and 146 did not. A SLN falsely negative either at macroscopic or FS examination was found in 33 (12.8%) cases. Overall, the rate of recall for ALND was 11.6% as compared to 8.4% in T2-patients. Using the experimental protocol, the institution reached a 9.6% cost saving, as compared to the standard procedure.

Conclusions : Omission of SLN intra-operative staging in T1-N0 patients is rather safe. It provides the institution with both management and economical advantages.

Keywords: breast cancer, sentinel lymph node, intra-operative evaluation, axillary lymph node dissection

Introduction

Resection of the primary tumor together with axillary lymph node dissection (ALND) has long been the standard surgical management of early-stage breast cancer. However, axillary metastases are found in only ~40% of the cases [1, 2]; the remaining patients derive no benefit from axillary surgery but unnecessarily face common morbidities from ALND [3]. For patients with early-stage tumor (T1-T2) and clinically negative lymph nodes (N0), this problem is now obviated by the use of the sentinel lymph node biopsy (SLNB). This minimally invasive, safe and acceptably accurate procedure has a high negative predictive value for axillary status [4,5,6] and is nowadays the recommended method for axilla staging [7, 8, 9].

Nevertheless, several aspects need further evaluation: 1) is ALND mandatory for all patients with metastatic SLN?; 2) what is the prognostic significance of SLN micrometastases, particularly those evidenced only by immunohistochemistry, and of isolated tumor cells? 3) can patients presenting both SLN micrometastasis and small-size tumor be spared ALND? 4) is it necessary to always perform SLNB, and when needed, ALND during the initial surgery or could these procedures be postponed in specific instances?

This last question emerges from several considerations [8,10,11]: screening mammography has increased the proportion of patients presenting a ≤ 1 cm tumor; these patients have a low probability of nodal disease as the incidence of positive SLN increases with tumor size; the presence of SLN micrometastases is predominantly associated with pT1a-1b tumors; intra-operative false-negative SLN staging on frozen sections (FS) is largely due to the failure to detect micrometastasis by hematoxylin-

eosin;; pT1c-pT2-patients mostly benefit from FS examination since the sensitivity of the procedure increases with tumor size.

Based on these considerations, the present study was designed to investigate whether intra-operative SLN staging on FS could be omitted in T1-N0-patients and deferred to definitive evaluation on paraffin sections (PFS). As for risk/benefit and cost/benefit, we hypothesized that this approach could provide patients with shorter surgery duration and hospital stay without substantially increasing the rate of second surgery for ALND, but allowing more efficient use of human resources and logistic facilities.

Patients and methods

Study hypothesis

The main hypothesis was that intra-operative SLN evaluation on FS could be omitted, with measurable efficiency gains, in all patients clinically staged T1a-T1b, and in the subgroup of T1c-patients presenting a SLN macroscopically free of disease. We investigated whether this approach was associated with an unacceptably high rate of recall for ALND, thereby counterbalancing/nullifying the advantages deriving from the reduced duration of the initial surgery. The rate of delayed ALND in T2-patients due to false-negative SLN on FS, was used as reference. Indeed, an overview of our whole case series across the period 1998-2004 has given an acceptable false-negative rate of 8-9%.

A second objective was to assess the accuracy and negative predictive value of the macroscopic evaluation performed by the pathologist in T1c-patients.

A third objective was to estimate the economical and organizational implications of the experimental procedure.

Patient population

This single-center, uncontrolled study was conducted at the National Cancer Research Institute of Genoa, Italy. The protocol, which introduced a modification in our current surgical procedures, that is intra-operative SLN evaluation on FS for all patients, was approved by Institutional Ethical Committees and conducted in accordance with International Good Clinical Practice Guidelines. Patients satisfying the following criteria were selected: primary infiltrating breast carcinoma (cytologically C5), small-size tumor (T1-T2) as estimated by mammography and/or ecography, clinically

negative axillary nodes. Eligible patients who had undergone previous surgery on the same breast and/or the ipsilateral axilla, or presented a bilateral, multifocal or multicentric tumor were excluded. All enrolled patients were informed on study aims and implications and signed a consent form.

Surgical protocol (Figure 1)

In all patients, SLN was identified and retrieved as previously described [12].

Patients clinically staged T1a, T1b or T1c represent the experimental group undergoing the intra-operative protocol under investigation. Information on T2-patients treated according to our standard intra-operative protocol is also provided to allow comparisons with surgical practices in other institutions.

Experimental intra-operative protocol

No intra-operative SLN evaluation was performed in T1a-T1b-patients (tumor size $\leq 1\text{cm}$); SLN diagnosis was deferred to the definitive examination on PFS and no axillary dissection was performed in concomitance with surgery.

In T1c-patients (tumor size $>1\text{cm}$ but $\leq 2\text{cm}$), SLN was subjected to intra-operative macroscopic evaluation as follows: the pathologist first appraised SLN dimension and consistency as well as the status of the capsula. The SLN was then bisected along its major axis and both cut surfaces were assessed for color, nodularity, hemorrhage and necrosis. If none of these parameters was suspicious, the SLN was considered negative and embedded in paraffin for definitive post-operative evaluation; no axillary dissection was performed in concomitance with surgery. If the SLN presented areas possibly metastatic, FS were analyzed. If metastases were found, the surgeon proceeded with ALND. If the SLN was clearly metastatic, FS were anyway

analyzed to confirm the diagnosis of node disease and ALND was immediately performed.

Standard intra-operative protocol

All T2-patients (tumor size $>2\text{cm}$ but $\leq 5\text{cm}$) underwent SLNB on FS, which was immediately followed by ALND if the SLN was metastatic.

Intra-operative SLN evaluation on frozen sections

The SLN was bisected along its major axis. Five frozen sections, each $4\text{-}\mu\text{m}$ thick, were cut every $50\text{ }\mu\text{m}$ in each half and stained with hematoxylin-eosin.

Definitive post-operative SLN evaluation on paraffin sections

The bisected SLN was fixed in formalin for 24 hours and embedded in paraffin. In each half, 10 sections, each $4\text{-}\mu\text{m}$ thick, were cut at every $50\text{ }\mu\text{m}$ (first 5) and every $150\text{ }\mu\text{m}$ (next 5). All sections, but the second and the ninth, were stained with hematoxylin-eosin. If the diagnosis resulted negative or ambiguous, the second and the ninth sections were tested by immunohistochemistry for the presence of cytokeratins, as previously described [12].

Economical and organizational evaluations

We considered 4 types of surgical procedures and estimated their respective costs including surgery room occupation, medical and nursing staff time, histological SLN assessment and patient care: procedure #1) tumor excision with SLN retrieval but no evaluation on FS; procedure #2) tumor excision with SLNB on FS but no ALND; procedure #3) tumor excision with SLNB on FS and ALND; procedure #4) second

surgery for delayed ALND. Based on costs of personnel and hospital care at our institution, the estimates of procedures #1, #2, #3 and #4 were 1150, 1467, 2550 and 1795 euros, respectively.

Results

Patient characteristics

Between January 2005 and December 2007, 558 T1-T2-N0 patients were admitted for surgery at our institution. Among them, 33 were not eligible for the study because they had undergone previous surgery on the same breast (n=26), or presented a bilateral (n=5) or multifocal (n=2) tumor. The study thus included 525 patients whose characteristics are summarized in Table 1

Compliance with protocol

Considering all 525 patients, a total of 989 SLNs were identified and removed (median 2.0 node/patient, range 1 to 6). Table 2 reports both intra-operative SLN evaluation and ALND performed during surgery, as well as the compliance with the protocol assigned according to the clinical T.

Experimental protocol

Among the 137 T1a-T1b-patients, 118 did not undergo any intra-operative SLN evaluation and, consequently, no concomitant ALND was performed. SLN status was assessed only at definitive examination on PFS, in compliance with the protocol. For the other 19 T1a-T1b-patients, the surgeon specifically requested intra-operative SLN examination on FS because of the dubious macroscopic appearance of the node. Six of those patients presented SLN metastases and underwent concomitant ALND.

For all 258 T1c-patients, SLN was macroscopically evaluated. In 146 cases, it appeared negative, and neither further SLN analysis nor ALND was performed. Ten other patients had a clearly metastatic SLN, which was histologically confirmed, and

received immediate ALND. For the remaining 102 patients, the macroscopic evaluation resulted unclear and was thus followed by histological analysis on FS. Metastases were found in 43 cases and concomitant ALND was performed. The other 59 patients who presented a histologically negative SLN were spared ALND.

Standard protocol

Among the 130 T2-patients, 126 received histological SLN analysis. Fifty-one of them presented metastases and underwent immediate ALND. Other 75 patients had a negative SLN. For the last 4 patients, SLN assessment on FS was unfeasible due to the exceeding adiposity of the node. The SLN was thus macroscopically evaluated and resulted negative in all 4 cases. None of these 79 patients with negative SLN received ALND.

SLN status at definitive diagnosis

Table 3 summarizes the results of the definitive diagnosis of the SLN on PFS as compared with the intra-operative evaluation.

Experimental protocol (Table 3A)

Among the 118 T1a-T1b-patients whose SLN was not evaluated during surgery, 12 resulted positive on PFS. Six of them presented SLN micrometastases (foci > 0.2 mm but ≤ 2 mm) and other 6 had SLN macrometastases (foci > 2 mm). All 12 patients were thus recalled to undergo ALND. For the remaining 106 patients, the SLN was free of disease, which obviated the need for ALND.

Upon intra-operative macroscopic evaluation, the SLN of 146 T1c-patients was considered negative. The diagnosis was correct in 121 of the cases. By contrast, the

SLN was falsely negative for 25 patients, resulting at definitive diagnosis micrometastatic or macrometastatic in 12 and 13 of the cases, respectively. All these 25 patients thus received delayed ALND. For the 131 patients (112 T1c and 19 T1a-T1b-patients) whose SLN was macroscopically either clearly positive or dubious, additional intra-operative examination on FS evidenced 8 cases with micrometastasis, 51 (39.8%) cases with macrometastasis and 72 cases free of disease. The 51 macrometastases were all confirmed at definitive examination while 2 of the 8 micrometastases resulted to be macrometastases. Among the 72 SLNs diagnosed disease-free on FS, 9 were found positive on PFS. Seven of these SLNs presented micrometastases and 2 had macrometastases. Thus, for this subgroup of 131 patients, the prevalence of metastatic SLN was 51.9% (95% CI 48.8 - 55.0). The accuracy and the negative predictive value of the intra-operative SLN evaluation on FS were 93.1% (95% CI 91.4 – 94.5) and 87.5% (95% CI 85.3 – 89.4), respectively. The rate of recall for delayed ALND was 6.9% (95% CI 5.5 – 8.7).

Accuracy of intra-operative macroscopic SLN examination for the subgroup of T1-patients

Overall, among the 258 T1c-patients, 86 presented SLN metastases, (24 micrometastases and 62 macrometastases). Fifty-three of these positive SLNs were identified by macroscopic evaluation for a sensitivity of 61.6% (95% CI 58.6 – 64.6), while 51 SLNs were false-positive at macroscopic evaluation for a specificity of 70.3% (95% CI 67.4 – 73.1). Positive and negative predictive values of SLN macroscopic evaluations were 54.5% (95% CI 51.4 – 57.6) and 82.9% (95% CI 80.4 – 85.1), respectively.

Standard protocol (Table T3B)

All T2-patients, except for the 4 cases with lipomatous SLN, received intra-operative SLN analysis on FS, without preliminary macroscopic evaluation. Micrometastases and macrometastases were found in 6 and 46 cases, respectively. SLN positivity was confirmed on PFS for all these 52 patients. Among the remaining 78 patients diagnosed SLN negative on FS, 67 were truly negative while 11 presented micrometastatic (n=8) or macrometastatic (n=3) at definitive evaluation. Prevalence of metastatic SLN in this subgroup was 48.5% (95% CI 45.4 – 51.6). Accuracy and negative predictive value of the diagnosis on FS were 91.5% (89.6 – 93.1) and 85.9% (95% CI 83.6 – 87.9), respectively. The rate of second surgery for ALND was 8.4% (95% CI 6.8 – 10.3), which is in line with the \approx 8 to 9% rate of recall we observed at our institution across the 1998-2004 period.

Risk/benefit and cost/benefit evaluations

Benefit evaluation

Table 3A shows that, overall, 46 out of the 395 patients treated according to the experimental procedure had to undergo a second surgery for ALND. Thus, the risk of not identifying metastatic SLN(s) in this settings is slightly higher as compared with the expected risk of having false-negative SLN(s) on standard FS (11.6% versus the \approx 8.0% estimated from our 1998-2004 institutional report).

Cost evaluation

Table 4 compares, within this group of 395 patients, the actual costs of the experimental protocol with the theoretical costs the institution would have if all patients were treated according to the standard protocol. Table 4A summarizes the cost of each of the 4 surgical procedures used in the study. .

All 118 T1a-T1b-patients not receiving any intra-operative SLN evaluation underwent procedure #1 (Table 4B). Twelve of them were also recalled for second surgery. The total cost was thus 157,600 euros. If these patients were treated with the standard protocol, 106 would have procedure #2. Considering a $\approx 8\%$ false-negative rate on FS, 1 of the other 12 patients would receive both procedure #2 and recall for ALND. The remaining 11 patients would undergo procedure #3. Overall, the theoretical cost of the standard procedure would be 186,900 euros. For this subgroup of T1a-T1b-patients, the actual cost was thus $\approx 15.7\%$ less than the theoretical one.

When we analyzed on the same line the subgroup of 146 T1c-patients who underwent only macroscopic SLN evaluation, we obtained an actual cost of 212,800 euros (Table 4C), which includes 146 procedures #1 and 25 recalls for ALND. The standard protocol would foresee, for a total cost of 242,700 euros, 123 procedures #2 including 2 cases of false-negative SLN needing delayed ALND, and 23 procedures #3. The actual cost thus represented 87.7% of the theoretical one.

The remaining 131 T1c-patients who underwent both macroscopic and histological SLN evaluations were treated essentially as the standard protocol. Actual and theoretical costs are thus equivalent.

Table 4D summarizes the global cost evaluation for all 395 patients of the experimental group. Overall, 264 patients did not have histological SLN examination (procedure #1) , 63 presented a histologically negative SLN and did not receive ALND

(procedure #2), 59 with positive SLN underwent concomitant ALND (procedure #3) and 46 with false-negative SLN had delayed ALND (procedure #4). The total cost of the experimental procedure was thus 629,100 euros. If the standard protocol were applied, 299 of these patients, that is those with a negative SLN, would have procedure #2, 59 patients with positive SLN would receive procedure #3 and other 9 patients with false-negative SLN would have procedure #4. Among the remaining 37 patients who did not have intra-operative histological SLN assessment, 3 would have a delayed ALND based on the expected 8% rate of false-negative node, which raises the number of procedure #4 to 12. The other 34 patients would be correctly diagnosed with a positive SLN and undergo concomitant ALND. The total theoretical cost would be 697,400 euros. Using the experimental protocol, the institution thus reached an overall 9.8% saving, corresponding to $\approx 70,000$ euros.

Discussion

Rate of delayed ALND

We investigated whether intra-operative SLN evaluation could be omitted for patients clinically staged T1-N0, without excessively jeopardizing their post-surgery course while allowing more efficient use of human resources and logistic facilities. The main parameter under assessment was the rate of delayed ALND as compared to that we usually observe when applying standard surgical procedures. This rate of 8-9% is provided by the group of T2-patients here included as reference and is similar to that observed across 69 other studies [8].

For the group of T1a-T1b-patients whose SLN was not evaluated at surgery, the rate of delayed ALND was 10.2%, which is quite acceptable as compared to the 8.4% rate observed for the T2-patients. Among the 146 T1c-patients whose SLN was evaluated only macroscopically, the node was falsely negative in 25 cases, thus giving a rate of delayed ALND as high as 17.1%. However, in most cases, the pathologist could not have detected these metastases as they were either micrometastases $<0.2\text{mm}$ ($n=12$), or sparse metastatic cells originating from infiltrating lobular carcinomas ($n=4$), or metastases embedded in a lipomatous SLN ($n=3$).

Risk and benefit considerations

a) in the present settings

Overall, 46 of the 395 patients of the experimental group needed a second surgery for completion of axillary lymph node dissection. This corresponds to a 3.2% increase of delayed ALND as compared to the 8.4% reference rate. In terms of

cost/benefit, the overall cost of these 395 experimental procedures was 9.8% less than if all patients were treated according to the standard procedures.

The limited, though non-negligible, risk of delayed ALND and the economical implications are not the sole factors to be taken into account when considering our experimental protocol as a possible routine option for T1-N0-patients. Indeed, this protocol warrants both shorter surgery duration and hospital stay for the majority of patients; in turn, this allows more efficient management of human resources and use of surgery rooms. When intra-operative SLN examination is not performed, surgery duration is reduced by 23 % or 34% as compared to a surgery that includes SLNB with negative result or SLNB with positive result and subsequent ALND, respectively. Thus, more patients can be treated by the same staff and waiting lists can be shortened. by simply scheduling surgery, on fixed days, for only T1-N0 patients.

b) in the absence of any intra-operative SLN evaluation

We are aware that at some institutions, intra-operative SLN evaluation is never performed for T1-T2-N0 patients but is straightly deferred to the definitive diagnosis on PFS. Considering the T1-patients of our study, those with a T1c-tumor and a SLN macroscopically unclear or positive received intra-operative SLN examination. If this intra-operative evaluation were not performed, the management of human resources and logistic facilities would further improve. However, the additional economical advantage would be insignificant (less than 1.5%) and patients would suffer major distress knowing that the possibility to be recalled for a second surgery is greater than 1 over 10. On the same line, if the SLN of the T2-patients were evaluated only at definitive

analysis, time and cost savings would be negligible due a rate of delayed ALND as high as 40%.

Conclusions

The experimental protocol here evaluated (no SLN evaluation or macroscopic examination) seems to be rather safe for the subgroup of T1-N0-patients. Furthermore, it is beneficial for the institution, in terms of efficiency and costs. Alternatively, the possibility not to perform any intra-operative evaluation but to always defer SLN assessment to post-surgery definitive diagnosis might be considered for all T1-N0-patients. A third option is to let the patients, fully informed on the risks and implications of the procedure, freely choose whether to undergo intra-operative SLN evaluation and, if needed, immediate ALND. Intra-operative SLN examination should remain the standard procedure for all T2-N0-patients.

Conflict of interest statement

None of the authors has any of interest regarding the manuscript.

References

1. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. *Cancer* 2006; 106:4-16.
2. Krag DN, Anderson SJ, Julian TB, et al. National Surgical Adjuvant Breast and Bowel Project. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. *Lancet Oncol* 2007; 8:881-8.
3. 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
4. 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.
5. Giuliano AE, Jones RC, Brennan M, Statman R. Sentinel lymphadenectomy in breast cancer. *J Clin Oncol* 1997; 15:2345-50.
6. 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.
7. Schwartz GF, Giuliano AE, Veronesi U; Consensus Conference Committee. Proceedings of the consensus conference on the role of sentinel lymph node biopsy in carcinoma of the breast, April 19-22, 2001, Philadelphia, Pennsylvania. *Cancer* 2002; 94:2542-51.
8. Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol* 2005; 23:7703-20.

9. Silverstein MJ, Lagios MD, Recht A, et al. Image-detected breast cancer: state of the art diagnosis and treatment. *J Am Coll Surg* 2005; 201:586-97.
10. Weiser MR, Montgomery LL, Susnik B, Tan LK, Borgen PI, Cody HS. Is routine intraoperative frozen-section examination of sentinel lymph nodes in breast cancer worthwhile? *Ann Surg Oncol* 2000; 7:651-5
11. Chan SW, LaVigne KA, Port ER, Fey JV, Brogi E, Borgen PI, Cody HS 3rd. Does the benefit of sentinel node frozen section vary between patients with invasive duct, invasive lobular, and favorable histologic subtypes of breast cancer? *Ann Surg* 2008; 247:143-9.
12. Canavese G, Catturich A, Vecchio C, Tomei D, Gipponi M, Villa, et al. Sentinel node biopsy compared with complete axillary dissection for staging early breast cancer with clinically negative lymph nodes: results of randomized trial. *Ann Oncol* 2009; 20:1001-7

Legends to Figures

Figure 1 : Study design and protocol both for intra-operative evaluation of the sentinel lymph node and total axillary dissection.

SLN, sentinel lymph node; H&E, hematoxylin-eosin; ALND, axillary lymph node dissection

Table 1. Patient characteristics (n = 525)

Characteristic	n	(%)
Age (years) Median (range)	63 (23 – 85)	
Age by category		
≤ 45 y	126	(24.0)
46 – 55 y	102	(19.4)
56 – 65 y	163	(31.0)
> 65 y	134	(25.5)
Clinical T		
T1a		
T1b	28	(5.3)
T1c	109	(20.8)
T2	258	(49.1)
	130	(24.8)
Pathological T		
pT1a	27	(5.1)
pT1b	106	(20.2)
pT1c	250	(47.6)
pT2	141	(26.9)
pT3	1	(0.2)
Tumor site		
Right	248	(47.2)
Left	277	(52.8)
Quadrant		
QSE	215	(41.0)
QSI	60	(11.4)
QII	47	(9.0)
QIE	31	(5.9)
QC	24	(4.6)
>1 Quadrant	148	(28.1)
Tumor histology		
Ductal	431	(82.1)
Lobular	60	(11.4)
Other	34	(6.5)

Pathological N		
pN0	348	(66.3)
pN1mic	37	(7.0)
pN1a	115	(21.9)
pN2a	11	(2.1)
pN2	7	(1.3)
pN3a	7	(1.3)
Grading		
G1	96	(18.3)
G2	319	(60.8)
G3	109	(20.8)
Gx	1	(0.2)
Hormonal receptor status		
ER + / PgR +	397	(675.6)
ER - / PgR +	2	(0.4)
ER + / PgR -	50	(9.5)
ER - / PgR -	65	(12.4)
Unknown	11	(2.1)
Ki67		
≤ 15%	197	(37.5)
> 15%	328	(62.5)
c-erB-2		
Negative	438	(83.4)
1 +	27	(5.1)
2 +	24	(4.6)
3 +	25	(4.9)
Unknown	11	(2.1)

Table 2 : Compliance to the protocol established for both intra-operative SLN evaluation and axillary lymph node dissection, stratified by clinical T.

SLN evaluation (H.E. histological staining)	Axillary dissection	T1a –1b (total=137) n compliance	T1c (total=258) n compliance	T2 (total=130) n compliance
no	no	118 (as protocol)	146 (as protocol - macroscopic negative)	4 [§] fatty SLN
yes	no	13 [#] SLN dubious	59 (as protocol - macroscopic unclear - H.E. negative)	75 (as protocol)
yes	yes	6 [#] SLN dubious	43 (as protocol - macroscopic unclear - H.E. positive)	51 (as protocol)
yes	yes	- -	10 (as protocol - macroscopic positive)	- -

[#] intra-operative histological diagnosis performed upon explicit request from the surgeon.

[§] macroscopic evaluation only (intra-operative histological assessment not feasible).

Table 3 : SLN status at definitive diagnosis as compared to the intra-operative assessment.**A. Experimental protocol (T1a, T1b and T1c patients)**

SLN status	No evaluation		Macroscopic evaluation – negative		Macroscopic evaluation – positive or unclear followed by intra-operative H.E .histological staining*			
	T1a – T1b (n=118)		T1c (n=146)		T1c (n=112)		T1a – T1b (n=19)	
	Intra	Definitive	Intra	Definitive	Intra	Definitive	Intra	Definitive
Micrometastasis	-	6	-	-	8	neg 0 pos 8 - micro 6 - macro 2	-	-
Macrometastasis	-	6	-	-	45	neg 0 pos 45	6	neg 0 pos 6
Negative	-	106	146	neg 121 pos 25 - micro 12 - macro 13	59	neg 51 pos 8 - micro 6 - macro 2	13	neg 12 pos 1 - micro 1
Test in % (95% CI)					<i>T1c</i>	<i>Total</i>	<i>T1a-T1b</i>	
Recall for ALND	10.2 (8.5-12.2)		17.1 (14.9-19.6)		7.1 (5.7-8.9)	6.9 (5.5-8.7)	5.3 (4.1-6.9)	
Accuracy	-		-		92.9 (91.1-94.3)	93.1 (91.4-94.5)	94.7 (93.1-95.9)	
Negative Predictive Value	-		82.9 (80.4-85.1)		86.4 (84.1-88.4)	87.5 (85.3-89.4)	92.3 (90.5-93.8)	
Prevalence of metastatic SLN	10.2 (8.5-12.2)		17.1 (14.9-19.6)		54.5 (51.4-57.6)	51.9 (48.8-55.0)	36.8 (33.9-40.8)	

* including the 19 T1a-1b patients who underwent SLN intra-operative histological evaluation upon explicit request from the surgeon

B. Standard protocol (T2 patients)

SLN status	Intra-operative H.E. histological staining) (n=130)	
	Intra	Definitive
Micrometastasis	6	neg 0 pos 6 - micro 5 - macro 1
Macrometastasis	46	neg 0 pos 46
Negative	78	neg 67 pos 11 - micro 8 - macro 3
Test in % (95% CI)		
Recall for ALND	8.4 (6.8-10.3)	
Accuracy	91.5 (89.6-93.1)	
Negative Predictive Value	85.9 (83.6-87.9)	
Prevalence of metastatic SLN	48.5 (45.4-51.6)	

H.E. : haematoxylin-eosin; 95% CI : 95% confidence intervals

Table 4 : Comparative cost evaluation between the experimental and the standard protocols**A. Description of the procedures**

Procedure	Tumor resection	Pre- and post-surgery room (min)	Surgery room and staff (min)	SLN histological evaluation (min)	Axillary dissection (min)	Hospital care (days)	Cost (euros)
# 1	yes	yes (45)	yes (60)	no	no	yes (1)	1,150
# 2	yes	yes (45)	yes (60)	yes (30)	no	yes (1)	1,467
# 3	yes	yes (45)	yes (60)	yes (30)	yes (30)	yes (3)	2,550
# 4	no	yes (45)	yes (45)	no	yes (45)	yes (3)	1,795

B. Cost evaluation for the 118 T1a-T1b patients undergoing no intra-operative SLN evaluation

Cost in euros (K=x1,000)	Actual cost				Theoretical cost			
Procedure type	1	2	3	4	1	2	3	4
N° procedure	118	-	-	12	-	106 + 1	11	1
Cost per procedure	136,0 K	-	-	21,6 K	-	157,0 K	28,1 K	1,8 K

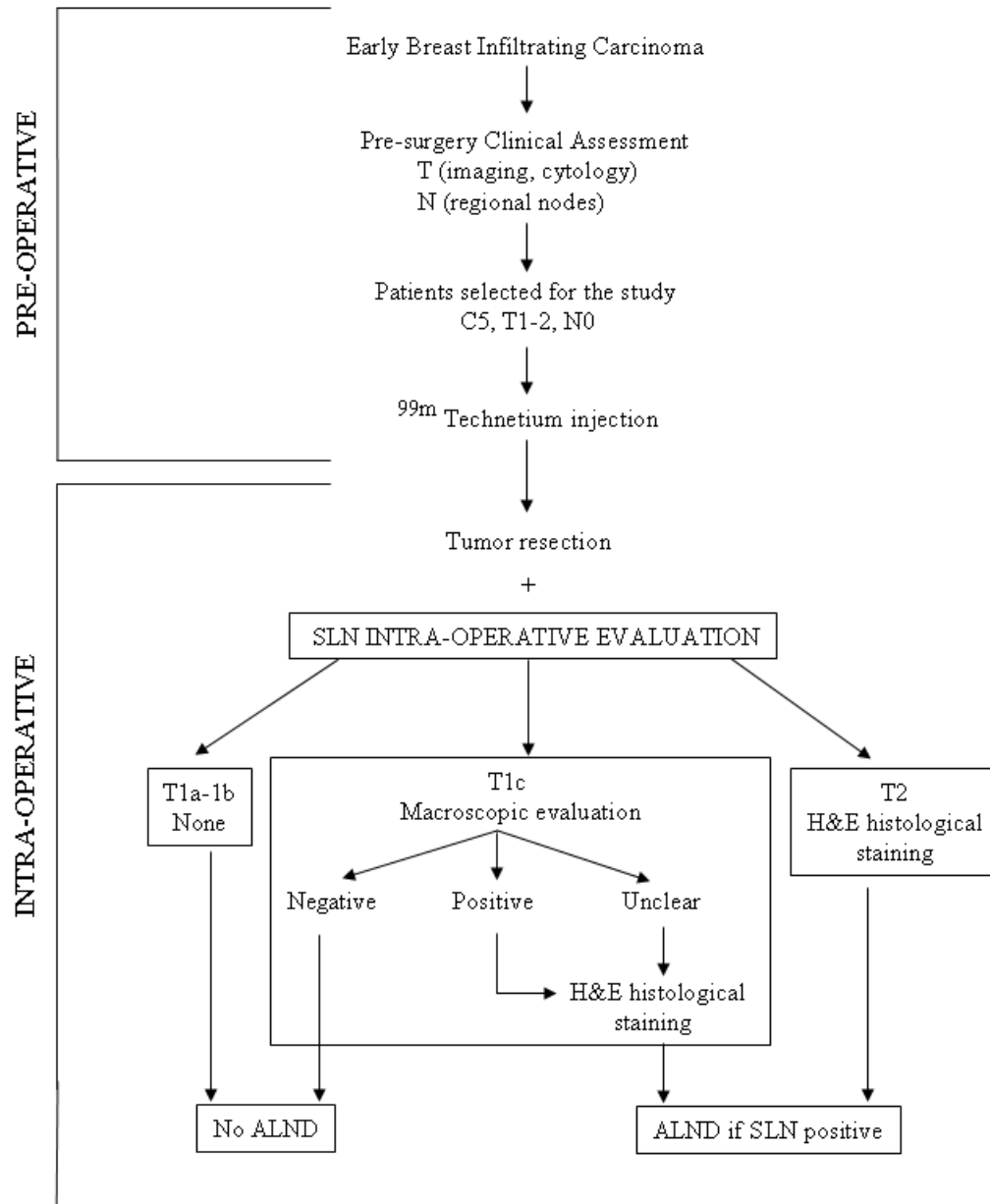
Total cost (%)	157,6 K (84.3)	186,9 K(100)
----------------	----------------	--------------

C. Cost evaluation for the 146 T1c patients undergoing only macroscopic SLN evaluation

Cost in euros (K=x1,000)	Actual cost				Theoretical cost			
Procedure type	1	2	3	4	1	2	3	4
N° procedure	146	-	-	25	-	121+2	23	2
Cost per procedure	167,9 K	-	-	44,9 K	-	180,4 K	58,7 K	3,6 K
Total cost (%)	212,8 K (87.7)				242,7 K (100)			

D. Cost evaluation for all 395 patients undergoing the experimental procedure

Cost in euros (K=x1,000)	Actual cost				Theoretical cost			
Procedure type	1	2	3	4	1	2	3	4
N° procedure	264	63	59	46	-	299	59 + 34	9 + 3
Cost per procedure	303,6 K	92,4 K	150,5 K	82,6 K	-	438,6 K	237,2 K	21,6 K
Total cost (%)	629,1 K (90.2)				697,4 K (100)			

**Figure 1**