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Sentinel lymph node biopsy is associated with improved survival compared to level I & II axillary lymph node dissection in node negative breast cancer patients

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Abstract

Objective: The few long-term follow-up data for sentinel lymph node (SLN) negative breast cancer patients demonstrate a 5-year disease-free survival of 96–98%. It remains to be elucidated whether the more accurate SLN staging defines a more selective node negative patient group and whether this is associated with better overall and disease-free survival compared with level I & II axillary lymph node dissection (ALND).

Methods: Three-hundred and fifty-five consecutive node negative patients with early stage breast cancer (pT1 and pT2 $\leq$ 3 cm, pN0/pN$_{SN}$0) were assessed from our prospective database. Patients underwent either ALND ($n = 178$) in 1990–1997 or SLN biopsy ($n = 177$) in 1998–2004. All SLN were examined by step sectioning, stained with H&E and immunohistochemistry. Lymph nodes from ALND specimens were examined by standard H&E only. Neither immunohistochemistry nor step sections were performed in the analysis of ALND specimen.

Results: The median follow-up was 49 months in the SLN and 133 months in the ALND group. Patients in the SLN group had a significantly better disease-free ($p = 0.008$) and overall survival ($p = 0.034$). After adjusting for other prognostic factors in Cox proportional hazard regression analysis, SLN procedure was an independent predictor for improved disease-free (HR: 0.28, 95% CI: 0.10–0.73, $p = 0.009$) and overall survival (HR: 0.34, 95% CI: 0.14–0.84, $p = 0.019$).

Conclusions: This is the first prospective analysis providing evidence that early stage breast cancer patients with a negative SLN have an improved disease-free and overall survival compared with node negative ALND patients. This is most likely due to a more accurate axillary staging in the SLN group.

Keywords: Disease-free and overall survival; Sentinel lymph node; Axillary dissection; Breast cancer; Long-term follow-up

Introduction

The sentinel lymph node (SLN) biopsy has become the standard staging method to evaluate the axillary lymph node status in early stage breast cancer patients in most institutions and has replaced level I & II axillary lymph node dissection (ALND).[1] The axillary lymph node status is among the most important prognostic factors in breast cancer patients and helps defining the need for subsequent adjuvant treatment. Many studies proved the accuracy and the high negative predictive value of the SLN procedure.[2] Since its introduction in clinical practice, axillary lymph node micro-metastases and isolated tumor cells are more likely to be detected[3–11] as a more thorough analysis including step sectioning and immunohistochemistry can be performed in fewer nodes.[12] Clearly, the systematic use of these techniques is not feasible for the assessment of all the nodes in ALND specimens due to time and financial constraints. In addition to improved staging, midterm follow-up

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data provided compelling evidence that axillary recurrences after SLN procedure are as low as after formal ALND.[13–15] Finally, randomized controlled trials and cohort studies showed a highly significant reduction of postoperative morbidity after SLN biopsy only.[14,16,24]

The few available long-term follow-up data demonstrated a 5-year disease-free survival and overall survival for SLN negative breast cancer patients of 96–98%.[17,18] However, it remains to be elucidated whether the more accurate SLN staging is associated with improved survival compared with level I & II ALND. Therefore, the objective of the present investigation – the first prospective analysis in the literature – was to evaluate if node negative breast cancer patients undergoing a SLN biopsy have an improved disease-free survival and overall survival compared to those having level I & II ALND.

Patients and methods

Three-hundred and fifty-five consecutive node negative patients with early stage breast cancer (pT1 or pT2 $\leq$ 3 cm, pN0/pN$_{SN}$0) were evaluated from our database. Data for both groups (SLN and ALND) were prospectively collected. Patients with lymph node macro-metastases, micro-metastases, or isolated tumor cells were excluded. Disease-free survival and overall survival were the primary endpoints. Patients underwent either ALND ($n = 178$) in the years 1990–1997 or SLN biopsy ($n = 177$) in 1998–2004. The SLN biopsy was declared as the standard procedure for early stage breast cancer patients at our institution in 1998. Patients with a positive SLN (not included in the present study) underwent a formal level I & II ALND. Conversely, no routine ALND was performed for SLN node negative patients thereafter. This explains why the two subsets of patients in our investigation – node negative breast cancer patients undergoing ALND versus SLN biopsy – are from two different time periods. Institutional review board approvals were obtained prior to performing this study.

Pathologic examination of ALND and SLN specimen

Intraoperative frozen sections were routinely performed for SLN biopsies. 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 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, Vector Laboratories, Burlingame, USA) was performed. Lu-5 (Bio Medicals, Augst, Switzerland) is a pan-cytokeratin monoclonal antibody that recognizes type I and II cytokeratin subfamilies of all epithelial and mesothelial cells.

In the ALND group the axillary lymph nodes larger than 5 mm in diameter were all bisected for permanent section. One section was examined from each half and stained with H&E only. Lymph nodes smaller or equal to 5 mm were embedded uncut. Neither frozen sections nor immunohistochemical analyses were performed for routine ALND.

SLN mapping

SLN mapping was performed by using a combination of a radiolabeled colloid and a vital blue dye in the SLN group only. ^{99m}Tc-labeled nanocolloid (Nanocoll®, Nycomed AG, Wädenswil, Switzerland) at a dose of 70 MBq was injected, peritumorally at four sites, whereas the dose at the injection site closest to the axilla was placed both peritumorally and subdermally. Preoperative lymphoscintigraphy was performed to identify lymphatic flow to axillary and/or parasternal lymph nodes. Hot spots were marked on the skin. Furthermore, up to 5 ml of isosulfan blue (Lymphazurin®, Ben Venue Labs Inc., Bedford, Ohio, USA and Hospital Pharmacy, University Hospital Zurich) or 2–4 ml of patent blue V (Guerbet Group, Roissy, France) were injected as described above 5–10 min prior to incision. Due to their nearly identical chemical structure patent blue V has very similar lymphatic penetration and flow properties compared with isosulfan blue. Patent blue V is commercially available in Switzerland and approved by Swissmedic, the Swiss Federal Agency for Therapeutic Products, whereas isosulfan blue was only approved for study purposes.

The SLN were intraoperatively identified through blue coloration and detection of radioactivity using a handheld gamma probe (Navigator®, USSC, RMD Waterton, MA, USA).

Operative techniques

In the SLN group hot and/or blue sentinel lymph nodes were excised through a small incision and labeled separately. Dissection was continued until all hot and blue nodes were removed and the background count of the axilla was less than 10% of the hottest lymph node ex vivo. In the ALND group axillary lymph node dissection was performed as a level I & II clearance (Berg).[19] Preoperative informed consent was obtained from all patients.

Adjuvant therapy

After breast-conserving surgery patients received postoperative breast radiation therapy with 45 Gray over 5 weeks and a boost of 10 Gray to the tumor site which was intraoperatively clip-marked. Radiotherapy was applied identically for both patient subsets. Adjuvant therapy

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consisted of hormonal treatment (Tamoxifen 20 mg daily, orally for 5 years) and/or chemotherapy (Adriamycin + Cyclophosphamide or Epirubicin + Cyclophosphamide) every 3 weeks for a total of 12 weeks. In low-risk patients, elderly patients, and patients with contraindications for anthracyclines, 6 cycles of CMF (Cyclophosphamide + Methotrexate + 5-FU) were given. Chemotherapy agents and regimens did not substantially change in the two time periods 1990–1997 and 1998–2004. During these two time periods no new chemotherapeutic agents were introduced into clinical practice at our institution. Only after 2005 (and thus after all patients were enrolled in our study), taxanes, trastuzumab, and aromatase inhibitors were increasingly used for specific indications in breast cancer patients.[20] Furthermore, as all patients in the present analysis were node negative and had early stage breast cancer with tumor sizes equal to or smaller than 3 cm, only a minority of these patients received adjuvant chemotherapy. The indication for adjuvant therapy was based on the recommendations of the St. Gallen Consensus Conference.[21–23]

Postoperative follow-up

The follow-up diagnostic procedures were identical for both groups with clinical breast and axillary lymph node examination every four months for the first 5 years, afterwards once every year. Mammography was done annually.

Statistical analyses

Disease-free survival was calculated from surgery to relapse, overall survival from surgery to death. Patients without relapse or death were censored at the last date of clinical visit. Survival probabilities for disease-free and overall survival were estimated using Kaplan–Meier method. Follow-up time was estimated using inversed Kaplan–Meier method. Between-group comparisons without adjusting for other factors were carried out using χ^2 test for categorical variables, Wilcoxon test for continuous variables and log-rank test for follow-up time, disease-free, and overall survival. The impact of patient and tumor characteristics on disease-free and overall survival was investigated using univariate and multivariate Cox regressions, with Wald test for individual covariates. Backward elimination procedure with staying p-value 0.05 was applied to select variables for the reduced multivariate Cox model. To further investigate the robustness of our findings and take into account the differential follow-up times between the ALND and the SLN groups, two additional analyses were performed. First, the incidence rate of respective event per person-year was calculated for disease-free and overall survival. The corresponding 95% confidence intervals for the incidence rate difference were constructed using normal approximation. Second, as a cautious, conservative approach, the proportion of patients who were followed up for at least 3, 4, or 5 years or had experienced an event by the respective time were compared between the two patient groups by Fisher's exact test. The level of statistical significance was set at 0.05. All statistical tests were two-sided, without adjustment for multiple testing. For compilation of data Microsoft Excel database Software (Microsoft Corporation, Redmond, WA, USA) was used. Statistical analyses were performed using SAS software (version 9.1, SAS Institute Inc., Cary, NC, USA).

Results

The patient and tumor characteristics of the SLN and ALND groups are listed in Table 1.

The majority of patients in both groups (SLN versus ALND) were postmenopausal (75.1% versus 75.3%) with a median age of 59 years, and a median tumor size of 15 mm versus 16 mm, respectively. Estrogen-receptor and

Table 1
Patient and tumor characteristics

	SLN ($n = 177$) No.	ALND ($n = 178$) No.	p-value
Age (years)			
Median	59	59	0.99
Range	(32–88)	(29–85)	
Menopausal status			
Premenopausal	44	44	0.98
Postmenopausal	133	134	
Tumor size in mm			
Median	15.0	16.0	0.06
Range	(2–30)	(1–30)	
T stage			
T1a	11	10	0.69
T1b	34	27	
T1c	94	96	
T2	38	45	
Histology			
Ductal	150	136	0.05
Lobular/other	27	42	
Histological grading			
G1	49	27	0.0004
G2	86	77	
G3	42	74	
Estrogen receptor status			
Positive	155	157	0.86
Negative	22	21	
Progesteron receptor status			
Positive	123	122	0.85
Negative	54	56	
No. of SLN per patient			
Median	2		–
Range	(1–11)		
No. of axillary lymph nodes per patient			
Median		17	
Range		(4–35)	–

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progesteron-receptor positivity were approximately 88% and 70% in both patients subsets, respectively. With the exception of grading and follow-up time, there were no significant differences in the baseline characteristics, follow-up procedures, and adjuvant treatments between the two groups (SLN versus ALND, Tables 1 and 2). Only 16.4% of the SLN patients and 10.1% of the ALND patients received adjuvant chemotherapy as all patients had early stage, node negative disease. A median number of two lymph nodes per patient in the SLN group were removed. The overall quality of the axillary dissection in our series was high, with a largely sufficient median of 17 nodes removed and analyzed per patient. In only 16 of the 178 ALND patients (16/178 = 9%) less than 10 lymph nodes were removed with the axillary specimen. Four of these 16 patients died from metastatic disease.

The median follow-up was 49 months (1–91) in the SLN group and 133 months (9–190) in the ALND group. Axillary recurrences were observed in 1.1% of SLN and 1.7% of ALND patients. Distant metastases occurred in 1.1% of SLN and 14.6% of ALND patients. Six patients in the SLN group died during follow-up, with two of them due to distant metastases. In the ALND group 49 of 178 patients died, 31 of them due to metastatic disease. Of the 31 tumor related deaths, 26 patients died from known metastatic disease. Five patients developed local recurrence and died from medical conditions unrelated to breast cancer. The 5-year overall survival was 96.7% in the SLN group and 88.5% in the ALND group (Fig. 1) ($p = 0.034$). The 5-year disease-free survival was 96.0% and 87.2% in the SLN and ALND group, respectively (Fig. 2) ($p = 0.008$).

In univariate analysis, lower tumor stage, lower grading, and absence of adjuvant chemotherapy were associated with significantly improved disease-free survival but not overall survival (Table 3). Younger patients' age and menopausal status were associated with improved overall survival but not disease-free survival (Table 4). After adjusting for potential confounding factors, the SLN procedure (compared with ALND) was an independent predictor for significantly improved disease-free survival (hazard ratio: 0.28, 95% confidence interval: 0.10–0.73, $p = 0.009$) and overall survival (hazard ratio: 0.34, 95% confidence interval: 0.14–0.84, $p = 0.019$) in both the full and the reduced multivariable Cox models. Similarly, the use of adjuvant chemotherapy was found to be a significant predictor for worse overall and disease-free survival in the full and reduced multivariable Cox model. Younger age was a prognostic factor for a better overall survival.

Additional independent predictors were tumor stage for disease-free (Table 3) as well as age and menopausal status for overall survival (Table 4). For disease-free survival the incidence rate was 0.75% per person-year in the SLN group and 2.6% in the ALND group. The 95% confidence interval for the incidence rate difference did not include zero; hence the difference was statistically significant at the level of 0.05. For overall survival the corresponding incidence rates were 0.88% and 2.94%, respectively. Again, the 95% confidence interval for the incidence rate difference did not include zero.

Using a cautious, conservative statistical approach by excluding patients with less than 3 years of follow-up, clear trends towards improved disease-free and overall survival were found in patients undergoing SLN biopsy versus those having ALND. These differences did not quite reach statistical significance as the sample size decreased (due to the exclusion of these patients) and resulting lower power. However, it is well conceivable that the survival differences between the ALND and SLN groups will further increase with longer follow-up.

Table 2
Adjuvant therapy and follow-up

	SLN ($n = 177$) No.	ALND ($n = 178$) No.	p-value
Adjuvant therapy			
Hormonal therapy (H)	130	128	0.09
Chemotherapy (C)	18	11	
H + C	11	7	
None	18	32	
Follow-up in months			
Median	49	133	<0.0001
Range	(1–91)	(9–190)	

Discussion

This is the first prospective analysis providing evidence that patients with a negative SLN tend to have a significantly improved disease-free and overall survival compared with node negative ALND patients. The significant survival benefit of node negative patients having SLN biopsy highlights yet another important advantage of the SLN concept in breast cancer in addition to lower morbidity.[24]

Axillary recurrence rate and survival after ALND in node negative patients

ALND provides excellent regional control in node negative as well as node positive early breast cancer patients, with axillary recurrence rates ranging from 0% to 2%.[25–28] In multivariable analysis the axillary node status did not turn out as an independent predictor for axillary recurrences.[26] In an investigation from our institution, an axillary recurrence rate of only 1.3% was found in all 390 breast cancer patients undergoing standard level I and II ALND between 1986 and 1996.[29] As axillary recurrences worsen the prognosis of breast cancer patients, it is crucial to achieve similar regional control after ALND and SLN procedure alone.[26–28]

The favourable overall survival of node negative early stage breast cancer patients after ALND is well documented. In a population based analysis of 96,030 patients

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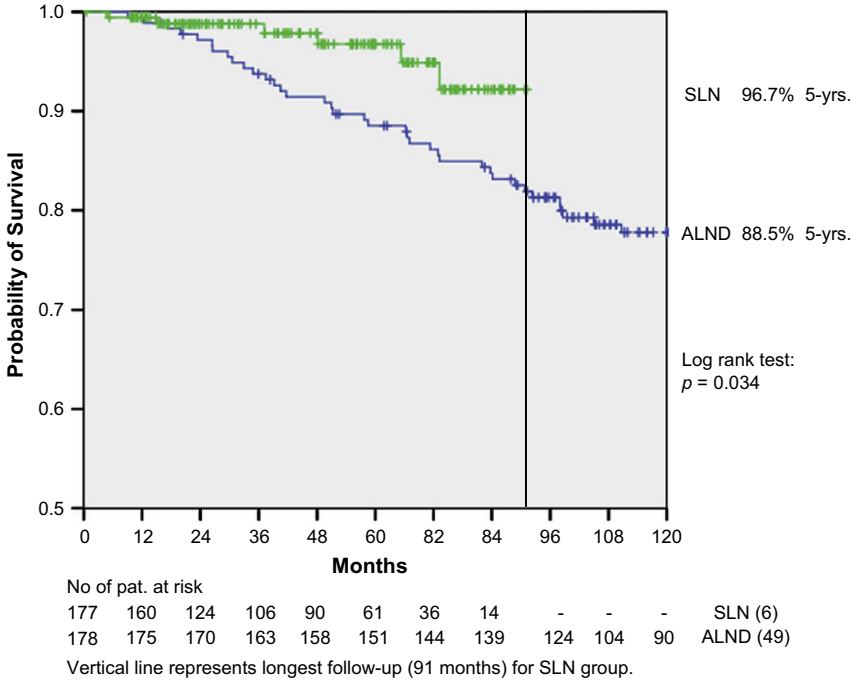

Figure 1. Kaplan–Meier life table analysis of overall survival (OS) SLN versus ALND. The "patients at risk" represents the number of patients in each group, who remain in the analysis at a given point in time. The number in parentheses represents the total of events.

with stage I and II disease, Winchester et al. found a 5-year overall survival of 96% for stage I and 88% for stage II patients.[30] Furthermore, large series examined stage I patients with tumor diameters of 1 cm or less and reported an overall survival rate of 92% and a disease-free survival of 93% after 8 years of follow-up regardless of hormone receptor status and use of adjuvant therapy.[31] Further trials with longer follow-ups revealed an overall survival of 65% after 10 years[32] and 47% (stage I and II) to 59% (stage I) after 20 years.[33,34] In the present investigation the 5-year overall

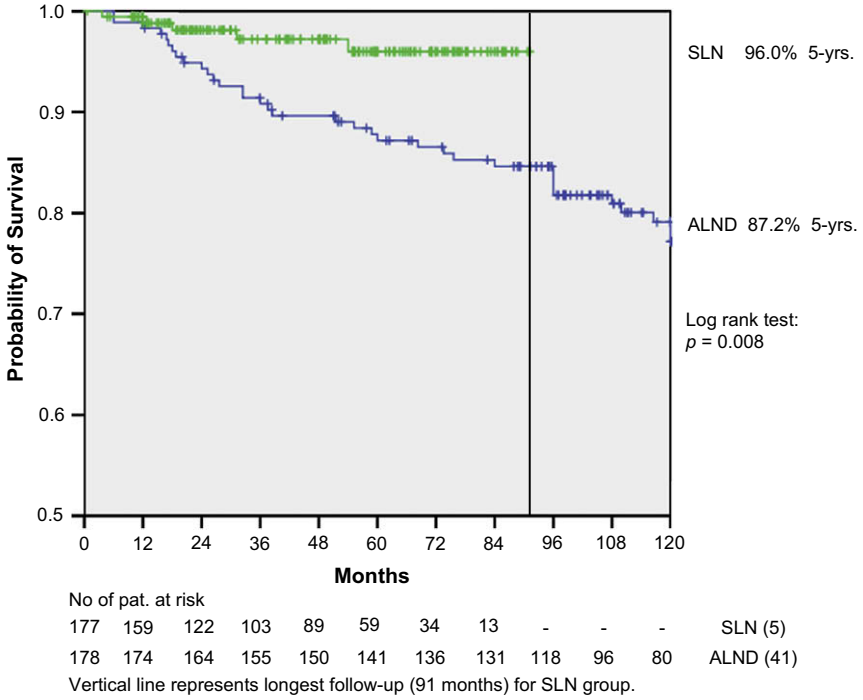

Figure 2. Kaplan–Meier life table analysis of disease-free survival (DFS) SLN versus ALND. The "patients at risk" represents the number of patients in each group, who remain in the analysis at a given point in time. The number in parentheses represents the total of events.

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Table 3
Univariate and multivariate Cox regressions of disease-free survival

Variable	Category	No. events/No. patients	Univariate analysis			Full multivariate model[a]			Reduced multivariate model[b]		
			HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Axillary surgery	SLN	5/177	0.29	0.11–0.76	0.012	0.28	0.11–0.75	0.011	0.28	0.10–0.73	0.009
	ALND	41/178	1.00								
Tumor stage	pT2 (≤3cm)	18/83	2.24	1.24–4.04	0.008	1.80	0.96–3.37	0.065	2.06	1.14–3.74	0.017
	pT1a-c	28/272	1.00								
Adjuvant therapy	Chemotherapy	11/47	2.75	1.39–5.46	0.004	3.15	1.41–7.03	0.005	2.88	1.45–5.73	0.003
	Hormone/none	35/308	1.00								

HR: hazard ratio; CI: confidence interval.
[a] Full multivariate model: including all covariates.
[b] Reduced multivariable model: containing only covariates that are associated with the outcome at a statistical level of <0.05.

survival in the ALND group was 88.5%. Given that all patients were diagnosed node negative, this finding seems to be worse than expected from the literature. However, 25% of the patients in both the SLN and ALND subset in the present study had a tumor size between 2 and 3 cm (pT2), therefore, partially representing a stage II disease.

Occult disease in the ALND specimen impact patients' outcomes

In a recent study by Tan et al. 368 patients with axillary node negative breast cancer, who were treated between 1976 and 1978 by mastectomy, axillary dissection, but no systemic therapy were re-examined.[35] The lymph nodes were re-analyzed by applying serial sectioning and immunohistochemistry. A total of 23% of patients (83 of 368) – who were initially classified as pN0 by single section and H&E analysis – were found to be node positive. On multivariable analysis, pattern of staining, number of positive nodes, number of metastatic cells, and cluster size were all significantly related to disease-free and overall survival. In breast cancer patients staged node negative by conventional single section pathology and H&E, occult axillary node metastases detected by step sectioning and use of immunohistochemistry were, therefore, considered prognostically significant.[35]

Dowlatshahi et al. reviewed different articles, in which negative axillary lymph nodes from breast cancer patients were re-sectioned to determine whether nodal metastases were missed during standard histopathology and to assess the prognostic significance of missed nodal metastases.[12] Twenty-four of 25 studies identified lymph node metastases in 7%–33% of patients initially staged as node negative. Most studies with a sufficient number of patients found disease-free survival and/or overall survival to be significantly worse among patients with occult nodal disease.[12]

Axillary recurrence rate and survival after SLN biopsy in node negative patients

Similar to node negative breast cancer patients undergoing level I and II ALND, the prognosis of those having SLN biopsy alone is excellent. After 3–4 years of follow-up axillary recurrence rates of 1% or less and distant metastases between 1.3% and 2.7% have been reported.[15,36] Torrenga

Table 4
Univariate and multivariate Cox regressions of overall survival

Variable	Category	No. events/No. patients	Univariate analysis			Full multivariate model[a]			Reduced multivariate model[b]		
			HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Axillary surgery	SLN	6/177	0.39	0.16–0.96	0.040	0.36	0.14–0.89	0.027	0.34	0.14–0.84	0.019
	ALND	49/178	1.00								
Age	>=60	39/175	3.20	1.75–5.83	0.0002	2.19	1.10–4.40	0.027	2.20	1.11–4.36	0.024
	<=59	16/180	1.00								
Menopausal status	Postmenopausal	50/267	4.08	1.60–10.40	0.003	3.28	1.06–10.16	0.039	3.33	1.10–10.11	0.034
	Premenopausal	5/88	1.00								
Adjuvant therapy	Chemotherapy	8/47	1.55	0.73–3.31	0.252	2.85	1.23–6.59	0.015	2.98	1.35–6.58	0.007
	Hormone/none	47/308	1.00								

HR: hazard ratio.
[a] Full multivariate model: including all covariates.
[b] Reduced multivariable model: containing only covariates that are associated with the outcome at a statistical level of <0.05.

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et al. found a 3.5-year overall survival rate of 98% and a disease-free survival rate of 99%.[37] Recent studies revealed a 5-year overall survival for SLN negative patients ranging from 96% to 98%.[17,18] The systemic recurrence rate was between 2.3% and 6%.[14,17,38,39] The results of the present study confirm these findings with a 96.0% disease-free survival and a 96.8% overall survival for the SLN negative group.

Since the introduction of the SLN procedure into clinical practice, small tumor infiltrates in axillary lymph nodes are more frequently detected.[4,6–8,10,40] This is due to the fact that pathologists can focus their attention on a few lymph nodes, which can be analyzed more thoroughly using step sectioning and immunohistochemistry. The detection rate of small tumor infiltrates varies according to different histopathological techniques and protocols. Current literature reports that 15%–48% of all SLN metastases are micro-metastases, leading to an upstaging of 9%–25% of initially node negative patients.[4,6–8,10,11,40] These small tumor infiltrates may have been missed using single section and standard H&E analysis. Therefore, the node negative SLN patients represent a more selective group of patients who are truly node negative. The more accurate staging in patients undergoing SLN procedure is most likely to explain the better clinical outcomes in patients undergoing the SLN procedure in the present investigation.

Interestingly, in addition to the SLN procedure, age was found to be an independent prognostic factor associated with improved disease-free and overall survival. In fact, younger women had better outcomes compared to elderly patients. This could be explained by the fact that younger women received more aggressive adjuvant therapy compared to elderly patients.

Survival differences between SLN biopsy alone versus ALND in diagnosed node negative patients

The only two studies examining the outcome between node negative patients undergoing SLN biopsy alone versus ALND were published by Cox et al.[41] in 2006 and by Kuijt et al.[42] in 2007. These are both retrospective studies which used a historical control group of node negative patients who received a routine ALND in the pre-SLN era. Cox et al. found no statistically significant difference for overall and disease-free survival between the two groups. The median follow-up was 7 years for the ALND group, but only two years for the SLN group.[41] Kuijt et al. described 5-year survival rates of 85% for ALND negative and 89% for SLN negative breast cancer patients. After correction for potential confounders in a multivariate Cox regression analyses, the hazard ratio for overall mortality of ALND negative compared to SLN negative patients without completion ALND demonstrated no significant difference. The authors concluded that survival after a SLN biopsy without completion ALND is at least equivalent to a conventional ALND in node negative breast cancer patients.[42]

Therefore, the present analysis is the first prospective one in the literature which compares both techniques with an adequate follow-up and provides evidence that there is in fact a statistically significant and clinically relevant survival benefit of node negative patients having SLN biopsy.

In a recent New England Journal of Medicine publication, Veronesi et al. compared overall and disease-free survival in patients undergoing SLN biopsy versus ALND in node negative patients. However, even patients who underwent ALND had a SLN biopsy and thus all patients benefited from more accurate and thorough histopathologic analysis.[14] The same applies for the NASBP-B32, ALMANAC, and SNAC studies. This explains their findings of no significant overall and disease-free survival difference.[14]

Moreover, performing a prospective randomized study, which assigns breast cancer patients to SLN biopsy versus level I & II ALND would be impracticable and ethically questionable.

Better survival after SLN biopsy due to a more accurate staging

As the SLN biopsy is a staging procedure more than a therapeutic intervention, the survival benefit found in our study is most likely due to an improved accuracy of detecting tumor tissue in the SLN. The SLN biopsy allows for a more accurate histopathological examination with step sectioning and immunohistochemistry detecting small macro-metastases, and micro-metastases. In fact, in 5–30% of the patients with early breast cancer micro-metastases and isolated tumor cells can be identified using the appropriate techniques.[11,43] We recently found that the detection of micro-metastases led to an upstaging of 18% in early stage breast cancer patients.[15] Clearly, the introduction of the SLN procedure for early stage breast cancer patients has led to a stage migration. However, the relevance of micro-metastases remains a matter of great debate. Although the detection of SLN micro-metastases might change the management of these patients, preliminary results suggested that micro-metastases did not affect outcomes significantly.[15] Otherwise missed lymph node metastases could potentially alter the indication for adjuvant therapy. Local and axillary recurrence rates are very low in early stage breast cancer patients undergoing breast-conserving therapy and adjuvant radiotherapy to the breast, regardless of whether SLN biopsy or ALND was performed. However, distant metastases are more likely to occur in the group of patients, in whom a metastatic spread to lymph nodes was missed. As axillary lymph node metastases are recognized as a systemic manifestation of the disease with an important impact on overall survival, patients undergoing ALND who are wrongly classified as pN0 are more likely to have a poorer prognosis.

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Limitations of our study

The main limitation of this study is the comparison of patients in two time periods. However, follow-up procedures and adjuvant treatment were comparable for both patient groups (SLN and ALND groups) in the present study. Only after 2005 (and thus after all patients were enrolled in our study), taxanes, trastuzumab, and aromatase inhibitors were increasingly used for specific indications in breast cancer patients. Most importantly, as all patients had early stage, node negative disease, only a small fraction received adjuvant chemotherapy.

Second, although most patient and tumor characteristics were similar in the SLN versus the ALND group, there were significantly more patients with grade 3 tumors in the ALND group compared to the SLN group. However, grading was not a significant predictor for a worse disease-free and overall survival after adjusting for other factors in multivariable Cox Proportional Hazard Regression analysis.

Third, the percentage of lobular carcinoma was higher in the ALND group, although, not significantly. However, histological tumor type (ductal versus lobular) was not a significant predictor for overall or disease-free survival neither in univariate nor multivariable analysis.

Summary

In summary, the present analysis shows that patients with a negative SLN have an improved overall and disease-free survival compared with node negative ALND patients. This survival benefit of node negative patients having SLN biopsy, most likely due to a more accurate staging, highlights yet another important advantage of the SLN concept in breast cancer.

Conflict of interest

No financial disclosures. No conflicts of interest to disclose. No funding for this study.

All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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