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REVIEW

Safety of avoiding routine use of axillary dissection in early stage breast cancer: a systematic review

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Abstract Physicians are moving away from routine axillary lymph node dissection (ALND) in clinically node-negative breast cancer. We conducted a systemic review on the safety of this policy. Pubmed and Cochrane library were searched for. Sixty-eight studies were included: studies of clinically node-negative patients in the pre-sentinel node (SN) era; observational studies of SN-negative patients, without ALND; comparative studies of SN-negative patients, with a non-ALND and an ALND group; SN-positive studies, of patients without ALND. Primary endpoint was the pooled axillary recurrence rate (ARR) of each category; secondary endpoint was overall survival (OS) rate. In pre-SN studies, with larger tumors and less systemic therapy, ARR without ALND after 5–10 years follow-up was 12–18%, with 5% reduced OS. In the observational SN-negative studies, with median follow-up of 36 months, the pooled ARR was 0.6% (95% CI 0.6–0.8). In the comparative SN-negative studies, pooled ARR was 0.4% (95% CI 0.2–0.6) without ALND versus 0.3% (95% CI 0.1–0.6) with ALND at 31 and 47 months, respectively, and no survival disadvantage. In SN-positive studies, ARR was up to 1.7% (95% CI 1.0–2.7) at 30 months. For patients with an H&E positive SN the ARR without ALND was 5% after 23 months, which may imply rates as high as 13 and 18% after 5 and 8 years. In conclusion, this systematic review confirms the safety of omitting ALND in SN-negative patients. There is a potential role for avoiding ALND in selected SN-positive patients, but eligibility criteria and the role of systemic therapy need further to be elucidated.

Keywords Breast cancer · Sentinel node · Axillary lymph node dissection · Axillary recurrence · Survival

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Introduction

Axillary lymph node dissection (ALND) has long been considered the golden standard in the work-up of early-stage breast cancer patients. It offered as such the best opportunity for staging and prognostication to select patients requiring additional treatment. Whether ALND also offers a therapeutic advantage is questioned [1].

Nowadays, approximately 60–70% of breast cancer patients have node-negative disease, due to an earlier diagnosis of breast cancer [2]. Obviously, if the axillary lymph nodes are truly negative, there can be no possible benefit from performing an ALND. In the late 1990s, the sentinel lymph node (SN) procedure was introduced [3, 4]. The intrinsic hypothesis is that SN biopsy will identify

patients with a negative axilla on pathology. The false-negative rate of the SN procedure is on average 8.4%, ranging from 0 to 29% [5]. Based on the low false-negative rate, the SN procedure was rapidly implemented in routine daily practice, even before the first randomized trial on the safety of the SN procedure was finalized [6, 7].

In The Netherlands at least 70% of breast cancer patients undergo an SN procedure. Of these patients, in 65% an SN only is carried out, implying, that in daily practice in nearly 50% of newly diagnosed breast cancer patients ALND is avoided [7]. (Completion) ALND is still the standard of care for patients with axillary metastases being identified by SN biopsy, including micrometastases [5].

To this end, many series have reported on axillary recurrence rates (ARRs). A few randomized trials evaluated the safety of the SN procedure. Recently, attention was drawn to the fact that there is a trend towards omitting ALND in patients with micrometastatic involvement of the SN, in contrast to the ASCO recommendations and despite lack of data on the safety of this strategy [8].

The aim of our study was to provide a systematic review on the safety of withholding ALND to clinically node-negative breast cancer patients. For this purpose, we reviewed ARRs in the pre-SN era of patients who did or did not undergo an ALND, and we reviewed ARRs of patients with a negative or positive SN in observational series and randomized trials that did or did not undergo a completion ALND. As secondary endpoint we reviewed survival rates in relation to axillary surgery type.

Methods

Literature search strategy

We performed a systematic review of the literature. Pubmed and the Cochrane Library were searched for (1st of January 1985 through 30th September 2009) with the use of the Medical Subject Heading terms “breast neoplasm”, “sentinel node”, “axillary lymph node dissection”, “recurrence”, and “survival”. We only included studies which were published in English language. Studies were included irrespective of number of patients included, except for case reports.

Study inclusion criteria

The following criteria were applied to the papers that were identified by the literature search. Studies were included when they studied ALND and/or axillary staging by the SN procedure if follow-up information was provided. Endpoints had to be available in terms of ARR and/or overall survival (OS) rates. Studies that reported on detection methods using molecular biology approaches like reverse transcriptase polymerase chain reaction, and studies in which neoadjuvant chemotherapy was administered were excluded. If duplicate or updated studies were identified, only the most recent study was included. Only full papers published in peer-reviewed journals and based on original data were included. Retrospective large database studies analyzing OS were only included if more than 1,000 patients were included. To prevent overlap of data from studies that described subpopulations besides a total population, only the total population was taken into account, and the most recent paper. For cohort studies and series based on overlapping selections, only the largest study was taken into account.

Data extraction

Two independent investigators (MP and JV) extracted data to rule out potential bias or errors. Discrepancies were resolved by consensus, if necessary through arbitrage by a third investigator (VTH). The following data were extracted from the included papers: number of patients studied, tumor size or stage, follow-up time, false-negative rate, ARR, OS, type of surgery, number of nodes excised, use of adjuvant systemic therapy, and use of axillary radiotherapy. Complete data were not always obtainable for every characteristic evaluated in each study. For some studies the range for time of follow-up had to be estimated based on date of inclusion versus date of analysis and/or date of manuscript submission. If not provided in the text or tables in the original paper, data with respect to ARRs were extracted from the recurrence-free survival curves. In some series, patients with in situ carcinoma were included; these patients were omitted in our tables, with recalculation of the ARR for invasive cancers only.

Definitions

The false-negative rate was obtained by dividing the number of patients who were SN-negative but non-SN positive by the number of patients who had a positive SN or a positive non-SN. This shows the reliability of the SN procedure, i.e., the sensitivity of the SN procedure is 1 minus the false-negative rate. This is essentially different from the percentage of patients with a negative SN, having a positive non-SN (1 minus negative predictive value). This percentage was collected or calculated and shown in the table regarding the validation and randomized studies. If a different definition was used in a paper, or if in situ carcinoma was included in the denominator, the rate was recalculated.

Of note, if in a study axillary recurrence was reported as either isolated or in combination with local or distant relapse, the total number of axillary recurrences was

counted. In most papers median (or mean) tumor size and T-stage were only described for the total population, both with a negative SN and positive SN. This overall number was then used in the tables.

Statistical analyses

Most studies were very small and only reported summary statistics for the exposure and the recurrence, such as median exposure time and number of recurrences. As no estimates of efficacy were reported, for example a 5 or 10 years recurrence rate, a routine meta-analysis was impossible. Hence, we used a more informal approach and calculated the overall recurrence by dividing the total number of recurrences by the total number of patients in all studies. In addition, we estimated the median exposure by the weighted median of the median exposure times in the studies, with study size as weight.

For the single group studies, we were able to calculate Kaplan–Meier estimates of the pooled 5 and 8 years ARRs. As we did not have the individual patient data, we had to estimate the follow-up duration for each patient. For patients who did not have a recurrence, we used three different scenarios. Middle scenario: almost all studies reported minimal, median and maximal duration of follow-up. In this scenario, we assumed that the follow-up durations were uniformly distributed, with half of the durations between the minimum and median follow-up and half of the durations between the median and maximum follow-up. For three studies [9–11], no minimal follow-up was reported, and we assumed it to be 0. When no maximal follow-up was reported (one study) [12], we assumed it to be twice the upper quartile. Worst case scenario: we assumed that 40% of the follow-up durations were equal to the minimum follow-up. The others were uniformly distributed, as in the middle scenario. In the worst case scenario, the follow-up duration is low, so the estimate of the recurrence rate will be high. Best case scenario: we assumed that 40% of the exposures were equal to the maximum follow-up duration. The others were uniformly distributed, as in the middle scenario.

In most studies, for patients that had a recurrence, the time of the recurrence was reported, so no assumptions about the follow-up duration were required. For the four studies, that only reported median, minimal and maximal duration till recurrence, we followed a similar approach as described above, using a middle, a worst and a best case scenario. For two studies with one event, the duration till recurrence was not reported and we set it to the median follow-up [13].

The worst and best case scenarios are extremely conservative, because they assume worst and best case scenarios in every individual study. In practice, different studies probably had different follow-up patterns that more or less cancelled each other out. We therefore think that the middle scenario is the most realistic.

In addition to the approach above we investigated the results when the exposure data were not uniformly distributed, but followed a Weibull distribution.

Further, we calculated pooled survival rates for the three randomized SN studies. For the large database pre-SN studies we were not able to calculate pooled survival rates, because of large heterogeneity between studies.

All reported P values are two-sided, and confidence intervals (CI) are at 95% level. All analyses were performed in SAS (version 8.2).

Results

This search strategy resulted in 61 abstracts. The reference lists of selected papers were searched for additional papers, leading to the identification of in total 68 eligible studies which included follow-up of different axillary treatment strategies.

We decided to categorize the included studies according to type of axillary surgical approach. In this way, we aimed to show more clearly the differences and similarities between studies on the issue of ARR and OS. The first category consisted of studies of patients with clinically node-negative disease who did or did not undergo a conventional ALND, in the pre-SN era, with a long-term follow-up. The second category consisted of observational studies of patients who had a negative SN and who did not undergo a completion ALND. The third category consisted of comparative studies with a non-ALND and an ALND group. All Patients had a negative SN: the patients in the SN learning phase underwent an SN and ALND, whereas the more recent patients did not undergo a completion ALND anymore (i.e., validation and application phase studies). We also included randomized studies assessing the safety of the SN procedure in this category. The fourth category included observational studies that reported follow-up data on patients with a positive SN who did not undergo a completion ALND. The last category concerned studies that reported on at least 5-years follow-up data on survival rates in either pre-SN or SN era.

ARRs with versus without conventional ALND: Pre-SN studies

In order to evaluate the role of ALND in patients with clinically node-negative disease in the pre-SN era, we included three randomized trials comparing ALND versus no axillary treatment [14, 15] (Table 1).

In the NSABP B-04 trial, after a follow-up of 10 years the ARR was 18.4% in the total mastectomy group as compared to 1.4% in the radical mastectomy group,

Table 1 Axillary recurrence rates with versus without axillary lymph node dissection (ALND) in patients with clinically node-negative breast cancer

Study	Patients (*N*)	pT1 (%)	Node positive with ALND (%)	Follow-up (months)	Axillary recurrence with ALND (%)	Axillary recurrence no ALND (%)
Guy I [14]	232	17	24	60–120	0.9	18.8
Guy II [14]	258	38	–	60–120	1.4	12.5
NSABP-B0 [15]	727	–	39	120	1.4	18.4

including ALND, even though it was noted that a small number of lymph nodes was excised in one-third of the patients in the "no axillary treatment arm" [15]. Site of recurrence was only reported for the first event, which may have resulted in an underreported ARR.

ALND was compared to axillary radiotherapy in five randomized studies [14, 16–18]. In two of these, the Guy I and Guy II trials, the radiotherapy dosage in the no-ALND arms was considered inadequate to modern standards for axillary radiotherapy [14], and for that reason these two latter studies were considered of interest for our systematic review. The ARRs were 18.8 and 12.5% without ALND compared to 0.9 and 1.4% with ALND, in the Guy I and Guy II trials, respectively, after 5–10 years of follow-up, in agreement with findings in the B-04 trial. The difference in outcome between the Guy I and Guy II trial could be explained by the fact that there were significantly more patients with T1 tumors in the Guy II trial.

ARRs for a negative SN, without ALND: observational studies

Of 50 observational SN studies [9–13, 19–63], information on ARRs was available of patients who had a negative SN and who had not undergone a completion ALND (Table 2; Fig. 1). There was a large difference in tumor size and administered systemic therapy between studies.

Overall, follow-up of more than 26,000 patients was reported. The median and maximum follow-up duration of all studies pooled was 36 and 144 months, respectively. With a median follow-up duration of 36 months, the ARR was 0.6% (95% CI 0.6–0.8).

Figure 1 shows the Kaplan–Meier curves for the middle, best and worst case scenarios. According to the middle scenario, the 5- and 8-years ARRs were 1% (95% CI 0.8–1.1) and 1.4% (95% CI 1.1–1.6), respectively. In the worst case scenario, the recurrence rates were approximately 0.1% worse.

ARRs for a negative SN, with and without ALND: comparative studies

The third category consisted of studies in which patients with a negative SN were randomized between a completion ALND or not, and of studies in which patients with a negative SN in the learning/validation phase routinely underwent a completion ALND, whereas the next patients with a negative SN did not undergo a completion ALND anymore (SN application phase) (Table 3).

In total, 12 studies [10, 12, 13, 24, 33, 35, 41–43, 52, 54, 64] were available with follow-up information, of which three [10, 13, 41] were randomized. Overall, follow-up of 8,542 patients was reported. The ARR was 0% in all but three "SN and ALND" study arms, leading to an overall recurrence rate of 0.3% (95% CI 0.1–0.6). As in one of these it was actually unclear whether the only patient with an axillary recurrence had a negative or positive SN, the recurrence rate may even be lower [10]. The median follow-up duration in these studies was 47 months, with a maximum of 102 months.

On the other hand, the pooled recurrence rate for SN-negative patients who did not undergo a completion ALND was 0.4% (95% CI 0.2–0.6), which is still low but slightly higher compared with the SN-negative ALND-treated patients, especially when considering the shorter median follow-up duration of only 31 months, with a maximum of 98 months.

The false-negative rate ranged from 4.1 to 22.2%. Conversely, the percentage of patients with a negative SN having a positive non-SN varied from 2.0 to 9.2%. This latter rate reflects the potential long-term risk of axillary recurrence if no systemic treatment is offered.

ARRs for a positive SN, without ALND: observational studies

One population-based study [65] and 15 single centre studies [12, 23, 35, 42, 43, 46, 50, 55, 66–72] reported on patients with a positive SN who did not undergo a completion ALND (Table 4).

From the National Cancer Data Base of the United States of America, nearly 100,000 patients with clinically node-negative breast cancer who had a positive SN were identified [65]. Of these, 21% underwent SN only ($n = 1{,}988$ patients). In this population-based study, 1% (95% CI 0.6–1.5) of the patients had a recurrence, while the median duration of follow-up was 64 months, with a maximum of 72 months. The authors themselves noted already that recurrences may have been underreported to cancer registries. Patients classified as 'micrometastases'

Table 2 Axillary recurrence after sentinel (SN)-only in SN-negative breast cancer patients in relation to tumor size and type of AST: Single group studies

Source (reference)	No. patients	% T1 or median (range)	% chemotherapy/ hormonal therapy	Median FU, months (range)	Timing of recurrence, months	Axillary recurrence (%)
2009 Canavese (R) [10]	77	87%[a]	NR	68 (±17)	–	0
2009 Veronesi [11]	3548	84%	19/81	48 (−132)	29 (range 2–86)	0.9
2009 Kiluk [19]	1530	14 mm	26/53	60 (0–144)	23, 46, 102, 110	0.3
2009 Gauthier [20]	194	15 mm (1–31)	27/77	40 (7–72)	–	0
2009 Groetelaers [21]	254	71%[a]	NR	73 (60–100)	40	0.4
2009 Sanli [22]	121	81%	37 (total)	44 (15–76)	24, 31, 32	2.5
2009 Bulte [23]	503	71%[a]	21/23[a]	46 (11–64)	3, 30, 51	0.6
2009 Kim [24]	293	82%[a]	NR	40 (24–49)	8, 12, 16	1.0
2008 Zavagno (R) [13]	218	81%[a]	"To most"	56 (IQ 42–63)	NR	0.5
2008 Ploeg [25]	748	75%[a]	21/23	46 (0–98)	10, 44	0.3
2008 Christiansen [26]	3717	68%[a]	NR	20 (0–62)	Range 0–50	0.5
2008 Poletti [27]	804	79%	18/82	39 (4–97)	4, 11, 18, 19, 22, 72	0.7
2008 Bergkvist [28]	2246	14 mm (5–30)	NR	37 (0–75)	21 (4–51)	1.2
2008 Kuijt [29]	100	15 mm (3–31)	13/39	78 (4–103)	14, 20, 33, 79, 90	5.0
2008 Wely [30]	392	NR	NR	65 (33–123)	27 (4–63)	2.8
2008 Heuts [31]	344	63%	NR	43 (1–96)	17, 21, 26	0.9
2007 Domenech [32]	91	85%	NR	49 (26–63)	–	0
2007 Konstantiniuk [33]	1394	70%[a]	24/79[a]	34 (0–102)	0–48	0.4
2007 Susini [34]	165	95%	40/67	46 (12–72)	–	0
2007 Takei [35]	822	39%[a]	75 (total)	34 (2–83)	9, 18, 21, 29	0.5
2006 Rosing [9]	89	19 mm (±14)	NR	26 (–48)	NR	1.1
2006 Schulze [12]	25	100%[a]	3/68[a]	47 (±15)	–	0
2006 de Kanter [36]	149	56% T1c	13 (total)	65 (50–79)	10, 12, 14, 56	2.7
2006 Leikola [37]	205	81%	45/55	36 (0–36)	24, 36	1.0
2006 Nagashima [38]	241	8 mm (±9)	16/76	27 (6–66)	–	0
2006 Paajanen [39]	107	63%[a]	44/57[a]	31 (13–49)	–	0
2006 Palesty [40]	335	83%	32/76	33 (2–76)	5, 14	0.6
2006 Veronesi (R) [7, 41]	167	100%	47/90[a]	79 (15–97)	86	0.6
2005 Fan [42]	237	13 mm (1–60)	NR	31 (0–70)	5, 18	0.8
2005 Jeruss [43]	592	74%[a]	42/70[a]	27 (1–98)	22	0.2
2005 Khakpour [44]	202	NR	44/86	26 (6–80)	–	0
2005 Kokke [45]	113	14 mm (2–35)	19/18	38 (24–54)	29	0.9
2005 Langer [46]	122	72%[a]	20/76	42 (12–64)	14	0.8
2005 Sanjuan [47]	158	17 mm (0–36)	NR	21 (4–45)	17	0.6
2005 Soni [48]	101	75[a]	21/71	22 (6–42)	35	1.0
2005 Snoj [49]	50	13 mm (5–25)	NR	32 (10–50)	26	2.0
2005 Swenson [50]	580	85%[a]	42/58	33 (2–73)	11, 24, 36	0.5
2005 Zavagno [51]	479	90%	53/47	36 (12–68)	–	0
2004 Imoto [52]	112	56%	32/17	44 (36–53)	3–22	4.5
2004 Torrenga [53]	104	15 mm (4–50)	19 (total)	57 (48–83)	24	1.0
2004 Naik [54]	2340	89%	NR	31 (1–75)	19, 29, 38	0.1
2004 van der Vegt [55]	106	71%[a]	24 (total)	35 (17–59)	26	0.9
2004 Wessem [56]	56	58%	NR	28 (16–39)	24	1.8
2003 Badgwell [57]	159	71	NR	32 (24–34)	–	0
2003 Blanchard [58]	685	78	26/NR	29 (7–46)	41	0.1
2003 Estourgie [59]	361	NR	NR	16 (1–34)	22	0.3
2003 Ponzone [60]	150	80	NR	15 (3–35)	–	0

Table 2 continued

Source (reference)	No. patients	% T1 or median (range)	% chemotherapy/ hormonal therapy	Median FU, months (range)	Timing of recurrence, months	Axillary recurrence (%)
2002 Chung [61]	206	81	27/47	26 (2–50)	4, 11, 40	1.5
2002 Hansen [62]	238	85	25/56	39 (6–69)	–	0
2002 Loza [63]	168	NR	NR	21 (1–48)	30	0.6

R indicates part of a randomized trial, *NR* patients received systemic therapy, but exact percentage was not reported, *AST* adjuvant systemic therapy

[a] Characteristics including patients with a positive SN; DCIS excluded, whenever information was available

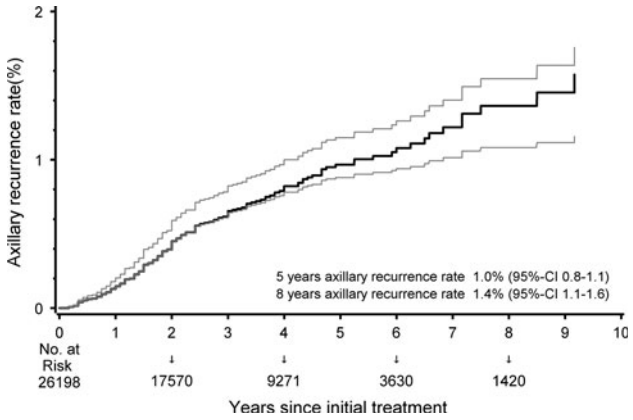

Fig. 1 Kaplan Meier curves for the percentage axillary recurrence among patients with a negative SN who did not undergo a completion ALND, based on 50 observational series (Table 2). As the curves cannot be determined with certainty, the *bold line* shows the recurrence for the middle scenario, whereas the other *lines* indicate the recurrence for extreme best case and worst case scenarios, respectively. The numbers at risk correspond to the middle scenario

who did not undergo ALND probably included patients with isolated tumor cells according to the 6th edition of AJCC classification [73], implying that a substantial number of patients actually may have had "node-negative disease" according to current definition.

The pooled single centre studies resulted in 1.7% (95% CI 1.0–2.7) recurrences, with a median and maximum follow-up duration of 30 and 98 months, respectively. Overall, follow-up was reported from 962 patients.

In the largest single centre study from the MSKCC ($n = 287$), patients with SN positive/no ALND had compared with the SN positive/ALND patients more favorable tumors with a lower median predicted risk of non-SN metastases (9 vs. 37%, $P < 0.001$) [67]. The SN metastasis size was not reported, but SN positivity was detected by serial sectioning and/or immunohistochemistry in 39% of patients, indicating small volume disease in many patients. Of note, in the "no ALND" group, still a substantial number of nodes was excised, that is, 4 or more nodes (SN and non-NSs) in 14% of patients. And, 15% of patients received radiotherapy to the axilla and/or supraclavicular nodes. In their series, axillary recurrences developed in 2.0% of SN positive/no ALND patients at a median follow-up of 23 months versus in 0.4% of SN positive/ALND patients at 30 months ($P = 0.004$). Of importance, the highest ARR was seen in the subgroup of SN positive/no ALND patients whom SNs were positive on routine H&E. In these patients the ARR was 5% after 23 months of follow-up.

In the second largest study, from the MD Anderson Cancer Center, 196 patients with a positive SN did not undergo completion ALND [66]. Twenty-three patients had non-SNs removed, and relatively many SNs (median 4, range 1–14) were excised. Radiotherapy covering part of the axilla was used in 64% of patients. The calculated risk of positive non-SNs based on the MSKCC nomogram was 9.8%, in line with the low risk profile according to the MDACC risk model. At a median follow-up of 30 months, no axillary recurrences were observed.

OS in randomized and large database studies: pre-SN and SN studies

Before the SN era, six randomized trials have assessed the role of ALND with respect to survival in clinically node-negative breast cancer patients (Table 5). Three of six studies, among others the NSABP-B04, did not show a statistically significant survival benefit, but likely due to lack of power. In a Bayesian meta-analysis, the combination of trials including almost 3,000 patients showed a 5.4% (95% CI 2.7–8.0) survival benefit in favor of ALND [74]. Although three studies used axillary radiotherapy in patients who did not undergo an ALND, these studies were yet included in the analysis [16–18]. Of note, essentially none of the patients were treated with systemic therapy.

In addition, six large pre-SN database-studies, including in total 160,459 patients, showed a survival benefit in direct proportion to the number of lymph nodes removed (Table 5) [75–80]. Although it was noted that treatment choices may have been influenced by age, presence of co-morbidity and likelihood of nodal involvement, these were not always taken into account in multivariate analyses. Only one study corrected for use of systemic therapy and

Table 3 Studies in which breast cancer patients with a negative SN were randomized between a completion axillary lymph node dissection (ALND)-or-not, and of studies in which patients with a negative SN in the learning/validation phase routinely underwent a completion ALND, whereas the next patients with a negative SN did not undergo a completion ALND anymore (SN application phase)

Source[a]	Only SN-negative patients are included	No. patients	%T1 (or median, range in mm)	Follow-up, months (median, range)	Axillary recurrence (%)	Pos. non-SNs (%)	False-negative rate (%)
Randomized trials							
2009 Canavese [10]	SN and ALND	88	74[b]	Mean 67 (±16)	1.1[d/NR]	9.2	22.2
	SN only	79	87[b]	Mean 67 (±16)	0		
2008 Zavagno [13]	SN and ALND	233	82[b]	56 (IQ 42–63)	0	7.7	16.7
	SN only	218	81[b]	56 (IQ 42–63)	0.5		
2006 Veronesi [7, 41]	SN and ALND	174	100	79 (5–97)	0	4.6	8.8
	SN only	167	100	79 (5–97)	0.6		
Studies reporting on validation and next application phase							
2009 Kim [24]	SN and ALND	174	73[b]	40 (24–49)[c]	0		
	SN only	293	73[b]	40 (24–49)[c]	1.0		
2007 [33] Konstantiniuk	SN and ALND	355	69[b]	47 (0–102)	0.8	3.7	6.5
	SN only	1394	70[b]	31 (0–87)	0.4		
2007 Takei [35]	SN and ALND	56	30	34 (2–83)[c]	0		
	SN only	1062	34	34 (283)[c]	0.4		
2006 Schulze [12]	SN and ALND	56	100	66 ± 22	0	7.1	12.1
	SN only	25	100	47 ± 15	0		
2005 Fan [42]	SN and ALND	39	13 (1–60)[b]	31 (0.3–70)[c]	0	5.1	
	SN only	237	13 (1–60)[b]	31 (0.3–70)[c]	0.8		
2004 Jeruss [43]	SN and ALND	30	71[b]	27 (1–98)[c]	3.3	2.0	
	SN only	557	71[b]	27 (1–98)[c]	0.2		
2004 Imoto [52]	SN and ALND	97	31	62 (53–71)	0		
	SN only	112	56	44 (36–52)	4.5		
2004 Naik [54]	SN and ALND	326	66	32 (1–74)	0		
	SN only	2340	89	31 (1–75)	0.1		
2002 Shivers [64]	SN and ALND	250	96%T1,2[b]	16 (12–42)[c]	0	2.0	4.1
	SN only	180	96%T1,2[b]	16 (12–42)[c]	0		

Positive non-SN rate and false-negative rate were calculated only for those studies that provided full information on the validation phase including patients with a positive SN

NR not reported, *IQ* interquartile range

[a] Only studies that included consecutively all patients with a negative SN irrespective of non-SN status and with follow-up information with and without ALND were included (so, different from the main results of randomized trials, in which intent-to-treat analyses was performed irrespective of SN status). Only patients with negative SN are included in this table

[b] T size also included of patients from other categories (e.g., Positive SN)

[c] Follow-up time in validation studies: only median provided for total study population, whereas in reality follow-up of "SN and ALND" group was somewhat longer than of the more recent "SN only" group. In some studies, the range of follow-time was estimated from date of inclusion versus date of analysis

[d] Unclear whether this one patient with an axillary recurrence had a positive or a negative SN

observed that the risk of death by omission of ALND was diminished when systemic therapy was used [77]. Another interesting observation was that even when all regional lymph nodes were pathologically negative, the number of nodes removed was associated with survival [78, 79].

The three published studies randomizing patients to ALND or to SN followed by ALND only if the SN was involved did not show a survival benefit of ALND, and concluded that completion ALND can be avoided in patients with negative SNs [10, 13, 41]. Pooled analysis of the three randomized trials also showed no significant differences in 5-year OS, with a hazard ratio of –0.2 (95% CI −2.4%, 2.2%).

Discussion

In patients with clinically node-negative breast cancer the necessity of axillary surgery has been a matter of debate for many years. Leaving out ALND in *all* clinically node-negative patients is potentially harmful [74]. With the introduction of the SN procedure a strategy to identify the patients who might not need axillary surgery became available. The aim of our study was to provide a systematic review to estimate ARRs in patients with clinically node-negative breast cancer, who did or did not undergo ALND. In this systematic review, we found that patients with a negative SN had a pooled ARR of only 0.6% at 36 months.

Table 4 Axillary recurrence rate in studies on selected SN-positive breast cancer patients who did not undergo completion axillary lymph node dissection (ALND)

Source	No. patients	% T1	% chemo/hormonal therapy	RT axilla %	SN status	Median FU (months)	Axillary recurrence %
2009 Bulte [23]	20	71[a]	21/23[a]	NR	20 "micro"	46 (11–64)	0
2009 Bilimoria [65]	1,988	63	71/41	NR	530 "micro"; 1,458 macro	64 (60–72)	0.6/1.2
2007 Takei [35]	120	30	92	54	Not specified	34 (2–83)[a]	0
2007 Hwang [66]	196	72	56/27	64	67 itc; 90 micro; 39 macro	30 (1–62)	0
2007 Park [67]	287	78	NR	15	Not specified	23 (6–87)	2.1 (5.0)[c]
2006 Schulze [12]	6	100[a]	3/68[a]	–	1 itc; 4 micro; 1 macro	49 ± 17[a]	0
2006 Pejavar [68]	16	80[a]	30/34[a]	100	Not specified	24–60[a]	0
2006 Haid [69]	10	77[a]	32/93[a]	–	2 itc; 6 micro; 2 macro	47 (7–90)	0
2005 Fan [42]	38	71	NR	63	27 micro; 11 macro	29 (6–76)	2.6
2005 Jeruss [43]	73	57[a]	85/70[a]	–	73 "micro"	27 (1–98)	0
2005 Langer [46]	27	72[a]	20/76[b]	–	27 "micro"	42 (12–64)	0
2005 Swenson [50]	67	82[a]	42/58[a]	–	32 itc; 31 micro; 4 macro	33 (2–73)	1.5
2005 Chagpar [70]	15	89[a]	33	–	2 itc; 12 micro; 1 macro	40 (1–54)	0
2004 Vegt [55]	10	85[a]	NR	100	4 micro; 6 macro	35 (17–59)	0
2003 Fant [71]	31	81	100	3	27 "micro"; 4 macro	28 (21–48)	0
2003 Guenther [72]	46	67	100	2	23 itc; 16 "micro"; 7 macro	32 (4–61)	0

"micro": before 2002 there was no distinction between itc/micro, and these were, therefore, referred to as "micro"

NR patients received systemic therapy, but exact percentage was not reported

[a] Total group, not specified separately for SN-positive patients

[b] For all SN only including both SN negatives as positives

[c] Axillary relapse rate if positive SN was detected by H&E

In contrast, in SN-positive studies the ARR was about 3 times higher, up to 1.7% (95% CI 1.0–2.7) at 30 months. For patients with a positive SN by H&E examination these rates were even higher.

The SN procedure is based on the premise that it improves identification of patients with *pathologically* node-negative disease. Indeed, series including patients with a negative SN who did not undergo completion ALND show low ARRs of 1% after 5 years of follow-up (Fig. 1). The results of the comparative studies, i.e. summary statistics of the follow-up duration and overall recurrence, are more difficult to interpret (Tables 2, 3). The observational study results may illustrate this. The overall recurrence rate in these studies was 0.6%, the median follow-up was 36 months and the maximal follow-up was 12 years. One may be tempted to assume that 0.6% is the recurrence rate at median follow-up, or at least for some time point between the median and the maximum follow-up duration. However, the Kaplan–Meier graph in Fig. 1 shows that the recurrence rate at median follow-up is already 0.8% and it is steadily increasing to more than 1.5% after 9 years. So, in reported studies the ARR continued to increase over time, which was different from what we had expected. Based on the comparative studies, we conclude that omitting ALND in SN-negative patients is associated with a small increase in risk of axillary recurrence. However, based on the single group studies, we conclude that this risk seems to be acceptable as long as techniques are validated and selection criteria do not change dramatically from the criteria in validated studies. New prospective randomized survival and regional recurrence data from the NSABP B-32 were very recently presented at ASCO [81]. In B-32, including 2,011 pathologically node-negative patients undergoing SN alone and 1,975 randomized to SN plus confirmatory axillary dissection, the SN biopsy false-negative rate was 9.8% with a sample size large enough to detect a 2% difference in survival between the control and experimental arms [81, 82]. Median follow-up was 95 months. ARRs were 0.6 and 0.4%, 5-year OS rates were 95.0 and 96.4%, respectively, both statistically not different. This recent study supports the view that in SN-negative breast cancer patients with a T1 or (small) T2 tumor, omission of ALND can be regarded as safe.

In daily practice there is a shift toward omitting completion ALND in SN-positive patients [8, 65, 83]. At first glance, ARRs in series and a population-based registry seem not worse as opposed to series in SN-negative patients (Table 4 vs. Tables 2 and 3). However, these low recurrence rates in SN-positive patients may be explained

Table 5 OS rates of clinically node-negative breast cancer patients: randomized trials, ALND vs. no ALND (Orr); pre SN-database studies ($n = 160{,}459$), and randomized trials, SN with on indication ALND vs. ALND in all patients (pooled analysis 1,179)

Trial	No. patients	FU (years)	Comparison	Individual studies OS (%)	HR OS in MVA for ALND	Summary statistics OS benefit ALND	Remarks
Orr's meta-analysis [74]	2,936					5.4% (95% CI 2.7. 8.0)	Essentially no AST
Guy's I [14]	370	10	No ALND vs. ALND	44 vs. 52			
Guy's II [14]	258	10	No ALND vs. ALND	57 vs. 73			
B-0 [41, 5]	727	10	No ALND vs. ALND	54 vs. 58			
Curie [16]	658	5	No ALND vs. ALND	93 vs. 97			
SES [17]	498	10	No ALND vs. ALND	52 vs. 61			
Copenhagen [18]	425	10	No ALND vs. ALND	46 vs. 50			
Database studies	160,459						
White, RI-TR [75]	1,126	5	No ALND vs. ALND	64 vs. 88	0.21 for BCS and 0.48 for MRM		$P < 0.001$; MVA not including AST
Bland, NCDB [76]	6,753	10	No ALND vs. ALND	85 vs. 94	nd		OS for stage I: BCS + RT, no AST
Weir, BCCA [77]	2,278	10	<10 vs. 10 + nodes resected	No AST: 75 vs. 80; AST: 75 vs. 79	NS		$P = 0.06$ (no AST); $P = 0.57$ (with AST)
Krag, SEER [78]	72,102	10	<10 vs. 10 + nodes resected	pN0: 75 vs. 78; pN1-3: 54 vs. 65	0.95(0.93–0.97) for pN0/ 0.91(0.76–0.94) for pN1-3		MVA not for AST; OS rates shown for patient category of 50 to 80 years
Polednak, SEER [79]	69,543	5	<10 vs. 10 + nodes resected		0.65 (95% CI 0.51–0.83)		MVA not for AST, HR shown for 1–3 nodes
Axelsson, DBCG [80]	8,657	9	<10 vs. 10 + nodes resected	75%	0.90 (95% CI 0.82–0.99)		None of the patients used AST
Randomized SN studies	1,179					−0.2 (95% CI −2.4, 2.2)	Pooled analyses on 5-years OS rates
Canavese [10]	225	5	SN/ALND vs. ALND	97 vs. 97			Well balanced, but no info on AST
Zavagno [13]	697	5	SN/ALND vs. ALND	95 vs. 96			Well balanced, but no info on AST
Veronesi [41]	257	5	SN/ALND vs. ALND	98 vs. 96			Well balanced, but no info on AST

RI-TR Rhode Island Tumor Registry, *NCDB* National Cancer Data Base, *BCCA* British Columbia Cancer Agency, *SEER* Surveillance, Epidemiology and End Results, *DBCG* Danish Breast Cancer Group, *FU* follow-up, *ALND* axillary lymph node dissection, *SN* sentinel node, *OS* overall survival, *AST* adjuvant systemic therapy, *HR* hazard ratio, *MVA* multivariate analysis, *BCS* breast conserving surgery, *MRM* modified radical mastectomy, *nd* note done, *NS* not significant, *RT* radiotherapy

by more favorable tumor characteristics, the presence of isolated tumor cells (even if they were classified as "micrometastases"), a considerable number of patients being treated by axillary radiotherapy, and finally, the number of nodes removed during the SN procedure being higher than normally expected. Of note, the MSKCC reported that in patients identified with a positive SN by H&E examination, the ARR was 5% at a median follow-up of 23 months, even though these were highly selected patients [67]. In a cohort study from The Netherlands (the MIRROR study), patients with SN micrometastases (0.2–2.0 mm) who did not undergo a completion ALND were also shown to have an increased risk of axillary recurrence of 5% at 5 years follow-up [84].

The results of the observational SN-negative studies may help to interpret the results for SN-positive patients. On the one hand, the single group SN-negative studies had a median follow-up duration of 36 months and an overall recurrence of 0.6%. The 5 and 8 year recurrence rates were 1 and 1.4%, respectively. For the studies in SN-positive patients, the overall recurrence was 1.7%, i.e., 1.7/0.6 = 2.8 times higher than for the single group studies. Therefore, the 5 and 8 year recurrence rates in SN-positive patients may be (1.7/0.6)*1 = 2.8% and (1.7/0.6)*1.4 = 4%, respectively. If we also take the median follow-up of 30 months for the SN-positive studies into account, the rates will be (36/30)*2.8 = 3.4% and (36/30)*4 = 4.8%, respectively. In a similar way, we find that for patients identified with a positive SN by H&E examination in the MSKCC study, the ARR after 5 and 8 years may be as high as (5/0.6)*(36/23)*1 = 13% and (5/0.6)*(36/23)*1.4 = 18%. Although these calculations are rather speculative, they are not implausible. They suggest that in many patients with a positive SN withholding ALND may not be safe. Concerns regarding safety of general omission of ALND in clinically node-negative but SN-positive patients are based on the survival rates in conventional ALND versus no-ALND studies [74]. However, in these studies most of the patients did not receive adjuvant systemic therapy. Recently, we showed that isolated tumor cells and micrometastases were associated with a reduced 5-year rate of disease-free survival among women with favorable early-stage breast cancer who underwent an SN procedure and who did not receive adjuvant systemic therapy [85]. Among patients who received systemic therapy, the 5-year disease-free survival rate was significantly improved with an absolute benefit of nearly 10%, including a reduction in locoregional recurrence rate. Therefore, with more patients undergoing systemic therapy, the need for axillary treatment may change. In the studies reported so far, the rate of systemic therapy was highly varying and, therefore, impossible to analyse. This is a limitation of a systematic review on published data instead of a meta-analysis on individual data. Considering the number of trials and low number of patients included, an individually based analysis was considered not possible.

Survival outcomes for the node-positive ACoSOG Z0011 trial were presented at ASCO [82]. Patients with one or two H&E positive SNs were randomized to observation or ALND. The trial unfortunately failed to reach its targeted accrual. This otherwise would have been the most robust possible test of the null hypothesis that regional lymph node dissection does not improve breast cancer outcomes. That noted, among the 856 patients randomized and analyzed in an intent-to-treat analysis, at a median follow-up of 6.2 years there were no statistically significant differences in ipsilateral breast tumor or axillary recurrence. Five-year regional recurrence rate was 0.9% for SN only compared to 0.5% for ALND ($P = 0.11$), with 5-year OS rates of 92.5 and 91.9%, respectively ($P = 0.24$). Of note, 82% of patients had received adjuvant systemic therapy. In 50% of patients the SN contained micrometastatic disease.

How should we now interpret these new findings together with existing data? On the one hand, conventional pre-SN studies showed reduced survival rates from omission of ALND in clinically node-negative breast cancer patients. In SN-positive series, the overall ARR was 2.8 times higher than for the single group studies in SN-negative patients, with estimated ARR after 5 and 8 years as high as 13 and 18%. On the other hand, in the one randomized phase III study omission of ALND did not result in high ARRs or reduced survival. One explanation could be the increasing use of systemic therapy over the last decade that also reduces the risk of locoregional recurrences. Another explanation could be the increased use of pre operative screening of the axilla by ultrasound, causing stage migration of clinically node-negative disease. Apparently, the challenge will be to better define the patients that still need to undergo a completion ALND versus those who do not. The risk of non-SN metastases, if the axilla is left untreated, is on average 8% for SN-negative disease, 12% for SN isolated tumor cells, 29% for micrometastases and 38% for macrometastases [86, 87]. The risk of non-SN involvement is not only associated with SN status, but also with primary tumor size and presence or absence of lymph vessel invasion [86]. In the ACoSOG Z0011 study, 27% of patients in the ALND group had positive non-SNs. Further research on predictive nomograms and on impact of modern adjuvant systemic therapy is needed to improve selection of patients who will not benefit from further axillary surgery. In the decision process the risk of arm morbidity should be taken into account, because even though morbidity from axillary surgery in the NSABP-B32 was lower than expected, shoulder deficit, arm volume difference, arm numbness and tingling occurred at least twice as frequently in the ALND arm as compared to the SN alone arm.

We conclude that the SN procedure can be regarded as nearly optimal to identify patients who do not need an ALND, that is, patients who have a negative SN. However, additional eligibility criteria and the role of systemic therapy need further to be elucidated to determine a potential role for avoiding ALND in selected SN-positive patients.

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