EUROPEAN JOURNAL OF CANCER 45 (2009) 3124–3130

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Review

Accuracy of sentinel node biopsy after neoadjuvant chemotherapy in breast cancer patients: A systematic review

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ARTICLE INFO

Article history:
Received 7 June 2009
Received in revised form 2 August 2009
Accepted 4 August 2009
Available online 26 August 2009

Keywords:
Breast cancer
Sentinel lymph node biopsy
Neoadjuvant chemotherapy
Review

ABSTRACT

Background: As neoadjuvant chemotherapy (NAC) is increasingly used to downstage patients with breast cancer, the timing of the sentinel node (SN) biopsy has become an important issue. This review was conducted to determine the accuracy of SN biopsy following NAC.

Methods: We searched Medline, Embase and Cochrane databases from 1993 to February 2009 for studies on patients with invasive breast cancer who underwent SN biopsy after NAC followed by an axillary lymph node dissection (ALND).

Results: Of 574 eligible studies, 27 were included in this review with a total study population of 2148 patients. The pooled SN identification rate was 90.9% (95% confidence interval (CI) = 88.0–93.1%) and the false-negative rate was 10.5% (95% CI = 8.1–13.6%). Negative predictive value and accuracy after NAC were 89.0% (95% CI = 85.1–92.1%) and 94.4% (95% CI = 92.6–95.8%), respectively. The reported SN success rates were heterogeneous and several variables were reported to be associated with decreased SN accuracy, i.e. initially positive clinical nodal status.

Conclusions: There is a potential role for SN biopsy following NAC which could be considered on an individual basis. However, there is insufficient evidence to recommend this as a standard procedure. Further research with subgroup analysis using variables reported to be associated with decreased SN accuracy is required in order to clearly define its value in the subgroups of breast cancer patients.

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.08.001

1. Introduction

Lymph node status, even after neoadjuvant chemotherapy (NAC), is a strong predictor of disease-free and overall survival in breast cancer patients.[1–3] A sentinel node (SN) biopsy is an accurate method to assess nodal status and has now replaced traditional axillary lymph node dissection (ALND) as an initial staging procedure in early-stage, clinically node-negative breast cancer patients.[4,5] Several studies indicated that SN biopsy is also feasible for patients with large primary breast tumours,[6–8] provided there is no clinical nodal involvement.[9]

NAC, initially introduced to downstage locally advanced breast cancer to facilitate surgery, results in an improved disease-free and overall survival, which is comparable with the effect of adjuvant chemotherapy.[10–13] More recently, the indication for NAC has been extended to selected patients with an earlier stage disease to allow breast-conserving surgery.[14,15] Another potential advantage of a neoadjuvant approach is the opportunity to observe chemosensitivity *in situ*, providing prognostic information and the ability to identify effective novel therapies.[16]

Following NAC, nodal staging was traditionally performed by an ALND at the time of breast surgery, which is associated with substantial morbidity.[17,18] Therefore, a less aggressive approach to the axilla is desirable. In fact, this raises not only the question whether these patients could be staged by SN biopsy, but also the question of what the optimal timing is for this procedure with respect to the NAC.

Performing an SN biopsy before NAC, on the one hand, assures accurate assessment of initial nodal status, avoiding the possible negative effects of lymphatic scarring or uneven nodal tumour response. On the other hand, performing SN biopsy after NAC could be an attractive strategy as NAC may downstage nodal status in a number of patients (20–40%).[14,19] Before such a strategy can be recommended as a routine procedure, validation of the safety and predictive value of SN biopsy following NAC is required.

Numerous, generally retrospective, small and single-institution studies assessed the feasibility of SN biopsy after NAC, with varying conclusions. This systematic review was conducted to give an overview of these studies and provide recommendations regarding the role of SN biopsy following NAC.

2. Methods

2.1. Literature search strategy

The electronic databases of Medline, Embase and Cochrane were searched from 1993 to February 2009 using free text and controlled terms for breast cancer, SN and NAC. The year 1993 was selected because this was the year of the first publication on the SN. Articles published in English, German, French or Dutch were considered. Two reviewers (C.H.M. van Deurzen and B.E.P.J. Vriens) independently evaluated titles and abstracts of the identified papers. Potentially relevant articles were retrieved to review the full text.

2.2. Study inclusion criteria

To be included in this review, studies had to fulfil the following criteria. First, the patients had received NAC for invasive breast carcinoma. Second, the patients underwent an SN biopsy after NAC, which was followed by an ALND. The patients receiving neoadjuvant endocrine therapy only were excluded.

2.3. Data extraction

Data extraction was carried out independently by the two reviewers who abstracted data on entry criteria, size, clinicopathologic characteristics, SN biopsy technique, SN success rates, SN and non-SN status. Any disagreement was resolved by consensus. In some instances, the corresponding authors were contacted for additional information.

SN accuracy parameters were recalculated according to standard definitions in order to facilitate comparison across studies. The identification rate was defined as the number of patients who underwent a successful SN biopsy divided by the total number of patients in whom an SN biopsy was attempted. The result from each successfully identified SN was categorised as true-positive, true-negative or false-negative, taking the outcome of the complete ALND as reference standard. A true-negative SN was defined as a negative SN and a negative ALND, a false-negative as a negative SN with a positive lymph node in the ALND and a true-positive as a positive SN with or without a positive ALND. Based on these definitions, it was assumed that there were no false-positive cases.

The calculated SN accuracy parameters included sensitivity (true positive/(true positive + false negative)), false-negative rate (false negative/(false negative + true positive)) and negative predictive value (true negative/(true negative + false negative)). Accuracy was computed as the sum of all true-positive and true-negative patients, divided by the number of patients with a successfully identified SN.

2.4. Statistical analysis

A random effects model with an exact likelihood approach was used to calculate pooled SN accuracy parameters and 95% confidence intervals (CIs).[20] The extent to which clinical nodal status explained between-study heterogeneity was explored by the use of meta-regression analysis using the same model.[21] The variation in accuracy parameters in the individual studies was displayed graphically using forest plots. The 95% CIs for the individual studies were calculated by use of the Rothman spreadsheet.[22] Systematic differences between small and large studies were assessed by the use of a funnel plot. Two-sided P-values < 0.05 were considered significant. Statistical analyses were performed using SAS version 9.1.

3. Results

The initial electronic search identified 574 potentially relevant articles of which we screened the title and abstract. After screening, the full texts of 66 articles were obtained. After full-text review and exclusion of overlapping series, 27 arti-

cles that met the inclusion criteria of this review remained for data extraction, including single- (N = 23) and multicentre (N = 4) series. The total study population comprised 2148 patients. The main characteristics and results of these studies are listed in Table 1.

Overall, studies were heterogeneous regarding clinicopathologic characteristics. Patients generally presented with large primary breast tumours (range cT 1–4). The upper outer quadrant of the breast was the most common primary tumour location.

SNs were usually identified by using a combination of radiocolloid and blue dye that was injected peritumourally. A combination of anthracycline and cyclophosphamide was the most frequently used chemotherapy. The majority of studies (19/27) included both clinically node-negative and node-positive patients, and the remainder were restricted to clinically node-negative (5/27) or node-positive (3/27) patients.

The overall, pooled SN identification rate was 90.9% (95% CI = 88.0–93.1%).

The false-negative rate, sensitivity, negative predictive value and accuracy after NAC were 10.5% (95% CI = 8.1–13.6%), 89.5% (95% CI = 86.4–91.9%), 89.0% (95% CI = 85.1–92.1%) and 94.4% (95% CI = 92.6–95.8%), respectively. Forest plots displayed large interstudy variation in SN accuracy parameters (Fig. 1).

Overall, the pooled rate of SN involvement was 49% (95% CI = 32.0–66.2%). Patients with SN involvement had a pooled risk of 61.5% (95% CI = 52.7–69.6%) for non-SN involvement.

3.1. *SN after NAC, in studies including cN0 versus cN+ patients only*

Meta-regression analysis revealed that clinical nodal status at initial diagnosis, before NAC, did not contribute significantly to between-study heterogeneity regarding SN accuracy parameters. The pooled SN identification rate in studies restricted to clinically node-negative patients (N = 5 studies, 266 patients) was 92.7% compared to 88.2% in studies restricted to clinically node-positive (N = 3 studies, 342 patients) patients. The pooled negative predictive value was 90.6% in clinically node-negative patients compared to 87.1% in clinically node-positive patients. The pooled accuracy was comparable for both groups (94.4% and 94.5%, respectively). The effect of clinical tumour size could not be assessed since this was reported heterogeneously in the included studies. A funnel plot did not indicate systematic differences in SN

Table 1 – Overview of breast cancer studies reporting on SN accuracy following neoadjuvant chemotherapy.

First author	N	cT	cN	IR (%)	FNR (%)	Sens (%)	NPV (%)	Accuracy (%)	SN+ only (%)	SN and non-SN+ (%)[a]
Nason[23]	15	2–4	0–1	87	33	67	57	77	46	100
Cohen[c,24]	38	2–3	0–1	82	17	83	81	90	48	M
Fernandez[25]	40	1–4	0–1	85	20	80	78	88	47	75
Tafra[26]	29	1–2	0	93	0	100	100	100	56	M
Brady[27]	14	1–4	0–1	93	0	100	100	100	77	40
Stearns[28]	34	3–4	0–1	85	14	86	73	90	62	72
Schwartz[29]	21	1–3	0–1	100	9	91	91	95	48	30
Balch[30]	32	2–4	0–1	97	5	95	92	97	58	44
Piato[b,31]	42	1–2	0	98	17	83	88	93	37	100
Vigario[b,32]	37	1–2	0	97	39	61	72	81	M	M
Shimazu[33]	47	2–4	0–1	94	12	88	73	91	66	69
Lang[34]	53	1/2–4	0–1	94	4	96	96	98	46	M
Patel[d,35]	42	2–4	0–1	95	0	100	100	100	48	M
Shen[c,36]	69	1–4	1	93	25	75	62	82	48	73
Mamounas[d,37]	428	1–3	0–1	85	11	89	93	96	36	44
Jones[38]	36	2–4	0–1	81	11	89	85	93	55	63
Tanaka[39]	70	1–3	0–1	90	5	95	96	98	30	58
Yu[40]	127	3	0	91	7	93	90	96	55	63
Tausch[41]	167	1–4	0–1	85	8	92	91	96	49	44
Kinoshita[42]	104	2–4	0–1	93	10	90	93	96	37	56
Lee[43]	219	1–4	1	78	5.6	94	87	96	69	M
Newman[44]	54	1–3	1	98	8	92	85	94	62	M
Yamamoto[45]	20	1–3	0–1	100	14	86	93	95	30	100
Gimbergues[46]	129	1–3	0–1	94	14	86	89	93	40	52
Hino[47]	55	2–3	0–1	71	0	100	100	100	46	72
Papa[48]	31	2–3	0	87	16	84	73	89	59	M
Classe[49]	195	0–3	0–1	90	12	88	95	97	26	43
Total	2148			90.9	10.5	89.5	89.0	94.4	49.0	61.5

N = number of patients; cT = clinical tumour diameter; cN = clinical nodal status: 0 = cN0, 1 = clinical nodal involvement (either cN1 or cN2), 0–1 = combination of patients with clinical node-positive and node-negative diseases.
IR = identification rate; FNR = false-negative rate; NPV = negative predictive value; M = missing data.
a Percentage of patients with non-SN involvement among patients with a positive SN.
b Potential overlap of patients.
c,d Some overlapping patients.

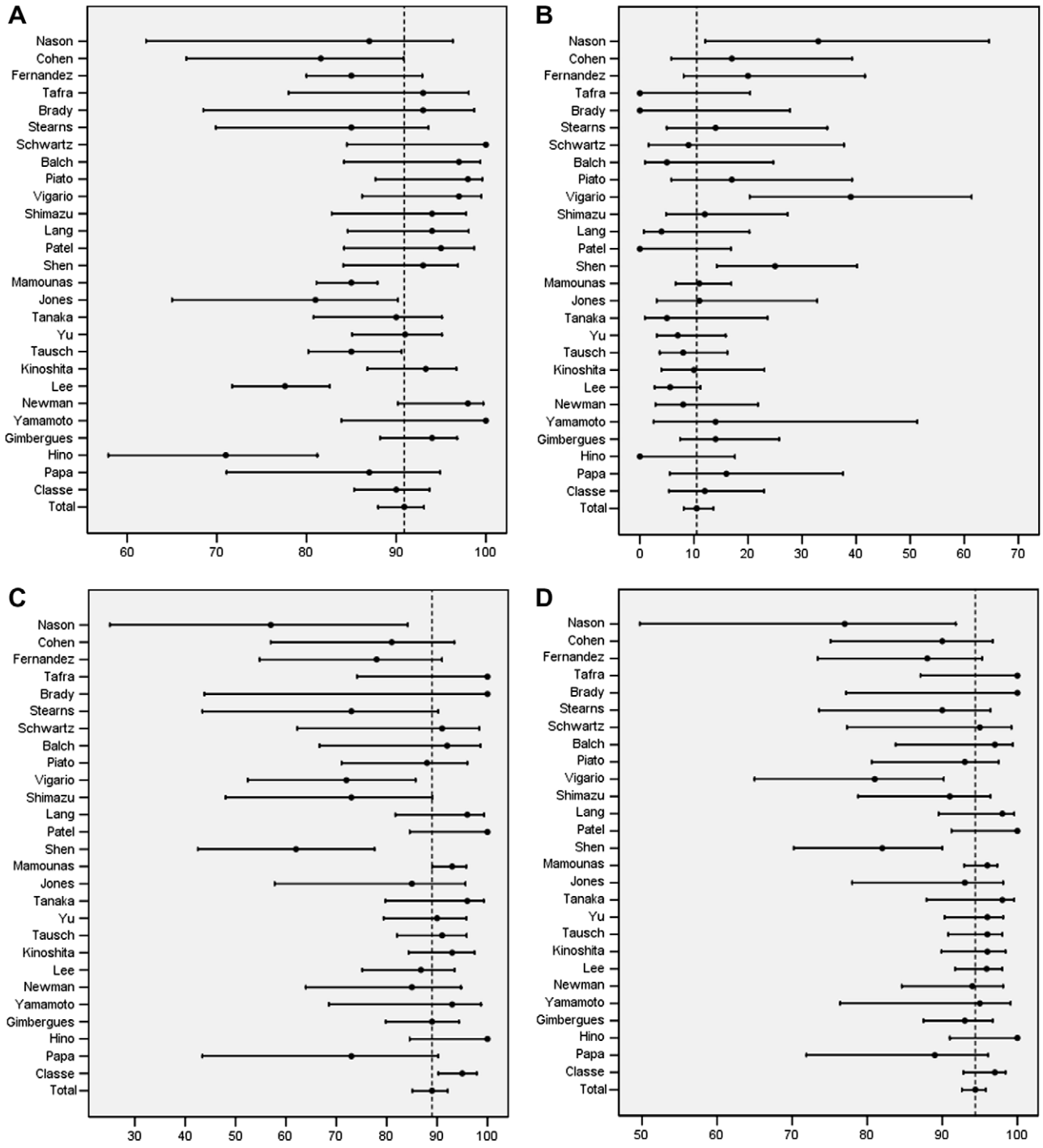

Fig. 1 – Forest plots of SN identification rate (A), false-negative rate (B), negative predictive value (C) and accuracy (D) of an SN biopsy following NAC in breast cancer patients. The width of the horizontal line represents the 95% CI of the individual studies. The 95% CI of the pooled estimate is displayed as a vertical line.

accuracy parameters between larger and smaller studies (data not shown).

3.2. *Features influencing SN accuracy*

A minority of studies performed statistical analysis regarding clinicopathologic features influencing SN accuracy following NAC.

Classe and colleagues[49] ($N = 195$) reported a significantly lower SN identification rate in patients with clinical nodal involvement compared to clinically node-negative patients ($P = 0.008$). Hino and colleagues[47] reported that clinical breast tumour size after NAC, clinical axillary nodal status after NAC and Body Mass Index were significantly associated with SN identification rate ($P = 0.0003$, $P = 0.048$ and $P = 0.008$, respectively).

Both Mamounas and colleagues[37] ($N = 428$) and Gimbergues and colleagues[46] ($N = 129$) reported an increased SN false-negative rate with increasing primary tumour size (P = NS and $P = 0.045$, respectively). Gimbergues and colleagues[46] concluded that clinical nodal status before NAC was the main factor influencing the SN false-negative rate after NAC. They reported no false-negative cases in clinically node-negative patients compared to a false-negative rate of 30% in clinically node-positive patients ($P = 0.003$). Tausch and colleagues[41] ($N = 169$) also reported a trend toward a higher false-negative rate in initial clinically node-positive patients although this was not significant ($P = 0.39$). Mamounas and colleagues[37] ($N = 428$), Kinoshita[42] ($N = 104$) and Classe and colleagues[49] ($N = 195$) on the other hand reported no effects of clinical nodal status on the SN false-negative rate.

Another factor reported to affect a successful SN biopsy is the response to chemotherapy. Tauch and colleagues[41] reported a significantly lower sensitivity among patients with a complete response compared to the group of patients with any other type of response ($P = 0.048$). However, this finding is contradicted by Mamounas and colleagues[37] who reported a trend towards a lower sensitivity in patients with a poor tumour response.

4. Discussion

This systematic review was conducted to give an overview of the current literature regarding the accuracy of an SN biopsy in breast cancer patients following NAC. We calculated a pooled SN identification rate and false-negative rate of 90.9% and 10.5%, respectively. These rates do not differ substantially from prior multicentre studies evaluating SN success rates without NAC, reporting an identification rate of 88–97% and a false-negative rate of 5–10%.[50–55] However, these rates are largely based on early SN studies and these rates are not generally accepted any more according to current treatment guidelines. The reported pooled false-negative rate of 10.5% in this review is substantially higher than the generally accepted 5% rate without NAC and therefore the SN biopsy following NAC cannot be recommended as the standard of care. Besides, several clinicopathologic factors have been reported to be associated with decreased SN accuracy following NAC, including clinical nodal status, primary tumour size, Body Mass Index and response to chemotherapy.

The largest cohort to date, the NSAPB B-27 multicentre randomised trial ($N = 428$),[37] evaluating the sequencing of chemotherapy, reported an identification rate, a false-negative rate and an accuracy of 85%, 11% and 96%, respectively. They concluded that these rates are comparable to those obtained from multicentre studies evaluating SN biopsy following breast cancer diagnosis and suggest that this procedure is feasible following NAC, which is consistent with the results of a meta-analysis by Xing and colleagues.[56] Lee and colleagues[43] reported the largest cohort ($N = 219$) restricted to clinically lymph node-positive patients published to date. They reported an SN identification rate of 78% after NAC, which was significantly lower ($P < 0.001$) compared to the patients who did not receive NAC. However, the false-negative rate and accuracy did not significantly differ between these two groups. They concluded that an SN biopsy is feasible in patients who reach clinically complete axillary clearance by NAC.

NAC downstages nodal status in a substantial proportion of patients (20–40%),[14,19] which could be an important advantage of nodal staging after NAC compared to nodal staging before NAC. Other potential advantages of this first approach are avoidance of a delay for NAC and that the patients with a negative SN following NAC require only one surgical procedure instead of two. Performing an SN procedure before NAC on the other hand results in two surgical procedures regardless of SN status (one for the SN procedure and one for surgery of the primary tumour). However, Kilbride and colleagues[57] recently reported that knowing nodal status before NAC (by ultrasound with FNA or SN biopsy) provides important prognostic information regarding the risk of recurrence, which may be useful in further treatment planning (i.e. adjuvant irradiation).

Theoretically, NAC could have several negative effects on the accuracy of the SN biopsy. First, both primary tumours and metastatic lymph nodes respond to chemotherapy yielding reactive changes like fibrosis which may affect lymphatic drainage patterns. Second, chemotherapy could induce an uneven tumour response in axillary lymph node eradication. These effects would likely result in decreased SN accuracy after NAC. A few studies included both patients with an SN biopsy before/without NAC and after NAC,[38,43,48] and reported a significantly decreased SN identification rate after NAC.

When comparing SN success rates between heterogeneous studies (i.e. between studies including patients treated with NAC versus studies including patients without NAC), one must take into account that the false-negative rate depends on the probability of nodal involvement. Among patients with a lower probability of nodal involvement, there is more variation in the false-negative rate because the sample size is smaller.[58] This also holds true for the comparison of the SN false-negative rate of initially clinically node-positive patients (who have a high risk of SN and non-SN involvement) versus clinically node-negative patients. The clinical significance of an unsuccessful SN procedure on the other hand may also differ. Previous studies reported minimal impact of false-negative SNs before or without systemic therapy regarding local recurrences, but this might not hold true in this 'high risk' group treated with NAC.

In conclusion, the SN accuracy parameters following NAC are not substantially different from prior multicentre studies evaluating SN success rates without NAC. Since about half of the included patients in this review had a negative SN, this could substantially reduce the extent of axillary surgery. However, the included series contain methodological weaknesses and several features have been reported to be associated with a decreased SN accuracy after NAC in individual studies. Given the limited power for subgroup analyses, no definitive conclusions can be drawn regarding the precise value of SN biopsy in subgroups of breast cancer patients, i.e. those with clinical nodal involvement. Besides, none of the authors of the published studies on SN biopsy after NAC abandoned an ALND yet and it is unsure whether surgeons are now comfortable in doing so. Awaiting further data on the safety of SN biopsy after NAC, it can be performed before NAC with the

same outcome as without NAC. Nevertheless, the conclusions of this systematic review at least warrant a clinical trial with long-term follow-up to evaluate the safety of omission of an ALND in patients with a negative SN after NAC. Future advances in molecular profiling and imaging techniques may further help to determine which patients are most likely to have negative axillary nodes following a specific chemotherapeutic regimen, in which omission of an ALND could be more easily accepted for patients with a negative SN after NAC. We believe that performing an SN biopsy following NAC could for the time being anyway be considered on an individual basis (i.e. clinically node-negative patients following NAC), but there is insufficient evidence to recommend this as a standard procedure.

Conflict of interest statement

None declared.

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