

Sentinel Node Biopsy After Primary Chemotherapy in Breast Cancer: A Note of Caution from Results of ABCSG-14

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■ **Abstract:** Over the past years, experience has been increasing with lymphatic mapping and sentinel node biopsy (SNB) after preoperative chemotherapy for breast cancer, with a wide range of results reported in the literature and final conclusions on the diagnostic value and clinical consequences of this sequential approach still missing. Between 1999 and 2002, the Austrian Breast and Colorectal Cancer Study Group (ABCSG) conducted a prospective randomized multicenter trial comparing three versus six preoperative cycles of epirubicin/docetaxel + granulocyte colony-stimulating factor for operable breast cancer. Of the 292 patients recruited to the trial overall, 111 were enrolled in a prospective subprotocol for performing LM and SNB in addition to obligatory axillary lymph node dissection (ALND) after PC. SNB after PC identified at least one sentinel node in 100 of 111 patients (identification rate 90%). In six cases, a false-negative SN was identified, resulting in a false-negative rate of 13% (6 of 47). We only found little correlation between patients and tumor characteristics and the identification rate or false-negative rate. Lymphatic mapping and SNB after primary chemotherapy failed to predict histologic infiltration of the sentinel node with sufficient sensitivity. The routine use of SNB after primary chemotherapy should therefore be discouraged. ■

Key Words: false-negative rate, primary chemotherapy, sensitivity, sentinel node biopsy, sequence of chemotherapy and sentinel node biopsy

Sentinel node biopsy, SNB, is increasingly accepted as an alternative to axillary lymph node dissection of level I and II for T1 and T2 breast tumors in patients undergoing tumor resection and receiving adjuvant endocrine and/or cytotoxic therapy according to the histologic results of this initial staging of

primary and axilla (1). In this setting, SNB was introduced as a diagnostic procedure to reduce morbidity resulting from extensive surgical evaluation of the axilla. In a meta-analysis of 69 phase-II reports a sensitivity of 93% was reached (2). This was nearly the value of 95% considered the critical threshold of acceptance for clinical practice at the beginning of the sentinel era as for e.g., outlined by the consensus of the American Society of Breast Surgeons in 2000 (3). At present, the results of large trials randomizing between SNB and axillary lymph node dissection have demonstrated a distinct advantage for SNB regarding

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morbidity, but we are still waiting for long-term data pertaining axillary and distant recurrences (4). Only one small randomized trial has been reported with a median follow-up of 79 months concerning these questions, yet it is with excellent results (5).

In turn, primary chemotherapy has become a widespread approach for breast cancer treatment. Primary chemotherapy was initially developed to render locally advanced breast tumors operable and to increase the rate of breast-conserving therapy (6–8). While primary chemotherapy failed to improve overall survival versus postoperative chemotherapy for the entire collective (9–12), the subgroup of patients experiencing a pathological complete response (pCR) experienced a significant improvement in overall survival (13). Primary chemotherapy is furthermore considered an *in vivo* test for the efficacy of new drugs or novel systemic treatment regimens with pCR serving as a surrogate marker for an improvement of outcome (14). Therefore, primary chemotherapy is no longer exclusively used for large tumors, but rather offered to a wider range of patients at high risk. Only a proportion of these patients present clinical signs of axillary node involvement at diagnosis and might therefore be candidates for avoiding axillary lymph node dissection.

The combination and optimal sequence of SNB and primary chemotherapy is one of various controversial issues with respect to state-of-the-art recommendations for lymphatic mapping and SNB. The recently published ASCO guidelines for SNB in early-stage breast cancer (1) do not recommend SNB after PC in view of insufficient evidence as yet. According to this recommendation, however, SNB before primary chemotherapy is deemed acceptable although the level of evidence is still very limited.

In light of these open questions, we previously investigated the feasibility and sensitivity of SNB after primary chemotherapy in a retrospective analysis, employing the data base of the Austrian Sentinel Node Study Group, and achieved an 86% identification rate and a false-negative rate of 8% (15–17). To substantiate these promising findings in a prospective manner, the combination of SNB and primary chemotherapy was evaluated in a prospective subprotocol of the ABCSG-Trial 14 with the goal to achieve a false-negative rate comparable to SNB without primary chemotherapy. This randomized multicenter trial studied the outcome in terms of the rate of pCR, comparing three versus six cycles of an otherwise identical preoperative chemotherapy regimen (18).

METHODS

Patients

The Austrian Breast and Colorectal Cancer Study Group, ABCSG-14, was open for patients with operable breast cancer that had been histologically proven by core needle biopsy. All tumor sizes with the exception of T4d tumors (inflammatory disease) and all clinical nodal stages were eligible. Presence of distant disease at the time of diagnosis was excluded by clinical investigation, chest x-ray, liver ultrasound and bone scan.

The protocol was approved by the institutional review boards in all participating centers. All patients submitted written informed consent and were stratified according to clinical tumor size (T1, T2, T3, T4a–c), clinical lymph node status (positive, negative), menopausal status (premenopausal, postmenopausal), hormone receptor status (negative, positive, not determined), Her2 status (negative, positive, not determinable), grading (G1, G2, Gx, G3, not determined), and participating center.

Patients were randomly assigned to two treatment groups receiving either three cycles (control group) or six cycles (experimental group) of a preoperative epirubicin 75 mg/m² and docetaxel 75 mg/m² combination combined with granulocyte colony-stimulating factor according to standard recommendations (19). Details concerning the treatment regimens have been published previously (18).

Response to Preoperative Chemotherapy

Information regarding tumor size and status of axillary nodes was obtained clinically at randomization, on day 1 of each cycle of chemotherapy and immediately before surgery. Mammography and ultrasound of the affected breast were specified after three cycles for all patients and after six cycles for patients on the experimental arm to investigate response.

Clinical complete response (CR) was defined in the absence of evidence of a palpable tumor in the breast. Patients who had no invasive cancer in the final surgical sample of the breast were classified as showing pathological complete response (pCR). A reduction in tumor size by $\geq 50\%$ at the time of surgery was defined as partial remission (PR). Any increase in tumor size was considered progressive disease (PD). In these cases, chemotherapy was to be discontinued at any time of preoperative therapy and the patient was administered salvage surgery. All tumors that did not

meet the above-mentioned criteria were specified as stable disease.

Surgery

Final surgery was performed 2–4 weeks after the last scheduled cycle of chemotherapy. Adequate surgery was defined as breast-conserving therapy with axillary lymph node dissection level I and II or as modified radical mastectomy, with obligatory free margins in all cases. At least eight lymph nodes were always removed from the axilla, as per protocol.

While endoscopic techniques for axillary dissection were prohibited in this trial, surgeons were invited to perform an SNB in the framework of axillary lymph node dissection according to a subprotocol of ABCSG-14 in patients without evidence of clinically palpable axillary lymph nodes at the time of surgery. The injection site and the method were at the discretion of the surgeon. However, participating institutions were requested to prove their experience with SNB (at least 50 procedures with a sensitivity of $\geq 95\%$) to avoid including learning curves. Every lymph node which was stained blue or was hot was defined as sentinel lymph node.

The method of SNB put to use, the number of removed SNs, and the pathological findings were documented in the subprotocol case report form. Each SN was worked up with routine hematoxylin and eosin staining in slides of 250 μm and additional immunohistochemical staining in 500 μm step sections against cytokeratin antibodies following the guidelines of the Austrian Society of Pathology (20).

To obtain information regarding the identification rate and the applied method of lymphatic mapping, the operative reports of 196 patients in centers participating in the subprotocol and pathology reports of all identified SNs were centrally subjected to review.

Statistics

The identification rate was calculated for statistical analysis. This rate represents the proportion of patients in whom at least one SN could be successfully identified by the procedure.

The false-negative rate is defined as the ratio of the number of patients in whom histological and histochemical evaluation showed tumor infiltration although the SN identification had predicted a negative result to the number of patients with axillary lymph node metastases in per cent.

Sensitivity is the reciprocal value of the false-negative rate and defined as the ratio of the number of patients with a positive SNB to the number of patients with axillary lymph node metastases in (percentage)%.

The false-negative rate and identification rate were recorded and comparisons were made by analyzing simple proportions.

Comparisons between identification rate and false-negative rate values between the respective variable levels were done in grouped comparisons according to patient and tumor characteristics—age, menopausal status, clinical tumor size before chemotherapy, histopathological tumor grading, estrogen receptor, progesterone receptor, Her2-status, tumor location in the breast, clinical axillary status before treatment, response to primary chemotherapy, method and injection site of SNB—using exact chi-squared tests and additional Mantel–Haenszel exact trend tests (21) when applicable. All p-values are given two-sided unless otherwise stated and $p < 0.05$ was considered as indicating a statistically significant difference. All analyses were carried out using the statistical software package SAS (version 8.02, SAS Institute, Cary, NC).

RESULTS

A total of 111 patients from 11 centers were enrolled in the SNB subprotocol. The mean age was 48.4 years (range 28–70); 68 patients (58.1%) were premenopausal, 49 patients (41.9%) were postmenopausal. 57 patients received three cycles and 60 patients received six cycles of primary chemotherapy.

A pCR was achieved in 12 patients (11%). An additional 14 patients (13%) had a clinical CR. A PR was obtained in 39 patients (35%), SD was observed in 28 patients (25%). Five patients (4%) showed PD during preoperative chemotherapy. In 13 patients (12%) clinical response could not be accurately defined.

Sentinel node biopsy, SNB after primary chemotherapy was attempted in 111 patients. Only blue dye was used in 28 (25%) cases, radionuclide was used as a single method in 13 (12%), and the combination of both methods was applied in 70 (63%) cases.

For the 111 patients who had SNB after primary chemotherapy, the following results were achieved: At least one SN was found and removed in 100 patients (identification rate of 90%). In 51 cases only one SN was identified; in 32 cases two SNs were found; and in 17 cases three or more SNs were successfully identified. The median number of removed nodes was 1.79.

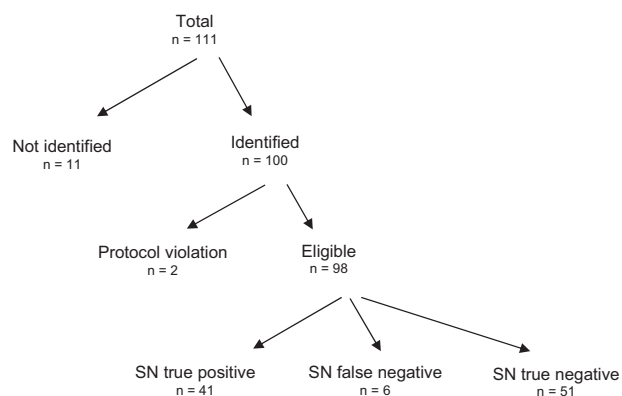


Figure 1. Flow-chart of patients who underwent SNB after primary chemotherapy ($n = 111$).

When only blue dye was applied, 23 of 28 SNB (82%) were successful. The use of radionuclide alone resulted in an 85% identification rate (11/13). The combination of both methods reached an identification rate of 94% (66/70).

The identification rate was significantly lower when lymphatic mapping was performed in women >50 years of age ($p = 0.029$) and in patients clinically progressing on chemotherapy ($p = 0.017$).

No statistically significant difference was found in identification rate according to histopathological tumor grading, hormone receptor status (both estrogen and progesterone receptors), menopausal status, tumor stage, Her2-status, tumor location, clinical nodal status before chemotherapy, therapy arm, pathological response to chemotherapy, injection method and injection site.

Of the 100 patients undergoing successful identification of at least one SN after primary chemotherapy (Figure 1), one patient was lost for assessment because the pathologist did not analyse the SN separately from the axillary nodes. In another case which was eliminated from further evaluation, SNB was the only axillary procedure without the required axillary lymph node dissection.

From the 98 patients left for systematic analysis of accuracy, 41 patients (41.4%) had a histologically involved SN. In 18 patients (18.2%), the SN was the only involved node. The SN was free of tumor cells while finding other positive axillary nodes in six cases, resulting in a false-negative rate of 12.8% (6/47). In 51 patients (52.5%), the negative SN was proven true by a negative axilla.

No statistically significant difference was found in the false-negative rate according to patients' age,

Table 1. False-Negative Rate According to Patient and Tumor Characteristics for SNB After PC

Factors	False-negative results/Positive axillary results	False-negative rate (%)	p-value
Age			
≤50 years	4/28	14	NS
>50 years	2/19	11	
Clinical tumor size			
≤3 cm	4/26	15	NS
>3 cm	2/21	10	
Grading			
1	0/1	0	NS
2	3/29	10	
3	3/16	19	
Hormone receptor status			
Negative	3/12	25	NS
Positive	3/35	9	
Her-2 status			
-, +, ++	4/37	10	NS
+++	2/8	25	
Tumor location			
Upper outer	3/13	23	NS
Upper inner	2/20	10	
Lower outer	0/6	0	
Lower inner	1/3	33	
Central	0/2	0	
Multicentric	0/3	0	
Clinical nodal status before preoperative chemotherapy			
Negative	4/26	15	NS
Positive	2/21	10	
Number of chemotherapy cycles			
3	3/28	11	NS
6	3/19	16	
Tumor response			
pCR	2/2	100	0.0139
No pCR	4/45	9	
Injection method			
Single-modality mapping	0/14	0	NS
Combination (blue dye and isotope)	6/33	18	

histopathological tumor grading, hormone receptor status for estrogen and progesterone, menopausal status, tumor stage, Her2-status, tumor location, clinical nodal status before chemotherapy, therapy arm, clinical response to chemotherapy or injection method (Table 1).

Ten of 12 patients with pCR in the breast showed also free nodes in the axillary basin. Both remaining patients with pathological complete response in the breast but residual tumor cells in axillary nodes had false-negative SNs, while four of 45 without a pathological complete response were false negative. This difference was statistically significant ($p = 0.0139$).

DISCUSSION

The published reports of SNB after primary chemotherapy are marked by a wide range of results with

Author	Number of Centers	<i>n</i>	Method	Identification rate (%)	False-negative rate (%)
Breslin et al. (32)	s.i.	51	mixed	84	12
Nason et al. (31)	s.i.	15	both	79	33
Fernandez et al. (28)	s.i.	40	tracer	81	20
Julian et al. (24)	s.i.	31	mixed	94	0
Tafra et al. (33)	m.c.	29	both	93	0
Brady et al. (25)	s.i.	14	n.a.	93	0
Stearns et al. (34)	s.i.	34	blue dye	85	14
Miller et al. (26)	s.i.	35	mixed	86	0
Piato et al. (35)	s.i.	42	tracer	98	17
Balch et al. (23)	s.i.	32	both	97	5
Reitsamer et al. (36)	s.i.	30	both	96	7
Kang et al. (27)	s.i.	54	mixed	72	11
Tanaka et al. (37)	s.i.	70	blue dye	90	5
Le Bouedec et al. (38)	s.i.	74	tracer	92	14
Yu et al. (39)	s.i.	127	blue dye	91	9
Peley et al. (40)	s.i.	17	both	59	0
Kinoshita et al. (41)	s.i.	77	both	94	11
Mamounas et al. (29)	m.c.	428	mixed	85	11
Tausch et al. (17)	m.c.	167	mixed	85	8
Shen et al. (42)	s.i.	69	n.a.	93	25
Gimbergues (43)	s.i.	129	tracer	94	14
Total		1,565		87.7	10.7

s.i., single institution trial; m.c., multicenter trial.

respect to identification rate and false-negative rate as the most relevant outcome measures of that procedure (22). Results from single-institution series with lower numbers of patients differ distinctly, with excellent identification rate of up to 97% (23) and a sensitivity of 100% (24–26) as one extreme. Conversely, SNB identification rates of 72% (27) and high false-negative rates up to 33% (28) are reported on the poor end of the range.

The NSABP B-27 sentinel subprotocol ($n = 428$) and the NSABP B-32 trial ($n = 2,807$) can show a similar false-negative rate in patients after PC and in untreated patients (11% resp. 10%) (29,30). But comparing all data of SNB after PC with the results published in the meta-analysis of lymphatic mapping in early-stage breast carcinoma by Kim et al. (2), the identification rates of SNB after primary chemotherapy are significantly lower than identification rates of SNB in untreated patients (i.e., 87.7% versus 96.4%, $p < 0.0001$; OR = 3.69; 95% CI 3.05–4.46 (23–29,31–43). Further the false-negative rate seems to increase substantially if SNB is performed after primary chemotherapy (i.e., 10.7% versus 7.3%, $p = 0.0036$; OR = 0.66; 95% CI 0.50–0.87) (Table 2). As a result, the question arises as to whether SNB after PC can be recommended as a standard procedure in the same way it has become standard in surgery for non-pretreated patients.

The retrospective data on SNB after primary chemotherapy generated by the Austrian Sentinel

Table 2. Phase II-Trials of Sentinel Node Biopsy After Primary Chemotherapy

Node Study Group demonstrated an identification rate of 86% and an encouraging false-negative rate of 8% (17). These results, however, were collected retrospectively from a large nationwide data base which is maintained by a group with a special scientific interest in SNB. The false-negative rate (from 8% to 13%) from our previous retrospective report to this prospective investigation is noteworthy. It means for this report that every eighth nodal positive case will be missed. It may be seen as an example of a reporting bias that raises concerns about the validity of basing treatment recommendations on retrospective analyses. In any case, we argue that treatment modalities deemed as potentially state-of-the-art need to be validated in a prospective manner. While setting out to do so for SNB after primary chemotherapy, our results have clearly shown that SNB following primary chemotherapy yields insufficient results even in the hands of a specialized and experienced group and therefore far from being a recommendable standard.

There are several potential reasons for the limited value of SNB after as compared to SNB without primary chemotherapy: it is well-known that primary chemotherapy for breast cancer can induce downstaging of axillary nodes in addition to downsizing of the primary tumor (44). In this regard, (a) the exact effect of chemotherapy on the microarchitecture of the histologically involved and not involved lymph nodes is not fully established. Different types of chemotherapy might affect the lymphatic parenchyma of the lymph

Table 3. Phase II-Trials of Sentinel Node Biopsy Before Primary Chemotherapy

Author	Number of Centers	n	Method	Identification rate (%)	False-negative rate (%)
Schrenk et al. (53)	s.i.	21	mixed	100	0
Sabel et al. (54)	s.i.	26	n.a.	100	n.a.
Jones et al. (55)	s.i.	52	mixed	100	n.a.
Ollila et al. (56)	s.i.	21	both	100	n.a.
Van Rijk et al. (57)	s.i.	25	both	100	n.a.
Total		145		100	n.a.

s.i., single institution trial.

nodes differently depending on their lymphotoxic effects. This might alter the ratio of tumor cells and lymphocytes and impact on the sensitivity of the method. (b) Neoangiogenesis is under strict tumor control and dependent on the growth kinetics and size of a tumor (45). Therefore, not only chemotherapy itself but also the treatment effect on the lymph node metastases as well as the volume of node infiltration might influence the results of SN analyses. (c) Furthermore, primary chemotherapy is known to potentially induce lymph node fibrosis (28,46), possibly resulting in a pathway to a false (-negative) node for tracer and blue dye. If the “leading” vessel thus becomes non-functional, SNB may identify the wrong lymph node.

Although the false-negative rate was high in this study, the absolute number of false-negative results is nevertheless too low and the identification rate too high to allow adequate statistical workup of risk factors for false-negative results. However, despite these limitations, the correlation between a pCR after primary chemotherapy and a false-negative result of SNB achieved the level of statistical significance. This is in apparent contrast to the results of an as yet single available report of lymphatic mapping after preoperative endocrine therapy (47) which reported a sensitivity rate of 100% of SNB. Whether this difference is due to the much lower frequency of pCR after neoadjuvant endocrine treatment as compared to primary chemotherapy (48,49) remains to be determined. However, a more concentric shrinkage of lymph node metastases has been reported following endocrine treatment (47). This finding might support the view that differences in the interaction of treatment modalities with tumor biology and the interaction of tumor cells with their specific microenvironment during tumor regression and in fact differences in the biology of tumor regression could influence the accuracy of SNB.

Other authors have proposed a role for the number of initially involved lymph nodes as determined by clinical means and the false-negative rate following pri-

mary chemotherapy. In a recent report of 4,117 patients from the University of Louisville Breast Cancer Sentinel Lymph Node Study (50), a low number of positive axillary nodes was identified as a factor associated with false-negative SNB, whereas other authors with lower numbers of cases have found that SNB after primary chemotherapy is more effective in the presence of a clinically negative axilla prior to the start of chemotherapy (42,51,52). In summary, it is currently impossible to define a subset of patients in whom SNB after primary chemotherapy can be recommended.

Although SNB after primary chemotherapy is widely performed in clinical practice, our data discourage this approach and clearly support the restrictive view of the ASCO panelists (1). Therefore, the question arises concerning alternative sequences for procedures like the performance of a SNB before primary chemotherapy (reverse procedure). In one of our centers six patients were analyzed in this way outside of the trial protocol reported. At least one SN was found in all of the six patients, with no single false-negative case. It is noteworthy, that all publications (53–57) about this “reverse” procedure so far report a 100% identification rate (Table 3). In 20 cases with pre-treatment SNB, results were confirmed by subsequent axillary lymph node dissection, and not a single false-negative case has been detected (53). While these results seem promising, a drawback of this “reverse” procedure is that potential axillary downstaging cannot be exploited for its use as a prognostic factor or surrogate marker in clinical trials. Further disadvantages of this approach are the patients’ inconvenience associated with an additional surgical intervention, uncertainty about the value of this approach in patients with large tumors (49,58–63) and the incapability to detect skip metastases eliminated by the primary chemotherapy. Currently the reverse approach has not been adequately compared with SNB after primary chemotherapy e.g., in a randomized fashion. The only retrospective analysis (55) directly comparing

the results of SNB before and after chemotherapy showed an improvement of identification rate with SNB before PC and a false-negative rate after PC of 11%. Clearly, this new concept needs further evaluation in large prospective clinical trials.

Since SNB before PC seems to be more sensitive than SNB after PC, the ABCSG will prospectively investigate this procedure in a larger number of patients within its just closed neo-adjuvant protocol ABCSG-24, the ultimate aim for the future being to preserve both the breast and the axilla in a selected subgroup of our patients. Until then, the use of SNB after PC is discouraged and should only take place in the framework of clinical trials.

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APPENDIX

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