

Management of the axilla for ipsilateral breast cancer recurrence after previous sentinel lymph node biopsy and breast conserving therapy

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Abstract The sentinel lymph node biopsy (SLNB) is the standard procedure for axillary staging in patients with primary breast cancer. Of these patients, 10–15% will develop local breast cancer recurrence. Optimal management of the axilla for these patients is still not established. The aim of this review is to assess the role of secondary lymph node biopsy in patients with ipsilateral breast cancer recurrence. The MEDLINE–PubMed databases were searched from 2006 to 2010 for publications addressing the role of secondary SLNB for ipsilateral breast cancer recurrence. Following terms were used: breast cancer recurrence, sentinel node biopsy, lymphatic drainage, follow-up lymphatic mapping. Twenty-two publications reporting a second SLNB at the time of ipsilateral relapse were identified. The detection rate of a new sentinel node (SN) was 45–97%. The detection rate varied depending on the type of previous surgery. A high rate of extra-axillary re-SN was reported (32%). In 8–35% cases, a histologically positive re-SN was diagnosed. The optimal management of the axilla in the setting of local recurrence is still not established. Prospective trials are needed to facilitate evidence-based recommendations for this situation.

Keywords Breast cancer recurrence · Sentinel node biopsy · Follow-up lymphatic mapping · Axillary surgery

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Abbreviations

AGO	German Gynecological Oncology
ASCO	American Society of Clinical Oncology
ALND	axillary lymph node dissection
BCT	breast conserving therapy
LSG	lymphoscintigraphy
SLNB	sentinel lymph node biopsy
SN	sentinel node

Background

The objectives of primary surgical therapy of breast cancer are the removal of the tumor (therapeutic aim) and the assessment of lymph node status for selecting appropriate adjuvant treatment (diagnostic aim). Standard therapy for primary breast cancer includes breast-conserving surgery in the majority of cases. Lymph node status is determined in clinically node-negative patients by the sentinel lymph node biopsy (SLNB). The sentinel lymph node is the hypothetical first node (or several nodes) reached by cancer spread from the primary tumor [1, 2]. This concept entails removal of selected lymph nodes at the highest risk of metastatic growth and thus the assessment of nodal status by a minimally invasive procedure. In addition, the incidence of axillary recurrence after negative findings on SLNB is comparable to that following axillary lymph node dissection (ALND) [3, 4]. ALND is indicated in the case of positive lymph nodes. The diagnostic value of ALND has drastically diminished after the introduction of SLNB and is the standard of care in cases where SLNB is not feasible [5].

Approximately 10–15% of patients after breast conserving therapy (BCT) or mastectomy suffer from local recurrence [6]. Adequate treatment for such a relapse

following BCT consists generally of mastectomy, whereas thoracic recurrence after mastectomy is treated by wide excision [7].

The optimal surgical approach for lymph node re-staging in patients who have been previously treated with SLNB is still under debate. The exact fate of drainage patterns after previous axillary surgery or radiation therapy that alters or disrupts lymphatic pathways is not known [8, 9]. Limited data from experimental studies suggest that disruption of lymphatic vessels may only be temporary and a new lymphatic network will be built up by collaterals and retained open lymphatic vessels [10]. Further research is needed to assess exact changes in lymphatic pathways and thus allow a definite statement with regard to the clinical and oncological relevance of secondary lymph node staging [11–15].

Various studies have already confirmed the feasibility and efficacy of SLNB after a biopsy of the breast [16]. Accordingly, previous breast biopsy is not considered a contraindication for SLNB in the American Society of Clinical Oncology (ASCO) recommendations [17]. However, SLNB after axillary surgery has not been widely studied. In addition, guidelines from ASCO and German Society of Senology recommend against SLNB in women who have undergone prior axillary surgery [17, 18]. At present, there are emerging reports of successful second SLNB in patients with a local recurrence following a previous SLNB and/or axillary dissection. Therefore, the objective of this review is to discuss the potential role of second axillary sentinel node biopsy for ipsilateral breast cancer recurrence based on current literature.

Methods

The MEDLINE–PubMed databases were searched from 2006 to 2010 for publications addressing the role of secondary SLNB for ipsilateral breast cancer recurrence. The following terms were used: breast cancer recurrence, sentinel node biopsy, lymphatic drainage, and follow-up lymphatic mapping. The reference lists of selected publications were also checked for other possible relevant publications. Case reports were excluded. Twenty-two publications were identified in the PubMed database. All authors investigated the possibilities and limitations of lymph node re-staging (re-SLNB) after axillary intervention for primary breast cancer by using radionuclide labeling and lymphoscintigraphic detection of sentinel nodes.

Findings

Detection rate of SN after previous axillary surgery

The Medline research yielded 22 publications investigating the role of secondary sentinel lymph node biopsy after previous axillary surgery. The detection rate of a sentinel node (SN) after previous axillary surgery (SLNB or ALND) was 45–97% (mean 73%, Table 1). In the largest study including 117 cases, a SN was identified in 55% of the patients [19]. The extent of primary axillary intervention had a significant impact on the detection of a re-SN. A new sentinel node could be identified in 78% of patients who had initially only a SLNB. In contrast, the detection rate

Table 1 Review of publications including at least 20 patients

Author	N	Initial ALND/ SLNB/none	Radiotracer injection	Detection (%)	SN axillary/ extraaxillary	SN pos (%)
Palit 2008 (review) [22]	287	77/131/0	Review	73	n.a./32%	15
Van der Ploeg 2010 [24]	115	12/36/67	Intratumoral	83	70%/51%	12/115 (10)
Port 2007 ^a [19]	117	63/54/0	Peritumoral ^c	55	69%/30%	10/64 (16)
Intra 2007 ^a [20]	65	0/65/0	Peritumoral	97	97%/8%	7/65 (11)
Cox 2008 [38]	56	0/56/0	Periareolar / peritumoral	80	98%/2%	9/45 (20)
Axelsson 2008 [12]	47	43/1/3	Peritumoral ^d	45	24/7	7/20 (35)
Koizumi 2008 [9]	31	16/3/12	Peritumoral	95	61%/36%	4/28 (14)
Schrenk 2008 [15]	23	12/11/0	Peritumoral	63	100%/31%	3/16 (19)
Boughey 2006 ^a [8]	21	12/5/4	Peritumoral	69	100%/46%	1/13 (8)
Karam 2008 ^b [39]	20	11/4/5	Above mastectomy scar	75	15/2	2/13 (15)

^a Included into the review by Palit et al.

^b Re-SLNB after previous mastectomy

^c Tracer injection at the axillary aspect of the recurrence site in the breast

^d Tracer injection sub- or intracutaneously over the tumor

after ALND was only 38%. In addition, the identification of a re-SN was inversely correlated with the number of previously removed lymph nodes. The highest detection rate of 97% was reported by Intra et al. [20] (65 cases); however, only patients with initial breast conserving therapy and SLNB were included in the analysis.

Lymphatic drainage patterns after previous axillary surgery

Based on current reports, four main regions of lymphatic drainage in case of intramammary recurrence have been identified: ipsi- and contralateral axilla, parasternal nodes, as well as infra- and supraclavicular lymph nodes [1, 21–23] (Fig. 1). Extra-axillary lymphatic drainage in case of a re-SLNB was consistently observed in up to 40% of patients (Table 1). The probability of identifying an extra-axillary SN correlated with the number of previously removed lymph nodes. The detection rate reported by Boughey et al. [8] was 50% for patients who had over ten lymph nodes removed, 30% for patients with one to ten lymph nodes and 0% for those who had no previous axillary surgery. Mastectomy also appeared to affect the rate of extra-axillary SN [8]. Van der Ploeg et al. [24] identified extra-axillary drainage in 47% of patients previously treated by BCT and SLNB. Interestingly, the percentage of extra-axillary drainage was highest (60%) in patients who had undergone non-oncological plastic surgery. Intra et al. [20] observed no extra-axillary lymphatic drainage but none of the patients had undergone a complete ALND before. In five of 63 (8%) patients, an additional re-

SN outside the axilla was detected. Nonetheless, all five patients had also axillary re-SN. The type of surgery may also affect SN detection. Boughey et al. [8] reported lower SN identification rates in patients who had undergone previous mastectomy compared with those who had undergone breast-conserving therapy (50% vs. 65%); however, this difference was not significant.

Positive sentinel lymph node in patients with local recurrence

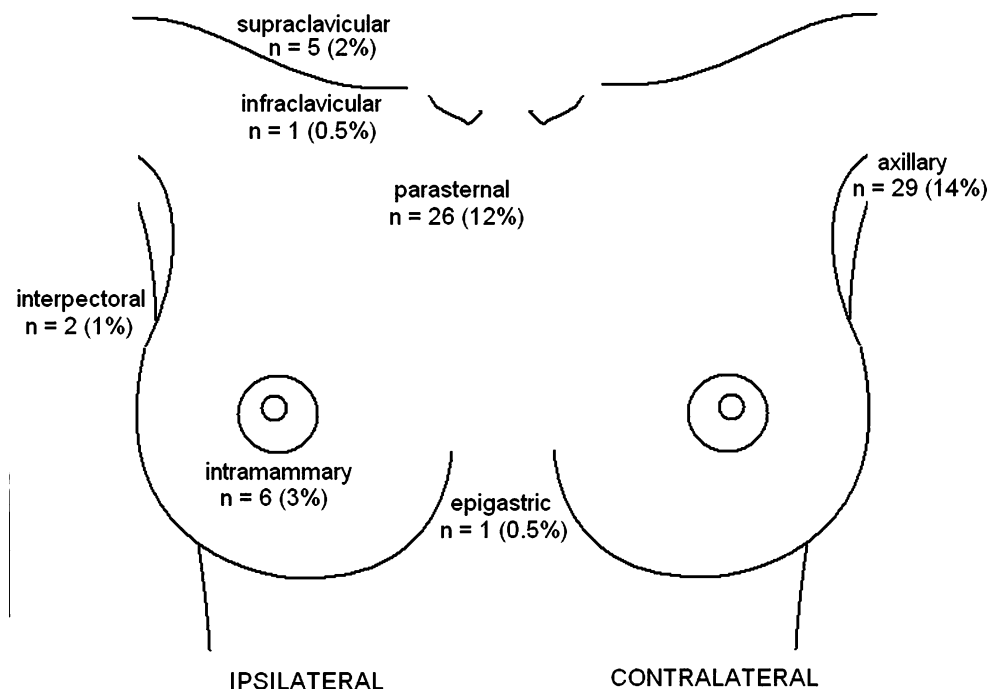
The rate of metastatic re-SN in case of local relapse was observed to be between 8% and 35% (Table 1). The review by Palit et al. [22] reported a mean rate of 15%. Interestingly, in seven out of 31 cases with extra-axillary SN, the lymph node metastasis was localized outside the axilla. In four out of these seven patients, the metastatic node was detected in the contralateral axilla (Table 1).

Discussion

The breast develops new lymphatic drainage patterns after damage to the primary lymphatic system caused by therapy. The topography of this new pattern is significantly more variable than the one of an untreated breast. The exact mechanisms and time needed for a new drainage pattern to evolve remain to be clarified.

According to recent studies, the lymphatic pattern may depend on the type of primary surgery the patient received

Fig. 1 Frequency and localization of extra-axillary sentinel nodes (modified after Palit et al. [22]). Patients number, $n=287$; SN detection rate, 210/287 (73%); extra-axillary SN 68/210 (32%)



previously. The drainage system following oncological therapy (SLNB, ALND, radiation therapy) is notably variable. Consequently, mammary gland tissue and the skin do not necessarily share a common lymphatic drain (in contrast to an untreated breast). Therefore, periareolar or intradermal injection for sentinel node labeling may not match the draining pattern of the tumor. For a re-SLNB a peri- or intratumoral injection seems more appropriate. Further, lymphoscintigraphy (LSG) may contribute to the successful identification of the SN. While the clinical feasibility of LSG in primary breast cancer remains controversial, it vitally contributes to lymphatic mapping in case of local recurrence as these patients are more likely to present with an extra-axillary or contralateral sentinel node [24, 25].

Extra-axillary sentinel nodes

The incidence of extra-axillary drainage after prior treatment mentioned in literature is significantly higher than in non-treated breast and ranges between 20% and 67% [13, 22, 24]. This finding underlines the crucial role of lymphoscintigraphy. It is particularly important since failure to identify an extra-axillary SN may lead to down-staging of the disease and alter treatment decisions [26]. All authors (Table 1) used LSG for preoperative lymphatic mapping. In a study reported by van der Ploeg et al. [24], SPECT/CT was performed when conventional imaging failed to identify an axillary SN. The high incidence of extra-axillary drainage in a recurrent setting is a strong argument for performing a LSG [27]. Preoperative LSG reveals altered drainage patterns and allows sentinel nodes from unpredictable locations to be visualized and biopsied. Otherwise, these are sites of potential nodal involvement that would be overlooked. Thus, re-SLNB and lymphoscintigraphy may improve the surgical staging.

The clinical relevance of extra-axillary SN and, in particular, the internal mammary chain SN is under discussion [28–31]. Further, the feasibility of SLNB of the internal mammary chain nodes remains controversial as its lymphatic pattern lacks regularity observed in axillary lymph nodes. Here, the lymphatic flow from the breast reaches the internal mammary nodes through tiny vessels of each intercostal space. This raises the question of whether the ‘sentinel’ node concept applies to this nodal station, as there is not a node which predicts whether the other lymph nodes are involved. This observation may explain why the use of sentinel node technique in internal mammary chain does not necessarily increase nodal positivity rates (11% in radioguided SLNB group vs. 10% in patients with biopsy of one intercostal space without sentinel technique) [26].

Development of alternative lymphatic patterns depends to some extent on the type of surgery the patient received at

primary operation. Boughey et al. reported increased incidence of alternative drainage in patients with >10 axillary lymph nodes removed previously. Similarly, successful SN detection may depend on the type of axillary surgery. Port et al. [19] from Memorial Sloan-Kettering Cancer Center reported a significantly higher SN detection rate after a previous SLNB than a previous ALND. However, current guidelines do not distinguish between previous SLNB and ALND in recommendations for therapy of local recurrence.

With regard to therapy in patients with only extra-axillary SN, axillary lymph node dissection is typically performed. However, recent studies have shown that such patients may be spared ALND [32]. Several authors suggested that pursuing extra-axillary nodes may improve staging and lead to a better selection of patients who might benefit from radiotherapy to the internal mammary chain and from adjuvant therapy [33, 34]. The German Gynecological Oncology (AGO) breast group currently does not make a recommendation for or against SLNB of the internal mammary chain in primary setting (\pm , level of evidence 2b; Guidelines 2010, www.ago-online.de). In the case of a local ipsilateral in-breast recurrence after previous axillary surgery, AGO recommends against SLNB (level of evidence 3b).

SLNB after plastic breast surgery

Similarly, the practicability of SLNB in women with previous non-oncologic types of breast surgery such as breast augmentation or reduction mammoplasty remains unclear. Guidelines from ASCO and AGO did not make a recommendation for or against SLNB in these cases due to insufficient data (AGO guideline: level of evidence 4). However, recent studies confirm the feasibility of the SLNB technique for identifying the sentinel node in patients with previous esthetic breast surgery. Rodriguez Fernandez et al. reported a SN identification rate of 100% in patients with previous esthetic surgery (augmentation or reduction). All patients underwent lymphoscintigraphy prior to surgery [25]. Several smaller studies suggest that SLNB may also be feasible after transaxillary approach [35, 36]. Interestingly, van der Ploeg et al. [24] describe a high percentage (60%) of extra-axillary drainage in patients who had undergone plastic surgery.

SLNB after radiation therapy

Radiation therapy of the breast or its regional lymph nodes may alter lymphatic patterns. This may have consequences for lymphatic mapping and SN detection afterwards. Recently, van der Ploeg et al. [37] examined lymphatic drainage in 22 breast cancer patients who underwent mantle field radiation therapy for Hodgkin’s lymphoma in the past.

This treatment includes radiation of axillary, supra- and infraclavicular, mediastinal lymph nodes. Lymphatic y4mapping yielded a lymph node in 86% of the patients. Nonvisualization and extra-axillary SN were more frequently encountered than in patients without history of radiation therapy. Similarly, the detection of contralateral sentinel nodes in patients with breast cancer recurrence seems to increase after previous radiation therapy. Koizumi et al. [9] showed lymphatic drainage to contralateral nodes in seven out of ten cases with previous irradiation.

Clinical relevance of lymph node status in recurrent breast cancer

Another important issue is the purpose of SLNB in relapse setting. Up to 35% of patients who are diagnosed with local recurrence have histologically positive lymph nodes. Whether the removal of metastatic nodes may improve local control of the disease, and thus disease-free survival, is currently being debated. Current guidelines do not provide universal recommendations for or against axillary surgery in recurrent cases. Regarding diagnostic value, positive node status may imply more aggressive or advanced disease. Thus, nodal assessment may contribute to optimized staging and improve treatment decisions. Interestingly, a high rate of extra-axillary and even contralateral SN has been observed. The question remains as to whether contralateral re-SN metastasis should be classified as an M1 (palliative) situation or a locally restricted and thus curable disease. Contralateral metastatic lymph nodes are mostly diagnosed after previous axillary dissection [24]. In such cases, contralateral nodes may merely reflect the nearest direct drainage site and not distant metastasis.

What is the clinical and prognostic relevance of positive re-SN status in comparison to primary disease? No consensus has been reached so far regarding the optimal systemic therapy for breast cancer local recurrence. Future studies must clarify whether selected patients' groups benefit from secondary chemotherapy. Reevaluation of lymph node status may provide additional data and thus enable individualized and optimized treatment.

Conclusions

The adequate treatment of lymphatic pathways in the case of ipsilateral breast cancer recurrence remains to be clarified. In primary breast cancer, SLNB is a staging procedure that provides prognostic information for tailored adjuvant treatment. In contrast, the clinical implications of a positive lymph node in the case of a local recurrence are not defined. Chemotherapy is in general not recommended in

this situation. The oncologic significance of positive nodes with respect to prognosis and further tumor spread is unclear. Whether patients with a positive re-SN derive any benefit from adjuvant chemotherapy or radiotherapy is highly speculative and deserves further evaluation.

Current data is insufficient due to small patient groups, inhomogeneous collectives and partly contradictory results. However, review of the literature provides important insights into the development of new lymphatic pathways of the treated breast. Since we will be confronted more often with local recurrences in patients treated only with SLNB, an evidence-based recommendation for re-SLNB is necessary.

Although the role of re-SLNB remains unclear, the following clinical recommendations can be derived from this review: a re-SLNB is feasible in the majority of patients who have undergone previous SLNB. Re-SLNB can be performed in order to detect and remove tumor burden in the lymph nodes. The procedure does, however, not appear mandatory. Axillary dissection is not indicated if an SN cannot be detected.

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