Review Article

Axillary surgery in oncologic breast surgery: a narrative review

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Background and Objective: With the improved survival for breast cancer there is now an increased focus on quality of life after treatment. Axillary surgery is known to be associated with significant risk of arm morbidity feared by the patients, and several studies have shown de-escalation is possible in different settings. In this review, an overview will be given on new techniques and procedures for de-escalation of axillary surgery in breast cancer patients and the subsequent implications for adjuvant systemic treatment.

Methods: This study is a narrative review. PubMed was searched for relevant publications in English published between January 2018–June 2023. Only publications with major impact on clinical practice have been included with main emphasis on meta-analysis. In addition, Clinicaltrial.gov has been searched for on-going studies.

Key Content and Findings: New tracer techniques are described as well as the on-going reduction in axillary lymph node dissection (ALND) at primary surgery even in node positive patients, and the axillary staging possibilities after down-staging of the axilla by neoadjuvant treatment. Finally axillary staging at local recurrence and in case of ductal carcinoma in situ is described.

Conclusions: ALND is no longer routinely recommended in many node positive patients and further de-escalation is investigated. The lack of knowledge on precise axillary status will require cooperating studies between oncologists and breast surgeons in order to avoid escalation of systemic treatment due to the lack of applicability of trial eligibility criteria. Furthermore, investigations on the use of axillary imaging for staging are needed.

Keywords: Breast cancer; axillary surgery; de-escalation

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Introduction

Background

Axillary lymph node dissection (ALND) was previously the standard procedure for staging of the axilla in breast cancer. This procedure is associated with considerable arm morbidity (1,2) and is redundant in women without lymph node metastases. In 1994, the sentinel lymph node dissection (SLND) was introduced in the treatment of breast cancer (3) as a procedure to identify patients without lymph node metastases who could be spared an ALND. It was subsequently confirmed in a randomized trial that SLND could accurately stage the axilla, by removing only few lymph nodes, in clinically node negative breast cancer patients undergoing primary surgery (4). A meta-analysis from 2006, including 69 studies conducted between 1970 and 2003 with data from more than 8,000 patients, did find a detection rate for the sentinel node on 96% and a false negative rate (FNR) on 7.0% (5). In the following years, the use of the procedure in breast cancer rapidly increased and

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Table 1 The search strategy summary

Items	Specification
Date of search	20th of June 2023
Databases and other sources searched	PubMed, Clinicaltrial.gov, References, National Guidelines
Search terms used	1#: invasive breast cancer AND surgery AND sentinel node AND axilla NOT neoadjuvant
	2#: breast cancer AND sentinel lymph node AND technique AND detection rate
	3#: breast cancer AND four node sampling AND false negative rate
	4#: RCT AND breast cancer AND sentinel node AND metastases
	5#: invasive breast cancer AND sentinel node biopsy AND neoadjuvant
	6#: invasive breast cancer AND sentinel node biopsy AND neoadjuvant AND radiotherapy AND axillary surgery
Timeframe	January 2018–June 2023
Inclusion criteria	Only English, mainly meta-analysis and systematic reviews were included when available
Selection process	Selected by main author

RCT, randomised controlled trial.

has now replaced ALND as standard procedure for staging of the axilla in clinically node negative primary breast cancer. The introduction of the SLND in breast cancer treatment spares each year hundreds of thousands of women an ALND and the following risk of arm morbidity (2). Numerous studies have shown that the risk of lymphedema and arm morbidity associated to ALND can be reduced by the SLND. In a meta-analysis from 2013 based on 72 studies it was shown that the incidence of lymphedema was 16.6%: 19.9% after ALND but only 5.6% after SLND (6).

Rationale and knowledge gap

With the improved survival for breast cancer and the increasing focus on quality of life after treatment efforts should continue in de-escalating axillary surgery. New tracer techniques for the sentinel node procedure have been introduced during recent years, and further de-escalation of axillary surgery after neoadjuvant treatment (NACT), in case of ductal carcinoma in situ (DCIS) or non-detection of sentinel node and at local recurrence is being investigated. The significance of this de-escalation for the decision for adjuvant treatment is basically unknown.

Objective

In this review, an overview will be given on new techniques and procedures for further de-escalation of axillary surgery in breast cancer patients and the subsequent implications for adjuvant treatment. I present this article in accordance with the Narrative Review reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-362/rc).

Methods

A PubMed search with keywords (invasive breast cancer AND surgery AND sentinel node AND axilla NOT neoadjuvant) and (breast cancer AND sentinel lymph node AND technique AND detection rate) and (breast cancer AND four node sampling AND false negative rate) and (RCT AND breast cancer AND sentinel node AND metastases) and (invasive breast cancer AND sentinel node biopsy AND neoadjuvant) and (invasive breast cancer AND sentinel node biopsy AND neoadjuvant AND radiotherapy AND axillary surgery) was conducted for the period January 2018–June 2023. Relevant publications in English were screened manually for their title, abstract, and even full text to determine their true relevance. Articles on the development of axillary staging in breast cancer were identified. References from the searched articles and other supplementary articles were also studied.

Only publications with major impact on clinical practice have been included with main emphasis on meta-analysis. In addition, Clinicaltrial.gov has been searched for on-going studies. For summary of search strategy see *Table 1*.

Tracer technique

The most commonly used method for detection of the sentinel node is the use of radioactive tracer, often in combination with blue dye. A significantly higher detection rates has been found when using a combination of both tracers. A meta-analysis including 11 studies with 1,236 patients found a detection rate of 85% with the use of blue dye alone, 94% with the use of radioactive tracer and 95% with a combination of blue dye and radioactive tracer (7). A high detection rate of the sentinel node is crucial due to a current recommendation of ALND in case of non-detection of sentinel node. In recent years, several new tracers have been introduced without the use of radioactivity. These were compared in a meta-analysis from 2019 (8). When using indocyanine green (ICG) fluorescence a detection rate of 97.9% was found, and for superparamagnetic iron oxide the detection rate was 97.4%. However, these new tracers have some limitations. Studies have shown a higher average number of removed sentinel nodes when using ICG compared to radioactive tracer and blue dye, due to diffusion of ICG to other lymph nodes if the time between injection and removal of the lymph nodes is too long (9,10). When using the superparamagnetic tracer, metal instruments cannot be used during SLND, and the tracer can produce artefacts on a subsequent magnetic resonance imaging (MRI). These limitations should be considered when using the tracers. It should be noted that the superparamagnetic tracer has the advantage of remaining in the sentinel node for a longer period which can be used in delayed axillary staging of patients with DCIS upstaged for invasive cancer at surgery.

De-escalating axillary surgery

Omission of ALND at primary surgery

The possibility of a more extensive examination of the fewer lymph nodes removed by SLND in clinically node negative breast cancer patients resulted in identification of more micrometastases and isolated tumor cells (ITCs) (11). The prognostic gain from removing additional lymph nodes by ALND in these patients was soon questioned. Two large American cohort studies from the Surveillance Epidemiology, and End Results (SEER) database, including 6,838 patients with micrometastases (12), and from the National Cancer Database (NCDB), including 2,203 patients with micrometastases (13), compared the prognosis of patients with micrometastases in the sentinel node with and without ALND. No significant difference was found in overall survival and axillary recurrence rate. In addition, a Danish cohort study including 2,074 patients with micrometastases or ITC in the sentinel node from the Danish Breast Cancer Group (DBCG) database, where adjustments were made for comorbidity and adjuvant treatment, found no significant difference in axillary recurrence or survival between patients with and without ALND (14). Finally, results from two randomized European trials on patients with micrometastases or ITC in the sentinel node randomized to ALND or no further treatment of the axilla; the European IBSCSG 23-01 study with 934 patients (15) and the Spanish AATRN 048/13/2000 trial with 233 patients (16), found no difference in axillary recurrence rate or survival between groups. The axillary recurrence rate was very low on 1–2%. Based on these studies, ALND is no longer recommended for patients with micrometastases or ITC in the sentinel node.

Subsequently, randomized trials were initiated including clinically node negative breast cancer patients with macrometastases in the sentinel node. In the American ACSOG Z0011 study, included patients with breast-conserving surgery and up to two positive sentinel nodes, patients were randomized to either ALND or no further treatment of the axilla (17). No difference in loco-regional recurrence, overall survival and disease-free survival was found after 10 years of follow-up. However only 60% of the included patients had macrometastases in the sentinel node. In the Italian SINODAR-ONE study, 889 patients were included; all with macrometastases in the sentinel node. No difference in 3-year survival or risk of recurrence was found between patients with and without ALND (18); 25% of patients in this study had a mastectomy.

In the European AMAROS trial (19), and the Hungarian OTOASOR trial (20), including 1,425 and 526 patients respectively, with sentinel node metastases, patients were randomized to either ALND or axillary radiotherapy. No difference in axillary recurrence or survival after 10 and 8 years of follow-up respectively was seen. Again only 60% of patients had macrometastases and only 18% underwent mastectomy. To further substantiate the evidence of omitting ALND in patients with macrometastases in the sentinel node, the SENOMAC trial (21) and the POSNOC study (22) have randomized patients with macrometastases in 1–2 sentinel nodes to either ALND or no further axillary surgery. Inclusion has now been completed and the results are awaited. Today, the St Gallen consensus guidelines no longer recommend ALND in clinically node negative

breast cancer patients with T1–T2 and one or two positive sentinel nodes treated by breast-conserving surgery and radiotherapy or mastectomy and axillary radiotherapy (23).

ALND is still recommended in breast cancer patients diagnosed as node positive by preoperative histologic confirmation. This group of patients is being considered having larger metastatic burden in the axilla. Larger cohort studies have compared the tumor burden in the axilla of breast cancer patients who were diagnosed as node positive by preoperative histologic confirmation, with patients who were diagnosed as node positive by SLND and found that patients diagnosed as node positive preoperatively had a significantly larger metastatic burden in the axilla (24-26). The randomized TAXIS trial is currently investigating whether ALND can be replaced by axillary radiotherapy in patients with histologically confirmed node positive disease. In this study, the metastatic lymph node is marked before surgery and removed together with the sentinel node at surgery. Patients are then randomized to either ALND or axillary radiotherapy (27) (ClinicalTrials.gov Identifier: NCT03513614). Until the results of this study might allow reduction of ALND in this group of patients, the only possibility to reduce axillary surgery in clinically node positive patients is down-staging by NACT.

Omission of axillary staging at primary surgery

Recently, randomized studies have been initiated to investigate whether axillary surgery can be completely omitted at primary surgery in patients who are clinically node negative, e.g., the Italian SOUND study (ClinicalTrials.gov: NCT02167490), the German INSEMA study (ClinicalTrials.gov: NCT02466737) and the Dutch BOOG 13-08 study (ClinicalTrials.gov: NCT02271828). Results from most of these studies are not yet available and the St Gallen Guidelines continue to recommend staging with SLND at primary surgery for all clinically node negative breast cancer patients (23). In 2023 the first results on 5-year distant disease-free survival were published from the SOUND trial, including 1,405 clinically node negative breast cancer patients with tumor size <2 cm, randomized to SLND or no axillary surgery (28). No significant difference was found between groups, indicating that axillary surgery can be safely omitted in breast cancer patients with small, clinically node negative disease. The question that remains to be answered is how to handle the missing information on precise nodal status when planning adjuvant treatment in these patients.

Non-detection of sentinel node

Despite the high detection rate of new tracers, the sentinel node is not detected in a few percent of the patients. Recommendations for management of patients with non-detection of the sentinel node is non-existing in most international guidelines, and if described, ALND is recommended. There is only sparse evidence on the proportion of patients with metastases in the axilla in case of non-detection of the sentinel node. A Dutch cohort study included 76,472 patients, of whom 1,924 (2.5%) had non-detection of the sentinel node. Of these, 1,552 subsequently underwent ALND (29); 22% of these patients had lymph node metastases whereof half had three or more metastatic lymph nodes. In a multivariate analysis, non-detection was significantly associated with risk of spread to three or more lymph nodes [odds ratio (OR) =2.86]. In a Danish cohort study including 20,498 patients (30), 242 (1.2%) patients had non-detection of the sentinel node, 92 of these patients (38%) had metastases at the subsequent ALND. This proportion of axillary metastases is comparable to the proportion of patients having non-sentinel node metastases if macrometastases is found in the sentinel node. As many guidelines no longer recommend ALND in patients with breast conserving surgery and 1–2 macrometastases in the sentinel node, is seems reasonable to look for alternative staging methods than ALND for patients with non-detection of the sentinel node.

Before the introduction of SLND for axillary staging in breast cancer, the procedure "Low axillary sampling" or "four node sampling" was studied for staging of the axilla (31,32). In 2001, MacMillan *et al.* found that lymph nodes removed by four node sampling contained the sentinel node in 80% of the 200 included patients (33) and in 2006 Tanaka *et al.* compared four node sampling with ALND for staging of the axilla in 237 patients and found sampling as accurate as ALND with an FNR for sampling of 7.1% (31). Likewise in 2002, Ahlgren *et al.* found that five node sampling was as accurate as ALND in 415 patients with screening-detected breast cancer with an FNR of 6.7% (34). Finally in 2013, Parmar *et al.* did show that level I axillary sampling was as accurate as SLND for staging the axilla in 478 clinically node negative breast cancer patients (32). It is likely that some degree of publication bias exists for studies where axillary sampling have shown a high FNR. In addition, the sampling procedure is not well-defined in the mentioned studies. In some studies, the axillary level I is removed, in others lymph nodes are removed in the area where the

sentinel node is expected to be found, while others remove a certain number of lymph nodes, usually four, from level I. Still, four node sampling could be a loophole for avoiding ALND in case of non-detection of the sentinel node and has now been re-introduced as method for axillary staging in case of non-detection of the sentinel node in breast cancer surgery in Denmark.

Significance of de-escalating axillary surgery on adjuvant treatment

In the effort to de-escalate axillary treatment to save patients from the risk of maybe life-long arm morbidity (2) the total number of positive axillary lymph nodes will be unknown in an increasing number of patients, and the selection of patients who benefit from adjuvant chemotherapy will be hampered.

Axillary nodal status is one of the most important prognostic factors in breast cancer. Accordingly, nodal status is included in the decision for adjuvant systemic treatment. This has become increasingly important along with the more tailormade approach for different risk subgroups to avoid overtreatment. Especially de-escalation of adjuvant chemotherapy in patients with estrogen receptor (ER) positive, human epidermal growth factor receptor 2 (HER2) negative subtypes has received increasing attention during recent years. The benefit from adjuvant chemotherapy in patients with luminal subtypes and 1–3 positive nodes has been investigated in the RxPONDER trial and the MINDACT trial (35,36). Based on these results the St Gallen guidelines no longer recommend routine use of adjuvant chemotherapy in postmenopausal ER positive, HER2 negative patients with 1–3 lymph node metastases and a low genomic risk signature (23). In case of four or more lymph node metastases adjuvant chemotherapy is recommended to all postmenopausal ER positive, HER2 negative patients.

Likewise, the treatment with abemaciclib has been shown to decrease risk of recurrence in ER-positive, HER2 negative, node-positive, high-risk breast cancer patients in the MonarchE trial. High-risk patients were defined as having either four or more positive axillary lymph nodes, or between one and three positive axillary lymph nodes and either grade 3 disease or tumor size of 5 cm or larger (37).

To implement the results of these trials, a complete axillary status with exact number of positive nodes is needed to identify patients for de- or escalation of adjuvant treatment. The impact of omitting ALND in node positive breast cancer patients on the recommendations for adjuvant treatment has until now only been sparsely investigated, and the magnitude and impact on prognosis is basically unknown.

Weber *et al.* have recently investigated the omission of ALND on the recommendation for adjuvant systemic treatment in the TAXIS trial (27). They found no significant impact on adjuvant treatment between treatment arms (38). Patients included in the TAXIS trial is however diagnosed as node positive preoperatively. This group of patients is expected to have a higher tumor burden in the axilla compared to clinically node negative patients (25). The majority of node positive breast cancer patients, where ALND is no longer recommended, is however clinically node negative but with macrometastases in the sentinel node. The impact of omitting ALND on adjuvant treatment in this group is expected to be even smaller than in the TAXIS trial. When comparing clinically node negative patients with macrometastases in the sentinel node randomized to either ALND or axillary radiotherapy in the AMAROS trial and in the OTOASOR trial no significant difference was found in the administration of adjuvant systemic treatment between groups (39,40). The indication for adjuvant chemotherapy was based on Adjuvant Software and institutional protocols respectively. Since then, the use of genomic testing and Recurrence score have been included in the guidelines.

The decision for adjuvant systemic treatment will be further challenged with the expected results from trials investigating complete omission of axillary staging, like the SOUND trial (28). The significance of de-escalating axillary surgery in today's adjuvant setting is basically unknown and should be investigated in planned clinical trials concerning de-escalation of axillary surgery.

Axillary staging after NACT

The feasibility and accuracy of axillary staging with SLND in patients treated by neoadjuvant chemotherapy has been questioned. Fibrosis of the lymphatic vessels due to treatment response and an un-even response to chemotherapy in different lymph nodes have been proposed. Nevertheless, studies have shown a high detection rate above 90% of the sentinel node (41) and SLND is now considered as feasible after NACT. The FNR for SLND varies between patients with cN0 and cN1 disease before NACT. A meta-analysis Geng *et al.* from 2016 (41) including patients who were cN0 before NACT found an

FNR of 6% which is comparable to the FNR for patients with SLND at primary surgery. In addition, the prospective French multicenter study, GANEA2, included 419 clinically node negative patients staged by SLND after NACT, with omission of ALND if no metastases were found in the sentinel node. Only one axillary recurrence was observed after 3 years of follow-up (42). According to these studies, the SLND is now considered safe for axillary staging after NACT in clinically node negative breast cancer patients.

Four prospective studies have investigated the accuracy of the SLND after NACT in patients who are cN1–N2 before NACT. In the American ACOSOC Z1071 study, 687 breast cancer patients with metastases to the axilla before NACT underwent SLND and ALND after NACT. The detection rate for the sentinel node was 92.9% and the FNR 12.6% (43). In the German SENTINA study, a group of 360 patients with metastases to the axilla before NACT had a detection rate of 80% for the sentinel node after NACT and an FNR of 14% (44). The Canadian SN-FNAC study, including 153 node positive patients, found a sentinel node detection rate of 87.6% and an FNR of 13.3% after NACT (45). However, the FNR was only 9.6% if patients with ITC in the sentinel node were considered node positive. In the French GANEA2 study, 351 patients were included who were clinically node positive before NACT, who were staged with SLND and ALND after NACT. The detection rate was 79.5% and the FNR was 11.9% (42). All four studies found a lower FNR if more sentinel node were removed, or if two tracers were used. However, it is often not technically possible to remove more than 1–2 sentinel nodes during surgery (46). Studies suggest that marking of the metastatic lymph node before NACT and removal of this marked lymph node along with the sentinel node after NACT [called targeted axillary dissection (TAD)] can lower the FNR for axillary staging after NACT to the same level or lower than for SLND at primary surgery. A systematic review and meta-analysis from 2022 included a total of 30 studies where clinically node positive patients treated by NACT were staged by TAD at surgery. The review included a total of 1,920 patients, of whom 849 underwent ALND. There was an overall FNR for the TAD of 5.5% (47). The largest study to date investigating the FNR for TAD after NACT is the Dutch prospective RISAS study. They found an FNR on 2.5% (48).

There is still only limited evidence on the risk of axillary recurrence after staging with TAD without subsequent ALND. An abstract from SABCS 2022 of the EUBREAST-06 study showed that only 0.5% of 478 cN^+ patients staged with TAD after NACT without subsequent ALND developed axillary recurrence after 3 years of follow-up (49). It should be noted that the recurrence rate after SLND alone, with removal of three or more sentinel nodes, was not significantly different from the recurrence rate after TAD. In addition, an Italian study, investigating 222 patients being node positive before NACT and staged by SLND alone after NACT, found a recurrence rate on less than 2%, despite 74% having ≤2 sentinel nodes removed. This indicates that the high FNR found in previous studies when staging cN^+ patients with SLND alone after NACT does not translate into a high risk of axillary recurrence (50). The recurrence rate of node positive breast cancer patients treated by NACT and staged as node negative after NACT with omission of ALND, is now investigated in the ongoing prospective Dutch MINIMAX study (clinicaltrials.gov ID NCT04486495) and the European prospective multicenter study AXSANA (clinicaltrials.gov ID NCT04373655), to determine the optimal staging procedure and treatment of these patients.

Several methods exist for marking of the malignant lymph node at TAD. This can be done as a two-step procedure with clip-marking of the metastatic lymph node before NACT and re-marking with a surgically detectable marker before surgery using radioactive iodine seed, magnetic seed, hooked wire, radiofrequency identifiers, markings using radar reflection or ink marking on the skin. However, studies have shown highly variable detection rates for the marked lymph node when remarking before surgery, especially in case of pathological complete response (pCR) of the lymph node, diminishing the contrast between coil and lymphatic tissue (51,52). This challenge is eliminated by using a one-step marking procedure placing a marker that will still be surgically detectable at surgery before NACT. This marker must not interfere with MRI performed during NACT. A radioactive iodine seed (46) or markers using radar reflection (53) can be used as a one-step marker.

Residual tumor cells in the lymph nodes after NACT may represent chemotherapy-resistant disease and is associated with a poorer survival. In the American NSABP B18 study patients with macro- or micrometastases (<2 mm) after NACT had a significantly worse survival than patients who became node negative (54). In addition, patients with micrometastases and ITCs after NACT have a high incidence of non-sentinel node metastases (55). In a retrospective cohort study of 702 patients, non-sentinel node metastases were found in 64% of the patients with micrometastases in the sentinel node and in 17% of

patients with only ITC in the sentinel node. However, it should be mentioned that the result in the ITC group was based on only 6 patients. Due to an expected high risk of residual, chemotherapy-resistant metastatic burden in the axilla after NACT, ALND is recommended in most centers in case of residual metastases found at axillary staging after NACT. The risk of axillary recurrence and survival after NACT, if ALND is omitted despite metastases found at staging, is currently being investigated in several studies. In the prospective Italian NEONOD 2 study, ALND is performed for macrometastases in the sentinel node, but no further treatment in case of ITC or micrometastases (56). The primary endpoint is disease free survival. The retrospective OPBC-05/EUBREAST-14R/ICARO study, includes patients with residual ITC after NACT treated with either ALND, axillary radiotherapy or observation and is investigating 3-year axillary recurrence rate. In the American ALLIANCE A011 202 study (ClinicalTrials.gov identifier: NCT01901094), patients with limited residual metastases in the sentinel node after NACT are randomized for ALND or axillary radiotherapy, to compare recurrence free survival. In this trial patients with ITC are treated as node negative. Likewise, in the TAXIS trial (27), survival is compared for node positive patients with residual disease in the axilla staged by targeted axillary surgery after NACT. Patients are randomized to either ALND or axillary radiotherapy. Here, however, patients with ITC are also included. Results from these trials might allow further de-escalation of axillary surgery after NACT by replacing ALND by axillary radiotherapy in patients with residual disease in the axilla.

The axillary response to NACT vary between subtypes and only around 15–20% of node positive patients with luminal subtypes will achieve an axillary pCR (57). This means that patients with luminal subtypes and 1–2 positive lymph nodes, who could be spared an ALND if offered primary surgery, would most likely be offered an ALND after NACT. As long as ALND is recommended for all patients with residual axillary metastases after NACT, these patients will get more and not less axillary surgery after NACT. This should be taken into consideration when planning treatment.

Axillary staging at recurrence

After several decades with the use of SLND as staging procedure in primary breast cancer, a small proportion of patients is now coming back with a local recurrence, who still have the majority of their lymph nodes left in the axilla. Previously, ALND was recommended in these patients due to uncertainty of the reliability of SLND after prior axillary surgery. Today, no consensus guidelines exist on the optimal axillary staging procedure in case of local recurrence. It could be argued that the lymphatic pathways have been interrupted and/or damaged by the first surgical procedure and/or subsequent radiotherapy (58). This could result in a less feasible and accurate SLND in these patients. Smaller studies suggest that re-SLND is reliable in patients who have previously undergone SLND and as a method for identifying lymphatic metastases in patients with locally recurrent breast cancer who have previously undergone ALND. A systematic review from 2018 includes 34 of these studies with a total of 1761 patients with ipsilateral local recurrence where re-SLND had been used (59); 48% of the patients had previous surgery with SLND and 47% had previous surgery with ALND, while 5% had no previous axillary surgery. The detection rate for SLND was 75.7% after previous SLND, but somewhat lower (46.1%) after previous ALND. The FNR was only 4.1%. Only 1.3% patients had an axillary recurrence after in average 31.7 months of follow-up. Information on adjuvant treatment was available for 296 patients. Of these, 116 were node positive after re-SLND. In 63.8% of these patients, re-SLND led to a change in the adjuvant treatment. Re-SLND is thus both technically possible and safe and leads to a change of adjuvant treatment. One thousand six hundred and eighty-seven patients underwent scintigraphy prior to surgery with re-SLND. Sentinel node was identified by scintigraphy in 64.7%; 39.2% of patients had aberrant drainage, 19.8% after previous SLND, and 72.6% after previous axillary drainage. It is therefore recommended to perform scintigraphy prior to re-SLND to increase the detection rate.

No studies so far have investigated whether ALND can be omitted, or replaced by axillary radiotherapy in patients with no previous irradiation, in case of metastases at re-SLND.

Axillary staging of patients with DCIS

Around 1/4 of patients with DCIS on preoperative biopsy are upstaged to invasive cancer at final postoperative pathology and should be offered axillary staging (60,61). In a retrospective Danish multicenter study, 34% of patients who were upgraded to invasive carcinoma had metastases in the axilla, of which 36% had macrometastases (60). The

risk of axillary metastases is thus not insignificant in patients with DCIS who are upgraded to invasive carcinoma. Several risk factors have been suggested for upstaging of DCIS to invasive cancer at final pathology. In a meta-analysis by Brennan *et al.* mass-forming DCIS, DCIS >2 cm and high grade DCIS were significantly associated with upstaging to invasive carcinoma (61). The increased risk of upstaging to invasive carcinoma in these patients could justify removal of the sentinel node at primary surgery for DCIS. SLND is also recommended in patients where the lymphatic drainage for the sentinel node may be hampered by the planned surgery for DCIS, e.g., mastectomy (60,61).

It has been shown that the risk of arm morbidity is significantly lower after SLND than after ALND. Still, removal of the sentinel node it not without risk of morbidity (6). Even when limiting axillary staging to patients with DCIS with high risk of upstaging to invasive carcinoma, some of these patients will be offered a redundant SLND.

In contrast to a radioactive tracer, the superparamagnetic tracer remains in the sentinel node for weeks after injection allowing the sentinel node to be detected and removed after the pathological results from primary surgery is known without a new tracer-injection. The feasibility of this concept has been shown in the SentiNot Study including 254 patients (62), and a multicenter randomized trial, SentiNot 2.0, has been initiated. Removing the sentinel node at a second surgery in case of DCIS with invasion is found at final histopathology, can spare patients with only DCIS on final histopathology an SLND, thereby de-escalating axillary surgery in DCIS patients.

Conclusions

With the improved survival for breast cancer there is now an increased focus on quality of life after treatment. Accordingly, treatment should be de-escalated wherever possible without affecting prognosis. Axillary surgery is known to be associated with significant risk of arm morbidity feared by the patients, and several studies have shown de-escalation possible in different settings. ALND is no longer routinely recommended in many node positive patients. Patients diagnosed as node positive by imaging before surgery can be offered NACT and subsequent axillary staging to verify a possible axillary complete response permitting omission of ALND, and in patients diagnosed as node positive by SLND, ALND can be replaced by axillary radiotherapy. Still knowledge gaps exist, and more evidence is needed on handling of patients with non-detection of the sentinel node and on the safety of complete omission of axillary surgery in selected patients. In addition, only limited evidence exists on whether the de-escalation of axillary surgery can be extended to patients with local recurrence. The de-escalation of axillary surgery will however lead to a lack of knowledge on precise nodal status. This will require cooperating studies between oncologists and breast surgeons in order to avoid escalation of systemic treatment due to the lack of applicability of trial eligibility criteria. A possible solution for axillary staging without axillary surgery could lay in the evolving and increasingly more precise imaging modalities. However, imaging of the axilla is beyond the scope of this review.

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Footnote

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