Review Article

De-escalation of axillary treatment in early breast cancer—a narrative review of current trials

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Background and Objective: In the era of de-escalation and minimally invasive locoregional treatments across many fields of surgical oncology, the treatment of the axilla in breast cancer has garnered significant interest. While the knowledge of axillary lymph node involvement is crucial for multidisciplinary management, the surgical approach to the axillary basin can have potential disadvantages that may impact the quality of life. The objective of this narrative review is to examine studies about de-escalation of axillary treatment in various clinical scenarios, namely the settings of upfront surgery and neoadjuvant systemic treatments. Moreover, trials investigating omission of axillary surgery were examined.

Methods: As of July 2024, a comprehensive literature search, compilation, and analysis were conducted across PubMed, Scopus, Web of Sciences, and ClinicalTrials.gov.

Key Content and Findings: In patients with clinically node-negative lymph nodes and up to two positive sentinel nodes, avoiding axillary lymph node dissection is a safe option. As for patients receiving neoadjuvant systemic treatment, axillary lymph node dissection is unnecessary if no residual tumor burden remained in the lymph nodes after surgery. Additionally, studies have shown that axillary radiotherapy can be as effective as axillary dissection in certain cases. The avoidance of any axillary surgery might be proposed to highly select sub-groups patients with small tumors and negative on clinical and ultrasound evaluation lymph nodes.

Conclusions: To date, determining the appropriate axillary treatment remains a complex decision that must be made by multidisciplinary teams with expertise in personalized breast cancer treatment.

Keywords: Breast cancer; axillary lymph nodes; surgery; radiotherapy; neoadjuvant

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Introduction

Axillary status continues to remain one of the most powerful predictors of survival in breast cancer, hence its knowledge plays a fundamental role in multidisciplinary strategy for patients at all stages of the disease. From the 1990s, systematic axillary lymphadenectomy (ALND), has been progressively replaced by sentinel node biopsy (SNB), with the aim of achieving knowledge about the state of axillary lymph nodes without removing the entire axillary basin in patients with no axillary metastases (1-3). In the last decade, the management of axillary nodes in breast cancer has further evolved, such that necessity of performing the SNB

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Table 1 The search strategy summary

Items	Specification
Date of search	15/07/2024
Databases and other sources searched	PubMed, Scopus, Web of Sciences, ClinicalTrials.gov
Search terms used	"breast cancer", "early", "clinical trial", "axillary lymphadenectomy", "sentinel node biopsy", "radiotherapy, "de-escalation", "neoadjuvant"
Timeframe	January 2009–July 2024
Inclusion and exclusion criteria	Inclusion criteria: (I) articles focused on early breast cancer; (II) articles discussing innovative clinical trial designs; (III) English language; (IV) humans; (V) last 15 years
	Exclusion criteria: (I) non-English articles; (II) reviews, editorials, letters, conference abstracts; (III) non-human studies; (IV) articles not focused on breast cancer or clinical trial design innovations; (V) studies including patients with stages IIIB or beyond
Selection process	The screening and selection were conducted independently by two reviewers. Any disagreements were resolved by discussion and consensus

in all invasive breast cancers and the imperative to carry out an ALND in all patients with SNB involvement have been questioned.

It is not surprising that in the current era of de-escalation of breast cancer management, the treatment of axilla represents a focal point. In fact, the advances in the understanding of the biological behavior of breast cancer subtypes, as well as the advent of targeted therapies, paved the way for further de-escalation of axillary interventions, mostly for patients with no or minimal nodal disease (4-8).

This review aims to report findings from recent clinical trials evaluating the clinical outcomes of reduced axillary treatment in patients with early-stage breast cancer. For clarity, we identified three different scenarios: upfront surgery, neoadjuvant systemic treatments, and omission of axillary surgery. We present this article in accordance with the Narrative Review reporting checklist (available at https://tbcr.amegroups.com/article/view/10.21037/tbcr-24-45/rc).

Methods

We performed an extensive search across major databases to identify trials on de-escalation of axillary treatment published over the past 15 years in patients with early breast cancer, i.e., stage I, stage IIA, stage IIB, and stage IIIA breast cancers. We applied stringent criteria to screen and select articles for inclusion. Studies that also included patients with stages IIIB or beyond were excluded. The search strategy is detailed in *Table 1*. Additionally, relevant guidelines were reviewed to complement the literature review. This comprehensive approach enabled us to compile a representative collection of studies to support the discussion in this review.

Management of positive lymph nodes in patients who undergo upfront surgery

The advent of SNB marked a fundamental change towards the improvement in quality of life of women affected by breast cancer. For years, the treatment of early breast cancer involved ALND in case of histologically-proven positive SNB or omitting resection of the axillary lymph nodes when SNB revealed no evidence of cancer cells. That clinical practice has allowed for the sparing of ALND to the majority of breast cancer patients, thus avoiding or minimizing the morbidity of complete axillary removal, including lymphedema, nerve damage, reduced mobility in the shoulder and arm, and chronic pain (3). Shortly after the introduction into clinical practice of the SNB, the actual requirement to perform complete ALND in presence of micrometastases (i.e., metastases greater than 0.2 mm but no more than 2 mm) or isolated tumor cells (ITCs) in the sentinel node was questioned (4,9). The main studies focusing on axillary staging in the setting of upfront surgery are summarized in *Table 2*.

The IBCSG 23-01 Trial was designed to determine whether ALND could be safely omitted in breast cancer patients having micrometastases in the sentinel lymph

Table 2 Trials investigating the management of positive lymph nodes in patients who undergo upfront surgery

Study	Type of trial	Eligibility criteria	Patient groups	Primary endpoint	Status
IBCSG 23-01 (9)	Phase III randomized controlled trial	cT1–T2, N0 with one or more micrometastatic SN	• ALND • No ALND	Disease-free survival	Concluded
ACOSOG Z0010 (10)	Prospective, multicenter study	cT1–T2, N0, who had BCS, SNB, and breast RT	• SN metastases • SN-negative • Bone marrow micrometastases	Overall survival	Concluded
AATRM 048/13/2000 (11)	Randomized clinical study	T <3.5 cm, cN0, with SN micrometastasis	• ALND • No ALND	Disease-free survival	Concluded
MIRROR (12)	Retrospective cohort study	Early-stage BC with either ITCs, micrometastases, or no nodal involvement	• pN0(i–) without AST • pN0(i+)/pN1mi without AST • pN0(i+)/pN1mi with AST	Disease-free survival	Concluded
ACOSOG Z0011 (13)	Randomized controlled trial	cT1–T2, N0 with 1 or 2 SN containing metastases, who had BCS and breast RT	• SN alone • ALND	Overall survival	Concluded
SINODAR-ONE (14)	Randomized controlled trial	T1–T2 undergoing either BCS or mastectomy, with one or two macrometastatic SN	• ALND followed by adjuvant therapy • SN alone followed by adjuvant therapy	Overall survival	Re-opened, ongoing
POSNOC trial (15)	Randomized controlled trial	T ≤5 cm, with one or two SN with macrometastases	• Adjuvant therapy alone • Adjuvant therapy plus ALND or axillary RT	Five-year axillary recurrence rate	Ongoing
SENOMAC (16)	Randomized controlled trial	cN0 breast cancer and 1–2 SN macrometastases, undergoing either BCS or mastectomy	• SN alone • ALND	Breast cancer-specific survival at 5 years	Concluded
AMAROS (17)	Randomized clinical trial	cT1–T2, N0, with positive SN	• ALND • Axillary RT	Five-year axillary recurrence	Concluded
OTOASOR (18)	Randomized clinical trial	cT <3 cm, N0, with positive SN	• ALND • Regional nodal irradiation	Axillary recurrence-free survival	Concluded

SN, sentinel node; ALND, axillary lymph node dissection; BCS, breast conserving surgery; SNB, sentinel node biopsy; RT, radiotherapy; BC, breast cancer; ITCs, isolated tumor cells; AST, adjuvant systemic therapy.

nodes. Participants were randomly allocated to either ALND or no additional axillary treatment beyond SNB. The primary endpoint was disease-free survival, while secondary endpoints included overall survival and the occurrence of lymphedema. The results of the trial showed that there was no difference in disease-free survival between the patients submitted to ALND and those that did not receive further axillary treatment. The findings of the IBCSG 23-01 trial have greatly influenced the surgery of breast cancer towards a more conservative approach to axillary lymph nodes with minimal metastatic disease (9,19).

The American College of Surgeons Oncology Group (ACOSOG) Z0010 trial showed that the detection of occult metastases in sentinel nodes and bone marrow did not significantly affect survival, implying a restricted impact of these findings on management strategy of breast cancer (10).

The treatment of micrometastatic disease in the SNB was also addressed by the prospective randomized clinical trial AATRM 048/13/2000. Patients with T<3.5 cm, N0

and micrometastases in the SNB were randomly assigned to either ALND or clinical follow-up. The results showed no differences in disease-free survival and no cancer-related deaths among the two study groups, suggesting that SNB effectively control locoregional and distant disease (11).

The MIRROR trial aimed to evaluate the clinical relevance of micrometastases and ITC in sentinel nodes in terms of disease-free survival and overall survival in patients with early breast cancer. Patients received no further axillary treatment or ALND or radiotherapy, based on the presence of micrometastases or ITC. The finding of the trial showed that patients with micrometastases or ITC who did not receive additional axillary treatment (ALND or radiotherapy) had slightly worse outcomes than those who did, although the difference was not substantial to alter clinical practice decisions. However, the trial demonstrated that even minor load of cancer cells in sentinel nodes could have prognostic significance (12).

The ACOSOG Z0011 was a crucial clinical study that has greatly impacted the management of axillary lymph nodes in breast cancer surgery. This study investigated whether ALND could be safely omitted in patients with one or two metastatic sentinel lymph nodes. Patients with clinical T1–2N0M0 breast cancer undergoing lumpectomy with planned whole-breast irradiation, having one or two metastatic sentinel nodes, were randomized to receive either standard ALND or no further axillary treatment. The results revealed no significant differences in overall survival or disease-free survival between the two groups over a median follow-up of 6.3 years. In detail, the 5-year disease-free survival was 83.9% in the SNB group in comparison to 82.2% in the ALND group. The 5-year overall survival was about 92.5% in the SNB alone group and 91.8% in the ALND group. These findings revealed that ALND might not be mandatory for all patients receiving lumpectomy and radiation therapy with limited sentinel node metastasis (13,20,21). The ACOSOG Z0011 trial has significantly influenced the clinical management of breast cancer, prompting less invasive strategies for axillary surgery in patients receiving breast conserving surgery. Several national breast cancer treatment guidelines now advise against standard ALND for patients who meet the Z0011 criteria, focusing on a tailored treatment approach that reduces morbidity linked to lymph nodes complete removal while still ensuring effective cancer control. Despite the widespread dissemination of the ACOSOG Z0011 trial, some limitations and potential pitfalls linked to selection bias, differences in surgical technique and radiotherapy protocols have been discussed in oncology community. To note, this study did not include patients receiving neoadjuvant chemotherapy (NAC), those undergoing partial breast irradiation, or those undergoing mastectomy, thus the results should not be extrapolated for these groups.

The potential extension of the ACOSOG Z0011 results to the patients undergoing mastectomy has been explored by the SINODAR-ONE multicenter randomized clinical trial. The trial explored the role of ALND in patients undergoing either breast-conserving surgery or mastectomy for T1–2 breast cancer with one or two sentinel lymph nodes with macrometastases. Patients were randomly assigned in a 1:1 ratio to either no additional axillary treatment or the removal of ≥10 axillary level I/II non-sentinel lymph nodes (SLNs) followed by adjuvant therapy. The results demonstrated that the 3-year survival and relapse rates for T1–2 breast cancer patients with one or two macrometastatic SLNs who received only SNB and adjuvant therapy were not inferior to those of patients who underwent ALND (14,22).

The POSNOC trial has the main objective to determine the necessity and effectiveness of additional treatments, such as ALND or axillary radiotherapy, after a positive SNB. Patients with one or two SLNs testing positive were randomized to either no further axillary treatment or additional treatment (either ALND or axillary radiotherapy). The primary objective of the trial is to compare disease-free survival between the two groups. The results of the POSNOC trial, which is still ongoing, might provide further evidence to possibly broaden less invasive axillary treatments to patients with breast cancer and limited axillary disease (15).

The SENOMAC trial randomized patients with up to two macrometastases in their sentinel nodes to undergo completion ALND or no further axillary surgery. Interestingly, clinically node-negative T1–3 (i.e., tumors larger than 5 cm), undergoing breast-conserving surgery or mastectomy whether or not submitted to NAC were included. The SENOMAC trial aims to explore whether completion ALND is necessary in cases of limited spread to sentinel lymph nodes. This investigation will include not only patients undergoing any type of breast surgery but also those who have received neoadjuvant treatment and those with larger tumors (16).

The randomized, multicenter trial AMAROS was an important study primarily investigating the role of radiotherapy in the treatment of axillary nodes. Clinically node-negative breast cancer patients with positive SNB

were randomly assigned to receive either ALND or axillary radiotherapy. Both patients undergoing breast-conserving surgery and those undergoing mastectomy were included. The results showed that axillary radiotherapy was comparable to ALND in preventing axillary recurrence in patients with positive SNB. To note, the occurrence of arm lymphedema was significantly lower in the radiotherapy group, implying that radiotherapy has the potential to be an effective alternative to ALND in patients with positive sentinel lymph nodes, with reduced side effects (17).

The trial OTOASOR arrived at similar results. Patients with T<3 cm N0 breast cancer and positive SNB were randomized to either ALND or regional nodal irradiation. The long-term follow-up demonstrated that regional nodal irradiation does not increase the risk of axillary relapse compared to ALND. This suggests that axillary radiotherapy could be an effective alternative for selected patients with positive nodes (18).

Management of axillary lymph nodes in the setting of neoadjuvant treatments

Neoadjuvant systemic treatments have been used increasingly in the modern management of breast cancer, especially among patients diagnosed with triple negative or HER2 positive breast cancer. This trend has generated new insights on the role of axillary treatment in particular patient subgroups. In fact, one of the main purposes of neoadjuvant treatments is to downstage the disease burden in both the breast and axillary lymph nodes, in order to reduce the extent of surgery and refine personalized treatment based on biological tumor characteristics and response to neoadjuvant protocols. Particular interest has been directed towards patients with metastatic lymph nodes before the start of neoadjuvant therapy who downstage to node-negative at the time of surgery. The main studies focusing on axillary staging in the setting of neoadjuvant systemic treatments are summarized in *Table 3*.

The ACOSOG Z1071 (Alliance) clinical trial was designed to determine the false-negative rate for SNB following chemotherapy in patients initially presenting with biopsy-proven cN1 breast cancer. The false negative rate was not found to be 10% or less in women with cN1 breast cancer with 2 or more sentinel nodes examined who received NAC. Based on this finding, the trialists suggested that a greater sensitivity would be necessary to support the use of SNB as an alternative to ALND after NAC (23).

The SENTINA was a four-arm, prospective, multicentre cohort study investigating the timing of SNB in patients scheduled for NAC. The primary endpoint of the study was to evaluate the false-negative rate of SNB after NAC for patients who converted from cN1 to ycN0 disease. The results demonstrated that SNB was a reliable method before NAC, while after systemic treatment or early SNB, the procedure had a lower detection rate and a higher false-negative rate in comparison with SNB carried out before NAC. The authors suggested caution about the limitations of SNB planned after NAC (24).

The potential of omitting ALND after NAC was explored by the SN FNAC study, where patients with biopsy-proven node-positive breast cancer (T0–3, N1–2) underwent both SNB and ALND after NAC. SNB was considered positive even in presence of ITC. The false negative rate was <10% by using immunochemistry, and the potential for avoiding ALND was around 30%. Thus, the authors recommended evaluation of SNB with immunohistochemistry in the setting of NAC (25).

The GANEA 2 study investigated the accuracy and safety of SNB after NAC in breast cancer patients, being the SNB false negative rate the main endpoint. The results showed that in patients with no initial node involvement (cN0), a negative SNB after NAC enables the safe avoidance of an ALND. Furthermore, residual tumor in the breast and absence of lympho-vascular invasion after NAC enables the identification of patients with initially involved node with a low risk of axillary lymph nodes involvement (26).

The OPBC-03/TAXIS trial is an ongoing international phase-III study evaluating the non-inferiority of axillary radiotherapy compared to ALND in terms of disease-free survival for patients with clinically node-positive breast cancer. This trial is unique as it investigates the de-escalation of axillary surgery in patients undergoing upfront surgery and also includes those with residual disease following NAC. Patients in the experimental arm receive tailored axillary surgery (TAS), involving the removal of sentinel lymph nodes and nodes suspected of containing cancer identified and marked using imaging prior to surgery, ensuring they are targeted during the procedure, followed by radiotherapy, while those in the control arms receive standard ALND followed by radiotherapy. The TAXIS trial is important as it investigates whether TAS, a less invasive approach that tailors the extent of surgery to the disease burden, can achieve safe oncological outcomes with reduced treatment-related morbidity related to ALND (27).

The ongoing Alliance A011202 is a randomized phase III trial comparing ALND to axillary radiotherapy in

Table 3 Management of axillary lymph nodes in the setting of neoadjuvant treatments

Study	Type of trial	Eligibility criteria	Patient groups	Primary endpoint	Status
ACOSOG Z1071 (23)	Phase II prospective, non-randomized study	Invasive BC, N1–2, NAC	All patients received SNB and ALND	False-negative rate of SN in identifying residual axillary disease	Concluded
SENTINA (24)	Prospective cohort study	Invasive BC, cN0–1, NAC	• SNB before NAC • SNB after completing NAC • SNB after conversion to node-negative after NAC • ALND for node-positive after NAC	False-negative rate of SNB after NAC for patients who converted from cN1 to ycN0	Concluded
SN FNAC study (25)	Prospective study	T0–3, N1–2, NAC	All patients received SNB and ALND	False-negative rate of SNB after NAC for patients who converted from cN1 to ycN0	Concluded
GANEA 2 (26)	Prospective trial	T0–3, N0–1, NAC	• cN0 • pN1	False-negative rate of SNB after NAC in pN1	Concluded
OPBC-03/ TAXIS (27)	Phase III randomized controlled study	BC, N+ (cytologically or histologically proven), NAC or upfront surgery	• TAS followed by ALND and regional nodal irradiation • TAS followed by axillary radiotherapy	Rate of imaging-guided localization of the suspicious node clipped under imaging guidance	Ongoing
Alliance A011202 (28)	Phase III randomized controlled study	T1–3, N1, NAC	Positive SNB • ALND and regional nodal radiation therapy • Axillary and regional nodal radiation therapy without ALND	Invasive breast cancer recurrence-free interval	Recruiting concluded
ADARNAT (29)	Phase III randomized study	Invasive BC, positive SNB, NST	• Axillary RT alone • ALND alone	5-year axillary recurrence rate	Ongoing
NSABP B-51 (30)	Phase III randomized study	T1–3, N1, NAC	• Post-BCS: whole-breast irradiation with or without RNI • Post-mastectomy: chest wall RT with RNI or observation	Invasive breast cancer recurrence-free interval	Recruiting concluded

BC, breast cancer; NAC, neoadjuvant chemotherapy; SNB, sentinel node biopsy; ALND, axillary lymph node dissection; SN, sentinel node; TAS, targeted axillary surgery; NST, neoadjuvant systemic treatment; RT, radiotherapy; BCS, breast conserving surgery; RNI, regional nodal irradiation.

cT1–3N1 breast cancer patients with positive SNB after NAC. Essentially, the trial aims to assess, in patients with positive sentinel lymph node(s) after completion of NAC, whether radiotherapy to the undissected axilla and regional lymph nodes is not inferior to ALND with radiotherapy to the regional lymph nodes but not to the dissected axilla in terms of invasive breast cancer recurrence-free interval (28).

The ADARNAT trial is a multicenter, randomized, open-label, phase 3 clinical trial designed to evaluate the efficacy and safety of axillary radiation compared to ALND in breast cancer patients with positive SNB following neoadjuvant systemic therapy. Participants are randomly assigned to receive either axillary radiotherapy without ALND (study arm) or ALND alone (control arm). Both groups are scheduled to receive level 3 and supraclavicular radiotherapy. The primary objective is to determine if radiotherapy is non-inferior to ALND in terms of 5-year axillary recurrence rates (29).

Table 4 Omission of axillary surgery in patients with invasive breast cancer

Study	Type of trial	Eligibility criteria	Patient groups	Primary endpoint	Status
INSEMA (31)	Phase III randomized controlled trial	cT1–2N0, BCS	• No axillary surgery • SNB (if 1–2 positive SNB, randomization: SNB alone *vs.* ALND)	Invasive disease-free survival	Recruiting concluded
SOUND (32)	Phase III randomized controlled trial	cT1N0, US-negative axilla, BCS	• SNB • No axillary surgery	Distant disease-free survival	Concluded
BOOG 13-08 (33)	Phase III randomized controlled trial	cT1–2N0, BCT	• SNB • No axillary surgery	5-year regional recurrence rate	Ongoing
SOAPET (34)	Prospective, phase II clinical study	T1–2N0 (clinical, imaging including LymphPET), BCT	Stage 1: LymphPET imaging and SNB Stage 2: • Negative axillary assessment: no axillary surgery • Positive axillary assessment: SNB	Negative predictive value of LymphPET	Ongoing
NAUTILUS (35)	Phase III randomized controlled trial	cT1–2N0, US-negative axilla, BCS	• SNB • No axillary surgery	5-year invasive disease-free survival	Recruiting concluded

BCS, breast conserving surgery; SNB, sentinel node biopsy; ALND, axillary lymph node dissection; US, ultrasound; BCT, breast conserving therapy.

The NRG Oncology/NSABP B-51/RTOG 1304 trial is a phase III randomized clinical study aimed at determining whether regional nodal irradiation is necessary for breast cancer patients who initially have biopsy-confirmed positive axillary lymph nodes, which become pathologically negative (ypN0) after undergoing NAC. Patients with clinical stage T1–3, N1 breast cancer before NAC were randomized to receive either chest wall irradiation with regional nodal irradiation or observation in case of mastectomy, or whole-breast irradiation with or without regional nodal irradiation in case of breast conserving surgery. The results suggest that for patients whose axillary lymph node involvement resolves after NAC, omitting regional nodal irradiation does not compromise oncological outcomes and may reduce treatment-related toxicity (30).

Omission of axillary surgery in patients with invasive breast cancer

The omission of any axillary surgery has gained interest as an appealing practice for patients with early-stage breast cancer who present with clinically negative lymph nodes. This shift is underpinned by pivotal trials aiming to demonstrate the oncologic safety of such an approach in carefully selected patient groups. The main studies focusing on possible omission of axillary surgery in selected groups of patients with early breast cancer are resumed in *Table 4*.

The INSEMA trial includes cT1–2N0 patients who are scheduled for breast-conserving surgery followed by radiotherapy. This non-inferiority trial demonstrated that early-stage breast cancer patients who undergo a less extensive axillary surgery achieve 5-year invasive disease-free survival outcomes that are not inferior to those of patients receiving standard treatment (31).

The Italian SOUND trial examined the safety of omitting axillary surgery in patients with breast cancers up to 2 cm and negative preoperative axillary ultrasonography. This phase III noninferiority study involved 1,405 patients randomized to either no axillary surgery or SNB. The results indicated that avoiding axillary surgery was noninferior to SNB in terms of 5-year distant disease-free survival, suggesting that these patients can safely skip axillary surgery without impacting their treatment outcomes (32).

The Dutch prospective non-inferiority randomized multicenter BOOG 13-08 trial examines clinically node-negative T1–2 invasive breast cancer patients undergoing breast-conserving therapy (BCT), in order to determine if SNB can be safely omitted in these patients. Participants are randomized to either undergo SNB or follow a watchful waiting approach without SNB. Primary and

secondary endpoints include distant disease-free survival and overall survival. The estimated study completion date is April 2027 (33).

The SOAPET trial consists of two phases. The first phase will assess the negative predictive value of preoperative axillary assessment, which includes routine imaging exams and lymphPET/CT. In the second phase, SNB will be omitted for patients with negative preoperative axillary assessments. The estimated completion date for the SOAPET trial is 2027 (34).

The ongoing NAUTILUS trial is a Korean prospective, multicenter, randomized study involving candidates for breast conserving surgery with clinically T1–2N0 tumors and negative axillary ultrasound. The participants are randomized to either undergo SNB or no axillary surgery. The primary endpoint is the 5-year invasive disease-free survival. The secondary endpoints are overall survival, axillary recurrence rate, distant metastasis-free survival, and quality of life (35).

A recent study evaluated survival and recurrence in 125 estrogen receptor-positive/HER2-breast cancer patients, aged 65 or older who received breast conserving surgery and no SNB After a median follow-up of 36.7 months, rates of axillary recurrence were extremely low, demonstrating prospective data to support omission of SNB in this patient population (36).

Results summary and future perspectives

In the era of de-escalation treatments in many fields of surgical oncology, a compelling transition towards less invasive surgical techniques aims at reducing morbidity while maintaining or enhancing oncologic outcomes. This approach is particularly significant in breast cancer treatment, where efforts focus on reducing the extent of axillary surgery without compromising the effectiveness of cancer management. Axillary staging remains a crucial aspect of breast cancer management, due to its important prognostic role. Although research is ongoing to reduce the extent of surgical interventions, thorough axillary staging is still necessary in specific cases. This comprehensive approach helps ensure accurate diagnosis, guides treatment decisions, and influences overall patient outcomes.

In this scenario, two important issues need to be taken into account. First, the potential harms of unnecessary ALND or SNB, particularly lymphedema and axillary web syndrome, represent significant sequelae that remain difficult to treat and compromise quality of life. On the other hand, an improper evaluation of axillary status can negatively influence decision on postoperative systemic treatments with relevant effects on overall prognosis. Moreover, patients with unrecognized or untreated lymph node metastases may experience severe local symptoms.

Many trials have highlighted the advantages of de-escalating axillary treatment in different clinical settings. In patients with positive nodes, it seems reasonable to apply the results of studies that demonstrated that omission of complete ALND in presence of up to two sentinel nodes with macrometastases do not affect survival rates. Among these trials, the ACOSOG Z0011 is probably the most well-known and the most frequently recommended in current guidelines. This trial is a landmark study in breast cancer treatment, significantly impacting surgical practice, since it has demonstrated that for women with limited sentinel lymph node metastasis undergoing breast-conserving surgery and systemic therapy, ALND could be safely omitted without affecting survival rates. Nonetheless, it should be remarked that inclusion criteria are highly selective, and restricted to patients who undergo breast conserving surgery (20,21).

Omission of ALND in node positive patients converting to node negative after NAC is an exciting opportunity. However, the treatment of this subgroup of patients remains heterogeneous across different countries, and even within various breast centers of the same country. The ongoing international, prospective, multicenter cohort study AXSANA seeks to determine the best practices for axillary surgery by comparing various techniques, with the goal of optimizing treatment outcomes and reducing morbidity associated with traditional ALND (37,38). On a practical basis, sparing ALND in selected patients with positive lymph nodes that convert to negative after NAC seems to be a rational option. Evidence-based medicine has shown the dramatic effects of neoadjuvant treatments on both breast and axillary basin, with high rates of complete pathologic response especially in patients with triple-negative or HER2-positive breast cancer.

The omission of any surgical evaluation of axillary lymph nodes is probably the most attractive setting. It undoubtedly has important advantages, as it reduces surgical morbidity and improves patient quality of life (31,32). SNB, although it is a minimally invasive approach when compared to ALND, may be challenging to perform in some situations and may have long-lasting complications. A correct preoperative patient selection and an accurate use of imaging modalities, to assess the axillary lymph nodes

for the presence of disease are of the utmost importance when no axillary surgery is planned. Imaging is crucial in determining the extent of disease spread and planning appropriate treatment strategies.

Axillary radiotherapy instead of axillary lymph node dissection is an emerging strategy that aims to reduce surgical morbidity while maintaining effective disease control. Among studies exploring the potential of axillary radiotherapy, the AMAROS trial was a pivotal phase III study that evaluated the management of the axilla in patients with a positive SNB, after either breast conserving surgery or mastectomy. The trial compared ALND with axillary radiotherapy. The findings of the AMAROS trial have impacted clinical practice by establishing axillary radiotherapy as a viable alternative to ALND for selected breast cancer patients, offering reduced surgical complications while maintaining comparable survival outcomes (17). Current trials are also evaluating the efficacy and safety of axillary radiotherapy, and the adoption of this approach is expected to increase as evidence supports its benefits. This shift highlights the importance of continuously updating clinical guidelines and ensuring that multidisciplinary teams are well-informed to provide personalized treatment plans for breast cancer patients. Also, the safety of omitting radiotherapy is under investigation in low-risk breast cancer, as assessed by genomic risk scores and Oncotype Dx (39,40). The randomized TAILOR RT trial has been comparing the effects on low-risk breast cancer receiving usual care that includes regional radiation therapy, with receiving no regional radiation therapy (41).

Importantly, decision on postoperative management of breast cancer with new systemic treatments are still based also on axillary status. Adjuvant therapy decisions for patients with higher-risk hormone receptor-positive/HER2-negative breast cancer and lymph node involvement may include the recommendation for cyclin-dependent kinase 4/6 (CDK4/6) inhibitors (42,43). This is because CDK4/6 inhibitors have been shown to improve outcomes in this patient population by targeting key regulators of the cell cycle, thereby inhibiting cancer cell proliferation. The use of CDK4/6 inhibitors in combination with endocrine therapy has demonstrated significant benefits in reducing the risk of recurrence and improving survival rates in clinical trials (44,45). The decision to include CDK4/6 inhibitors in adjuvant therapy should be based on a thorough assessment of the patient's overall risk profile, including factors such as tumor size, grade, nodal involvement, and other biomarkers.

Conclusions

The treatment of the axilla poses a significant challenge in the modern management of breast cancer patients. The multitude of trials underscores the complexity of the issue and the variability among breast centers in different countries. Profound differences exist in patient selection criteria and SNB evaluation methods. In patients with clinically node-negative lymph nodes and up to two positive sentinel nodes, avoiding axillary lymph node dissection is a safe option. As for patients receiving neoadjuvant systemic treatment, axillary lymph node dissection is unnecessary if no residual tumor burden remained in the lymph nodes after surgery. Additionally, studies have shown that axillary radiotherapy can be as effective as axillary dissection in certain cases. The avoidance of any axillary surgery might be proposed to highly select sub-groups patients with small tumors and lymph nodes that are negative on clinical and ultrasound evaluation. In the coming years, there will likely be a progressive de-escalation in axillary treatment, with ALND reserved for fewer patients. In this context, the adoption of guidelines based on results of current trials and a thorough multidisciplinary team approach is crucial to determine the appropriate treatment for each breast cancer patient.

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Footnote

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References

1. Giuliano AE, Chung AP. Long-term follow-up confirms the oncologic safety of sentinel node biopsy without axillary dissection in node-negative breast cancer patients. Ann Surg 2010;251:601-3.
2. Veronesi U, Paganelli G, Viale G, et al. Sentinel lymph node biopsy and axillary dissection in breast cancer: results in a large series. J Natl Cancer Inst 1999;91:368-73.
3. Fancellu A, Cottu P, Feo CF, et al. Sentinel node biopsy in early breast cancer: lessons learned from more than 1000 cases at a single institution. Tumori 2012;98:413-20.
4. Morrow M. De-escalating and escalating surgery in the management of early breast cancer. Breast 2017;34 Suppl 1:S1-4.
5. Jatoi I, Benson JR, Toi M. De-escalation of axillary surgery in early breast cancer. Lancet Oncol 2016;17:e430-41.
6. Fisher CS, Margenthaler JA, Hunt KK, et al. The Landmark Series: Axillary Management in Breast Cancer. Ann Surg Oncol 2020;27:724-9.
7. Gnant M, Harbeck N, Thomssen C. St. Gallen/Vienna 2017: A Brief Summary of the Consensus Discussion about Escalation and De-Escalation of Primary Breast Cancer Treatment. Breast Care (Basel) 2017;12:102-7.
8. Fancellu A, Sanna V, Sedda ML, et al. Benefits of Organized Mammographic Screening Programs in Women Aged 50 to 69 years: A Surgical Perspective. Clin Breast Cancer 2019;19:e637-42.
9. Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol 2013;14:297-305.
10. Giuliano AE, Hawes D, Ballman KV, et al. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. JAMA 2011;306:385-93.
11. Solá M, Alberro JA, Fraile M, et al. Complete axillary lymph node dissection versus clinical follow-up in breast cancer patients with sentinel node micrometastasis: final results from the multicenter clinical trial AATRM 048/13/2000. Ann Surg Oncol 2013;20:120-7.
12. de Boer M, van Deurzen CH, van Dijck JA, et al. Micrometastases or isolated tumor cells and the outcome of breast cancer. N Engl J Med 2009;361:653-63.
13. Olson JA Jr, McCall LM, Beitsch P, et al. Impact of immediate versus delayed axillary node dissection on surgical outcomes in breast cancer patients with positive sentinel nodes: results from American College of Surgeons Oncology Group Trials Z0010 and Z0011. J Clin Oncol 2008;26:3530-5.
14. Tinterri C, Gentile D, Gatzemeier W, et al. Preservation of Axillary Lymph Nodes Compared with Complete Dissection in T1–2 Breast Cancer Patients Presenting One or Two Metastatic Sentinel Lymph Nodes: The SINODAR-ONE Multicenter Randomized Clinical Trial. Ann Surg Oncol 2022;29:5732-44.
15. Goyal A, Mann GB, Fallowfield L, et al. POSNOC-POsitive Sentinel NOde: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy: a randomised controlled trial of axillary treatment in women with early-stage breast cancer who have metastases in one or two sentinel nodes. BMJ Open 2021;11:e054365.
16. de Boniface J, Frisell J, Andersson Y, et al. Survival and axillary recurrence following sentinel node-positive breast cancer without completion axillary lymph node dissection: the randomized controlled SENOMAC trial. BMC Cancer 2017;17:379.
17. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol 2014;15:1303-10.
18. Sávolt Á, Péley G, Polgár C, et al. Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial. Eur J Surg Oncol 2017;43:672-9.
19. Galimberti V, Cole BF, Viale G, et al. Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial. Lancet Oncol 2018;19:1385-93.

20. Giuliano AE, Ballman K, McCall L, et al. Locoregional Recurrence After Sentinel Lymph Node Dissection With or Without Axillary Dissection in Patients With Sentinel Lymph Node Metastases: Long-term Follow-up From the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 Randomized Trial. Ann Surg 2016;264:413-20.
21. Giuliano AE, Ballman KV, McCall L, et al. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA 2017;318:918-26.
22. Tinterri C, Canavese G, Gatzemeier W, et al. Sentinel lymph node biopsy versus axillary lymph node dissection in breast cancer patients undergoing mastectomy with one to two metastatic sentinel lymph nodes: sub-analysis of the SINODAR-ONE multicentre randomized clinical trial and reopening of enrolment. Br J Surg 2023;110:1143-52.
23. Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 2013;310:1455-61.
24. Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 2013;14:609-18.
25. Boileau JF, Poirier B, Basik M, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. J Clin Oncol 2015;33:258-64.
26. Classe JM, Loaec C, Gimbergues P, et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. Breast Cancer Res Treat 2019;173:343-52.
27. Weber WP, Matrai Z, Hayoz S, et al. Association of Axillary Dissection With Systemic Therapy in Patients With Clinically Node-Positive Breast Cancer. JAMA Surg 2023;158:1013-21.
28. Boughey J, Haffty B, Buchholz T, et al. Alliance A011202: A Randomized Phase III Trial Comparing Axillary Lymph Node Dissection to Axillary Radiation in Breast Cancer Patients (cT1-3 N1) Who Have Positive Sentinel Lymph Node Disease After Receiving Neoadjuvant Chemotherapy. Available online: https://www.alliancef orclinicaltrialsinoncology.org/main/cmsfile?cmsPath=/Public/Annual%20Meeting/files/A011202-Boughey-May2019.pdf
29. Garcia-Tejedor A, Ortega-Exposito C, Salinas S, et al. Axillary lymph node dissection versus radiotherapy in breast cancer with positive sentinel nodes after neoadjuvant therapy (ADARNAT trial). Front Oncol. 2023;13:1184021.
30. Mamounas EP, Bandos H, White JR, et al. Loco-regional irradiation in patients with biopsy-proven axillary node involvement at presentation who become pathologically node-negative after neoadjuvant chemotherapy: Primary outcomes of NRG Oncology/NSABP B-51/RTOG 1304. Presented at: 2023 San Antonio Breast Cancer Symposium; December 5-9, 2023; San Antonio, TX. Abstract GS02-07.
31. Reimer T, Stachs A, Veselinovic K, et al. Patient-reported outcomes for the Intergroup Sentinel Mamma study (INSEMA): A randomised trial with persistent impact of axillary surgery on arm and breast symptoms in patients with early breast cancer. EClinicalMedicine 2023;55:101756.
32. Gentilini OD, Botteri E, Sangalli C, et al. Sentinel Lymph Node Biopsy vs No Axillary Surgery in Patients With Small Breast Cancer and Negative Results on Ultrasonography of Axillary Lymph Nodes: The SOUND Randomized Clinical Trial. JAMA Oncol 2023;9:1557-64.
33. Clinicaltrials.gov. Omitting Sentinel Node Procedure in Breast Cancer Patients Undergoing Breast Conserving Therapy. Available online: https://clinicaltrials.gov/ct2/show/NCT02271828
34. Clinicaltrials.gov. Sentinel Node Biopsy Vs Observation After Axillary PET (SOAPET). Available online: https://clinicaltrials.gov/ct2/show/NCT04072653
35. Jung JG, Ahn SH, Lee S, et al. No axillary surgical treatment for lymph node-negative patients after ultrasonography [NAUTILUS]: protocol of a prospective randomized clinical trial. BMC Cancer 2022;22:189.
36. Chung AP, Dang CM, Karlan SR, et al. A Prospective Study of Sentinel Node Biopsy Omission in Women Age≥65 Years with ER+ Breast Cancer. Ann Surg Oncol 2024;31:3160-7.
37. Banys-Paluchowski M, Gasparri ML, de Boniface J, et al. Surgical Management of the Axilla in Clinically Node-Positive Breast Cancer Patients Converting to Clinical Node Negativity through Neoadjuvant Chemotherapy: Current Status, Knowledge Gaps, and Rationale for the EUBREAST-03 AXSANA Study. Cancers (Basel) 2021;13:1565.
38. Hartmann S, Kühn T, Hauptmann M, et al. Axillary Staging after Neoadjuvant Chemotherapy for Initially Node-Positive Breast Carcinoma in Germany: Initial

Data from the AXSANA study. Geburtshilfe Frauenheilkd 2022;82:932-40.
39. Whelan TJ, Smith S, Parpia S, et al. Omitting Radiotherapy after Breast-Conserving Surgery in Luminal A Breast Cancer. N Engl J Med 2023;389:612-9.
40. Jagsi R, Griffith KA, Harris EE, et al. Omission of Radiotherapy After Breast-Conserving Surgery for Women With Breast Cancer With Low Clinical and Genomic Risk: 5-Year Outcomes of IDEA. J Clin Oncol 2024;42:390-8.
41. The University of Chicago Medicine. CLINICAL TRIAL / NCT03488693. Available online: https://www.uchicagomedicine.org/find-a-clinical-trial/clinical-trial/cirb220521
42. Gaillard T, Piketty J, Feron JG, et al. Rethinking surgical revisions: impact of the MonarchE trial on axillary dissection in hormone-positive HER2-negative early breast cancer patients potentially eligible for abemaciclib. Br J Cancer 2024;130:1141-8.
43. Toi M, Boyle F, Im YH, et al. Adjuvant Abemaciclib Combined with Endocrine Therapy: Efficacy Results in monarchE Cohort 1. Oncologist 2023;28:e77-81.
44. Giraudo A, Sabatier R, Rousseau F, et al. The Use of Cyclin-Dependent Kinase 4/6 Inhibitors in Elderly Breast Cancer Patients: What Do We Know? Cancers (Basel) 2024;16:1838.
45. Agostinetto E, Arecco L, de Azambuja E. Adjuvant CDK4/6 Inhibitors for Early Breast Cancer: How to Choose Wisely? Oncol Ther 2024;12:19-29.

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