Review Article

Axillary management in older women with early operable invasive breast carcinoma: a narrative review

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Background and Objective: Breast cancer management in older women presents challenges due to competing comorbidities and life expectancy concerns. Traditional axillary surgeries as part of treatment of breast cancer are being reconsidered, particularly in two settings (I) early operable disease with positive sentinel lymph node biopsy (SLN+) and (II) cases of early operable clinically node-negative disease (cN0). Current guidelines and emerging evidence suggest that axillary lymph node dissection (ALND) may not always be necessary, especially in patients with low-risk disease. The objective of this study is to offer an updated synthesis of current guidelines and discuss the latest evidence from significant clinical studies.

Methods: A literature search was conducted using the PubMed database and articles up to Nov 2023 were included for analysis.

Key Content and Findings: Recent trials, including AMAROS and OTOASOR, demonstrate the non-inferiority of radiotherapy compared to ALND in early breast cancer with positive sentinel lymph node biopsy (SLNB), offering a shift towards de-escalation of axillary surgery. Similarly, studies like IBCSG 10-93 highlight the potential benefits of omitting axillary surgery in clinically node-negative tumours, showing improved quality of life without compromising oncological outcomes. Despite promising findings from these studies, challenges remain, including disparities between real-world evidence and controlled trials. Variation in clinical management persists, influenced by factors such as trials designs, restricted inclusion criteria, and clinician interpretation. Ongoing trials are still needed to further elucidate the role of axillary surgery, particularly in older women, by assessing quality of life outcomes, the need for comprehensive geriatric assessment tools, and individualised treatment decisions.

Conclusions: While evidence supporting the use of radiotherapy or adjuvant systemic therapy for managing axillary lymph nodes continues to grow, the reduction in both ALND and SLNB in older women may be on the horizon, emphasising the importance of tailored treatment approaches based on patient characteristic.

Keywords: Axillary surgery; breast cancer; older women

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Introduction

Breast cancer is a highly prevalent disease, annually affecting approximately 2.3 million individuals and ranking fifth among the leading causes of cancer-related mortality worldwide (1). Axillary lymph nodes serve as predictors of disease spread and influence patient survival. Thus, their management plays a crucial role in disease control and prognosis (2).

Traditionally, patients with early invasive breast cancer with clinically node-positive disease at presentation will be offered radical axillary lymph node dissection (ALND); clearance of all lymph nodes in the axilla region. If the patient has clinically-node negative disease at presentation (non-palpable, radiologically undetectable), they will be offered sentinel lymph node biopsy (SLNB) for pathological confirmation of nodal status (3,4). This procedure involves the removal of the sentinel or 'gatekeeping' axillary nodes; the site of initial drainage of the breast.

There are numerous methods to help detect the sentinel lymph nodes (SLNs) intraoperatively, including implantable magnetic devices, blue or radioactive dyes; often these are used in combination (5,6). If the SLNB is found to be positive, the current standard of care is to offer ALND to clear the remaining axillary lymph nodes. If the SLNB is negative (or contains micrometastatic disease), then no further axillary treatment is recommended (7).

Compared to their younger counterparts, the older adult population (>65 years) with breast cancer, have distinct challenges owing to higher prevalence of multiple comorbidities, lower predicted life expectancy and concerns regarding quality-of-life (QOL) post-surgery (8). In older women, breast cancer may not be the major determinant of survival (9,10). Instead, the cause of mortality may be attributed to other comorbidities. These observations have led to important trials looking at de-escalation of adjuvant therapy in older women with low-risk node-negative breast cancer (11). This raises an important question about the necessity of axillary surgeries in this demographic regardless of their SLN status. As older women are more likely to die with the breast cancer rather than from it, having extensive axillary surgery alongside surgery to the breast may not be necessary (3).

This review aims to offer an updated synthesis of current guidelines and discuss the latest evidence from significant clinical studies to address these specific challenges in the management of breast cancer among older patients, focusing on two areas: positive SLNB (SLN+) and clinically node-negative disease (cN0). We present this article in accordance with the Narrative Review reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-24-22/rc).

Methods

A literature search was conducted using the PubMed database, employing a combination of keywords and phrases related to the topics of "Older women" and "Sentinel Lymph Node Biopsy" in breast surgery. Articles in the database were searched from earliest available date, starting from 1996 up to November 2023 (*Table 1*). Both peer-reviewed articles with full-text availability and grey

Table 1 The search strategy summary

Items	Specification
Date of search	November 2023
Database	PubMed
Search terms used	'Older women' and 'sentinel lymph node biopsy'
Timeframe	Articles from 1996 to November 2023 were included
Inclusion and exclusion criteria	Inclusion: English full text
	Exclusion: Case reports
Selection process	A senior breast trainee underwent a search independently. This was cross-checked by the breast consultant and breast oncologist. Upon disagreement or ambiguity, discussion among the reviewers and articles were chosen
Additional considerations	Clinical trials or cutting-edge studies deemed relevant were selected for the purpose of this concise mini-review

literature were considered for analysis. Case reports were excluded in these studies. Studies that were deemed to be influential to guidelines were selected. The selection of articles was performed independently by a senior breast specialty trainee and then cross-checked by a second reviewer, consultant in breast surgery and third reviewers in breast consultant oncologist. In cases of ambiguity or disagreement, discussions among the reviewers were held to reach a consensus. Additionally, a systematic review of this topic is currently underway to provide a more comprehensive and in-depth analysis when the results from future studies become available for publication.

Landmark trials in the field

Early operable disease with positive SLNB

Firstly, the EORTC 10981-22023 AMAROS trial was an international randomised controlled trial across Europe and the UK. AMAROS compared ALND (744 patients) against axillary radiotherapy (681 patients) in individuals with T1–T2 breast tumours and positive SLNB after mastectomy or lumpectomy. They discovered a similar cancer locoregional recurrence rate over 5 years (0.43% *vs.* 1.19%) and no significant difference in overall survival (OS) or disease-free survival (DFS) rates between the groups (92% *vs.* 82%). However, ALND was associated with a doubled incidence of lymphedema (25% *vs.* 13%) during the 5-year follow-up. Importantly, 95% of patients in this trial had positive sentinel nodes equating to two or fewer, making it particularly relevant to low-nodal disease as suggested by the guidelines (12-14).

Secondly, the OTOASOR trial, led by a Hungarian group, with a smaller sample size of 526, further supported the AMAROS trial's findings with a follow-up over 8.9 years that axillary radiotherapy is as effective as ALND in terms of the DFS rates (72.1% *vs.* 77.4%). Importantly, the AMAROS trial showed that only 33% of the time ALND found additional positive lymph nodes which is similar to the findings of 38.5% in OTOASOR trial. Findings from these two trials question the benefit of ALND in removing more axillary lymph nodes as additional metastasis is not always found (15).

Additionally, ACOSOG Z0011 trial was a USA based multi-centre, randomised controlled non-inferiority trial. Z0011 compared SLNB alone (446 patients) with adjuvant conventional therapy against ALND (445 patients) in individuals with T1–T2 tumours and positive SLNB sentinel nodes after breast-conserving surgery (BCS). Despite additional positive lymph nodes being removed in ALND, the 10-year follow-up showed no significant differences in OS (83.6% *vs.* 86.3%), DFS (78.2% *vs.* 80.2%), or loco-regional recurrence rates (8.8% *vs.* 7%) between ALND and SLNB alone with standard adjuvant therapy. The authors conclude not routinely supporting ALND in small tumours undergoing BCS, adjuvant systemic therapy with whole-breast radiotherapy is sufficient to treat the residual disease (16).

The findings of the Z0011 study did not support additional surgery especially in the low volume disease, which are now being further explored in the POSNOC trial (17), recruiting 1,900 women with up to two SLNs positive and T1/2 tumours. The primary outcome of this randomised controlled trial compares the current gold standard of axillary treatment (surgery or radiotherapy) against systemic adjuvant therapies only. Secondary outcomes include arm morbidity, quality of life and anxiety and is stratified for age (under and over 50 years). The trial recruited patients that were originally excluded from Z0011, including those treated with mastectomy, the radiotherapy details are also being carefully analysed. Results from this important trial are pending.

These studies are in support for clinicians to use radiotherapy or even systemic therapy to replace axillary surgery to avoid unnecessary complications in older women patients (12-14). However, the observed results can only apply to a specific population and do not extend beyond the trial's inclusion criteria, such as patients with more than two positive SLNs, or those who underwent mastectomy without radiation, and those receiving neoadjuvant therapy. Furthermore, the precise effect of radiotherapy and the specific isodose level administered to the axillary region is yet to be established.

Early operable clinically node-negative disease

Clinically or radiologically undetectable lymph nodes may still harbour positive disease, leading to false negative results. Variation in guidelines is likely attributed to inference from the clinical trials beyond the primary research outcome of interests that the trials were not was designed to answer, these limitations contribute to the lack of generalisability and subject to clinician's interpretation.

The CALGB43 trial conducted by Hughes *et al.* (18) examined the impact of adjuvant radiotherapy with tamoxifen in 636 women (>70 years old) with estrogen

receptor-positive (ER^+) T1 tumours following lumpectomy. In the trial, 62% of patients did not undergo axillary staging via SLNB, and only 3% developed axillary recurrence. The author hence suggests that survival outcomes were not affected by axillary staging, leading to the inference that SLNB may not be necessary in older women with small, endocrine sensitive tumours. Subsequently, the American Internal Medical Foundation and the combined American Society of Clinical Oncology and Cancer Care Ontario guidelines (19) supported avoiding axillary surgery, and advocating for tamoxifen, with or without radiotherapy, is a sufficient adjunct therapy for managing low-risk breast cancer in older women. However, it is essential to note that while this observation appears clinically reasonable, the study was not adequately powered to make meaningful comparisons of axillary recurrence rates and assess the benefit of SLNB in this study population (18).

Martelli *et al.* conducted a retrospective analysis in older women (>70 years) with T1 tumours and no clinically palpable lymph nodes revealing that, over a median follow-up period of 15 years, adjuvant systemic therapy with tamoxifen yielded comparable oncological outcomes to those achieved with axillary surgery (20). In patients who did not undergo axillary surgery or SLNB, the incidence of axillary lymphadenopathy was as low as 5.8%. The author later concludes that this risk is deemed clinically acceptable to neglect SLNB. Yet, this is a retrospective study which subjects to biases. It could mean that clinicians had already pre-selected the patients who were more likely to benefit from conservative management.

The International-Breast-Study-Group-10-93 (IBCSG 10-93) trial investigated the quality of life for older women patients (>60 years old) with clinically node-negative ER^+ tumours receiving axillary surgery compared to those without (using tamoxifen only), after removal of primary tumour. It discovered that patients without axillary surgery reported better quality of life, with insignificant differences in DFS and OS compared to those undergoing axillary surgery (21). At the first immediate follow-up, the benefits of avoiding axillary surgery included lower rates of arm stiffness and pain (15% *vs.* 39% and 7% *vs.* 23%, respectively) with systemic endocrine therapy. However, this trial was not blinded which makes both clinicians and patients prone to reporting biases immediately after the operation. Furthermore, the nature of axillary surgery (SLNB or ALND) was not specified in this study which further could over-exaggerate effects of axillary surgery. Interestingly, both groups demonstrated improvement in the arm pain and stiffness symptoms over time, with insignificant difference in QOL at the two-year follow-up (7,22-24).

Current guidelines

Guideline recommendations may be shaped by patient expectations and societal factors, varying by country (25). In the UK, free public healthcare emphasises cost-effectiveness, necessitating careful evaluation of the harms and costs of omitting SLNB in clinically negative tumours whilst maintaining efficiency and safety (25). Conversely, in countries like China and the USA, where patients bear healthcare costs either through personal finances or insurance patients may possess more autonomy in requesting treatments, even if they deviate from established guidelines, albeit at their own risk and judgement (26).

Early operable disease with positive SLNB

There are current guidelines to support the use of axillary radiotherapy following a positive SLNB in older women who present with early breast cancer, rather than ALND.

The European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG) jointly published a paper in 2021 advocating for discussion of axillary radiotherapy in older adults (>70 years) with SLN-positive breast cancer. They suggested that ALND might not always be necessary, particularly in patients with a low nodal burden or ER-positive tumours that respond well to endocrine treatment. Instead, radiotherapy could be considered, especially if only one or two SLNs are positive. This guidance is similar in National Comprehensive Cancer Network (NCCN) (27), where if <2 SLNB were found to have positive, radiological SLNB mapping to decide the need of ALND. This reflects a significant shift from the 2012 recommendation where ALND was a routine procedure for all patients with positive SLNB (12,22).

Similarly, the American Society of Breast Surgeons 2022 guidelines state that in patients with positive SLNB, ALND is recommended under restricted criteria: in patients who had BCS with two or more positive sentinel nodes or in patients who underwent mastectomy with three or more positive sentinel nodes (23).

The UK National Institute for Health and Care Excellence (NICE) encourages clinicians to discuss the risks and benefits of ALND and advises using alternative

therapies such as radiotherapy (24) in such cases.

Across different guidelines, there is a consensus that in patients with positive SLNB (after clinically negative axilla at presentation) use of radiotherapy is acceptable in lieu of ALND in older women (22-24) although there remain questions for radiation oncologists around extent of nodal irradiation, dose and fractionation of the radiation treatment (25).

Early operable clinically node-negative disease

Patients with unknown or clinically negative nodal status traditionally require SLNB for staging. Currently, guidelines from EUSOMA and SIOG have advocated that while SLNB remains the standard for axillary care in radiologically negative cases, it can be omitted in patients with cT1N0 luminal A-like tumours. These tumours are defined as <2 cm, clinically undetectable lymph node status, ER-positive, human epidermal growth factor receptor 2 (HER2)-negative (22).

Similar recommendations are seen in the Arbeitsgemeinschaft-Gynäkologische-Onkologie (AGO) Breast Committees in Germany guidelines published in 2022. The routine use of SLNB in patients >70 years with clinically negative lymph node status (cN0) under certain conditions which aligns with EUSMOA and SIOG guidelines, including T1, ER^+, $HER2^-$ disease (7), is not required.

Both European and American guidelines suggest that SLNB may be unnecessary in advancing age or in cases of serious co-morbidities (28). For instance, the American Society of Breast Surgeons explicitly mentions that in patients aged ≥70 years with cT1–2N0 hormone receptor-positive breast cancer, axillary staging might be unnecessary and the EUSOMA/SIOG guidelines advise avoiding SLNB in those with limited life expectancy (22).

However, in NCCN guidelines, it recommends that if any suspicious of lymph nodes seen on the imaging, SLN mapping should be performed to risk stratify patients and determine the need for further axillary treatment, which is a less invasive approach than SLNB. However, a pilot trial demonstrated a low accuracy of SLNB mapping which has 28% false-negative rate, this raised the concerns about premature escalation and underscored the need of SLNB (27,29).

Despite some countries adopting de-escalation strategies, organisations like NICE in the UK continue to recommend SLNB as the primary staging approach for all nodal-negative breast cancer cases, regardless of age or co-morbidities. Unlike SLNB-positive tumours, there is a lack of consensus and clearly defined criteria for when SLNB could be omitted in the older women population (7,22-24).

Ongoing trials and relevant studies since publication of guidelines

The above trials mentioned have generated hypotheses that have prompted ongoing trials with focused research questions to evaluate the benefits of omitting ALND and SLNB. Current trial evidence is summarised in *Tables 2*,*3* and ongoing studies in *Table 4*.

Early operable disease with positive SLNB

Since the latest guidelines previously discussed were published (30), more studies have emerged to the literature supporting the replacement of ALND in early breast cancer with positive SLNB. However, none of the contemporary trials are designed for older women, yet they represent a large sample size where the observed effect could be easily extrapolated to older population with shorter life expectancy.

The SINODAR-ONE trial is a multicentre-randomised controlled trial conducted in Italy. It compares the effect of ALND and standard adjuvant therapy *vs.* no axillary surgery and adjuvant therapy (which includes radiotherapy) in 879 patients (median age 54 years old) with early breast tumours (T1–T2) and positive SLNB (up to two SLNs removed). In this trial, over 89% of tumours were ER^+ and progesterone receptor-positive (PR^+). Five-year recurrence and OS rates were similar in both arms, with a 6.9% recurrence rate and 98.9% OS rate in the ALND group (P=0.44), *vs.* a 3.9% recurrence rate and 98.8% OS rate in the no further surgery group (P=0.98). Despite inclusion criteria allowing up to 5-cm tumours, the median tumour size remains less than 2 cm. Although the results are based on short-term follow-up data, they provide additional evidence to support the notion that in cases of low-nodal SLNB positive cancer, no further axillary surgery is needed after SLNB (31).

The SENOMAC trial is an international randomised controlled trial led by a Danish research group. It has expanded the tumour size criteria to larger than 5 cm (up to T3) and aims to compare the benefits of ALND in cases of SLNB-positive cancer. The trial includes more patients undergoing mastectomy as the primary surgery rather than only breast-conserving therapy, and patients receiving neo-

Table 2 Clinical trials for positive-SLNB tumour advocating omission of ALND

Study [year]	N	Primary comparison	Study population	Age (years)	Primary outcome
AMAROS trial [2014]	4,823	ALND *vs.* ART	SLNB positive, tumour ≤5 cm	Median [IQR]: 56 [48–64] in ALND, 55 [48–63] in radiotherapy	5-year axillary recurrence rate: 0.43% ALND *vs.* 1.19% radiotherapy
OTOASAR trial [2017]	2,073	ALND *vs.* ART	SLNB positive, tumour ≤3 cm	Mean [range]: 54.5 [26–74] in ALND, 55.2 [27–74]	97-month axillary recurrence rate: 2% ALND *vs.* 1.9% ART
ACOSOG Z0011 trial [2017]	891	ALND *vs.* SLNB alone	SLNB positive, tumour ≤5 cm	Median [range]: 54 [25–90] in ALND, 56 [24–92] in SLNB alone	10-year OS: 83.6% ALND *vs.* 86.3% SLNB
IBCSG23-01 [2019]	931	ALND *vs.* SLNB alone	SLNB positive, micro-metastasis, tumour ≤5 cm	Median [range]: 53 [28–81] in ALND, 54 [26–81] in SLNB alone	5-year DFS: 84.4% ALND *vs.* 87.8% SLNB (P=0.16)
SINODAR ONE trial [2022]	889	ALND *vs.* SLNB alone	SLNB positive, tumour ≤5 cm	Mean (SD): 56.1 (9.3) in ALND, 56.2 (9.6) in SLNB alone	5-year OS: 98.9% ALND *vs.* 98.8% SLNB (P=0.94)
SENOMAC trial [2022]	976	ALND *vs.* SLNB alone	SLNB positive, tumour size up to T3	Median [range]: 61 [34–87] in ALND, 62 [23–92] in SLNB alone	5-year cancer-specific survival yet to publish

All trials included patients who had their primary tumour removed and recruitment was not confined to tumour biology. Z11 trials patients all had BCS + breast radiotherapy. All patients had standard adjuvant therapy in both ALND and SLNB group. SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; ART, axillary radiotherapy; IQR, interquartile range; SD, standard deviation; OS, overall survival; DFS, disease-free survival.

Table 3 Clinical trials for clinically-node negative tumour advocating omission of SLNB

Study [year]	N	Primary comparison	Study population	Age (years)	Primary outcome
CALGB43 trials[†] [2013]	636	Tam *vs.* TamRT	Clinically negative axillae with ER^+ tumour ≤2 cm	>70 years old (no information on breakdown)	10-year OS: 67% Tam *vs.* 66% TamRT
IBCSG 10-93 trial[†] [2006]	473	TamA *vs.* Tam	Clinically negative-node tumour size T3	Median [range]: 74 [60–91]	6-year DFS: 67% TamA *vs.* 66% Tam (P=0.69); OS: 75% TamA *vs.* 73% Tam (P=0.77)
INSEMA [2022]	5,154	SLNB alone *vs.* no SLNB	Ultrasound proven negative-node, tumour ≤5 cm	Median [range]: 62 [24–89]	5-year DFS yet to be published
SOUND [2023]	1,463	SLNB alone *vs.* no SLNB	Clinically negative tumour ≤2 cm	Median [IQR]: 60 [52–68]	5-year distant DFS: 97.7% SLNB *vs.* 98% no SLNB, P=0.67

All trials included patients who had their primary tumour removed. [†], the authors of both trials infer results of SLNB omission from a subgroup of patient that did not undergo SLNB which was not the primary intention of the trials. SLNB, sentinel lymph node biopsy; Tam, tamoxifen alone; TamRT, tamoxifen + radiotherapy; TamA, ALND + tamoxifen; ALND, axillary lymph node dissection; IQR, interquartile range; OS, overall survival; DFS, disease-free survival; ER^+, estrogen receptor-positive.

adjuvant systemic therapies. The primary outcome of the SENOMAC trial incorporates an extensive assessment of health-related quality of life, which is more holistic than in previous trials such as AMAROS or OTOASOR. In their 1-year follow-up, despite significant arm and breast symptoms experienced in the ALND group compared to SLNB only, overall, there was no difference in the global quality of health (32).

A further provocative development is to add genomic information into prognostic staging for breast cancer alongside traditional pathological and clinical staging. The use of genomic expression profile tests has been shown to be helpful in identifying those patients who will not benefit from adjuvant chemotherapy regardless of patient age. The MA39 study is randomising a planned 2,140 patients with low-risk node positive disease to further axillary treatment (radiotherapy) on the basis of a low Oncotype DX score (33).

These trials are waiting for longer follow-up data.

Table 4 Summary of the ongoing trials

Trials	Primary result anticipated
ALND *vs.* adjuvant radiotherapy	
SERC	2031
SINODAR ONE	2022, published
SENOMAC	2022, published
Omission of SLNB	
BOOG 2013-08	2027
NAUTILUS	2025
INSEMA	2023, published
SOAPET	2027

ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.

Early operable clinically node-negative disease

Zhong *et al.* conducted a retrospective study in China comparing outcomes in older women (>70 years old) with clinically-node negative breast cancer who underwent BCS without any adjuvant radiotherapy or SLNB to those who underwent mastectomy with ALND. The study included 450 patients, with up to 97% having T1–T2 tumours (34). While both groups showed no significant differences (P=0.90) in recurrence-free survival or breast cancer-specific survival, the no radiotherapy/SLNB group experienced an insignificant (P=0.78) higher recurrence rate (7% *vs.* 6.1%). Older women in this group also had significantly (P<0.01) higher ipsilateral breast recurrence (5.3% *vs.* 0%) overall compared to those who received ALND. Despite being a retrospective study with indirect comparison, the evidence suggests that omitting axillary surgery and radiotherapy in older women could increase the risk of breast cancer recurrence after BCS (34).

In an attempt to narrow the evidence gap for older women, Rana *et al.* performed meta-analysis of nine studies of a mixture of observational studies and clinical trials evaluating the effect of SLNB (35). This provides a large amount of data to evaluate the oncological outcome in women over 70 years old with clinically negative-node tumours who underwent surgery. Among the 3,591 patients analysed for recurrence, there was a reduced risk of recurrence with SLNB [relative risk (RR) =0.59], although not reaching statistically significance (P=0.21, I^2=46.6%), and among 48,523 patients, there was a lower risk of mortality if SLNB was performed (RR =0.51, P<0.01, I^2=78.1%); however, the authors could not explain their findings and a full paper is awaited (35).

Similarly, a Canadian observational population comprising 22,621 older women individuals real-world data, highlighted that SLNB omission correlated with worse OS and breast cancer-specific survival, even after adjusting for baseline confounding factors including a Charlson comorbidity score through propensity matching. Interestingly, despite propensity matching, in the older women group, mainly with tumours <2 cm (which accounted for around 70% of the breast tumours), omission of SLNB showed they would receive lower rates of radiotherapy (25% *vs.* 47%) and chemotherapy (4% *vs.* 8%) compared to those who received SLNB. Even after adjusting for both radiotherapy and chemotherapy treatments, this real-world study revealed worse OS outcomes in older women patients who had SLNB omission (36).

In contrast to the observational studies described, the SOUND trial conducted across Italy, Spain, Switzerland, and Chile examined the impact of omitting SLNB in 1,405 patients with small tumours (up to 2 cm). Employing a more consistent recruitment design, all patients had ultrasound-proven negative lymph nodes, eliminating biases from undiagnosed positive SLNs. Approximately one-third of participants were older women (over 65 years old), with over 90% having ER^+ and HER-negative tumours. The study demonstrated that omitting SLNB was non-inferior to its inclusion in terms of axillary recurrence rate (0.7% *vs.* 0.4%), ipsilateral breast recurrence rate (0.9% *vs.* 1%), breast cancer-related mortality (0%), and distant metastasis (2% *vs.* 1.8%). Notably, the median tumour size was approximately 1.1 cm, predominantly consisting of non-overexpressing ER^+ tumours. Published in 2023, the findings from the SOUND trial support the safe management of low-risk tumours with systemic therapy, even without definitive pathological confirmation of axillary nodal status (37).

Additionally, the INSEMA trial in Australia/Germany, expected to complete in 2024, addresses the problems encountered in previous Z011 trial. With an expanded tumour size criteria of up to 5 cm, INSEMA includes 5,154 patients undergoing two randomisation processes to investigate effect of radiotherapy in SLNB-positive and omission of SLNB in SLNB-negative tumours. It also aims to determine the optimal therapeutic isodose level for effective radiotherapy in different axillary levels which acts as quality assurance process. The study design incorporates clinician and patient-reported outcomes, including QOL assessments such as EORTC QLQ-C30 and BR23 modules,

comparing QOL between SLNB and no axillary surgery. Initial analysis shows no significant difference (P=0.78) in global QOL between groups which is like the SOUND trial, though arm symptoms were more pronounced in the SLNB group during the first week post-operation (mean difference 23.6 *vs.* 13.6). However, at 18 months, these differences tended to diminish (mean difference at around 17 *vs.* 14), with no statistical difference in global breast symptoms (P=0.30). In subgroup analysis, arm symptoms were more pronounced in the <60 years group compared to the older women group, suggesting that these arm symptoms may be even less pronounced in the older women population. These data imply that omission of SLNB is better with respect to arm function. Conversely, one could interpret that the impact of SLNB on patient global QOL is similar or non-inferior to its omission, with even longer follow-up, SLNB may have minimal impact on patient QOL at all, as seen in the IBCSG 10-93 trial (38,39).

Conclusions

It is noteworthy to observe the disparity between real-world evidence from observational studies, such as the one conducted by Castelo (36) on axillary surgery/SLNB demonstrating omission of SLNB to have worsened OS outcome, and findings from controlled trial environments that did reciprocate similar finding (34). This suggests potential clinician biases in real-world settings that may skew results. For instance, some high-risk older women patients with poor prognoses may have SLNB omitted to preserve dignity, possibly leading to adverse outcomes. Additionally, even guidelines and evidence suggest the benefit of omission of ALND in positive node disease, 49% of surgeons from a national survey remains favours the axillary surgery in their practice. Hence, emphasis should be placed on educating surgeon and helping them to interpret and made aware of evidence from clinical trials to better inform their practice (40).

Despite ongoing high-quality trials, most are not specifically designed for the older women population and lack geriatric end-point assessments (41), instead trials opt for universal recruitment and extrapolate findings to older women patients or those with comorbidities (*Tables 2,3*). Designing trials requires significant financial and time investments to ensure adequate long-term follow-up, which may not be feasible or in the best interest of older women patients. A potential solution to ensure high-quality evidence for managing breast cancer in the older women is the establishment of a national database where researchers can publish trial data, enabling integration of primary data for meaningful subgroup analyses and adequate power calculations specific to the older women population.

Another aspect to consider is the pre-operative functional status of the older women population, as age alone may not reflect physiological age or fitness levels. Validated scoring systems assessing quality of life and functional status post-surgery exist and their routine collection in clinical practice and trial data would improve applicability of data. The development and use of a comprehensive geriatric assessment tool may better risk-stratify patients for axillary surgery omission (42). Alongside consideration of individual patient characteristics, this approach may provide tailored treatment decision rather than advocating for blanket de-escalation of axillary surgery.

Clinicians should carefully consider the functional status, quality of life and the biology of the tumour when considering omitting axillary surgery for patients. We expect to see evidence to support the use of radiotherapy or even adjuvant systemic therapy to manage the axillary lymph nodes in the early breast cancer in the next years. There is likely to be reduction in both ALND and SLNB in the older women population.

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Footnote

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appropriately investigated and resolved.

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