Impact of Sentinel Lymph Node Biopsy on Management of Older Women With Clinically Node-Negative, Early-Stage, ER+/HER2−, Invasive Breast Cancer: A Systematic Review and Meta-Analysis

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Abstract

In 2016 the Choosing Wisely guidelines advised against routine performance of a sentinel lymph node biopsy (SLNB) in women ≥ 70 years of age with clinically node negative (cN0), early-stage, oestrogen receptor positive/ human epidermal growth factor receptor 2 negative (ER+/HER2−), invasive breast cancer. The argument in favour of its continued performance is that it may serve as a useful guide for subsequent management. This systematic review was performed in accordance with the PRISMA guidelines. Studies reporting on rate of adjuvant chemotherapy, adjuvant radiotherapy and performance of completion axillary lymph node dissection (cALND) post SLNB in women aged ≥ 65 years with cN0, early-stage, ER+/HER2−, invasive breast cancer were included. A random effects meta-analysis was performed with summary estimates made using the Mantel–Haenszel method. Dichotomous outcomes were reported as odds ratios (ORs) with 95% confidence intervals (CIs). Ten retrospective studies across 4 countries. Of 105,514 patients, 15,509 had a positive SLNB and 90,005 had a negative SLNB. On meta-analysis, a positive SLNB was significantly associated with receipt of adjuvant chemotherapy (OR 4.64 (95% CI 3.18, 6.77), $P < .00001$), adjuvant radiotherapy (1.71 (95% CI 1.18, 2.47), $P = .005$) and undergoing completion axillary lymph node dissection (OR 68.97 (95% CI, 7.47, 636.88), $P = .0002$). Adjuvant treatment decisions continue to be influenced by SLNB positivity in the era of the Choosing Wisely guidelines. The effects of a positive SLNB and subsequent treatments on outcomes remain inconclusive. However, it is likely clinicians are continuing to over-investigate and over-treat this cohort.

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Introduction

Breast cancer incidence and life expectancy are rising, leading to an increased prevalence of breast cancer amongst women over 65 years of age.[1] Older patients with breast cancer are a distinct population. Notably, most breast cancers in older patients are estrogen receptor (ER) positive.[2,3] Additionally, older patients may have increased co-morbidities and a reduced expected overall survival (OS) compared to younger cohorts.[4] Therefore, the risk versus benefit of treatment becomes an increasingly important consideration.[5] Despite these clinical challenges older patients with breast cancer remain underrepresented in clinical trials.[6] This has created a deficit in the high-quality evidence needed for effective, individualized treatment strategies for this cohort.

In recent years, several efforts have been made to de-escalate surgical intervention in the older population with BC. In 2016, the Society of Surgical Oncology (SSO) published the "Choosing Wisely" guidelines.[7] In an attempt to prevent the overtreatment of older individuals, these guidelines made several recommendations on topical issues in the management of older patients with BC.[8] One important recommendation advised against routine sentinel lymph node biopsy (SLNB) in women ≥ 70 years of age, with early-stage, clinically node negative (cN0), estrogen receptor positive/ human epidermal growth factor receptor negative (ER+/HER2−) BC.[7] These recommendations came following 2 randomized control trials (RCTs) which concluded that axillary lymph node dissection (ALND) offered no benefit in OS to older women with early-stage, ER+/HER2− BC who underwent ALND, provided they were

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willing to take hormone therapy.[9,10] However, recent studies suggest that surgeons are continuing to perform SLNB in this cohort.[11,12] Proponents of SLNB argue that, while removal of positive nodes may not influence outcomes, a SLNB may serve as a useful guide for subsequent treatment decisions.[11]

A less invasive alternative for axillary staging to the SLNB is the axillary ultrasound (AUS). The encouraging results of the recent SOUND (NCT02167490) trial may potentially be further supported by several ongoing trials that are comparing different imaging modalities to SLNB.[13-16] Additionally, the widespread commercial availability of personalized genomic tests such as Oncotype Dx (ODx) have important treatment implications in this cohort. Following the promising results of the TAILORx and RxPONDER trials, ODx may be used to guide adjuvant chemotherapy decisions in select patients.[17]

To our knowledge, this is the first systematic review and meta-analysis of the influence of SLNB on adjuvant chemotherapy, adjuvant radiotherapy and completion ALND (cALND) in older women with cN0, early-stage, ER+/HER2−, invasive breast cancer. This study also aimed to evaluate the impact of nodal positivity on outcomes in this cohort.

Methods

This systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).

Search Strategy

An electronic search was performed on 02/03/2024 on Medline Ovid, Embase, CINAHL, Scopus, Web of Science and Cochrane for relevant studies. Search terms included "sentinel lymph node biopsy," "breast cancer" and "older patients," and were linked with Boolean operators, "AND" and "OR." Included studies were limited to those published in the English language. Only studies published after the "Choosing Wisely" guidelines were included (August 2016).

Inclusion and Exclusion Criteria

Studies meeting the following inclusion criteria were included: studies reporting adjuvant radiotherapy or adjuvant chemotherapy receipt post SLNB; due to the global heterogeneity in the definition of "older age," studies including patients ≥ 65 years were included; studies involving patients with ER+/HER2−, cN0, early-stage disease. Studies meeting any of the following exclusion criteria were excluded from this meta-analysis: receipt of adjuvant therapy was not reported for positive and negative SLNB; studies without subset data for patients aged ≥ 65 years; review articles, summaries, editorials, letters, case reports and case series with less than 5 patients; studies involving > 5% male patients; studies involving ductal carcinoma in-situ (DCIS); studies of a neo-adjuvant cohort; non-English language articles.

Selection Process

Two independent reviewers (G.R.D) and (G.P.D) performed the literature search. Duplicate studies were removed manually, before titles and abstracts were screened, followed by full text review. Studies meeting the inclusion criteria were included for data extraction. In instances of disagreement between reviewers, a third author (SH) arbitrated whether the study be included.

Data Extraction and Quality Assessment

The following data were extracted from all eligible articles: name of first author; journal of publication; country of study; year of publication; study design; mean age of participants; number of positive SLNBs; number of negative SLNBs; number of patients who received adjuvant chemotherapy, adjuvant radiotherapy and underwent cALND after a positive and negative SLNB; outcome data post positive and negative SLNB. Authors were contacted in instances of insufficient raw data. Quality of methodology and risk of bias assessment was conducted in accordance with the Newcastle-Ottawa scale.

Statistical Analysis

Random effects meta-analyses were performed to produce summary estimates of the odds of receiving adjuvant chemotherapy, adjuvant radiotherapy and undergoing cALND in those with a positive SLNB (SLNB+) versus a negative SLNB (SLNB-). Dichotomous outcomes were reported as odds ratios (ORs) with 95% confidence intervals (CIs) following estimation by Mantel–Haenszel method. I^2 was used to assess heterogeneity of studies included in each analysis, with an I^2 of greater than 50% considered "high." A leave-one-out sensitivity analysis was performed to assess the influence of individual studies on heterogeneity. A P-value of $< .05$ was considered significant for all analyses. In cases where data was not reported in the text but Sankey graphs were available, the graph was digitalized and converted into bar chart data by choosing 2 known points on the continuous axes along the bars using Webplotdigitizer (Version 5, URL: https://automeris.io/), and data then extracted. Where means were not reported, they were estimated using median and interquartile range or overall range.[18,19] Forest plots were created and sensitivity analysis performed using Review Manager (*RevMan*) version 5.4 (*Nordic Cochrane Centre, Copenhagen, Denmark*).

Results

Literature Search

The initial search produced 4160 articles. After duplicates were removed (n=827), 3333 abstracts remained for screening. Of these, 151 texts were reviewed in full. Six of these articles met the inclusion. References of the included articles were reviewed, yielding 3 further articles for inclusion. A final article, recently written by the authors, was also included following publication, leaving 10 articles for qualitative and quantitative synthesis. Summary in Figure 1.

Study Characteristics

Data were extracted for 10 studies, published across 4 countries between 2018 and 2024.[12,20-28] All studies were retrospective in nature. Of 105,514 SLNBs included, 15,509 were positive and 90,005 were negative. Most studies included women with cN0, early-stage, ER+/HER2− invasive breast cancer only. Summary in Table 1.

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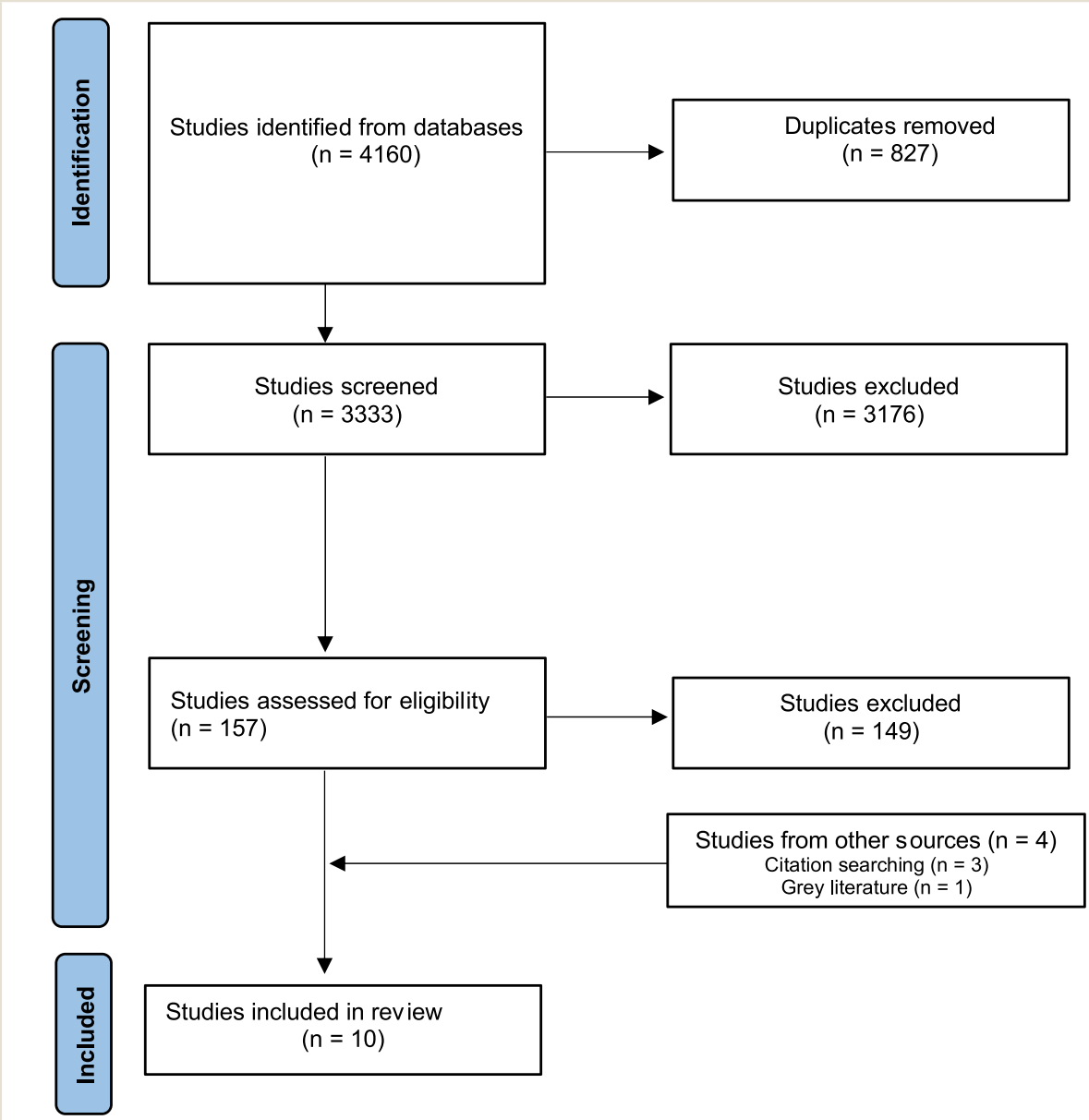
Figure 1 PRISMA flow diagram of study selection.



Adjuvant Chemotherapy Post SLNB

Eight studies including 104,080 patients reported on adjuvant chemotherapy receipt post SLNB. A positive SLNB was associated with increased receipt of chemotherapy in all individual studies and statistically significantly overall (OR 4.64 (95% CI 3.18, 6.77), $P < .00001$) (Figure 2). Gu et al. and McKevitt et al.'s studies contributed most significantly to the I^2 value of 71% (Supplemental Table 1).

Adjuvant Radiotherapy Post SLNB

Ten studies including 105,675 patients reported on adjuvant radiotherapy receipt post SLNB. A positive SLNB was associated with increased receipt of adjuvant radiotherapy in 8 studies. Adjuvant radiotherapy receipt was significantly associated with a positive SLNB overall (OR 1.71 (95% CI 1.18, 2.47), $P = .005$), (Figure 3). Laws et al. and Tamirisa et al. contributed most towards the I^2 value of 92% (Supplemental Table 2).

cALND Post SLNB

Five studies including 3,916 patients reported on rate of cALND post SLNB. A positive SLNB was associated with a significantly increased likelihood of undergoing a cALND in all studies and overall (OR 68.97 (95% CI, 7.47, 636.88), $P = .0002$)(Figure 4). Sensitivity analysis revealed that removal of McKevitt et al.'s study

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Table 1 Characteristics of Included Studies

Author	Year	Country	Study design	Patient cohort	Patients (n)	Mean age ±SD (years)	Positive nodes (n)	Negative nodes (n)	LOE	NOS
Di Lena	2023	Canada	RC	Women ≥ 70 years with cN0, T1-3, ER+/HER2−, invasive breast cancer	118	77.0 ± 8.1	27	91	3	8
Gu	2022	China	RC	Women ≥ 70 years with,cN0, invasive breast cancer[a]	376	74.6 ± 3.6	65	311	3	8
Laws	2020	Canada	RC	Women > 70 years with cN0, T1-3, ER+/HER2−, invasive breast cancer	312	75.8 ± 4.6	72	240	3	7
Carleton	2021	USA	RC	Women ≥ 70 years with, cN0, T1-3 ER+/HER2−, invasive breast cancer	1373	77.7 ± 7.4	159	1214	3	6
McKevitt	2021	Canada	RC	Women ≥ 70 years with cN0, T1-3 ER+/HER2−, invasive breast cancer	2662	75.4 ± 5.2	665	1997	3	7
Davey	2021	Ireland	RC	Women > 65 years with cN0, T1/2, ER+/HER2−, invasive breast cancer	253	73.2 ± 5.5	50	203	3	7
Christian	2019	USA	RC	Women ≥ 70 years with cN0, T1, ER+/HER2−, invasive breast cancer	40	76.2	2	38	3	7
Sun	2020	USA	RC	Women ≥ 70 years with cN0, T1-3, ER+, invasive breast cancer[b]	371	74.7 ± 4.5	120	251	3	6
Tamirisa	2018	USA	RC	Patients ≥ 70 years with cN0, T1-3, invasive breast cancer[c]	99764	80 ± 5.9	14290	85474	3	6
Daly	2024	Ireland	RC	Women ≥ 70 years with T1-3, ER+/HER2−, invasive breast cancer	255	75 ± 4.5	59	196	3	6

Abbreviations: RC, retrospective cohort; SD, standard deviation; cN0, clinically node negative; T, T stage; ER, Estrogen Receptor; HER2, human epidermal growth receptor 2; LOE, level of evidence; NOS, Newcastle-Ottawa Score.
[a] 99.1% ER or PR+/ 79.3% HER2−.
[b] 97.4% HER2−.
[c] 98.8% female, 89% ER+/ 95.5% HER2−.

Figure 2 Forest plot illustrating likelihood of receipt of adjuvant chemotherapy post positive versus negative SLNB.

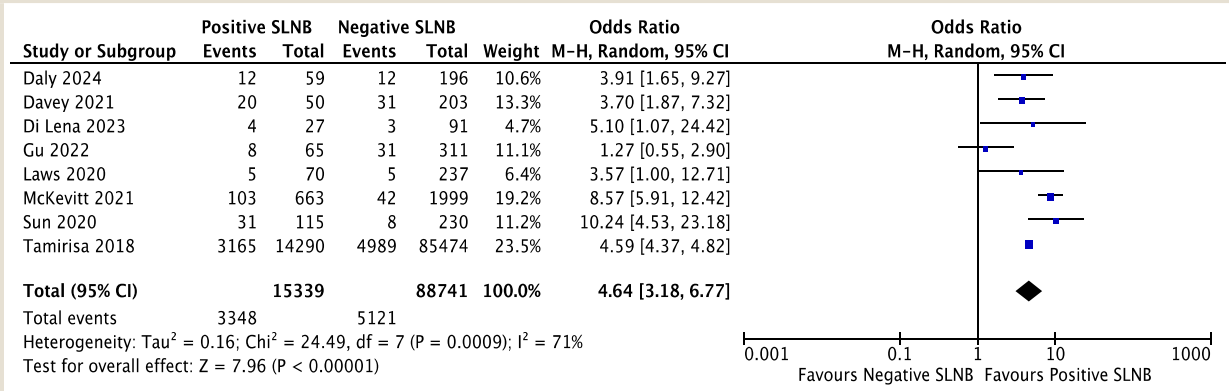

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Figure 3 Forest plot illustrating likelihood of receipt of adjuvant radiotherapy post positive versus negative SLNB.

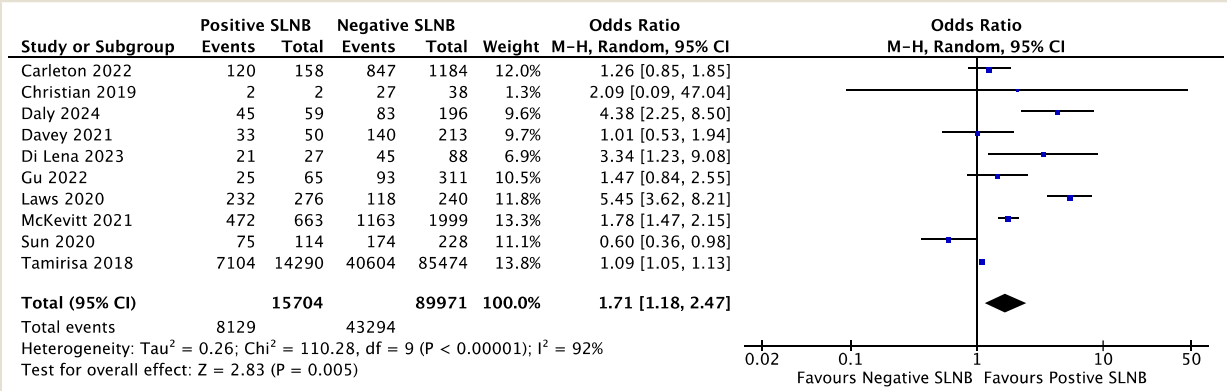
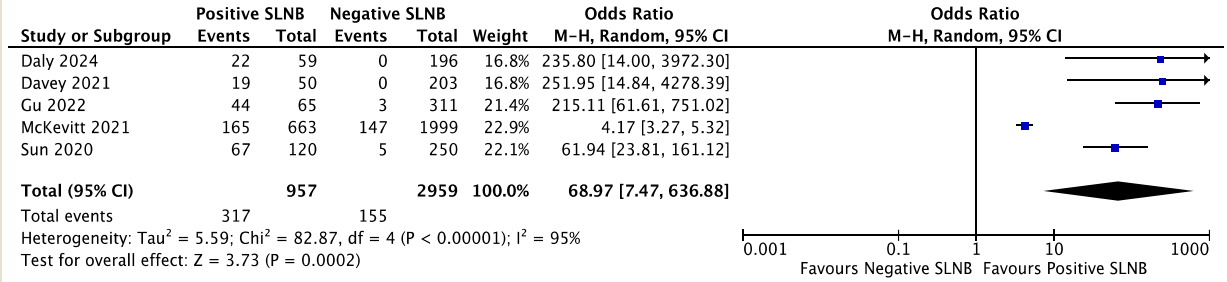


Figure 4 Forest plot illustrating likelihood of undergoing of cALND post positive versus negative SLNB.



reduced the I^2 from 95% to 3%, however, a positive SLNB was strongly associated with the performance of cALND in all studies (Supplemental Table 3).

Outcomes Post SLNB

Four studies, including 4,782 patients, compared outcomes post positive and negative SLNB. Only 1 study found significantly different outcomes between groups. Sun et al. reported significantly worse overall survival (OS) (HR 1.68 (95% CI 1.1, 2.6), $P = .02$) and increased distant recurrence (DR) (HR 3.12 (1.1, 9.0), $P = .04$) in patients with a positive SLNB. Summary in Table 2.

Discussion

The key findings of this systematic review and meta-analysis were that, in older women with ER+/HER2−, cN0, early-stage breast cancer, a positive SLNB was significantly associated with an increased likelihood of receiving adjuvant chemotherapy and radiotherapy, and undergoing a completion cALND compared to those with a negative biopsy result.

The findings of this meta-analysis come despite the publication of the "Choosing Wisely" guidelines which advise against routine performance of SLNB in this cohort. Proponents of the continued performance of SLNB in the older cohort argue that it offers import information that may guide adjuvant therapy. In 2021, Minami et al. surveyed 29 surgical, medical and radiation oncologists on their attitudes regarding the "Choosing Wisely" guidelines.[29] Several concerns were reported including scepticism surrounding the strength of the evidence supporting the guidelines, fear of an increased risk of locoregional recurrence (LRR) and the increased need for alternative investigations when SLNB was omitted.[29] NCT02564848 is a prospective clinical trial examining the safety of omitting SLNB in 125 women ≥ 65 years of age who underwent BCS for T1-2/cN0, ER+ breast cancer.[30] Preliminary results have reported an axillary recurrence rate of just 1.6% at 3 years.[30] These initial results are undeniably positive and long-term follow up of this study may promote many clinicians to change their practice.

This study suggests that adjuvant chemotherapy was significantly more likely to be prescribed in those with a positive SLNB. However, in the era of precision oncology, individual tumour biology has an increasing role in chemotherapy selection. The advent of genomics has allowed individual patient tumors to be analyzed on a molecular level. OncotypeDX (ODx) is a commercially available predictive tool used to evaluate the risk of distant recurrence in the first 5-10 years.[31] The promising results of the TailorX trial, followed by the Rxponder trial, have

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Table 2 Summary of Reported Outcomes Post Positive SLNB

Author	Patients (n)	Follow-up (years)	Outcome	HR (95% CI)	*P*-value
McKevitt	2662	5	BCSS	1.5 (0.8-2.7)	.2
Carleton	1373	5	DFS	0.86 (0.26-2.86)	.81
Sun	371	15	OS	1.68 (1.1-2.6)	.02*
			LRR	1.57 (0.3-9.4)	.62
			DRFS	3.12 (1.1-9.0)	.04*
Gu	376	5.8[a]	DFS	1.09 (0.54-2.22)	.81
			DDFS	1.78 (0.55-5.75)	.34
			BCSS	0.99 (0.32-3.05)	.99
			OS	1.29 (0.57-2.9)	.54

Abbreviations: HR, hazard ratio; BCSS, breast cancer-specific survival; DFS, disease-free survival; OS, overall survival; LRR, locoregional recurrence; DR; distant recurrence; DDFS, distant disease-free survival;
[a] Median, range (0.25-11.92).
* statistically significant.

shown no significant benefit of receiving adjuvant chemotherapy compared to endocrine therapy alone in postmenopausal patients with, ER+/HER2− breast cancer, with 1-3 positive nodes a "low" ODx score.[17,32] The 2 studies included in this meta-analysis that included ODx score in multivariable analysis, found that a "high" ODx score was a stronger predictor of receipt of chemotherapy than a positive SLNB.[20,21]

The increased use of radiotherapy in those with a positive SLNB comes despite several studies observing that radiation after BCS does not improve distant disease-free survival (DFS)or OS.[9,33-35] Clinicians decisions may have been influenced by recent trials such as PRIME II and LUMINA require knowledge of nodal status to participate.[35,36]

Several randomised control trials with long-term follow up have reduced indications for ALND in early-stage breast cancer and that shown that while ALND may reduce risk of LRR its performance does not improve survival in this cohort.[37-39] However, in this study, surgeons were evidently encouraged to perform cALND in patients with a positive SLNB. Proponents of cALND may argue that as life expectancies increase, so too should the threshold for omission of cALND. Many would criticize this approach and condemn it for being overly-invasive and a cause of unnecessary morbidity.

AUS has gained increasing interest as a possible replacement for SLNB in patients with early-stage breast cancer, serving as a less invasive means of staging the axilla. The argument in favour of performing AUS only is strongest in the older population as over-investigation and over-treatment is a critical consideration. The recent SOUND (NCT02167490) trial assessed whether the omission of axillary staging in patients without radiological evidence of axillary metastasis on pre-operative AUS would affect outcomes in patients with T1 breast cancer.[13] In 1405 women included, no difference in DFS at 5 years was found between those who underwent SLNB and those who did not.[13] However, the SOUND trial was underpowered to report on whether SLNB positivity increased receipt of adjuvant therapies, possibly confounding results. Other RCTs, NAUTILUS (NCT04303715) and BOOG 2013-08 (NCT02271828), are also evaluating the omission of SLNB in patients with early-stage disease.[14,15] Importantly, these trials include patients with both T1 and T2 (< 5 cm) disease.[14,15] Alternatively, the SOAPET trial (NCT04072653) is evaluating dedicated axillary positron emission tomography (DA-PET) in combination with pre-operative AUS and MRI as a replacement for SLNB in women with T1/T2 disease.[16] SLNB is being omitted in patients with a low risk DA-PET, AUS, MRI and clinical examination.[16] If the results of this trial are promising, and considering that nuclear imaging modalities have become increasingly accessible, DA-PET may become an integral tool in future axillary staging. Furthermore, a previous study has shown that surveillance is more cost-effective than SLNB post negative AUS in postmenopausal women with hormone positive disease. Future studies may further elucidate the discrepancy in cost-effectiveness in the older cohort which is likely greater.[40]

Future studies may integrate ODx and AUS and allow for an increasingly tailored, minimally invasive approach in guiding adjuvant treatment decisions for this cohort. However, further randomised trials with long-term follow-up are needed to conclusively identify the patients in whom SLNB may be safely omitted.

This systematic review and meta-analysis has a number of inherent limitations. Firstly, all included studies were retrospective in nature. Therefore, it is likely that both selection and reporting biases influenced results to varying degrees across studies; in a manner that is challenging to quantify. Most studies included patients that underwent SLNB prior to the publication of the "Choosing Wisely" guidelines. Thus, as precision oncology is continually evolving and changing, it is likely that the included studies do not perfectly reflect current treatment practices today. While studies included in this meta-analysis predominantly included women ≥ 70 with ER+/HER2−, early-stage, invasive breast cancer, a degree of heterogeneity in the patients included existed between studies. Furthermore, data regarding chemotherapy regimens used or whether patients received partial or whole breast irradiation was not widely available. Additionally, the paucity of outcome data reported in these studies did not allow for the performance of meta-analysis. The influence of SLNB on patient quality of life was similarly poorly reported. Therefore, the crucial question of whether sentinel node

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status or the receipt adjuvant therapies influenced outcomes remains unanswered.

Information on functional status and comorbidities was not widely available for analysis; and treatment decisions were rarely reported for different stages and grades. Therefore, the provided data lacked the necessary granularity for the performance of subgroup analysis. This is key information, as functional age, influenced by mental and physical capacity, rather than chronological age should most impact decision making with regard to adjuvant therapy. Similarly, as breast cancer treatment becomes more personalised, specific tumour stage, grade and biology have an increasing impact on optimising individualised patient management. Regional differences in both life expectancy and survival post breast cancer diagnosed are commonly recognised.[41,42] Importantly, the definition of "older age" varies considerably and must be interpreted in both a geographical and patient specific context.[43] Of the 4 countries represented in this meta-analysis, sensitivity analysis revealed no clear jurisdictional differences in adjuvant treatment options selected between studies.[24] While further studies are required to understand the validity of this observation, it is clear that different regions will benefit from different breast cancer treatment guidelines. These variations further emphasise the importance of avoiding over-reliance on age-based guidelines and that guidelines should be considered in the context of the patient as an individual.

Conclusion

Despite recent guidelines encouraging the de-escalation of SLNB in older women with ER+/HER2−, cN0, early-stage breast invasive breast cancer, it is likely that a positive SLNB continues to impact adjuvant treatment decisions in this cohort. As life expectancies increase, the challenge of optimising outcomes while preventing over-treatment is increasingly difficult to overcome in older patients. However, less-invasive diagnostic modalities such as AUS and genomic testing may replace SLNB as a guide for adjuvant management of early-stage disease. Ongoing prospective trials may better inform surgeons as to the true value of SLNB in this cohort and allow for enhanced patient management. Future research should focus on the influence of SLNB on both survival outcomes and patient quality of life on long-term follow-up in order to offer optimal personalised treatments in the older cohort.

Disclosure

The authors have stated that they have no conflicts of interest.

CRediT authorship contribution statement

Gordon R. Daly: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Gavin P. Dowling:** Writing – original draft, Methodology, Conceptualization. **Mohammad Said:** Data curation. **Yazan Qasem:** Data curation. **Sandra Hembrecht:** Formal analysis. **Gavin G. Calpin:** Formal analysis, Conceptualization. **Ma'en M. AlRawashdeh:** Data curation. **Arnold D.K. Hill:** Writing – review & editing, Supervision, Conceptualization.

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Supplementary materials

Supplemental Table 1 Leave-one-out sensitivity analysis of studies comparing adjuvant chemotherapy receipt post SLNB

Study omitted	OR (95% C.I.)	I^2	Tau^2	*P* value
Daly 2024	4.71 (3.09, 7.16)	75%	0.18	0.0005
Davey 2021	4.77 (3.09, 7.34)	75%	0.19	0.0005
Di Lena 2023	4.60 (3.09, 6.85)	75%	0.17	0.0004
Gu 2022	5.48 (3.92, 7.66)	60%	0.09	0.02
Laws 2020	4.71 (3.15, 7.05)	75%	0.17	0.0005
McKevitt 2021	4.02 (2.69, 6.01)	56%	0.13	0.03
Sun 2020	4.21 (2.84, 6.24)	71%	0.15	0.002
Tamirisa 2018	4.48 (2.51, 7.99)	73%	0.4	0.001

Supplemental Table 2 Leave-one-out sensitivity analysis of studies comparing adjuvant radiotherapy receipt post SLNB

Study omitted	OR (95% C.I.)	I^2	Tau^2	*P* value
Carleton 2022	1.79 (1.18, 2.71)	93%	0.3	<0.0001
Christian 2019	1.70 (1.17, 2.47)	93%	0.26	<0.0001
Daly 2024	1.54 (1.06, 2.23)	92%	0.23	<0.0001
Davey 2021	1.81 (1.22, 2.69)	93%	0.27	<0.0001
Di Lena 2023	1.62 (1.11, 2.37)	92%	0.25	<0.0001
Gu 2022	1.74 (1.17, 2.60)	93%	0.27	<0.0001
Laws 2020	1.42 (1.05, 1.92)	85%	0.13	<0.0001
McKevitt 2021	1.72 (1.06, 2.78)	91%	0.41	<0.0001
Sun 2020	1.95 (1.31, 2.89)	92%	0.26	<0.0001
Tamirisa 2018	1.84 (1.15, 2.95)	87%	0.39	<0.0001

Supplemental Table 3 Leave-one-out sensitivity analysis of studies comparing completion ALND performance post SLNB

Study omitted	OR (95% C.I.)	I^2	Tau^2	*P* value
Daly 2024	53.60 (4.90, 586.91)	96%	5.37	<0.0001
Davey 2021	52.92 (4.83, 579.72)	96%	5.38	<0.0001
Gu 2022	48.78 (94.81, 495.12)	94%	4.66	<0.0001
McKevitt 2021	111.77 (53.60, 233.07)	3%	0.02	<0.0001
Sun 2020	74.86 (3.89, 1442.35)	95%	8.06	<0.0001

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