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RESEARCH ARTICLE

The value of sentinel lymph-node biopsy after neoadjuvant therapy: an overview

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Abstract

Purpose We conducted a systematic review to analyse the performance of the sentinel lymph-node biopsy (SLNB) after the neoadjuvant chemotherapy, compared to axillary lymph-node dissection, in terms of false-negative rate (FNR) and sentinel lymph-node identification rate (SLNIR), sensitivity, negative predictive value (NPV), need for axillary lymph-node dissection (ALND), morbidity, preferences, and costs.

Methods MEDLINE, Embase, Scopus, and The Cochrane Library were searched. We assessed the quality of the included systematic reviews using AMSTAR2 tool, and estimated the degree of overlapping of the individual studies on the included reviews.

Results Six systematic reviews with variable quality were selected. We observed a very high overlapping degree across the included reviews. The FNR and the SLNIR were quite consistent (FNR 13–14%; SLNIR ~ 90% or higher). In women with initially clinically node-negative breast cancer, the FNR was better (6%), with similar SLNIR (96%). The included reviews did not consider the other prespecified outcomes.

Conclusions It would be reasonable to suggest performing an SLNB in patients treated with NACT, adjusting the procedure to the previous marking of the affected lymph node, using double tracer, and biopsy of at least three sentinel lymph nodes. More well-designed research is needed.

PROSPERO registration number: CRD42020114403.

Keywords Breast cancer · Neoadjuvant chemotherapy · Preoperative chemotherapy · Sentinel lymph node

Background

Neoadjuvant chemotherapy (NACT) has become a generalized approach to the treatment of breast cancer, with the aim of reducing the size of the primary tumor and to facilitate performing a conservative surgery. In addition, it will also allow an earlier evaluation of the clinical efficacy and changes in the regimens [1], as well as the conservation of the breast in operable cancers, with higher rates of complete pathological responses [2].

Sentinel lymph-node status is an important prognostic factor and sentinel node biopsy (SLNB) is considered the reference procedure for lymph-node staging of early breast cancer lesions [3, 4]. SLNB is usually undergone before performing the axillary lymph-node dissection (ALND). ALND is a more accurate method to evaluate the spread of the disease to the loco-regional lymph nodes, but is in turn a more complex procedure and is associated with important morbidities in the short and long term such as lymphedema, nerve injury, worse quality of life, etc [4, 5].

There is still a debate about the value of SLNB after neoadjuvant treatment, especially for clinical-positive lymph node initially [6]. There are also concerns about the increase in false-negative rate (FNR) and the decrease in sentinel lymph-node identification rate (SLNIR) after NACT. Although infrequent (near 3%), the occurrence of loco-regional relapses in sentinel lymph-node biopsy negative breast cancer patients is another matter of concern [7].

SLNIR and FNR are considered as the most clinically relevant performance characteristics of this procedure [8].

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The SLNIR is defined as the proportion of successfully completed SLNB. FNR represents in turn people who had a negative index test result, but were classified by the reference standard as having the target condition [9]. These patients may be denied, or experience delays in receiving effective treatment.

When synthesizing the available evidence on a given topic, researchers can identify multiple relevant systematic reviews addressing the same (or very similar) clinical questions and that includes many of the same primary studies (overlapping) [10]. The simple sum of data coming from an increasing number of studies/reviews, where primary studies can be counted more than once, will result in an artificial and disproportionate statistical power, and hence, in biased and falsely reliable results [11, 12].

We aimed to assess the performance of SLNB after NACT, in terms of FNR, SLNIR, sensitivity, negative predictive value (NPV), need for axillary lymph-node dissection (ALND), morbidity, preferences, and costs. We sought also to assess the quality of the existing systematic reviews, as well as to know the degree of study overlapping across the published systematic reviews.

Methods

Literature review

To find relevant studies to answer the clinical question, we designed a search strategy in MEDLINE (accessed via PubMed), Scopus, and The Cochrane Library. We also carried out a manual search of relevant reviews and studies, and contacted experts in the field (PS, AP, FJC, and SS) to find out if they were aware of other unpublished or on-going studies. The search was first conducted in December 2018, and lastly updated in November 2020 (see Appendix 1. Search strategy).

Eligibility criteria

Systematic reviews including prospective or retrospective studies evaluating the value of SLNB for decision-making after neoadjuvant chemotherapy, followed by ALND, were considered for inclusion. An attempt was made to identify relevant economic evaluations for the question, as well as studies on the importance given by patients to the outcomes of interest.

Risk of bias

We assessed the quality of the systematic reviews using the AMSTAR 2 tool [13]. We considered the items related to literature search, risk-of-bias assessment/impact, appropriateness of meta-analytical methods, and assessment and impact of publication bias as the most important ones.

Examining overlapping

We used the approach described by Pieper y cols. [11], and included only the prospective studies identified in the reviews. We calculated the measure of the "covered area" (CA) according to the formulae

$$CA = \frac{N}{rc},$$

where N is the number of included publications (including double counting), r is the number of rows (studies), and c is the number of columns (reviews). We then calculated the "corrected cover area" (CCA), a measure that takes into consideration the differences in the number of studies included by every separate review, using the formulae

$$CCA = \frac{N - r}{rc - r}.$$

Summary of findings

We elaborated a narrative synthesis of the results of the reviews and the studies obtained from the search of the literature. The main characteristics of the included reviews/studies are provided, as well as the main findings of the reviews for each of the outcomes of interest.

Results

The last search was performed in November 2020. After the analysis of the abstracts and the potentially relevant full-text articles, we selected six systematic reviews [14–19]. Consultation with experts did not yield any other additional information (see Table 1 Characteristics of the included systematic reviews).

Quality assessment

Using AMSTAR 2 tool, four reviews [15, 16, 18, 19] reached a good quality assessment. One review [17] failed to report data on a previous protocol and the potential deviations from it, as well as the impact of the risk of bias assessment on the results of the review. In the other systematic review [14], literature search was limited to PubMed/Ovid, and provided not enough information about the impact of the risk of bias on both the individual studies. (See Table 2 AMSTAR 2 Assessment, and Fig. 1 AMSTAR 2 Assessment).

Table 1 Characteristics of the systematic reviews

Review	Country	No. of studies included	Primary study design	Participants
El Hage Chehade 2016	UK	19 observational studies published until January 2016. Bibliographic searches in PubMed. Only articles in English	18 prospective studies, one retrospective study	3398 women with breast cancer and diagnosis of axillary lymph node metastases by physical examination or by echography, scheduled to receive NACT and SLNB followed by ALND
Geng 2016	China	16 observational studies published between 2000 and 2015. Bibliographic searches in PubMed, Embase, The Cochrane Library. Only articles in English	11 prospective studies, 5 retrospective studies	1456 women with invasive, clinically node-negative breast cancer receiving NACT, and who underwent SLNB followed by ALND (range 9 to 575 per study)
Mocellin 2016	Italy	71 studies published between entre 2000 and 2014. Bibliographic searches in PubMed, Cochrane y Scopus until December 2014. No language restrictions	32 prospective studies, 39 retrospective studies	7451 women with locally advanced breast cancer who underwent SNB after NACT; pathology evaluation of the lymph node dissection following SLNB (media 103 patients per study; range 14 to 689 per study)
Tee 2018	Ireland	13 studies published between 2007 and 2017. Bibliographic searches in PubMed, Ovid MEDLINE, Embase and Web of Science until April 2017. Only articles in English	12 prospective studies, one retrospective study	1921 women with breast cancer with node-positive disease and confirmation by pathology, SLND after NACT followed by ALND (range 51 to 689 patients per study)
Shirzadi 2019	Iran	36 studies published between 2000 and 2016. Bibliographic searches in PubMed, ISI Web of Sciences, Scopus, and Cochrane databases until November 2016. Only articles in English	22 prospective studies, 14 retrospective studies	2609 patients with breast cancer undergoing SLNB after NACT, and undergoing ALND regardless of SLNB pathology (range 9 to 529 patients per study)
Simons 2019	The Netherlands	27 studies published between 2007 and 2018. Bibliographic searches in MEDLINE and Embase until April 2018. No language restrictions	16 prospective studies, 11 retrospective studies	2217 patients with cN + breast cancer, confirmed by pathology. SLNB after NACT followed by ALND (range 11–637 patients per study)

NACT neoadjuvant chemotherapy; *ALND* axillary lymph-node dissection; *SLNB* sentinel lymph node biopsy

Table 2 AMSTAR 2 assessment

Item	El Hage Chehade 2016	Geng 2016	Mocellin 2016	Tee 2018	Shirzadi 2019	Simons 2019
PICO question	Yes (patients: women with breast cancer with metastases of the axillary lymph nodes; Intervention: SLNB followed by ALND. Outcomes: FNR, IR, pCR)	Yes (patients: women with invasive, clinically node-negative breast cancer; Intervention: SLNB followed by ALND; Outcomes: IR, sensitivity, FNR, NPV, AR)	Yes (Patients with locally advanced breast cancer after NACT; Intervention: SLNB after neoadjuvant chemotherapy; Outcomes: IR, FNR)	Yes (Patients: women with breast cancer who had a node-positive disease; Intervention: SLNB followed by ALND. Outcomes: FNR, receptor status, tumor subtype, nodal pCR)	Yes (Patients: women with node-positive breast cancer who received NACT, and who underwent SLNB and ALND regardless of SLNB pathology. Outcomes: FNR, IR)	Yes (Patients: women with node-positive breast cancer who received NACT, and who underwent SLNB and ALND. Outcomes: ax-pCR rate, AR, FNR, IR)
Previous protocol	No	No	No	No	No	No
Selection of study design	No	No	Yes (retrospective or prospective studies)	No	No	Yes (controlled trials, cohort and case–control studies)
Search strategy	No (Medline-Ovid)	Yes (PubMed, Embase, The Cochrane Library)	Yes (PubMed, Cochrane, Scopus)	Yes (PubMed, Ovid MEDLINE, Embase and Web of Science)	Yes (PubMed, ISI Web of Sciences, Scopus, The Cochrane Library)	Yes (MEDLINE, Embase)
Duplicate study selection	Yes (two authors)	Partially Yes (no described, but probably yes)	Yes (two authors)	Yes (two authors)	Yes (two authors)	Yes (two authors)
Duplicate data extraction	No (not clear)	Yes (two authors)	Yes (two authors)	No (not clear)	Yes (two authors)	Yes (two authors)
Excluded studies described	Partial Yes (not meeting inclusion criteria, statistical reason)	Yes	Yes	Yes	Yes	Yes
Included studies described	Partial Yes (lack of details)	Yes	Yes	Partial Yes	Yes	Yes
RoB assessment	No (only publication bias)	Yes (QUADAS-2)	Yes (QUADAS-2)	Partial Yes (publication, small effect study bias)	Yes (QUADAS-2)	Yes (QUADAS-2)
Sources of funding of individual studies	No	No	No	No	No	No
Methods for meta-analysis	Partially Yes (no model described, meta-regression)	Yes (fixed-effects model meta-analysis)	Yes (random effects meta-analysis)	Yes (random effects meta-analysis)	Yes (random effects meta-analysis)	Yes (random effects meta-analysis)
Impact of RoB on meta-analysis	No (only publication bias)	No	Yes (examination for bias using sensitivity analysis)	No (only publication bias)	Yes (examination for bias using sensitivity analysis)	No
RoB in individual studies (Discussion)	No	No	No	No	No	No
Heterogeneity	Yes (I^2 statistic)	Yes (I^2 statistic)	Yes (I^2 statistic, χ^2-based Cochran's Q test)	Yes (I^2 statistic)	Yes (I^2 statistic, χ^2-based Cochran's Q test)	Yes (I^2 statistic, χ^2)
Publication bias	Yes (funnel plots)	Yes (funnel plots, Begg's test)	Yes (funnel plots)	Yes (funnel plots)	Yes (Egger's tests)	No
Conflict of interest	Yes	Yes	No	Yes	Yes	Yes

RoB risk of bias; *SLNB* sentinel lymph-node biopsy; *ALND* axillary lymph-node dissection; *pCR* pathological complete response; *IR* identification rate; *FNR* false-negative rate; *NPV* negative predictive value; *AR* accuracy rate

Risk of bias

The main flaws of the included studies were found in the domains "Patient selection" and "Index test", where most of the studies were qualified as high risk of bias; therefore, we judged the quality of the evidence as low.

Overlapping

The six systematic reviews included in total 107 prospective studies, corresponding to 51 primary studies. Using the method described by Pieper et al. [11] we calculated a CA of 35.0%, and a CCA of 22%, showing a very high overlapping across the five included reviews.

Outcomes of interest

See Table 3. Summary of findings.

False-negative rate (FNR)

FNR were very similar across five systematic reviews [14, 16–19], ranging between 13 and 17%.

El Hage Chehade 2016 found that the pooled estimate for the FNR was 13% (95% CI 10.8–15.6%). In this review, median age, tumor histology, tumor size, receptor status, and chemotherapy regimen had no effect on pCR, although authors describe a cN1 disease marginally associated with an increased pCR rate when compared with N2 or N3 disease ($p = 0.06$).

In Mocellin 2016, the calculated FNR was 14.2% (95% CI 12.5–16.0%). No statistically significant differences were found between patients with clinically negative nodes before NACT (FNR 23.5%, 95% CI 15.8–33.5%) and patients with nodes clinically positive before NACT (FNR 15.2%, 95% CI 12.4–18.5%).

The systematic review by Tee et al. found a pooled estimate of 14% for the FNR (95% CI 11–17%). No differences were found when FNR was analysed according to the mapping technique (single mapping: 19% [95% CI 1–27%], dual mapping: 11% [95% CI 6–15%], $I^2 = 40.5\%$ [moderate heterogeneity], $p = 0.12$). The review did find differences in the FNR when the analysis was performed according to the number of lymph nodes removed (one lymph node removed: 20% [95% CI 13–27%], two lymph nodes removed: 12% [IC 95% 5–19%], three or more nodes removed: 4% [95% CI 0–9%] [$I^2 = 78.2\%$ [high heterogeneity]; $p = 0.00$]).

In the meta-analysis by Shirzadi 2019, the pooled FNR was 13% (95% CI 7–18%). In the subgroup analysis considering the number of tracers used, the pooled FNR for single and dual tracers was 9% (95% CI 3–15%) and 14% (95% CI 10–19%), respectively, ($I^2 = 91.3\%$, high heterogeneity). Egger's test showed evidence of publication bias.

Finally, Simons 2019 reported an FNR of 17% (95% CI 14–20%). No differences were observed with the use of single tracer when compared to dual tracers (16 vs 13%; $p = 0.53$), or when immunohistochemistry (IHC) analysis was used or not (15 vs 17%; $p = 0.47$). Removal of at least 3 SLNs was associated with a lower FNR, when compared to < 3 SLNs (8 vs 22%; $p < 0.0001$).

The systematic review and meta-analysis by Geng et al., which included only women with initially clinically node-negative breast cancer, found a pooled FNR of 6% (95% CI 3–8%). No significant differences were found between studies with and without IHC staining ($p = 0.241$) (only H&E staining: 11% (95% CI 4–18%; six studies); H&E combined with IHC staining: 4% (95% CI 1–7%; six studies).

Sentinel lymph-node identification rate (SLNIR)

Sentinel lymph-node identification rates (SLNIR) were also very similar across the six systematic reviews, ranging from 89 to 96%.

El Hage Chehade 2016 found a pooled estimate of 90.9% (95% CI 87.6–93.4%). Mocellin 2016 reported an SLNIR of 89.6% (95% CI 87.8–91.2), while the systematic review by Tee et al. found that pooled SLNIR was 90% (95% CI 87–93%), with a high heterogeneity ($I^2 = 75.2\%$).

The systematic review by Geng 2016 found a pooled SLNIR of 96% (95% C: 95–97%). No significant differences were found when different mapping methods were used ($p = 0.18$) (only blue dye mapping: 96% (95% CI 91–100%, three studies; only radiocolloid: 96% (95% CI 94–99%; four studies; both blue dye and radiocolloid: 97% (95% CI 96–98%; six studies).

In the meta-analysis performed by Shirzadi 2019, the pooled SLNIR was 89% (95% CI 85–94%). The subgroup analysis according to the type of tracer showed that the pooled SLNIR for single and dual tracers was 92% (95% CI 87–96%) and 89% (95% CI 80–98%), respectively ($I^2 = 80.5\%$; high heterogeneity).

Finally, the systematic review by Simons et al. found an SLNIR of 89% (95% CI 87–92%).

Evidence on the use of resources

We identified a study about costs conducted in Hong Kong, which evaluated the resource needs derived from performing a sentinel lymph-node biopsy using gammagraphy [20]. However, this study "excluded patients who had undergone neoadjuvant chemotherapy, because there is still an open discussion on the influence of neoadjuvant chemotherapy on sentinel node identification". Therefore, these findings are not applicable to the population of interest for this review.

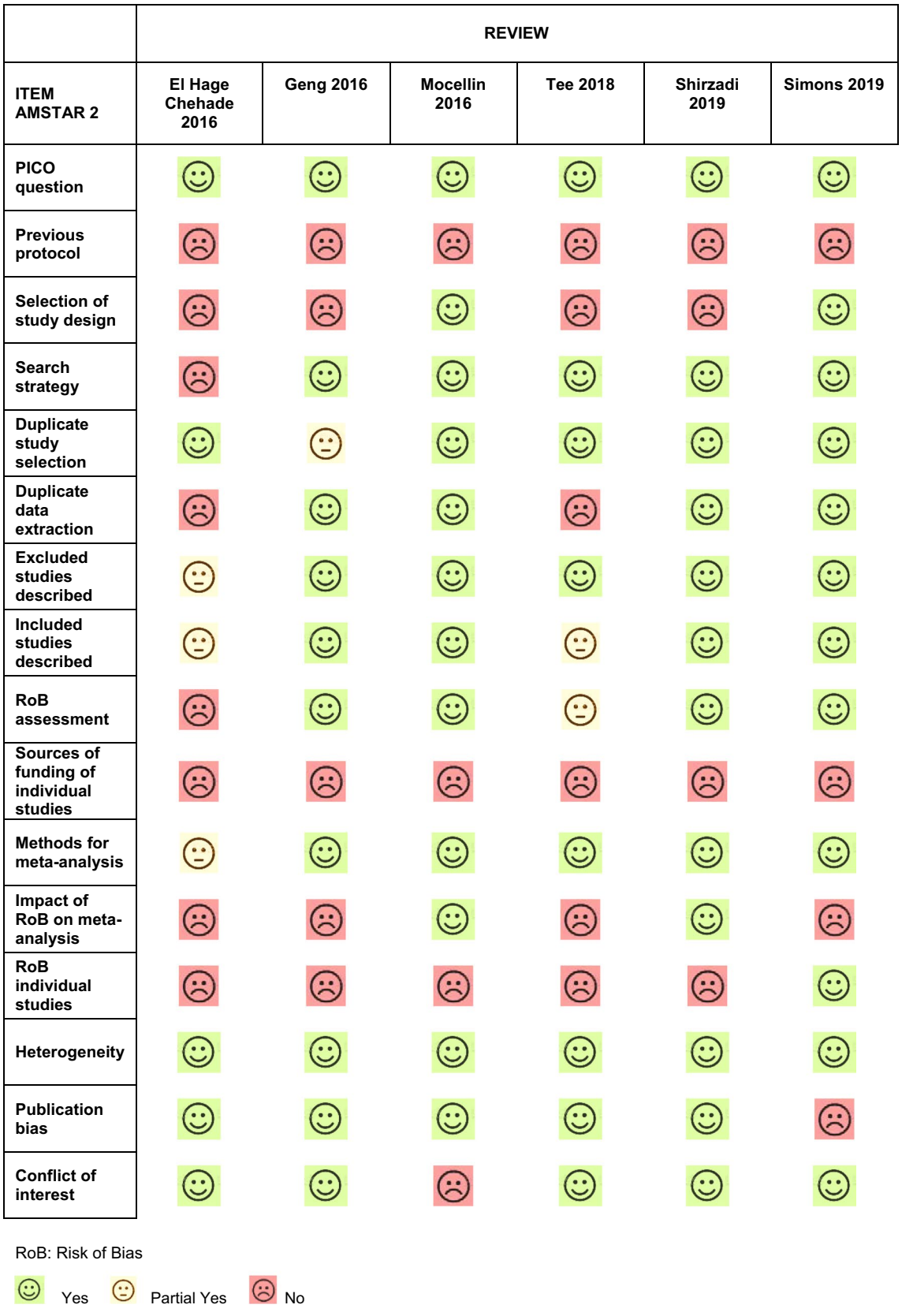

Fig. 1 AMSTAR 2 assessment

Table 3 Summary of findings

Outcome	Review	Number of studies	Results	Subgroup analysis
False-negative rate (FNR)	El Hage Chehade 2016	19	13% (95% CI 10.8–15.6%); range 5.1–25%	cN1 disease was marginally associated with an increased pCR rate when compared with N2 or N3 disease ($p=0.06$), eight studies
	Mocellin 2016	65	14.2% (95% CI 12.5–16.0)	Clinically negative nodes before NACT: 23.5% (95% CI 15.8–33.5) five studies; clinically positive nodes before NACT: 15.2% (95% CI 12.4–18.5), 15 studies
	Tee 2018	13	14% (95% CI 11–17%); range 8–25%	Single mapping: 19% (95% CI 1–27%); dual mapping: 11% (95% CI 6–15%), four studies One lymph node removed: 20% (95% CI 13–27%); two lymph nodes removed: 12% (IC 95% 5–19%); three or more nodes removed: 4% (95% CI 0–9%), six studies
	Shirzadi 2019	36	Node- group: 7% (95% CI 5–9%); range 0–22% Node + to node- group: 13% (95% CI 7–18%); range 0–29.2%	Node- group: single tracer: 4% (95% CI 1–7%), dual tracer: 8% (95% CI 5–11%), 23 studies Node + to node- group: single tracer: 9% (95% CI 3–15%), dual tracer: 14% (95% CI 10–19%), 13 studies
	Simons 2019	16	17% (95% CI 14–20%)	Single tracer: 16%, dual tracer: 13% ($p=0.53$), five studies IHC used: 15%, IHC not used: 17% ($p=0.47$), 14 studies Removal of at least 3 SLNs: 8%, removal < 3 SLNs: 22% ($p<0.0001$), six studies
Sentinel lymph node identification rate (SLNIR)	El Hage Chehade 2016	17	90.9% (95% CI 87.6–93.4%); range 77.6–98%	_
	Mocellin 2016	71	89.6% (95% CI 87.8–91.2)	Clinically negative nodes before NACT: 94.0% (95% CI 86.0–97.6), seven studies; clinically positive nodes before NACT: 89.5% (95% CI 85.0–92.7), 16 studies
	Tee 2018	13	90% (95% CI 87–93%); range 77.9–98%	_
	Shirzadi 2019	36	Node- group: 94% (95% CI 92–96%); range 81–100% Node + to node- group: 89% (95% CI 85–94%); range 80.1–100%	Node- group: single tracer: 97% (95% CI 95–99%), dual tracer: 91% (95% CI 86–94%); 23 studies Node + to node- group: single tracer: 92% (95% CI 87–96%), dual tracer: 89% (95% CI 80–98%); 13 studies
	Simons 2019	16	89% (95% CI 87–92%); range 78–96%	_

pCR pathological complete response; *NACT* neoadjuvant chemotherapy; *IHC* immunohistochemistry; *SLN* sentinel lymph node

Discussion

In the last years, SLNB has gained prominence in patients with non-metastatic breast cancer, as a minimally invasive alternative to ALND.

The overview included six systematic reviews focused mainly on the false-negative rate and the sentinel node identification rate, with fairly consistent results for both outcomes in five of them (FNR 13–14%; SLNIR ~ 90% or higher). The rest of the outcomes of interest intended to investigate were not considered in the individual reviews.

The identification rates showed in general acceptable values (~ 90% or higher). False-negative rates were also consistent (13–14%), although several authors agree that values

below 10% would be advisable. In the subgroup analyses of two of the included reviews [18, 19], there were no significant differences according to the use of single and dual tracers, with a trend to higher FNRs when dual tracers are used in Shirzadi 2019. These results contrast with those from the ACOSOG Z1071 trial, where the clip placement in the biopsy-proven positive node at time of initial diagnosis and removal of this clipped node during axillary surgery showed to be an effective intervention to decrease the FNR from 12.6 to 6.8% [21]. In the study by Caudle et al., the use of Targeted Axillary Dissection (TAD) led to an FNR of 2%, compared to 10% when SLNB was performed alone [22]. Is important to notice the lack of randomized trials aimed to assess the role of the marking the affected lymph node to guide the clinical practice.

Subgroup analyses showed that FNR was also lower when more than one node was removed [17, 19]. A recent article by Classe et al. [23], a report from the GANEA2 study, found an overall FNR of 11.9% (95% CI 7.3–17.9%) in women with pN1 sentinel nodes, with significant differences according to the number of resected SLNs (19.3% for cases of one SLN versus 7.8% for cases of two or more SLNs; $p = 0.041$). Despite these findings, it is not clear yet how to manage patients for which metastases in less than 3 sentinel nodes are identified. Two on-going studies, the POSNOC trial [24] and the SENOMAC trial [25] will include women with no more than two metastatic sentinel nodes, and will contribute to shed light on this particular group of patients.

From the included systematic reviews, there is limited evidence about using single or double mapping. Tee 2018 found lower FNRs when dual mapping was used, but results came from only four studies. In a recent study by Arjunan et al. [26], in 44 women, most of them (86.3%) classified as N1 at diagnosis, and found a higher FNR with the single method of SLN mapping (33–50%), compared to the use of both method simultaneously (11%). The study reported also better results for the SLNIR when the dual method was used (100%) compared to 66.7% each when only the single method of SLN mapping was performed. To reduce the rate of false negatives in initially N1 tumors, it is recommended to map them prior to initiating neoadjuvant chemotherapy, although in some cases, the identified node is not the sentinel node, or the FNR is unacceptably high [27].

It is important to note that decisions about which cN + patients should be treated with SLNB after NAC must rely not only on the performance of the procedure but also on other methods, like lymphoscintigraphy [28], TAD [22], ultrasound-guided biopsy [29], determination of molecular subtypes [30], and breast pCR [31].

There are several clinical practice guidelines that address this important topic, and have issued recommendations about the SLNB in the NACT context. For example, the consensus of the Working Group of Radioguided Surgery of the Spanish Society of Nuclear Medicine and Molecular Imaging [32] states that, in patients with breast cancer undergoing neoadjuvant treatment, SNB is an alternative to avoid performing unnecessary axillary emptying. It states that, in patients node-positive at diagnosis, patients should be carefully selected according to the TN status (T1-3, N1), using a combined technic for lymph mapping (radiotracer plus staining), placing a clip on the pathological node and removing it during the biopsy, and completing the ALND, even if the SNB results in isolated tumor cells or micrometastases.

In the same line, the American Society of Clinical Oncology Clinical Practice Guideline [33] recommends that SNB should be offered to women with operable breast cancer receiving preoperative/neoadjuvant treatment. Such recommendation is based on an updated review of the literature, including randomized controlled trials, systematic reviews, meta-analyses, and clinical practice guidelines.

Finally, a more recent multidisciplinary guidance elaborated by the Association of Breast Surgery, Faculty of Clinical Oncology of the Royal College of Radiologists, UK Breast Cancer Group, National Coordinating Committee for Breast Pathology, and British Society of Breast Radiology [34] recommends for women with clinically node-positive axilla (cN1), that patients can be safely considered for SNB after NACT, and that four nodes should be removed using dual mapping.

Strengths

To perform this overview, we developed a structured and extensive bibliographic search complemented with manual search in relevant articles and reviews, and several recognized experts in the field were consulted for potentially relevant studies.

Key steps like article selection, data extraction, and risk-of-bias assessment were performed independently by two authors with experience in systematic review methodology, and the interpretation of the data and the conclusions were discussed and agreed upon with a panel of experts with extensive clinical and research experience.

In the analysis of the information, we implemented a useful method to detect the degree of overlapping among the reviews, which contributed to the knowledge of the real value of the sentinel lymph-node biopsy in the context of NACT.

Limitations

The six systematic reviews included a heterogeneous mix of women, i.e., women either with negative or positive SLNs before NACT, or with positive SLNs that became negative or remained positive after the treatment, and even some of them with an unknown status before and/or after the therapy. It

is valid to consider that the outcomes would be different for these varied groups of patients; therefore, this fact precludes drawing firm conclusions about the applicability, accuracy, and safety of the procedure.

One significant limitation is that was not possible to make a separate analysis of the performance of SLNB for different subtypes of breast cancer (HER2 and triple-negative, very sensitive to neoadjuvant treatment) and luminal or hormonal (not very sensitive).

The very high degree of overlapping detected means that several studies were considered simultaneously in two or more of the reviews, giving rise to apparently consistent results and to a supposedly high certainty from the available evidence. This fact is one of the classically described limitations of overviews, which has been recognized as resulting in a fictitious increase in statistical power [11, 12]. In this case, we decided to describe the overlap and recognize it as a possible limitation of the study, instead of adopting formal statistical approaches to deal with this issue.

Another potential flaw to consider is the lack of information on important outcomes for patients, such as satisfaction with treatment and costs. Given this limitation, the decisions on the most convenient procedure for an individual case should be taken along with patients, after providing them with the available information on the accuracy and possible adverse events associated with each procedure.

As implications for research, it is advisable that future studies develop new axillary markers, easier to locate in the operating room and not requiring a nuclear medicine service. Thresholds for residual tumor burden in lymph nodes that are considered susceptible to treatment by radiotherapy and without performing lymphadenectomy should be also established.

Conclusions

From the analysis of the six available systematic reviews, it would be reasonable to suggest performing a sentinel lymph-node biopsy in patients treated with NACT. However, for patients with positive LN initially, it is advisable to adjust the procedure to a number of technical requirements (previous marking of the affected lymph node, using double tracer, and biopsy of at least three sentinel lymph nodes), having established a correct staging of the tumor [32]. As the evidence from well-designed studies is still limited, such recommendation is based on the results of two clinical trials (ACOSOG Z1071, [21] SN FNAC [31]) which have shown a significant reduction in the false-negative rate with the biopsy of at least three lymph nodes, previously marking the affected lymph node and using a double tracer. It is important to have a precise definition of the indication, for example according to the staging proposed by the recommendations of the Radioguided Surgery Working Group of the Spanish Society of Nuclear Medicine and Molecular Imaging, [32] which addresses the feasibility of marking possible positive lymph nodes and their subsequent identification.

Appendix 1: MEDLINE/EMBASE search strategy

MEDLINE
PubMed

#1 “Breast Neoplasms”[Mesh].
#2 breast[tiab].
#3 #1 OR #2
#4 “Sentinel Lymph Node Biopsy”[Mesh].
#5 sentinel lymph node*[tiab].
#6 sentinel node biops*[tiab].
#7 SLNB[tiab].
#8 SLN[tiab].
#9 lymph node positivity[tiab].
#10 #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11 node positive[tiab].
#12 positive lymph node*[tiab].
#13 axillary[tiab].
#14 ALND[tiab].
#15 ALN[tiab].
#16 #11 OR #12 OR #13 OR #14 OR #15
#17 “Neoadjuvant Therapy”[Mesh].
#18 neo adjuvant chemotherapy[tiab].
#19 neoadjuvant chemotherapy[tiab].
#20 NAC[tiab].
#21 preoperative chemotherapy[tiab].
#22 pre operative chemotherapy[tiab].
#23 primary[ti].
#24 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
#25 #3 AND #9 AND #15 AND #24

EMBASE

#1 (neoadjuvan* NEAR/5 (chemotherapy OR treatment)):ti,ab.
#2 (sentinel NEXT/5 node* NEXT/2 biops*):ti,ab.
#3 #1 AND #2

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Declarations

Conflict of interest The authors have no competing interests to declare that are relevant to the content of this article. Juan Carlos Vazquez

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Ethical approval Not applicable.

Research involving human participants and/or animals Not applicable.

Informed consent Not applicable.

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