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Systematic Review

Oncological, surgical, and cosmetic outcomes of endoscopic *versus* conventional nipple-sparing mastectomy: meta-analysis

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Abstract

Background: Endoscopic nipple-sparing mastectomy has been developed to improve the cosmetic outcomes of conventional nipple-sparing mastectomy. This meta-analysis compares surgical, quality of life and oncological outcomes of endoscopic nipple-sparing mastectomy *versus* conventional nipple-sparing mastectomy.

Methods: PubMed and Embase were systematically reviewed to identify literature relevant to endoscopic nipple-sparing mastectomy and conventional nipple-sparing mastectomy literature published through to August 2023. The risk of bias was assessed using the Newcastle–Ottawa Scale, and proportional and pairwise random-effects meta-analysis was performed. Surgical (operative time, duration of hospital stay, blood loss, necrosis, overall complications), quality of life (cosmesis, pain, nipple-areolar complex sensitivity) and oncological outcomes (margin positivity, recurrence, metastasis and breast cancer-specific mortality rate) were evaluated.

Results: Of 1286 articles retrieved, 51 endoscopic nipple-sparing mastectomy studies and 12 conventional nipple-sparing mastectomy reviews were analysed; 10 non-randomized comparative studies (656 patients) were included in the pairwise analysis and 36 studies (comparative and single-group cohort studies; 2612 patients) in the proportional meta-analysis. Results showed no differences in oncological outcomes (mean follow-up of up to 52 months), comparable overall (OR = 0.49; $P = 0.100$) and necrotic complications (OR = 0.45; $P = 0.150$), and improved cosmetic satisfaction (OR = 1.88; $P = 0.020$). Comparing only single-incision endoscopic nipple-sparing mastectomy to conventional nipple-sparing mastectomy significantly reduced postoperative necrosis (OR = 0.19; $P = 0.008$). The proportional meta-analysis produced oncological and surgical outcome rates comparable to or lower than conventional nipple-sparing mastectomy rates. However, longer operative time (weighted mean difference = 43.08 min; $P < 0.00001$) and duration of hospital stay (weighted mean difference = 0.72 days; $P = 0.0007$) were observed.

Conclusion: Endoscopic nipple-sparing mastectomy does not affect oncological outcomes in up to 52 months mean follow-up when compared with conventional nipple-sparing mastectomy and provides better cosmetic satisfaction, with a reduced risk of necrosis after single-incision endoscopic nipple-sparing mastectomy. As such, endoscopic nipple-sparing mastectomy may become a viable breast surgery option.

Introduction

Breast cancer is one of the most prevalent cancers worldwide, accounting for 12.5% of all new annual cancer cases[1,2]. Significant progress in breast cancer treatment over the last three decades includes advancements in the understanding of intratumour heterogeneity, enhanced systemic treatments and more precise surgical techniques. The evolution of breast cancer surgery stems from a commitment to improve both the oncological and aesthetic outcomes of breast surgery, specifically through the application of minimally invasive techniques and the preservation of the nipple–areolar complex (NAC) during mastectomy[3–5].

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Since preservation of the NAC is considered key for promoting psychological wellbeing and cosmetic satisfaction[6], nipple-sparing mastectomy (NSM) has been increasingly performed in patients with prophylactic and therapeutic indications, who have been deemed ineligible for conservative breast surgery. Multiple meta-analyses between 2012 and 2021 suggested the oncological safety and non-inferiority of conventional NSM (C-NSM) compared with skin-sparing mastectomy (SSM) and modified radical mastectomy (MRM), provided lack of clinical or radiological evidence of nipple involvement and adequate removal of retro-areolar breast tissue is confirmed, which may require frozen biopsy at the time of surgery[6–8]. These analyses have also improved the definition of C-NSM patient selection, effectiveness and oncological safety, showing acceptably low rates of local recurrence and distant metastasis. However, limitations of the C-NSM technique, primarily the presence of visible scars, can impact postoperative cosmetic satisfaction[9,10]. Furthermore, the association of some C-NSM technique incision placements to NAC ischaemic necrosis impacts reconstruction-related surgical outcomes, particularly in large or ptotic breasts[11–14].

The literature outlines some 15 possible incisions for C-NSM, each with specific advantages and drawbacks[15,16]. For instance, incisions made beneath the breast (inframammary) provide restricted access to the upper regions, requiring deep retraction, a second axillary incision for axillary dissection, the use of headlights and uncomfortable positioning[17,18], and the weight of the prosthesis rests on the scar. Alternately, incisions positioned closer to the NAC reduce these challenges but introduce potential complications related to the disruption of the NAC vascular supply, consequently increasing the risk of necrosis[19,20]. Incision placement may also be related to long-term NAC dysaesthesia, which is sufficient to impact quality of life (QoL). The position of the mammary incision is a factor that contributes to the disruption of the intricate superficial neural network responsible for sensory function within the mastectomy flap tissue, influencing postoperative breast sensitivity[18]. This aspect underscores the importance of considering the neurological implications associated with various incision approaches in breast surgery[21].

Minimally invasive nipple-sparing mastectomy (MI-NSM) procedures, including endoscopic and robotic nipple-sparing mastectomy techniques, have been developed to address incision-related complications, cosmetic satisfaction and neurological concerns associated with C-NSM, in part by relocating the surgical incision from the peri-areolar region, inframammary fold, or surface of the breast to the axillary and lateral chest areas[22]. In particular, endoscopic nipple-sparing mastectomy (E-NSM) has been demonstrated to be feasible, as the better optics of endoscopic instruments have enabled precise mammary gland resection through small, off-the-breast, axillary incisions while leaving no visible scarring on the surface of the breast[15,23–30].

Even though minimally invasive mastectomy has been acknowledged as a viable choice for specific patients, several opinion articles, international protocols and consensus statements have been released, underscoring potential advantages but stressing the necessity for additional evidence[31–33]. A 2010 systematic review demonstrated that endoscopic subcutaneous mastectomy (ESM) can be used to achieve disease control with high rates of overall survival and low rates of local recurrence and distant metastasis[34]. This study, however, combined E-NSM with endoscopic skin-sparing mastectomy (E-SSM) data. A more recent systematic review, covering 20 years of endoscopic-assisted breast surgery (EABS), concluded that EABS was comparable to open techniques in oncological and surgical outcomes but lacked a formal quantitative analysis of E-NSM *versus* C-NSM techniques[35]. While both systematic reviews provided valuable analyses of the safety and efficacy of endoscopic *versus* open breast procedures, no prior systematic review has attempted to quantitatively synthesize the results of E-NSM publications through meta-analysis. Furthermore, the first endoscopic mastectomies, performed since 1994, used a gasless technique that required multiple small incisions in addition to the axillary incision, including a peri-areolar one[5]. This gasless method with a self-retractor almost always necessitated an axillary incision of at least 5 cm, whereas the newer gas-inflated E-NSM technique, aided by the more recent development of single-port devices, typically requires a smaller incision of only 2.5–3 cm. In the last decade, many researchers have adopted this newer method to reduce complications and improve cosmetic outcomes[5]. Hence, the introduction of the gas-inflated single-incision E-NSM has revitalized research, resulting in new data from prospective enrolment trials and necessitating an updated systematic review of the topic.

This systematic review and meta-analysis aims to compare E-NSM to C-NSM in oncological, surgical and cosmetic outcomes.

Methods

This systematic review and meta-analysis was conducted in accordance with the 2020 PRISMA statement[36]. No review protocol was registered or published before the initiation of the review project.

Selection criteria for published literature

A comprehensive systematic literature search of PubMed and Embase was conducted to identify studies relevant to E-NSM, published between the dates of the creation of the electronic databases and August 2023. Accepted E-NSM publications included studies relevant to single-incision endoscopic NSM and those relevant to endoscopy-assisted NSM, in which surgical space is created with physical retraction, rather than CO_2 gas insufflation, or multiple incisions are used. An additional systematic literature search of PubMed and Embase, targeting systematic reviews relevant to C-NSM, was performed to establish current practice/state of the art (SOTA). Search terms, databases and filters used to identify literature relevant to E-NSM or to C-NSM can be found in *Tables S1, S2* in the *Supplementary material*.

The inclusion criteria were: publications relevant to establishing the oncological, cosmetic and safety outcomes, side effects, risks and benefits of E-NSM; there were no language-based exclusion criteria for this systematic review; translations for non-English full-text publications were sought when abstracts met the inclusion criteria and could not be excluded based on any of the five exclusion criteria listed. Exclusion criteria were: publications not relevant to establishing the oncological, cosmetic and safety outcomes, side effects, risks and benefits of E-NSM; publications in which the population was limited (less than 10 patients); publications that did not evaluate the procedure in live human participants; publications that were expert opinions, editorials or laboratory studies; publications that were not of high methodological quality and scientific validity, including study protocols and conference abstracts more than 3 years old.

Additional studies relevant to E-NSM, discovered by reviewing references of relevant publications or identified during

additional author-specific and C-NSM literature searches, were also included.

Since C-NSM is a procedure that has been extensively researched, the C-NSM publications search was restricted to higher-level evidence (systematic reviews and meta-analyses). The inclusion criteria were:

systematic reviews and meta-analyses relevant to establishing the oncological, cosmetic and safety outcomes, side effects, risks and benefits of C-NSMs. The exclusion criteria were: publications not relevant to establishing the oncological, cosmetic and safety outcomes, side effects, risks and benefits of C-NSMs; publications that were expert opinions or editorials; publications that were not of high methodological quality and scientific validity (including all studies ranked lower than Oxford Centre for Evidence-Based Medicine (OCEBM) level 1).

After removing duplicate titles and conference abstracts that copied a data set from a separate publication by the same author(s), screening and assessment of eligibility for each record was performed independently by two authors. First, abstracts of each record were screened to determine if inclusion or exclusion criteria were met. If the abstract met the inclusion criteria or could not be excluded with confidence, the full text of the publication was acquired. Finally, the full text was evaluated to determine if the publication met the inclusion criteria for eligibility.

Data extraction

Critical appraisal and data extraction were independently performed by two authors and any disparities were resolved after discussion. To verify the safety and efficacy of the procedure, published literature reviews, practice guidelines and consensus statements related to E-NSM were accepted and reviewed. However, the quantitative analysis was conducted solely on patient data from case series, cohort studies or randomized clinical trials (RCTs). This way, duplication of data from clinical studies represented in published reviews and independently accepted within this review was avoided.

While publications with completely or mostly overlapping patient populations were excluded from analysis of shared outcomes, publications with both unique and minimal (suspected) overlapping patient populations were included. The criteria used to appraise the clinical data is adapted from OCEBM[37]; for the purposes of this review, systematic reviews of non-randomized studies were considered level 1 and any non-controlled/non-comparative studies, including multi-institute cohort studies, were considered level 4. Publications were appraised to determine the suitability of the clinical data and the weight of the evidence provided by the data.

Risk-of-bias assessment

A formal risk-of-bias assessment was performed on the non-randomized comparative studies included in the pairwise analysis to establish appropriate selection of patients, cohort comparability and adequate reporting of patient demographic information, follow-up intervals and study results, using the Newcastle–Ottawa Scale. This risk-of-bias assessment was independently performed by two authors, after which all publications were reviewed by both authors, with any disagreement in study grade resolved after discussion.

Outcomes of interest

Oncological study outcomes analysed were local recurrence (including recurrence in the chest wall and lymph nodes in the axillary region), distant metastasis, margin positivity and breast cancer-specific mortality rate. Surgical outcomes analysed were operative time, estimated blood loss (EBL), duration of hospital stay, overall complications (including but not limited to necrosis, wound dehiscence, ischaemia, wound infection and implant exposure) and necrosis (including skin, fat, and NAC necrosis). QoL and cosmetic outcomes analysed were patient cosmetic satisfaction, postoperative pain and NAC sensation loss. Not all included publications reported on all the above outcomes. Mortality rate and distant metastasis were calculated over the total number of patients rather than the total number of procedures for each study. In articles that reported cosmetic satisfaction as an incidence rate, outcomes categorized as 'satisfied' to 'very satisfied' or 'good' to 'excellent' were pooled into the overall incidence of patient satisfaction; all other reported outcomes (that is 'fair' or 'poor') were considered unsatisfactory. Covariates of interest, systematically extracted during the data extraction phase, included incidence of pre- and/or postoperative radiotherapy usage, reconstruction type, follow-up duration, use of manual retraction *versus* CO_2 insufflation for creation of working space and surgical indications.

Statistical methods

For included comparative cohort studies relevant to E-NSM with propensity score matching, patient outcomes of propensity-matched cohorts were extracted for pairwise data analysis. For pairwise meta-analysis of included comparative cohort studies, random-effects meta-analysis was performed on RevMan Web[37] to analyse E-NSM *versus* C-NSM intervention groups. For categorical outcomes (for example incidence of local recurrence and incidence of necrosis), the odds ratio (OR), 95% confidence interval, and heterogeneity were determined using random-effects Mantel–Haenszel meta-analysis. For continuous study variables (for example mean operative time), the weighted mean difference (WMD), 95% confidence interval and heterogeneity were calculated using random-effects Inverse Variance meta-analysis, analysing study data from publications that reported a mean and standard deviation (s.d.) for the given outcome or from which a standard deviation could be estimated from a provided confidence interval (c.i.) using the RevMan SD calculator[37].

In addition, a proportional meta-analysis of single-group safety and oncological data (extracted from single-group cohort studies and case series and experimental arms of comparative clinical studies) was conducted using the random intercept logistic regression model, a maximum-likelihood estimator of heterogeneity, and logit transformation with the R meta and metafor packages. The calculated weighted incidence rates for safety and oncological outcomes were then compared with accepted ranges of equivalent outcomes from high-level C-NSM literature. For the proportional meta-analysis, outlier analysis was conducted to identify studies with 95% c.i. falling outside the 95% c.i. of the pooled incidence rate for each outcome. Identified outlier studies were not excluded from the proportional meta-analysis but were further analysed to identify potential confounding factors.

For both the pairwise and proportional meta-analysis, heterogeneity was assessed, using the calculated I^{2}%, as 'minimal' (0–25%), 'moderate' (25–50%), 'substantial' (50–75%) or 'high' (75–100%). When the results of pairwise meta-analysis indicated substantial or high heterogeneity, sensitivity analysis was performed. The sensitivity analysis was two-fold: first, a leave-one-out meta-analysis was performed for each heterogenous outcome, in which each study was removed from

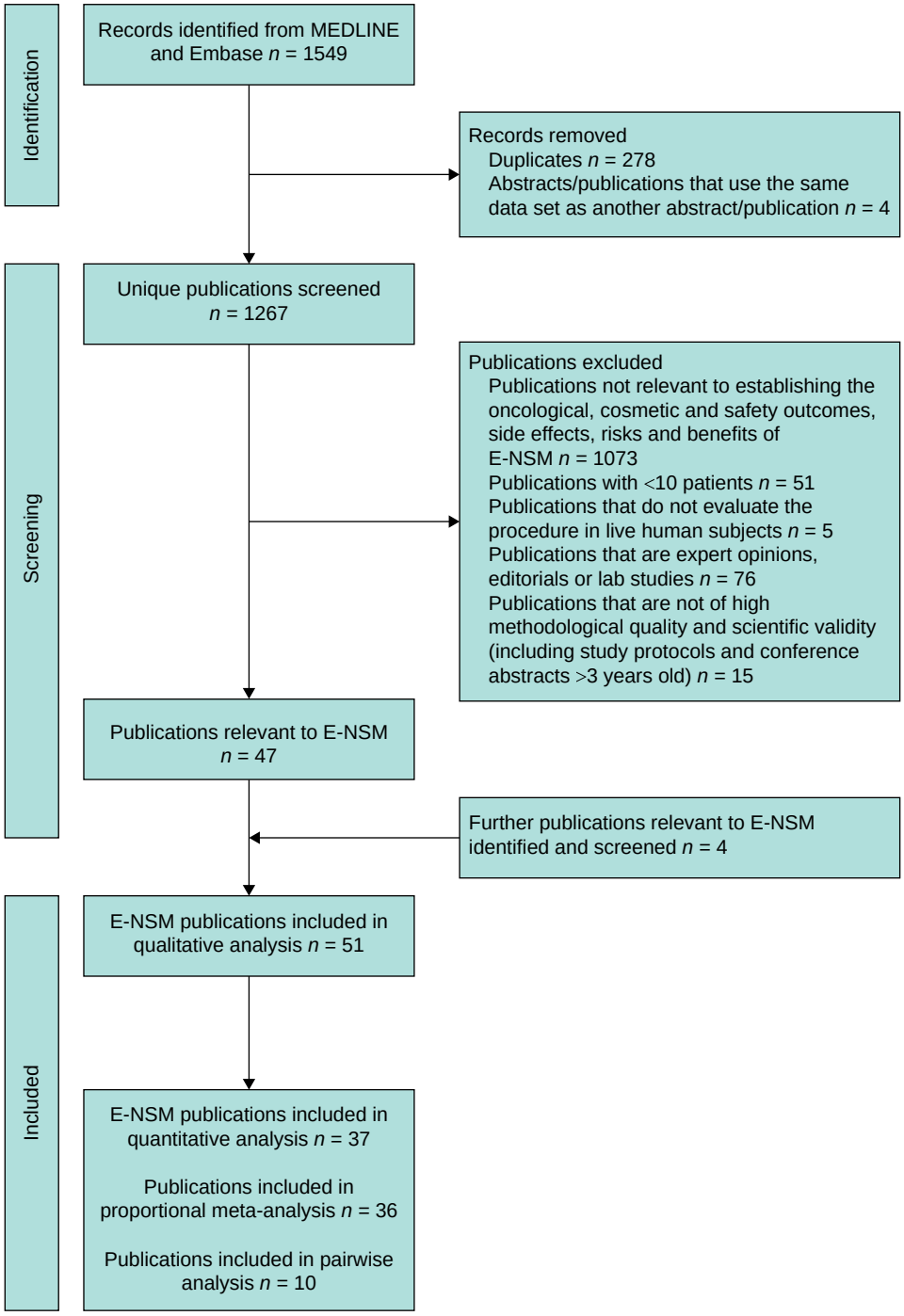

Fig. 1 PRISMA flow chart of endoscopic nipple-sparing mastectomy (E-NSM) literature search

the meta-analysis in turn to determine the robustness of the meta-analysis and impact of individual study contribution. If highly influential individual studies were identified in this process, the impact of the study characteristics and interventional factors on the outcome of interest were examined through subgrouping of studies by potentially influential characteristics and repeating the pairwise meta-analysis.

Results

Study characteristics

The search for published clinical data relevant to E-NSM yielded 1549 records from PubMed and Embase. After removing duplicate titles and excluding conference abstracts that duplicated a data set from a separate publication by the same author(s), 1267 unique records remained for screening. Of these, 47 publications relevant to E-NSM were identified. The remaining publications were excluded based on the exclusion criteria provided in the section above. An additional four publications, including studies identified from references of relevant publications or author-specific literature searches, were accepted for analysis (*Fig. 1*). The final 51 accepted publications included 2 systematic reviews, 18 non-randomized comparative cohort studies, 26 single-group cohort studies or case series, and 5 practice guidelines, narrative reviews or textbook chapters, all of which were included in the qualitative analysis. Of the 51

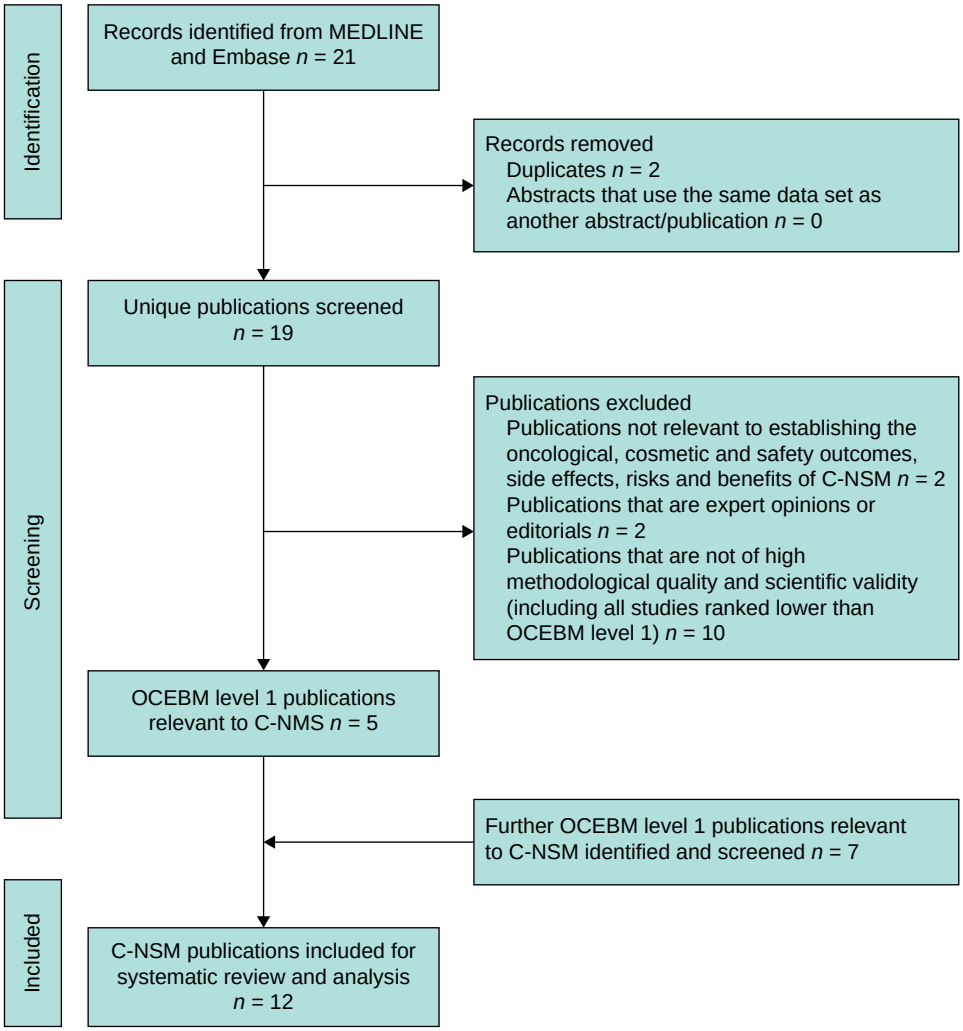

Fig. 2 PRISMA flow chart of conventional nipple-sparing mastectomy (C-NSM) systematic review literature search
OCEBM, Oxford Centre for Evidence-Based Medicine.

reviewed publications, 37 were included in the quantitative analysis; 36 studies (representing 2612 patients who underwent E-NSM) were included in the proportional meta-analysis and 10 studies (representing 656 patients who underwent E-NSM) were included in the pairwise analysis. Publications from which E-NSM patient-specific data could not be extracted for statistical analysis, including guidance documents, reviews and publications in which results from patients undergoing E-NSM were combined with those from patients undergoing other minimally invasive breast surgeries, were included only for qualitative analysis.

The search for high-level clinical evidence related to C-NSM on PubMed and Embase yielded 21 records. After removing duplicate titles and excluding publications according to the criteria listed in the section above, five systematic reviews relevant to C-NSM were accepted for analysis. An additional 7 C-NSM systematic reviews or meta-analyses were identified during the search for publications relevant to E-NSM and were also included for analysis, with a total of 12 C-NSM publications included for systematic review and analysis (*Fig. 2*).

Details of these searches, including search terms, filters and PICO (population, intervention, comparison, and outcomes) justification, are provided in *Supplementary material, Tables S1, S2*. The included studies relevant to E-NSM were OCEBM level 1, 3, 4 and 5 evidence (*Supplementary material, Table S3*). The included publications relevant to C-NSM were all systematic reviews (OCEBM level 1).

The results of the risk-of-bias assessment of non-randomized comparative studies included in the pairwise analysis are documented in *Supplementary material, Tables S4–S8*.

Pooled analysis: oncological outcomes

When compared with C-NSM, E-NSM resulted in statistically equivalent rates of local recurrence (OR 0.97 (95% c.i. 0.45 to 2.09), $I^2 = 0\%$; $P = 0.94$; *Fig. 3*) and distant metastasis (OR 0.63 (95% c.i. 0.20 to 1.99), $I^2 = 0\%$; $P = 0.43$; *Fig. 3*), and the estimated overall incidence of recurrence (1.29% (95% c.i. 0.62 to 2.64); *Supplementary material, Fig. S1*) or metastasis (1.66% (95% c.i. 0.76 to 3.57); *Supplementary material, Fig. S2*) following E-NSM was also comparable to that found in C-NSM literature. While the average follow-up times for E-NSM cohorts were shorter than those for patients who underwent C-NSM, some medium/longer-term oncological data suggesting low recurrence and metastasis rates for patients who underwent E-NSM was included in the analysis. Mean follow-up for oncological outcomes was up to 52.1 months in comparative studies, and median follow-up ranged from 8 to 74 months across all E-NSM publications.

There was no difference in the pooled margin positivity rate in E-NSM when compared with C-NSM (OR 0.79 (95% c.i. 0.15 to 4.12),

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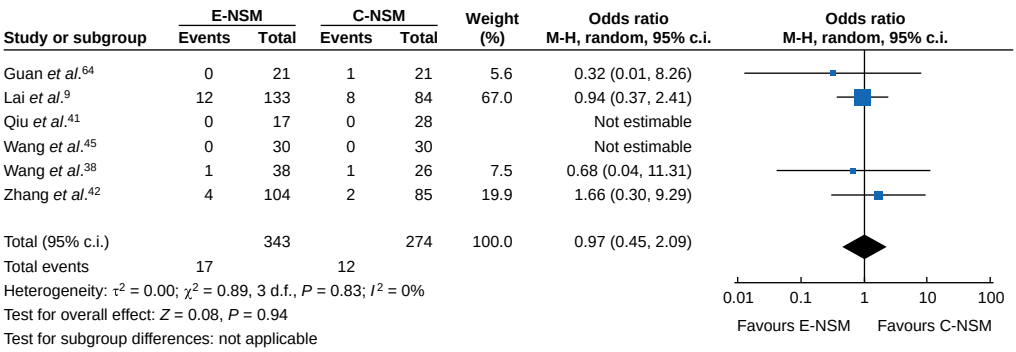

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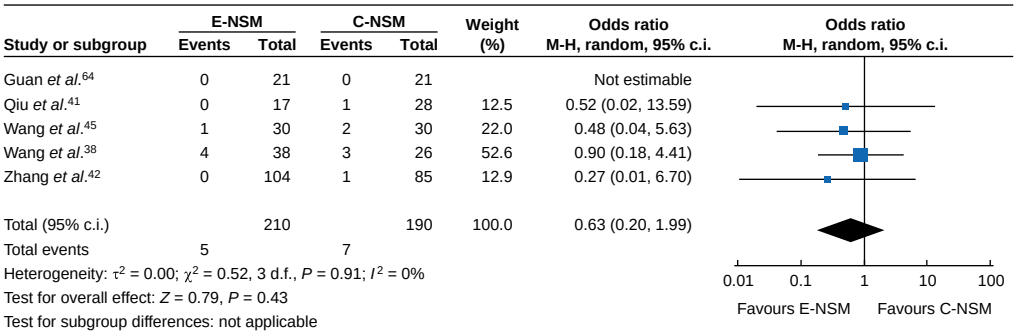

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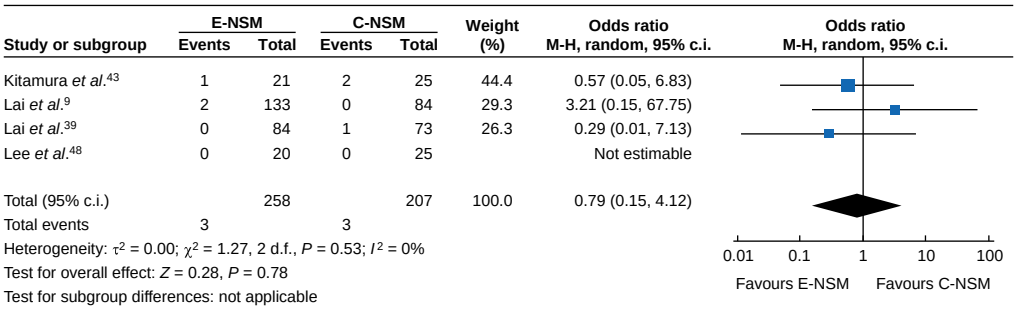

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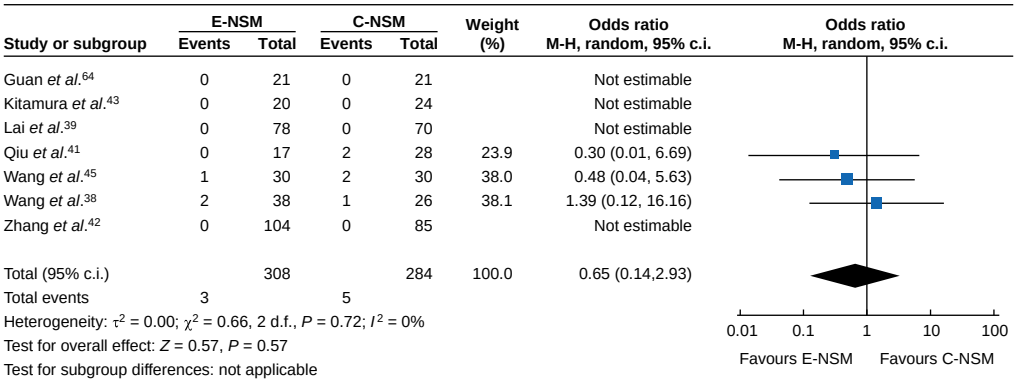

Fig. 3 **a** Local recurrence in endoscopic nipple-sparing mastectomy (E-NSM) *versus* conventional nipple-sparing mastectomy (C-NSM); **b** distant metastasis in E-NSM *versus* C-NSM; **c** margin positivity in E-NSM *versus* C-NSM; **d** breast cancer-specific mortality rate in E-NSM *versus* C-NSM. Note: Lai *et al.*[9] did not provide statistical comparison of patient demographics between E-NSM and C-NSM; Wang *et al.*[38] reported greater BMI and significant differences in tumour stage in the C-NSM cohort; Lai *et al.*[39] reported more patients with substantial breast ptosis in the E-NSM group. M–H, Mantel–Haenszel.

Table 1 Outcome rates from systematic reviews of conventional nipple-sparing mastectomy (C-NSM)

Study ID	Aim	*Publications/ sample size (*n*)	Follow-up	Local recurrence (%)	Distant metastasis (%)	Positive margins (%)	Mortality rate (%)	Overall complications (%)	Necrosis (%)
De la Cruz *et al.* 2023[40]	R-NSM *versus* C-NSM	6 797	90 days– 32.1 months	Early recurrence: 0–8	NR	0–4.6	NR	RCT: 31.4, case-control: 56.3	RCT: 14.4, case-control: 13.3
Blanckaert *et al.* 2021[6]	Oncological safety of C-NSM + BR	14 5980	60–97 months	NAC rec.: 0–4.1 5 year LR: 0–10, LRR: 0–7.4	1.6–15.6	NR	Overall survival: 93.1–100	NR	Partial NAC: 0.2–9.4 Full NAC: 0–3.3
Tondu *et al.* 2020[14]	BR after C-NSM in large/ptotic	31 629	3 months to 22 years	0.37	0.74	NR	NR	0–46.91	Partial NAC: 14, full NAC: 11, skin flap: 12
Agha *et al.* 2019[8]	C-NSM *versus* SSM	14 1419	18–101 months	42 of 1082 (3.88)	NR	NR	6.14	22.6	NAC: 15, skin flap: 3.4
Daar *et al.* 2019[13]	Incision location for C-NSM	51 6407	3–74 months	0–7.2	NR	NR	NR	NR	overall: 6.97 (95% c.i. 5.34–8.79); <0.0001
Karian *et al.* 2017[12]	Delay techniques of BR following C-NSM	5 101	NR	NR	NR	Retro-areolar: 6.9	NR	7.9–8.9	Partial NAC: 8.9, full NAC: 0, skin flap: 7.9
De La Cruz *et al.* 2015[7]	Oncological safety of C-NSM *versus* SSM/MRM	20 5594	10.5–135.6 months	Local recurrence.: <3 years: 5.4, 3–5 years: 1.4 >5 years: 11.4 NAC, rec.: <3 years: 2.1 3–5 years: 1.0 >5 years: 3.4, weighted averages	NR	NR	Overall survival: <3 years: 97.2 3–5 years: 97.9 >5 years: 86.8, disease-free survival: <3 years: 93.1, 3–5 years: 92.3 >5 years: 76.1	NR	NR
Endara *et al.* 2013[3]	BR after C-NSM	48 5166	0.2–210 months	Locoregional: 1.8	2.2	NR	NR	22	7.7

*Number of publications included and reviewed in each systematic review. BR, breast reduction; C-NSM, classical nipple sapring mastectomy; LR, local recurrence; LRR, locoregional recurrence; MRM, modified radical mastectomy; N/A, not applicable; NAC, nipple areola complex; NR, not reported; RCT, randomized clinical trial; R-NSM, robotic nipple-sparing mastectomy; SSM, skin sparing mastectomy.

$I^2 = 0\%$; $P = 0.78$; *Fig. 3*). The estimated overall incidence of margin positivity in E-NSM procedures was 1.46% (95% c.i. 0.52 to 4.03) (*Supplementary material, Fig. S1*), which was comparable to rates reported in systematic literature relevant to C-NSM (*Table 1*).

The estimated rate of patient breast cancer-specific mortality rate after E-NSM (0.50%) was extremely low, though confidence in this result is also impacted by the lack of long-term oncological data (*Supplementary material, Fig. S2*). Pairwise analysis similarly showed comparable breast cancer-specific mortality rates in E-NSM *versus* C-NSM (OR 0.65 (95% c.i. 0.14 to 2.93), $I^2 = 0\%$; $P = 0.57$; *Fig. 3*).

Pooled analysis: surgical outcomes

The mean operative time was significantly longer for E-NSM than for C-NSM (WMD 43.08 min (95% c.i. 25.14 to 61.02), $I^2 = 71\%$; $P < 0.00001$; *Fig. 4*). Additionally, the average duration of hospital stay was significantly longer in patients undergoing E-NSM surgery *versus* C-NSM, with a WMD of 0.72 days (95% c.i. 0.30 to 1.14, $I^2 = 15\%$; $P = 0.0007$; *Fig. 4*). Finally, there was no significant difference in estimated procedural blood loss between E-NSM and C-NSM techniques (WMD −5.93 ml (95% c.i. −30.08 to 18.23), $I^2 = 80\%$; $P = 0.63$; *Supplementary material, Fig. S3*).

While the results of the pairwise analysis did not reach significance, the pooled incidence of overall complications trended lower for E-NSM than for C-NSM (OR 0.49 (95% c.i. 0.21 to 1.15) $I^2 = 77\%$; $P = 0.10$; *Fig. 5*). The estimated overall incidence rate of complications after E-NSM, pooled across all included primary research studies reporting overall complications as an outcome, was also comparable to or lower than reported rates in C-NSM systematic reviews (*Table 1*), at 16.54%, though with substantial heterogeneity in results (*Fig. 6*). In an additional pairwise analysis of complications specifically related to postoperative loss of implant viability, including severe capsular contracture requiring surgical repair, prosthesis exposure or incision disruption, and full implant loss, the pooled incidence rate trended non-significantly lower in E-NSM *versus* C-NSM (OR 0.35 (95% c.i. 0.10 to 1.22), $I^2 = 8\%$; $P = 0.10$; *Supplementary material, Fig. S3*). When necrotic complications (including full-thickness and partial skin, fat and NAC necrosis) were isolated as an outcome of interest in the pairwise analysis, the pooled incidence rate of necrosis also trended non-significantly lower for E-NSM than C-NSM (OR 0.45 (95% c.i. 0.16 to 1.32), $I^2 = 52\%$; $P = 0.15$; *Fig. 5*).

One publication included in the meta-analysis reported a significantly higher rate of partial NAC necrosis than other E-NSM publications; this was partially attributed by the authors to the use of a two-dimensional endoscopic dual-areolar-axillary-incision in early E-NSM cases. After a single-axillary-incision approach was introduced, rates of necrosis at their institute dropped significantly ($P < 0.01$)[9]. Leave-one-out sensitivity analysis revealed that this study considerably impacted the significance and heterogeneity of overall complications and necrosis meta-analysis results, as the reduction in both outcomes in E-NSM *versus* C-NSM reached significance with the removal of this article from the pairwise analysis ($P = 0.01$ and $P = 0.007$ respectively; *Supplementary material, Tables S15, S16*), and the heterogeneity of both analyses was substantially reduced. As a correlation between the use of dual-incision E-NSM and the prevalence of necrotic outcomes was identified by the author, the pairwise meta-analysis for necrosis was further modified to exclude all articles in which dual- or multiple-incision E-NSM patient data was used. The results of this sensitivity analysis demonstrated a significant reduction in odds of necrosis following single-incision E-NSM *versus* C-NSM (OR 0.19 (95% c.i. 0.06 to 0.65), $I^2 = 0\%$; $P = 0.008$; *Fig. 7*), with minimal heterogeneity in study results. In the

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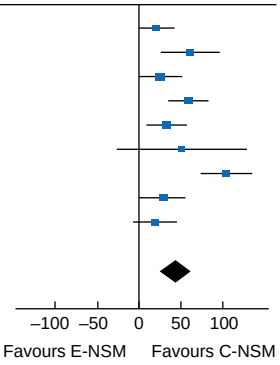
Study or subgroup	E-NSM Mean (min)	E-NSM s.d. (min)	E-NSM Total	C-NSM Mean (min)	C-NSM s.d. (min)	C-NSM Total	Weight (%)	Mean difference IV, random, 95% c.i. (min)
Guan *et al.*[64]	185	43	21	165	33	21	13.0	20.00 (–3.18, 43.18)
Kitamura *et al.*[43]	237	60	21	176	60	25	10.2	61.00 (26.19, 95.81)
Lai *et al.*[9]	208	94	133	183	101	84	12.1	25.00 (–1.86, 51.86)
Lai *et al.*[39]	248.6	87.2	84	190.2	64	73	12.9	58.40 (34.67, 82.13)
Lee *et al.*[48]	269.1	39.6	20	235.9	43.8	25	12.7	33.20 (8.79, 57.61)
Qiu *et al.*[41]	451.7	154.9	17	400.9	67.3	28	4.0	50.80 (–26.94, 128.54)
Wang *et al.*[38]	300.97	64.77	38	196.88	59.79	26	11.1	104.09 (73.23, 134.95)
Zhang *et al.*[42]	233	49	70	204	79	40	12.0	29.00 (1.96, 56.04)
Zhang* *et al.*[42]	198	42	34	178	80	45	12.0	20.00 (–7.31, 47.31)
Total (95% c.i.)			438			367	100.0	43.08 (25.14, 61.02)

Heterogeneity: $\tau^2 = 505.59$; $\chi^2 = 27.38$, 8 d.f., $P = 0.0006$; $I^2 = 71\%$
Test for overall effect: $Z = 4.71$, $P < 0.00001$
Test for subgroup differences: not applicable



b

Study or subgroup	E-NSM Mean (days)	E-NSM s.d. (days)	E-NSM Total	C-NSM Mean (days)	C-NSM s.d. (days)	C-NSM Total	Weight (%)	Mean difference IV, random, 95% c.i. (days)
Lai *et al.*[9]	6	1.4	133	5.2	1.7	84	55.5	0.80 (0.37, 1.23)
Lai *et al.*[39]	5.8	1.6	84	5.1	2	73	38.4	0.70 (0.13, 1.27)
Lee *et al.*[48]	14.4	4.5	20	12	6.2	25	1.7	2.40 (–0.73, 5.53)
Qiu *et al.*[41]	10.2	3.1	17	11	3.5	28	4.3	–0.80 (–2.76, 1.16)
Total (95% c.i.)			254			210	100.0	0.72 (0.30, 1.14)

Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 3.54$, 3 d.f., $P = 0.32$; $I^2 = 15\%$
Test for overall effect: $Z = 3.40$, $P = 0.0007$
Test for subgroup differences: not applicable

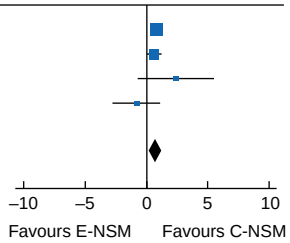


Fig. 4 **a** Operative time in endoscopic nipple-sparing mastectomy (E-NSM) *versus* conventional nipple-sparing mastectomy (C-NSM); **b** duration of hospital stay in E-NSM *versus* C-NSM. Note: Qiu *et al.*[41] and Lai *et al.*[39] utilized flap or flap + implant-based immediate breast reconstruction (IBR); Lai *et al.*[9] used tissue expander, flap + implant-, flap- or implant-based IBR or no IBR; and Wang *et al.*[38] used implant-based IBR or tissue expanders. All other publications used implant-based IBR. *Zhang *et al.*[42] reported operative time separately for patients undergoing nipple sparing mastectomy + immediate breast reconstruction (NSM + IBR) with axillary lymph node dissection (ALND) *versus* NSM + IBR with sentinel lymph node biopsy (SLNB). Asterisk denotes SLNB cohort. IV, indipendent variable.

proportional meta-analysis, the estimated overall incident rate of necrosis (including skin, fat and NAC necrosis) from E-NSM publications (3.84% (95% c.i. 2.41 to 6.07); *Fig. 6*) was also comparable to or lower than rates reported in C-NSM literature (*Table 1*).

Pooled analysis: cosmesis and quality of life

Postoperative pain, measured as patient-reported visual analogue scale (VAS) scores in two studies, was significantly lower after E-NSM *versus* C-NSM immediately after surgery, though this significant reduction was not sustained days after surgery (*Supplementary material, Table S9*). The incidence of patient-reported cosmetic satisfaction was significantly improved in E-NSM (OR 1.88 (95% c.i. 1.09 to 3.26); $P = 0.02$; $I^2 = 0\%$; *Fig. 8*), with low heterogeneity of results, and average breast satisfaction scores were higher following E-NSM procedures in comparative studies (*Supplementary material, Table S10*)[38,3941].

The loss of NAC sensation was not consistent among the results of the included comparative studies (*Supplementary material, Table S11*). In a multivariate analysis performed by one author group, including 460 patients, E-NSM and patients who underwent robotic NSM showed decreased nipple and/or skin sensation compared with patients who underwent C-NSM[44]. The same group, in a separate multi-institutional analysis, also reported better mean(s.d.) nipple sensitivity scores after C-NSM (1.7(1)) *versus* E-NSM (1.5(1.2), $P < 0.01$)[39]. On the other hand, in a separate study, another author group reported significantly reduced rates of pressure, temperature and vibration sensation loss in E-NSM *versus* C-NSM 3 months after surgery[45]; and the fourth study reported no significant differences in incidence of sensory abnormalities or pain in the surgical area in E-NSM *versus* C-NSM[42].

Discussion

This analysis highlights that E-NSM and C-NSM are equally safe and effective for therapeutic procedures in patients with breast cancer and risk-reduction mastectomy procedures in high-risk mutation carriers.

The results of the meta-analyses provided robust evidence in support of the short-term oncological safety of E-NSM when compared with C-NSM, with mean follow-up intervals up to 52.1 months in comparative studies, and median follow-ups ranging from 8 to 74 months across all E-NSM publications. While overall rates of recurrence, metastasis and breast cancer-specific mortality rate were equivalent for E-NSM and C-NSM, there was a paucity of long-term follow-up data (more than 5 years) for patients undergoing E-NSM procedures, preventing quantitative comparison of long-term oncological safety. However, the equivalence of pathological margin status after E-NSM and C-NSM procedures in patients with breast cancer indicates comparable resection efficacy.

From pairwise analysis, there was no difference in estimated blood loss between E-NSM and C-NSM ($P = 0.63$), indicating that sufficient haemostasis, comparable to C-NSM, was achieved

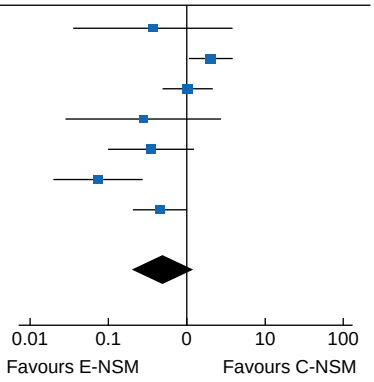
a

Study or subgroup	E-NSM Events	E-NSM Total	C-NSM Events	C-NSM Total	Weight (%)	Odds ratio M-H, random, 95% c.i.
Kitamura *et al.*[43]	1	21	3	25	8.2	0.37 (0.04, 3.82)
Lai *et al.*[9]	45	133	17	84	18.8	2.02 (1.06, 3.83)
Lai *et al.*[39]	20	84	17	73	18.2	1.03 (0.49, 2.16)
Lee *et al.*[48]	1	20	4	25	8.4	0.28 (0.03, 2.69)
Qiu *et al.*[41]	6	17	17	28	14.5	0.35 (0.10, 1.23)
Wang *et al.*[38]	4	38	16	26	14.1	0.07 (0.02, 0.27)
Zhang *et al.*[42]	12	104	19	85	17.8	0.45 (0.21, 1.00)
Total (95% c.i.)		417		346	100.0	0.49 (0.21, 1.15)
Total events	89		93			

Heterogeneity: $\tau^2 = 0.91$; $\chi^2 = 26.09$, 6 d.f., $P = 0.0002$; $I^2 = 77\%$

Test for overall effect: $Z = 1.64$, $P = 0.10$

Test for subgroup differences: not applicable



b

Study or subgroup	E-NSM Events	E-NSM Total	C-NSM Events	C-NSM Total	Weight (%)	Odds ratio M-H, random, 95% c.i.
Guan *et al.*[64]	0	21	3	21	9.0	0.12 (0.01, 2.54)
Kitamura *et al.*[43]	0	21	0	25		Not estimable
Lai *et al.*[9]	23	133	7	84	26.0	2.30 (0.94, 5.63)
Lai *et al.*[39]	0	84	1	73	8.2	0.29 (0.01, 7.13)
Lee *et al.*[48]	0	20	2	25	8.7	0.23 (0.01, 5.06)
Qiu *et al.*[41]	0	17	5	28	9.3	0.12 (0.01, 2.36)
Wang *et al.*[38]	2	38	6	26	17.7	0.19 (0.03, 1.00)
Zhang *et al.*[42]	4	104	5	85	21.1	0.64 (0.17, 2.46)
Total (95% c.i.)		438		367	100.0	0.45 (0.16, 1.32)
Total events	29		29			

Heterogeneity: $\tau^2 = 0.94$; $\chi^2 = 12.43$, 6 d.f., $P = 0.05$; $I^2 = 52\%$

Test for overall effect: $Z = 1.45$, $P = 0.15$

Test for subgroup differences: not applicable

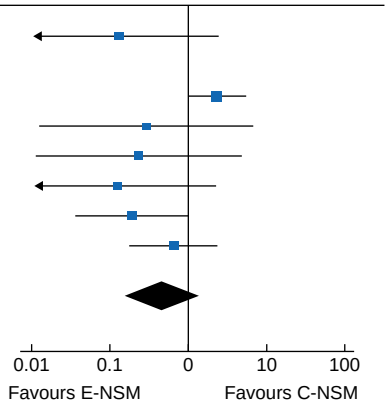


Fig. 5 **a** Overall complications in endoscopic nipple-sparing mastectomy (E-NSM) *versus* conventional nipple-sparing mastectomy (C-NSM); **b** necrosis in E-NSM *versus* C-NSM. Note: Lai *et al.*[9] did not provide statistical comparison of patient demographics between E-NSM and C-NSM; Wang *et al.*[38] reported greater BMI and significant differences in tumour stage in the C-NSM cohort; Lai *et al.*[39] reported more patients with substantial breast ptosis in the E-NSM group. M–H, Mantel–Haenszel.

with endoscopic coagulation devices. Additionally, as overall complication and necrosis rates trended (non-significantly) lower after E-NSM, the longer operative time and duration of hospital stay reported for patients who underwent E-NSM do not appear to be associated with or due to delayed healing[23]. Rather, the difference in duration of hospital stay is likely related to surgeon caution during initial or early experience with the surgical technique, which may decrease as surgeons gain familiarity with E-NSM procedures.

The length of operative time required for E-NSM can also be reduced with gained surgeon experience, as evidenced by the sharp or significant decrease in E-NSM operative time after approximately 10 to 18 procedures[46–49]. While not as robustly studied, the learning curve was reported to impact post-E-NSM surgical complications as well, as two author groups reported significantly lower overall complication rates in the mature phase of their respective studies[46,49]. Taken together, the available clinical evidence suggests that the low rates of postoperative surgical complications associated with E-NSM may be further reduced with gained experience.

While no significant differences in surgical complications between E-NSM and C-NSM were calculated, overall complications, necrotic complications and loss of implant viability trended non-significantly lower for E-NSM procedures. Only one author group reported higher rates of overall complications (34.8% *versus* 20.2%) and NAC necrosis (17.2% *versus* 8.3%) in patients who underwent E-NSM *versus* C-NSM[9]. These authors reported that the shift from a dual-areolar-axillary-incision E-NSM technique to a single-axillary-incision E-NSM significantly decreased the rate of NAC ischaemia/necrosis (grade II and III) from 22.8% to 9.4% throughout their study. As the sensitivity analysis comparing only single-incision E-NSM to C-NSM resulted in a significant reduction in the calculated necrosis rate, it is possible that the use of an additional areolar incision in dual- or multiple-incision E-NSM is correlated with increased risk of postoperative NAC necrosis[50]. Due to the relatively high rates of overall complications and necrosis reported, this publication and another that similarly utilized multiple incisions for E-NSM were the only studies identified as outliers in the proportional meta-analysis[51].

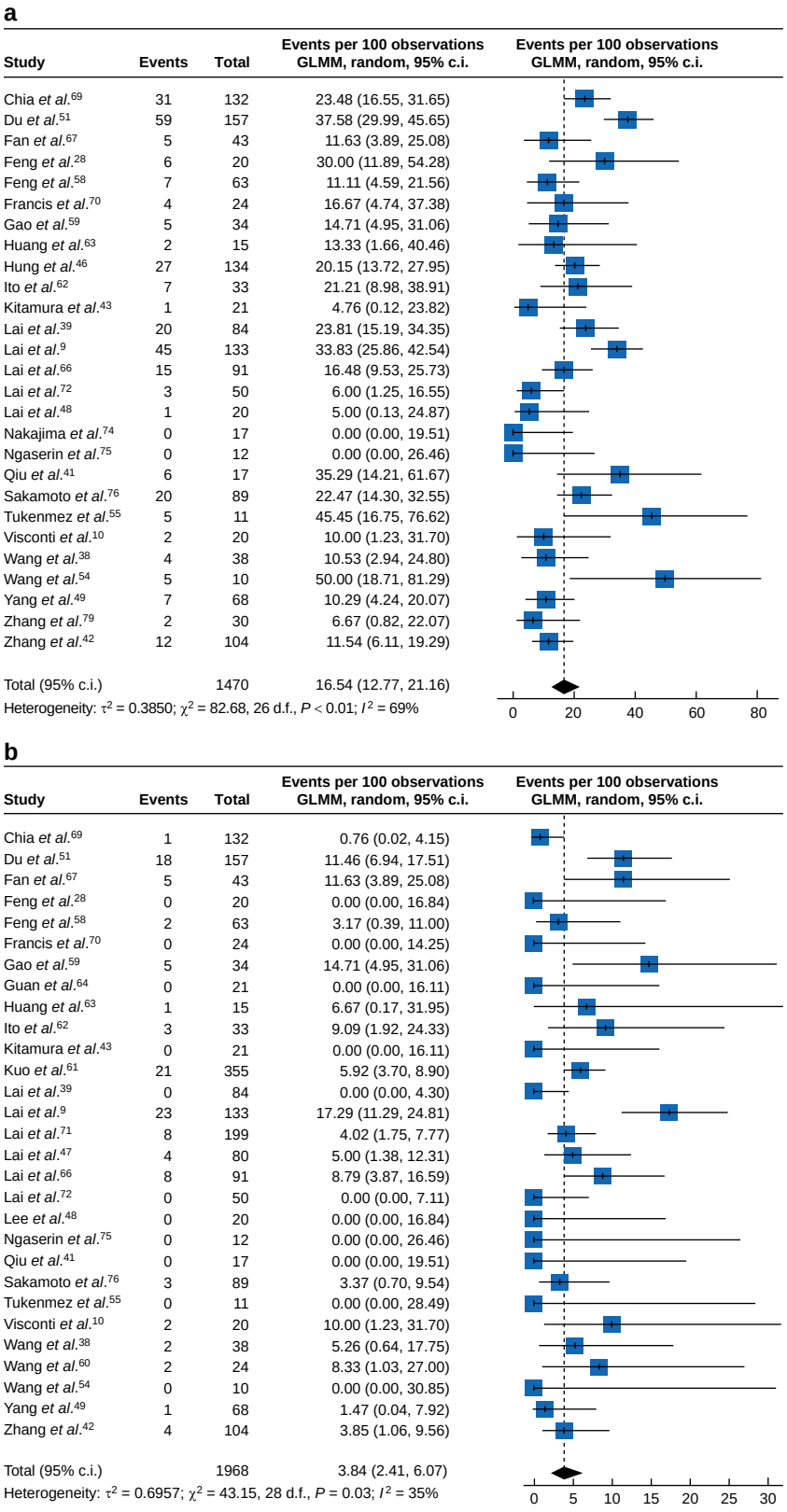


Fig. 6 **a** Estimated incidence of overall complications for endoscopic nipple-sparing mastectomy (E-NSM); **b** estimated incidence of necrosis for E-NSM.

Other factors correlated with increased rates of NAC or skin flap ischaemia/necrosis were autologous breast reconstruction[29,30,39], patient age, breast size (mastectomy specimen weight) and type of skin incision[52]. Indeed, the main incisions used in minimally invasive NSM (axillary incisions) have been significantly associated with lower NAC or skin flap necrosis rates than those used in C-NSM ($P < 0.01$)[52], which may be due to the preservation of the vascular supply to the NAC and skin envelope[53]. In a

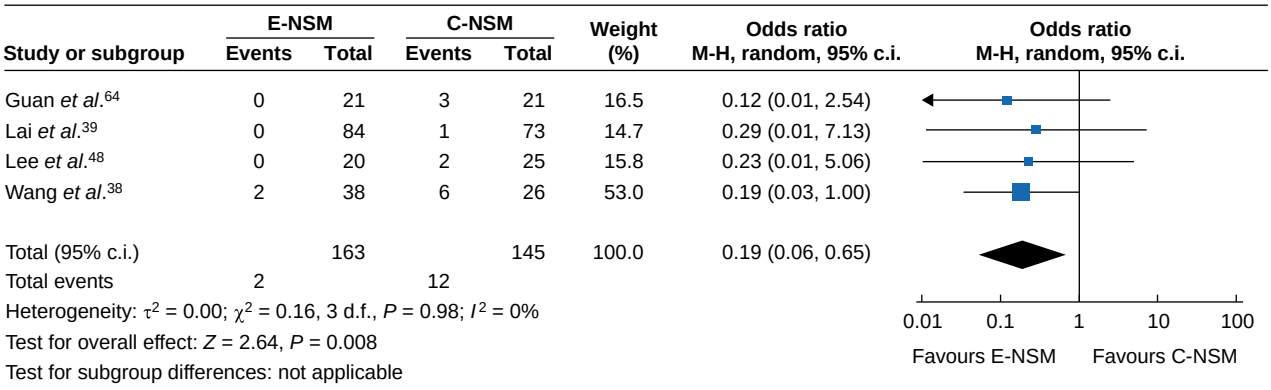


Fig. 7 Necrosis in single-incision endoscopic nipple-sparing mastectomy (E-NSM) *versus* conventional nipple-sparing mastectomy (C-NSM)
M–H, Mantel–Haenszel.

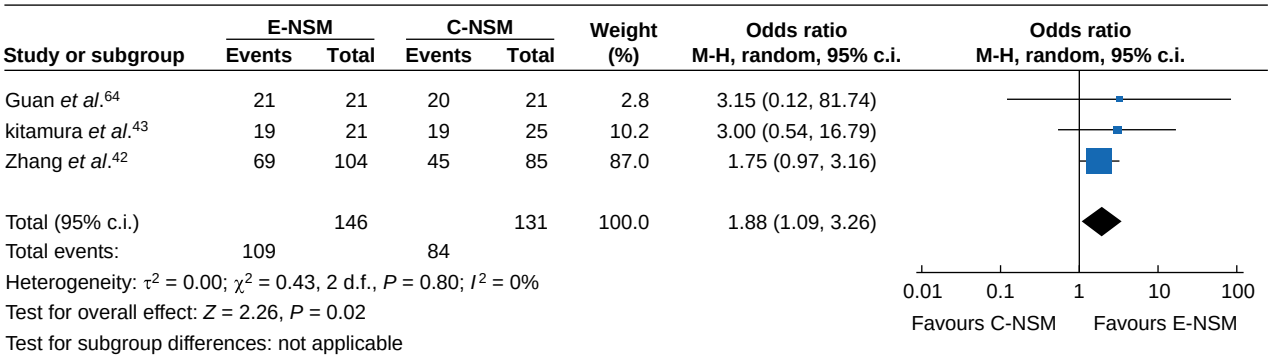


Fig. 8 Percentage of patients satisfied with cosmetic results in endoscopic nipple-sparing mastectomy (E-NSM) *versus* conventional nipple-sparing mastectomy (C-NSM)
Note: all authors utilized immediate implant-based reconstruction. Kitamura *et al.*[43] reported use of postoperative irradiation in both groups (E-NSM: 1 of 21 cases *versus* C-NSM: 2 of 25 cases; $P = 0.1851$), as did Zhang *et al.*[42] (numbers not specified). M–H, Mantel–Haenszel.

recent report, preservation of blood supply to the NAC following single-axillary-port E-NSM was visually confirmed using indocyanine green angiography, and this mitigation of vascular network injury was credited for the low rate of ischaemic or necrotic complications in patients who underwent E-NSM[38].

It is noteworthy, however, that an association between decreased NAC necrosis and increased preservation of NAC sensation in patients who underwent E-NSM was not consistently reported, which may be due in part to variations in dissection and sensation assessment methods between studies. One author group reported better nipple sensation preservation rates in patients who underwent C-NSM *versus* E-NSM[39,44], postulating that relative over-thinning of the retro-areolar tissue in the E-NSM group may have contributed to higher rates of NAC sensation abnormality. Due to the risk of NAC ischaemic necrosis associated with peri-areolar incisions, surgeons may have been prompted to leave thicker skin flaps during C-NSM procedures[44]. On the other hand, a separate author group reported a significantly lower rate of NAC sensation loss in patients who underwent E-NSM *versus* patients who underwent C-NSM[45], though the use of a skin-lifting retraction method and shorter time interval between surgery and NAC sensation assessment may have impacted results[45]. A fourth study reported no difference in the incidence of sensory abnormalities or pain between groups[42]. Considering anatomical structures, the superficial skin nerves and the blood supply to the nipple following a mastectomy depend on small vessels that traverse the subcutaneous tissue, originating from larger branching arteries such as the internal mammary, anterior intercostal and lateral thoracic arteries, with less reliance on branches from the axillary artery or posterior intercostal arteries. In single-incision E-NSM, this nerve and vascular network is largely preserved due to the use of a distant axillary incision.

Importantly, the results of pairwise meta-analysis demonstrated that patient-reported cosmetic satisfaction was significantly greater following E-NSM *versus* C-NSM. The studies which were excluded from the pooled analysis due to variability in assessment methods also reported superior or significantly superior cosmetic scores after E-NSM[38,39,41]. In previously published evidence reviews of E-NSM, patient cosmetic satisfaction was largely attributed to scar placement and length of skin incision[23]. Our analysis also suggests that this improvement in cosmetic satisfaction could be related to smaller incision size, aesthetically superior scar location and decreased scar visibility afforded by minimally invasive techniques. Meanwhile, less positive aesthetic outcomes were often correlated with specific reconstruction methods shared between minimally invasive and open techniques[28,41,54].

In contrast to C-NSM, E-NSM can provide a magnified view while creating adequate space for dissection[22,23,28,35,55]. The use of CO_2 insufflation in E-NSM creates positive pressure that can improve visualization by lifting the skin in a uniform fashion

while reducing bleeding. Moreover, the magnification provided by an endoscope allows for precise identification of anatomical structures, enabling delicate surgical manipulation and wide dissections of the breast parenchyma while avoiding normal tissue damage[23,28,35,56]. Other advantages of E-NSM, consistently reported in the literature, included significantly shorter incision sizes[9,38,39,42,43,57], hidden or invisible scars[9,38,41,43,48,58,59], minimized tissue trauma[55,60], and general improvements in cosmetic and/or QoL outcomes, including psychological, sexual and physical wellbeing[10,38,41,45,46,57,60–65]. Beyond length of operative time and duration of hospital stay, reported disadvantages included greater cost and/or demand for specialized equipment[9,27,63], technical difficulties and substantial learning curves[45,66], smaller working space, rigid instrumentation, potential for instrument collision or inconsistent optical windows (for two-dimensional E-NSM only)[47,55,66], and difficulties operating on large or ptotic breasts[67].

This review had several limitations. Due to the lack of randomization, there was substantial risk of bias in the analysed comparative studies. While most studies frequency matched or reported no significant differences in patient demographic factors, indications for surgery and reconstruction type, a small subset of studies reported between-group differences that may have biased the results of our analysis; in particular, there were significant differences in follow-up time between cohorts in multiple publications. Several studies also reported results using the 'intention-to-treat' principle. While a small number of patients who underwent E-NSM were converted to E-SSM due to positive nipple biopsy results in these studies, outcomes were reported over the original patient sample, somewhat confounding results. Furthermore, differences in surgeon experience, endoscopic or endoscopy-assisted NSM surgical techniques, methods of assessment for cosmesis and QoL outcomes, and types of immediate breast reconstruction contributed to the overall heterogeneity of the study set. In addition to these limitations from study design, the potential for duplication bias due to overlapping patient populations also impacts confidence. While over 50 publications relevant to E-NSM were identified, most studies included patient data from a small number of databases or hospitals. Publications with clearly duplicated patient populations were excluded from the analysis when reported outcomes were shared. However, publications with both minimal (suspected) overlapping and unique patient populations were included in the analysis, leading to a potential inflation of patient numbers, particularly for the proportional meta-analysis.

Despite these limitations, there are several strengths of this systematic review that differentiate it from the most recently published systematic reviews relevant to E-NSM and address gaps in the research. This review extends the collected E-NSM data more than 3 years past the evaluation interval of the previous systematic review[35] and is the first pairwise meta-analysis comparing E-NSM to C-NSM. Additionally, no prior systematic review on minimally invasive (MI-)NSM conducted a proportional meta-analysis. Much of the available evidence on the safety and efficacy of E-NSM comprises reports of early institutional or surgeon experience, including case series, retrospective single-institute chart reviews and broader multicentre studies. By conducting a proportional meta-analysis, we were able to quantitatively evaluate this wide pool of non-controlled clinical data in support of the comparative analysis. Finally, our review maintained a strict focus on E-NSM procedures only, without conflating them with E-SSM, endoscopic breast-conserving surgery, or other variations of endoscopic or robotic breast surgery[34].

Overall, the findings of this study were in line with those of prior reviews of E-NSM techniques. The estimated recurrence rate calculated in our review was within range of E-NSM recurrence rates reported in an earlier systematic review, though our calculated rates of margin positivity and metastasis were lower, possibly reflecting refinement of the E-NSM technique in more recent years (see *Supplemental material, Table S12*)[34]. Notably, in published reviews of minimally invasive robotic nipple-sparing mastectomy (R-NSM), which like E-NSM, is primarily performed through a hidden axillary incision, some similar procedural and safety outcomes were reported. Indeed, the results of a recently published meta-analysis showed significantly longer operative time and duration of hospital stay for R-NSM *versus* C-NSM and identified that the robotic technique might reduce overall complications, including necrosis, though these results were not significant[40]. Additionally, in the only published study directly comparing outcomes of endoscopic-assisted and robotic NSM, no differences in oncological outcomes, overall breast satisfaction, morbidity rate or mortality rate were reported, though R-NSM resulted in less EBL (mean(s.d.) 32(29) *versus* 79(62) ml, $P < 0.01$) and a shorter learning curve, and E-NSM required a shorter operative time (mean(s.d.) 215(70) *versus* 241(61) min, $P = 0.01$) and lower operative costs (mean(s.d.) 6855(936) *versus* 10 587(554) Euro, $P < 0.01$)[66]. Taken together, available evidence suggests shared clinical outcomes between E-NSM and R-NSM methods.

The addition of more recent E-NSM publications in our study allowed us to identify a trend towards lower rates of overall complications and necrosis for E-NSM procedures when compared with C-NSM. However, somewhat unexpectedly, a corresponding consistent reduction in the incidence of NAC sensation loss was not observed. While multiple authors have identified procedural aspects of MI-NSM that may correlate to specific postoperative complications like NAC necrosis and sensation loss, there is a paucity of research comparing patient outcomes following MI-NSM based on technique-related variables. Future research would benefit from direct comparison of E-NSM port and incision variations (number, length and placement), dissection extent (skin flap/ retro areolar tissue thickness) and endoscope dimensionality (two-dimensional *versus* three-dimensional). Additionally, objective outcome assessment tools and adequate follow-up are likely prerequisites to validly compare NAC sensation preservation rates, and direct comparative testing of autologous *versus* prosthetic reconstruction methods after MI-NSM may clarify the increased rates of complications sometimes observed after flap-based breast reconstruction[28,30,41,54,68–80]. While most patients included in this review underwent implant-based reconstruction, the refinement of autologous reconstructive options in more recent years might be expected to impact surgical outcomes. Finally, in published clinical studies comparing MI-NSM to conventional techniques, long-term (more than 5 years) follow-up for oncological outcomes was lacking. To confirm the long-term oncological safety of E-NSM, additional controlled research studies with careful patient selection and adequate follow-up are required.

Overall, patients undergoing E-NSM may have significantly greater odds of satisfactory cosmetic results than those undergoing conventional surgery. The analysed clinical evidence suggests that this benefit is not correlated to an increased risk of

cancer recurrence, as no significant differences in oncological outcomes were detected through meta-analyses of early recurrence, metastasis and breast cancer-specific mortality rates. While concordant long-term follow-up data is still needed to establish the oncological safety equivalence to C-NSM, there was no significant difference in breast tissue resection efficacy, as evaluated through the surrogate measure–margin positivity. Furthermore, the results of the meta-analyses demonstrated non-significant reductions in surgical complications and necrosis of the skin, fat and NAC following E-NSM, and a significant reduction of necrosis following single-incision E-NSM, although an association of E-NSM techniques to improved NAC sensation preservation was only demonstrated in some studies. Therefore, further research is needed to strengthen the correlations between operative techniques and surgical outcomes. Regardless, increased costs, longer operative time, and lengthier duration of hospital stays associated with E-NSM are important limitations to widespread adoption, though these later two disadvantages can be ameliorated with surgeon experience. While limited by the quality of available evidence, our findings suggest that E-NSM can be considered a safe and cosmetically advantageous surgical option for both prophylactic and therapeutic indications.

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Disclosure

Authors A.C. and C.R. are employed by Applied Medical. G.R. is a consultant for Applied Medical. The authors declare no other conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

Data are available from the corresponding author upon reasonable request.

Author contributions

Ayla Carroll (Investigation, Writing—original draft), Carlos Robles (Investigation, Writing—original draft), Hung-Wen Lai (Resources, Supervision), Lidia Blay (Validation, Writing—review & editing), Piotr Pluta (Writing—review & editing), Gauthier Rathat (Writing—review & editing), Guillermo Peralta (Writing—review & editing), Rami Younan (Supervision, Visualization), Giada Pozzi (Writing—review & editing), Daniel Martinez Campo (Writing—review & editing), Robert Milligan (Supervision, Visualization), Glenn Vergauwen (Writing—review & editing), Paolo Carcoforo (Visualization) and Antonio Toesca (Validation, Visualization, Writing—review & editing).

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