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Nipple- and areola-sparing mastectomy for the treatment of breast cancer (Review)

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[Intervention Review]

Nipple- and areola-sparing mastectomy for the treatment of breast cancer

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ABSTRACT

Background

The efficacy and safety of nipple-sparing mastectomy and areola-sparing mastectomy for the treatment of breast cancer are still questionable. It is estimated that the local recurrence rates following nipple-sparing mastectomy are very similar to breast-conserving surgery followed by radiotherapy.

Objectives

To assess the efficacy and safety of nipple-sparing mastectomy and areola-sparing mastectomy for the treatment of ductal carcinoma in situ and invasive breast cancer in women.

Search methods

We searched the Cochrane Breast Cancer Group's Specialized Register, the Cochrane Center Register of Controlled Trials (CENTRAL), MEDLINE (via PubMed), Embase (via OVID) and LILACS (via Biblioteca Virtual em Saúde [BVS]) using the search terms "nipple sparing mastectomy" and "areola-sparing mastectomy". Also, we searched the World Health Organization's International Clinical Trials Registry Platform and ClinicalTrials.gov. All searches were conducted on 30th September 2014 and we did not apply any language restrictions.

Selection criteria

Randomised controlled trials (RCTs) however if there were no RCTs, we expanded our criteria to include non-randomised comparative studies (cohort and case-control studies). Studies evaluated nipple-sparing and areola-sparing mastectomy compared to modified radical mastectomy or skin-sparing mastectomy for the treatment of ductal carcinoma in situ or invasive breast cancer.

Data collection and analysis

Two review authors (BS and RR) performed data extraction and resolved disagreements. We performed descriptive analyses and meta-analyses of the data using Review Manager software. We used Cochrane's risk of bias tool to assess studies, and adapted it for non-randomised studies, and we evaluated the quality of the evidence using GRADE criteria.

Main results

We included 11 cohort studies, evaluating a total of 6502 participants undergoing 7018 procedures: 2529 underwent a nipple-sparing mastectomy (NSM), 818 underwent skin-sparing mastectomy (SSM) and 3671 underwent traditional mastectomy, also known as modified radical mastectomy (MRM). No participants underwent areola-sparing mastectomy. There was a high risk of confounding for all reported outcomes. For overall survival, the hazard ratio (HR) for NSM compared to SSM was 0.70 (95% CI 0.28 to 1.73; 2 studies; 781 participants) and the HR for NSM compared to MRM was 0.72 (95% CI 0.46 to 1.13; 2 studies, 1202 participants). Local recurrence was evaluated in two studies, the HR for NSM compared to MRM was 0.28 (95% CI 0.12 to 0.68; 2 studies, 1303 participants). The overall risk of complications was different in NSM when compared to other types of mastectomy in general (RR 0.10, 95% CI 0.01 to 0.82, 2 studies, P = 0.03; 1067 participants). With respect to skin necrosis, there was no evidence of a difference with NSM compared to other types of mastectomy, but the confidence interval was wide (RR 4.22, 95% CI 0.59 to 30.03, P = 0.15; 4 studies, 1948 participants). We observed no difference among the three types of mastectomy with respect to the risk of local infection (RR 0.95, 95% CI 0.44 to 2.09, P = 0.91, 2 studies; 496 participants). Meta-analysis was not possible when assessing cosmetic outcomes and quality of life, but in general the NSM studies reported a favourable aesthetic result and a gain in quality of life compared with the other types of mastectomy. The quality of evidence was considered very low for all outcomes due to the high risk of selection bias and wide confidence intervals.

Authors' conclusions

The findings from these observational studies of very low-quality evidence were inconclusive for all outcomes due to the high risk of selection bias.

PLAIN LANGUAGE SUMMARY

Nipple- and areola-sparing mastectomy for the treatment of breast cancer

Review question

We reviewed the evidence about the effectiveness and safety of nipple-sparing mastectomy (that is, removing the breast tissue but preserving the entire skin, nipple and areola) compared to traditional mastectomy (that is, removing the skin that overlies the breast including nipple and areola) or skin-sparing mastectomy (that is, removing the breast tissue including the breast and areola but preserving all the skin envelope).

Background

Traditional surgical therapy for breast cancer is mastectomy. A traditional mastectomy consists of the removal of the entire breast tissue and the nipple-areola complex. The chance of cancer returning to the region of the mastectomy after this type of surgery is about 2.3% after 20 years. Rising interest in improving the cosmetic results has led to the introduction of nipple-sparing mastectomy or areola-sparing mastectomy as an alternative to conventional mastectomy. Nipple-areola complex preservation results in higher psychological satisfaction and the perception of less mutilation among women. Nipple-sparing mastectomy has been proposed for the treatment of breast cancer. This technique retains the entire natural envelope of the skin and areola complex, and aims to create an aesthetic result that is closer to the natural state than breast reconstruction techniques. The efficacy and effectiveness of nipple- and areola-sparing mastectomy in the treatment of breast cancer is questionable.

Study characteristics

The evidence is current to September 2014. We included 11 studies involving 6502 participants having 7018 surgical procedures (some participants had surgery on both breasts). Out of these, 2529 participants underwent nipple-sparing mastectomy, while there were no participants who had an areola-sparing mastectomy, 818 participants underwent skin-sparing mastectomy and 3671 underwent a traditional mastectomy. All participants in the studies were women and most of them (99.2%) had invasive breast cancer or ductal carcinoma in situ. We compared nipple-sparing mastectomy to conventional mastectomy and skin-sparing mastectomy in two different analyses.

Key results

It was not possible to conclude whether or not survival following nipple-sparing mastectomy was similar to traditional mastectomy and skin-sparing mastectomy. Results were also inconclusive for differences in local recurrence and adverse events following different types of mastectomy. In practice the decision to select nipple-sparing mastectomy over other types of mastectomy should be done through shared decision making after extensive discussion of the risks and benefits. Generally the nipple-sparing mastectomy studies reported a favourable aesthetic result and a gain in quality of life compared with the other types of mastectomy. However, due to the lack of numerical data, it was not possible to pool the results of different studies.

Quality of the evidence

The quality of the evidence included in this review was very low. The studies had a number of methodological flaws. Poor reporting meant that the effect of the type of mastectomy on survival could not be determined for a number of studies. Also, differences between surgery groups in tumour stage and whether or not adjuvant radiotherapy was used may have affected the results. This is likely to have an impact on the findings and future research is likely to change the current findings.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Nipple-sparing mastectomy for breast cancer treatment

Patient or population: women with breast cancer
Setting: breast cancer therapy centres
Intervention: nipple-sparing mastectomy
Comparison: modified radical mastectomy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with other types of mastectomies	Risk with nipple-sparing mastectomy				
Overall survival	Study population		HR 0.72 (0.46 to 1.13)	1202 (2 observational studies)	⊕◯◯◯ VERY LOW[1,2]	We were unable to conclude non-inferiority because of the high risk of confounding. The quality of evidence was downgraded to very low due to the risk of bias and imprecision
	882 per 1000	785 per 1000 (626 to 910)				
Local recurrence	Study population		HR 0.28 (0.12 to 0.68)	1311 (2 observational studies)	⊕◯◯◯ VERY LOW [3]	Conclusions could not be drawn because of the high risk of residual confounding. The quality of the evidence was graded as very low due to the risk of bias
	17 per 1000	5 per 1000 (2 to 12)				
Overall complications	Study population		RR 0.10 (0.01 to 0.82)	1067 (2 observational studies)	⊕⊕◯◯ LOW [4]	We downgraded the quality of evidence from low to very low due to inconsistency (i.e. the magnitude of effects across the stud-

						ies)
	184 per 1000	18 per 1000 (2 to 151)				
Skin necrosis	Study population		RR 4.22 (0.59 to 30.03)	1948 (4 observational studies)	⊕◯◯◯ VERY LOW [5,6]	We downgraded the quality of evidence from low to very low due to a wide confidence interval
	19 per 1000	82 per 1000 (11 to 583)				
Infection	Study population		RR 0.95 (0.44 to 2.09)	496 (2 observational studies)	⊕⊕◯◯ LOW	
	48 per 1000	45 per 1000 (21 to 100)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ Confidence interval; __RR:__ Risk ratio; __OR:__ Odds ratio; __HR:__ Hazard ratio

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]There was no adjustment for confounding in Sakurai 2013 and we classified this as a serious risk of bias. We we were unable to conclude non-inferiority because of the high risk of confounding
[2]The confidence interval of included studies both increased and decreased risk for nipple-sparing mastectomy versus modified radical mastectomy
[3]Imprecision was downgraded because of the high risk of residual confounding due to lack of adjustment for tumour stage and radiotherapy. Adam 2014 matched the participants by tumour stage, Horiguchi 2001 seemed to have more initial tumours (Stages 0 and 1) in the NSM group (83 out of 123; 67.5%) than the MRM group (277 out of 910; 30.4%) and this fact may have influenced the results. Only 7.9% (103 out of 1303 participants) received radiotherapy, 7.2% (81 out of 1113 participants) in the modified radical mastectomy group and in 11.6% (22 out of 190 participants) in the nipple-sparing mastectomy. No one

received the treatment in Horiguchi 2001, probably because in that period the indication for radiotherapy treatment was more limited. Probably more patients would now receive post-mastectomy radiotherapy, which would have an impact on the local recurrence rate

[4]There was evidence of considerable heterogeneity on statistical testing, I^2 = 85%, P = 0.01

[5]There was evidence of considerable heterogeneity on statistical testing, I^2 = 79% , P = 0.008

[6]Confidence intervals fail to exclude both clinically important and clinically unimportant harms.

BACKGROUND

Description of the condition

Breast cancer is the most frequent non-skin cancer in women (23% of all cancers in women) with an estimated 1.67 million new cases and over 521,907 deaths reported worldwide in 2014 (Ferlay 2012).

Description of the intervention

The technique of subcutaneous mastectomy for the treatment of benign breast disease for women with a strong family history of breast cancer was first reported by Freeman 1962. In 1980, Gentil 1980 proposed nipple-sparing mastectomy (NSM) for prophylactic contralateral mastectomy and to treat breast cancer. The traditional method of mastectomy consists of the removal of the skin that overlies the breast including the nipple-areola complex. Today, NSM is commonly used for women who are considered to be high risk and who are undergoing surgery as primary prevention for breast cancer (Hartmann 2001; Josephson 2000; Lostumbo 2010; Pennisi 1989).

How the intervention might work

The surgical management of breast carcinoma has evolved during the last two decades and improvements in the techniques mean that more conservative surgery and better cosmetic results can be achieved without compromising oncological safety (Morrow 2002). Although the techniques for breast conserving surgery in the treatment of breast cancer are well-established, many women prefer or require mastectomy to obtain local control of their disease. This is particularly true in cases of multifocal tumours and/or small volume breasts in relation to the tumour, extensive ductal carcinoma in situ, women with clinical contraindications for radiotherapy and treatment of local recurrences (Singletary 2003). Conventional surgical therapy in these situations is mastectomy with the removal of the nipple-areola complex. This type of surgery has a cumulative incidence of local recurrence of about 2.3% after 20 years (Veronesi 1990).

Rising interest in improved cosmesis (i.e. cosmetic outcome) has led to the introduction of NSM or areola-sparing mastectomy as an alternative to radical mastectomy (Chung 2008; Gerber 2009; Simmons 2002). Nipple-areola complex preservation results in higher psychological satisfaction and the perception of less mutilation among women (Loewen 2008).

Occult nipple involvement in breast cancer ranges from 0% to 58% (Andersen 1979; Banerjee 2008; Lagios 1979; Laronga 1999; Loewen 2008; Luttges 1987; Menon 1989; Morimoto 1985; Parry 1977; Quinn 1981; Rusby 2008; Santini 1989; Schecter 2006; Smith 1976; Verma 1997; Vyas 1998; Wetheim 1980) and areola involvement is 0.9% in people with tumours less than 2 cm (Simmons 2002). This wide range may be explained by differences in the thoroughness of the pathological examinations and the study methods. The factors most commonly associated with the pathological involvement of the nipple are the size and region of the tumours, the distance of the tumours from the nipple, and axillary metastasis (Benediktsson 2008; Caruso 2006; Lagios 1979; Schecter 2006).

Despite the promising approach with nipple-sparing and areola-sparing mastectomy, the evidence from published studies seems preliminary. These studies include a small number of participants and a relatively short follow-up period (Benediktsson 2008; Caruso 2006; Gerber 2009; Horiguchi 2001; Petit 2009a; Sacchini 2006). In these non-randomised studies, the incidence of local recurrence ranges from 1.6% to 28% without radiotherapy (Benediktsson 2008; Caruso 2006), and 1.4% to 8.5% with radiation of the nipple-areola complex (Benediktsson 2008; Petit 2009a; Petit 2009b). Surgical complications such as skin necrosis (i.e. death of localised tissue or cells) have been described in up to 11% of patients without radiotherapy (Sacchini 2006) and up to 15% with the addition of radiotherapy to the nipple-areola complex (Petit 2009a).

Why it is important to do this review

NSM has been proposed for the treatment of breast cancer. This technique retains the entire natural envelope of the skin and areola complex, and aims to create an aesthetic result that is closer to the natural state than breast reconstruction techniques. The efficacy and effectiveness of NSM in the treatment of breast cancer is questionable, but it is estimated that local recurrence rates are very similar to those for breast-conserving surgery followed by radiotherapy (Veronesi 1990; Veronesi 2002). No systematic reviews or articles have been published that have assessed the relevant studies with regards to their internal and external validity, and the risk of bias. Therefore, a systematic review on this topic is warranted.

OBJECTIVES

To assess the efficacy and safety of nipple-sparing mastectomy and areola-sparing mastectomy for the treatment of ductal carcinoma in situ and invasive breast cancer in women.

METHODS

Criteria for considering studies for this review

Types of studies

We searched for randomised controlled trials (RCTs) as they provide the highest level of evidence. As no RCTs were found, we expanded our criteria to include non-randomised comparative studies (cohort and case-control studies).

Types of participants

Women with a diagnosis of ductal carcinoma in situ or invasive breast cancer, regardless of age, time of onset, or disease stage. The diagnosis must have been in accordance with the histopathological criteria of the World Health Organization (WHO) (Lakhani 2012).

We included women who had undergone breast reconstructive surgery.

Types of interventions

Nipple-sparing mastectomy (NSM) (that is, removal of all glandular breast tissue and preservation of the entire skin, nipple and areola) and areola-sparing mastectomy (that is, removal of all glandular breast tissue and nipple, and preservation of the entire skin and areola) compared with conventional mastectomy (removal of the skin that overlies the breast including the nipple and areola, also known as modified radical mastectomy (MRM)) for the treatment of ductal carcinoma in situ or invasive breast cancer, regardless of any adjuvant therapy.

We included studies where women underwent breast reconstructive surgery.

Types of outcome measures

Primary outcomes

Overall survival, considered separately for ductal carcinoma in situ and early breast cancer if possible.

Secondary outcomes

- Local recurrence incidence rate and time-to-recurrence during the follow-up period, considered separately for ductal carcinoma in situ and early breast cancer if possible.
- Adverse events: local surgical complications and overall complications (systemic surgical complications, e.g. thromboembolic events)
    - Local Complications
        - Explantation of implant/expander
        - Hematoma
        - Seroma
        - Rehospitalization
        - Skin necrosis (nipple, areola or flap necrosis)
        - Skin necrosis with revision surgery
        - Infection
- Cosmetic results: participants' and professionals' opinions
- Quality of life including satisfaction with the decision to have NSM, satisfaction with the cosmetic outcome, satisfaction with the medical process, psychological well-being, impact on body image, and impact on primary relationships and sexuality.

Search methods for identification of studies

See: Breast Cancer Group for search methods used in reviews. There were no language restrictions on included studies. We undertook full translations of all non-English language papers using local resources.

Electronic searches

We searched the following databases.

- The Cochrane Breast Cancer Group's Specialised Register. The Cochrane Breast Cancer Group searched their Specialised Register on 30 September 2014. Details of the search strategies used by the Group for the identification of studies and the procedure used to code references are outlined in the Group's module (onlinelibrary.wiley.com/o/cochrane/clabout/articles/BREASTCA/frame.html). We extracted trials with the key words 'surgery', 'nipple sparing mastectomy', 'areola sparing mastectomy' and 'breast conserving surgery'
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2014, issue 9) (Appendix 1) on 30 September 2014.
- MEDLINE (via Pubmed) (Appendix 2) on 30 September 2014.
- Embase (via OVID) (Appendix 3) on 30 September 2014.
- LILACS (via Biblioteca Virtual em Saúde (BVS)) (Appendix 4) on 30 September 2014.
- The WHO International Clinical Trials Registry Platform (ICTRP) search portal (www.who.int/ictrp/en/) for all prospectively registered and ongoing trials (Appendix 5) on 30 September 2014.
- ClinicalTrials.gov (www.clinicaltrials.gov/) (Appendix 6) on 30 September 2014.

Searching other resources

Bibliography Searching

We searched bibliographies of all included studies and review papers in order to identify other potentially suitable studies. We obtained a copy of the full article for each reference reporting a potentially eligible trial, where possible. We contacted the study authors to provide additional information when it was not available.

Unpublished Literature

We contacted experts in this field and sent letters to all authors of included studies requesting information on unpublished data or ongoing studies.

Data collection and analysis

Selection of studies

Two review authors (BS, RR) independently examined the titles and abstracts of articles identified in the search as potentially relevant trials. From this initial assessment, we obtained full versions of all potentially relevant articles. We consulted a third review author (JLBB) to help to resolve any disagreements.

Data extraction and management

We extracted and recorded the data onto data extraction forms which we had developed for this review. Two review authors (BS and RR) independently undertook full data extraction and consulted a third review author (JLBB) to help resolve disagreements. We sought unpublished data concerning outcomes of interest from study authors by letter as stated above.

We included the following information from individual studies on data extraction forms:

- publication details;
- study design, study setting, inclusion/exclusion criteria;
- patient population (e.g. age, type of surgical procedure, histological classification);
- details of intervention;
- outcome measures; and
- withdrawals, length and method of follow-up and the number of participants followed up.

For non-randomised studies we also recorded the following information:

- methods used to control for confounders;
- adjusted and unadjusted outcome measures.

Assessment of risk of bias in included studies

We applied the Cochrane tool for assessing risk of bias as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a), the Cochrane EPOC Group's risk of bias criteria (Cochrane EPOC Group 2013), and recommendations by Norris 2013. Two review authors (BS, RR)independently assessed the methodological quality of each study and risk of bias for the following domains: selection bias, performance/detection bias, attrition bias, reporting bias and other bias. For each risk of bias domain and its associated specific questions outlined below, we assigned either 'High risk', 'Low risk', or 'Unclear risk'.

Selection Bias

Was the allocation sequence adequately generated?

- Scored "Low risk" if a random component in the sequence generation process was described (e.g. referring to a random number table).
- Scored "High risk" when a non-random method was used (e.g. performed by date of admission). Non-randomised studies should be scored "High risk".
- Scored "Unclear risk" if not specified in the paper.

Was the allocation adequately concealed?

- Scored "Low risk" if participants or investigators enrolling participants could not foresee assignment (e.g. because a centralised randomisation scheme, an on-site computer system or sealed opaque envelopes were used).
- Scored "High risk" if participants or investigators enrolling participants could possibly foresee assignments. Non-randomised studies were scored "High risk".
- Scored "Unclear risk" if not specified in the paper.

For non-randomised studies, we also considered the following questions.

Were baseline characteristics similar?

- Scored "Low risk" if baseline characteristics of the study and control group were reported and similar. Important baseline characteristics were adjuvant radiotherapy, age, surgical techniques, stage of disease, ductal carcinoma in situ or invasive breast cancer, and chemotherapy. We considered intervention and control groups similar for categorical variables if category membership agreed within no more than a 2 percentage point difference between groups. We considered mean ages within two years and tumour sizes within 1 cm similar. When we used statistical tests to compare baseline characteristics between groups, we took statistical significance into account, but as the study may have been underpowered due to small sample sizes, we also considered the magnitude of the difference.
- Scored "Unclear risk" if it was not clear in the paper (e.g. characteristics were mentioned in the text, but no data were presented).
- Scored "High risk" if there was no report of characteristics in text or tables or if there were differences between control and intervention groups.

Was there adequate adjustment for confounding?

- Scored "Low risk" if appropriate methods were used to adjust for potential confounding (e.g. adjuvant radiotherapy, age, surgical techniques, stage of disease, ductal carcinoma in situ or invasive breast cancer, and chemotherapy).

- Scored “Unclear risk” if the methods used to adjust for confounding were not reported in the paper.
- Scored “High risk” if no appropriate methods were used to adjust for potential confounding.

Performance/detection bias

Was knowledge of the allocated interventions adequately prevented during the study?

- Scored “Low risk” if the study authors stated explicitly that the primary outcome variables were assessed blindly, or the outcomes were objective, e.g. overall survival, hospitalisation time
- Scored “High risk” if the outcomes were not assessed blindly
- Scored “Unclear risk” if not specified in the paper

Attrition bias

Were incomplete outcome data adequately addressed?

- Scored “Low risk” if missing outcome measures were unlikely to bias the results (e.g. reasons for missingness unlikely to be related to true outcome, missing outcome data balanced and small numbers across study groups with similar reasons for missing data or missing data were imputed using appropriate methods).
- Scored “High risk” if missing outcome data were likely to bias results.
- Scored “Unclear risk” if not specified in the paper.

Reporting bias

Were reports of the study free from selective outcome reporting?

- Scored “Low risk” if there was no evidence that outcomes were selectively reported (e.g. the study had a protocol pre-specifying the outcomes, or all relevant outcomes described in the methods section were reported in the results section).
- Scored “High risk” if some pre-specified outcomes were subsequently omitted from the results.
- Scored “Unclear risk” if not specified in the paper.

Were reports of the study free from selective analysis reporting?

- Scored “Low risk” for each outcome if there was no evidence that analyses were selectively reported (e.g. analyses were defined in the methods section of the protocol or paper).
- Scored “High risk” if there was evidence of selective analysis reporting (e.g. multiple adjusted analyses were carried out and only one reported, or unusual cut-points were used for categorizing an outcome).
- Scored “Unclear” risk if unclear from the paper.

Classification of study designs

We included various study designs and defined them as follows:

- Prospective cohort study: a group of exposed and non-exposed individuals who were followed over time to compare incidence (or rate of death from disease) between the groups (Gordis 1996). In prospective cohort studies, the recruitment, exposure/intervention, and outcomes must all have occurred after setting up the study.
- Retrospective cohort study: a group of exposed and non-exposed individuals who were followed over time to compare incidence (or rate of death from disease) between the groups (Gordis 1996). In retrospective cohort studies, outcomes could have occurred prior to setting up the study or collected afterwards, or both.
- Case-control study: a study that compared people with a specific outcome of interest (cases) with people from the same source population but without the outcomes (controls), to examine the association between the outcome and exposure.

Measures of treatment effect

We reported time-to-event outcomes (e.g. overall survival and local recurrence) as hazard ratios (HRs) with 95% confidence intervals (CIs). Where necessary we estimated HRs using the methods of Parmar 1998.

We reported dichotomous outcomes (e.g. distant disease, explantation of implant/expander, hematoma, seroma, rehospitalization, skin necrosis (nipple, areola or flap necrosis), skin necrosis (nipple, areola or flap necrosis) with revision surgery, infection and cosmetic results) as risk ratios (RRs) with 95% CIs. Participants reported as lost-to-follow-up were excluded from the analyses.

We reported continuous outcomes (e.g. quality of life) as mean differences (MDs) or standardised mean differences (SMD) with 95% CIs.

Considering the current approach for ductal carcinoma in situ or invasive breast cancer, it seemed reasonable to consider the treatment effect for the primary outcome as a non-inferiority question. Thus, the non-inferiority bound for the HR was 1.13 (based on a 10-year death rate of 24% for conventional mastectomy with a cut-off value of 27% for nipple/areola-sparing mastectomy, 1.13 = 0.27/0.24). For local recurrence the non-inferiority bound for the HR was 2.67 (based on 3% 10-year local recurrence for conventional mastectomy with a cut-off value of 8% for nipple/areola-sparing mastectomy, 2.67 = 0.08/0.03). Non-inferiority could be claimed if the upper limit of the two-sided 95% confidence interval was less than the non-inferiority bound.

Outcomes relating to adverse events were assessed for superiority.

Unit of analysis issues

The unit of analysis was the individual participant.

Two studies were three-arm studies. The three surgical interventions in the Gerber 2009 and Kim 2010 studies contributed to the NSM versus SSM comparison and also the NSM versus MRM comparison.

Dealing with missing data

Where data were missing or unsuitable for analysis (e.g. intention-to-treat analysis was not used), we contacted the study authors to request further information as indicated in the Characteristics of included studies table. Where data were missing to the extent that the study could not be included in the meta-analysis, and attempts to retrieve data were exhausted, we presented the results in the review and discussed them in the context of the findings.

Assessment of heterogeneity

We assessed statistical heterogeneity using the Chi^2 statistic (P value less than 0.1). We also assessed heterogeneity between studies using the I^2 statistic to examine the percentage of total variation across studies due to heterogeneity rather than chance (Higgins 2003). An I^2 value of 30% to 60% may represent moderate heterogeneity, while values greater than 50% may be considered substantial heterogeneity (Deeks 2011).

We investigated the following factors as potential causes of heterogeneity in the included studies using the framework below.

- Clinical diversity: included study location and setting, full characteristics of participants, co-morbidity and treatments that participants were probably receiving on trial entry. We considered how outcomes were measured, the definition of outcomes, and how they were recorded. Depending upon the extent of the clinical diversity, we either analysed studies separately or presented the results using a narrative approach.
- Methodological diversity: included assessment of the randomisation process, study quality, and analytical method.

Assessment of reporting biases

We searched for protocols of included trials using PubMed (National Library of Medicine) and through the UK and other trial registries, where possible. We contacted study authors to attempt to establish a full data set or reasons for the non-reporting of certain outcomes as outlined in the Characteristics of included studies table.

Data synthesis

We synthesised data using Cochrane's statistical software, Review Manager (RevMan) (RevMan 2014).

We based the choice of using a fixed-effect or random-effects model for data synthesis on the extent of the heterogeneity. Where substantial clinical or methodological heterogeneity existed, we used a random-effects model. Otherwise we used a fixed-effect model (Deeks 2011).

We combined data using the inverse variance method and the log-HR for time-to-event outcomes, the log-RR for dichotomous outcomes and the MD for continuous outcomes. For random-effects meta-analysis we used the DerSimonian and Laird method (Deeks 2011).

Where the data were too diverse for combining effect sizes in a meaningful or valid manner, we presented the results of individual studies in table and graphical format and used a narrative approach to summarise the data.

We used the criteria of the GRADE working group to evaluate the evidence. The quality of evidence for each outcome was classified as high, moderate, low or very low quality. The classification criteria considered the study design, the risk of bias, the inconsistency of data, subjectivity (indirectness, or indirect evidence), imprecision and publication bias (Guyatt 2008).

Subgroup analysis and investigation of heterogeneity

As we expected a small number of published studies, we anticipated that it would not be possible to perform subgroup analyses. However, we will consider the following subgroups in future updates of this review.

- Participants who received adjuvant radiotherapy versus participants who did not have radiotherapy.
- Younger (< 50 years) versus older (≥ 50 years) women.
- Surgical techniques.
- Cancer stage based on the TNM (the size and/or extent of the primary tumour (T), the amount of spread to nearby lymph nodes (N), and the presence of metastases (M) or secondary tumours) classification system (NCI 2013).
- Systemic therapy (chemotherapy or endocrine therapy) versus no systemic therapy.

Sensitivity analysis

We planned to conduct sensitivity analyses by excluding either studies of low methodological quality or, if RCT evidence was available, quasi-randomised studies. This was not possible due to a lack of good quality studies, but will be considered for future updates of this review.

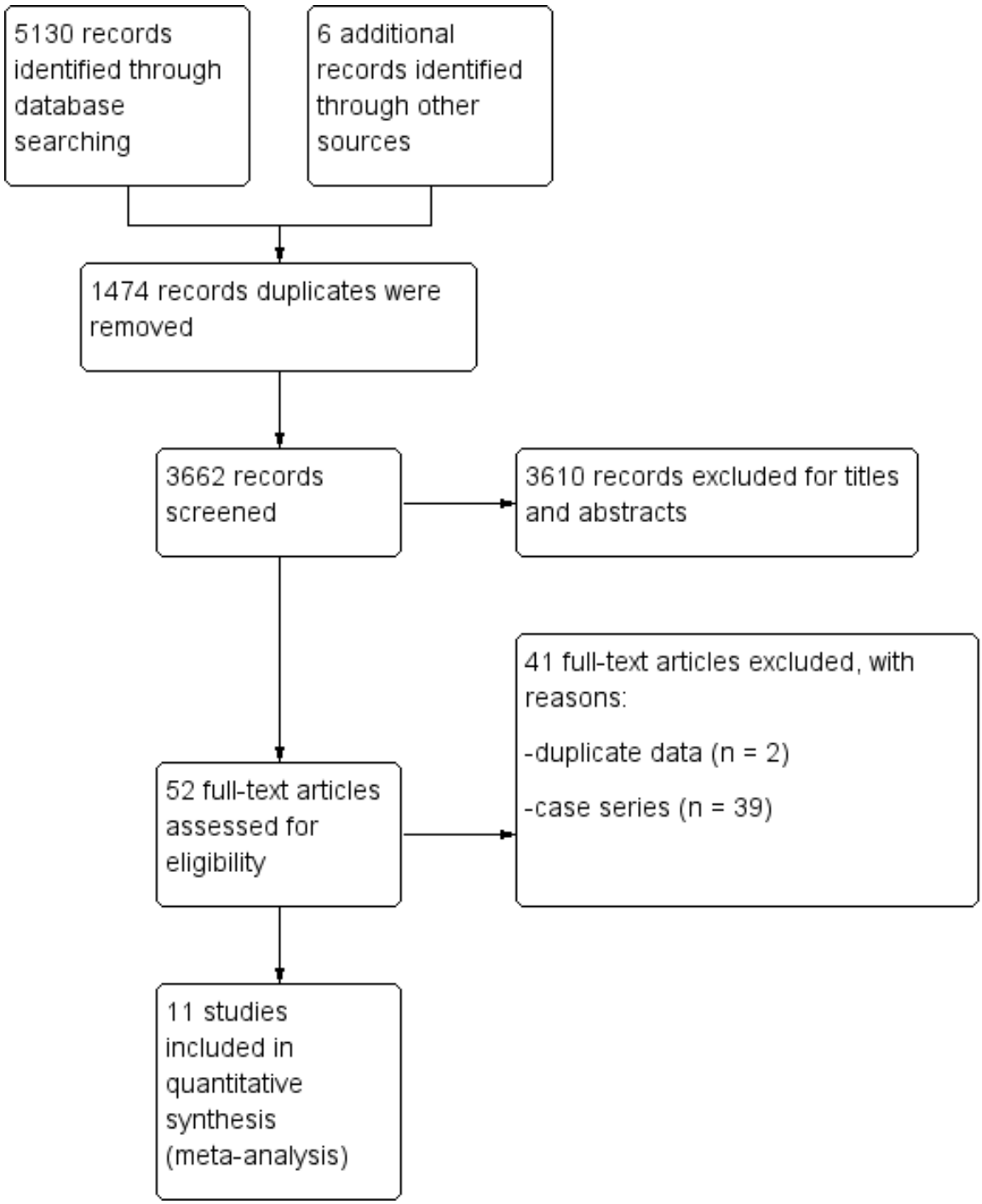
RESULTS

Description of studies

Results of the search

See: Figure 1.

Figure 1. Study flow diagram



Based on our search strategy, we identified and screened 5130 references, with an additional six references identified from other sources. After removing duplicates, we screened the title and abstracts of 3662 references. Of these, we discarded 3610 records and assessed 52 full-text articles. We excluded 41 articles due to being either case series or duplicate data. Eleven cohort studies met the inclusion criteria for this review. There were no RCTs or quasi-RCTs.

Included studies

We included 11 studies in the review (Adam 2014; Boneti 2011; Burdge 2013; Gerber 2009; Horiguchi 2001; Kim 2010; Oura 1994; Poruk 2015; Sakurai 2013; Shi 2012; Stanec 2014). See: Characteristics of included studies table.

Study design

All studies were cohort studies; 10 were retrospective (Adam 2014; Boneti 2011; Burdge 2013; Horiguchi 2001; Kim 2010; Oura 1994; Poruk 2015; Sakurai 2013; Shi 2012; Stanec 2014) and one was prospective (Gerber 2009).

Characteristics of participants

In total, the studies included 6502 participants involving 7018 procedures, as 516 participants underwent bilateral surgery. Out of these, 2529 participants underwent nipple-sparing mastectomy (NSM), while there were no participants who had areola-sparing mastectomy, 818 participants underwent skin-sparing mastectomy (SSM) and 3671 underwent a modified radical mastectomy (MRM).

The mastectomy indications were 99.2% for invasive breast carcinoma or ductal carcinoma in situ and 0.8% for prophylaxis, that mostly involved the contralateral breast after invasive breast cancer. It was possible to identify the indications for NSM in 10 studies.

The criteria for mastectomy varied across the included studies. In six studies, the criteria comprised any tumour without skin or areola involvement (Boneti 2011; Burdge 2013; Kim 2010; Poruk 2015; Sakurai 2013; Shi 2012). Four studies considered tumours located at least 2 cm from the nipple-areola complex (Adam 2014; Gerber 2009; Oura 1994; Stanec 2014).

Eleven studies classified the stage of the tumour. Eight studies used the AJCC classification (Gerber 2009; Horiguchi 2001; Kim 2010; Oura 1994; Poruk 2015; Sakurai 2013; Shi 2012; Stanec 2014). In total, 387 participants had Stage 0, 1992 participants had stage 1; 2776 participants had stage 2; 655 participants had stage 3 and 11 participants had stage 4 tumours (refer to Table 1). In the three remaining studies, one study (Burdge 2013) enrolled participants with, at least, stage 2 (NSM: mean tumour size was 3.4 cm (± 2.2 cm) and SSM: mean tumour size was 4.6 cm (± 2.9 cm)). The Boneti 2011 study described the mean tumour size and there was no difference between groups (the mean tumour size was 1.9 cm (± 1.6 cm) in the NSM group and 2.1 cm (± 1.7 cm) in the SSM group, P = 0.42 in SSM group) and Adam 2014 described the tumour size according to TNM staging (NSM: T1 - 37 participants (53.6%), T2 - 14 participants (20.3%), T3 - three participants (4.3%), T4 - one participant (1.4%); MRM T1 - 111 participants (53.9%), T2 - 46 participants (22.3%), T3 - nine participants (4.4%), T4 - one participant (0.5), P = 0.86). In two studies there were significant differences in staging between groups with more advanced disease in the SSM group (Poruk 2015) and MRM group (Horiguchi 2001) when compared to NSM. In six of the remaining studies there were differences between intervention and control groups of more than 2 percentage points for at least one tumour stage (Gerber 2009; Kim 2010; Oura 1994; Sakurai 2013; Shi 2012; Stanec 2014) (Table 2). Only two studies used appropriate methods to adjust for tumour stage (Kim 2010; Poruk 2015), while Adam 2014 matched participants in the intervention and control groups according to their tumour stage.

The mean age was described in 10 studies while one study (Horiguchi 2001) described the age groups as younger or older than 50 years (see Table 3). Two studies reported similar ages between intervention and control groups (Adam 2014; Boneti 2011). Three studies reported significant differences between groups (Gerber 2009; Horiguchi 2001; Poruk 2015) with the NSM group being younger on average. The remaining five studies reported more than two years' difference in mean age between intervention and control groups (Burdge 2013; Oura 1994; Sakurai 2013; Shi 2012; Stanec 2014). Only three studies used appropriate methods to adjust for tumour stage disease (Horiguchi 2001; Kim 2010; Poruk 2015). One study matched participants in the intervention and control groups according to three age categories (Adam 2014).

Interventions

Five studies compared NSM and MRM (Adam 2014; Horiguchi 2001; Oura 1994; Sakurai 2013; Shi 2012), four studies compared NSM and SSM (Boneti 2011; Burdge 2013; Poruk 2015; Stanec 2014) and two studies contained three arms involving NSM, SSM and MRM (Gerber 2009; Kim 2010).

Regarding adjuvant therapy, only two studies described chemotherapy (Gerber 2009; Poruk 2015). Poruk 2015 reported that use of both neoadjuvant and adjuvant chemotherapy was higher in the SSM group (neoadjuvant: 17%: 22/131 participants and adjuvant: 57%: 74/131 participants) compared to the group receiving NSM (neoadjuvant: 8.5%: 11/130 participants and adjuvant: 44.5%: 57/130; P = 0.04 and 0.05, respectively). There was no difference between NSM and SSM groups for neo- or adjuvant chemotherapy in Gerber 2009: 90% (43/48 participants) in the NSM group versus 88% (53/60) in the SSM group, but it was lower in the MRM group: 83% (109/130).

Radiotherapy was a co-intervention in seven studies. In five studies, radiotherapy was performed according to tumour stage (Adam 2014; Boneti 2011; Gerber 2009; Poruk 2015; Stanec 2014). In

the remaining two studies, all participants received radiotherapy (Burdge 2013; Shi 2012). Only two studies compared radiotherapy between intervention groups. Poruk 2015 reported 28% of radiotherapy treatment (36 out of 130 participants) for the NSM group versus 50.4% (65 out of 131 participants) for the SSM group (P < 0.001). Gerber 2009 did not find a difference in radiotherapy treatment between the NSM and SSM groups: 29% (14 out of 48 participants) and 27% (16 out of 60 participants) respectively, but it was lower for the MRM group: 24% (31 out of 130 participants).

In three studies, participants did not receive radiotherapy (Horiguchi 2001; Oura 1994; Sakurai 2013).

Follow-up

Six studies had a mean follow-up of 60 months or greater (Gerber 2009; Horiguchi 2001; Kim 2010; Oura 1994; Sakurai 2013; Shi 2012). The shortest follow-up ranged from 3 to 102 months (mean: 25.3 months; Boneti 2011) while the longest ranged from 0 to 231 months (mean: 87 months; Sakurai 2013). Boneti 2011 used methods to adjust for differential follow-up between intervention and control groups; this study had a mean follow-up of 25.3 months for the NSM group and 38.2 months for the SSM group (P < 0.001). (See Table 4.)

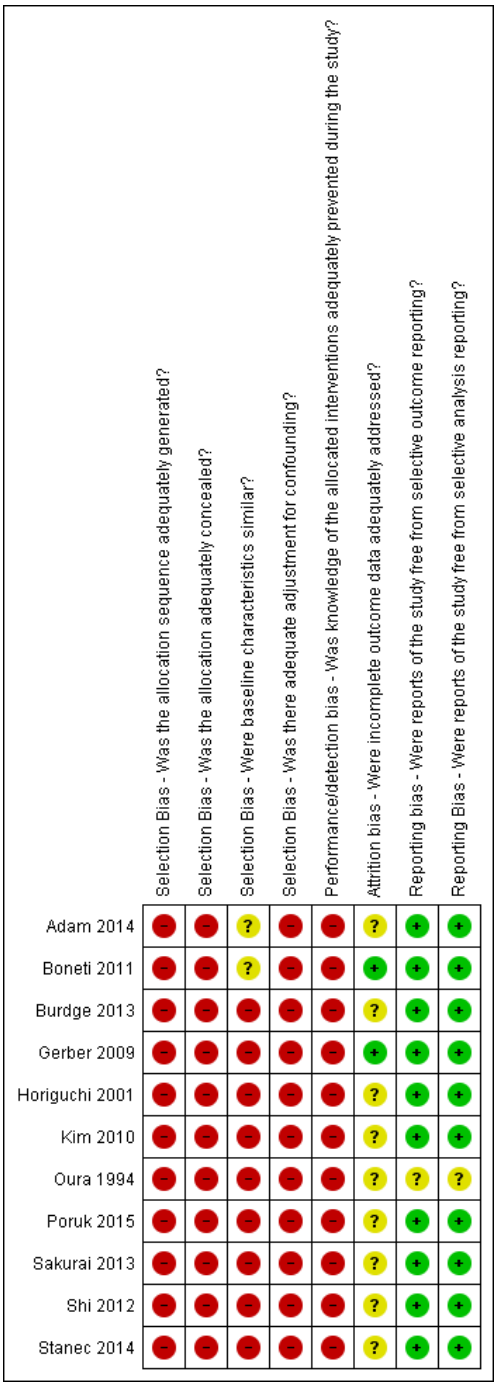
Excluded studies

Of the 41 excluded studies, all were case series with two being duplicate reports. See Excluded studies.

Risk of bias in included studies

The risk of bias for each of the selected studies is shown in Figure 2. Overall, we identified 11 relevant studies (11 cohort) published between 2001 and 2014. The major implication for risk of bias assessment was selection bias due to the lack of random assignment to intervention or control. None of the studies performed adequate adjustment for confounding, and there were differences in baseline characteristics between intervention and comparison groups for some studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

The most common source of potential bias was selection bias. All studies were cohort studies; 10 were retrospective (Adam 2014; Boneti 2011; Burdge 2013; Horiguchi 2001; Kim 2010; Oura 1994; Poruk 2015; Sakurai 2013; Shi 2012; Stanec 2014) while one was prospective (Gerber 2009). Therefore none had an allocation sequence adequately generated and concealed, and so all were judged as having a high risk of bias.

Differences in baseline characteristics between mastectomy groups were observed for nine studies (Burdge 2013; Gerber 2009; Horiguchi 2001; Kim 2010; Oura 1994; Poruk 2015; Sakurai 2013; Shi 2012; Stanec 2014). For two studies (Adam 2014; Boneti 2011) the stage of disease and age at baseline of participants were similar, but differences in chemotherapy and radiotherapy between groups were not reported.

None of the studies used appropriate techniques to deal with all the potential confounders that were pre-specified for this review. Some studies partially adjusted for confounding. Adam 2014 matched participants for age, tumour stage and follow up, but made no adjustment for adjuvant radiotherapy, surgical techniques or chemotherapy. Horiguchi 2001 adjusted for age, lymph node status and oestrogen receptor status for local recurrence, but did not adjust for tumour stage, surgical techniques or chemotherapy. Kim 2010 adjusted overall survival for age, tumour stage and oestrogen receptor status, but did not adjust for radiotherapy use, surgical techniques or chemotherapy use. Poruk 2015 controlled for age, stage, and surgery laterality, but did not adjust for radiotherapy or chemotherapy use. The remaining studies made no adjustment for confounding.

Blinding

Blinding of participants and surgeons was not possible because of the nature of the procedure. The lack of blinding may have influenced the results for some outcomes. The time to event outcomes were judged as low risk of bias. Adverse events, cosmesis and quality of life were judged as high risk of bias due to the lack of blinding.

Incomplete outcome data

Three studies reported loss-to-follow-up. Stanec 2014 reported almost 12%, which may have been high enough to influence results, so the risk of bias was considered to be unclear, Boneti 2011 reported 5% and Gerber 2009 reported 3%. The low rates of attrition in Boneti 2011 and Gerber 2009 were unlikely to have affected their results and they were classified at low risk of bias. It was impossible to determine if the remaining studies had any missing outcome measures (Adam 2014; Burdge 2013; Horiguchi 2001; Kim 2010; Oura 1994; Poruk 2015; Sakurai 2013; Shi 2012). These studies and Stanec 2014 were considered to have unclear risk of bias.

Selective reporting

Ten of the eleven studies (Adam 2014; Boneti 2011; Burdge 2013; Gerber 2009; Horiguchi 2001; Kim 2010; Poruk 2015; Sakurai 2013; Shi 2012; Stanec 2014) appeared to be free from selective outcome and analysis reporting, because the defined statistical methods and outcomes in the methods section of the study were employed and reported in the results section.

Other potential sources of bias

We did not identify any other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Nipple-sparing mastectomy for breast cancer treatment; **Summary of findings 2** Nipple-sparing mastectomy for breast cancer treatment

The 11 cohort studies, involving 13 treatment comparisons, enrolled 6502 participants. Four studies included participants who underwent either nipple-sparing mastectomy (NSM) or skin-sparing mastectomy (SSM) (Boneti 2011; Burdge 2013; Poruk 2015; Stanec 2014), five studies included participants who underwent either NSM or modified radical mastectomy (MRM) (Adam 2014; Horiguchi 2001; Oura 1994; Sakurai 2013; Shi 2012) and two studies involved three treatment comparisons, that is, NSM, SSM and MRM, and therefore these latter two studies contributed data for the analysis related to NSM versus SSM, and NSM versus MRM (Gerber 2009; Kim 2010).

We tried to analyse the outcomes of overall survival and local recurrence in two different comparisons: NSM versus SSM, and NSM versus MRM. When this was not possible (e.g. for adverse effects), we drew the comparison between NSM versus other types of mastectomy (i.e. SSM or MRM, or both).

For most studies, we could not calculate the HRs because outcomes were not reported in sufficient detail. Many studies only reported outcomes at the end of follow-up, rather than at specific time points.

It was not possible to stratify the analyses for participants with DCIS and those with invasive breast cancer, as had originally been planned, because insufficient data were available.

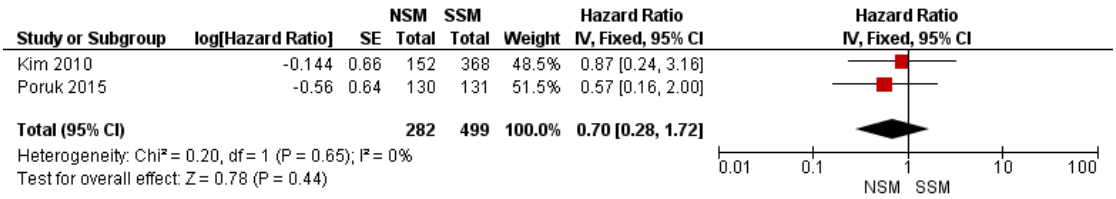
Overall survival

Overall survival was evaluated in four of the 11 studies (Adam 2014; Kim 2010; Poruk 2015; Sakurai 2013).

Nipple-sparing mastectomy versus skin-sparing mastectomy

Two studies involving 781 participants evaluated overall survival for NSM versus SSM (Kim 2010; Poruk 2015), both of which had adjusted for some confounders including age and tumour stage. The HR was 0.70 (95% CI 0.28 to 1.72; 2 studies; 781 participants; Analysis 1.1; Figure 3) with no heterogeneity across studies (I^2 = 0%; P =0.65). The confidence interval is too wide to draw any conclusions, and indeed crossed the specified non-inferiority bound of 1.13. We downgraded the evidence for this outcome from low to very low quality due to imprecision, as further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

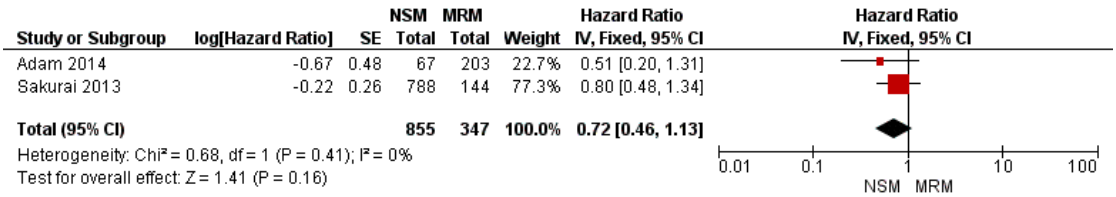
Figure 3. Forest plot of comparison: 1 Overall survival, outcome: 1.1 NSM vs SSM - overall survival.



Nipple-sparing mastectomy versus modified radical mastectomy

Two studies involving 1202 participants evaluated overall survival for NSM versus MRM (Adam 2014; Sakurai 2013). Adam 2014 matched participants for age and tumour stage, but the larger study, Sakurai 2013 did not adjust for confounding. The HR was 0.72 (95% CI 0.46 to 1.13; 2 studies, 1202 participants; Analysis 1.2; Figure 4) with no heterogeneity (I^2 = 0%, P = 0.41). Although the confidence interval did not cross the specified non-inferiority bound of 1.13, we were unable to conclude non-inferiority because of the high risk of confounding. We downgraded the quality of evidence from low to very low due to the risk of bias and imprecision.

Figure 4. Forest plot of comparison: 1 Overall survival, outcome: 1.2 NSM vs MRM - overall survival.



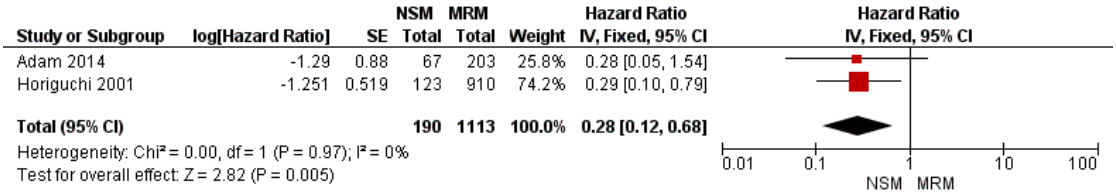
Local recurrence

Eleven studies with 13 treatment comparisons described local recurrence (Adam 2014; Boneti 2011; Burdge 2013; Gerber 2009; Horiguchi 2001; Poruk 2015; Kim 2010; Oura 1994; Sakurai 2013; Shi 2012; Stanec 2014).

In total, there were 144 events in 2105 women who had undergone NSM. The recurrent events occurred in 38 out of 118 (32.2%) women in the nipple or areola, or both, 80 out of 118 (67.8%) women in the mastectomy flap or regional lymph nodes while the location was not described in 26 participants.

Two studies involving 1303 participants evaluated the HR for local recurrence for NSM versus MRM (Adam 2014; Horiguchi 2001). One study matched participants for age and tumour stage (Adam 2014), and the other adjusted for age, lymph node status and oestrogen receptor status. The HR was 0.28 (95% CI 0.12 to 0.68, P = 0.005; 2 studies, 1303 participants; Analysis 2.1; Figure 5) with no heterogeneity (I^2 = 0%, P= 0.97). However we were unable to draw firm conclusions because of the high risk of residual confounding. We graded the quality of the evidence as very low due to the risk of bias.

Figure 5. Forest plot of comparison: 2 Local recurrence, outcome: 2.1 NSM vs MRM - local recurrence.



Adverse events

We evaluated overall complications for two studies involving 1067 participants (Sakurai 2013; Shi 2012). Neither study made any adjustment for confounding. The RR was 0.10 (95% CI 0.01 to 0.82, P = 0.03; 2 studies, 1067 participants; Analysis 3.1) with significant heterogeneity (I^2 = 85%; P = 0.01). We downgraded the quality of evidence from low to very low due to inconsistency (i.e. the magnitude of effects across the studies).

Local surgical complications

Explantation of implant/expander

Two studies reported on explantation of the implant/expander (Boneti 2011; Burdge 2013). Burdge 2013 described the necessity of implant removal in 5% of the participants (3 out of 60 participants) and Boneti 2011 described the necessity of implant removal for 1% of participants (2 out of 281 in NSM group and 3 out of 227 in the SSM group).

In terms of capsular contracture, three studies described an incidence of 3.1% (9 out of 293 participants; Boneti 2011),10% (6 out of 60 participants; Burdge 2013) and 15% (22 out of 145 participants; Stanec 2014).

Hematoma

Two studies evaluated hematomas (Shi 2012; Stanec 2014). Shi 2012 reported that 2 out of 35 participants had a hematoma or infection in the NSM group while 5 out of 100 participants had a hematoma (two participants) or infection (three participants) in the MRM group. Stanec 2014 reported that 9 out of 252 participants had a hematoma in the NSM group while 3 out of 109 participants had a hematoma in the SSM group.

Seroma

Two studies evaluated seromas (Shi 2012; Stanec 2014). Shi 2012 described an incidence of 2.9% (one participant) in the NSM group versus 14% (14 participants) in the MRM group (P = 0.13). Stanec 2014 described seroma of the donor site and axilla as a frequent postoperative complication with 25.6% of participants (108/361) being treated with aspirative punction in the NSM and SSM groups.

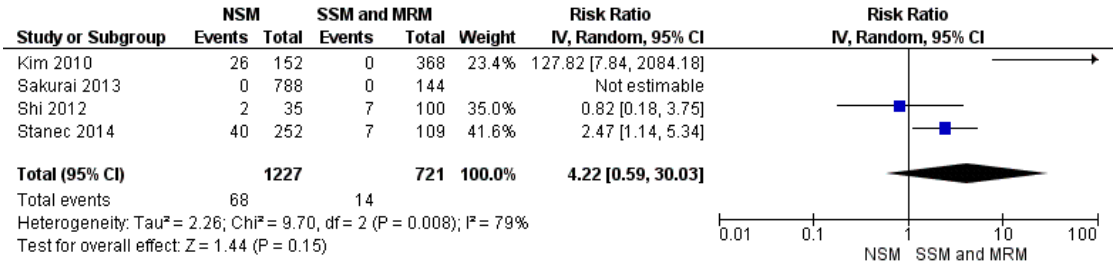
Rehospitalization/re-exploration

Boneti 2011 described that 0.7% (2 out of 281 breasts) in the NSM group versus 0.4% (1 out of 227 breasts) in the SSM group required further exploration for postoperative bleeding. Stanec 2014 described that 1.1% of participants (4 out of 361) needed further exploration for the drainage of breast abscesses.

Skin necrosis (nipple, areola or flap necrosis)

Four studies described skin necrosis (Kim 2010; Sakurai 2013; Shi 2012; Stanec 2014). The RR was 4.22 (95% CI 0.59 to 30.03, 4 studies, P = 0.15; 1948 participants; Analysis 3.2; Figure 6) with significant heterogeneity (I^2 = 79%; P = 0.008). We downgraded the quality of evidence from low to very low due to a wide confidence interval.

Figure 6. Forest plot of comparison: 3 Adverse events, outcome: 3.2 Skin necrosis.



Skin necrosis with revision surgery

Only two studies described this outcome (Boneti 2011; Stanec 2014). Boneti 2011 showed 0.9% (4 out of 404) of participants had nipple necrosis with revision surgery and Stanec 2014 described 3.6% (13 out of 361) of participants needing further exploration.

Infection

Two studies involving 496 participants evaluated infections following NSM versus other types of mastectomy (Shi 2012; Stanec 2014). Neither study made any adjustment for confounding. The RR was 0.95 (95% CI 0.44 to 2.09, P = 0.91, 2 studies; 496 participants; Analysis 3.3) with no significant heterogeneity (I^2 = 0%; P = 0.39).

Due to a lack of data, it was not possible to perform subgroup analysis or analyse thromboembolic events as proposed in the protocol.

Cosmetic results

Five studies performed an evaluation of the aesthetic outcome after NSM (Boneti 2011; Burdge 2013; Gerber 2009; Shi 2012; Stanec 2014). Boneti 2011 and Burdge 2013 asked the participants to rate their cosmetic result on a scale from 0 to 10 (with 10 being the most favourable outcome). In Boneti 2011, the NSM group gave a mean score of 9.2 versus 8.3 in the SSM group (P = 0.04). In Burdge 2013, the average rating was 8 by the participants and 9 by the doctors for both groups in total.

In three studies, cosmesis was assessed through personal opinion and the evaluation was either excellent, good, average or poor (Gerber 2009; Shi 2012; Stanec 2014).

Stanec 2014 described the aesthetic outcome by the type of primary reconstruction (that is, latissimus dorsal, implant and deep inferior epigastric perforators (DIEP)). The best results were with autologous reconstruction with almost 90% of participants having excellent or good evaluations compared to almost 70% of participants with implants. Unsatisfactory reconstruction was higher for participants who had implants (18.6%) compared to participants who had autologous reconstruction (7%).

Gerber 2009 described excellent and/or good results for almost 98% of the SSM group and 100% for the NSM group (P = 0.004). After 59 months of follow-up, satisfaction (excellent and/or good) decreased to 88% in the SSM group and 96% in the NSM group (P = 0.025).

Shi 2012 asked the participants if they were satisfied with the local aesthetic (yes or no). The participants in the NSM group who received breast reconstruction felt more satisfied with the resulting aesthetic appearance (34 out of 35 participants) than those in the MRM group (20 out of 100 participants, P < 0.001).

Quality of life

Only one study reported this outcome. Shi 2012 used a psycho-

logical questionnaire and the NSM group had higher levels of self-confidence (33 out of 35 versus 30 out of 100 participants, P < 0.001), social activity (35 out of 35 versus 60 out of 100 participants, P < 0.001) and sexual activity (31 out of 35 versus 82 out of 100 participants, P = 0.52) compared to the MRM group.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Nipple-sparing mastectomy for breast cancer treatment

Patient or population: women with breast cancer
Setting: breast cancer therapy centres
Intervention: nipple-sparing mastectomy
Comparison: skin-sparing mastectomy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with other types of mastectomies	Risk with nipple-sparing mastectomy				
Overall survival	Study population		HR 0.70 (0.28 to 1.72)	781 (2 observational studies)	⊕◯◯◯ VERY LOW [1]	
	928 per 1000	841 per 1000 (521 to 989)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **OR:** Odds ratio; **HR:** hazard ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]We downgraded the quality of evidence due to: (a) risk of bias of included studies: non-randomised studies with low quality, and imprecision: wide confidence intervals that crossed null effect and comprised both directions of effect

DISCUSSION

Summary of main results

In general the results were inconclusive because none of the included studies had used appropriate methods to deal with confounding. In particular, the modified radical mastectomy (MRM) and skin-sparing mastectomy (SSM) groups tended to have participants with more advanced disease than the nipple-sparing mastectomy (NSM) group, and the use of radiotherapy tended to be different in the different treatment groups. Currently, the indications for postmastectomy radiation have been extended and this will probably have an impact on the results in future studies.

Overall survival

The results of this review were inconclusive as to whether there was a difference in overall survival between NSM and other types of mastectomy (SSM and MRM) due to a lack of studies reporting survival outcomes in sufficient detail to extract hazard ratios, and the high risk of confounding.

Evidence from two studies involving 781 people contributed data to the overall survival outcome for NSM compared to SSM. The results were inconclusive because the confidence interval was wide. Only one of these studies had more than five years of follow-up (Kim 2010), the other had a mean follow-up of about 25 months (Poruk 2015).

Evidence from two studies involving 1202 people contributed data to the overall survival outcome for NSM compared to MRM. The confidence interval did not cross the non-inferiority bound, but we were unable to draw any conclusions because of the high risk of residual confounding.

Local recurrence

For local recurrence, we could extract hazard ratios for only two studies comparing NSM to MRM, involving 1303 participants. The confidence interval indicated a lower risk of local recurrence in the NSM group, but we were unable to draw any conclusions due to the high likelihood of residual confounding due to lack of adjustment for tumour stage and radiotherapy.

Adam 2014 matched the participants assigned to each group taking into account the tumour stage. However, Horiguchi 2001 seemed to have more initial tumours (Stages 0 and 1) in the NSM group (83 out of 123 participants; 67.5%) than in the MRM group (277 out of 910 participants; 30.4%) and this imbalance may have influenced the results.

Only 7.9% (103 out of 1303 participants) received radiotherapy: 7.2% (81 out of 1113 participants) in the MRM group and 11.6% (22 out of 190 participants) in the NSM group. No one received this treatment in Horiguchi 2001, probably because during that period the indication for radiotherapy treatment was more limited. Probably more patients would now receive post-mastectomy radiotherapy, which would have an impact on the local recurrence rate.

Adverse events

Again, we could not draw any firm conclusions because of the high risk of confounding. There seemed to be evidence that the global rate of complications was lower in the NSM group. The frequency of this outcome was 0.85% versus 18.4% for NSM and other types of mastectomy respectively. This was lower than in the published meta-analysis of Endara 2013, which evaluated 6615 women undergoing NSM for therapeutic or prophylactic purposes and observed an incidence of 22% for overall complications. There was no evidence that infection differed between treatment groups in this review. One possible reason for the lower frequency in this Cochrane review is due to the presence of retrospective cohort studies, where the reporting of medical data may be flawed.

Strengths of this systematic review

Strengths of this systematic review include the following.

- A sensitive search strategy was carried out for all electronic databases (so as to avoid missing relevant studies). In addition, a manual search was made of reference lists of relevant studies and we screened clinical trials registries
- We applied a rigorous method recommended by Cochrane (Higgins 2011b) when conducting the review.
- The methodological quality of observational studies included was evaluated and considered in the presentation of findings. We also evaluated the quality of evidence through an appropriate tool (GRADE).

Main limitations

The main limitations of this systematic review are a result of the limited strength of the evidence due to the methodological deficiencies of the existing studies.

- The evidence in this review came from observational studies (mostly retrospective and low methodological quality), subject to important biases which increased the uncertainty of the results and limited the quality of existing evidence.
- It was not possible to calculate the hazard ratio for the assessment of survival data for all studies because many studies did not report time-to-event analyses in sufficient detail.
- Inability to perform the subgroup analyses initially proposed in the published protocol. The proposed analyses included: presence or absence of adjuvant treatment, participant age, surgical technique performed, and tumour staging according to the TNM system.
- This was a systematic review that used aggregated data (in which the subject of analysis was the study), and not a meta-analysis of individual data (in which the subject of analysis is the person or the participant). Therefore, only data published or

provided subsequently by the authors of the studies were available.

Overall completeness and applicability of evidence

In this systematic review, the evidence was incomplete due to a lack of good-quality studies in this area which have used appropriate methods to adjust for confounding. Additional research is therefore likely to have an important impact on the estimated effect. Decisions regarding choice of surgical method should be made jointly by the surgeon and woman after extensive information on the risks and benefits is provided.

Quality of the evidence

See the 'Summary of findings' tables: Summary of findings for the main comparison; Summary of findings 2.

Potential biases in the review process

This systematic review has several strengths. We asked a specific clinical question and the search strategy was comprehensive. We included publications of all relevant studies irrespective of language. Finally, we rigorously applied the GRADE criteria for each of the relevant outcomes (Guyatt 2008)

There were several potential biases in the review process. We made efforts to limit the bias in several ways: two review authors assessed the eligibility for inclusion and independently assessed the risks of bias. Although the review authors' views varied, we decided to accept the final conclusions after extensive discussion and reaching a consensus. Carrying out reviews, however, may require a number of subjective judgements, and it is possible that a different review team may have reached different decisions regarding the assessments of eligibility and risks of bias. Feedback from readers will serve to improve the next review update.

Agreements and disagreements with other studies or reviews

We found a meta-analysis by de La Cruz 2015 addressing the same clinical question as our Cochrane review. The de La Cruz 2015 meta-analysis included eight studies and the authors found no difference between NSM and MRM/SSM: 3.4 % risk difference in overall survival (P = 0.073), 9.6 % risk difference in disease-free survival (P = 0.056), and a 0.4 % risk difference in local recurrence (P = 0.567). These results are quite similar to our results and it was not possible to conclude that NSM was not inferior to other surgeries, because of the limited methodological quality and risk of bias of the included studies.

The most important methodological differences between the meta-analysis by de La Cruz 2015 and our review are:

- de La Cruz 2015 limited their search to Pubmed, Scopus and Google Scholar, included only studies in English, and used outcome (survival) in the search strategy. We included additional searches in Embase and CENTRAL databases, we did not use a language limit and did not specify any outcomes in the search strategy. Limiting the search string by outcome enhances specificity but reduces sensitivity which is not recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

- de La Cruz 2015 used the risk difference to compare time-to-event outcomes between intervention groups. We performed these analyses using hazard ratios (which was more appropriate). Moreover, we split the analysis into two subgroups NSM versus SSM and NSM versus MRM because we considered SSM and MRM to be different control groups, which could influence the results.

- de La Cruz 2015 did not assess the methodological quality and risk of bias of the included studies nor the overall quality of the evidence for each outcome. We did both assessments in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* using the 'Risk of bias table' and GRADE approach, respectively (Higgins 2011b).

AUTHORS' CONCLUSIONS

Implications for practice

- The evidence was inconclusive regarding the difference in overall survival and local recurrence between the nipple-sparing mastectomy (NSM) group and other types of mastectomy (modified radical (MRM) and skin-sparing mastectomy (SSM)). Additional research is likely to have an important impact on the estimated effect.

- No firm recommendations can be made to health professionals or patients and decisions should be made jointly after extensive discussion about the risks and benefits before performing a NSM.

- Health Managers should not adopt this as a health policy for the time being, but it could be adopted in some special cases.

Implications for research

- This review showed the shortage of well-conducted studies to evaluate the efficacy and safety of NSM in people with invasive breast cancer and ductal carcinoma in situ.

- Well-designed cohort studies are still needed.

- For planning and development of these studies, some suggestions are:

  - Use the CONSORT Statement to guide study methods (Schulz 2010)

  - Describe and adjust for all potential confounders

  - Use standardised criteria defining endpoints, quality of life and follow-up

  - Longer follow-up is needed to allow observation of long-term outcomes.

  - Studies need to adjust appropriately for follow-up time in the analysis of outcomes by using survival analysis methods or person-years of follow-up as the denominator for the incidence rates for events of interest

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adam 2014

Methods	• Retrospective matched cohort study • Conducted at the Department of Breast Surgery Karolinska University Hospital, Stockholm, Sweden • The cases were identified by registry data from the Swedish Breast Cancer Register - 1:3 to patients operated by conventional mastectomy. Matching variables were age, tumour stage and year of surgery. • 270 participants • Intervention group: 67 NSM • Control group: 203 MRM randomly selected • Follow-up was performed during an outpatient clinic visit (medical record) • The median follow-up time was 36 months (4 to 162 months) for NSM and 35 months for MRM (range 0 to 160 months).
Participants	**Inclusion criteria** • Breast cancer confirmed by pathological methods • ALL NSMs performed during 2000 to 2012 were from Karolinska University Hospital for breast cancer treatment • The participants selected for the NSM procedure had a tumour of at least 2 cm, no skin involvement, no pathological nipple discharge and no signs • Intraoperative biopsies of mammary gland specimens resected from below the nipple-areola complex (NAC) confirmed that both the NAC and the skin were not cancerous to perform the NSM procedure. • The Intervention cases (NSM participants) were from Karolinska University Hospital and the control group were women with breast cancer operated at any hospital in the Stockholm and Gotland region by conventional mastectomy without immediate breast reconstruction

Interventions	• Intervention group:
	  ○ NSM with immediate breast reconstruction
	• Control group:
	  ○ MRM
	In addition to surgery, participants in both groups received adjuvant treatment as recommended by the National Comprehensive Cancer Network (NCCN) guidelines

Outcomes	• Primary outcomes
	  ○ Local recurrence - specified as histologically proven recurrent breast cancer in the ipsilateral skin, chest wall or the NAC.
	• Secondary endpoints were
	  ○ local recurrence-free survival, calculated from the date of surgery until the date of diagnosis for a local recurrence
	  ○ disease-free survival (DFS), calculated from the date of surgery to the first event of any local, regional or distant recurrence
	  ○ breast cancer-specific survival, calculated from the date of surgery to death due to breast cancer, or the date of medical record review

Adam 2014 (*Continued*)

	○ overall survival, calculated from the date of surgery to death from any cause, or to the date of medical record review in all other cases.
Notes	There were no NAC recurrences in the study group. The study author was contacted to provide the absolute number of people alive and local recurrence

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection Bias - Was the allocation sequence adequately generated?	High risk	Retrospective matched cohort
Selection Bias - Was the allocation adequately concealed?	High risk	Retrospective matched cohort
Selection Bias - Were baseline characteristics similar?	Unclear risk	Tumour stage and age at baseline were similar in both groups. Adjuvant chemotherapy and radiotherapy use were not reported
Selection Bias - Was there adequate adjustment for confounding?	High risk	Participants were matched for age, tumour stage and year of study. No adjustment was made for adjuvant radiotherapy, surgical techniques or chemotherapy
Performance/detection bias - Was knowledge of the allocated interventions adequately prevented during the study?	High risk	The lack of blinding may have influenced the results for some outcomes. Time-to-event outcomes are generally more objective and therefore less likely to be prone to bias. Surgical reports, however, could be influenced by knowledge of the procedure
Attrition bias - Were incomplete outcome data adequately addressed?	Unclear risk	It was not mentioned in the methods section
Reporting bias - Were reports of the study free from selective outcome reporting?	Low risk	There was no evidence that outcomes were selectively reported
Reporting Bias - Were reports of the study free from selective analysis reporting?	Low risk	There was no evidence of selective reporting of analysis

Boneti 2011

Methods	• Retrospective cohort • Conducted at the Division of Breast Surgical Oncology, Department of Surgery, Winthrop P. Rockefeller Cancer Institute (Boneti, Santiago, Diaz, Robertson, Westbrook, Henry-Tillman, Klimberg), Division of Plastic Surgery, Department of Surgery (Yuen), and Department of Pathology (Korourian), University of Arkansas for Medical Sciences, Little Rock, Arkansas • 293 participants • Intervention group: 141 NSM • Control group: 152 SSM • The median follow-up was 25 months for NSM group and 38 months for SSM group • 1998 to 2010
Participants	**Inclusion criteria** • Informed consent signed • Breast cancer confirmed by pathological methods • The NSM procedure was offered to participants. The participants chose one surgical approach over the other for aesthetic reasons. • Intraoperative biopsies of mammary gland specimens resected from below the NAC confirmed that both the NAC and the skin were not cancerous to perform the NSM procedure **Exclusion criteria** • Exclusion criteria included locally advanced disease, inflammatory breast cancer, collagen vascular disease, smoking within the previous 6 months • Radiation was a relative exclusion (depended on skin radiation damage)

Interventions	• Intervention group:
	  ○ NSM
	• Control group:
	  ○ SSM
	• Both groups:
	  ○ Chemotherapy was recommended for participants when the estimated benefit of chemotherapy outweighed the risks
	  ○ participants with original tumours larger than 5 cm, 4 or more positive lymph nodes, or chest wall invasion diagnosed on the final pathology report were given 5,000 units of external beam conformal radiation to the total skin after all surgery and systemic therapy were completed
	  ○ Breast reconstruction was performed either immediately via implant or with expanders followed by implants.

Outcomes	• Local recurrence • Adverse events • Cosmetic results
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Boneti 2011 (*Continued*)

Selection Bias - Was the allocation sequence adequately generated?	High risk	Retrospective cohort study
Selection Bias - Was the allocation adequately concealed?	High risk	Retrospective cohort study
Selection Bias - Were baseline characteristics similar?	Unclear risk	Mean tumour size and mean baseline age was similar between intervention groups. Adjuvant chemotherapy and radiotherapy use were not reported
Selection Bias - Was there adequate adjustment for confounding?	High risk	No adjustment was made for potential confounders
Performance/detection bias - Was knowledge of the allocated interventions adequately prevented during the study?	High risk	The lack of blinding may have influenced the results for some outcomes. Time-to-event outcomes are generally more objective and therefore less likely to be prone to bias. Surgical reports, however, could be influenced by knowledge of the procedure
Attrition bias - Were incomplete outcome data adequately addressed?	Low risk	Missing outcome measures were unlikely to bias the results. 15 participants were lost to follow-up within the first 3 months after the mastectomy operation
Reporting bias - Were reports of the study free from selective outcome reporting?	Low risk	There was no evidence that outcomes were selectively reported
Reporting Bias - Were reports of the study free from selective analysis reporting?	Low risk	There was no evidence that analyses were selectively reported

Burdge 2013

Methods	• Retrospective cohort • Conducted at the Division of Breast Surgical Oncology, Winthrop P. Rockefeller Cancer Institute, University of Arkansas for Medical Sciences, Arkansas Breast Cancer, New York, NY • 60 participants • Intervention group: 39 NSM • Control Group: 21 SSM • Follow-up: SSM group was 38.2 months ± 26.3 months; NSM was 25.3months ± 18.8 months • 2001 to 2012
Participants	**Inclusion criteria** ○ Subpopulation of 60 participants from 527 who underwent SSM or NSM

	○ Prior radiotherapy was not an exclusion criteria: 5 participants had previously elected to undergo breast-conserving therapy and subsequently elected NSM or SSM after a new diagnosis of DCIS **Exclusion criteria** ○ Locally advanced disease with involvement of the skin ○ Inflammatory breast cancer ○ Collagen-vascular disease ○ Known to smoke within the previous 6 months
Interventions	• Intervention group: ○ NSM • Control group: ○ SSM • Both groups: ○ 60 participants were identified with either locally advanced disease that underwent neoadjuvant chemotherapy followed by SSM or NSM with immediate reconstruction and prior or subsequent radiotherapy
Outcomes	• Local recurrence • Cosmetic results by personal opinion
Notes	Only participants with advanced disease

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection Bias - Was the allocation sequence adequately generated?	High risk	Retrospective cohort study
Selection Bias - Was the allocation adequately concealed?	High risk	Retrospective cohort study
Selection Bias - Were baseline characteristics similar?	High risk	Baseline characteristics of the intervention and control groups were different There were significant differences in age and stage between groups with younger participants in the NSM group and more advanced disease in the SSM group
Selection Bias - Was there adequate adjustment for confounding?	High risk	There was no adjustment for confounding
Performance/detection bias - Was knowledge of the allocated interventions adequately prevented during the study?	High risk	The lack of blinding may have influenced the results for some outcomes. Time-to-event outcomes are generally more objective and therefore less likely to be prone to bias. Surgical reports, however, could

Burdge 2013 (*Continued*)

		be influenced by knowledge of the procedure. The lack of blinding may have influenced the results for some outcomes. Cosmesis measurements were based on self-report and therefore could be prone to bias
Attrition bias - Were incomplete outcome data adequately addressed?	Unclear risk	It was not mentioned in the methods section
Reporting bias - Were reports of the study free from selective outcome reporting?	Low risk	They were defined in the methods section of the paper
Reporting Bias - Were reports of the study free from selective analysis reporting?	Low risk	The analyses were reported as pre-defined in the methods section of the paper

Gerber 2009

Methods	• Prospective cohort study
	• Conducted at the Department of Obstetrics and Gynecology, University of Rostock and Institute of Medical Informatics and Biometry, University of Rostock, Rostock, Germany
	• 246 participants selected with an indication for MRM, no skin involvement, and tumour margins of greater than 2 cm from the nipple.
	• Intervention group: 60 NSM
	• Control group:
	  ○ 48 SSM
	  ○ 130 MRM
	• Follow-up 101 months (range 26 to 156)
	• 8 participants were lost for unknown reasons during follow-up.
	• 1994 to 2000

Participants	**Inclusion criteria** • Informed consent signed • Breast cancer confirmed by pathological methods • Selected participants with an indication for MRM • The SSM procedure was offered to participants. The participants chose one surgical approach over the other for aesthetic reasons. • Intraoperative biopsies of mammary gland specimens resected from below the nipple-areola complex (NAC) confirmed that both the NAC and the skin were not cancerous to perform the NSM procedure. If it was positive the SSM was performed. **Exclusion criteria** • Skin involvement • Tumour margins of greater than 2 cm from the nipple

Interventions	• Intervention group:
	  ○ NSM
	• Control group:
	  ○ SSM

	○ MRM In addition to surgery, participants in all groups received adjuvant treatment according to AJCC staging
Outcomes	• Local-regional recurrence (LR) was defined as histologically proven recurrent tumour occurring in either the ipsilateral breast skin, the NAC, or in the chest wall after MRM and tumour spread in the internal mammary, supraclavicular, infraclavicular, ipsilateral axillary nodes, or in the non breast skin of the ipsilateral chest wall. • Distant Metastases (DM) - all other sites of tumour recurrence. • Breast cancer-specific deaths were included for the analyses of the overall survival (OS) end point • Cosmetic results by personal opinion
Notes	Insufficient reporting of data to estimate the hazard ratio for overall survival analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection Bias - Was the allocation sequence adequately generated?	High risk	Non-random method was used
Selection Bias - Was the allocation adequately concealed?	High risk	No method of allocation was used. It was chosen by participants
Selection Bias - Were baseline characteristics similar?	High risk	Baseline age was different between intervention groups (P = 0.001). Differences in tumour stage were apparent (e.g. % tumour stage 1 was 18.3 for NSM group, 22.9 for SSM group and 26.9 for MRM group), although not statistically significant (P = 0.47). The MRM group had fewer participants with adjuvant chemotherapy (83% MRM vs 90% NSM and 88% SSM) and radiotherapy (24% MRM vs 29% NSM and 27% SSM)
Selection Bias - Was there adequate adjustment for confounding?	High risk	There was no adjustment for confounding
Performance/detection bias - Was knowledge of the allocated interventions adequately prevented during the study?	High risk	The lack of blinding may have influenced the results for some outcomes. Time-to-event outcomes are generally more objective and therefore less likely to be prone to bias. Surgical reports, however, could be influenced by knowledge of the procedure

Gerber 2009 (*Continued*)

Attrition bias - Were incomplete outcome data adequately addressed?	Low risk	Missing outcome measures were unlikely to bias the results. 8 participants were lost to follow-up for unknown reasons
Reporting bias - Were reports of the study free from selective outcome reporting?	Low risk	The outcomes were not selectively reported
Reporting Bias - Were reports of the study free from selective analysis reporting?	Low risk	There was no evidence that analyses were selectively reported - analyses were pre-defined in the methods section

Horiguchi 2001

Methods	• Retrospective cohort • Conducted at the Second Department of Surgery and Department of Emergency and Critical Care Medicine, Gunma University Faculty of Medicine, Japan • 1041 participants • Intervention group: 131 NSM • Control Group: 910 MRM • Follow-up: NSM group was 66 months and MRM was 88 months • 1983-1999
Participants	**Inclusion criteria** • Breast cancer confirmed by pathological methods • Intraoperative biopsies of mammary gland specimens resected from below the nipple-areola complex (NAC) confirmed that both the NAC and the skin were not cancerous to perform the NSM procedure. If it was positive the SSM was performed. **Exclusion criteria** • participants who underwent a non curative surgery
Interventions	• Intervention group: ○ NSM • Control group: ○ MRM • Both groups: ○ In addition to surgery, participants in both groups received adjuvant treatment as recommended by Breast cancer Japanese Society ○ Chemotherapy regimens ◇ Before 1990 consisting of 5-fluorouracil and cyclophosphamide and mitomycin ◇ After 1990 consisting of 5-fluorouracil for lymph node negative and 5-fluorouracil and cyclophosphamide followed by UFT (mixed compound of tegafur and URACIL) ○ No participants received radiotherapy ○ Hormonal therapy was indicated for oestrogen receptor-positive and/or progesterone receptor-positive participants

Horiguchi 2001 (*Continued*)

Outcomes	• Overall survival • Local recurrence
Notes	• The groups were different in age, stage, nodal status. Methods to adjust for confounders were performed • Insufficient reporting of data to estimate the hazard ratio for overall survival analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection Bias - Was the allocation sequence adequately generated?	High risk	Retrospective cohort study
Selection Bias - Was the allocation adequately concealed?	High risk	Retrospective cohort study
Selection Bias - Were baseline characteristics similar?	High risk	Baseline characteristics of the intervention and control groups were different There were significant differences in age and stage between groups with younger participants in the NSM group and more advanced disease in the MRM group
Selection Bias - Was there adequate adjustment for confounding?	High risk	The HR for local recurrence was adjusted for age, lymph node status and oestrogen receptor status using a multivariable Cox proportional hazards model. Participants did not have radiotherapy. Tumour stage, surgical techniques and chemotherapy were not adjusted for
Performance/detection bias - Was knowledge of the allocated interventions adequately prevented during the study?	High risk	The lack of blinding may have influenced the results for some outcomes. Time-to-event outcomes are generally more objective and therefore less likely to be prone to bias. Surgical reports, however, could be influenced by knowledge of the procedure
Attrition bias - Were incomplete outcome data adequately addressed?	Unclear risk	It was not mentioned in the methods section
Reporting bias - Were reports of the study free from selective outcome reporting?	Low risk	There was no evidence that outcomes were selectively reported

Horiguchi 2001 (*Continued*)

Reporting Bias - Were reports of the study free from selective analysis reporting?	Low risk	There was no evidence that analyses were selectively reported

Kim 2010

Methods	• Retrospective cohort study • Conducted at the Departments of Surgery and Plastic Surgery, College of Medicine, Asan Medical Center, University of Ulsan, Seoul, Korea • 2420 participants • All participants had breast cancer (Stage 0 - 3a) • Intervention group: 152 NSM • Control group: ○ 368 SSM ○ 1990 MRM • Follow-up - NSM group was 60 months and SSM was 67 months. The follow-up of MRM was not described • 2001 to 2006
Participants	**Inclusion criteria** • The indications for SSM or NSM were any stage, any tumour size, and any tumour areola distance with indications for mastectomy. • Participants with a clinically normal nipple and no skin involvement were offered the option of NSM **Exclusion criteria** • Not mentioned
Interventions	• Intervention group: ○ NSM - The procedure involved 2 types of skin incision ◇ A periareola skin incision and a lateral extension ◇ The other was a lateral incision without a periareola skin incision ◇ The NAC dissection was done by monopolar cautery using a low level of cutting current. A thin layer of glandular tissue was taken from under the areola for frozen sectioning ◇ The NAC was preserved when palpation, shape, and colour of the nipple were normal and when NAC ducts were confirmed as tumour-free in frozen biopsies. • Control groups: ○ SSM ○ MRM - The procedure involved an areola incision with lateral extension • Both groups: ○ All reconstructive procedures were performed by a single plastic surgeon using a TRAM flap reconstruction. ○ Adjuvant systemic treatment was performed according to the contemporary recommendations of the St. Gallen consensus meeting and NCCN guidelines irrespective of the surgical method.
Outcomes	• Overall survival • Local recurrence

Kim 2010 (*Continued*)

	• Distant recurrence	
Notes	Specific methods were used to adjust for potential confounders	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Selection Bias - Was the allocation sequence adequately generated?	High risk	Retrospective cohort study
Selection Bias - Was the allocation adequately concealed?	High risk	Retrospective cohort study
Selection Bias - Were baseline characteristics similar?	High risk	Baseline characteristics of the intervention and control groups were different There were apparent differences in tumour stage between intervention and control groups, e.g. % tumour stage 1 was 46.1 for NSM, 40.8 for SSM and 26.7 for MRM. Mean baseline age was within 2 years difference between NSM and SSM groups (41.5 years vs 42.8 years respectively), but was not reported in the MRM group. Adjuvant chemotherapy and radiotherapy use were not reported
Selection Bias - Was there adequate adjustment for confounding?	High risk	The HR for overall survival was adjusted for age, tumour stage and oestrogen receptor status using a multivariable Cox proportional hazards model. Radiotherapy, surgical techniques and chemotherapy were not adjusted for
Performance/detection bias - Was knowledge of the allocated interventions adequately prevented during the study?	High risk	The lack of blinding may have influenced the results for some outcomes. Time-to-event outcomes are generally more objective and therefore less likely to be prone to bias. Surgical reports, however, could be influenced by knowledge of the procedure
Attrition bias - Were incomplete outcome data adequately addressed?	Unclear risk	It was not specified in the methods section
Reporting bias - Were reports of the study free from selective outcome reporting?	Low risk	There was no evidence that outcomes were selectively reported

Kim 2010 (*Continued*)

Reporting Bias - Were reports of the study free from selective analysis reporting?	Low risk	There was no evidence that analyses were selectively reported (e.g. analyses were defined in the methods section of the paper)

Oura 1994

Methods	• Retrospective cohort study
	• 493 participants
	• Intervention group: 299 NSM
	• Control group: 194 MRM
	• All participants had breast cancer (Stage I-II)
	• Follow-up
	  ○ Stage 1 - 49 months for NSM and 85 months for MRM
	  ○ Stage 2 - 38 months for NSM and 73 months for MRM
	• 1993

Participants	**Inclusion criteria** • Stage I and II **Exclusion criteria** • Not mentioned

Interventions	• Intervention group:
	  ○ NSM
	• Control group:
	  ○ MRM
	• Both groups:
	  ○ In both groups, immunochemical endocrine therapy was enforced as an adjuvant therapy depending on the degree of lymph node metastasis and progress.
	  ○ participants in all groups received adjuvant treatment according to stage

Outcomes	• Overall survival • Local recurrence
Notes	• No radiotherapy • Data extraction was completed separately by two authors (Dr Maki Kawasaki, and Dr Rintaro Mori) from The Japanese Cochrane Centre • Insufficient reporting of data to estimate the hazard ratio for overall survival analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Selection Bias - Was the allocation sequence adequately generated?	High risk	This was a retrospective study using data from case notes
Selection Bias - Was the allocation adequately concealed?	High risk	This was a retrospective study using data from case notes

Oura 1994 (*Continued*)

Selection Bias - Were baseline characteristics similar?	High risk	There were differences in baseline characteristics between groups. Mean ages for those with stage 1 and stage 2 tumours respectively were 49 and 48 in the NSM group and 56 and 54 in the MRM group. 81.6% had stage 1 tumours in the NSM group vs 63.9% in the MRM group. Adjuvant chemotherapy was not reported. No participants underwent radiotherapy
Selection Bias - Was there adequate adjustment for confounding?	High risk	There was no adjustment for confounders
Performance/detection bias - Was knowledge of the allocated interventions adequately prevented during the study?	High risk	The lack of blinding may have influenced the results for some outcomes. Time-to-event outcomes are generally more objective and therefore less likely to be prone to bias. Surgical reports, however, could be influenced by knowledge of the procedure
Attrition bias - Were incomplete outcome data adequately addressed?	Unclear risk	It was not specified in the methods section
Reporting bias - Were reports of the study free from selective outcome reporting?	Unclear risk	There was no protocol and the definitions of outcomes were not provided in the methods section
Reporting Bias - Were reports of the study free from selective analysis reporting?	Unclear risk	The analyses of outcomes were not prespecified in the methods section of the study report

Poruk 2015

Methods	• Retrospective cohort study • Conducted at the Huntsman Cancer Institute at the University of Utah, USA • 261 participants • All participants underwent mastectomy for either the treatment or prophylaxis of breast cancer • Intervention groupL 130 NSM • Control Group: 131 SSM • Follow-up: the NSM group had 25.8 months and SSM had 29 months of follow-up • 2005 to 2011
Participants	**Inclusion criteria** • Participants who underwent a NSM or SSM between April 2005 and April 2011 • Did not mention the indication for NSM **Exclusion criteria**

Poruk 2015 (*Continued*)

	• Was not mentioned
Interventions	• Intervention group: ○ NSM ○ 130 participants ○ 25 for prophylactic reasons • Control group: ○ SSM was defined as any mastectomy with a skin island (as measured by the pathologist) of less than 10 cm ○ 131 participants ○ 11 for prophylactic reason • Both groups: ○ In addition to surgery, participants in all groups received adjuvant treatment according to AJCC staging
Outcomes	• Local recurrence • Overall survival • Distance metastases
Notes	The groups were different in age and stage. Methods to adjust for these confounders were performed

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection Bias - Was the allocation sequence adequately generated?	High risk	Retrospective cohort study
Selection Bias - Was the allocation adequately concealed?	High risk	Retrospective cohort study
Selection Bias - Were baseline characteristics similar?	High risk	Baseline characteristics of the intervention and control groups were different There were significant differences in staging and age between groups with more advanced disease in the SSM group, and NSM group were younger. There were differences in adjuvant chemotherapy and use of radiotherapy between the intervention and control groups
Selection Bias - Was there adequate adjustment for confounding?	High risk	The study controlled for age, stage, and surgery laterality. Chemotherapy and radiotherapy were not adjusted for
Performance/detection bias - Was knowledge of the allocated interventions adequately prevented during the study?	High risk	The lack of blinding may have influenced the results for some outcomes. Time-to-event outcomes are generally more objec-

Poruk 2015 (*Continued*)

		tive and therefore less likely to be prone to bias. Surgical reports, however, could be influenced by knowledge of the procedure
Attrition bias - Were incomplete outcome data adequately addressed?	Unclear risk	It was not mentioned in the methods section
Reporting bias - Were reports of the study free from selective outcome reporting?	Low risk	The outcomes were free from selective reporting - all relevant outcomes in the methods section were reported in the results section
Reporting Bias - Were reports of the study free from selective analysis reporting?	Low risk	The reported analyses were defined in the methods section of the paper

Sakurai 2013

Methods	• Retrospective cohort study • Conducted at the Kihoku Hospital, Wakayama Medical University, Wakayama, Japan • 932 participants • Intervention group: 788 NSM • Control group: 144 MRM • The median follow-up was 78 months • 1985-2004
Participants	**Inclusion criteria** • Breast cancer confirmed by pathological methods • The NSM procedure was offered to participants. The participants chose one surgical approach over the other for aesthetic reasons. • Intraoperative biopsies of mammary gland specimens resected from below the nipple-areola complex (NAC) confirmed that both the NAC and the skin were not cancerous to perform the NSM procedure. • Participants were reached by phone to sign a verbal informed consent. Written consent was not obtained. **Exclusion criteria** • Not mentioned

Interventions	• Intervention group:
	  ○ NSM
	• Control group:
	  ○ MRM
	• Both groups:
	  ○ Did not provide information about adjuvant chemotherapy and hormone therapy

Outcomes	• Overall survival • Disease-free survival • Local recurrence

Sakurai 2013 (*Continued*)

Notes	None of participants in the NSM cohort received radiotherapy	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Selection Bias - Was the allocation sequence adequately generated?	High risk	Non-random method was used
Selection Bias - Was the allocation adequately concealed?	High risk	Non-randomised study
Selection Bias - Were baseline characteristics similar?	High risk	Baseline characteristics of the intervention and control groups were different between intervention and control groups. E.g. % tumour stage 2 was 46.3 in the NSM group and 24.3% in the MRM group. Mean age was 51 in the NSM group vs 58 in the MRM group. Adjuvant chemotherapy and radiotherapy use were not reported
Selection Bias - Was there adequate adjustment for confounding?	High risk	There was no adjustment for potential confounders
Performance/detection bias - Was knowledge of the allocated interventions adequately prevented during the study?	High risk	The lack of blinding may have influenced the results for some outcomes. Time-to-event outcomes are generally more objective and therefore less likely to be prone to bias. Surgical reports, however, could be influenced by knowledge of the procedure
Attrition bias - Were incomplete outcome data adequately addressed?	Unclear risk	Not specified in the paper
Reporting bias - Were reports of the study free from selective outcome reporting?	Low risk	There was no evidence that outcomes were selectively reported
Reporting Bias - Were reports of the study free from selective analysis reporting?	Low risk	For each outcome, there was no evidence that analyses were selectively reported (analyses were defined in the methods section of paper)

Shi 2012

Methods	• Retrospective cohort study • Conducted at the Department of Breast Surgery, The first Hospital, Jilin University, Japan • 135 participants • Intervention group: 35 NSM • Control group: 100 MRM randomly selected • 2000 to 2008 • Follow-up was performed over the telephone or during an outpatient clinic visit. • All participants were followed up over the course of 10 to 104 months. • The median follow-up time was 68 months. • In total, 23 participants were followed for more than 54 months.
Participants	**Inclusion criteria** • Informed consent signed • Breast cancer confirmed by pathological methods • The NSM procedure was offered to participants. The participants chose one surgical approach over the other for aesthetic reasons. • Intraoperative biopsies of mammary gland specimens resected from below the nipple-areola complex (NAC) confirmed that both the NAC and the skin were not cancerous to perform the NSM procedure. **Exclusion criteria** • Cases with evidence of distant metastasis were excluded from the study.
Interventions	• Intervention group: ◦ NSM ◦ Three types of incision were used: an S-shaped incision ending at the inferior border of the breast parallel to the areola a fusiform incision with a radial incision to the areola extending in the direction of the axilla on the lateral breast an arc-shaped incision parallel to the axillary fold. • Control group: ◦ MRM - the breast skin was then moved upward to the inferior clavicle margin and downward to the superior border of rectus abdominis, internal to the parasternal line and external to the leading edge of the latissimus dorsi muscle. The fascia was peeled from the surface of the pectoralis major muscle, and the prosthesis was implanted between the pectoralis major and pectoralis lesser. Axillary fat and lymph nodes were removed • Both groups: In addition to surgery, participants in both groups received adjuvant treatment as recommended by the National Comprehensive Cancer Network (NCCN) guidelines, including: ◦ chemotherapy regimens consisting of FAC (5-fluorouracil + adriamycin + cyclophosphamide), TAC (taxol + adriamycin + cyclophosphamide), or CMF (cyclophosphamide + methotrexate + 5-fluorouracil) ◦ radiotherapy with a total dose of 50 Gy in 25 fractions was optimal for all participants in the study group. In the control group, participants with tumours ≥ 3 cm in diameter and metastatic axillary lymph nodes were treated with radiotherapy ◦ hormonal therapy was indicated for oestrogen receptor-positive and/or

Shi 2012 (*Continued*)

	progesterone receptor-positive participants
Outcomes	• Overall survival • Local recurrence • Distant recurrence • Adverse events • Cosmetic results • Quality of life
Notes	• All participants in the intervention group (NSM) received radiotherapy • Insufficient reporting of data to estimate the hazard ratio for overall survival analyses

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Selection Bias - Was the allocation sequence adequately generated?	High risk	A retrospective cohort study
Selection Bias - Was the allocation adequately concealed?	High risk	A retrospective cohort study
Selection Bias - Were baseline characteristics similar?	High risk	Baseline characteristics of the intervention and control groups were different There were significant differences in staging and age between groups with more advanced disease and younger participants in the SSM group when compared to NSM. Adjuvant chemotherapy was not reported. All participants underwent radiotherapy
Selection Bias - Was there adequate adjustment for confounding?	High risk	There was no adjustment for confounding
Performance/detection bias - Was knowledge of the allocated interventions adequately prevented during the study?	High risk	The lack of blinding may have influenced the results for some outcomes. Time-to-event outcomes are generally more objective and therefore less likely to be prone to bias. Surgical reports, however, could be influenced by knowledge of the procedure. Quality of life and cosmesis measurements were based on self-report and therefore could be prone to bias
Attrition bias - Were incomplete outcome data adequately addressed?	Unclear risk	It was not mentioned in the methods section

Shi 2012 (*Continued*)

Reporting bias - Were reports of the study free from selective outcome reporting?	Low risk	There was no evidence that outcomes were selectively reported
Reporting Bias - Were reports of the study free from selective analysis reporting?	Low risk	There was no evidence that there was selective reporting of analyses

Stanec 2014

Methods	• Retrospective cohort study • Conducted at the Department of Plastic, Reconstructive and Aesthetic Surgery, University Hospital Dubrava, Zagreb, Croatia • 361 participants • All participants underwent mastectomy for breast cancer treatment and prophylactic reasons (47 participants) • Intervention group: 252 NSM • Control group: 109 SSM • Follow-up: mean 63 months • 1997 to 2012
Participants	**Inclusion criteria** • Breast cancer confirmed by pathological methods • The NSM procedure was offered to participants. The participants chose one surgical approach over the other for aesthetic reasons. • Intraoperative biopsies of mammary gland specimens resected from below the nipple-areola complex (NAC) confirmed that both the NAC and the skin were not cancerous to perform the NSM procedure **Exclusion criteria** • Not mentioned

Interventions	• Intervention group:
	  ○ NSM
	  ○ Autologous reconstruction with latissimus dorsi flap (LD)
	• Control group:
	  ○ SSM
	• Both groups:
	  ○ Did not mention adjuvant therapy

Outcomes	• Overall survival • Local recurrence • Adverse events • Cosmetic results
Notes	• Cosmetic results were evaluated by personal opinion • We contacted the study author to provide the absolute number of complications • Insufficient reporting of data to estimate the hazard ratio for overall survival analyses
Risk of bias	

Stanec 2014 (*Continued*)

Bias	Authors' judgement	Support for judgement
Selection Bias - Was the allocation sequence adequately generated?	High risk	Retrospective cohort study
Selection Bias - Was the allocation adequately concealed?	High risk	Retrospective cohort study
Selection Bias - Were baseline characteristics similar?	High risk	Baseline characteristics of the intervention and control groups were different. E.g. tumour stage 2 was 34.2% in the NSM group and 21.9% in the SSM group. Mean age was 50.9 in the NSM group vs 53.2 in the SSM group. Adjuvant chemotherapy and radiotherapy use were not reported
Selection Bias - Was there adequate adjustment for confounding?	High risk	No adjustment was made for confounders
Performance/detection bias - Was knowledge of the allocated interventions adequately prevented during the study?	High risk	The lack of blinding may have influenced the results for some outcomes. Time-to-event outcomes are generally more objective and therefore less likely to be prone to bias. Surgical reports, however, could be influenced by knowledge of the procedure. Cosmesis measurements were based on self-report and therefore could be prone to bias
Attrition bias - Were incomplete outcome data adequately addressed?	Unclear risk	Outcomes were unavailable for around 12% of participants This could be high enough to influence results
Reporting bias - Were reports of the study free from selective outcome reporting?	Low risk	There was no evidence that outcomes were selectively reported
Reporting Bias - Were reports of the study free from selective analysis reporting?	Low risk	There was no evidence that analyses were selectively reported

AJCC: American Joint Committee on Cancer
DCIS: ductal carcinoma in situ
DFS: disease-free survival
DM: distant metastases
LR: local recurrence
MRM: modified radical mastectomy
NAC: nipple areolar complex
NSM: nipple-sparing mastectomy
SSM: skin-sparing mastectomy

TM: total mastectomy

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Algaithy 2012	Case series
Alperovich 2014	Case series
Babiera 2010	Case series
Benediktsson 2008	Case series
Caruso 2006	Case series
Chattopadhyay 2014	Case series
Crowe 2008	Case series
de Alcantara Filho 2011	Case series
Eisenberg 2014	Case series
Fortunato 2013	Case series
Garcia-Etienne 2009	Case series
Garwood 2009	Case series
Jensen 2011	Case series
Leclère 2014	Case series
Lohsiriwat 2013	Case series
Maxwell 2011	Case series
Missana 2007	Case series
Munhoz 2013	Case series
Nava 2012	Case series
Ohno 2013	Case series
Paepke 2009	Case series
Peled 2014	Case series

(*Continued*)

Petit 2003	Case series
Petit 2006	Case series
Petit 2009b	Case series/duplicate database
Petit 2012	Case series/duplicate database
Rache Simmons 2004	Case series
Radovanovic 2010	Case series
Reefy 2010	Case series
Regolo 2008	Case series
Rusgby 2010	Case series
Sachinni 2006	Case series
Salgarello 2010	Case series
Schneider 2012	Case series
Sookhan 2008	Case series
Spear 2011	Case series
Stolier 2008	Case series
Tancredi 2013	Case series
Voltura 2008	Case series
Wagner 2012	Case series
Wijayanayagam 2008	Case series

Characteristics of studies awaiting assessment *[ordered by study ID]*

Seki 2015

Methods	• Retrospective cohort study • Keio University Hospital, Tokyo, Japan • 678 participants. Propensity score was used to reduce the selection bias and matched only 66 participants in each group • All participants underwent mastectomy for breast cancer treatment • Intervention group: 121 NSM • Control group: 557 total mastectomy (TM) • Follow-up: mean 28 months for NSM and 43 for TM • 2003 to 2013
Participants	**Inclusion criteria** • Stage 0-3 breast cancer • NSM eligible criteria: patient without indication for breast conservative surgery by magnetic resonance imaging, ultrasonography and mammography • Intraoperative biopsies of mammary gland specimens resected from below the nipple-areola complex (NAC) confirmed that both the NAC and the skin were not cancerous to perform the NSM procedure. **Exclusion criteria** • Suspicion of involvement neoplastic of NAC

Interventions	• Intervention group:
	  ○ NSM: 66
	• Control group:
	  ○ MRM: 66
	• Both groups:
	  ○ Both groups:In addition to surgery, participants in all groups received adjuvant treatment according to AJCC staging

Outcomes	• Overall survival • Local recurrence • Adverse events
Notes	

Shimo 2015

Methods	• Retrospective cohort study • Department of Breast and Endocrine Surgery, St. Marianna University School of Medicine, Kanagawa, Japan • 1218 participants • All participants underwent mastectomy for breast cancer treatment and prophylactic reasons (47 participants) • Intervention group: 413 NSM • Control group: 878 TM • Follow-up: mean 46.8 months for NSM and 51.3 for TM • 2000 to 2013
Participants	**Inclusion criteria** • Stage 0-3 breast cancer • NSM eligible criteria: patient without indication for breast conservative surgery and no clinical or image (MRI) suspected of involvement neoplastic of NAC and patient preference. • Intraoperative biopsies of mammary gland specimens resected from below the nipple-areola complex (NAC)

Shimo 2015 (*Continued*)

	confirmed that both the NAC and the skin were not cancerous to perform the NSM procedure **Exclusion criteria** • Suspicion of involvement neoplastic of NAC

Interventions	• Intervention group:
	  ○ NSM: 413
	• Control group:
	  ○ MRM: 878
	• Both groups:
	  ○ Both groups:In addition to surgery, participants in all groups received adjuvant treatment according to AJCC staging

Outcomes	• Overall survival • Local recurrence • Adverse events
Notes	

DATA AND ANALYSES

Comparison 1. Overall survival

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NSM vs SSM - overall survival	2	781	Hazard Ratio (Fixed, 95% CI)	0.70 [0.28, 1.72]
2 NSM vs MRM - overall survival	2	1202	Hazard Ratio (Fixed, 95% CI)	0.72 [0.46, 1.13]

Comparison 2. Local recurrence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NSM vs MRM - local recurrence	2	1303	Hazard Ratio (Fixed, 95% CI)	0.28 [0.12, 0.68]

Comparison 3. Adverse events

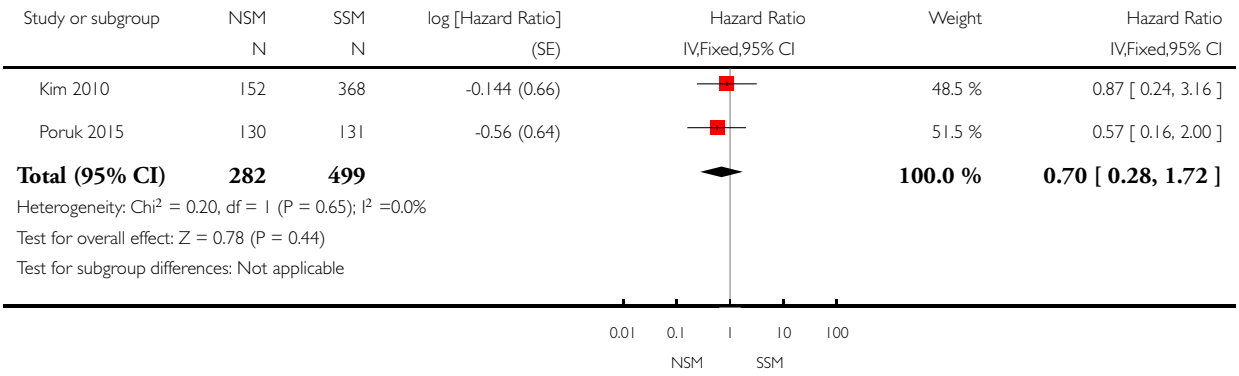
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall complication	2	1067	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 0.82]
2 Skin necrosis	4	1948	Risk Ratio (IV, Random, 95% CI)	4.22 [0.59, 30.03]
3 Infection	2	496	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.44, 2.09]

Analysis 1.1. Comparison 1 Overall survival, Outcome 1 NSM vs SSM - overall survival.

Review: Nipple- and areola-sparing mastectomy for the treatment of breast cancer

Comparison: 1 Overall survival

Outcome: 1 NSM vs SSM - overall survival

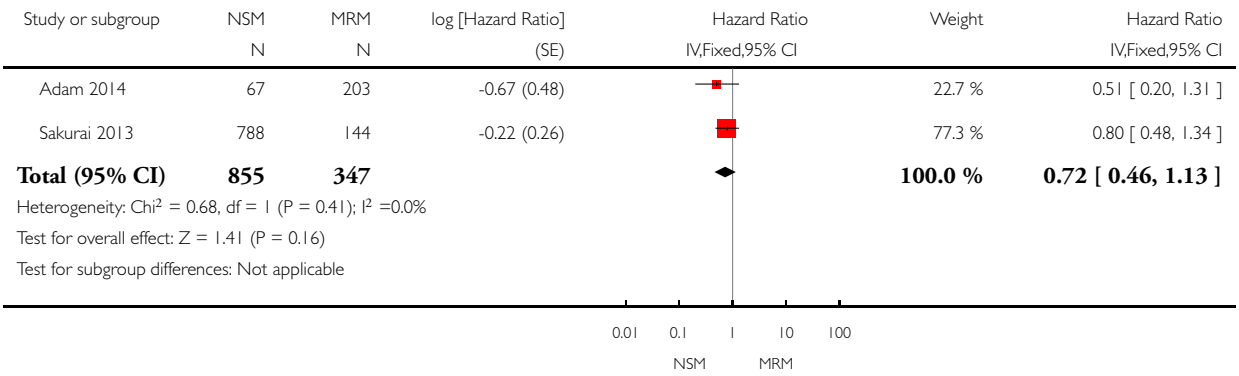


Analysis 1.2. Comparison 1 Overall survival, Outcome 2 NSM vs MRM - overall survival.

Review: Nipple- and areola-sparing mastectomy for the treatment of breast cancer

Comparison: 1 Overall survival

Outcome: 2 NSM vs MRM - overall survival

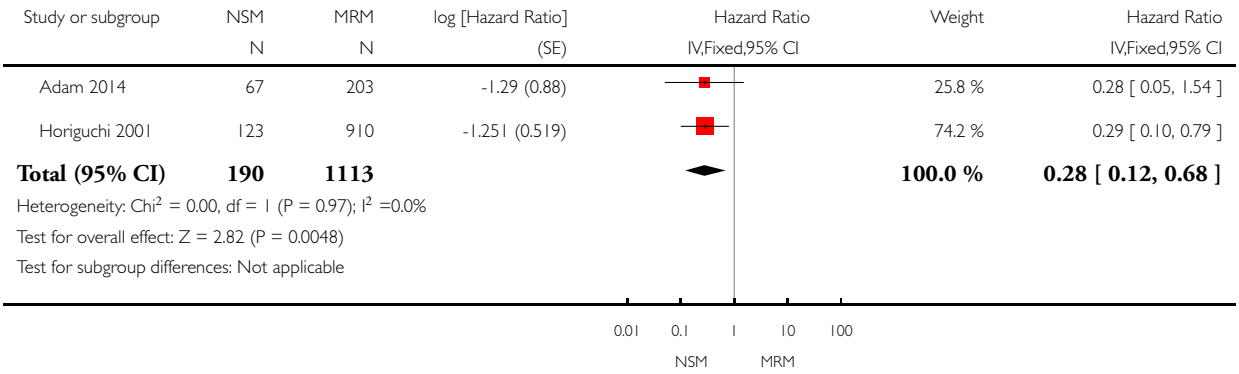


Analysis 2.1. Comparison 2 Local recurrence, Outcome 1 NSM vs MRM - local recurrence.

Review: Nipple- and areola-sparing mastectomy for the treatment of breast cancer

Comparison: 2 Local recurrence

Outcome: 1 NSM vs MRM - local recurrence

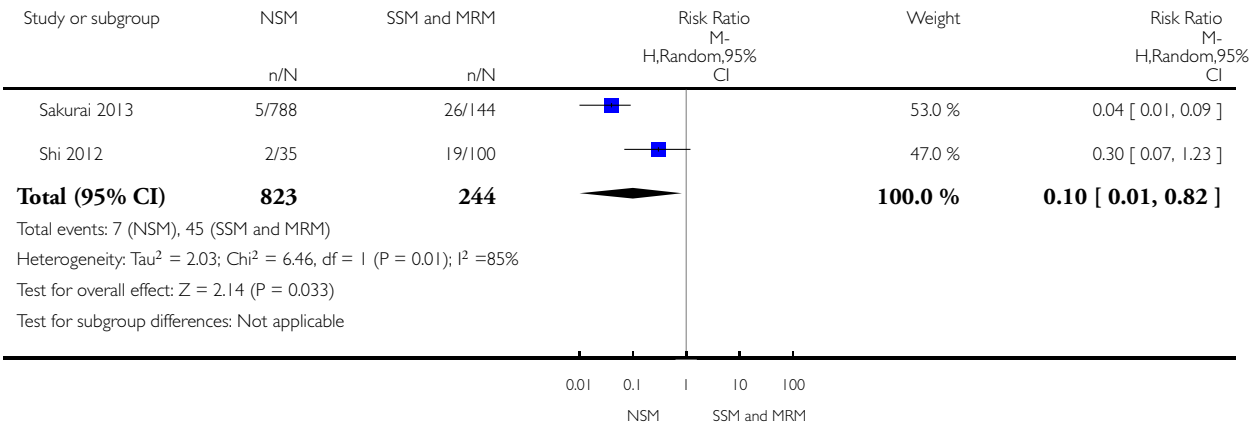


Analysis 3.1. Comparison 3 Adverse events, Outcome 1 Overall complication.

Review: Nipple- and areola-sparing mastectomy for the treatment of breast cancer

Comparison: 3 Adverse events

Outcome: 1 Overall complication

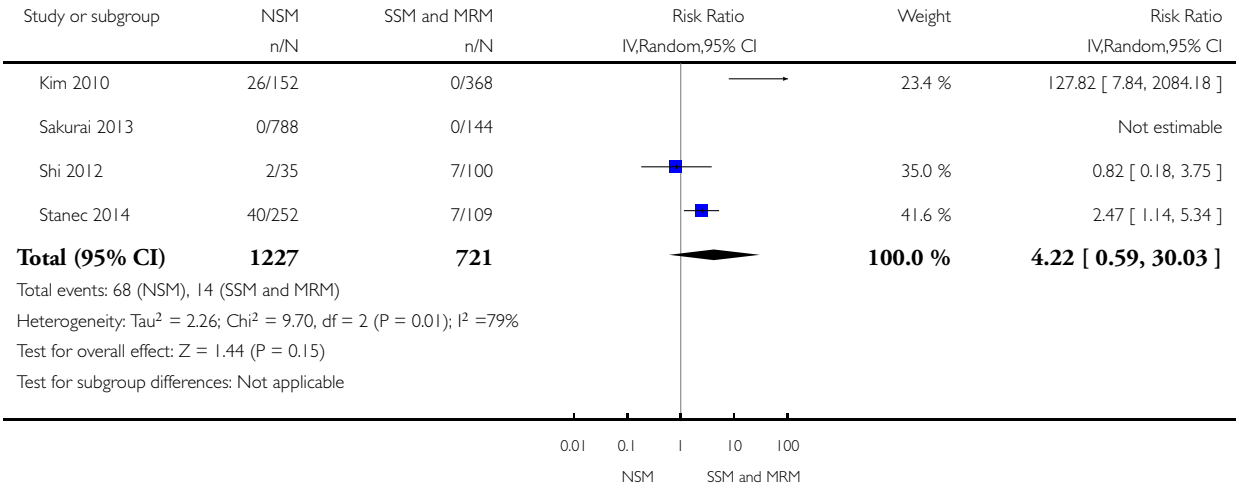


Analysis 3.2. Comparison 3 Adverse events, Outcome 2 Skin necrosis.

Review: Nipple- and areola-sparing mastectomy for the treatment of breast cancer

Comparison: 3 Adverse events

Outcome: 2 Skin necrosis

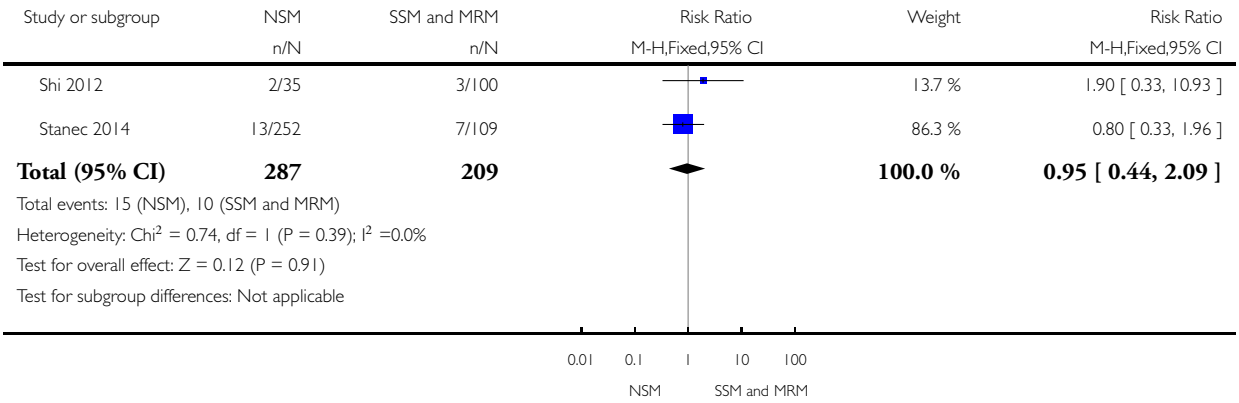


Analysis 3.3. Comparison 3 Adverse events, Outcome 3 Infection.

Review: Nipple- and areola-sparing mastectomy for the treatment of breast cancer

Comparison: 3 Adverse events

Outcome: 3 Infection



ADDITIONAL TABLES

Table 1. Tumour stage by study

Study	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Adam 2014	Study did not use the AJCC classification				
Boneti 2011	Study did not use the AJCC classification				
Burdge 2013	Study did not use the AJCC classification				
Gerber 2009	0	22	168	13	0
Horiguchi 2001	71	289	581	102	0
Kim 2010	173	752	1274	311	0
Oura 1994	0	368	125	0	0
Poruk 2015	34	70	77	34	6
Sakurai 2013	26	361	399	140	5
Shi 2012	10	0	81	14	0
Stanec 2014	73	130	71	41	0
Total	387	1992	2776	655	11

AJCC: American Joint Committee on Cancer

Table 2. Number of participants by tumour stage and intervention

Study	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	NSM; SSM; MRM	NSM; SSM; MRM	NSM; SSM; MRM	NSM; SSM; MRM	NSM; SSM; MRM
Adam 2014	This study did not use the AJCC classification				
Boneti 2011	This study did not use the AJCC classification				

Table 2. Number of participants by tumour stage and intervention *(Continued)*

Burdge 2013	This study did not use the AJCC classification				
Gerber 2009[1]		11(18.3);11(22.9) ;35 (26.9)	44(73.3);36(75.0) ;88(67.7)	5(8.3);1(2.1);7(5.4)	0;0;0
Horiguchi 2001[2]	19(14.3); 0;52(5.7)	64(48.1); 0;225(24. 7)	48(36.1); 0; 533(58. 6)	2(1.5); 0; 100(11.0)	0;0;0
Kim 2010[3]	19(12.5);65(17.7); 89(4.5)	70(46.1); 150 (40.8) ;532(26.7)	55(36.2);121(32.9) ;1098(55.2)	8(5.3);32(8.7)271 (13.6)	0;0;0
Oura 1994	0;0;0	244(81.6); 0; 124 (63.9)	55(18.4); 0; 70(36. 1)	0;0;0	0;0;0
Poruk 2015[4]	24(23.3); 10 (8.5); 0	36(35.0); 34(28.8); 0	34(33.0); 43(36.4); 0	7(6.8); 27(22.9);0	2(1.9);4(3.4); 0
Sakurai 2013	21(2.7); 0; 5(3.5)	304(38.6); 0; 57(39. 6)	364(46.3); 0; 35(24. 3)	95(12.1); 0; 45(31. 3)	3(0.4); 0; 2(1.4)
Shi 2012	2 (5.7); 0; 8 (8.0)	10 (28.6); 0; 20(20)	18 (51.4); 0; 63 (63. 0)	5(14.3); 0; 9(9.0)	0;0;0
Stanec 2014	51(19.8); 22(22.9); 0	97(37.7);33(34.4);0	88(34.2); 21(21.9); 0	21(8.2); 20 (20.8); 0	0;0;0
Total	136(7.4); 97(15.4) ;154(4.4)	836(45.8);228(36. 2);993(28.6)	706(38.7);221(35. 1);1887(54.4)	143(7.8);80(12.7); 432(12.5)	5(0.3); 4(0.6); 2(0. 1)

Numbers are given by absolute values with percentages in brackets.
AJCC: American Joint Committee on Cancer
MRM: modified radical mastectomy
NSM: nipple-sparing mastectomy
SSM: skin-sparing mastectomy
[1]Stage 0 and 1 have been combined; P = 0.47
[2]P < 0.01
[3]P = 0.21
[4]P = 0.001

Table 3. Mean age of participants by intervention

Age	NSM	SSM	MRM	Comments
Adam 2014	49 (24-74)	-	48.5 (21-87)	P = 0.38

Table 3. Mean age of participants by intervention (*Continued*)

Boneti 2011	51.2 (10.9)	53,1 (11.5)	-	P = 0.24
Burdge 2013	48.1 (10.4); (29-75)	53.9 (10.4); (29-73)	-	
Gerber 2009	46 (10)	48 (10)	58 (6)	P = 0.001
Horiguchi 2001	<= 50 y: 57 >50 y: 76	-	<= 50 y: 504 50 y >: 406	P < 0.01
Kim 2010	41.5 (7.4)	42.8 (6.6)	data not available	P = 0.06
Oura 1994	Stage 1: 49 Stage 2: 48	-	Stage 1: 56 Stage 2: 54	
Poruk 2015	45 (12)	55 (14.5)	-	P < 0.001
Sakurai 2013	51 (25-89)	-	58 (31-88)	
Shi 2012	35.6	-	50.8	
Stanec 2014	50.9	53.2	-	

MRM: modified radical mastectomy
NSM: nipple-sparing mastectomy
SSM: skin-sparing mastectomy

Table 4. Mean follow-up (in months) by intervention

Follow-up (months)	NSM	SSM	MRM	Comments
Adam 2014	35	-	36	
Boneti 2011	25.3 (18.8) 3-102	38.2 (26.3) 4-144	-	P < 0.001
Burdge 2013	25 (18.8)	38 (26.3)	-	

Table 4. Mean follow-up (in months) by intervention (*Continued*)

Gerber 2009	101 (32-126)	101 (32-126)	101 (32-126)	
Horiguchi 2001	66	-	81	
Kim 2010	60	67	not mentioned	
Oura 1994	Stage 1: 49 Stage 2: 38	-	Stage 1: 85 Stage 2: 73	
Poruk 2015	25.8 (18)	29.9 (15.7)	-	P = 0.86
Sakurai 2013	87 (10-252)	-	87 (0-231)	
Shi 2012	68 (10-104)	-	68 (10-104)	
Stanec 2014	43	58	-	

MRM: modified radical mastectomy
NSM: nipple-sparing mastectomy
SSM: skin-sparing mastectomy

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Breast Neoplasms] explode all trees
#2 breast cancer or breast neoplasm or breast adenocarcinoma or breast carcinoma or breast tumour or breast tumor
#3 #1 or #2
#4 MeSH descriptor: [Mastectomy, Segmental] explode all trees
#5 MeSH descriptor: [Mastectomy, Subcutaneous] explode all trees
#6 segmental mastectom* or subcutaneous mastectom* or breast conserving surger* or partial mastectom* or nipple-sparing mastectom* or areola-sparing mastectom* or local excision mastectom* or limited resection mastectom*
#5 #4 or #5 or #6
#6 #3 and #7

Appendix 2. MEDLINE search strategy

#	Searches
1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	placebo.ab.
5	Clinical Trials as Topic/
6	randomly.ab.
7	trial.ti.
8	(crossover or cross-over).tw.
9	Pragmatic Clinical Trials as Topic/
10	pragmatic clinical trial.pt.
11	or/1-10
12	Case-Control Studies/
13	Control Groups/
14	Matched-Pair Analysis/
15	Retrospective Studies/
16	((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab
17	or/12-16
18	Cohort Studies/
19	Longitudinal Studies/
20	Follow-Up Studies/
21	Prospective Studies/
22	Retrospective Studies/
23	cohort.ti,ab.

(*Continued*)

24	longitudinal.ti,ab.
25	prospective.ti,ab.
26	retrospective.ti,ab.
27	or/18-26
28	exp Breast Neoplasms/
29	(breast cancer or breast neoplasm or breast carcinoma or breast tumour or breast tumor).mp
30	or/28-29
31	exp Mastectomy, Segmental/
32	exp Mastectomy, Subcutaneous/
33	segmental mastectom*.mp.
34	subcutaneous mastectom*.mp.
35	breast conserving surger*.mp.
36	partial mastectom*.mp.
37	nipple-sparing mastectom*.mp.
38	areola-sparing mastectom*.mp.
39	local excision mastectom*.mp.
40	limited resection mastectom*.mp.
41	(limited resection adj5 mastectom*).mp.
42	or/31-41
43	and/30,42
44	Animals/
45	Humans/
46	44 not 45
47	43 not 46

(*Continued*)

48	and/11,47
49	and/17,47
50	and/11,47

Appendix 3. Embase search strategy

#1 random* OR factorial* OR crossover* OR cross NEXT/1 over* OR placebo* OR (doubl* AND blind*) OR (singl* AND blind*) OR assign* OR allocat* OR volunteer* OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single blind procedure'/exp
#2 'case control study'/syn OR ('case control' OR 'case base' OR 'case matched' OR retrospective) NEXT/3 (analys* OR design* OR evaluation* OR research OR stud* OR survey* OR trial*)
#3 (cohort OR concurrent OR incidence OR longitudinal OR followup OR 'follow up' OR prospective OR retrospective) NEXT/1 (analys* OR design* OR evaluation* OR research OR stud* OR survey* OR trial*) OR 'prospective method'/exp OR 'retrospective study'/syn
#4 'breast neoplasms'/exp OR 'breast neoplasms' OR 'breast cancer'/exp OR 'breast cancer' OR 'breast carcinoma'/exp OR 'breast carcinoma' OR 'breast tumour' OR 'breast tumor'/exp OR 'breast tumor'
#5 'segmental mastectomy'/exp OR 'segmental mastectomy'
#6 'subcutaneous mastectomy'/exp OR 'subcutaneous mastectomy'
#7 'breast conserving surgery'/exp OR 'breast conserving surgery'
#8 'partial mastectomy'/exp OR 'partial mastectomy'
#9 'nipple-sparing mastectomy'
#10 'areola-sparing mastectomy'
#11 'local excision mastectomy'
#12 'limited resection mastectomy'
#13 'limited resection' NEAR/5 mastectom*
#14 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15 #4 AND #14
#16 #15 AND [humans]/lim AND [embase]/lim
#17 #1 AND #16
#18 #2 AND #16
#19 #3 AND #16

Appendix 4. LILACS search strategy

Search strategy
#1(Mastectomia Segmentar) OR (Mastectomia Segmental) OR (Mastectomy, Segmental) OR (Lumpectomy) OR (Partial Mastectomy) OR (Breast-Conserving Surgery) OR (Ex E04.466.701)
#2(Mastectomy, Subcutaneous) OR (Mastectomia Subcutânea) OR (Mastectomia Subcutânea) OR (Ex E04.466.823)

(*Continued*)

#3(Breast Neoplasms) OR (Neoplasias de la Mama) OR (Neoplasias da Mama) OR (Cancer of Breast) OR (Breast Cancer) OR (Breast Tumors)
#4 #1 OR #2
#5 #3 AND #4

Appendix 5. WHO ICTRP search portal search strategy

Basic searches

1. Nipple-sparing mastectomy AND breast cancer
2. Areola-sparing mastectomy AND breast cancer[ft1]

Advance searches

Title: Nipple and areola sparing mastectomy for the treatment of breast cancer
Recruitment Status: ALL
Condition: breast cancer
Intervention: nipple-sparing mastectomy OR areola-sparing mastectomy OR mastectomy OR breast conserving surgery OR NAC
Recruitment Status: ALL
Condition: breast cancer
Intervention: nipple AND areola AND mastectomy
Recruitment Status: ALL

Appendix 6. ClinicalTrials.gov search strategy

Basic searches

1. Nipple-sparing mastectomy AND breast cancer
2. Areola-sparing mastectomy AND breast cancer

Advance searches

Title: Nipple and areola sparing mastectomy for the treatment of breast cancer
Recruitment: All Studies
Study Results: All Studies
Study Type: All Studies
Gender: All Studies
Condition: breast cancer
Intervention: nipple-sparing mastectomy OR areola-sparing mastectomy OR mastectomy OR segmental mastectomy OR breast conserving surgery OR NAC
Recruitment: All Studies
Study Results: All Studies
Study Type: All Studies
Gender: All Studies
Condition: breast cancer

Intervention: nipple AND areola AND mastectomy
Recruitment: All Studies
Study Results: All Studies
Study Type: All Studies
Gender: All Studies

HISTORY

Protocol first published: Issue 1, 2011

Review first published: Issue 11, 2016

Date	Event	Description
9 November 2012	Amended	The previous version of this protocol included nipple-, areola- and skin-sparing mastectomy for breast cancer. Due to nipple- and areola-sparing mastectomy being different treatments to skin-sparing mastectomy, the scope of this protocol has been revised to review nipple- and areola-sparing mastectomy only
9 November 2012	Amended	The scope of this protocol has changed to include nipple- and areola-sparing mastectomy only. In addition, the types of studies have been extended to include non-randomised study designs

CONTRIBUTIONS OF AUTHORS

Bruna Salani - background, objectives, outcome definitions and protocol organization, screened studies for inclusion, extracted data, completed the first draft

Rachel Riera - methodological topics and protocol organization, drafted sections of the review

Marcos Desidério Ricci - screened studies for inclusion, extracted data.

Tiago B de Castria- outcome definition and statistical analysis.

Alvaro Atallah - methodological topics.

Jessica Barrett - methodological topics, statistical analysis, drafted sections of the review.

José Luiz Barbosa Bevilacqua - idealization, background, objectives and outcome definitions.

DECLARATIONS OF INTEREST

BS: none known

RR: none known

MDR: none known

TBDC: none known

AA: none known

JB: none known

JLBB: none known

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.
- Medical Research Council, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We included study design filters to the search strategies to ensure that our search results were as relevant and comprehensive as possible to comply with Cochrane search requirements.

- We included skin-sparing mastectomy as a comparator in this version of the review. During the data extraction process, we identified articles that included two different control groups, that is, modified radical mastectomy and skin-sparing mastectomy. Due to the importance of the information presented, we have chosen to present data using both types of surgeries as a comparator to nipple-sparing mastectomy.

- Due to lack of data, it was not possible to perform subgroup analysis or comparisons of thromboembolic events as proposed initially in the protocol. We have included the analysis of overall complications as described in most studies. This outcome also included surgical systemic complications.