Ann Surg Oncol (2015) 22:3241–3249
DOI 10.1245/s10434-015-4739-1

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Overall Survival, Disease-Free Survival, Local Recurrence, and Nipple–Areolar Recurrence in the Setting of Nipple-Sparing Mastectomy: A Meta-Analysis and Systematic Review

Lucy De La Cruz, MD[1], Alison M. Moody[2], Erryn E. Tappy[2], Stephanie A. Blankenship, MS[2], and Eric M. Hecht, MD, MSPH[3]

[1]Department of Surgery, University of Miami Miller School of Medicine, Miami, FL; [2]University of Miami Miller School of Medicine, Miami, FL; [3]Department of Public Health Sciences, University of Miami Miller School of Medicine, Miami, FL

ABSTRACT

Background. Nipple-sparing mastectomy (NSM) is an increasingly common procedure; however, concerns exist regarding its oncological safety due to the potential for residual breast tissue to harbor occult malignancy or future cancer.

Methods. A systematic literature review was performed. Studies with internal comparison arms evaluating therapeutic NSM versus skin-sparing mastectomy (SSM) and/or modified radical mastectomy (MRM) were included in a meta-analysis of overall survival (OS), disease-free survival (DFS), and local recurrence (LR). Studies lacking comparison arms were only included in the systematic review to evaluate mean OS, DFS, LR, and nipple–areolar recurrence (NAR).

Results. The search yielded 851 articles. Twenty studies with 5594 patients met selection criteria. The meta-analysis included eight studies with comparison arms. Seven studies that compared OS found a 3.4 % risk difference between NSM and MRM/SSM, five studies that compared DFS found a 9.6 % risk difference between NSM and MRM/SSM, and eight studies that compared LR found a 0.4 % risk difference between NSM and MRM/SSM. Risk differences for all outcomes were not statistically significant. The systematic review included all 20 studies and evaluated OS, DFS, LR, and NAR. Studies with follow-up intervals of <3 years, 3–5 years, and >5 years had mean OS of 97.2, 97.9, and 86.8 %; DFS of 93.1, 92.3, and 76.1 %; LR of 5.4, 1.4, and 11.4 %; and NAR of 2.1, 1.0, and 3.4 %, respectively.

Conclusions. This study did not detect adverse oncologic outcomes of NSM in carefully selected women with early-stage breast cancer. Use of prospective data registries, notably the Nipple-Sparing Mastectomy Registry, will add clarity to this important clinical question.

In 2015, an estimated 231,840 women will be diagnosed with breast cancer, the second leading cause of cancer mortality in women.[1] Surgery is currently the mainstay of treatment for breast cancer. Surgical techniques have evolved since the nineteenth century, from the Halsted radical mastectomy to more conservative tissue-sparing techniques.[2] Today, procedures that preserve the breast skin envelope and/or the nipple–areolar complex (NAC) are increasingly common. A study utilizing the National Cancer Institute's Surveillance, Epidemiology, and End Results database demonstrated a 202 % increase in NSM between 2005 and 2009 in the US.[3]

Historically, progression to less invasive surgical management of breast cancer has not produced worse outcomes. A recent meta-analysis of retrospective studies comparing patients undergoing skin-sparing mastectomy (SSM) with patients undergoing conventional mastectomy showed no significant difference in local recurrence (LR) between the two treatment groups.[4] However, concerns exist regarding the oncological safety of nipple-sparing mastectomy (NSM) due to the potential for residual glandular breast tissue to harbor occult malignancy or future cancer. These concerns warrant careful examination as

Electronic supplementary material The online version of this article (doi:10.1245/s10434-015-4739-1) contains supplementary material, which is available to authorized users.

First Received: 14 April 2015;
Published Online: 5 August 2015

L. De La Cruz, MD
e-mail: lcruzclaver@gmail.com

studies included in a comprehensive review of NAC histopathology revealed the average incidence of occult malignancy in the NAC was 11.5 % overall and 7.9 % in the four most recent studies published in 2011.[5] Due to the lack of consensus regarding the safety of NSM, the National Comprehensive Cancer Network does not recommend NSM for surgical management of breast cancer, with the exception of patients enrolled in a clinical trial.[6]

The purpose of the current study was to summarize the totality of evidence and assess differences in oncological safety between NSM and modified radical mastectomy (MRM) and/or SSM. We performed a meta-analysis and systematic literature review to assess overall survival (OS), disease-free survival (DFS), LR, and nipple–areolar recurrence (NAR) in patients undergoing NSM.

METHODS

Study Selection

A search was conducted through the MEDLINE database using PubMed. Our search terms included: ((((‘Breast’[Mesh] AND ‘Female’[Mesh]) AND (‘Mastectomy’[Mesh] OR ‘Mastectomy, Subcutaneous’[Mesh])) OR ‘Carcinoma, Ductal’[Mesh]) OR ‘Carcinoma, Ductal, Breast’[Mesh]) AND ‘Nipples’[Mesh]. We filtered all articles from 1967 to 2014, selecting those containing the key terms ‘nipple–sparing mastectomy’, ‘subcutaneous mastectomy’, ‘skin-sparing mastectomy’, and/or ‘survival’. Further searches were conducted using Google Scholar and Scopus. A manual search of bibliographies of relevant articles was performed. All searches were conducted in July 2014 and repeated in January 2015. Abstracts were screened to identify studies that measured OS, DFS, LR, and/or NAR following NSM.

Data Extraction

Three investigators performed the search and independently reviewed and extracted data from each study. Discrepancies in coding required agreement between authors to be considered resolved.

Definitions of Outcomes of Interest

Included studies reported at least one of the following outcomes:

- *OS*: people in the study and/or control group who were alive from the time of surgery to date of last follow-up.
- *DFS*: people in the study and/or control group who were alive from the time of surgery to date of last follow-up without the development of local or distant disease recurrence or a new breast tumor.
- *LR*: cancer that has occurred in the ipsilateral breast, chest wall or lymph nodes following surgery and prior to date of last follow-up.
- *NAR*: recurrence of cancer in the NAC following surgery and prior to date of last follow-up.

Inclusion and Exclusion Criteria

Studies were selected based on the following inclusion criteria:

- Report on women undergoing NSM in the setting of breast cancer.
- Report on OS, DFS, LR, and/or NAR.
- Available in English.

Studies were excluded by any one of the following criteria:

- The NAC was not fully preserved.
- Only non-oncologic outcomes (i.e. cosmetic result, NAC necrosis) were reported.
- Combined outcome measures for therapeutic and prophylactic NSMs were reported and could not be delineated. Study authors were contacted via email in an attempt to obtain isolated data for patients undergoing therapeutic NSMs only.

Statistical Analysis

For all studies, we reported one or more of the primary outcomes of interest (OS, DFS, LR, and NAR). In addition, we extracted follow-up time, mean age, most common pathology, tumor stage, use of neoadjuvant and/or adjuvant chemotherapy, use of radiotherapy, use of hormonal therapy, tumor size, tumor-to-nipple distance (TND), and lymph node status. Studies were categorized by the presence or absence of an internal comparison between NSM and MRM/SSM. Studies that included a comparison arm were included in the meta-analysis to determine risk differences for OS, DFS, and LR between treatment groups. Studies both with and without comparison arms were included in the systematic review and evaluation of mean OS, DFS, LR, and NAR.

A study-level meta-analysis was performed using Comprehensive Meta-Analysis Software. We first calculated the degree of heterogeneity across the studies and tested its significance using both Cochran’s Q test and an I^2 statistic to determine the underlying statistical model. When the Q statistic is not significant, the fixed effects model, which assumes that the observed effects are different from the true population value due to sampling error, is chosen. Otherwise the random effects model, which assumes that study effects are uniquely different regarding sampling error and other differences, is chosen. We used the random effects model as

it is considered more appropriate and conservative when evaluating observational studies in a meta-analysis.

The effect size of each study was calculated by subtracting the proportion of affected individuals from those unaffected. A weighted average of effect sizes was then computed as a summary measure. A risk difference of zero favors the null hypothesis, meaning there is no difference in outcome measures between patients treated with either therapy. Statistically significant differences were considered at the $p < 0.05$ level.

RESULTS

Our literature search yielded 851 articles. Twenty studies published from 2006 to 2014 met the inclusion and exclusion criteria and were selected for the systematic review of OS, DFS, LR, and NAR (Fig. 1).[7–26] In aggregate, the 20 studies included 2207 patients who underwent therapeutic NSM. Eight studies published comparison arms and were included in a meta-analysis of OS, DFS, and LR.[7–14] Twelve additional studies lacked comparison arms.[15–26] Tables 1 and 2 provide baseline characteristics of studies with and without comparison arms, respectively.

Meta-analysis of Overall Survival (OS), Disease-Free Survival (DFS), and Local Recurrence (LR)

Characteristics of Studies Included in the Meta-analysis of NSM Versus MRM/SSM The meta-analysis included 4663 patients; 1398 (30 %) underwent NSM, 698 (15 %) underwent SSM, and 2567 (55 %) underwent MRM. Patients undergoing NSM, SSM, and MRM had a mean age of 45.5, 50.6, and 55.6 years, respectively. Follow-up time ranged from 25.3 to 101 months. All studies reported invasive ductal carcinoma (IDC) as the most common tumor pathology. Six of the eight studies reported stage I and II as the most common tumor stage.

Four of the eight studies reported use of neoadjuvant and adjuvant chemotherapy in patients who underwent NSM and MRM/SSM;[7–10] two studies reported use of adjuvant radiotherapy;[7,10] four studies reported estrogen receptor, progesterone receptor, and HER2/neu status;[7,11,12,14] and three studies reported lymph node status.[7,10,11] Investigators of the aforementioned studies found no statistically significant differences between treatment groups with regard to use of neoadjuvant and adjuvant chemotherapy, use of radiotherapy, estrogen receptor status, progesterone receptor status, HER2/neu status, and lymph node status. Six studies reported tumor size ranging from 1.6 to 5 cm in NSM patients, 1 to 4.6 cm in SSM patients, and 2 to 5 cm in MRM patients.[7–9,12–14]

Summary of Results

In the meta-analysis, seven of the eight studies reported OS, five reported DFS, and eight reported LR. Five studies provided information for all three analyses. Seven studies were retrospective, one study was prospective, and all were non-randomized.

The Q and I^2 statistics for risk difference between patients undergoing NSM versus MRM/SSM were 12.8

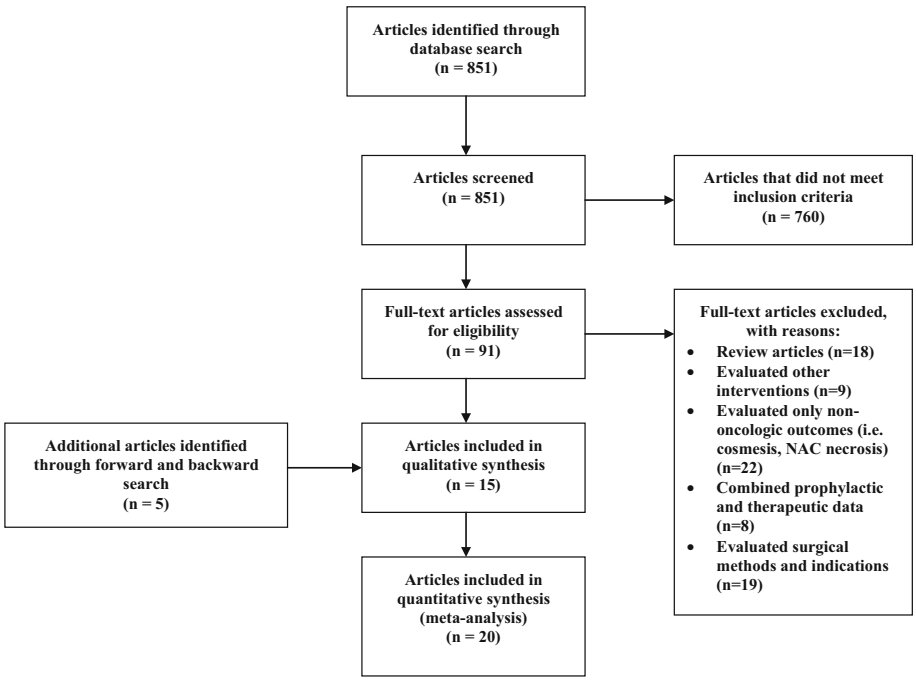

FIG. 1 Literature review process. *NAC* nipple–areolar complex

TABLE 1 Characteristics of studies with comparison arms included in the meta-analysis of NSM versus MRM/SSM

Author, year of publication	Study type	Period	Country	Comparison arm	No. of patients		Follow-up (months)		Age (years)		Most common pathology		Most common stage		Neoadjuvant and/or adjuvant chemotherapy (%)		Radiotherapy (%)	
					NSM	MRM/SSM	NSM	MRM/SSM	NSM	MRM/SSM	NSM	MRM/SSM	NSM	MRM/SSM	NSM	MRM/SSM	NSM	MRM/SSM
Adam et al., 2014[7]	R	2000–2012	Sweden	MRM	67	203/–	36	35/–	–	–/–	IDC	IDC/–	I	I/–	37.3/–	46.3/–	31.9	39.3/–
Boneti et al., 2011[8]	R	1998–2010	US	SSM	152	–/141	25.3	–/38.2	51.2	–/53.1	IDC	–/IDC	–	–/–	45.1	–/46.1	–	–/–
Burdge et al., 2013[9]	R	2001–2012	US	SSM	39	–/21	25.3	–/38.2	48.1	–/54	IDC	–/IDC	IIIA	–/IIIA	–	–/–	–	–/–
Gerber et al., 2009[10]	P	1994–2000	Germany	MRM/SSM	60	130/48	101	101/101	46	58/48	IDC	IDC/IDC	II	II/II	88.3	89.5/83.8	26.7	23.8/29.2
Kim et al., 2010[11]	R	2001–2006	South Korea	MRM/SSM	152	1990/368	60	–/67	41.5	–/42.8	IDC	IDC/IDC	I	II/I	–	–/–	5.3	–/8.2
Poruk et al., 2015[12]	R	2005–2011	US	SSM	105	–/120	25.8	–/29.9	45	–/55	IDC	–/IDC	I	–/II	61.9	–/82.9	89.7	–/84.8
Sakurai et al., 2013[13]	R	1985–2004	Japan	MRM	788	144/–	87	87/–	51	58/–	IDC	IDC/–	II	I/–	–	–/–	0	–/0
Shi et al., 2012[14]	R	2000–2008	China	MRM	35	100/–	68	68/–	35.6	50.8/–	IDC	IDC/–	II	II/–	–	–/–	–	–/–

MRM modified radical mastectomy, *SSM* skin-sparing mastectomy, *R* retrospective, *P* prospective, *IDC* invasive ductal carcinoma

TABLE 2 Characteristics of studies without comparison arms

Author, year of publication	Study type	Period	Country	No. of patients			Follow-up (months)	Age (years)	Most common pathology	Most common stage	Positive lymph nodes (%)	Chemotherapy (%)		Radiotherapy (%)	Hormonal therapy (%)
				Total (n)	Therapeutic NSM (n)	Prophylactic NSM (n)						Neoadjuvant	Adjuvant		
Alperovich et al., 2013[15]	R	2006–2012	US	12	8	4	10.5	46.6	DCIS	0	–	–	–	–	–
Benediktsson and Perbeck, 2008[16]	P	1988–1994	Sweden	202	202	0	11.3	52.8	IDC	II	40.3	–	24.5	21.8	56.5
Caruso et al., 2006[17]	P	1994–2004	Italy	50	50	0	66	42	IDC	I	26.0	–	24.0	6.0	42.0
Crowe et al., 2008[18]	P	2001–2007	US	110	83	27	41	43	IDC	–	9.1	–	–	–	–
Jensen et al. 2011[19]	P	1997–2008	US	77	77	0	60.2	51	IDC	I	31.2	–	–	20.8	–
Nava et al., 2012[20]	P	–	Italy	65	58	7	36	48	IDC	I	32.8	13.7	44.8	17.2	65.5
Paepke et al., 2009[21]	P	2003–2006	Germany	96	94	2	34	–	IDC	I	–	–	–	–	–
Sacchini et al., 2006[22]	R	–	US/Brazil/Italy	123	68	55	24.6	45	IDC	I	8.9	–	–	–	–
Sood et al., 2014[23]	R	2008–2012	Australia	87	76	11	15.7	47	IDC	I	–	–	46.1	27.6	46.1
Sookhan et al., 2008[24]	R	2005–2007	US	20	9	11	10.5	44	DCIS	0	5.6	–	–	5.6	–
Tancredi et al., 2013[25]	P	2007–2012	Italy	55	55	0	21.7	46	IDC	II	31	–	3.6	–	–
Voltura et al., 2008[26]	R	2002–2007	US	34	29	5	18	48	IDC	II	26.5	5.9	35.3	14.7	–

NSM nipple-sparing mastectomy, *R* retrospective, *P* prospective, *IDC* invasive ductal carcinoma, *DCIS* ductal carinoma in situ

and 53 % with regard to OS (degrees of freedom [df] = 6, $p = 0.047$); 19 and 78.9 % with regard to DFS (df = 4, $p = 0.001$); and 7.3 and 4.3 % with regard to LR (df = 7, $p = 0.397$). These estimates suggest we should reject the null hypothesis of homogeneity across studies and determine the average effect size using the random effects model.

Under the random effects model, the weighted average risk difference for OS, DFS, and LR was 3.4 % ($p = 0.073$), 9.6 % ($p = 0.056$), and 0.4 % ($p = 0.567$), respectively, all in favor of NSM (Fig. 2), although these risk differences were not statistically significant.

To assess oncological safety of NSM over longer follow-up intervals, a subgroup analysis of studies with >5-year follow-up time was performed. This group had similar results to the overall group. OS had a risk difference of 1.2 % ($p = 0.628$), DFS had a risk difference of 2.7 % ($p = 0.400$), and LR had a risk difference of 0.6 %

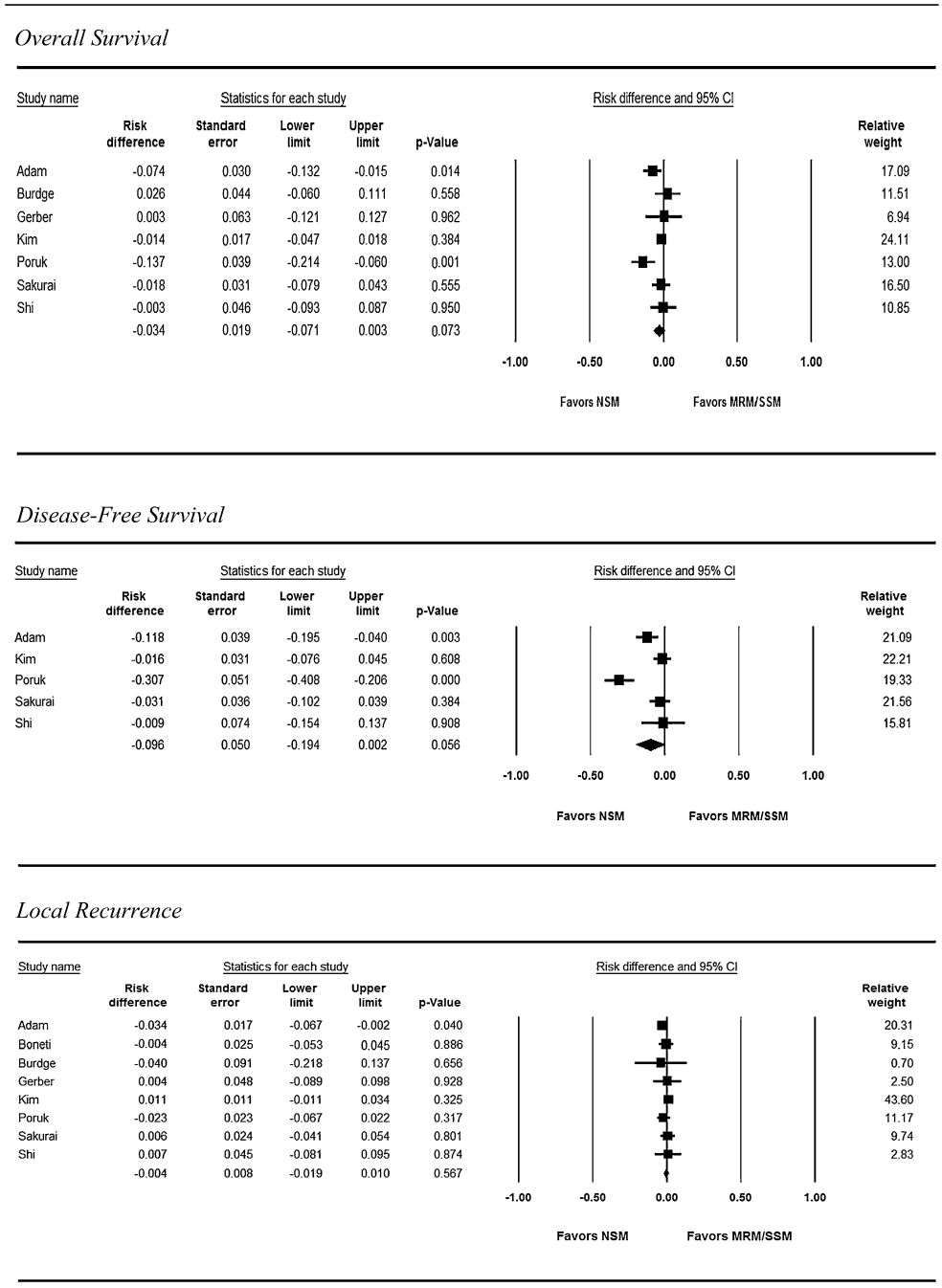

FIG. 2 Forest plots evaluating overall survival, disease-free survival, and local recurrence in NSM versus MRM/SSM. *NSM* nipple-sparing mastectomy, *MRM* modified radical mastectomy, *SSM* skin-sparing mastectomy

($p = 0.758$), all trending in favor of NSM; however, these risk differences were not statistically significant.

In several studies, patients undergoing NSM were younger than patients undergoing MRM/SSM. To further evaluate the potential effect of age on our study outcome measures, we conducted a subgroup analysis of those studies in which the mean age of patients in each treatment group was approximately equivalent. In those studies, OS had a risk difference of 1.4 % ($p = 0.399$) trending in favor of NSM, and LR had a risk difference of 0.9 % ($p = 0.39$) trending in favor of MRM/SSM, although these differences were not statistically significant. We were unable to evaluate the effect of age on DFS due to insufficient data.

To better evaluate the effects of cancer stage on our outcome measures, we conducted a subgroup analysis using the five studies that controlled for stage in the primary analysis. Risk differences for OS, DFS, and LR were 2.5 % ($p = 0.05$), 4.6 % ($p = 0.068$), and 0.3 % ($p = 0.768$), respectively, all trending in favor of NSM; however, these differences were not statistically significant.

Systematic Review of OS, DFS, LR and Nipple–Areolar Recurrence (NAR)

Characteristics of Studies Included in the Systemic Review Data were extracted from all 20 studies that reported OS, DFS, LR, and/or NAR in patients who had therapeutic NSM (Table 3), 12 of which lacked comparison arms. The mean age of patients was 46.2 years, with follow-up time ranging from 10.5 to 135.6 months. All studies reported on type of breast cancer, with 18 of 20 studies reporting IDC as the most common tumor pathology. Eighteen studies reported the most common cancer stage, with nine studies reporting stage I as the most common. Lymph node status was reported in 13 studies, and 5.6–71.8 % of patients had

TABLE 3 Average overall survival, disease-free survival, local recurrence and nipple-areolar recurrence according to follow-up interval

Author	No. of patients undergoing NSM (n)	Follow-up (months)	Overall survival (%)	Disease-free survival (%)	Local recurrence (%)	Nipple–areolar recurrence (%)
Follow-up <3 years	$n = 541$					
Alperovich et al.[15]	8	10.5	100	100	0	0
Boneti et al.[8]	152	25.3	–	–	4.6	–
Burdge et al.[9]	39	25.3	97.4	–	10.3	0
Poruk et al.[12]	105	25.8	96.2	92.4	1.9	0
Sacchini et al.[22]	68	24.6	98.5	95.6	2.9	0
Sood et al.[23]	76	15.7	98.7	91.9	7.9	1.3
Sookhan et al.[24]	9	10.8	100	100	0	0
Tancredi et al.[25]	55	21.7	100	92.7	0	3.6
Voltura et al.[26]	29	18	96.6	93.1	6.9	0
Weighted average (95 % CI)			97.2 (94.8–98.5)	93.1 (89.8–95.3)	5.4 (3.6–7.9)	2.1 (0.9–4.5)
Follow-up 3–5 years	$n = 454$					
Adam et al.[7]	67	36	96.2	94.1	0	0
Crowe et al.[18]	83	41	98.8	95.1	0	1.2
Kim et al.[11]	152	60	97.1	89	2	1.3
Nava et al.[20]	58	36	98.2	94.9	1.6	0
Paepke et al.[21]	94	34	98.9	94.7	1.1	0
Weighted average (95 % CI)			97.9 (95.9–98.9)	92.3 (89.3–94.4)	1.4 (0.7–3.2)	1.0 (0.4–2.6)
Follow-up >5 years	$n = 1212$					
Benediktsson and Perbeck[16]	202	135.6	76.4	51.3	25.7	–
Caruso et al.[17]	50	66	92	88	0	2
Jensen et al.[19]	77	60.2	100	100	0	0
Gerber et al.[10]	60	101	76.7	–	11.7	1.7
Sakurai et al.[13a]	788	87	88[a]	83[a]	4.6	3.7
Shi et al.[14]	35	68	94.3	82.9	5.7	2.9
Weighted average (95 % CI)			86.8 (78.6–92.2)	76.1 (73.3–78.8)	11.4 (9.4–13.8)	3.4 (2.4–4.8)

NSM nipple-sparing mastectomy, *CI* confidence interval

[a] 10-year follow-up data

positive nodes. The use of neoadjuvant and/or adjuvant chemotherapy was described in ten studies among 3.6–88.3 % of patients. Utilization of adjuvant radiation therapy was reported in 11 studies among 5.3–89.7 % of patients. Eight studies reported use of adjuvant hormonal therapy in 42.0–65.5 % of patients; five studies reported average TND ranging from 3.6 to 4.97 cm; and seven additional studies described specific inclusion criteria for TND, two of which included patients with TND >1 cm, and five of which included TND >2 cm.

Summary of Results

Weighted averages of OS, DFS, LR, and NAR were calculated based on the number of patients in each study in three follow-up intervals: <3 years, 3–5 years, and >5 years (Table 3). A total of 541 patients in nine studies were followed for <3 years, 454 patients in five studies were followed for 3–5 years, and 1212 patients in six studies were followed for >5 years. Studies with follow-up intervals of <3 years, 3–5 years, and >5 years had mean OS of 97.2, 97.9, and 86.8 %; DFS of 93.1, 92.3, and 76.1 %; LR of 5.4, 1.4, and 11.4 %; and NAR of 2.1, 1.0, and 3.4 %, respectively.

DISCUSSION

Across all studies, we found relatively high rates of OS and DFS and relatively low rates of LR and NAR in all three follow-up intervals. We also found no significant differences in OS, DFS, and LR between NSM and MRM/SSM. Finally, in a subgroup analysis of studies with >5-year follow-up time, we found no significant differences in OS, DFS, and LR between patients who received NSM versus patients who received MRM or SSM.

Our finding that NSM was not associated with adverse oncologic outcomes when compared with MRM/SSM has several possible explanations. First, when performing NSM, the investigators likely conducted careful patient selection. Another possibility relates to the hypothesis that cancer recurrence is more strongly associated with tumor biology (e.g. stage, grade, lymph node involvement, hormone responsiveness, and size) than surgical approach.[27–29] Finally, the research design utilizes study-level data, as opposed to individual-level data, and therefore may not have been sufficiently sensitive to account for all potential biases.

Our study has limitations. Many studies had missing data, such as tumor characteristics and adjuvant therapy, among other factors that may impact clinical outcomes. In addition, the data were derived from longitudinal observational studies, not randomized clinical trials (RCTs). As such, confounding factors, including patient demographics, family history, tumor size, TND, nodal status, hormonal status, genetic predisposition, and neoadjuvant and/or adjuvant therapy, may have influenced our study results. For example, women undergoing NSM in this meta-analysis were 5 and 10 years younger, on average, than women undergoing SSM and MRM, respectively. While subgroup analyses of studies that controlled for age and stage were consistent with our overall study results, we still cannot be certain that these factors did not have an impact on our overall findings. An additional subset of studies demonstrated no significant difference between treatment groups regarding chemotherapy, radiation therapy, hormone receptor status, and HER2/neu status, although these data were not reported in all studies and remain a potential confounder. Finally, observational studies are unable to control for inherent differences in patients who self-select more or less aggressive forms of treatment. Women with a family history of breast cancer or with genetic predispositions may be more likely to self-select a more aggressive form of treatment.

Our study has a number of strengths. By following a predetermined protocol in which investigators cannot select articles for inclusion that favor one outcome over another, meta-analyses limit article selection bias. In addition, our study is unlikely to be affected by publication bias as investigators would be equally motivated to publish both favorable and unfavorable outcomes regarding the oncological safety of NSM. Meta-analyses further benefit from generalizability if the studies included are representative of all studies ever performed on the topic of interest. Our meta-analysis includes a large representative sample of 4663 patients, and our results are likely generalizable to women between the ages of 35.6 and 61 years with ductal carcinoma in situ or stage I and II IDC, and TND >2 cm. Finally, our strongest finding is that all eight studies in the meta-analysis show uniform consistency in which NSM is not inferior to MRM/SSM.

CONCLUSIONS

Our study did not detect adverse oncologic outcomes of NSM in carefully selected women with early-stage breast cancer, and provides an enhanced basis for patients and surgeons to undergo shared decision making regarding the risks and benefits of NSM. These data require further validation. Although a large RCT would greatly minimize bias and perhaps provide the best evidence regarding the safety of NSM, RCTs have not been conducted for NSM because of ethical concerns.[10,30] Even if deemed ethical, patient preferences would not make effective randomization feasible. Despite the limitations of meta-analyzing observational studies, the Cochrane Collaboration states a

meta-analysis of observational studies may be used to "provide evidence of the effects, including benefit or harm, of interventions that cannot be randomized, or which are extremely unlikely to be studied in randomized trials."[31] In an environment where evidence from RCTs is unavailable, and is unlikely to become available, surgeons must work with the evidence at hand. Use of prospective data registries, notably the Nipple-Sparing Mastectomy Registry, will further aid in evaluation of the oncological safety of NSM.

ACKNOWLEDGMENT This manuscript includes preliminary data presented at the 16th Annual Meeting of the American Society of Breast Surgeons, and incorporates additional analyses that have undergone peer review. The authors would like to thank Dr. Beth-Ann Lesnikoski for reviewing our initial abstract presented at the meeting.

AUTHOR CONTRIBUTION Lucy De La Cruz conceptualized and designed the project. Eric Hecht, Stephanie Blankenship, Alison Moody, and Erryn Tappy drafted the initial manuscript. All authors reviewed, revised, and approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DISCLOSURES No external funding was secured for this study. Lucy De La Cruz, Alison M. Moody, Erryn E. Tappy, Stephanie A. Blankenship, and Eric M. Hecht have no financial relationships or conflicts of interest to disclose that are relevant to this article.

REFERENCES

1. American Cancer Society. Cancer facts and figures 2015. http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf. Accessed 22 Feb 2015.
2. Laronga C, Lewis JD, Smith PD. The changing face of mastectomy: an oncologic and cosmetic perspective. *Cancer Control*. 2012;19(4):286–94.
3. Agarwal S, Agarwal S, Neumayer L, Agarwal JP. Therapeutic nipple-sparing mastectomy: trends based on a national cancer database. *Am J Surg*. 2014;208(1):93–8.
4. Lanitis S, Tekkis PP, Sgourakis G, Dimopoulous N, Al Mufti R, Hadjiminas DJ. Comparison of skin-sparing mastectomy versus non-skin-sparing mastectomy for breast cancer: a meta-analysis of observational studies. *Ann Surg*. 2010;251(4):632–9.
5. Mallon P, Feron JG, Couturaud B, et al. The role of nipple-sparing mastectomy in breast cancer: a comprehensive review of the literature. *Plast Reconstr Surg*. 2013;131(5):969–84.
6. National Comprehensive Cancer Network. NCCN Guidelines For Patients®. Version 1.2014. Stages I and II breast cancer. http://www.nccn.org/patients/guidelines/stage_i_ii_breast/files/assets/common/downloads/files/stage_I_II_breast.pdf. Accessed 22 Feb 2015.
7. Adam H, Bygdeson M, de Boniface J. The oncological safety of nipple-sparing mastectomy: a Swedish matched cohort study. *Eur J Surg Oncol*. 2014;40(10):1209–15.
8. Boneti C, Yuen, J Santiago C, et al. Oncologic safety of nipple skin-sparing or total skin-sparing mastectomies with immediate reconstruction. *J Am Coll Surg*. 2011;212:686–93.
9. Burdge EC, Yuen J, Hardee M, et al. Nipple skin-sparing mastectomy is feasible for advanced disease. *Ann Surg Oncol*. 2013;20(10):3294–302.
10. Gerber B, Krause A, Dieterich M, Kundt G, Reimer T. The oncological safety of skin sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction: an extended follow-up study. *Ann Surg*. 2009;249(3):461–68.
11. Kim HJ, Park EH, Lim WS, et al. Nipple areola skin-sparing mastectomy with immediate transverse rectus abdominis musculocutaneous flap reconstruction is an oncologically safe procedure: a single center study. *Ann Surg*. 2010;251(3):493–8.
12. Poruk KE, Ying J, Chidester JR, Olson JR, Matsen CB, Neumayer L, et al. Breast cancer recurrence after nipple-sparing mastectomy: one institution's experience. *Am J Surg*. 2015;209(1):212–7.
13. Sakurai T, Zhang N, Suzuma T, Umemura T, Yoshimura G, Sakurai T, et al. Long-term follow-up of nipple-sparing mastectomy without radiotherapy: a single center study at a Japanese institution. *Med Oncol*. 2013;30(1):481.
14. Shi A, Wu D, Li X, et al. Subcutaneous nipple-sparing mastectomy and immediate breast reconstruction. *Breast Care (Basel)*. 2012;7(2):131–136.
15. Alperovich M, Tanna N, Samra F, et al. Nipple-sparing mastectomy in patients with a history of reduction mammaplasty or mastopexy: how safe is it? *Plast Reconstr Surg*. 2013;131(5):962–7.
16. Benediktsson KP, Perbeck L. Survival in breast cancer after nipple-sparing subcutaneous mastectomy and immediate reconstruction with implants: a prospective trial with 13 years median follow-up in 216 patients. *Eur J Surg Oncol*. 2008;34(2):143–148.
17. Caruso F, Ferrara M, Castiglione G, Trombetta G, De Meo L, Catanuto G, et al. Nipple sparing subcutaneous mastectomy: sixty-six months follow-up. *Eur J Surg Oncol*. 2006:32;937–40.
18. Crowe JP, Patrick RJ, Yetman RJ, Djohan R. Nipple-sparing mastectomy update: one hundred forty-nine procedures and clinical outcomes. *Arch Surg*. 2008;143(11):1106–10; discussion 1110.
19. Jensen JA, Orringer JS, Giuliano AE. Nipple-sparing mastectomy in 99 patients with a mean follow-up of 5 years. *Ann Surg Oncol*. 2011;18(6):1665–70.
20. Nava MB, Ottolenghi J, Pennati A, et al. Skin/nipple sparing mastectomies and implant-based breast reconstruction in patients with large and ptotic breast: oncological and reconstructive results. *Breast*. 2012;21(3):267–71.
21. Paepke S, Schmid R, Fleckner S, et al. Subcutaneous mastectomy with conservation of the nipple–areolar skin. *Ann Surg*. 2009;250:288–92.
22. Sacchini V, Pinotti JA, Barros AC, et al. Nipple-sparing mastectomy for breast cancer and risk reduction: oncologic or technical problem? *J Am Coll Surg*. 2006;203:704–14.
23. Sood S, Elder E, French J. Nipple-sparing mastectomy with implant reconstruction: the Westmead experience. *ANZ J Surg*. 2015;85(5):363–67.
24. Sookhan N, Boughey JC, Walsh MF. Nipple-sparing mastectomy: initial experience at a tertiary center. *Am J Surg*. 2008;196(4):575–77.
25. Tancredi A, Ciuffreda L, Petito L, Natale F, Murgo R. Nipple-areola-complex sparing mastectomy: five years of experience in a single centre. *Updates Surg*. 2013;65(4):289–94.
26. Voltura AM, Tsangaris TN, Rosson GD, et al. Nipple-sparing mastectomy: critical assessment of 51 procedures and implications for selection criteria. *Ann Surg Oncol*. 2008;15(12):3396–401.
27. Gilliland MD, Barton RM, Copeland EM III. The implications of local recurrence of breast cancer as the first site of therapeutic failure. *Ann Surg*. 1983;197:284–87.
28. Donegan WL, Perez-Mesa CM, Watson FR. A biostatistical study of locally recurrent breast carcinoma. *Surg Gynecol Obstet*. 1966;122:529–540.
29. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of Surgical Oncology–American Society for Radiation Oncology Consensus

guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *Int J Radiation Oncol Biol Phys*. 2014;88(3):553–64.
30. Gerber B, Krause A, Reimer T, et al. Skin-sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction is an oncologically safe procedure. *Ann Surg*. 2003;238(1):120–7.
31. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration. http://handbook.cochrane.org. Accessed 22 Feb 2015.