Original article

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Evolving indications and long-term oncological outcomes of risk-reducing bilateral nipple-sparing mastectomy

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Background: **Bilateral nipple-sparing mastectomy (NSM) is a technically feasible operation and is associated with excellent cosmetic outcomes. The aim of this study was to evaluate trends in patient characteristics, indications for surgery and long-term outcomes of bilateral NSM for breast cancer risk reduction over time.**

Methods: **A review of a single-centre experience with bilateral NSM performed between 2001 and 2017 for breast cancer risk reduction in patients without breast cancer was performed. Trends in patient characteristics and indications for surgery were evaluated over four time intervals: 2001–2005, 2006–2009, 2010–2013 and 2014–2017. Statistical analysis was performed using χ^2 tests.**

Results: **Over the study period, 272 NSMs were performed in 136 patients; their median age was 41 years. The number of bilateral NSMs performed increased over time. The most common indication was a mutation in breast cancer-associated genes (104 patients, 76·5 per cent), which included *BRCA1* (62 patients), *BRCA2* (35), *PTEN* (2), *TP53* (3) and *ATM* (2). Other indications were family history of breast cancer (19 patients, 14·0 per cent), lobular carcinoma *in situ* (10, 7·4 per cent) and a history of mantle irradiation (3, 2·2 per cent). The proportion of patients having a bilateral NSM for mutation in a breast cancer-associated gene increased over time (2001–2005: 2 of 12; 2006–2009: 9 of 17; 2010–2013: 34 of 41; 2014–2017: 61 of 66; $P < 0·001$). Mean follow-up was 53 months; no breast cancers were found during follow-up.**

Conclusion: **The use of bilateral NSM for breast cancer risk reduction is increasing and the indications have evolved over the past 16 years. These excellent long-term oncological results suggest that bilateral NSM is a good option for surgical breast cancer risk reduction.**

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Introduction

Risk-reducing simple mastectomy, subcutaneous mastectomy and skin-sparing mastectomy have all been demonstrated to be associated with breast cancer risk reduction in patients with a strong family history of breast cancer and in patients with mutations in *BRCA1* and *BRCA2* genes[1–3]. Over the past 15 years, nipple-sparing mastectomy (NSM) has emerged as an option for the treatment and prevention of breast cancer in selected patients[4,5]. These reports and others[6–14] have established the technical feasibility of NSM. Most reports of NSM have focused on patients with a diagnosis of breast cancer, not NSM performed for breast cancer risk reduction in high-risk patients; in one previous series[5] only 13 of 111 patients had bilateral NSM for breast cancer risk reduction. There have been several reports[9,11,15,16] of bilateral NSM for breast cancer risk reduction, but these focused only on patients with mutations in *BRCA1* and *BRCA2*. In addition, many of these series report only short-term oncological follow-up. The limited published experience, relatively short-term reported follow-up and presence of terminal ductal lobular units in the nipple–areolar complex have led some groups[17–20] to question the long-term oncological safety of NSM for risk reduction in patients with an increased risk of breast cancer.

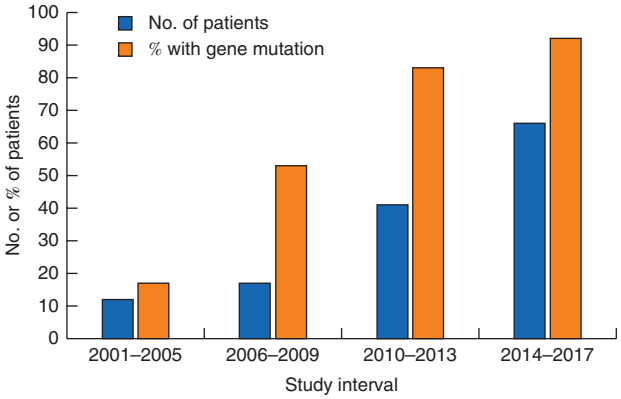

Fig. 1 Trends over time in use of risk-reducing bilateral nipple-sparing mastectomy and proportion of patients with pathogenic mutation in breast cancer genes

Since 2001, bilateral NSM for breast cancer risk reduction in high-risk patients with a genetic predisposition to breast cancer, a history of high-risk or atypical breast lesions, a strong family history of breast cancer, and history of mantle irradiation has been offered at Cleveland Clinic. The aims of this study were to determine whether the performance of risk-reducing NSM is increasing over time and whether the indications for risk-reducing bilateral NSM have changed over the past 17 years in the context of the increasing incorporation of more extensive germline genomic testing in clinical practice. It also aimed to ascertain whether bilateral NSM for risk reduction is oncologically safe and associated with low rates of subsequent breast cancer in high-risk patients with long-term follow-up.

Table 1 Reported series of risk-reducing bilateral nipple-sparing mastectomy

Reference	Institutions	Year	No. of risk-reducing NSMs	Median patient age (years)	Breast cancer risk category (%)	Follow-up (months)		New cancer (%)
						Mean	Median	
Sacchini *et al.*[7]	MSKCC Sao Paulo University European Oncology Institute University of Padua	2006	84	45	n.d.	n.a.	25	2
Crowe *et al.*[5]	Cleveland Clinic (Cleveland)	2008	26	43	n.d.	n.a.	n.a.	n.a.
Peled *et al.*[11]	UCSF	2014	52	41	*BRCA1* 54 *BRCA2* 46	37	n.a.	0
Yao *et al.*[9]	Northwestern University Massachusetts General Hospital	2015	298	41	*BRCA1* 62 *BRCA2* 46	33	n.a.	0·6
Manning *et al.*[15]	MSKCC*	2015	126	39	*BRCA1* 63 *BRCA2* 29 *BRCA* VUS 8	n.a.	26	0
Moo *et al.*[10]	New York Hospital – Cornell	2016	90	42	*BRCA1/2* 42 Other 58	n.a.	32	n.a.
Jakub *et al.*[16]	Mayo Clinic (Rochester, Phoenix, Jacksonville) UCSF Duke University Moffitt Cancer Center MSKCC University of Pennsylvania Georgetown University	2018	404	41	*BRCA1* 58 *BRCA2* 42	56	34	0
Grobmyer *et al.* (present series)	Cleveland Clinic (Cleveland)	2018	272	40	*BRCA1* 45.6 *BRCA2* 25.7 *PTEN* 1.5 *TP53* 2.2 *ATM* 1.5 Family history 14·0 LCIS/atypia 7·4 History of mantle irradiation 2·2	53	38	0

NSM, nipple-sparing mastectomy; MSKCC, Memorial Sloan Kettering Cancer Center; n.d., not defined; n.a., not available; UCSF, University of California, San Francisco; VUS, variant of unknown significance; LCIS, lobular carcinoma *in situ*.

Table 2 Characteristics of patients with genetic syndromes undergoing risk-reducing bilateral nipple-sparing mastectomy

Mutation	No. of patients	Age at bilateral NSM (years)*	Follow-up (months)		Breast cancer during follow-up
			Mean	Median	
BRCA1 or *BRCA2*	97	39 (20–67)	30	42	0
PTEN	2	30 (25–35)	54	54	0
TP53	3	29 (20–40)	26	32	0
ATM†	2	48·5 (47–50)	30	30	0

*Values are median (range). †Patients also had a significant family history of breast cancer. NSM, nipple-sparing mastectomy.

Methods

Approval for this study was obtained by the Cleveland Clinic Institutional Review Board. Local databases were reviewed to identify patients who underwent risk-reducing bilateral NSM at Cleveland Clinic between 2001 and 2017. Patients found to have occult cancer at the time of surgery, those who underwent contralateral risk-reducing mastectomy, and patients with breast cancer or a history of breast cancer were excluded from the analysis. The decision to perform a risk-reducing bilateral NSM was made by the patient and surgeon. Technical aspects of the procedures have been described previously[4,5]. The absence of cancer in the bilateral mastectomy specimens was confirmed by routine histological analysis. Follow-up was from the date of surgery to the date of last clinical follow-up at Cleveland Clinic.

The electronic medical record was reviewed to confirm and update data relevant to the study. Temporal trends were evaluated over four time intervals (2001–2005, 2006–2009, 2010–2013 and 2014–2017) to facilitate analysis of the data over time. The short-term technical outcomes of bilateral NSM have been well documented[4,5,7,8,14] and are beyond the scope of this report.

Statistical analysis

Statistical analysis was performed with the χ^2 test using StatView® 4 (SAS Institute, Cary, North Carolina, USA). $P < 0{\cdot}050$ was considered statistically significant.

Results

A total of 136 patients (135 women and 1 man) underwent risk-reducing bilateral NSM between October 2001 and May 2017. Their median age was 41 (range 20–67) years. The number of patients having risk-reducing bilateral NSM increased over the study interval (*Fig. 1*).

The most common indication for risk-reducing bilateral NSM for patients in this series was mutation in a breast cancer-associated gene (104 patients, 76·5 per cent): *BRCA1*, 62 (45·6 per cent); *BRCA2*, 35 (25·7 per cent); *PTEN*, two (1·5 per cent); *TP53*, three (2·2 per cent); and *ATM*, two (1·5 per cent) (*Table 1*). Other indications were a strong family history of breast cancer (19, 14·0 per cent), lobular carcinoma *in situ*/atypia (10, 7·4 per cent) and a history of mantle field irradiation (3, 2·2 per cent). The proportion of patients who had a risk-reducing bilateral NSM for mutation in a breast cancer-associated gene increased significantly over the study interval (2001–2005: 2 of 12 patients; 2006–2009: 9 of 17; 2010–2013: 34 of 41; 2014–2017: 61 of 66) ($P < 0{\cdot}001$) (*Fig. 1*). A risk-reducing bilateral NSM for patients with genetic mutations was first performed for *BRCA*, *PTEN*, *TP53* and *ATM* in 2004, 2013, 2013 and 2015 respectively.

Mean and median duration of follow-up for all patients in the series was 53 and 38 (range 0·5–326) months respectively; 61 patients had follow-up for more than 4 years. Follow-up for patients in the series with mutations in breast cancer predisposition genes (*BRCA1*, *BRCA2*, *PTEN* and *TP53*) are shown in *Table 2*. No patient undergoing risk-reducing bilateral NSM in this series developed breast cancer during follow-up.

Discussion

NSM has the advantage of preserving the nipple and skin envelope to optimize cosmesis following mastectomy, and it facilitates the reconstruction process[7,21]. Patient satisfaction with the appearance of the nipple–areolar complex is high after NSM, and the majority of patients are satisfied with their decision to undergo NSM[21]. It has been shown[22] that NSM is associated with higher patient psychosocial and sexual well-being compared with that in patients having skin-sparing mastectomy with removal of the nipple–areolar complex. Others[23] have found no difference in satisfaction with overall outcome between patients having NSM and skin-sparing mastectomy with reconstruction. It is noteworthy that not all patients are optimal candidates for risk-reducing NSM, particularly those with significant ptosis, very large breast size or high BMI, and those who are active smokers.

The present large single-centre experience of NSM for breast cancer risk reduction reinforces the oncological safety of this procedure, as no breast cancers developed among patients in this series. In a series of 63 patients of similar age with *BRCA* mutations undergoing surveillance, 12 per cent had developed breast cancer at a mean follow-up of 2·9 years[3]. Other series that have documented breast cancer risk reduction associated with bilateral NSM in patients with *BRCA* mutations are summarized in *Table 1*. The present series documents that the procedure has been used increasingly over time for breast cancer risk reduction, similar to the recent report of Jakub and colleagues[16]. The increased use of risk-reducing bilateral NSM may reflect growing acceptance of the procedure by physicians and patients, improvements in the cosmetic outcomes of these procedures, and increasing awareness of genetic testing and its importance in managing high-risk patients.

The indications for risk-reducing bilateral NSM have evolved over the past 16 years. In early reports of patients having risk-reducing mastectomy (simple mastectomy, subcutaneous mastectomy or skin-sparing mastectomy), a strong family history and/or a personal history of high-risk breast lesions such as lobular carcinoma *in situ* or atypical hyperplasia were the primary indications[1]. These are similar to the indications for most patients in the present series earlier in the study. In more recent time periods, the indications have shifted to primarily those with germline genetic mutations.

Patients with *BRCA1* and *BRCA2* mutations have up to an 87 per cent lifetime risk of developing breast cancer. Most other series have focused on risk-reducing NSM only for patients with *BRCA1* and *BRCA2* mutations, which did represent the most common indication for risk-reducing bilateral NSM in the present series. It is noteworthy that patients with other genetic mutations associated with increased breast cancer risk (including *PTEN*, *TP53* and *ATM*) underwent risk-reducing bilateral NSM in this series from 2013. Patients with *PTEN*, *TP53* and *ATM* have a significantly increased breast cancer risk of up to 85, 90 and 60 per cent respectively[24–26]. This series is the first to document the use of risk-reducing bilateral NSM in patients with these mutations. Previous experience was limited to a case report[27]. No patient in the present series with a *PTEN*, *TP53* or *ATM* mutation developed breast cancer following risk-reducing bilateral NSM. As multigene panel testing continues in practice, and penetrance estimates become more precise, it is anticipated that bilateral NSM for other genetic indications will become more common[28].

Three patients in the present series had risk-reducing bilateral mastectomy for a previous history of mantle irradiation. Patients with a history such as this for childhood cancer are known to be at increased risk of breast cancer[29]. Moskowitz and colleagues[29] reported a cumulative incidence of breast cancer of 30 per cent by age 50 years in these patients. NSM with immediate reconstruction has been shown[30] to be safe in these patients with a previous history of chest wall or breast irradiation. This is the first reported series of patients having risk-reducing bilateral NSM for this indication. No patient with a prevous history of mantle irradiation in this series developed breast cancer during follow-up.

Risk-reducing bilateral NSM has increased over time and indications have shifted increasingly towards patients with documented genetic mutations. The present large single-institution series supports the oncological efficacy of risk-reducing bilateral NSM for a variety of indications, including *BRCA1/2* and other breast cancer-associated genes that are increasingly being recognized.

Disclosure

The authors declare no conflict of interest.

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