Nipple-sparing mastectomy in patients with *BRCA1/2* mutations and variants of uncertain significance

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Background: Nipple-sparing mastectomy (NSM) is associated with improved cosmesis and is being performed increasingly. Its role in *BRCA* mutation carriers has not been well described. This was a study of the indications for, and outcomes of, NSM in *BRCA* mutation carriers.

Methods: *BRCA* mutation carriers who underwent NSM were identified. Details of patient demographics, surgical procedures, complications, and relevant disease stage and follow-up were recorded.

Results: A total of 177 NSMs were performed in 89 *BRCA* mutation carriers between September 2005 and December 2013. Twenty-six patients of median age 41 years had NSM for early-stage breast cancer and a contralateral prophylactic mastectomy. Mean tumour size was 1·4 (range 0·1–3·5) cm. Sixty-three patients of median age 39 years had prophylactic NSM, eight of whom had an incidental diagnosis of ductal carcinoma *in situ*. There were no local or regional recurrences in the 26 patients with breast cancer at a median follow-up of 28 (i.q.r. 15–43) months. There were no newly diagnosed breast cancers in the 63 patients undergoing prophylactic NSM at a median follow-up of 26 (11–42) months. All patients had immediate breast reconstruction. Five patients (6 per cent) required subsequent excision of the nipple–areola complex for oncological or other reasons. Skin desquamation occurred in 68 (38·4 per cent) of the 177 breasts, and most resolved without intervention. Debridement was required in 13 (7·3 per cent) of the 177 breasts, and tissue-expander or implant removal was necessary in six instances (3·4 per cent).

Conclusion: NSM is an acceptable choice for patients with *BRCA* mutations, with no evidence of compromise to oncological safety at short-term follow-up. Complication rates were acceptable, and subsequent excision of the nipple–areola complex was rarely required.

Introduction

It is estimated that 55–65 per cent of women with a *BRCA1* mutation and 45 per cent of those with a *BRCA2* mutation will develop breast cancer by the age of 70 years[1]. Women diagnosed with breast cancer who are known to have, or are subsequently found to have, a *BRCA* mutation usually undergo mastectomy, even for early-stage breast cancer amenable to breast-conserving therapy, owing to the high risk of developing a second cancer in the ipsilateral breast[2]. A contralateral prophylactic mastectomy (CPM) is commonly performed, and has been shown to improve survival in this high-risk group[3]. In addition, many asymptomatic women known to be *BRCA* mutation carriers choose to undergo risk-reducing bilateral mastectomy with immediate breast reconstruction[4].

Nipple-sparing mastectomy (NSM) is a preferred option for many patients with breast cancer when specific tumour and patient factors allow for this approach. In comparison to skin-sparing mastectomy, the nipple-sparing approach may allow a superior cosmetic outcome and higher levels of patient satisfaction[5], although studies comparing patient-reported outcomes for both techniques are lacking[6]. Several studies[7–9] have shown that preservation of the nipple–areola complex (NAC) is oncologically safe with no increased risk of local recurrence in women with sporadic breast cancer. It is also an option for many

patients undergoing prophylactic mastectomy who are not limited by such tumour factors, such as asymptomatic *BRCA* mutation carriers; however, its role in this high-risk population has seldom been reported. Because NSM necessitates leaving a small amount of breast tissue behind the NAC to provide a blood supply, its oncological safety in *BRCA* mutation carriers is of particular concern. In the present study, the indications for NSM and outcomes in a large series of *BRCA* mutation carriers and some patients with variants of uncertain significance treated at Memorial Sloan Kettering Cancer Center (MSKCC) are presented.

Methods

Patients with a documented *BRCA* mutation undergoing mastectomy for treatment of breast cancer (therapeutic) or risk reduction (prophylactic) were given the option of nipple-sparing *versus* conventional skin-sparing mastectomy following consideration of several patient and, where relevant, tumour characteristics. Relative contraindications to NSM included smoking history, larger breast size and ptosis. For therapeutic mastectomy, patients with skin or nipple involvement, central tumours close to the NAC or blood-stained nipple discharge were excluded. Patients with tumour or microcalcifications less than 1 cm from the nipple were excluded for NSM. All patients interested in NSM discussed the risks and benefits of this approach with their breast surgeon and plastic surgeon before surgery.

Patients were informed of the risks associated with preservation of the NAC, including risk of inadequate blood supply leading to skin desquamation or necrosis, possibly necessitating subsequent debridement or complete excision of the NAC. Concerns regarding oncological safety of nipple preservation, including limited long-term data on local recurrence rates, were discussed with all patients, including those undergoing prophylactic mastectomy. Assessment of the retroareolar tissue by frozen or permanent section was discussed as appropriate. Patients having frozen-section examination were advised that a positive result (preinvasive or invasive cancer) would require excision of the NAC at the time of mastectomy, and a positive result on permanent section would require a second operation for excision of the NAC.

Surgical technique

The most commonly performed incision for NSM was circumareolar with radial extension if required; however, the actual incision was decided on an individual basis following discussions between patient, breast surgeon and plastic surgeon. Although 11 different breast surgeons

performed NSMs on *BRCA* mutation carriers at the institution from September 2005 to December 2013, most operations were performed by only three surgeons. Similar to conventional skin-sparing mastectomy, NSM was performed with the aim of removing all glandular breast tissue. Infiltration of the retroareolar tissue with 10 ml saline was performed frequently following induction of anaesthesia, to help develop the tissue plane between the breast tissue and the NAC. A section of retroareolar tissue (the 'nipple margin') was removed for either intraoperative frozen-section examination or routine permanent section as deemed appropriate. Immediate breast reconstruction was performed in all patients by a plastic surgeon with a special interest in breast reconstruction.

Patient follow-up

Patients attended breast surgery and plastic surgery clinics after surgery until fully recovered; each visit was documented in the patient's electronic medical record. Subsequently, patients continued to attend for annual follow-up with a breast examination by the breast surgeon and plastic surgeon. Ultrasound imaging was performed only if a palpable abnormality was found on breast examination.

Data collection and outcome measures

Following approval by the MSKCC institutional review board, a prospectively maintained breast surgery database was used to identify all women with a *BRCA* mutation who underwent NSM. The electronic medical record of each patient was accessed, and relevant data were abstracted. These included indications for surgery, type of *BRCA* mutation, family history of breast and ovarian cancer, and type of reconstruction. All progress and clinic notes were reviewed to identify patients with postoperative complications, including haematoma, skin desquamation, necrosis and infection. Details of all interventions performed were recorded, such as evacuation of haematoma, surgical debridement and implant removal. Indications for subsequent excision of the NAC were determined. All pathology reports were reviewed to record preoperative and postoperative findings, including frozen and permanent sections of retroareolar tissue (nipple margin). For patients undergoing NSM for breast cancer, tumour characteristics, lymph node status and overall American Joint Committee on Cancer disease stage were recorded. For all patients, length of follow-up was calculated, and status at last follow-up determined from review of clinic notes (no evidence of disease, alive with disease, died from disease, died from other cause, or died from unknown cause). Recurrence events were captured for local, regional and distant disease.

Results

A total of 177 NSMs were performed in 89 patients with a documented *BRCA* mutation or variant of uncertain significance between September 2005 and December 2013, representing 25·5 per cent of the NSMs performed during that interval. Only one patient underwent unilateral NSM; all other patients had a bilateral procedure. All patients had immediate breast reconstruction. Patient characteristics, mutation types and indications for surgery are shown in *Table 1*. Twenty-six therapeutic mastectomies were performed in 26 patients with breast cancer, 17 as the initial surgical treatment and nine completion mastectomies following initial lumpectomy. Some 151 prophylactic mastectomies were performed in 89 patients, including 26 contralateral operations in the 26 patients with breast cancer, 108 prophylactic mastectomies in 54 patients with no previous breast cancer, and 17 prophylactic mastectomies in nine patients with a previous history of breast cancer. There was an incidental finding of ductal carcinoma *in situ* (DCIS) in nine (6·0 per cent) of the 151 prophylactic mastectomies. This included four patients undergoing a contralateral prophylactic mastectomy and four who had a bilateral prophylactic mastectomy, one of whom was diagnosed with bilateral DCIS. In addition, there was an incidental finding of atypia in eight prophylactic mastectomies (5·3 per cent). There was no incidental finding of invasive breast cancer.

Assessment of retroareolar tissue and excision of the nipple–areola complex

Assessment of the retroareolar tissue for evidence of disease differed between patients undergoing prophylactic and therapeutic NSM. In 23 of 26 therapeutic mastectomies for breast cancer, a separate nipple margin was excised for assessment; eight were sent for intraoperative frozen-section examination, all of which were negative and confirmed as negative on subsequent permanent section. One of the 23 samples assessed by permanent section in a patient with multicentric DCIS showed DCIS present less than 1 mm from the inked resection margin. This patient returned for excision of the NAC; no further DCIS was identified. One of the three patients who did not have excision of a separate nipple margin was found to have DCIS at the retroareolar ducts of the mastectomy specimen, and decided not to return for excision of the NAC.

For prophylactic NSM, a separate nipple margin was excised in 96 of 151 mastectomies. None was assessed by intraoperative frozen-section examination, and there was an unexpected diagnosis of DCIS in the nipple margin permanent section in two instances. In the first of these, there was an incidental finding of DCIS (single focus)

Table 1 Patient population

	n*
No. of women	89
No. of NSMs	177
Median (range) age (years)	
Prophylactic NSM	39 (25–59)
Therapeutic NSM	41 (26–59)
BRCA mutation type (n = 89)	
BRCA1	56 (63)
BRCA2	26 (29)
Genetic variant of uncertain significance	7 (8)
Family history (n = 89)	
Breast cancer	81 (91)
Ovarian cancer	36 (40)
Breast and ovarian cancer	32 (36)
Neither breast nor ovarian cancer	4 (4)
Indication for NSM (n = 177)	
Therapeutic	26 (14·7)
Current breast cancer	17 (65)
Completion mastectomy	9 (35)
Prophylactic	151 (85·3)
Contralateral prophylactic mastectomy	26 (17·2)
Prophylaxis (history of breast cancer)	17 (11·3)
Prophylaxis (no previous breast cancer)	108 (71·5)
Mean (range) tumour size (cm)†	1·4 (0·1–3·5)
T category (n = 26)	
Tis	6 (23)
T1	15 (58)
T2	5 (19)
N category (n = 26)	
N0	25 (96)
N0(i+)	1 (4)
Breast cancer stage (n = 26)	
0	6 (23)
I	15 (58)
II	5 (19)
III	0 (0)
IV	0 (0)
Molecular profile of patients with invasive breast cancer (n = 20)	
ER+/PR+, HER2−	11 (55)
ER+/PR+, HER2+	1 (5)
ER−/PR−, HER2+	1 (5)
ER−/PR−, HER2−	7 (35)
Type of reconstruction (n = 89)	
Tissue expander	80 (90)
Permanent implant	8 (9)
Autologous (DIEP) flap	1 (1)

*Number of women or tumours with percentages in parentheses, unless indicated otherwise. †For all patients undergoing therapeutic nipple-sparing mastectomy (NSM). ER, oestrogen receptor; PR, progesterone receptor; DIEP, deep inferior epigastric perforator.

in the retroareolar tissue of one breast, and the patient returned for excision of both NACs. No further disease was evident in the resected specimens. Similarly, in the second, a small focus of DCIS was identified in the nipple margin, but the patient decided not to return for excision of the NAC. She had no evidence of disease after more than 5 years of follow-up. In addition, one further patient

Table 2 Postoperative complications and reoperations in patients with breast cancer/*BRCA* mutation carriers undergoing nipple-sparing mastectomy during an 8-year period

	No. of breasts (*n* = 177)	No. of women (*n* = 89)
Excision of NAC	8 (4·5)	5 (6)
Necrosis requiring debridement	13 (7·3)	9 (10)
Infection	7 (4·0)	7 (8)
Haematoma	3 (1·7)	3 (3)
Complication requiring implant/tissue expander removal	6 (3·4)	6 (7)

Values in parentheses are percentages. NAC, nipple–areola complex.

with an incidental diagnosis of DCIS in both breasts, including retroareolar ducts on one mastectomy specimen, decided to have excision of both NACs despite negative nipple margins bilaterally. There was, however, no further evidence of disease in the resected specimens.

One patient who had bilateral prophylactic NSM complained of milk-like discharge from both nipples 1 year later, following childbirth. This patient returned for bilateral NAC excision. Another patient required a salvage latissimus dorsi reconstruction following infection that resulted in nipple necrosis and implant loss. There was no evidence of disease in any of these three resected NACs. In total, five (6 per cent) of the 89 patients underwent unilateral or bilateral excision of the NAC; the final pathology of the excised NAC was negative in all these patients.

Follow-up

Median follow-up for patients undergoing therapeutic NSM and prophylactic NSM was 28 (i.q.r. 15–43) and 26 (11–42) months respectively. In the therapeutic group, there were no local or regional recurrences, but two patients died. One patient was diagnosed with distant metastases 2 years after NSM for stage IIA breast cancer and died from her disease. The other patient died from metastatic ovarian cancer 3 years after NSM for DCIS. In the prophylactic group, there were no new diagnoses of breast cancer and or deaths during the follow-up period.

Complications

Some degree of skin desquamation was noted following NSM in 68 breasts (38·4 per cent) in 40 patients (45 per cent) during postoperative follow-up. This ranged from superficial epidermolysis to full-thickness necrosis requiring debridement, and most cases resolved fully on subsequent follow-up with no need for intervention. The most common complication was nipple–areola or flap

necrosis, which occurred in 13 breasts (7·3 per cent), and there were seven instances of infection (4·0 per cent). A combination of flap necrosis and infection resulted in implant loss from six breasts (3·4 per cent). A summary of surgical complications is shown in *Table 2*.

Discussion

Preservation of the NAC allows an improved cosmetic outcome, and there is evidence that this procedure is associated with higher psychosocial and sexual well-being compared with the more traditional skin-sparing mastectomy with or without nipple reconstruction (C. H. Wei *et al*., unpublished results). *BRCA* mutation carriers often undergo bilateral mastectomy for breast cancer treatment or as risk-reducing surgery, but the high breast cancer risk associated with these mutations understandably leads to concern among patients and physicians regarding the oncological safety of NSM.

In this study, NSM was performed successfully in almost all patients, with only eight (4·5 per cent) of 177 breasts subsequently requiring excision of the NAC. This was done for oncological reasons (to rule out residual DCIS following assessment of the separate nipple margin or the retroareolar ducts of the breast) in only three (1·7 per cent) of 177 breasts, and all excised NACs were negative for further disease. The overall rate of NAC loss of 4·5 per cent is lower than that observed in an earlier study[10] of NSM at MSKCC between 1998 and 2008, which reported NAC loss in ten (8·7 per cent) of 115 breasts, for occult disease (6) and wound-healing problems (4). All patients in this study undergoing therapeutic NSM had early-stage breast cancer with a mean tumour size of 1·4 cm. These factors would, of course, increase the likelihood of successful NSM, and only one patient undergoing therapeutic NSM had subsequent excision of the NAC. It is interesting that for the other two patients who had excision of the NAC owing to concerns regarding further disease, and for one further patient who declined excision, DCIS was an incidental finding following prophylactic NSM. Although this occurred in only three cases (2 in the nipple margin and 1 in the retroareolar ducts of the breast specimen), it highlights the importance of focused retroareolar tissue assessment and designation of a separate nipple margin even in *BRCA* mutation carriers undergoing prophylactic NSM. This procedure was performed in 96 of 151 prophylactic NSMs in this study, and the incidental diagnosis of DCIS in two (2 per cent) of 96 nipple margins justifies sending a separate nipple margin for permanent section in all *BRCA* mutation carriers undergoing prophylactic NSM.

The type of breast reconstruction performed in this group of patients was almost exclusively implant-based, with only one of 89 patients undergoing autologous flap reconstruction. This is consistent with a national trend in the USA towards increasing use of implant-based reconstruction and a decline in autologous reconstruction[11]. In addition, it is known that patients undergoing bilateral mastectomy are more likely to choose implant-based reconstruction[12], and 88 of 89 patients in the present study had a bilateral procedure.

Careful review of all follow-up clinic notes revealed that many patients in this study had some degree of skin desquamation (38·4 per cent of breasts); however, this was mostly superficial and reversible, with complete resolution on subsequent follow-up in most instances. Debridement was required, however, in 13 (7·3 per cent) of the 177 breasts, and this was performed either in the clinic under local anaesthesia or in the operating room. Although this included some cases of mastectomy skin flap necrosis, separate from the NAC, these were in the minority. The observed rate of skin flap necrosis in the present study is higher than published rates following skin-sparing mastectomy[13], which is not an unexpected finding, as the preserved NAC is particularly prone to vascular compromise following NSM, and the rates are similar to that reported by Peled and colleagues[14]. Patients are counselled before surgery regarding this risk, and are made aware that attempted removal of all glandular breast tissue inevitably results in thin mastectomy skin flaps, and that this is essential to minimize the risk of local recurrence or new primary breast cancer development in this high-risk population. It is reassuring, however, that only one patient in the present study ultimately required excision of the NAC due to necrosis and infection (0·6 per cent of breasts), compared with four instances (3·5 per cent) in an earlier report of NSM at MSKCC[10], possibly reflecting improvements in the technique and management of skin compromise with an increasing volume of procedures over time. The infection rate of 4·0 per cent was similar to that expected following skin-sparing mastectomy[13]. Patients can be warned before surgery that some degree of flap compromise is likely; however, most cases resolve fully with conservative management, and the risk of requiring debridement or removal of the NAC is low.

Twenty-six of 89 patients in this study underwent NSM for treatment of breast cancer, and there were no local or regional recurrences during a median follow-up of 28 months. All had early-stage node-negative disease, and one patient had isolated tumour cells on sentinel lymph node biopsy. This most likely reflects intensive screening of these patients with annual MRI and mammographic surveillance leading to early diagnosis, rather than a reluctance to perform NSM in patients with node-positive disease. Although the median follow-up of 28 months is short, studies[15,16] have shown that this time interval is associated with the highest risk for local recurrence following treatment of primary breast cancer. A review[15] of all mastectomies performed at MSKCC during a 4-year period, with a median follow-up of 6 years, showed that the median time to first local or regional recurrence was 1·8 years. The absence of any local or regional recurrences during the 28-month follow-up supports the view that NSM is oncologically safe in this patient group, but it is important to recognize the limitations of this study and that a longer follow-up in more patients is needed. In a similar study by Yao and colleagues[17], three of 51 *BRCA1/2* mutation carriers undergoing NSM for breast cancer had developed local or regional recurrence at mean follow-up of 32·6 months. One patient had a local recurrence and two had axillary lymph node recurrence. Of note, there were no recurrences at the NAC.

In addition to the risk of true local recurrence following mastectomy, the risk of a new primary breast cancer developing in residual breast tissue is of particular concern in the high-risk group of *BRCA* mutation carriers undergoing prophylactic or therapeutic mastectomy, and is regarded by some as a reason to avoid NSM in these patients. Only a few studies have reported on the incidence of new primary breast cancer postmastectomy in *BRCA* mutation carriers, and these have not shown an increased risk in such patients. Domchek and co-workers[18] reported that none of 247 *BRCA* mutation carriers undergoing prophylactic skin-sparing mastectomy developed breast cancer during a 3-year follow-up. In a smaller series of 26 *BRCA* mutation carriers undergoing skin-sparing mastectomy, Hartmann *et al.*[19] similarly reported that none developed breast cancer at 13 years' follow-up. More recently, Peled and colleagues[14] reported that none of 26 patients undergoing prophylactic NSM developed a new primary breast cancer at 51 months of follow-up, and Yao *et al.*[17] reported the development of a new breast cancer in only one of 150 *BRCA1/2* mutation carriers undergoing NSM for risk reduction. Although the present study had a relatively short follow-up of 26 months, it adds further support to this technique, as none of the 89 patients who had prophylactic NSM developed a new primary breast cancer during this time.

Within this large study of *BRCA* mutation carriers undergoing NSM, only 6 per cent of patients and 4·5 per cent of breasts subsequently required excision of the NAC for the finding of unexpected carcinoma or surgical complications. During the 26-month follow-up, there were no local or

regional recurrences, or new cancers, supporting the view that this procedure can be performed safely in patients with *BRCA* mutations or genetic variants of uncertain significance, although a larger cohort and longer follow-up are needed to determine the risk of subsequent cancers in the retained breast tissue.

Acknowledgements

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