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Original article

Nipple-sparing bilateral prophylactic mastectomy and immediate reconstruction with TiLoop® Bra mesh in BRCA1/2 mutation carriers: A prospective study of long-term and patient reported outcomes using the BREAST-Q

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ABSTRACT

Background: Although demand for prophylactic mastectomy is increasing over time among women at a high risk for breast cancer, there is a paucity of studies on long term patient-reported outcomes after this procedure.
Methods: Between January 2011 and January 2015, 46 patients documented BRCA1/2 mutation carriers, eligible for prophylactic nipple-sparing mastectomy (NSM) and immediate breast prosthetic reconstruction were registered at our Institution. Patients underwent NSM and subcutaneous reconstruction with implant covered by a titanium-coated polypropylene mesh (TiLoop®). The BREAST-Q questionnaire was given to patients prior to surgery and at 1 and 2 years follow-up points. Capsular contracture was evaluated by Baker scale. Surgical outcomes along with the changes in BREAST-Q score were analyzed over time.
Results: Complications were reported in only one case and after two years the capsular contracture rates were acceptable (grade I: 65,2%; grade II: 32,6%; grade III 2,2%). At one year and two year follow-ups patients reported high rates in the measures of overall satisfaction with breasts (72,5 and 73,7 respectively), psychosocial well-being (78,4 and 78,6), sexual well-being (58,8 and 59,4), physical well-being (77,6 and 80,6) and overall satisfaction with outcome (75,7 and 79,7). A statistically significant increase in all BREAST-domains from the preoperative to the postoperative period was reported at one and two years follow-ups ($p < 0,05$).
Conclusion: Following bilateral prophylactic NSM and immediate subcutaneous reconstruction with TiLoop®, patients demonstrated high levels of satisfaction and quality of life as measured by BREAST-Q. 2-years outcomes confirmed high patient comfort with increased scores from the preoperative baseline level.

1. Introduction

Considerable efforts have been made over the past decades toward the development of surgical management of breast cancer [1,2]. Surgical targets have rapidly evolved, aiming to optimize cosmetic outcomes and reduce patient morbidity, while still providing an oncologically-safe surgical procedure [3–6]. Surgeons moved from the radical mastectomy to the acceptance of breast conservation and aesthetic outcomes improvement as the achievable goals of surgical procedures. Skin sparing mastectomy (SSM)

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and Nipple sparing mastectomy (NSM) have low local recurrence rates, comparable with total mastectomy and allows for immediate breast reconstruction [2]. Several studies revealed similar survival outcomes for NSM patients compared to SSM patients in the cancer setting and NSM has also shown favorable outcomes for risk reduction (RR) surgery [3].

Though NSM has been validated as an oncologically safe option, there are still some concerns regarding the risk of tumor recurrence in patients at the highest risk of breast cancer, such as BRCA1/2 mutation carriers [3]. It is reported that the risk of developing breast cancer in women with a BRCA1/2 mutation is of between 60 and 80% and that prophylactic mastectomy reduce the risk of breast cancer by up to 95% [7–9]. Due to the lack of long-term outcomes data in literature, the adoption of NSM in this patient population remains a subject of controversy. A recent study on 201 BRCA1/2 mutation carriers reported that NSM is associated with a low rate of complications and risk of breast cancer, comparable with SSM [3].

Although there is a growing body of evidence on oncologic and surgical safety of NSM, in this group of women, there is a paucity of studies on patient-reported outcomes. Few studies have examined the impact of nipple preservation, following nipple sparing prophylactic mastectomy (NSPM) and immediate breast reconstruction on health-related quality of life (HRQOL) [4–6,8–10]. Previous evaluations of patient outcomes after NSM have shown high levels of satisfaction, but these studies have all been somewhat limited by their retrospective design and heterogeneous or small sample size populations. The increased demand for NSM highlight the need for objective evaluation of HRQOL outcomes [11,12].

The aim of this study was to determine whether NSM, with immediate breast reconstruction using silicone implants and TiLoop® Bra mesh, could be established as a safe procedure and examine how HRQOL is influenced by nipple-areola complex preservation in a BRCA1/2 mutation carrier population. We prospectively evaluated the HRQOL using the BREAST-Q, a validated patient-reported outcome instrument developed specifically for patients undergoing breast reconstruction.

2. Materials and methods

2.1. Patients

Between January 2011 and January 2015, patients with proven BRCA1 or BRCA2 gene mutation, undergoing prophylactic bilateral mastectomy at our institution, Azienda Ospedaliero-Universitaria Careggi, were enrolled for this study. These women, wanted and were suitable for nipple-sparing mastectomy and immediate breast prosthetic reconstruction; patients with “variants of uncertain significance” BRCA1/2 gene mutations were excluded. Inclusion criteria were documented BRCA1/2 mutation, body mass index (BMI) between 25 and 35 kg/m^2, no previous breast surgery, no evidence of cancer on clinical examination or imaging (magnetic resonance imaging (MRI), mammogram and ultrasound) and suitability for immediate reconstruction with subcutaneous implants. Prior to surgery, all patients were evaluated for both autologous or alloplastic breast reconstruction, taking into account patient preference, body habitus, co-morbidities and prior abdominal surgery. We enrolled in this study only patients willing to undergo prosthetic breast reconstruction, who refused autologous reconstruction or presenting any contraindication to these procedures. This study was approved by our institutional Ethics Committee and all patients provided written informed consent.

2.2. Operative technique

We have previously published our surgical technique for NSM and immediate reconstruction with implant and TiLoop® Bra mesh [13–15]. Briefly, the mastectomy was performed through an inframammary or lateral incision and skin flaps were raised in the subdermal plane. Once the breast tissue had been resected, the nipple tissue was cored out, while preserving the NAC skin. The excised tissue along with a specimen of the tissue underlying the NAC was sent to the pathologist for definitive histological evaluation. Patients underwent immediate reconstruction through definitive implant placement using a titanium-coated polypropylene mesh (TCPM), specifically TiLoop® Bra (TiLOOP® Bra, pfm medical, Cologne, Germany). The skin flaps were assessed and when considered adequate, after confirming definitive implant with a sizer, a TiLoop® Bra mesh bag was adjusted around the implant. Using absorbable sutures, a TiLoop® sheet was folded onto itself to create a bag which eventually functioned as a pocket for the breast implant. In the case of larger implants, two TCPM sheets were used and stitched together. The TCPM bag, with the implant inside, was then placed in a totally subcutaneous pre-pectoral position. Medial and lateral borders were secured to the muscular fascia with interrupted absorbable sutures. One vacuum drain was inserted in the inframammary fold and patients received oral antibiotics until surgical drains were removed. Patients were evaluated every two weeks for the first 2 months and follow-up visits were performed every 2 months thereafter. All the procedures were performed by the same surgeons.

2.3. Outcomes and measures

A secure digital database was prospectively created in order to collect data on patient demographics, BRCA mutation, medical history, family history, surgical complications and capsular contracture. Surgical complications were named as implant removal, skin-nipple necrosis, seroma, wound dehiscence, surgical site infection and hematoma. HRQOL and cosmetic outcome evaluation were conducted using the preoperative and the postoperative BREAST-Q modules for reconstructive surgery [16–24]. Enrolled patients received the preoperative questionnaire from the BREAST-Q reconstructive module after consultation with both the surgical oncologist and the plastic surgeon one month before the mastectomy. Patients were required to answer The BREAST-Q postoperative module at 1 and 2 years after mastectomy. At these time points, surveys were given directly to patients during their scheduled clinic visit. All aspects of the BREAST-Q reconstructive module (Satisfaction with Breasts, Satisfaction with Outcome, Psychosocial Well-being, Physical Well-being and Sexual Well-being) were included with exception of questions regarding abdominal donor site.

In keeping with the developers' guidance, patients who failed to answer more than half the items within each domain were excluded from the analysis for that particular domain [16,23,24].

Baker Scale was used for scoring capsular contracture during postoperative follow-ups, at one and two years after mastectomy. The completed questionnaires were reviewed by the senior authors (RD, CE) and our co-authors from the Breast Unit of Guy's Hospital, London.

2.4. Statistical analysis

Descriptive statistic accounted for patient sociodemographic, clinical characteristics, complications and capsular contracture grade. Using the QScore Scoring Software, BREAST-Q scores were converted from survey raw scores (1 through 4 or 5) to a continuous range from 0 to 100, with a higher score representing greater satisfaction or better HRQOL. The scores for each BREAST-Q matrix indexes were determined at each time point and then entered into

the database, along with the other data collected from patients and medical records. Both absolute BREAST-Q scores and changes in scores before and after treatment were analyzed. The Shapiro-Wilk test was used to verify for normal distribution of continuous variables. Consequently, Breast-Q scores were analyzed using Student *t*-distribution. P values less than 0.05 were considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 46 women BRCA1/2 mutation carriers were enrolled in to this study. Table 1 describes the demographic characteristics of participants. The 91,3% of the patients was Caucasian and the mean age at the time of NSPM was 43,2 years (range 23–65 years). The mean BMI was 28,4 kg/m^2 (range 25–35 kg/m^2). The mean time interval from patients' mutation diagnosis to surgery was 7.3 months (range 4–14 months). The drain was removed between the fourth and ninth postoperative day (mean value: 6,5 days). Complications were recorded in 1 patient, who developed necrosis of the breast skin flaps that required explantation. She underwent revision reconstruction using sub-pectoral expanders, followed by second stage replacement of the expander by definitive breast implant and lipofilling after 6 month. There were no cases of NAC necrosis and one patient had positive histological evaluation at the definitive analysis. Incidental stage 0, non invasive breast cancer was found in 1 patient. We did not detect any cases of severe capsular contracture (grade IV) at both follow-up points and, after two years, 30 patients were evaluated as grade I (65,2%), 15 patients as grade II (32,6%) and 1 patients grade III (2,2%). After one year in 7 cases an additional intervention in the form of lipofilling was required for either, visible implant creasing or implant edge palpability [25,26]. The mean volume of injected fat was 20,3 ml per breast. A one year follow-up clinic visit was scheduled in all cases before a second operation (Figs. 1 and 2).

3.2. Measure of HRQOL

All patients adequately answered for the five domains of the questionnaire. Tables 2 and 3 show the self-reported measures of HRQOL, evaluated with BREAST-Q questionnaire, at the preoperative setting compared to 1 year and 2 years respectively, after reconstruction. Significant increases from the base line were reported in the domains for overall satisfaction with breasts ($p < 0,05$), psychosocial well-being ($p < 0,05$) and sexual well-being ($p < 0,05$) at both follow-ups. The scores tended to improve overtime at the second follow-up. The measure for physical impact of the surgery declined from the preoperative to postoperative evaluations, but this was not observed to be statically significant. Overall satisfaction with outcome index, measured postoperatively, was higher and improved over time throughout the post-operative period, but this was not significant ($p = 0,091$).

Table 1
Demographic characteristics.

Patient characteristic	All patient (46)
Age [years, mean (range)]	43,2 (23–65)
BMI [kg/m^2, mean (range)]	28,4 (25–35)
Ethnicity (n, %)	
Caucasian	42 (91,3)
Hispanic	2 (4,3)
Asian	2 (4,3)
Marital status (n, %)	
Married	27 (58,7)
Divorced	4 (8,7)
Separated	2 (4,3)
Single	13 (28,3)
Comorbidities (n, %)	
Diabetes	3 (6,5)
Connective tissue diseases	1 (2,1)
Smoking (n, %)	
Never smoker	28 (60,9)
Past smoker	10 (21,7)
Active smoker	8 (17,4)
BRCA Mutation (n, %)	
BRCA1	30 (6,52)
RCA2	16 (34,8)

4. Discussion

Consequent to extensive coverage by the media there is an enhanced awareness amongst women about hereditary breast cancer. Newer testing guidelines and patient choice has led to an increase in BRCA mutation testing and genetic counseling, allowing patients to consciously consider prevention and therapy-related complications, while making decisions about surgical management of breast cancer [27–31]. The number of women seeking gene testing continues to rise and in Italy some medical societies are claiming implementation of specific health pathways, targeting toward early diagnosis and reduction of BRCA-related cancer risk rate [32]. Italian press named “right of gene” the request of introducing BRCA mutations screening among the basic healthcare services the national health system provides by law.

For women at highest risk for breast cancer, risk-reducing surgery has been associated with the greatest potential benefit in terms of decreasing the chance of developing breast cancer and demand for prophylactic mastectomy is increasing over time amongst this cohort of women [3]. In this regard, the value of a spared NAC for women psychological and sexual functions has been described before. However, little is known about the impact of these risk-reducing strategies on quality of life, and more research is needed in order to achieve robust and sound scientific evidence [3–8].

Our prospective study looks at the immediate and long term surgical and BREAST-Q outcomes for a series of 46 patients who underwent NSM and immediate reconstruction with TiLoop® Bra mesh. Our data demonstrates the safety and reliability of this technique, reporting satisfactory long term results with low complication rates and high patient satisfaction. 2-year outcomes for quality of life confirm high patient satisfaction following prophylactic mastectomy and suggest that NSM and TiLoop® immediate pre-pectoral breast reconstruction has the potential for providing a valid and safe aesthetic alternative. Furthermore, 2 years following surgery, patients reported significantly high scores in the self-reported measures of overall satisfaction with breasts (73,7), psychosocial well-being (78,6) and sexual well-being (59,4). The patients demonstrated a significant increase in self-reported measures from the preoperative to the postoperative period at one and two years follow-ups. All the postoperative data were evaluated both in absolute terms and in relation to preoperative results, as changes in scores were considered a more reliable and comparable measurement. Indeed, recently Howard et al. prompted to define the precise “minimally important differences” for BREAST-Q scores and proposed new baseline scores for BREAST-Q results in NSM surgery [5]. This study prospectively analyzed a heterogeneous population of 39 patients undergoing NSM for cancer treatment ($n = 17$) or (Risk Reducing) RR ($n = 22$) and immediate 1- and 2-stage implant or autologous immediate breast reconstruction and demonstrated high levels of satisfaction and quality of life as measured by BREAST-Q [5]. Another prospective

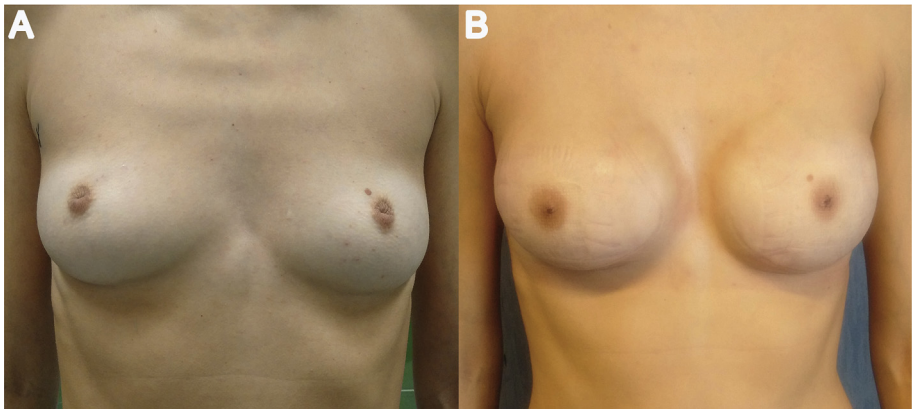

Fig. 1. A 42-year-old woman who underwent bilateral prophylactic NSM (inframammary fold incision) and direct-to-implant reconstruction: preoperative (left) and 2 year's postoperative (right).

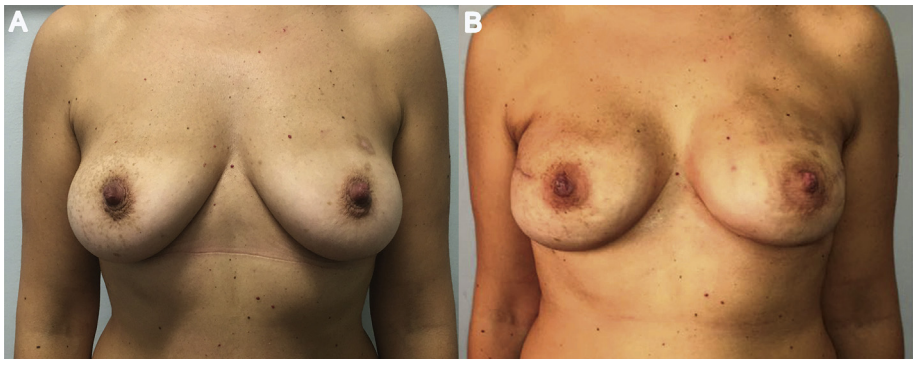

Fig. 2. A 38-year-old woman who underwent bilateral prophylactic NSM (lateral incision) and direct-to-implant reconstruction: preoperative (left) and 3 months' postoperative (right).

study designed by Peled at al, reported preoperative and one year follow-up outcomes of 28 NSM patients undergoing RR or cancer treating mastectomy and expander-implant reconstruction, evaluated with the BREAST-Q [4]. Other studies adopted BREAST-Q questionnaire for evaluating patients following NSM, but this was collected retrospectively and almost all the authors applied only the postoperative modules [6,10,21,22,33]. Furthermore as populations of these studies encompass woman with different characteristics, undergoing mastectomy for either therapeutic or prophylactic reasons and reconstruction with several techniques, it would be incongruous comparing our results with the measures provided by other authors. As postulated by Howard, preoperative measurements of breast health, psychosocial well-being, and sexuality establish a baseline measurement with which to determine if surgery decreases or increases these quality of life outcomes [5]. We agree that without a baseline measurement it is impossible to know if a score, even if high or at a long term follow-up after surgery, is actually a change from the baseline score. Nevertheless, our scores correlated well with the data from Howard's study, regarding only the small cohort of patients (n = 22) undergoing RR mastectomy [5].

Interestingly, as previously reported by other studies, we found in our clinical practice that RR and cancer patients who apply BREAST-Q questionnaire routinely at our institution scored relatively similar preoperative values (data not shown) [4,5]. It is possible that a new diagnosis of BRCA1 or 2- gene mutation would have a similar negative psychological impact as a cancer diagnosis in our patients series. Following this hypothesis, patients at high risk for breast cancer behave as they feel carriers of a disease rather than a simple gene mutation, affecting their psychological status and social life. However, RR patients scored high BREAST-Q results at 1-year and 2-years follow-up and expressed great overall satisfaction with outcome. We mainly ascribe these results to the relief experimented by patients after breast removal due to the decreased

Table 2
BREAST-Q scores recorded preoperatively and one year postoperatively, expressed as mean ± standard deviation. Changes in scores are expressed as delta (postoperative score minus preoperative score). *P < 0,05.

Domain	Preoperative mean (±SD)	Postoperative mean (±SD)	Delta mean	p-value
Satisfaction-breasts	59,3 (±12,2)	72,5 (±10,1)	13,2	0.0033*
Psychosocial wellness	66,4 (±13,7)	78,4 (±13,3)	12	0.0132*
Sexual well-being	52,7 (±14,4)	58,8 (±12,6)	6,1	0.0253*
Physical impact (chest)	80,9 (±10,4)	77,6 (±14,2)	−3.3	0.0984
Overall satisfaction with outcome	–	75,7 (±12,3)	–	–

Table 3
BREAST-Q scores recorded preoperatively and two year postoperatively, expressed as mean ± standard deviation. Changes in scores are expressed as delta (postoperative score minus preoperative score). *P < 0,05.

Domain	Preoperative mean (±SD)	Postoperative mean (±SD)	Delta mean	p-value
Satisfaction-breasts	59,3 (±12,2)	73,7 (±9,8)	14,4	0.0145*
Psychosocial wellness	66,4 (±13,7)	78,6 (±13,7)	12,2	0.0193*
Sexual well-being	52,7 (±14,4)	59,4 (±13,5)	6,7	0.0179*
Physical impact (chest)	80,9 (±10,4)	80,6 (±13,6)	−0,3	0.0846
Overall satisfaction with outcome	–	79,7 (±11,8)	–	–

likelihood of developing a breast cancer rather than to the simple breast aesthetic outcome. Indeed, in our study only three patients required a breast augmentation, while the others were satisfied with their breast shape and volume and did not ask for an augmentation. We believe that the reported increased scores could result as a merge of both the reduced risk of breast cancer concerning the patients and the acceptable aesthetic result provided by the subcutaneous reconstruction.

NSM and immediate breast reconstruction offers a safe option, providing a fast recovery and an appealing alternative from both an aesthetic and psychological point of view, improving cosmesis following mastectomy. In our opinion, among different reconstructive techniques, immediate one-stage reconstruction is a valid choice for preserving women's quality of life after mastectomy. In particular subcutaneous prosthetic reconstruction with TiLoop® Bra mesh guarantees higher levels of patient-reported outcomes [13–15]. The main advantages of this technique are the preservation of the pectoralis major muscle with reduced or absent muscular pain and a comparable rate of other minor complications, less invasiveness, reduction of surgical times (one-stage technique), early discharge and rapid recovery [13–15].

Furthermore in our study, we reported low complication rates. Comparing to cancer treating surgery, this good rate could be ascribed to several factors. First, our patients are mutation carriers undergoing prophylactic bilateral mastectomy for risk reducing purpose. Therefore, they did not undergo any chemotherapy or radiotherapy, which have been associated to an increased rate of postoperative complication, such as delayed healing, wound dehiscence, skin flaps and nipple necrosis and severe capsular contracture [27,28,34,35]. Another possible explanation of the low complications rate could rely on our subcutaneous reconstructive technique [34]. Indeed, it requires short intraoperative time. Tiloop does not require any rehydration or long treatment before use with an estimated setting time as low as 3–5 min, reducing the intraoperative time of exposure of the implant and the mesh, along with the possibility of intraoperative contamination and infections.

Nevertheless, we consider that our follow-up is short for drawing conclusion in the setting of capsular contracture and other implant-related complications; we believe that our complications rate could increase over time and we strictly follow up patients for contracture evaluation.

To our knowledge, this is the first study prospectively evaluating long-term outcomes after bilateral NSM and immediate breast reconstruction in a population of BRCA1/2 mutation carriers, applying BREAST-Q questionnaire to preoperative and postoperative points and analyzing scores and their changes over time. Indeed patients showed high levels of overall satisfaction with outcome and wellness. We believe that our data could help clinicians in counseling women at high risk for breast cancer and provide patients with reliable outcomes after prophylactic mastectomy.

Acknowledgments and conflict of interest

The authors have no commercial, proprietary, or financial interest in the products or companies described in this article. Our study was performed with respect to the ethical standards of the Declaration of Helsinki, as revised in Tokyo 2004. The study complies with the policy of the journal on ethical consent.

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