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ORIGINAL ARTICLE – BREAST ONCOLOGY

Update on the Feasibility and Progress on Robotic Breast Surgery

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ABSTRACT

Background. Robotic nipple-sparing mastectomy (RNSM) may allow for more precise anatomic dissection and improved cosmetic outcomes over conventional open nipple-sparing mastectomy; however, data regarding the feasibility and safety of the procedure are limited.

Objective. The aim of this study was to present and discuss perioperative surgical outcomes and early oncologic follow-up data on consecutive patients undergoing RNSM from June 2014 to January 2019.

Methods. Patients underwent RNSM and immediate robotic breast reconstruction through an axillary incision at a single institution. Perioperative data, complications at 3 months postoperatively, pathological data, and adjuvant therapies were recorded. Local recurrence-free, disease-free, and overall survival were analyzed.

Results. Overall, 73 women underwent 94 RNSM procedures. Indications were invasive breast cancer in 39 patients, ductal carcinoma in situ in 17 patients, and BRCA mutation in 17 patients. Mean surgery time was 3 h and 32 min. One-step reconstruction with implant occurred in 89.4% of procedures. The rate of complications requiring reoperation was 4.3%, and the rate of flap or nipple necrosis was 1.1%. Median follow-up was 19 months (range 3.1–44.8). No local recurrences occurred. Overall survival at 12, 24, or 60 months was 98% (95% confidence interval 86–100%).

Conclusion. We observed a low complication rate in 94 consecutive RNSM procedures, demonstrating the procedure is technically feasible and safe. We found no early local failures at 19 months follow-up. Long-term follow-up is needed to confirm oncologic safety. Future clinical trials to study the advantages and disadvantages of RNSM are warranted.

Nipple-sparing mastectomy is increasingly performed for the treatment and prevention of breast cancer and has acceptable oncologic outcomes in appropriately selected patients[1–4] The challenge of nipple-sparing mastectomy is achieving adequate exposure to perform precise dissection in areas that are remote from the skin incision. Robotic nipple-sparing mastectomy (RNSM) was developed in order to allow for enhanced visualization of tissue planes and better access to areas that are difficult to reach through conventional open nipple-sparing mastectomy incisions. Utilizing an incision off the breast in the mid-axillary line, the aim of RNSM was to achieve superior technical and cosmetic results while maintaining the same oncologic principles of standard mastectomy (i.e. anatomic dissection planes and removal of breast en bloc).[5–14]

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TABLE 1 Patient demographics/preoperative parameters [*N* = 73]

Age, years	
Mean	42
Median	42
Range	24–59
Body mass index (kg/m^2)	
Mean	20.5
Median	20.5
Range	16.4–24.4
Menopausal status [*n* (%)]	
Premenopausal	54 (74.0)
Postmenopausal	13 (17.8)
Perimenopausal	6 (8.2)
Ptosis of the breast [*n* (%)]	
0	23 (31.5)
1	15 (20.5)
2	24 (32.9)
3	5 (6.8)
Missing	6 (8.2)
Smoking history [*n* (%)]	
Never smoker	58 (79.5)
Past smoker	9 (12.3)
Current smoker	6 (8.2)
Family history of breast cancer [*n* (%)]	
No	30 (41.1)
Yes	43 (58.9)

We first described our technique of RNSM and immediate robotic breast reconstruction (IRBR) at the European Institute of Oncology in Milan[5–8] in 2014. Since that time, we have continued to study the advantages and disadvantages of RNSM through enrollment into prospective and randomized trials at our institution. We published feasibility and safety data on our first consecutive 29 RNSM and IRBR procedures, where we determined the procedure was technically feasible and safe.[7] The success in our early series justified a randomized prospective trial comparing RNSM with the open classical technique. This trial was fully accrued and has already closed.[15] We await long-term follow-up data for this trial but data maturation will be some years away. The aim of the current study was to analyze the perioperative data, postoperative complications, and early oncologic outcomes of consecutive patients undergoing RNSM and IRBR between June 2014 and January 2019.

METHODS

Women aged > 18 years who were candidates for nipple-sparing mastectomy and immediate breast reconstruction, and had RNSM with IRBR, were enrolled into a prospective institutional registry from June 2014 to January 2019. Indications for RNSM were invasive breast cancer, ductal carcinoma in situ (DCIS), or BRCA mutation carriers. All patients had negative preoperative assessment of the nipple–areola complex, with absence of skin involvement and low probability of having positivity of nipple–areola complex tissue intraoperative frozen section. Additionally, all patients had breast volume less than or equal to bra size C, no heavy smoking (defined as > 20 cigarettes/day), and were low and intermediate risk for anesthesia (American Society of Anesthesiologists Scale).

Exclusion criteria were previous thoracic radiation therapy for any reason; inflammatory breast cancer; skin involvement; preoperative diagnosis (radiological or cytological) of nipple–areola complex disease; pregnancy; patients with psychiatric, addictive, or any disorder that compromises the ability to give informed consent for participation in this study; uncontrolled diabetes mellitus; and high risk for anesthesia.

The protocol for this prospective study was approved by the Scientific Directorate Board. Prior to the operation, all patients gave their signed informed consent for RNSM and IRBR according to the established regulations.

The surgical procedure for RNSM and IRBR has been previously published,[6,7] and minimal technical modifications during assessment of the surgical technique were meticulously recorded to allow for understanding of the possible effect on outcomes. All procedures were carried out using the da Vinci Xi Surgical System® (Intuitive Surgical, Sunnyvale, CA, USA), with the exception of five procedures completed with the da Vinci Si Surgical System® (Intuitive Surgical).

Operation time, length of hospitalization, and number of complications were recorded. Complications were recorded at specific time points and included all complications up to 3 months postoperatively. Major complications included reoperations or implant loss, while minor complications included subcutaneous emphysema due to carbon dioxide insufflation, minor infections, necrosis, delayed wound healing, eschar/erythema to the nipple or skin flap, and seroma.

Data on patient age, body mass index, breast cancer characteristics (including tumor size, histologic subtype, grade, and nodal status), and adjuvant therapy (including receipt of radiotherapy, endocrine therapy, chemotherapy, and monoclonal antibodies) were collected. Local recurrence-free, disease-free, and overall survival were analyzed.

Patient characteristics, operation parameters, and complications were presented using contingency tables. Continuous variables were expressed as mean, median and range. Follow-up was calculated from the date of surgery to the date of last follow-up, the date of death, or the date of

TABLE 2 Pathological data

	N = 94
Robotic	
Histological examination [*n* (%)]	
Ca ductal	30 (31.9)
Ca lobular	6 (6.4)
Infiltrating other	3 (3.2)
In situ	21 (22.3)
Negative (prophylactic)	34 (36.2)
Pathological staging, dimension, cm	
Mean	1.7
Median (range)	1.6 (0.14–4.9)
Pathological staging, pT [*n* (%)]	
pT1a	4 (4.3)
pT1b	2 (2.1)
pT1c	20 (21.3)
pT2	13 (13.8)
pTis	21 (22.3)
pT0	34 (36.2)
Pathological staging, pN [*n* (%)]	
pNX	34 (36.2)
pN (SentNeg)	49 (52.1)
pN1mi	4 (4.3)
pN1a	4 (4.3)
pN2a	2 (2.1)
pN3a	1 (1.1)
Pathological staging, grading [*n* (%)]	
G1	6 (6.4)
G2	18 (19.1)
G3	13 (13.8)
Not available	2 (2.1)
Not applicable	55 (58.5)
Margins (oncologic patients) [*n* (%)]	
Negative	56 (100)
Positive	0 (0)
Biological characteristics of invasive carcinoma [*n* (%)]	*N* = 39
ER	
Negative	5 (12.8)
Positive	34 (87.2)
PR	
Negative	7 (17.9)
Positive	32 (82.1)
Ki-67	
< 20	15 (38.5)
≥ 20	24 (61.5)
PVI	
Negative	35 (89.7)
Positive	4 (10.3)
HER2	
0/+/++	35 (89.7)
Overexpressed (+++ or FISH +)	4 (10.3)

Data are expressed as *n* (%) unless otherwise specified

ER estrogen receptor, *PR* progesterone receptor, *PVI* peritumoral vascular invasion, *HER2* human epidermal growth factor receptor, *FISH* fluorescence in situ hybridization

diagnosis of a second primary cancer, whichever occurred first. Only first events that occurred during the median follow-up period were considered for analysis. All analyses were carried out using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Between June 2014 and January 2019, a total of 73 women (mean age 42 years) underwent 94 RNSM and IRBR procedures. Indications for the procedure were invasive breast cancer in 39 patients, DCIS in 17 patients, and BRCA mutation carriers without a cancer diagnosis in 17 patients. Patient demographics and preoperative parameters are listed in Table 1.

In the 39 patients with invasive cancer, mean tumor size was 1.7 cm. A majority of patients (34/39, 87.2%) had estrogen receptor (ER)-positive cancers without human epidermal growth factor receptor 2 (HER2) overexpression (HER2-negative in 35/39 patients, 89.7%). All tumor characteristics are listed in Table 2. In patients where the sentinel node biopsy was indicated, micrometastases were found in four (4.3%) patients and macrometastases were found in seven (7.5%) patients. In the seven patients with macrometastasis, axillary dissection was performed through robotic access incision, but using the standard open technique. Margins were negative in all oncological cases.

Mean surgery time was 3 h and 32 min (Table 3). All patients received retropectoral implant-based reconstruction. One-step reconstruction with implant occurred in 89.4% of cases, while the remaining patients received reconstruction with a tissue expander. The mean length of hospital stay (from admission to discharge) was 2 days.

Complications were defined as any postoperative event through 90 days. Minor and major complications were recorded as listed in the Methods section. Seroma was the most frequent event and occurred in five patients (5.3%) (Table 4). Infection occurred in two patients (2.1%), both of whom were treated with antibiotics, and one of two patients required explant of the implant. Hematoma requiring reoperation occurred in two cases (2.1%), and necrosis, erythema, and axillary web syndrome were found

TABLE 3 Perioperative data

No. of procedures	*N* = 94
Mastectomy procedure time (h:min)	
Mean	1:57
Median (range)	2:00 (0:47–3:50)
Reconstruction procedure time (h:min)	
Mean	1:35
Median (range)	1:15 (0:24–3:12)
Reconstruction [*n* (%)]	
Prosthesis	84 (89.4)
Expander	10 (10.6)
Length of hospital stay—admission to discharge (days)	
Mean	2
Median (range)	2 (1–8)
Duration of drainage (days)	
Mean	11
Median (range)	9 (4–40)
Drainage (ml)	
Mean	180
Median (range)	150 (40–700)

in one case each (1.1%). One patient required removal of the implant at almost 3 months during chemotherapy for implant exposure.

With regard to the 39 invasive breast cancer patients, radiotherapy was received in five (5.3%) patients. Chemotherapy was administered in 13 (33.3%) patients. Among the 34 patients with ER-positive disease, endocrine therapy was recommended in 100% of cases (87.2% of the total patients). Among the four patients with overexpressed HER2, three underwent trastuzumab therapy (Table 5).

Median follow-up for the 56 oncologic patients was 19 months (range 3.1–44.8), and the mean follow-up was 20 months (Table 5). No patients were lost at follow-up and no local recurrences occurred (Fig. 1). One woman received neoadjuvant treatment with carboplatinum, NAB-paclitaxel, and immunotherapy with atezolizumab for the triple-negative subtype. This patient was oligometastatic (bone only) at the time of surgery, and died after 4 months from brain metastasis. Disease-free survival (excluding the patient who died) was 100% (Fig. 2). Considering all oncologic patients (DCIS and infiltrating carcinoma), overall survival at 12 months was 98% (95% confidence interval 86–100%) and remained constant after 20, 24, or 60 months (Fig. 3).

TABLE 4 Complications through 90 days

Procedures	Total [*N* = 94]	Requiring reoperation [*N* = 94]
Infection	2 (2.1)	1 (1.1)[a]
Hematoma/hemorrhage	4 (4.3)	2 (2.1)
Necrosis	1 (1.1)	–
Axillary web syndrome	1 (1.1)	–
Implant exposure	1 (1.1)	1 (1.1)[a]
Eschar	4 (4.3)	–
Seroma	5 (5.3)	–
Erythema	1 (1.1)	–
Total loss of implant[a]	2 (2.1)	

Data are expressed as *n* (%)

[a]One explant of the implant for infection, one implant removed for implant exposure at almost 3 months during chemotherapy

TABLE 5 Proposed adjuvant treatment and follow-up [*N* = 39]

No. of subjects requiring radiation therapy	5 (12.8)
No. of subjects requiring chemotherapy	13 (33.3)
No. of subjects requiring monoclonal antibody	3 (7.7)
No. of subjects requiring hormonal therapy	34 (87.2)
Follow-up for 56 patients (months)	
Mean	20.0
Median (range)	19.0 (3.1–44.8)

Data are expressed as *n* (%) unless otherwise specified

DISCUSSION

In 94 prospectively studied, consecutive RNSM procedures with IRBR performed for the treatment or prevention of breast cancer, the operation was a technical success in all cases, and we had a very low complication rate. Major complications of reoperation and loss of implant occurred in only four cases (4%), and minor complications requiring only observation for resolution occurred in an additional 13% of patients. This rate is acceptable and is similar to our larger single-center experience of 1989 patients who underwent open nipple-sparing mastectomy and reconstruction,[3] as well as large restrospective studies evaluating postoperative outcomes of the conventional open technique.[16]

The technical advantages of the robotic system compared with the standard open technique are related to enhanced visualization, as well as incision placement. The robotic arms and camera allow for superior vision of the tissue planes and higher precision dissections as the robotic arms provide access at angles that are not possible with the

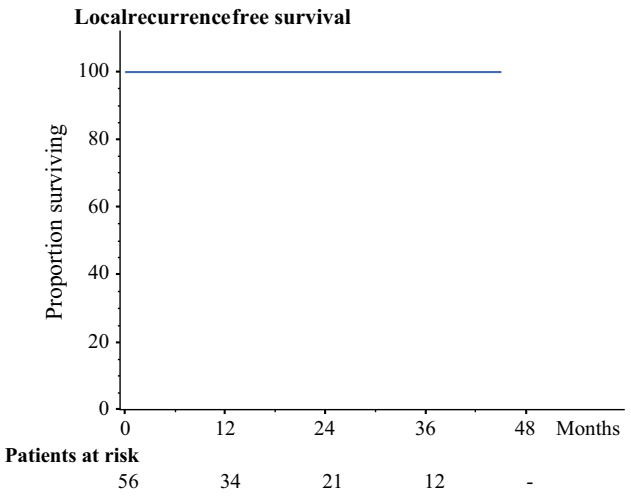

FIG. 1 Local recurrence-free survival. No patients were lost at follow-up

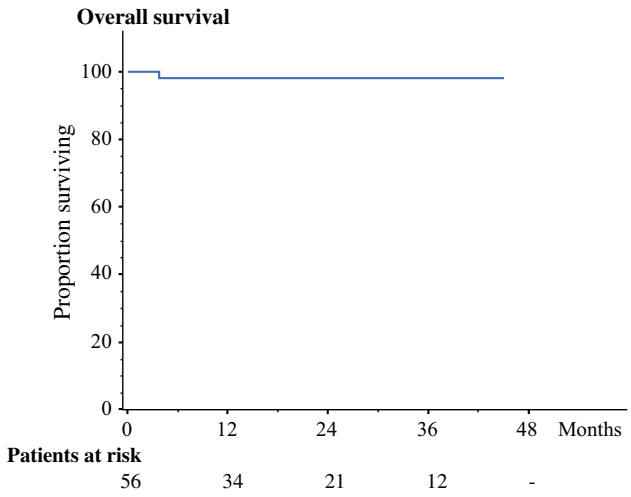

FIG. 3 Overall survival. No patients were lost at follow-up. Overall survival at 12, 20, 24, or 60 months was 98% (95% confidence interval 86–100%)

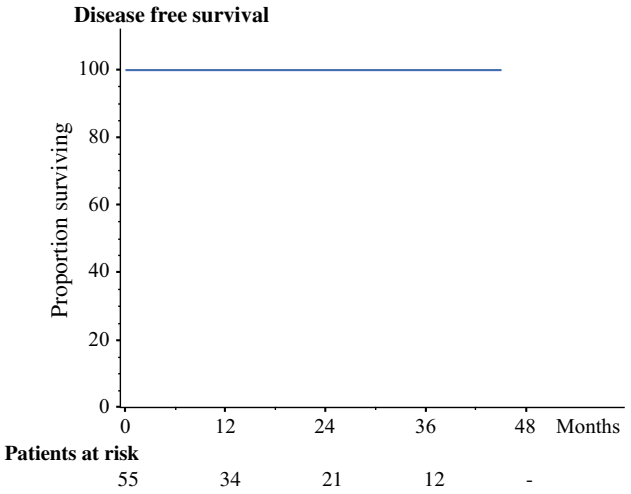

FIG. 2 Disease-free survival. No patients were lost at follow-up. One patient with metastatic disease was excluded from the disease-free survival analysis

retractors used in open surgery. In our experience, this allows for a more complete and anatomic dissection of the breast.

The robot allows for incision placement outside of the breast in the mid-axillary line. This offers cosmetic benefit but, more importantly, may have vascular advantages. The vascular supply to the nipple after nipple-sparing mastectomy relies on small vessels that traverse subcutaneous tissue from larger branching vessels off the internal mammary, anterior intercostal, and lateral thoracic arteries, with less reliance on branches from the axillary artery or posterior intercostal branches.[17] Options for open nipple-sparing mastectomy are the inframammary fold or a lateral extension off the nipple, which threaten these branches more than an incision placed in the mid-axillary line. This may contribute to our low rate of necrosis and no total nipple loss events.

Furthermore, it is equally conceivable that the minimal countertraction of 8 mmHg insufflation compared with manual retraction in an open procedure may also contribute to the low skin and nipple–areola complex necrosis rates.

Despite technical or cosmetic advantages that the robot may afford, the most important outcome is an oncologic outcome. We recognize this is essential to study long-term in any future study utilizing the robot for mastectomy; however, there is no reason to think that oncologic outcomes would be worse if a careful technique is utilized because both open and robotic procedures follow the same oncologic principles, i.e. they use anatomic dissection along tissue planes to remove the breast specimen completely en bloc. The specimen is then subjected to the same orientating protocol and pathologic analysis in both procedures. In fact, with the enhanced visualization and access to areas harder to reach when using the open technique, it is plausible that the robot may offer superior oncologic outcomes.

To provide preliminary data on oncologic safety, our study presents our short-term follow-up of all consecutively performed RNSMs performed over a 5-year period, with a median follow-up of 19 months. The local relapse rate and disease-free and overall survival rates were in line with a previous evaluation of nipple-sparing mastectomy in a large series of patients.[3] We acknowledge that most of the patients enrolled in that trial could be considered as low-risk in terms of prognosis, although they were all

young patients. Besides the relatively small median tumor size, the vast majority of patients were ER-positive and nodal involvement was limited.

CONCLUSION

As more centers perform RNSM with immediate breast reconstruction as part of prospective trials, it is important to ensure that local and distant recurrence rates are closely followed and remain within acceptable limits. In the meantime, our early data offer insight that the procedure is safe, and larger trials should continue to study the technology used.

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DISCLOSURES Antonio Toesca, Alessandra Invento, Giulia Massari, Antonia Girardi, Nickolas Peradze, Germana Lissidini, Claudia Sangalli, Patrick Maisonneuve, Andrea Manconi, Alessandra Gottardi, Jennifer L. Baker, Luca Bottiglieri, Paola Naninato, Gabriel Farante, Francesca Magnoni, Alessandra De Scalzi, Giovanni Corso, Marco Colleoni, Francesca De Lorenzi, Virgilio Sacchini, Viviana Galimberti, Mattia Intra, Mario Rietjens, and Paolo Veronesi declare that they have no conflicts of interest.

ETHICAL APPROVAL All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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