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Health-Related Quality of Life After Nipple-Sparing Mastectomy: Results From the INSPIRE Registry

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ABSTRACT

Introduction. Nipple-sparing mastectomy (NSM) with immediate breast reconstruction (IBR) is increasingly used for both breast cancer (TNSM) and risk reduction (RRNSM). The aim of the study is to report the results of the INSPIRE registry assessing health-related quality of life (HRQoL) comparing baseline and 1-year follow-up, regarding surgical indications and chemotherapy (CT) received.

Methods. INSPIRE is a prospective database including women undergoing NSM and IBR from 18 countries. HRQoL was measured using EORTC QLQC30 and QLQ-BR23 before surgery and after 1 year.

Results. A total of 677 women were included, of whom 537 (79.3%) underwent TNSM and 140 (21.6%) RRNSM: in total, 806 NSM (556 TNSM and 250 RRNSM). Nipple involvement was present in 7.73% of TNSM and incidental carcinoma in 1.2% of the RRNSM group. Out of the overall 537 patients with systemic treatment, 177 (32.96%) received neoadjuvant chemotherapy (NCT) and 118 (21.92%) adjuvant chemotherapy (CT). A total of 227 patients (28.16%) developed at least one complication postoperatively, 164 (29.5%) in the TNSM group and 63 (25.2%) in the RRNSM group. The TNSM group improved in global health status and emotional functioning after 1 year. No differences were found when comparing HRQoL at 1 year between patients who received NCT and those who received adjuvant CT. The RRNSM group showed improvement in HRQoL, with better emotional functioning and fatigue after 1 year.

Conclusions. This registry reports HRQoL findings after NSM. The impact of CT on worse HRQoL is independent from its timing. Patients with RRNSM showed an improved HRQoL at 1-year follow-up. Discussion of HRQoL outcomes with patients will facilitate the informed decision-making when considering NSM.

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Nipple skin-sparing mastectomy (NSM) has been increasingly performed in recent years, with its indication stretched from early-stage breast cancer to advanced breast cancer. Studies have shown that selected patients with

advanced breast cancer can benefit from NSM after systemic treatments.[1–3] Recent reports document how the oncologic outcomes of NSM are comparable with those of skin-sparing mastectomy, showing locoregional recurrence rates as low as 2% at the 3-year follow-up evaluation.[4–6]

As NSM techniques have evolved over time, complications have decreased to acceptably low rates.[7] Furthermore, excellent aesthetic outcomes and high levels of patient satisfaction have been achieved. This is particularly important for women considering bilateral mastectomy for risk-reducing (RR) purposes. However, most of the studies are single-institution retrospective studies collecting data from medical records and subject to confounding factors.

Currently, a randomized clinical trial of nipple-sparing techniques versus conventional mastectomy (followed by reconstruction) is neither feasible nor ethical. Consequently, well-designed, prospectively collected data produce evidence and reduce uncertainty regarding NSM.

The International Nipple-Sparing Mastectomy Registry (INSPIRE) is a prospective, non-randomized, international registry promoted by the European Society of Surgical Oncology (ESSO) and the EUropean REgistration of Cancer Care (EURECCA) to provide evidence-based information and assist in the treatment planning for future patients offered a mastectomy for cancer treatment or as an RR procedure.

To our knowledge, only two prospective NSM registries have been published (the American Society of Breast Surgeons [ASBS][8] and the Italian National Registry),[9] demonstrating that NSM is a safe and effective treatment. The ASBS registry also includes patient and doctor satisfaction using a scale of four points, from excellent to poor. The studies published compare satisfaction with NSM between breast cancer patients and those with RR NSM. No differences in baseline characteristics, patient satisfaction, or cosmesis/nipple-areola complex sensation was found (mean follow-up period, 31 months), although the breast cancer group showed a higher rate of flap infection in.

Nevertheless, neither of these two registries report any information regarding health-related quality of life (HRQoL), defined as patients' perception of their own physical, mental, and social health influenced by the diagnosis, treatment, post-treatment, and survivorship. The findings were collected using well-validated instruments.[10] The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) also has been shown to detect HRQoL differences in the general population. Therefore, it also was used for the high-risk patients' group in this study.[11]

Knowledge of QoL data on breast cancer patients will provide scientific evidence for clinical decision-making and convey helpful information concerning patients' experiences.

This study aimed to investigate and report HRQoL data and compare the two groups (breast cancer and RR groups).

MATERIALS AND METHODS

The INSPIRE Registry included the QLQ-C30 and the QLQ-BR23 questionnaires before surgery and 1 year afterward to evaluate the impact of NSM in terms of HRQoL on both breast cancer patients and RR NSM patients. The participants in the Registry were breast surgeons practicing at an institution with a breast cancer program that routinely offers NSM as a surgical option for breast cancer patients. The eligibility criteria specified patients older than 18 years scheduled for NSM and stratified them into two distinct groups (two parallel studies): patients affected by ductal carcinoma *in situ* (DCIS) or invasive breast cancer who require a therapeutic NSM (TNSM) and patients requiring RR mastectomy (RR NSM).

The indications for NSM were at the discretion of the participating surgeons. The absolute contraindications to NSM were evidence of nipple involvement, locally advanced breast cancer with skin involvement, inflammatory breast cancer, and bloody nipple discharge. Consecutive patients were prospectively entered into the Registry after signing the informed consent to avoid any selection bias.

Before surgery, 92.55% of the women underwent at least a mammogram, whereas 69.38% underwent at least magnetic resonance imaging (MRI), and 69.38% underwent at least one breast ultrasound. Only four patients did not undergo any preoperative imaging test, and all four of the women women underwent RR NSM. The indications for the imaging test were at the physician's discretion, and the distance from tumor to nipple was not limited as long as the nipple was not involved.

The primary objective of the INSPIRE registry was to assess patient satisfaction (using a QoL questionnaire) after NSM, whereas the secondary objectives were to investigate NSM's outcomes and complication rate from surgery plus adjuvant radiation therapy and to compare details relevant to surgical techniques and preoperative imaging

An International Quality Registry secured standardized collection of data on all patients undergoing NSM from the participating centers. Advanced Data Management, based in Leiden University Medical Center, Leiden, The

Netherlands, is NEN7510-certified, and Project Manager Internet Server meets the requirements for data safety and privacy set by international law.

From February 2016 to January 2019, 43 surgeons from 29 centers in 18 countries included patients in the database. No data about race/ethnicity are available because it was not included in the initial database.

Statistical Analysis

Standard descriptive statistics were used to summarize the data regarding baseline characteristics. Data on the intention-to-treat (ITT) population were analyzed. All the patients were included for the baseline analysis, but only those completing the questionnaires were taken into account for the HRQoL studies. To avoid confounding factors, patients' unilateral RR mastectomy and previous contralateral therapeutic mastectomy were included the study of baseline and surgical complications, but not in the HRQoL study.

The distribution of clinical factors between the groups was compared using Student's *t* test or the Mann-Whitney *U* test for continuous variables and the chi-square test for categorical variables. A receiver operating characteristic (ROC) regression was performed to evaluate the utility of the nipple-to-tumor distance measurement for predicting nipple involvement. A cut-point was described as optimal when the point classified most of the individuals correctly.

Differences between groups were compared using the analysis of variance (ANOVA) test. Multivariate regression was used to compare and explore the effect of confounding factors. Quality-of-life graphs were obtained, with the user command provided by Bascoul-Mollevi et al.[12] All calculations were performed with Stata software (Stata/SE 16; Stata Corp., College Station, TX). Two-tailed *p* values of 0.05 or lower were considered statistically significant.

RESULTS

Patients' Characteristics and Indications for NSM

Between February 2016 and January 2019, the Registry included 677 women, for a total of 806 NSMs (556 for TNSM and 250 for RR NSM). The mean age of the entire cohort was 44.7 years (range, 20–77 years): 45.3 years (range, 20–77 years) for the TNSM patients and 41.9 years (range, 26–68 years) for the RR NSM patients ($p = 0.0003$).

The median follow-up period was 10.32 months (range, 0–44.28 months): 9.72 months (range, 0–44.28 months) for the breast cancer group and 12.9 months (range, 0–32.2 months), for the RR group ($p = 0.003$).

TABLE 1 Baseline characteristics

TNSM *n* (%)	
No. of patients	537
No. of mastectomies	556
Unilateral	518
Bilateral	19
Median age: years (range)	45.3 (20–77)
Median BMI: kg/m^2 (range)	23.14 (16.4–38.1)
T status	
T0	6 (1.12)
Tis	74 (13.78)
T1	163 (30.35)
T2	203 (37.8)
T3	49 (9.12)
Unknown	42 (7.82)
Grade (%)	
1	54 (10.06)
2	186 (34.64)
3	109 (20.30)
Unknown/not performed	188 (35.01)
Nodal status	
cN0	379 (70.58)
cN+	119 (22.16)
Unknown	39 (7.26)
Hormone receptor status (DCIS)	
ER+PR+	47 (62.67)
ER+PR–	9 (12)
ER–PR+	0
ER–PR–	11 (14.67)
Unknown/not performed	8 (10.67)
HR status (excluding DCIS)	
ER+PR+	303 (66.30)
ER+PR–	66 (14.44)
ER–PR+	3 (0.66)
ER–PR–	72 (15.75)
Unknown/not performed	13 (2.84)
HER2 status (excluding DCIS)	
Positive	96 (20.79)
Negative	346 (75.71)
Unknown/not performed	16 (3.50)
Initial spread	
Unifocal	261 (48.61)
Multifocal	150 (27.93)
Multicentric	110 (20.48)
Unknown	16 (2.98)
BRCA status	
BRCA1+	68 (12.66)
BRCA2+	7 (1.30)
Total BRCA mutations	75 (13.97)

Table 1 (continued)

TNSM *n* (%)	
Not performed/unknown	387 (72.01)
Neoadjuvant therapy	
Yes	177 (32.96)
No	360 (67.04)
Adjuvant chemotherapy	
Yes	118 (21.97)
No	369 (68.72)
Unknown	50 (8.31)
Type of adjuvant chemotherapy	
AC + T (Adryamycin/cyclophosphamide + Taxanes)	38 (31.09)
TC (Taxotere/cyclophosphamide)	13 (10.92)
Adryamycin/epirubicin	10 (8.40)
T (Taxanes)	4 (3.36)
CMF (Cyclophosphamide/Methotrexate/5-Fluorouracil)	4 (3.36)
Other	41 (34.45)
Unknown	10 (8.13)
Genetic platform (excl DCIS or NCT)	
No gene profiling	220 (75.09)
Oncotype DX	22 (7.51)
Mammaprint	5 (1.71)
Other	4 (1.37)
Unknown	42 (14.33)
Adjuvant hormonal therapy	
Yes	337 (62.76)
No	143 (26.63)
Unknown	57 (10.31)
Type of adjuvant homone therapy	
Tamoxifen	190 (56.37)
Aromatase inhibitor	114 (33.83)
Other	5 (1.48)
Unknown	28 (8.32)
Adjuvant radiotherapy	
Yes	146 (27.19)
No	324 (60.34)
Unknown	67 (12.48)
Comorbidities	
Yes	104 (19.36)
Cardiovasc disease	35 (33.65)
Respiratory disorder	15 (14.42)
Diabetes	6 (5.77)
Psychiatric disorder	18 (17.3)
Alcohol use	5 (4.81)
Other	25 (24.05)
No	421 (78.39)
Unknown	7 (2.25)
Smoker	
Yes	59 (10.99)
No	446 (83.05)
Unknown	32 (5.96)
Menopausal status	
Premenopausal	338 (62.94)
Perimenopausal	62 (11.55)
Postmenopausal	127 (23.65)
Unknown	10 (1.86)
Previous breast surgery	
Yes	118 (21.22)
Cancer	61 (51.69)
DCIS	19 (16.1)
Benign	37 (31.36)
Unkonwn	1 (0.85)
No	435 (78.24)
Unknown	3 (0.54)
Previous radiation therapy to the breast	
Yes	27 (4.86)
No	523 (94.06)
Unknown	6 (1.08)
Cup size	
A	59 (10.99)
B	231 (43.02)
C	124 (23.09)
D+	45 (8.38)
Unknown	78 (14.53)
Breast ptosis	
No ptosis	154 (28.68)
Grade 1	159 (29.61)
Grade 2	95 (17.69)
Grade 3	25 (4.66)
Unknown	14 (19.37)
RR NSM group	
No. of patients	127
No. of mastectomies	250
Unilateral	4
Bilateral	123
Median age: years (range)	41.9 (26–68)
Median BMI: kg/m^2 (range)	23.18 (16.1–37.9)
Reason for NSM	
BRCA1 or 2	88 (69.29)
Family history	4 (3.15)
Atypia/LCIS	3 (2.36)
Other	21 (16.54)
Missing	11 (8.63)
Comorbidities	
Yes	12 (10)
- Cardiovasc disease	3 (25)
- Respiratory disorder	1 (8.33)

Table 1 (continued)

TNSM *n* (%)	
- Diabetes	2 (16.67)
- Psychiatric disorder	2 (16.67)
- Alcohol use	2 (16.67)
- Other[a]	2 (16.66)
No	101 (84.17)
Unknown	4 (5.83)
Smoker	
Yes	20 (25.75)
No	99 (77.95)
Unknown	8 (6.3)
Menopausal status	
Premenopausal	75 (59.06)
Perimenopausal	9 (7.09)
Postmenopausal	37 (29.13)
Unknown	6 (4.75)
Previous breast surgery	
Yes	49 (40.83)
Cancer/DCIS	39 (79.59)
Benign	10 (20.41)
No	69 (57.5)
Unknown	2 (1.67)
Previous breast RT	
Yes	16 (13.33)
No	92 (76.67)
Unknown	12 (10)
Cup size	
A	13 (10.24)
B	42 (33.07)
C	38 (29.92)
D+	9 (7.09)
Unknown	25 (19.69)
Breast ptosis	
No ptosis	31 (24.41)
Grade 1	32 (25.20)
Grade 2	29 (22.83)
Grade 3	7 (5.51)
Unknown	28 (22.05)

TNSM, therapeutic nipple skin-sparing mastectomy; BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; DCIS, ductal carcinoma *in situ*; NCT, neoadjuvant chemotherapy; RT, radiation therapy; RR, risk-reducing; NSM, nipple skin-sparing mastectomy; LCIS, lobular carcinoma *in situ*

[a]CDH1 E-cadherin mutation, Li-Fraumeni syndrome, PALB2 mutation or high risk of breast cancer after familial study without known mutation

Therapeutic NSM

The majority of the 537 women in the therapeutic NSM group (n = 415, 76%) had a diagnosis of invasive carcinoma. Of these women, 203 (37.8%) were affected by T2 tumors, 186 (34.64%) had histologic grade 2 cancers, 379 (70.58%) had a clinically negative axilla, and 301 (56.05%) had estrogen receptor-positive (ER+) and progesterone receptor-positive (PR+) tumors (Table 1).

The clinical median tumor size (based on preoperative imaging techniques including mammogram, ultrasound, or MRI) was 2.1 cm (range, 0.5–13 cm) for invasive carcinoma, 3.0 cm (range, 0–8.9 cm) for invasive carcinoma receiving neoadjuvant treatment, and 4.25 cm (range, 0.6–24.5 cm) for DCIS. The pathologic median tumor sizes were 3 cm (range, 0–12 cm) for invasive carcinoma and 1.6 cm (range, 0–9 cm) *in situ* carcinoma, respectively. Almost half of the patient population (n = 261, 48.61%) presented with unifocal disease. In terms of pathologic nodal status, 350 women (65.18%) were classified as pN0, 143 (26.63%) as pN1, 20 (3.72%) as pN2, and 14 (2.61%) as pN3. Information was missing for 10 of the women (1.86%).

In preoperative imaging studies, the median distance from the nipple was 3 cm (range, 0.3–7 cm) for the infiltrating carcinoma and 2.55 cm (range, 0.1–7 cm) for DCIS. For invasive carcinoma, the area under the curve (AUC) was 0.49 (95% CI, 0.38–0.61). Therefore, the optimal cutoff point (nipple-to-tumor distance) was 3.95 cm, with a sensitivity of 67% and a specificity of 41%. For DCIS, the AUC was 0.52 (95% CI, 0.33–0.73), and the optimal cutoff point was 5.25 cm, with a sensitivity of 60% and a specificity of 55%.

Of the 537 patients, 177 (32.96%) underwent neoadjuvant chemotherapy (NCT) and 118 (21.92%) had adjuvant chemotherapy. Eight patients (1.49%) received both NCT and adjuvant chemotherapy, which consisted mainly of adriamicyn + taxanes. Higher stage of disease, ER–/PR–, and human epidermal growth factor receptor 2-positive (HER2+) breast cancer were significantly associated to NCT. For 337 (70.21%) of the patients, some type of hormonal therapy was administered, and 83 patients (86.45% of the HER2+ breast cancer patients) received anti-HER2 therapy. Anti-HER2 therapy was not administered to six of the patients due to comorbidities (cardiovascular morbidities) or to seven of the patients (7.29%) due to unavailable data, considered as missing. Radiation therapy was given to 146 (27.19%) of the patients. The patient and tumor characteristics are reported in Table 1.

TABLE 2 Type of incision and reconstruction

	Total *n* (%)	RR NSM group *n* (%)	TNSM group *n* (%)	*p* Value
Type of reconstruction				0.0001
Tissue expander	348 (43.18)	81 (32.4)	267 (48.02)	
Implant	339 (42.07)	152 (60.8)	187 (33.63)	
Free TRAM	6 (0.7)	1 (0.4)	5 (0.9)	
DIEP	28 (3.48)	5 (2)	23 (4.14)	
Latissimus dorsi	30 (3.73)	3 (1.2)	27 (4.86)	
Other autologous	4 (0.5)	0	4 (0.72)	
Unknown	51 (6.34)	8 (3.2)	43 (7.73)	
Type of incision				0.0001
Periareolar (± lateral ext)	137 (17)	52 (20.8)	85 (15.29)	
Radial	110 (13.65)	21 (8.4)	89 (16.01)	
Inframmamary	323 (40.07)	95 (38)	228 (41.01)	
Inferior vertical	52 (6.45)	30 (12)	22 (3.96)	
Reduction mammoplasty	89 (11.04)	35 (14)	54 (9.71)	
Other	40 (4.96)	7 (2.8)	33 (5.94)	
Unknown	55 (6.82)	10 (4)	45 (8.09)	

RR risk-reducing, *NSM* nipple skin-sparing mastectomy, *TNSM* therapeutic nipple skin-sparing mastectomy, *TRAM* transverse rectus abdominis, *DIEP* deep inferior epigastric perforator

RR NSM

The Registry included 250 NSMs performed for 127 patients. Of these 127 patients, 88 (69.2%) were BRCA1/2 mutation carriers, and 123 (97%) underwent bilateral mastectomies. The majority (85%) did not have any comorbidities, and 13% had previous radiation therapy. None had previous breast surgery. The characteristics of the patients and tumors are summarized in Table 1.

Reconstruction Procedures

The most common type of surgical incision used in both groups was an inframammary operation (40%), followed by peri-areolar (± lateral extension) for 17% of the patients. Implant-based reconstruction was used most in both groups, with significantly more frequent use of the tissue expander in the TNSM group (54.76%) and direct implant in the RR NSM group (64.6%) ($p = 0.035$). The reconstruction characteristics in both groups are detailed in Table 2.

TNSM Nipple Involvement

Intraoperative nipple frozen sections were performed for 282 of the women (54.76%) in the TNSM group. Final pathology showed nipple involvement in 43 patients, whereas intraoperative pathology showed 10 patients with malignant cells and 5 patients with atypical cells. Nipple removal was performed for 42 women. An incidental carcinoma involving the nipple was found in three patients (1.2%) in the RR NSM group. In all three cases, the nipple was resected.

The patients with locally advanced breast cancer (stage 3) showed a trend toward higher nipple excision rates than those with early breast cancer (15.38% vs. 4.62%; $p = 0.09$).

Complications

At least one complication developed postoperatively for 227 patients (28.16%): 164 patients (29.5%) in the TNSM group versus 63 patients (25.2%) in the RR NSM group. The two groups did not differ significantly in rate of infection, seroma, hematoma, flap, or partial/total nipple necrosis. Seroma formation (10%) was the most frequent complication in both groups. Infection occurred in 3.23% of the patients.

The total nipple necrosis rate was 1.49%, and the partial nipple necrosis rate was 7.2% overall. Multivariate analysis showed that excision of the nipple due to necrosis was significantly associated with a reduction mammoplasty incision (Wise pattern) (RR, 7.97; 95% CI, 1.39–45.4), adjuvant radiotherapy (RR, 12.64; 95% CI, 1.64–96.97), and the presence of comorbidities at diagnosis (RR, 6.80; 95% CI, 1.51–30.64).

Multivariate analysis found that in reduction mammoplasty incision, independent factors for complications were postoperative radiation therapy (RDT) (RR, 4.83; 95% CI, 1.59–14.72), free transverse rectus abdominis (TRAM)

TABLE 3 Comparison of complications between groups

Type of complication	TNSM group *n* (%)	RR NSM group *n* (%)	Total *n* (%)	*p* Value
Partial nipple necrosis	37 (6.65)	21 (8.4)	58 (7.20)	0.22
Total nipple necrosis	9 (1.62)	3 (1.2)	12 (1.49)	0.67
Partial skin flap necrosis	37 (6.65)	10 (4)	47 (5.83)	0.25
Implant extrusion	8 (1.44)	5 (2)	13 (1.61)	0.56
Infection	22 (3.96)	4 (1.6)	16 (3.23)	0.09
Seroma	64 (11.51)	20 (8)	84 (10.42)	0.17
Hematoma/bleeding	28 (5.04)	7 (2.8)	35 (18.49)	0.19

TNSM therapeutic nipple skin-sparing mastectomy, *RR* risk-reducing, *NSM* nipple skin-sparing mastectomy

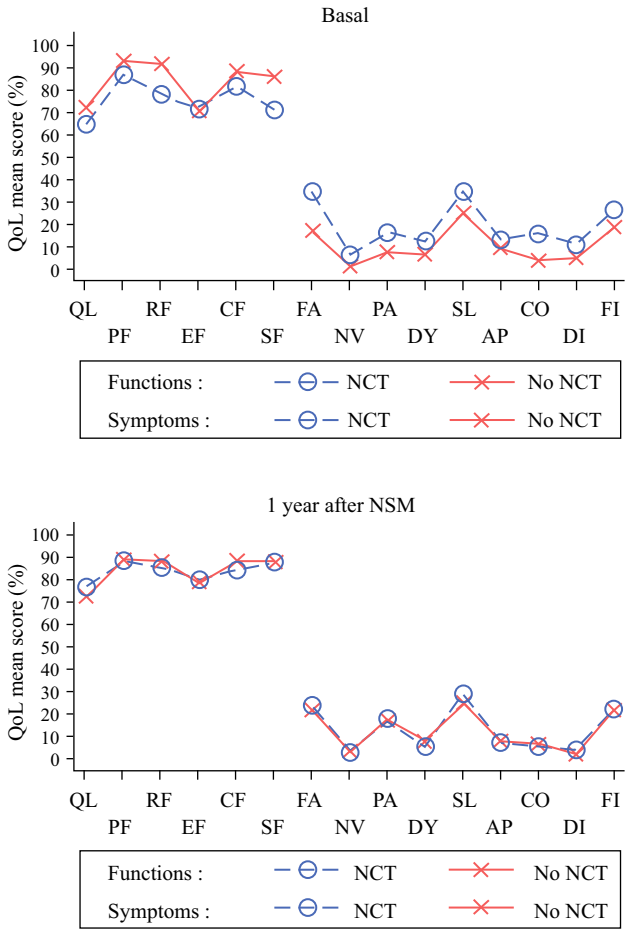

FIG. 1 HRQoL before surgery between the patients who received neoadjuvant chemotherapy and those who did not. Basal and 1 year follow up questionnaire

immediate reconstruction (RR,11.04; 95% CI, 1.16–105.02), current smoking habit (RR, 3.56; 95% CI, 1.6–7.98), and the presence of comorbidities at diagnosis (RR, 2.24; 95% CI, 1.13–4.44), as detailed in Table 3.

HRQoL (EORTC QLQ-C30)

Of the 664 patients, 511 (77%) completed the EORTC QLQ-C30 before surgery, and 290 (44%) completed it 1 year after surgery.

After 1 year, the breast cancer patients (TNSM) had significantly improved their global health status ($p = 0.03$), emotional functioning ($p = 0.002$), appetite loss ($p = 0.03$), and diarrhea ($p = 0.003$), but had significantly worsened their physical functioning ($p = 0.004$) and pain ($p = 0.003$). The RR NSM group demonstrated a significant improvement in emotional functioning ($p = 0.006$) and fatigue ($p = 0.03$) during 1-year follow-up period.

Subgroup analysis was performed to compare HRQoL before surgery between the patients who received NCT and those who did not. The basal questionnaire was completed by151 patients (29.5%) who received chemotherapy and 265 patients (51%) who did not. The patients who received NCT before surgery scored significantly lower in all items except emotional functioning ($p = 0.17$; Fig. 1; Table 4).

Functionality and symptoms did not differ significantly between the patients who received chemotherapy before and those who received chemotherapy after surgery, showing how the timing of chemotherapy did not have an impact on HRQoL.

HRQoL: Comparing TNSM and RR NSM Before Surgery and During the 1-Year Follow-up Period

The EORTC QLQ-C30 was completed preoperatively by 423 patients (83%) with TNSM and 88 patients (59%) with RR NSM. The breast cancer patients (TNSM) tended to present worse scores than the RR NSM group. These differences were more pronounced in the functional scales, with significantly lower scores for global health status ($p = 0.0001$) and social functioning ($p = 0.04$). The symptoms scale showed a significant increase in fatigue ($p = 0.04$) and diarrhea ($p = 0.007$; Fig. 2; Table 5).

When the two groups were compared 1 year after surgery, the differences in the functional and symptom scales remained significant. The breast cancer patients scored

TABLE 4 QLQ-C30 scores for TNSM patients with NCT versus no NCT before surgery (visit 0) and at the 1-year follow-up evaluation (visit 1).

Visit 0			
Item	Basal (n = 265) Mean score (range)	NCT (n = 151) Mean score (range)	p Value
Physical functioning (PF)	94.52 (40–100)	86.88 (40–100)	0.00001
Global health status (QL)	72.23 (0–100)	64.62 (16.67–100)	0.0004
Role functioning (RF)	92.24 (0–100)	78.47 (0–100)	0.00001
Emotional functioning (EF)	74.03 (8.3–100)	71.03 (8.3–100)	0.17
Cognitive functioning (CF)	87.82 (16.67–100)	81.89 (16.67–100)	0.004
Social functioning (SF)	88.48 (16.66–100)	70.97 (0–100)	0.00001
Fatigue (FA)	15.40 (0–100)	33.55 (0–88.89)	0.00001
Nausea & vomiting (NV)	2.05 (0–50)	5.96 (0–33.33)	0.00001
Pain (PA)	9.13 (0–83.33)	15.01 (0–100)	0.003
Dyspnea (DY)	5.76 (0–66.66)	11.7 (0–66.67)	0.0008
Insomnia (SL)	22.13 (0–100)	34.21 (0–100)	0.00001
Appetite loss (AP)	8.75 (0–66.67)	12.80 (0–66.67)	0.03
Constipation (CO)	5.79 (0–66.67)	14.79 (0–66.67)	0.00001
Diarrhea (DI)	5.03 (0–66.67)	10.59 (0–66.67)	0.0007
Financial difficulties (FI)	12.35 (0–100)	26.05 (0–100)	0.00001
Visit 1			
Item	Adjuvant (n = 46) Mean score (range)	NCT (n = 73) Mean score (range)	p Value
Physical functioning (PF)	88.69 (46.66–100)	88.28 (40–100)	0.87
Global health status (QL)	71.01 (16.67–100)	76.94 (25–100)	0.11
Role functioning (RF)	87.68 (0–100)	85.38 (0–100)	0.58
Emotional functioning (EF)	77.53 (0–100)	80.47 (16.67–100)	0.48
Cognitive functioning (CF)	87.68 (16.67–100)	84.70 (16.67–100)	0.42
Social functioning (SF)	87.03 (16.67–100)	87.89 (0–100)	0.82
Fatigue (FA)	21.01 (0–77.78)	23.43 (0–88.89)	0.58
Nausea & vomiting (NV)	2.89 (0–33.33)	2.51 (0–33.33)	0.81
Pain (PA)	16.66 (0–66.66)	17.35 (0–100)	0.87
Dyspnea (DY)	7.97 (0–66.66)	4.57 (0–66.66)	0.22
Insomnia (SL)	26.08 (0–100)	26.94 (0–100)	0.88
Appetite loss (AP)	6.52 (0–66.67)	7.31 (0–66.66)	0.81
Constipation (CO)	5.07 (0–66.67)	5.93 (0–100)	0.74
Diarrhea (DI)	1.44 (0–33.33)	4.11 (0–66.67)	0.18
Financial difficulties (FI)	22.96 (0–100)	20.55 (0–100)	0.68

QLQ-C30 Quality of Life Questionnaire-Core 30, *TNSM* therapeutic nipple skin-sparing mastectomy, *NCT* neoadjuvant chemotherapy

significantly worse in physical functioning (p = 0.0001), global health status (p = 0.004), role functioning (p = 0.0006), emotional functioning (p = 0.03), cognitive functioning (p = 0.009), fatigue (p = 0.0001), nausea and vomiting (p = 0.01), pain (p = 0.05), and appetite loss (p = 0.04; Fig. 2; Table 5).

QLQ Br23 Module in the TNSM Group

The QLQ-BR23 questionnaire was completed preoperatively by 423 TNSM patients (76%) and after 1 year by 226 patients (41%). Significant alterations were found during the 1-year follow-up period, with lower scores for sexual enjoyment (p = 0.0002) and increased arm

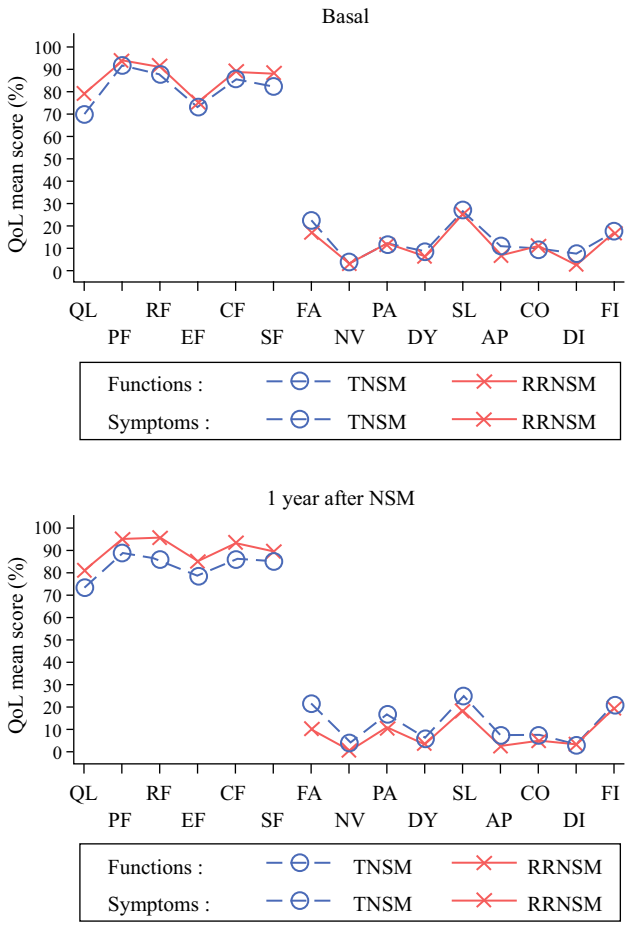

FIG. 2 HRQoL comparing TNSM and RR NSM before surgery and at 1 year follow up

symptoms (p = 0.001). A trend toward increased breast symptoms also was indicated (p = 0.09).

DISCUSSION

The INSPIRE Registry prospectively confirms the benefit of NSM in improving patient satisfaction and QoL. During the 1-year follow-up period, the TNSM group had significantly improved global health status (p = 0.03), emotional functioning (p = 0.002), appetite loss (p = 0.03), and diarrhea (p = 0.003). Nevertheless, the TNSM group had significantly worsened physical functioning (p = 0.004) and pain. The RR NSM group demonstrated significant improvement in emotional functioning, which may be explained by their relief after the decision to undergo RR surgery.

All the women undergoing NSM (regardless of indication) improved in the domains that may seem most likely to be improved by NSM such as emotional and psychosocial well-being.

Comparison of patient reported outcomes (PROs) between studies was difficult because many of the studies did not use the same questionnaires. We chose the EORTC QLQ-30/BR23 due to its comprehensiveness in measuring the impact of cancer across multiple domains of functioning, adding the EORTC QLQ-BR23, a breast-specific module, to assess body image, sexual functioning, sexual enjoyment, future perspective, and treatment effects.

Other studies have used the BREAST-Q, which has independent modules for breast cancer regarding types of surgery.[13,14] Although clinically relevant differences between the EORTC QLQ-C30/BR23 and the BREAST-Q are not well-defined, some literature describes half a standard deviation (0.5SD) difference between the two instruments, with the significant difference in domains detected by the BREAST-Q explained by the surgery-specific questions.[15]

Nevertheless, regardless of the measurement of PROs, the majority of previous studies with various methods of breast reconstruction have established that preserving the nipple positively influences overall patient satisfaction with the breast.[16,17] One strength in the INSPIRE trial was its baseline assessment of body image and QoL, whereas most studies lack the baseline questionnaires, and patients who undergo immediate breast reconstruction may begin the process at different levels of satisfaction with their breasts and QoL.

Similar to our results, the Mastectomy Reconstruction Outcome Consortium evaluated PROs among women undergoing immediate implant-based or autologous reconstruction.[13] The Consortium found that many patients are not fully recovered 3 months after surgery, and also that some of patients with expander reconstruction may have had replacement of implants close to the 1-year follow-up questionnaire, making the recovery longer.

For women undergoing NSM for RR procedures, our results matched the study by Metcalfe et al.[18] evaluating satisfaction of BRCA carriers undergoing prophylactic mastectomy. Even with a small sample size, they found improved satisfaction with breasts, outcome, and sexual well-being in the nipple-areola-sparing mastectomy group. This is consistent with the systematic review by Razdan et al.[19] showing that 69% to 100% of women undergoing NSM and reconstruction were highly satisfied after RR mastectomy.

For TNSM patients, clinicians need to take systemic treatments into account when evaluating QoL. Chemotherapy has the potential to have a negative impact on the QoL of breast cancer patients,[20] and our study confirmed that patients receiving NCT show a significant QoL deterioration on baseline questionnaires completed before NSM. However, when QoL was reassessed after the 1-year follow-up period, functionality and symptoms did not

TABLE 5 QLQC30 scores comparing the TNSM and RR NSM groups at baseline (visit 0) and at the 1-year follow-up evaluation (visit 1)

Visit 0			
Item	TNSM group (n = 423) Mean score (range)	RR NSM group (n = 88) Mean score (range)	p Value
Physical functioning (PF)	91.75 (46.66–100)	93.37 (16.6–100)	0.28
Global health status (QL)	69.45 (16.66–100)	78.83 (25–100)	0.0001
Role functioning (RF)	87.09 (0–100)	90.99 (16.66–100)	0.13
Emotional functioning (EF)	72.81 (8.33–100)	75.47 0–100)	0.30
Cognitive functioning (CF)	85.5 (16.66–100)	88.88 (16.66–100)	0.15
Social functioning (SF)	82.05 (0–100)	87.93 (0–100)	0.04
Fatigue (FA)	22.16 (0–88.88)	16.86 (0–88.88)	0.04
Nausea & vomiting (NV)	3.48 (0–33.33)	2.87 (0–50)	0.60
Pain (PA)	11.29 (0–83.3)	11.49 (0–100)	0.93
Dyspnea (DY)	8.07 (0–66.66)	6.13 (0–66.66)	0.33
Insomnia (SL)	26.92 (0–100)	24.90 (0–100)	0.55
Appetite loss (AP)	10.57 (0–66.66)	6.51 (0–100)	0.07
Constipation (CO)	9.13 (0–66.66)	10.34 (0–100)	0.60
Diarrhea (DI)	7.14 (0–66.66)	2.32 (0–66.66)	0.007
Financial difficulties (FI)	17.31 (0–100)	16.66 (0–100)	0.84
Visit 1			
Item (mean score, range)	TNSM group (n = 226) Mean score (range)	RR NSM group (n = 64) Mean score (range)	p Value
Physical functioning (PF)	88.55 (33.33–100)	94.89 (26.66–100)	0.0001
Global health status (QL)	72.97 (16.66–100)	80.72 (16.66–100)	0.004
Role functioning (RF)	85.87 (0–100)	95.57 (0–100)	0.0006
Emotional functioning (EF)	78.3 (16.66–100)	85.15 (0–100)	0.03
Cognitive functioning (CF)	85.88 (16.66–100)	93.23 (0–100)	0.009
Social functioning (SF)	85.14 (16.66–100)	89.32 (0–100)	0.16
Fatigue (FA)	21.32 (0–88.88)	9.72 (0–100)	0.0001
Nausea & vomiting (NV)	3.51 (0–50)	0.26 (0–66.66)	0.01
Pain (PA)	16.36 (0–100)	10.41 (0–66.66)	0.05
Dyspnea (DY)	5.53 (0–66.66)	3.64 (0–66.66)	0.33
Insomnia (SL)	24.66 (0–100)	18.26 (0–100)	0.13
Appetite loss (AP)	7.17 (0–66.66)	2.08 ((0–100)	0.04
Constipation (CO)	7.17 (0–100)	4.68 (0–100)	0.31
Diarrhea (DI)	2.86 (0–33.33)	3.12 (0–100)	0.86
Financial difficulties (FI)	20.51 (0–100)	19.04 (0–100)	0.71

QLQ-C30 Quality of Life Questionnaire-Core 30, *TNSM* therapeutic nipple skin-sparing mastectomy, *RR* risk-reducting, *NSM* nipple skin-sparing mastectomy

differ significantly between the patients receiving NCT and those undergoing adjuvant chemotherapy, and were significantly worse for the patients receiving no chemotherapy. To our knowledge, no data in the literature compare the effect of neoadjuvant versus adjuvant chemotherapy on QoL. When discussing optimal options and timing of chemotherapy with patients, they can be reassured that the impact on QoL is similar regardless of timing.

After acknowledgment of the differences between TNSM and RR NSM, it must be noted that the TNSM group had worse functional and psychosocial scores than the RR NSM group. Findings have shown that patients with

a diagnosis of breast cancer have increased anxiety before treatments and that QoL improves over time.[21] Similarly, the study by Härtl et al.[22] has shown that anxiety at diagnosis and before to surgery has an impact on QLQ-C30.

Nipple Involvement

No randomized trials have compared oncologic outcomes between NSM and skin sparing mastectomy (SSM). The use of NSM has expanded from early breast cancer to more advanced disease, and all data for oncologic outcomes come from retrospective institutional studies or meta-analyses. In the meta-analysis by de La Cruz et al.,[6] no significant differences in survival, disease-free survival, or local recurrence rates between NSM and modified radical mastectomy/SSM were found. Similarly, large multicentric trials have confirmed the oncologic safety of the procedure.[5,8,9] Due to this oncologic concern, a section of the retroareolar tissue usually is examined routinely to exclude cancer involvement. Nipple-areolar complex involvement in women undergoing therapeutic NSM ranges from 8% to 33%,[7,9,23,24] and multiple studies with follow-up periods ranging from 10 to 101 months have demonstrated low rates of locoregional recurrence.[23]

In our series, 54.76% of the patients underwent an intraoperative retroareolar pathology assessment, and the rate of nipple involvement was 5.34%. Final pathology showed that 7.73% of the patients had nipple invasion. In the multicenter registry from the American Society of Breast Surgeons, 96% of the patients had undergone intraoperative retroareolar pathology assessment with nipple involvement of 2.9%, although with only 1.2% rate of nipple resections performed due to positive margins.[8]

One of the primary controversies with the use of NSM is the distance from the tumor to the nipple-areola complex (TND). In our study, TND was not a reliable marker for nipple involvement, with an AUC of 0.5. Similarly, Fregatti et al.[25] showed that no difference in the rate of nipple involvement exists when TND is segregated into distances of >2 cm, 2–5 cm, and >5 cm. During a median follow-up period of 31 to 33 months, no nipple-areola complex recurrence occurred, showing that permanent section assessment of retroareolar tissue is the most accurate and cost-effective technique for evaluating nipple involvement. Studies also suggest that locoregional recurrence is associated with tumor biology rather than preservation of the nipple-areolar complex during NSM.[26]

During the past 15 years, NSM has emerged as an option for the prevention of breast cancer in high-risk patients and mutation carriers. Risk-reducing mastectomies for *BRCA* mutations carriers reduce the risk of subsequent breast cancer by 89–95%.[27,28] Women with *BRCA1* and *BRCA2* mutations usually represent the most common indication for RR NSM, similar to our study, in which 70% of the RR NSM procedures were performed for mutation carriers. In addition to the oncologic safety of the procedure,[27] findings of incidental carcinoma at the time of NSM have been reported. In the study of 384 RR NSMs by Valero et al.[28] a 1.6% rate of incidental invasive breast cancers was reported, similar to the rate of 1.2% in our study. Retroareolar tissue intraoperative assessment of the RR NSM patients was not performed as recommended by international guidelines.[29]

Complications

In our study, 227 patients (28.1%) experienced complications. Interestingly, the complication rate did not differ between the groups (29.5% in the TSNM group and 25.2% in the RR NSM group). The rates of complications from several studies and systematic reviews have ranged from 20% to 33%.[7,8,30,31] Most of the studies did not consider seroma as a complication, although in our study, it was reported as the most frequent complication.

A serious complication threatening nipple preservation is nipple necrosis. The early studies showed rates of complete nipple necrosis to be approximately 5% and rates of partial nipple necrosis to be 20%.[5,32,33]

Importantly, in many studies, rates of complications, including nipple necrosis, decreased over time. This decrease was attributed to improved surgeon expertise.[31] Numerous prospective multicentric studies, similar to INSPIRE, report lower complication rates, ranging from lower than 10% (partial necrosis) to lower than 2% (complete nipple necrosis).[8,9]

In our study, the significant independent factors for nipple necrosis were reduction mammoplasty incision (Wise pattern), adjuvant radiotherapy, and presence of comorbidities at diagnosis. Other studies also have shown that RDT and smoking are independent factors[9,34] and it is clear that RDT has a significant impact on the complication rate in NSM, whether it is given before NSM or after NSM.

Several studies have identified the type of surgical incision as one of the risk factors for nipple-areola complex necrosis, with the highest necrosis in periareolar incision. In our study, the highest necrosis was associated with incisions involving the nipple-areola complex (periareloar or Wise pattern).[31,34,35] When incisions for NSM are planned, it should be understood that avoiding periareolar incisions will prevent nipple necrosis. The inframammary fold incision was most commonly used in our study as well as in studies described in the recent literature, both for TNSM and the RR NSM.[8,36]

Infection is another complication that can influence the failure of the reconstruction. The infection rate in our study

was low (3.2%), similar to the rates in other prospective registries.[8]

CONCLUSION

Nipple skin-sparing mastectomy has become a popular surgical technique for early breast cancer as well as for high-risk women. Complications have decreased with increasing expertise. The INSPIRE Registry contributes to prospective evaluation of HRQoL for breast cancer patients and high-risk patients. Breast cancer patients undergoing NSM and chemotherapy have a poorer QoL than those who have no chemotherapy, although timing of chemotherapy does not influence QoL. Discussion of such HRQoL outcomes with patients will facilitate informed decision-making about treatments, not only for patients choosing RR NSM, but also for patients deciding on preservation of the nipple-areola complex when a mastectomy is indicated.

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