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Original article

Nipple sparing mastectomy: Surgical and oncological outcomes from a national multicentric registry with 913 patients (1006 cases) over a six year period

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ABSTRACT

Background: Nipple sparing mastectomy is deemed surgically and oncologically safe based on a long lasting literature data from reviews of single institution series. This study aims at evaluating surgical and oncological outcomes of NSM on a large multi-institutional scale, by means of the Italian National registry.
Methods: In July 2011 a panel of Italian specialists agreed upon and designed a National database of NSM. Centers with at least 150 cancers per year and following the National follow-up schedule guidelines could participate inserting any NSM case performed, retrospectively and prospectively from that moment on. In March 2015 analysis of data was accomplished. Dataset for this study consists of cases performed in the period between January 1st 2009 and December 31st 2014.
Results: 913 Women were included in the analysis, for a total of 1006 procedures. Prophylactic mastectomies were 124 (12.3%). MRI utilization increased over time. NSM failure rate, with NAC removal for any reason was 11.5%. NAC necrosis rate was 4.8%. Larger skin-flap necrosis rate was 2.3%. Major surgical complications rate was 4.4%. Oncological outcomes were calculated among primitive EBC cases only:

Abbreviations: sd, standard deviation; OR, odds ratio; CI, confidence interval; Ref., reference category; n.c., not computable; IHC, immunohistochemistry; FISH, fluoro in situ hybridization; MRI, magnetic resonance imaging; IORT, intra-operative radiation-therapy; ER, estrogen receptor; PgR, progesterone receptor.

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locoregional recurrences rate was 2.9%, NAC recurrence 0.7%. Systemic recurrence rate was 1.0%. Five deaths (0.7%) were registered.
Conclusions: More than 10% of NSM procedures are prophylactic mastectomies. MRI is gaining more importance over time. Surgical and oncological results show that NSM is effective. This National multicentric analysis enables a comparison of results with no geographical differences and a "safe" state of the art of NSM in Italy.

Introduction

Breast cancer surgical care had an impressive progress in 20th century [1]. Breast conservative surgery is the most common procedure [2]. Nonetheless mastectomy remains a frequent option, as a choice, as a prophylactic intervention and often as a mandatory indication.

Nipple sparing mastectomy (NSM) is deemed as an extension of breast conservative surgery. The definition of "conservative mastectomy" might appear a contradiction in terms, but becomes appropriate when considering conservation as the maintenance of body image [3].

In 1951 Rice and Strickler realized for a benign disease the first mastectomy with preservation of skin and nipple areola complex (NAC) [4]. In 1962 Freeman introduced the term subcutaneous mastectomy [5]. Nowadays, NSM for breast cancer is used in selected cases, with indications based on tumor's characteristics.

Once patients are carefully selected, NSM is considered appropriate and oncologically safe. There is a long lasting literature data regarding surgical and oncological effectiveness of NSM [6,7]. Despite that, there is a variation in the diagnostic and therapeutic strategy that involves NSM in breast cancer treatment from center to center. Moreover, selection criteria and thus indications are enlarging.

In order to evaluate such variations and reach homogeneous behaviors among specialists, an investigation based on a large set of historical data is necessary. Besides, a multicentric comparison is important to assess oncological and surgical results in accordance with international standards and to confirm the validity and reproducibility of the technique.

The aim of this study is to depict and describe the state of the art of NSM in an entire country, by collecting data from a six-year period using a National registry with contribution of various Italian centers. Primary end-points are the analysis of surgical and oncological outcomes.

Materials and methods

In July 2011 a panel of Italian breast specialists agreed upon and designed an open National database on NSM. The idea was to establish a centralized and homogeneous registry which gathers every single center database. The registry was created as a protected-by-password MySQL client (©2015, Oracle corporation).

Any Italian center with a volume of at least 150 breast cancers per year (according to the EUSOMA guidelines [8]) keen on participating had the possibility to contribute on a voluntary basis registering in a specifically created website (www.nipplesparingmastectomy.it).

Registry is made of 180 items, listed as: baseline patients characteristics, oncological parameters, surgical procedure details, pathological reports, adjuvant therapies, surgical outcomes and oncological outcomes. Follow-up schedule was: clinical examination every 3–6 months for the first 3 years, every 6–12 months for the following 2 years, and once a year ever after; mammogram once a year; further imagings and examinations only on clinical suspicion (according to Associazione Italiana Oncologia Medica, AIOM, follow-up schedule guidelines, http://www.aiom.it).

Each patient submitted to NSM, either prophylactic or therapeutic, could be included in the registry prospectively and retrospectively.

In March 2015 analysis of data for present study was accomplished. Inclusion criterion was: NSM cases referring to the period between January 1st 2009 and December 31st 2014 from centers with at least 15 cases included in the registry in the same period. Included cases from 2009 until 2011 were retrospective, while cases from 2011 to 2014 were prospective. The deadline for data update by every center was March 31st 2015.

Statistical analysis

Standard descriptive statistics were used to summarize data, with respect to demographic and preoperative characteristics. Demographics included patient age, smoking habits, diabetes status, hospital and survival status at last follow-up. Preoperative data were analyzed on all surgical procedures.

Four dichotomous (yes/no) response variables were considered: NAC necrosis, skin-flap necrosis, major surgical complications and loco-regional recurrence. Surgical outcomes were analyzed on all procedures, both prophylactic and therapeutic. On the contrary, oncological adverse outcomes (locoregional recurrences) were investigated among primitive early breast cancer cases only. Except for post-operative NAC necrosis, which was calculated excluding those cases with an intraoperative NAC removal, all other analyses were performed with the intent to treat criterion.

Logistic regression was used to investigate which factors were associated with each response variables. Independent variables of interest for surgical outcomes were: smoke, type of incision, neoadjuvant chemotherapy, preoperative radiation-therapy, type of reconstruction and geographical area. Instead, risk factors included in the locoregional recurrences analysis were: age above 45 years old, tumor's diameter greater than 3 cm, multifocality, pT, pN, ER, PgR, Ki67, HER2, neoadjuvant chemotherapy, adjuvant chemotherapy, hormone therapy, anti-HER2 target therapy, post-operative radiation-therapy and geographical area. Tumor diameter was defined as the biggest focus dimension and measured either by means of MRI, when performed, or mammogram, or eventually by ultrasound for lesion not visible at mammogram and not studied by MRI. The same imaging criterion was adopted to calculate the tumor to nipple distance by every center. In this case the distance was from the nearest focus of tumor and not from the biggest focus. An exact measure was not reported in database and therefore tumor to nipple distance was not used as a variable for statistical analysis.

Multiple logistic regression analyses were performed to account for several confounding variables simultaneously. Multiple logistic regression for surgical outcomes included all variables of interest, while in locoregional recurrences analysis only variables with a *p*-value less than 0.20 were included.

A two tailed *p*-value less than 0.05 was considered significant. All analyses were performed using STATA version 12.1 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP).

Results

Demographics and preoperative data

A total number of 913 women who fitted the inclusion criteria were included in the present study. Average age of patients was 47 years old (sd 9 years, range 21–77). Twenty-nine women (3.2%) had a BRCA1 mutation and 11 (1.2%) a BRCA2 mutation. Table 1 shows complete baseline patients characteristics.

A monolateral procedure was accomplished in 820 (89.8%) patients, while 93 (10.2%) had a bilateral intervention. Four patients had a bilateral intervention as a prophylactic procedure only, 58 had a bilateral procedure as a therapeutic procedure on one side and prophylactic on the other, while 31 patients had a therapeutic bilateral procedure. Therefore overall number of surgical procedures was 1006, among them 124 (12.3%) were prophylactic and 882 (87.7%) were therapeutic. Prophylactic mastectomies were performed either for BRCA mutations, for high-risk patients or for women choice. Procedures were performed in 15 different Italian hospitals, 5 of them located in Northern Italy, 4 in the Center and 6 in the South.

A preoperative mammography was performed in 892 (88.6%) cases among 1006. A preoperative ultrasound was completed in 895 (89.0%). Both diagnostic imagings were carried out in 822 cases (81.7%). Breast MRI was performed in 472 (46.9%) cases. Among 124 prophylactic cases, 53 (42.7%) had a pre-operative MRI study. A similar rate was recorded for therapeutic mastectomies with 419 (47.5%) MRI imagings out of 882 cases. MRI utilization increased over time with a more homogeneous pattern among different geographic areas as reported in Fig. 1.

Table 1
Baseline characteristics of patients included in the analysis.

	N = 913	%
Age		
<25	2	0.2%
25–39	178	19.5%
40–54	577	63.2%
55–69	147	16.1%
>69	9	1.0%
Smoke		
Never	572	62.7%
Occasionally	76	8.3%
5–15 cigarettes/die	59	6.5%
>15 cigarettes/die	23	2.5%
Missing	183	20.0%
Diabetes		
No	761	83.4%
Type I	3	0.3%
Type II	3	0.3%
Missing	146	16.0%
Overall survival		
Survivors	850	93.1%
Deaths	6	0.7%
Missing	57	6.2%
Hospital (city, area)		
San Giovanni Rotondo Hospital (Foggia, Southern Italy)	144	15.8%
San Paolo Hospital (Bari, Southern Italy)	138	15.1%
Careggi Hospital (Florence, Central Italy)	121	13.3%
Maugeri Hospital (Pavia, Northern Italy)	100	11.0%
Sant'Andrea Hospital (Rome, Central Italy)	89	9.7%
Cisanello Hospital (Pisa, Central Italy)	67	7.3%
Sant'Orsola Hospital (Bologna, Northern Italy)	52	5.7%
Montecchio Maggiore Hospital (Vicenza, Northern Italy)	36	3.9%
Valdese Hospital (Turin, Northern Italy)	35	3.8%
Campus Biomedico Hospital (Rome, Central Italy)	30	3.3%
Businco Hospital (Cagliari, Southern Italy)	26	2.8%
Cannizzaro Hospital (Catania, Southern Italy)	23	2.5%
Policlinico Hospital (Bari, Southern Italy)	20	2.2%
Humanitas Hospital (Catania, Southern Italy)	18	2.0%
Ramazzini Hospital (Carpi, Modena, Northern Italy)	14	1.5%

sd: standard deviation.

Outcomes

Among 1006 procedures 116 NACs were removed, resulting, as per an intent to treat criterion, in a 11.5% surgical strategy failure rate. Eighty-three NACs (71.5%) were removed intraoperatively, 6 (5.2%) were removed post-operatively for a full-thickness total NAC necrosis, 19 (16.4%) were removed post-operatively for positive margins at final pathology report, and 8 (6.9%) were eventually removed later on for local recurrence.

Surgical outcomes

NAC necrosis rate. Since 83 NACs were removed intraoperatively (78 cases for positive margin at frozen section and 5 cases for change in surgical technique), the post-operative NAC necrosis rate, either partial or total, was calculated on 923 procedures (subtracting 83 from overall 1006 cases). Thus, post-operative NAC necroses were 44 out of 923, 4.8% rate. Table 2 shows NAC necrosis risk factors univariate and multivariate analyses. Smoke resulted the only statistically significant risk factor for NAC necrosis.

Skin-flap necrosis rate. Skin-flap necrosis, considered as a large necrosis including NAC and/or surrounding breast skin envelope, either partial or total, was recorded in 23 cases among 1006. Therefore, skin-flap necrosis rate was 2.3%. Table 3 summarizes risks factors for skin-flap necrosis occurrence. Once again smoking was the only significant risk factor.

Major surgical complications rate. Major surgical complications data available from the registry were: surgical site infection, loss of prosthesis or autologous flap (reconstruction failure), and wound dehiscence. Major complications were considered those requiring readmission or prolongated hospitalization (more than 6 days for that specific cause). Major complications were overall 44 (4.4%): 26 (2.6%) reconstruction failures (either autologous flap loss or implant/tissue expander removal), 22 (2.2%) cases of wound dehiscence, and 15 (1.5%) surgical site infections. Table 4 reports

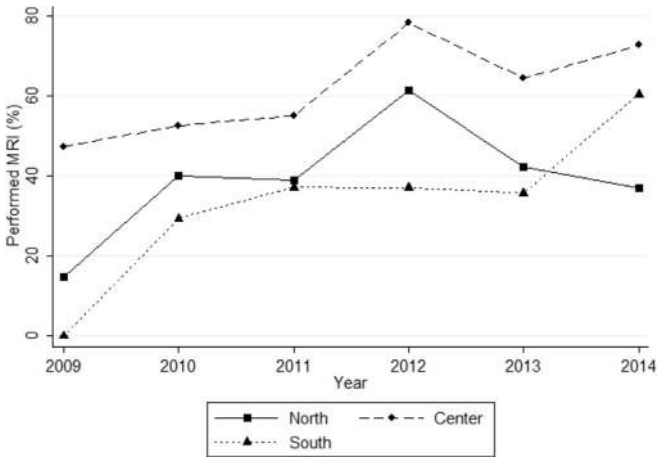

Fig. 1. MRI geographical distribution over time. Overall, MRI was performed in 45% of cases in Northern Italy, 63% in the Center and 36% in Southern Italy.

Table 2
Statistical analysis of NAC necrosis rate and related risk factors.

NAC necrosis (N = 44/923, 4.8%)	NAC necrosis cases[a] (*N* = 44)	Cases without NAC necrosis[a] (*N* = 879)	OR (95% CI) *p*-value	Adjusted OR (95% CI) *p*-value
Smoke	9/42 (21.4%)	80/690 (11.6%)	2.08 (0.96, 4.50) 0.063	2.47 (1.04, 5.87) **0.040**
Type of incision				
Lateral	25/44 (56.8%)	551/873 (63.1%)	Ref.	Ref.
Periareolar	2/44 (4.6%)	10/873 (1.2%)	4.41 (0.92, 21.2) 0.064	2.39 (0.22, 26.3) 0.476
Inframammary fold	9/44 (20.5%)	127/873 (14.5%)	1.56 (0.71, 3.43) 0.266	1.28 (0.42, 3.94) 0.668
Other	8/44 (18.2%)	191/873 (21.2%)	0.95 (0.42, 2.15) 0.908	0.65 (0.21, 2.03) 0.455
Type of reconstruction				
Tissue expander	27/42 (64.3%)	532/842 (63.2%)	Ref.	Ref.
Direct to implant	8/42 (19.0%)	247/842 (29.3%)	0.64 (0.29, 1.42) 0.273	0.54 (0.22, 1.34) 0.185
Autologous breast reconstruction	2/42 (4.8%)	35/842 (4.2%)	1.12 (0.26, 4.93) 0.875	0.73 (0.11, 4.79) 0.746
Autologous + tissue expander	0/42 (0%)	3/842 (0.4%)	n.c.	n.c.
Autologous + implant	5/42 (11.9%)	25/842 (3.0%)	3.94 (1.40, 11.1) 0.009	2.68 (0.58, 12.5) 0.209
Neoadjuvant chemotherapy	6/44 (13.6%)	87/879 (9.9%)	1.44 (0.59, 3.50) 0.424	1.25 (0.40, 3.89) 0.694
Preoperative radiation	1/40 (2.5%)	27/720 (3.8%)	0.66 (0.09, 4.97) 0.685	0.75 (0.09, 5.99) 0.782
Geographical area				
Center	16/44 (36.4%)	347/879 (39.5%)	Ref.	Ref.
North	12/44 (27.3%)	241/879 (27.4%)	1.08 (0.50, 2.32) 0.844	1.32 (0.45, 3.83) 0.611
South	16/44 (36.4%)	291/879 (33.1%)	1.19 (0.59, 2.43) 0.627	1.34 (0.49, 3.70) 0.561

Bold values are those statistically significant, as reported in the text.
[a] Statistical analyses were performed excluding missing data for every single item considered.

risk factors for having at least one of these complications in the post-operative course. A history of previous breast radiation therapy resulted as a significant risk factor for suffering of at least one major surgical complication.

Oncological outcomes

Oncological outcomes were considered locoregional recurrences and systemic recurrences. Oncological data analysis was conducted on patients who had a therapeutic procedure and an updated follow-up schedule. Moreover only primitive early breast cancer (EBC) patients were considered for this analysis, excluding recurrences, few cases of non-adenocarcinoma tumors and those who resulted to be advanced breast cancers at post-operative pTNM staging. Thus, included patients were 724 among 913. Thirty-one patients had a bilateral therapeutic intervention for EBC, therefore the overall number of cases was 755. Follow-up was calculated from date of intervention until last scheduled control. Mean duration of follow-up was 1101 days (range 125–2274). Overall disease free survival median from any event was 22 months (range 6–54). At last census 5 deaths (0.7%) were

Table 3
Statistical analysis of skin-flap necrosis rate and related risk factors.

Skin flap necrosis (*N* = 23/1006, 2.3%)	Skin-flap necrosis cases[a] (*N* = 23)	Cases without skin-flap necrosis[a] (*N* = 983)	OR (95% CI) *p*-value	Adjusted OR (95% CI) *p*-value
Smoke	5/20 (25.0%)	90/783 (11.5%)	2.57 (0.91, 7.23) 0.074	3.26 (1.06, 10.0) **0.039**
Type of incision				
Lateral	14/23 (60.9%)	625/977 (64.0%)	Ref.	Ref.
Periareolar	1/23 (4.3%)	13/977 (1.3%)	3.43 (0.42, 28.1) 0.250	9.16 (0.77,109) 0.080
Inframammary fold	5/23 (21.7%)	142/977 (14.5%)	1.57 (0.56, 4.44) 0.393	2.61 (0.70, 9.77) 0.153
Other	3/23 (13.0%)	197 (20.2%)	0.68 (0.19, 2.39) 0.547	0.28 (0.03, 2.32) 0.239
Type of reconstruction				
Tissue expander	14/23 (60.9%)	606/943 (64.3%)	Ref.	Ref.
Direct to implant	7/23 (30.4%)	260/943 (27.6%)	1.16 (0.46, 2.92) 0.744	1.35 (0.48, 3.81) 0.572
Autologous breast reconstruction	0/23 (0%)	42/943 (4.5%)	n.c.	n.c.
Autologous + tissue expander	0/23 (0%)	3/943 (0.3%)	n.c.	n.c.
Autologous + implant	2/23 (8.7%)	31/943 (3.3%)	2.79 (0.61, 12.8) 0.187	1.09 (0.14, 8.56) 0.937
Neoadjuvant chemotherapy	3/23 (13.0%)	95/983 (9.7%)	1.40 (0.41, 4.81) 0.591	1.74 (0.46, 6.64) 0.415
Preoperative radiation	1/22 (4.6%)	27/816 (3.3%)	1.39 (0.18, 10.7) 0.751	1.70 (0.19, 15.4) 0.638
Geographical area				
Center	5/23 (21.7%)	370/983 (37.6%)	Ref.	Ref.
North	12/23 (52.2%)	264/983 (26.9%)	3.36 (1.17, 9.66) 0.024	2.16 (0.53, 8.81) 0.283
South	6/23 (26.1%)	349/983 (35.5%)	1.27 (0.38, 4.21) 0.693	0.77 (0.18, 3.36) 0.725

Bold values are those statistically significant, as reported in the text.
[a] Statistical analyses were performed excluding missing data for every single item considered.

Table 4
Statistical analysis of having at least one major surgical complication with related risk factors.

Major complications ($N = 44/1006$, 4.4%)	Cases with at least one complication[a] ($N = 44$)	Cases without complications[a] ($N = 962$)	OR (95% CI) p-value	Adjusted OR (95% CI) p-value
Smoke	7/42 (16.7%)	88/761 (11.6%)	1.53 (0.66, 3.55) 0.322	1.28 (0.46, 3.56) 0.633
Type of incision				
Lateral	30/44 (68.2%)	609/956 (63.7%)	Ref.	Ref.
Periareolar	1/44 (2.3%)	13/956 (1.4%)	1.56 (0.20, 12.3) 0.673	2.80 (0.26, 29.8) 0.392
Inframammary fold	7/44 (15.9%)	140/956 (14.6%)	1.02 (0.44, 2.36) 0.972	1.30 (0.41, 4.09) 0.658
Other	6/44 (13.6%)	194/956 (20.3%)	0.63 (0.26, 1.53) 0.306	1.23 (0.45, 3.33) 0.685
Type of reconstruction				
Tissue expander	26/43 (60.5%)	594/922 (64.4%)	Ref.	Ref.
Direct to implant	14/43 (32.6%)	253/922 (27.4%)	1.26 (0.65, 2.46) 0.490	1.27 (0.59, 2.73) 0.537
Autologous breast reconstruction	0/43 (0%)	42/922 (4.6%)	n.c.	n.c.
Autologous + tissue expander	0/43 (0%)	3/922 (0.3%)	n.c.	n.c.
Autologous + implant	3/43 (7.0%)	30/922 (3.3%)	2.28 (0.65, 7.97) 0.195	2.28 (0.41, 12.5) 0.345
Neoadjuvant chemotherapy	4/44 (9.1%)	94/962 (9.8%)	0.92 (0.32, 2.64) 0.882	1.27 (0.41, 3.87) 0.679
Preoperative radiation	4/38 (10.5%)	24/800 (3.0%)	3.80 (1.25, 11.6) **0.019**	5.01 (1.46, 17.2) **0.010**
Geographical area				
Center	11/44 (25.0%)	364/962 (37.8%)	Ref.	Ref.
North	16/44 (36.4%)	260/962 (27.0%)	2.04 (0.93, 4.46) 0.075	1.88 (0.63, 5.64) 0.259
South	17/44 (38.6%)	338/962 (35.1%)	1.66 (0.77, 3.60) 0.196	1.40 (0.47, 4.15) 0.540

Bold values are those statistically significant, as reported in the text.
[a] Statistical analyses were performed excluding missing data for every single item considered.

recorded, four of them for breast cancer recurrence and one from other causes.

Locoregional recurrences. Locoregional recurrences were calculated on cases and not on patients. Out of 755 cases included in the analysis locoregional recurrences were 22 (2.9%). Five recurrences (22.7%) were on NAC, resulting in an NAC recurrence rate of 0.7%. Five more recurrences were registered on skin flap. Thus, the overall skin/NAC recurrence rate was 1.4%. Median time of locoregional recurrence appearance was 19 months (range 8–42).

In terms of tumor extension, majority of cases, 85.3%, has a tumor extension under 3 cm, while 14.7% of cases were over 3 cm. Tumor to nipple distance was not reported as a centimetric value but as a cut-off. Seven centers had 2 cm as cut-off limit for NSM indication (53.5% of EBC cases), 5 centers had 1 cm (35.5%), while the remaining 3 (11.0%) had no specific restriction and used MRI to ascertain NAC involvement. Nonetheless intraoperative frozen-section NAC examination was accomplished in 84.4% of EBC cases.

Table 5 shows analysis of risk factors for locoregional recurrence, by means of univariate and multivariate analyses. Tumor's diameter over 3 cm was a significant risk factor for locoregional recurrence among EBC cases. On the opposite a PgR positivity (at least >1%) was a significant protective factor for locoregional recurrence occurrence.

Systemic recurrences. Systemic recurrences were calculated on the number of patients with EBC. Seven patients out of 724 (1.0%) had distant metastasis, appeared with a median time span of 30 months after the operation (range 12–54).

Discussion

Despite that NSM safety versus skin-sparing and non-conservative mastectomies isn't proven by randomized trials, its adoption is so much widespread that such trials are definitely unlikely. This is because, notwithstanding the importance of randomized trials, there is a huge series of data in literature concerning surgical and oncological safety of NSM.

There are at least 14 reviews in last five years concerning NSM surgical and oncological outcomes, reporting approximately 80 studies.

Surgical outcomes results from literature show that NAC and skin-flap necroses vary from 1% to 30% according to Cohen [9]. In Mallon's review rates are 2.9% and 6.3% for full and partial NAC necrosis respectively [6]. In a 1001 cases series NAC total and partial necroses rates are 3.5% and 5.5% respectively [10].

In Mallon's review NAC recurrence rate is 0.9%, while overall skin-flap recurrence rate is 4.2% [6]. In Murthy's review all studies report a NAC recurrence rate of 0% except one reporting 1.6% and chest wall/axilla recurrence is between 0% and 8.5% [2]. In Veronesi's review local recurrence rate is between 0% and 20.8%, while only 8 NAC recurrences among 2262 cases are presented [3]. Petit (2012) presents a local recurrence rate in the breast and in the NAC of 3.6% and 0.8% respectively [11]. Sacchini (2006) reports two local recurrences among 123 cases and no NAC recurrences [12].

Majority of studies on NSM are single Institution series [13]. Feasibility and reproducibility of results are verified more significantly by a multicentric prospective study. Present study represents the effort to depict the state of the art of NSM on a National scale, with data from numerous Italian centers. To our knowledge this is the second in order of time and the largest as per number of cases National multi-institutional NSM study [13].

Patients are geographically distributed homogeneously, without significant bias. Mean age is lower than average peak age of breast cancer in Italy [14], since this procedure is generally reserved to younger ages for a reconstructive purpose. Prophylactic procedures are 12.3% of NSM cases performed in Italy, being the preferred approach in case of prophylactic mastectomy [15]. Magnetic resonance use is still different throughout the Nation. In Central Italy MRI was performed in 60.5% of cases versus 42.7% and 35.8% in North and South respectively. Nonetheless MRI is increasingly used timewise, according with recent data of its importance in detection of occult nipple involvement [16]. Moreover some centers use MRI

Table 5
Statistical analysis of EBC locoregional recurrences and related risk factors.

Locoregional recurrences ($N = 22/755$, 2.9%)	EBC recurrence cases[a] ($N = 22$)	EBC cases without recurrence[a] ($N = 733$)	OR (95% CI) p-value	Adjusted OR (95% CI) p-value
Age above 45 years old	12/22 (54.5%)	429/733 (58.5%)	0.85 (0.36, 1.99) 0.709	
Tumor's diameter greater than 3 cm	6/19 (31.6%)	95/668 (14.2%)	2.78 (1.03, 7.50) **0.043**	5.42 (1.45, 20.2) **0.012**
Multiple focality	10/22 (45.5%)	373/730 (51.1%)	0.80 (0.34, 1.87) 0.603	
pT				
pT0-X	0/22 (0%)	9/677 (1.3%)	n.c.	
pTis	3/22 (13.6%)	94/677 (13.9%)	Ref.	
pT1 (1mi-1a-1b-1c)	14/22 (63.6%)	380/677 (56.1%)	1.15 (0.33, 4.10) 0.824	
pT2	4/22 (18.2%)	179/677 (26.4%)	0.70 (0.15, 3.19) 0.645	
pT3	1/22 (4.6%)	15/677 (2.2%)	2.09 (0.20, 21.4) 0.535	
pN				
pN0-X	16/22 (72.7%)	450/671 (67.1%)	Ref.	
pN1	6/22 (27.3%)	188/671 (28.0%)	0.90 (0.35, 2.33) 0.824	
pN2	0/22 (0%)	33/671 (4.9%)	n.c.	
ER+	15/21 (71.4%)	526/626 (84.0%)	0.48 (0.18, 1.25) 0.133	4.59 (0.84, 25.1) 0.078
PgR+	9/21 (42.9%)	488/623 (78.3%)	0.21 (0.09, 0.50) **<0.001**	0.11 (0.02, 0.50) **0.004**
Ki67	13/20 (65.0%)	276/562 (49.1%)	1.92 (0.76, 4.89) 0.169	2.98 (0.76, 11.7) 0.119
HER2 (IHC ± FISH)	2/18 (11.1%)	86/548 (15.7%)	0.67 (0.15, 2.97) 0.600	
Neoadjuvant chemotherapy	5/22 (22.7%)	69/733 (9.4%)	2.83 (1.01, 7.91) **0.047**	1.37 (0.34, 5.55) 0.662
Adjuvant chemotherapy	9/19 (47.4%)	220/491 (44.8%)	1.11 (0.44, 2.78) 0.826	
Hormone therapy	10/20 (50.0%)	33/474 (70.3%)	0.42 (0.17, 1.04) 0.061	0.65 (0.16, 2.63) 0.546
Anti-HER2 target therapy	2/19 (10.5%)	69/451 (15.3%)	0.65 (0.15, 2.88) 0.572	
Postoperative radiation therapy	5/22 (22.7%)	68/598 (11.4%)	2.29 (0.82, 6.41) 0.114	2.11 (0.57, 7.81) 0.263
Geographical area				
Center	9/22 (40.9%)	251/733 (34.2%)	Ref.	
North	5/22 (22.7%)	226/733 (30.8%)	0.62 (0.20, 1.87) 0.393	
South	8/22 (36.4%)	256/733 (34.9%)	0.87 (0.33, 2.29) 0.781	

Bold values are those statistically significant, as reported in the text.
[a] Statistical analyses were performed excluding missing data for every single item considered.

to ascertain NAC involvement as the main surgical criterion for NSM indication instead of a centimetric tumor to nipple distance cut-off. Intraoperative histopathological NAC examination is performed in most EBC cases (84.4%) being an important indication for NSM. Despite Petit's results (2009) but in accordance with the findings of Veronesi (2013), IORT has gained no acceptance in Italy [10,17].

Present study shows an overall success rate of 88.5%, calculated considering NAC removals. NAC removal, for different reasons and at different times, with NSM "converted" to a skin-sparing mastectomy, can be considered as a surrogate of the correct surgical case selection and treatment achievement.

One of the primary end-points of the study, concerning all cases both prophylactic and therapeutic, is surgical outcomes: NAC necrosis, skin envelope necrosis and major surgical complications. Rates are 4.8%, 2.9% and 4.4% respectively, coherent with current literature [2,3,6,7,9,10,13,18–20]. Smoking is the sole significant risk factor confirmed at multivariate analysis for necrosis, both of NAC and skin-flap. A history of previous breast radiation therapy is a significant risk factor for at least one major surgical complication after NSM.

The other primary end-point of the study is oncological outcomes: locoregional and systemic recurrences, referred to primitive EBC cases only. Rates are once again coherent with published data [1–3,6,13,18,21,22].

As for locoregional recurrences (2.9% in present analysis), tumor's greatest focus dimension >3 cm is a significant risk factor. On the contrary, PgR positivity is significant at multivariate analysis as a protective factor. This confirms that less aggressive tumor biology, with hormone receptors positivity (PgR positive cases are almost always ER positive as well), is a good prognostic factor as highlighted in NCCN guidelines and recent meta-analysis [23,24], even with a relatively low number of registered events.

The numerosity of the sample and the great number of investigated parameters make this study a comprehensive picture of actual state of the art of NSM in Italy. This is corroborated by the almost homogeneous geographical distribution of participating centers, in a recent and relatively long period of time. National registry and present analysis represent a multicentric effort to depict NSM results on a wide scale.

Limits of the study are its retrospectivity as for a couple of years out of the six-year period of the cohort. Other limits are intrinsic in a voluntary and non controlled data registration, which might have biased the patients selection. Further limits come from the nature of the website registry, which allows the input of cases

even with missing items. Therefore some results might be distorted if missing data for any specific item are arbitrary rather than fortuitous.

In our opinion, even with such limits, the scope of registry has been attained and this work is a rare example of a NSM series from different Institutions and not from a single center. A nation-wide NSM analysis is possible and can make data comparable between centers and with current international literature.

Conclusions

In conclusion, NSM procedure represents a widespread surgical approach in Italy. Prophylactic mastectomies are more than 10% of all NSM. MRI is increasingly used as a pre-operative tool over time in all the different geographical areas. Surgical and oncological outcomes are coherent with published data. NAC necrosis rate is 4.8% and NAC recurrence is a rare event (0.7%). Smoke is a risk factor for necrosis. Previous radiation is a risk factor for major surgical complications. Tumors greater than 3 cm are at risk of locoregional recurrence, while tumor PgR positivity is a protective factor from locoregional recurrences. Results show that NSM is safe and effective, both surgically and oncologically, on a National scale.

Ethical standards statement

Study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

No Institutional Ethical Approval required.

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Conflict of interest statement

All Authors disclaim any conflict of interest.

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