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ORIGINAL ARTICLE – BREAST ONCOLOGY

Oncological Outcomes of Nipple-Sparing Mastectomy: A Single-Center Experience of 1989 Patients

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ABSTRACT

Background. Nipple-sparing mastectomy (NSM) is increasingly used in women with breast cancer who are not eligible for conservative surgery, but extensive outcome data are lacking and indications have not been established.

Objective. The aim of this study was to assess the oncological outcomes of NSM in a large series of patients with invasive or in situ breast cancer treated at a single center.

Methods. We analyzed 1989 consecutive women who had an NSM in 2003–2011, for invasive (1711 patients) or in situ cancer (278 patients) at the European Institute of Oncology, Italy, and followed-up to December 2016. Endpoints were local recurrences, recurrences in the nipple-areola complex (NAC), NAC necrosis, and overall survival (OS).

Results. After a median follow-up of 94 months (interquartile range 70–117), 91/1711 (5.3%) patients with invasive cancer had local recurrence (4.8% invasive disease, 0.5% in situ disease), and 11/278 (4.0%) patients with in situ disease had local recurrence (1.8% invasive disease, 2.2% in situ disease). Thirty-six (1.8%) patients had NAC recurrence, 9 with in situ disease (4 invasive and 5 in situ recurrences), and 27 with invasive disease (18 invasive and 9 in situ recurrences). NAC loss for necrosis occurred in 66 (3.3%) patients. There were 131 (6.6%) deaths, 109 (5.5%) as a result of breast cancer. OS at 5 years was 96.1% in women with invasive cancer and 99.2% in women with in situ disease.

Conclusions. The findings in this large series, with a median follow-up of nearly 8 years, indicate that NSM is oncologically safe for selected patients. The rate of NAC loss was acceptably low.

Nipple-sparing mastectomy (NSM) springs from Umberto Veronesi's maxim "from maximum tolerable treatment to minimum effective treatment".[1] It is also a direct result of the development of oncoplastic surgery in breast cancer, which associates tumor removal and preparation of skin flaps with immediate breast reconstruction and remodeling to give better aesthetic outcomes, without compromising local disease control. Immediate reconstruction allows women to avoid further surgery to restore body image.[2] NSM is closely similar to skin-sparing mastectomy (SSM), but the former is the real conservative innovation in that the nipple-areola complex (NAC) is preserved as well as the skin. NSM is associated with superior aesthetic outcomes and increased patient satisfaction compared with non-conservative mastectomy.[3] Furthermore, psychosocial and sexual wellbeing have been reported as being better in NSM patients than SSM patients.[4–7] Nevertheless, not all studies agree that NSM is better than SSM. For example, Van Verschuer et al.[8] assessed patient satisfaction, body image, and satisfaction with the NAC after a median follow-up of 65 months in SSM patients and 27 months in NSM patients ($p < 0.01$).

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The NAC was reconstructed in the SSM group. Satisfaction was better in the SSM group, while body image and NAC-specific satisfaction did not differ between the two groups.

One of the most important causes of dissatisfaction after NSM is loss of nipple sensation.[9] The review by Sisco and Yao noted that sensory outcomes after NSM were variable, with normal sensation self-reported in the range of 10–43%.[10] A Swedish study that investigated tactile, thermal, and nociceptive sensitivity after risk-reducing bilateral mastectomy (usually with regrafted NAC) in 46 patients (92 breasts) found total loss of NAC sensitivity in 62% of breasts, with altered sensitivity in the remaining 38%.[11–13] There are currently no widely accepted criteria for selecting patients for NSM. The guidelines of the National Comprehensive Cancer Network[14] suggest that NSM is acceptable when the cancer is at least 2 cm from the nipple, there is no instrumental or clinical evidence of disease in the nipple, and the primary is early stage with favorable biological characteristics. However, the local recurrence rate has been found to be low in studies where the tumor-nipple distance was < 2 cm, suggesting that 2 cm is too cautious and that absence of disease on intraoperative retroareolar frozen section is more important.[15,16]

The aim of the present study was to assess outcomes of NSM for invasive and in situ breast cancer in a large consecutive series of women treated at a single center. Primary endpoints were local recurrence, NAC recurrence, NAC necrosis, and overall survival (OS).

PATIENTS AND METHODS

We retrospectively analyzed data on 1989 consecutive women who had an NSM for invasive or non-invasive breast cancer at the European Institute of Oncology (IEO), Milan, Italy, from 2003 through 2011. The data were retrieved from our prospectively maintained institutional database, and the IEO Ethics Committee approved use of the data for our study. In this study, our eligibility criteria for SSM were closely similar to those for mastectomy, except the pathological secretion from the nipple (C4–C5) and Paget's disease were exclusion criteria. Patients with metastatic disease at presentation, phyllodes tumor, inflammatory or recurrent breast cancer, bilateral synchronous breast cancer, and other non-breast primary cancers, were not eligible for inclusion in this study. BRCA mutation carriers without breast cancer who underwent risk-reducing surgery were also excluded from the present series. However, those who received neoadjuvant treatment (with outcome contraindicating more conservative surgery) were eligible for inclusion. While a distance of < 2 cm between NAC and tumor was not an exclusion criterion for NSM, a positive intraoperative retroareolar frozen section was. The biological characteristics of the tumor were not considered in deciding eligibility.

Cases were discussed at weekly multidisciplinary meetings attended by breast surgeons, plastic surgeons, medical oncologists, radiation oncologists, and pathologists. During these meetings, treatment was decided and subsequently proposed to and approved by the patient. The autologous transplant option was decided on prior to surgery after extensive consultation with the patient. The decision for immediate implant versus tissue expander was taken by the plastic surgeon during mastectomy; the patient was informed of the most likely option but was also informed this could change depending on local conditions during mastectomy.

NSM was performed with or without sentinel node biopsy/axillary dissection. In all cases, the breast was immediately reconstructed, either with permanent implants, tissue expanders, or autologous flaps. A total of 1706 patients received immediate breast construction with definitive prosthesis, 290 received a temporary expander with second surgery for definitive reconstruction (typically 6 months later), and 15 received an autologous transplant (latissimus dorsi flap or pedicled transverse rectus abdominis myocutaneous flap).

The types of neoadjuvant and adjuvant treatment administered varied depending on histopathological features, stage, and comorbidities. Patients were seen every 6 months; contralateral breast mammography and bilateral ultrasound were performed yearly. Patients who did not present for 6-month follow-up were contacted to update their status, and were urged to present for check-up.

As described elsewhere,[17,18] experimental intraoperative radiotherapy with electrons (IORT) was administered to 1342 patients with invasive cancer and 197 with in situ disease. Briefly, 16 Gy was delivered to the NAC in a single fraction during surgery, with a lead-aluminum shield inserted over the pectoralis muscles to protect the thoracic wall. The remaining 369 patients with invasive cancer and 81 patients with in situ disease did not receive IORT. Initially, all patients were programmed for IORT to the NAC because we left some retroareolar tissue in the hope that this would reduce the necrosis rate. To reduce the risk of recurrence, we administered IORT. We soon realized that flap vascularization was the key to reducing necrosis,[19,20] and intraoperative retroareolar frozen section was a reliable way of ascertaining whether the NAC was disease-free. As a result, fewer and fewer women were administered IORT and we abandoned the practice in 2011.

In all cases, a retroareolar tissue sample was taken and examined intraoperatively by frozen section. It had to be disease-free in order to proceed with NSM (otherwise SSM was usually performed).

Statistical Methods

The cumulative incidence of local recurrence was assessed from date of surgery to date of any local relapse (including in situ and invasive recurrence of the NAC). Cumulative incidence functions were estimated according to Kalbfleisch and Prentice,[21] taking competing events into account, such as other primary cancer and distant relapse. The Gray test[22] was used to test the effects of influences of irradiation, neoadjuvant treatment, and tumor subtype on cumulative incidence of local recurrences.

OS was assessed from the date of surgery to death from any cause. OS curves were estimated using the Kaplan–Meier method,[23] and the log-rank test was used to assess the significance of differences in OS between subgroups. The analyses were performed using SAS statistical software (SAS Institute, Cary, NC, USA). All statistical tests were two-sided.

A multivariable Fine and Gray proportional subdistribution hazard model was run on patients with invasive disease only, to assess the independent effects of irradiation, neoadjuvant chemotherapy, and tumor subtype on the risk of local recurrence.

RESULTS

Characteristics of the 1989 patients and their disease type are shown in Table 1, according to whether they had invasive or in situ disease. A total of 399 NSMs (patients with invasive/in situ disease) were performed in 2003–2005, 729 in 2006–2008, and 861 in 2009–2011, in relation to an increase in the presentation of patients eligible for NSM, not because indications changed over the study period.

Table 2 shows additional treatments received. All 288 patients in the in situ group received sentinel node biopsy without axillary dissection. In the invasive group, 301 (17.6%) patients received upfront axillary dissection for clinically evident axillary involvement, and 891 (52.1%) patients received sentinel node biopsy, 519 of whom (30.3% of the invasive group) received axillary dissection for a positive sentinel node.

As expected, no patients with in situ disease received neoadjuvant treatment, while 121 (7.1%) patients with invasive disease received neoadjuvant chemotherapy and 19 (1.1%) received neoadjuvant hormonotherapy.

Eighty-one (29.1%) patients with in situ disease received no irradiation treatment, and 197 (70.9%) received IORT to the NAC. In the invasive group, 1342 (78.4%) patients received IORT to the NAC, 114 (6.7%) received external beam locoregional RT, and 255 (14.9%) received no irradiation.

TABLE 1 Characteristics of 1989 consecutive patients with breast disease who received nipple-sparing mastectomy

	In situ disease		Invasive carcinoma	
	N	%	*N*	%
No. of patients	278	100	1711	100
Year of surgery				
2003–2005	69	24.8	330	19.3
2006–2008	95	34.2	634	37.1
2009–2011	114	41.0	747	43.7
Age group, years				
< 35	11	4.0	147	8.6
35–49	170	61.2	1087	63.5
50–59	78	28.1	347	20.3
60+	19	6.8	130	7.6
Menopausal status				
Premenopausal	200	71.9	1320	77.1
Postmenopausal	78	28.1	391	22.9
Histotype				
Ductal	265	95.3	1385	80.9
Lobular	13	4.7	184	10.8
Other	–	–	142	8.3
Tumor size, pT				
Tis	278	100	10	0.6
pT1a/b	–	–	304	17.8
pT1c	–	–	513	30.0
pT2	–	–	738	43.1
pT3	–	–	129	7.5
Not evaluable	–	–	17	1.0
Positive lymph nodes				
0	278	100	864	50.5
1–3	–	–	558	32.6
4+	–	–	289	16.9
Grade				
Unknown			188	11.0
G1	38	13.7	195	11.4
G2	156	56.1	765	44.7
G3	84	30.2	563	32.9
Perivascular invasion				
No	278	100	1117	65.3
Yes	–	–	594	34.7
Tumor subtype				
Unknown	24	8.6	5	0.3
Luminal A	120	43.2	710	41.5
Luminal B (Ki67 ≥ 20%)	29	10.4	514	30.0
Luminal B (HER2-positive)	56	20.1	218	12.7
HER2-positive	44	15.8	121	7.1
Triple negative	5	1.8	143	8.4

HER2 human epidermal growth factor receptor 2

TABLE 2 Additional treatments received by 1989 consecutive patients with breast disease who received nipple-sparing mastectomy

	In situ disease		Invasive carcinoma	
	N	%	*N*	%
No. of patients	278	100	1711	100
SNB/AD				
AD only	0	–	301	17.6
SNB only	278	100	891	52.1
SNB plus AD	0	–	519	30.3
Neoadjuvant treatment				
None	278	100	1571	91.8
Chemotherapy	0	–	121	7.1
Hormonotherapy	0	–	19	1.1
Radiotherapy				
None	81	29.1	255	14.9
IORT to NAC	197	70.9	1342	78.4
External beam	0	–	114	6.7
Other adjuvant therapy				
None	133	47.8	57	3.3
HT	145	52.2	881	51.5
CT	0	–	236	13.8
CT followed by HT	0	–	537	31.4

SNB sentinel node biopsy, *AD* axillary dissection, *IORT* intraoperative radiation therapy, *NAC* nipple-areola complex, *HT* hormonotherapy, *CT* chemotherapy

A total of 145 (52.2%) in situ patients received adjuvant hormonotherapy, while the remainder received no adjuvant treatment. In the invasive group, 236 (13.8%) patients received adjuvant chemotherapy, 881 (51.5%) received hormonotherapy, and 537 (31.4%) received both.

Table 3 shows unfavorable events. There were 11 (4.0%) local recurrences in the in situ group [6 (2.2%) as in situ disease and 5 (1.8%) as invasive disease], and 91 (5.3%) local recurrences in the invasive group [9 (0.5%) as in situ disease and 82 (4.8%) as invasive disease]. Furthermore, there were no axillary or regional lymph node recurrences in the in situ group, but 3 (1.1%) in situ patients experienced simultaneous local and regional recurrence. In the invasive group 27 (1.6%) patients had axillary recurrence, 28 (1.6%) had regional nodal recurrence, and 6 (0.4%) had simultaneous local and regional recurrence. The cumulative incidence of local recurrences (including NAC recurrence) did not differ between groups that did and did not receive irradiation or neoadjuvant treatment (Table 4), but did vary significantly with tumor subtype (invasive group), with the highest incidence in patients with human epidermal growth factor receptor 2 (HER2)-positive and luminal B (HER2-positive) subtypes (Fig. 1). Among the 339 patients with HER2-positive invasive disease (218 luminal B; 121 estrogen receptor/progesterone receptor [ER/PR]-negative), 234 (69%) received trastuzumab or similar. Patients not administered trastuzumab had a significantly greater risk of local recurrence (10-year cumulative incidence 19.5%; 17.4% in luminal B and 25.9% in ER/PR-negative) than those administered trastuzumab (10-year cumulative incidence 6.9%; 4.3% in luminal B and 10.1% in ER/PR-negative) [$p < 0.003$].

TABLE 3 Unfavorable events including NAC removal for necrosis

	In situ		Invasive	
	N	%	*N*	%
No. of patients	278	100	1711	100
Vital status				
Alive	275	98.9	1583	92.5
Deceased	3	1.1	128	7.5
Events				
Locoregional recurrence				
Local recurrence	11	4.0	91	5.3
Local recurrence (in situ)	6	2.2	9	0.5
NAC recurrence (in situ)	5	1.8	9	0.5
Local recurrence (invasive)	5	1.8	82	4.8
NAC recurrence (invasive)	4	1.4	18	1.1
Axillary recurrence	0	0.0	27	1.6
Regional lymph node recurrence	0	0.0	28	1.6
Simultaneous local and regional	3	1.1	6	0.4
Distant metastasis	2	0.7	197	11.5
Other cancer	17	6.1	90	5.3
NAC removal for necrosis	6	2.2	60	3.5

NAC nipple-areola complex

Of the 450 cases with a negative frozen section (and not administered IORT to the NAC), 3 (0.6%) were found positive on definitive pathological examination and the NAC was removed in a subsequent operation. In 76/1539 (4.9%) patients who received IORT and had retroareolar disease on definitive pathological examination, the NAC was preserved; none of these cases experienced NAC recurrence.

NAC necrosis occurred in 6 (2.2%) patients with in situ disease and 60 (3.5%) patients with invasive disease, and was the most frequent unfavorable event affecting the NAC, although there were more NAC recurrences (2.8%) than cases of necrosis in the in situ group. NAC necrosis rates declined over time, from 4.8% in 2003–2005 to 1.4% in 2009–2011.

There were 3 deaths in the in situ group, 1 (0.4%) for breast cancer, 1 (0.4%) for other causes, and 1 (0.4%) unknown, and 128 (7.5%) deaths in the invasive group, 108 (6.2%) for breast cancer, 3 (0.2%) for other cancers, and 1 (0.1%) for cardiovascular disease. It was not possible to ascertain the cause of death for 16 (0.9%) patients. Five-

TABLE 4 Cumulative incidence of local recurrences (including NAC recurrences), overall and according to radiotherapy, neoadjuvant treatment and tumor subtype

	In situ disease				Invasive disease				
	Events/no. at risk	Cumulative incidence (95% CI)		*p* Value	Events/no. at risk	Cumulative incidence (95% CI)		*p* Value	HR[a] (95% CI)
		5-year	10-year			5-year	10-year		
Overall	11/278	3.4 (1.7–6.2)	3.9 (2.0–6.9)		91/1711	3.3 (2.5–4.3)	7.1 (5.5–8.8)		
Radiotherapy									
External					6/114	3.6 (1.1–8.4)	9.9 (2.8–22.5)	0.79	Ref.
IORT to NAC	7/197	3.2 (1.3–6.5)	3.2 (1.3–6.5)	0.51	76/1342	3.4 (2.5–4.5)	7.3 (5.6–9.2)		1.01 (0.44–2.32)
No RT	4/81	3.9 (1.1–10.1)	3.9 (1.1–10.1)		9/255	3.2 (1.5–6.0)	3.2 (1.5–6.0)		0.79 (0.28–2.23)
Neoadjuvant treatment									
No					85/1590	3.4 (2.6–4.4)	7.2 (5.6–9.1)	0.69	Ref.
Yes					6/121	3.3 (1.1–7.8)	5.6 (2.2–11.2)		0.84 (0.36–1.96)[b]
Tumor subtype									
Luminal A	1/120	1.0 (0.1–4.5)	1.0 (0.1–4.5)	0.10	26/710	2.2 (1.3–3.5)	5.2 (3.2–7.9)	0.008	Ref.
Luminal B (Ki67 $\geq$ 20%)	2/29	3.6 (0.2–15.7)	8.5 (0.1–24.4)		27/514	3.2 (1.9–5.0)	7.2 (4.4–10.7)		1.50 (0.87–2.56)
Luminal B (HER2-positive)	4/56	7.4 (2.3–16.5)	7.4 (2.3–16.5)		16/218	4.7 (2.4–8.2)	9.8 (5.2–16.2)		2.08 (1.12–3.89)
HER2-positive	4/44	7.3 (2.4–21.6)	7.3 (2.4–21.6)		14/121	7.0 (3.3–12.7)	14.1 (7.9–22.1)		3.21 (1.67–6.18)
Triple-negative	0/5	–	–		8/143	5.0 (2.2–9.6)	6.0 (2.8–11.0)		1.59 (0.71–3.54)

NAC nipple-areola complex, *CI* confidence interval, *HR* hazard ratio, *IORT* intraoperative radiation therapy, *RT* radiation therapy, *HER2* human epidermal growth factor receptor 2

[a]HRs derived from multivariable Fine and Gray model

[b]Excluding patients who received endocrine neoadjuvant treatment only

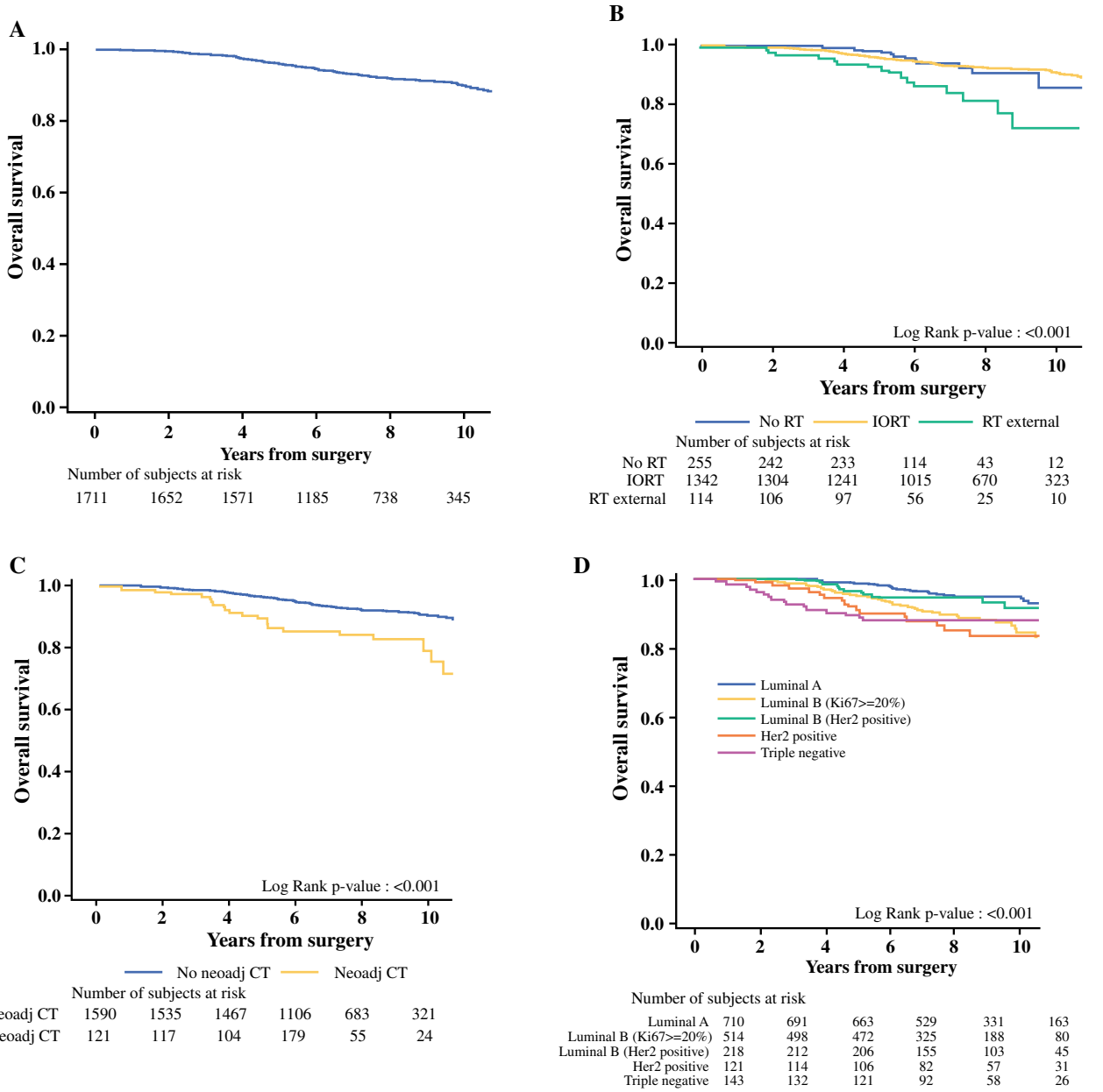

FIG. 1 Cumulative incidence of local recurrences in the invasive group: **a** overall; **b** by radiotherapy; **c** by neoadjuvant treatment; and **d** by subtype. *IORT* intraoperative radiation therapy, *Neoadj CT* neoadjuvant chemotherapy, *RT* radiation therapy

year OS was 99.2% in the in situ group and 96.1% in the invasive group. Corresponding figures for 10-year OS were 98.8% and 90.0%. Subgroups with biologically aggressive disease or advanced stage at diagnosis (for whom neoadjuvant chemotherapy or external radiotherapy was required) had significantly worse OS than other subgroups (Fig. 2).

The results of the multivariable Fine and Gray proportional subdistribution hazard model, which did not differ materially from those of the univariate analysis, are shown in Table 4. A multivariable analysis was not conducted on the in situ group because of the small number of events.

DISCUSSION

From January 2003 to December 2016, we performed approximately 5000 NSMs for breast disease at the IEO. In this study, we assessed patients treated from 2003 to 2011 in order to have a minimum follow-up of 5 years; 2011 patients were treated during this period but we only assessed the 1989 patients not lost to follow-up immediately after discharge.

The local recurrence rate (5.3%) in our invasive patients was closely similar to rates reported after traditional mastectomy.[24–26] As expected, local recurrences were more

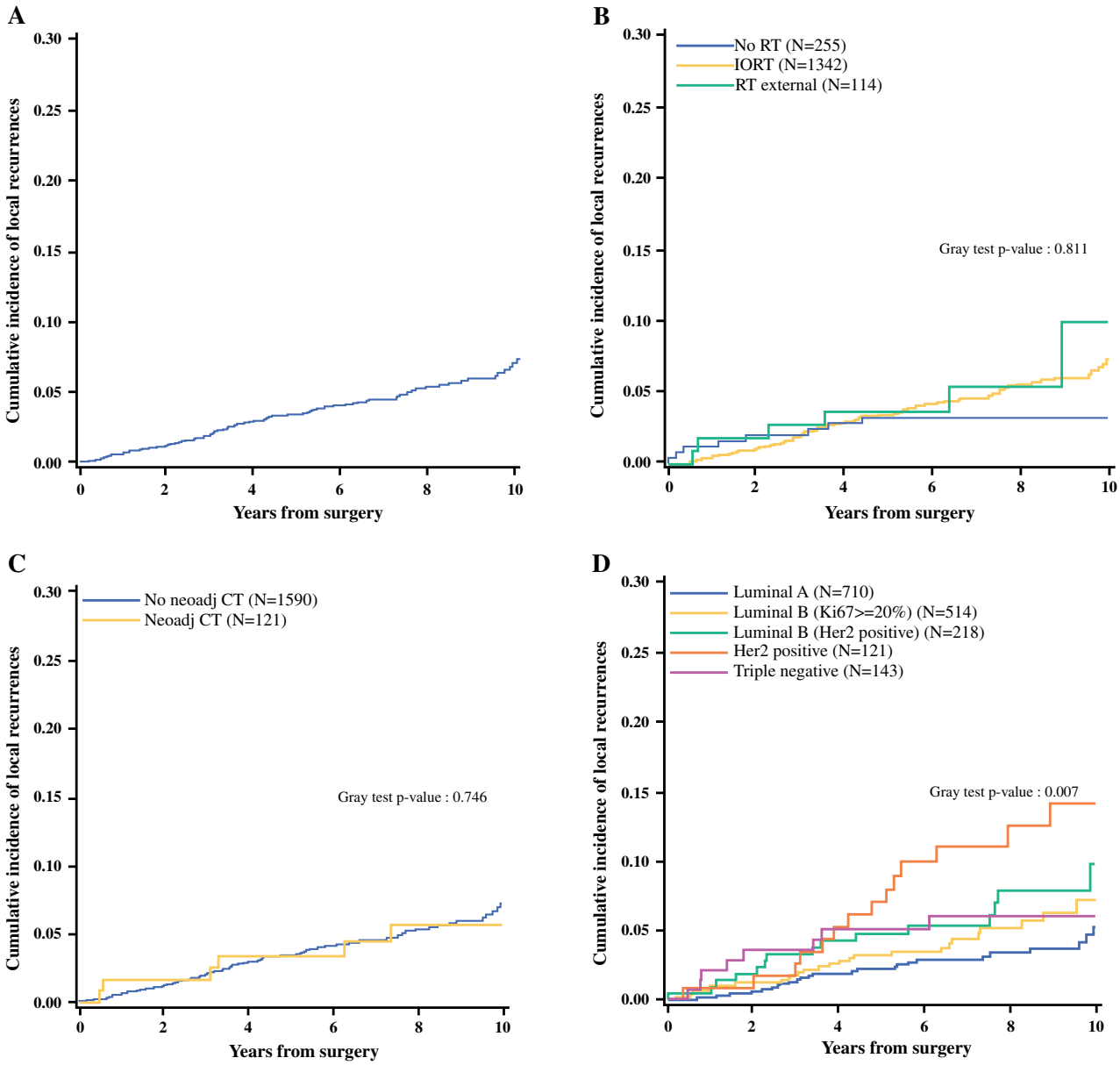

FIG. 2 Overall survival in the invasive group: **a** overall; **b** by radiotherapy; **c** by neoadjuvant (chemo)therapy; and **d** by subtype. *RT* radiation therapy, *IORT* intraoperative radiation therapy, *HER2* human epidermal growth factor receptor 2 , *Neoadj CT* neoadjuvant chemotherapy

frequent in patients with aggressive subtypes and those administered neoadjuvant chemotherapy or adjuvant external radiotherapy for more advanced-stage disease. Patients undergoing mastectomy without NAC preservation experienced similar variations in recurrence.[27–30]

With regard to unfavorable events in the NAC, it is noteworthy that of 278 in situ patients and 1711 invasive patients, only 9 (3.2%) and 27 (1.6%), respectively, had NAC recurrence. These data suggest that preserving the NAC is oncologically safe in the patients selected in our series (those with a negative intraoperative retroareolar frozen section).

We found that only 1 of the 121 patients administered neoadjuvant chemotherapy had NAC recurrence, suggesting that failure to obtain a satisfactory response to neoadjuvant treatment should not automatically exclude a patient from conservative mastectomy.

NAC necrosis is a major complication of NSM.[31] However, in our series, the NAC necrosis rate was contained (2.2% in situ; 3.5% invasive) and was slightly lower than reported elsewhere.[31] It is also noteworthy that NAC necrosis reduced with time, from 4.8% in 2003–2005 to 1.4% in 2009–2011. This is probably due to improvement in surgical technique in relation to a doubling of the

number of NSMs performed in our institute from 2009 to 2011. We found no similar decline in the literature.[31] Factors reported as predisposing to nipple necrosis include patient comorbidity (e.g. diabetes), periareolar surgical incision, type of reconstruction, thickness of the mastectomy flap, positive retroareolar frozen section, and smoking.[32,33] It is unclear whether high body mass index predisposes to NAC necrosis; one study reported a correlation,[34] while another did not.[35]

Ten-year OS in our series was high, in both the in situ (98.8%) and invasive (90.0%) groups. Furthermore, breast cancer-specific mortality was low (0.4% in situ, 6.2% invasive). These results indicate that NSM is oncologically safe.[36] The stratified survival analyses showed that patients with aggressive subtypes, as well as those who received neoadjuvant chemotherapy or external radiotherapy, had poorer survival than other groups. These findings are in line with those in patients who had non-conservative mastectomies,[37–39] and suggest that conducting NSM in patients in these poorer prognosis subgroups is not worse than performing a non-conservative mastectomy.

It is noteworthy that there was no difference in OS between patients who had IORT to the NAC and those who received no irradiation at all. In addition, the cumulative incidence of recurrences did not differ significantly between these two groups. These data provide further retrospective justification for our policy of no longer administering IORT to the NAC in patients receiving NSM.

CONCLUSIONS

Since the main aim of NSM, in combination with immediate breast reconstruction, is to provide better aesthetic outcomes, and hence improve patient quality of life, it is important to assess the complications of breast reconstruction and patient satisfaction. Unfortunately this was not possible in the present study because of database limitations. Nevertheless ample data of other studies[3–8] indicate that aesthetic outcomes are good, and women generally prefer NSM to less-conservative mastectomies. These findings, in addition to the finding of the present study that NSM is oncologically safe, suggest that NSM should be considered the standard of treatment for selected breast cancer patients unsuitable for more conservative surgical approaches, irrespective of the biological characteristics of the primary disease, and whether or not neoadjuvant chemotherapy is administered. We stress that a negative intraoperative retroareolar frozen section is necessary in order to proceed with NSM.

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REFERENCES

1. Veronesi U, Stafyla V, Luini A, et al. Breast cancer: from "maximum tolerable" to "minimum effective" treatment. *Front Oncol*. 2012;2:125.
2. Rietjens M, Urban CA, Rey PC, et al. Long-term oncological results of breast conservative treatment with oncoplastic surgery. *Breast*. 2007;16:387–95.
3. Jabor MA, Shayani P, Collins DR Jr, et al. Nipple-areola reconstruction: satisfaction and clinical determinants. *Plast Reconstr Surg*. 2002;110:457–63.
4. Wei CH, Scott AM, Price AN, et al. Psychosocial and sexual well-being following nipple-sparing mastectomy and reconstruction. *Breast J*. 2016;22:10–7.
5. Didier F, Radice D, Gandini S, et al. Does nipple preservation in mastectomy improve satisfaction with cosmetic results, psychological adjustment, body image and sexuality? *Breast Cancer Res Treat*. 2009;118(3):623–33.
6. Zhong T, Antony A, Cordeiro P. Surgical outcomes and nipple projection using the modified skate flap for nipple-areolar reconstruction in a series of 422 implant reconstructions. *Ann Plast Surg*. 2009;62:591–95.
7. Simmons RM, Adamovich TL. Skin-sparing mastectomy. *Surg Clin North Am*. 2003;83:885–99.
8. Van Verschuer VM, Mureau MA, Gopie JP, et al. Patient satisfaction and nipple-areola sensitivity after bilateral prophylactic mastectomy and immediate implant breast reconstruction in a high breast cancer risk population: NSM versus SSM. *Ann Plast Surg*. 2016;77:145–52.
9. Djohan R, Gage E, Gatherwright J, et al. Patient satisfaction following nipple-sparing mastectomy and immediate breast reconstruction: an 8-year outcome study. *Plast Reconstr Surg*. 2010;125:818–29.
10. Sisco M, Yao KA. Nipple-sparing mastectomy: a contemporary perspective. *J Surg Oncol*. 2016;113:883–90.
11. Gahm J, Hansson P, Brandberg Y, et al. Breast sensibility after bilateral risk-reducing mastectomy and immediate breast reconstruction: a prospective study. *J Plast Reconstr Aesthet Surg*. 2013;66:1521–27.
12. Sarhadi NS, Shaw Dunn J, Lee FD, et al. An anatomical study of the nerve supply of the breast, including the nipple and areola. *Br J Plast Surg*. 1996;49:156–64.
13. Schlenz I, Kuzbari R, Gruber H, et al. The sensitivity of the nipple-areola complex: an anatomic study. *Plast Reconstr Surg*. 2000;105:905–9.
14. NCCN clinical practice guidelines in oncology: breast cancer, version 2.2016. https://www.nccn.org/professionals/physician_gls/default.aspx. Accessed 12 Sep 2018.

15. Fortunato L, Loreti A, Andrich R, et al. When mastectomy is needed: is the nipple-sparing procedure a new standard with very few contraindications? *J Surg Oncol*. 2013;108:207–12.
16. Özkurt E, Tükenmez M, Güven E, et al. Favorable outcome with close margins in patients undergoing nipple/skin sparing mastectomy with immediate breast reconstruction: 5-year follow-up. *Balkan Med J*. 2018;35:84–92.
17. Orecchia R, Veronesi U. Intraoperative electrons. *Semin Radiat Oncol*. 2005;15:76–83.
18. Veronesi U, Gatti G, Luini A, et al. Intraoperative radiation therapy for breast cancer: technical notes. *Breast J*. 2003;9:106–12.
19. Gorai K, Inoue K, Saegusa N, et al. Prediction of skin necrosis after mastectomy for breast cancer using indocyanine green angiography imaging. *Plast Reconstr Surg Glob Open*. 2017;5(4):e1321.
20. De Lorenzi F, Yamaguchi S, Petit JY, et al. Evaluation of skin perfusion after nipple-sparing mastectomy by indocyanine green dye. Preliminary results. *J Exp Clin Cancer Res*. 2005;24(3):347–54.
21. Kalbfleisch JD, Prentice RL. The statistical analysis of failure time data. New York: Wiley; 1980.
22. Gray RJ. A class of k-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988;6:1141–54.
23. Altman DG, De Stavola BL, Love SB, et al. Review of survival analyses published in cancer journals. *Br J Cancer*. 1995;72:511–18.
24. Shimo A, Tsugawa K, Tsuchiya S, et al. Oncologic outcomes and technical considerations of nipple-sparing mastectomies in breast cancer: experience of 425 cases from a single institution. *Breast Cancer*. 2016;23:851–860.
25. Boneti C, Yuen J, Santiago C, et al. Oncologic safety of nipple skin-sparing or total skin-sparing mastectomies with immediate reconstruction. *J Am Coll Surg*. 2011;212:686–93.
26. Sakurai T, Zhang N, Suzuma T, et al. Long-term follow-up of nipple-sparing mastectomy without radiotherapy: a single center study at a Japanese institution. *Med Oncol*. 2013;30:481.
27. Laurberg T, Tramm T, Nielsen T, et al. Intrinsic subtypes and benefit from postmastectomy radiotherapy in node-positive premenopausal breast cancer patients who received adjuvant chemotherapy: results from two independent randomized trials. *Acta Oncol*. 2018;57:38–43.
28. Lai SF, Chen YH, Kuo WH, et al. Locoregional recurrence risk for postmastectomy breast cancer patients with T1-2 and one to three positive lymph nodes receiving modern systemic treatment without radiotherapy. *Ann Surg Oncol*. 2016;23:3860–69.
29. Scheer AS, Zih FS, Maki E, et al. Post-mastectomy radiation: should subtype factor into the decision? *Ann Surg Oncol*. 2016;23:2462–70.
30. Dominici LS, Mittendorf EA, Wang X, et al. Implications of constructed biologic subtype and its relationship to locoregional recurrence following mastectomy. *Breast Cancer Res*. 2012;14:R82.
31. Headon HL, Kasem A, Mokbel K. The oncological safety of nipple-sparing mastectomy: a systematic review of the literature with a pooled analysis of 12,358 procedures. *Arch Plast Surg*. 2016;43:328–38.
32. Lohsiriwat V, Rotmensz N, Botteri E, et al. Do clinicopathological features of the cancer patient relate with nipple areolar complex necrosis in nipple-sparing mastectomy? *Ann Surg Oncol*. 2013;20:990–6.
33. Garwood ER, Moore D, Ewing C, et al. Total skin-sparing mastectomy: complications and local recurrence rates in 2 cohorts of patients. *Ann Surg*. 2009;249:26–32.
34. Setälä L, Papp A, Joukainen S, et al. Obesity and complications in breast reduction surgery: are restrictions justified? *J Plast Reconstr Aesthet Surg*. 2009;62:195–99.
35. O'Grady KF, Thoma A, Dal Cin A. A comparison of complication rates in large and small inferior pedicle reduction mammaplasty. *Plast Reconstr Surg*. 2005;115:736–42.
36. De La Cruz L, Moody AM, Tappy EE, et al. Overall survival, disease-free survival, local recurrence, and nipple-areolar recurrence in the setting of nipple-sparing mastectomy: a meta-analysis and systematic review. *Ann Surg Oncol*. 2015;22:3241–49.
37. Medina-Franco H, Vasconez LO, Fix RJ, et al. Factors associated with local recurrence after skin-sparing mastectomy and immediate breast reconstruction for invasive breast cancer. *Ann Surg*. 2002;235:814–19.
38. Crowe JP Jr, Gordon NH, Antunez AR, et al. Local-regional breast cancer recurrence following mastectomy. *Arch Surg*. 1991;126:429–32.
39. Tokin C, Weiss A, Wang-Rodriguez J, et al. Oncologic safety of skin-sparing and nipple-sparing mastectomy: a discussion and review of the literature. *Int J Surg Oncol*. 2012;2012:921821.