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Review Article

Effectiveness of the Nipples-Saving Mastectomy (NSM): Review on the Results, Oncologic Safety and Surgical Complications

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ABSTRACT

Background: The nipples-saving mastectomy (NSM), most recent technique, allows the whole mammary gland removal preserving the nipple-areola compound (NAC), obtaining oncologic safe results. When indicated, NSM is validated by the great aesthetic results obtained.

Objectives: The objective of this review is the evaluation of the effectiveness and oncologic safety of the nipple-saving mastectomy, marking the most frequent complications. Moreover, the possibility to use the NSM procedure as prophylactic mastectomy in patients at high risk has been evaluated.

Research Methods: A bibliographic research about clinical studies and previous reviews related to nipples-saving mastectomy has been conducted. No limitation about language was performed.

Results: The study included 12 articles, for a total of 2859 patients and 3849 NSM. Patients candidate to NSM, either as a prophylactic or curative treatment of mammary carcinoma, must undergo a careful selection screening. Most frequently occurring surgery-related complications were necrosis and infections; though not altering the cosmetic results, that have been positively evaluated in almost all patients.

Conclusion: Preservation of the areola-nipple compound seems to be oncologically safe and does not increase local recurrences, compared to the previous techniques. Moreover, it is associated with better aesthetic results and patients' higher satisfaction.

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Introduction

Breast cancer (BC) is the most encountered malignant tumor in women [1]. Risk factors for mammary carcinoma include age, exposition to sexual hormones and genetic predisposition [2]. Oncologic risk evaluation and familiar/hereditary predisposition to the mammary and ovarian cancers represented the fundament of prevention so far, and the oncogenetic aims to develop diagnostic, therapeutic and preventive measures for subjects at risk [3]. Epidemiological studies have established the role of familiarity as a risk factor for breast cancer [4]. Some of the genetic mutations have been identified and the related risk

has precisely been assessed (> 50%) [5]. In familiar type, BC has an earlier occurrence age, a more frequent bilaterality, a vertical transmission and a higher association with other neoplasia. BRCA1, BRCA2, TP53 and PTEN were identified as genes associated to hereditary/familiar BC [6]. During the past years, different preventive measures have been diffused to reduce morbidity or mortality of mammary carcinoma, such as prophylactic surgery in patients with positive genetic test, without proven neoplasia. When breast surgery was born in 1894, the surgical technique was very invasive. The "radical mastectomy", introduced by William Stewart Halsted, included the removal of the entire breast with the skin, the superficial muscular level,

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the great pectoral and the small pectoral [7]. Patey introduced an innovative technique, known as “modified radical mastectomy” (MRM), which saved the great pectoral muscle [8].

The request of less invasive surgery techniques, led Madden to modify the procedure, introducing the small pectoral preservation [9]. In contemporary times, aesthetic results become desirable to improve the psychological acceptance of surgery for patients [10]. The saving-skin mastectomy (SSM) described in 1991 by Toth and Lappert, allows to preserve the cutaneous shell and the native infra-mammary crease (IMC) [11]. A meta-analysis carried out in 2010 revealed that SSM and MRM shared the same local recurrence rates [12]. The further evolution was the nipples-saving mastectomy (NSM), preserving the areola-nipple compound; its effectiveness and surgical radicality were long questioned because a bigger section of the mammary tissue was preserved. Then, when Hinton and co. assessed that NSM reached the same local recurrences and survival rates of MRM, the procedure obtained higher consensus [13]. Many studies have confirmed that the conservation of the NAC represents a safe technique, which doesn't increase the risk of local recurrences [14-16]. The purpose of this work is to provide a revision of Literature based on clinical retrospective studies applying the NSM procedure and to evaluate results, oncologic safety and surgical complications of the latter technique.

Research Methods

Electronic databases, such as PubMed, the Cochrane library and the abstract DARE database were checked up to April 2020; the research has been conducted by using English key words “Nipple sparing-saving mastectomy”, “breast cancer”, “mastectomy for cancer”. References of the more relevant articles were manually searched. The last research was concluded on April 15, 2020. The search was carried out by two Authors SP, GG and the obtained results were discussed with the senior Author NP. The inclusion criteria of the study comprised the report of patients affected by breast cancer undergoing NSM; as well as a case series regarding patients undergoing surgery for preventive treatment. The paper's language was not a choice criterion. All studies that failed to fulfil the established inclusion criteria and were about different surgical techniques apart from NSM or performed for benign diseases were excluded by the study.

Results

From the research performed, 12 articles have been selected for this work, for a total amount of 2859 patients and 3849 NSM, 772 proven procedures of oncologic prophylaxis related to the studies [17-28]. The average follow-up varies from 18 to 79 months (Table 1). Most common post-surgery complications were hematoma, occurring in 14.7% of patients of a series, capsular contractures, necrosis [19]. Higher local recurrence ranged from 1-7.3%, [18, 27]. Other complications registered have been summarized in (Table 2).

Table 1: Characteristics of the 12 selected articles.

Reference	Publication year	Patients	NSM performed	Average age, (range)	Average follow-up in months
Grobmyer <i>et al.</i> [17]	2018	136	272	41 (20-67)	53
Radovanovic <i>et al.</i> [18]	2018	435	441	49 (25-75)	79
Dull <i>et al.</i> [19]	2017	110	197	44 (20-77)	Nr
Shimo <i>et al.</i> [20]	2016	413	425	Nr	47
Moo <i>et al.</i> [21]	2016	413	721	Nr	32
Manning <i>et al.</i> [22]	2015	89	177	40	26
Yao <i>et al.</i> [23]	2014	201	397	Nr	33
Voltura <i>et al.</i> [24]	2008	36	51	Nr	18
Crowe <i>et al.</i> [25]	2008	110	149	43 (20-72)	Nr
Petit <i>et al.</i> [26]	2007	749	773	46 (20-73)	18
Sacchini <i>et al.</i> [27]	2006	123	192	45(22-70)	25
Crowe <i>et al.</i> [28]	2004	44	54	43 (29-72)	Nr

Nr: Not reported.

Table 2: Most encountered complications: the results are shown as number of NSM performed or number of patients. The values in parenthesis refer to the percentage values.

Reference	Complications	Number, (%)
Grobmyer <i>et al.</i> [17]	Nr	Nr
Radovanovic <i>et al.</i> [18]	Capsular contracture	33/441 (7,5)
	Infection	15/441 (3,4)
	Seroma	13/441 (2,9)
	Mayor cutaneous necrosis	12/441 (2,7)
	Minor cutaneous necrosis	11/441 (2,5)
	Hematoma	3/441 (0,7)
	Epidermolysis	2/441 (0,5)
	NAC necrosis	1/441 (0,2)
	Local recurrences	32/441 (7,3)

Dull <i>et al.</i> [19]	Necrosis Infections Hematoma Pulmonary edema Seroma	12/34 (35,3) 11/34 (32,3) 5/34 (14,7) 2/34 (5,9) 1/34 (2,9)
Shimo <i>et al.</i> [20]	Necrosis Local recurrences	6/425 (1,4) 25/425 (5,8)
Moo <i>et al.</i> [21]	Local recurrences Distant recurrences Local and distant recurrences	8/368 (2,2) 9/368 (2,4) 6/368 (1,6)
Manning <i>et al.</i> [22]	Necrosis Infection Hematoma	13/177 (7,3) 4/177 (4,0) 3/177 (1,7)
Yao <i>et al.</i> [23]	Necrosis NAC loss	10/397 (2,5) 7/397 (1,8)
Voltura <i>et al.</i> [24]	Local recurrences	2/36 (5,5)
Crowe <i>et al.</i> [25]	NAC partial loss Infection	2/110 (1,8) 1/110 (0,9)
Petit <i>et al.</i> [26]	NAC total necrosis Partial necrosis Infections Local recurrences	26/773 (3,4) 49/773 (6,3) 13/773 (1,7) 12/773 (1,5)
Sacchini <i>et al.</i> [27]	Necrosis Local recurrence	22/192 (11,4) 2/192 (1,0)
Crowe <i>et al.</i> [28]	Nr	Nr

Nr: Not reported; NAC: Areola-Nipple Compound.

Discussion

Radical mastectomy represented the Gold standard treatment for BC over a century. It led to the complete bosom removal, generating psychologic discomfort to the patient who felt disfigured. This technique's aim was the total eradication of the local disease when it has been discovered in advanced phases [7]. The nipples-saving mastectomy (NSM) has been associated to a better aesthetic result and to a decrease in the risk of developing BC [29]. Many studies performed in 2014 have recorded the probabilities to develop BC after NSM to 12,4% [1]. Patients' oncologic risk evaluation is composed by genetic tests, as the BRCA1 and BRCA2 mutations, involved in about 20% of familiar BC [30]. The alteration of these genes leads to uncontrolled cellular proliferation [31]. The estimated average cumulative risk of BC at the age of 70 is 57-65% in patients with BRCA1 mutations and 45-49% in BRCA2 alteration [32-35]. Another mutation gene is related to BC risk: p53, which applies in 50% of all kinds of cancer. Before undergoing mastectomy, accurate screening and selection phases are carried out. Contraindications to the NSM are neoplastic involvement of the nipple and tumor-nipple distance (TND) less than of 2,0 cm in NAC-negative tumors [36]. A recent study demonstrated that a tumor bigger than 2 cm results in a higher risk of nipple involvement [37].

I Choice of the Patient

Grobmyer *et al.* performed a review on NSM procedures, as a preventive surgery in 136 patients (135 women and 1 man) from 2001 to 2007 [17]. 104 patients presented genetic mutations; the BRCA1 in 62 patients, BRCA2 in 35 patients, PTEN in 2 patients, TP53 in 3 patients, ATM in 2 patients. Active smokers, people with big sizes of the bosom and ptosis

were. Dull and co-workers, analysed NSM procedures performed from 2008 to 2014, in patients with tumor-nipple distance higher than 2 cm [19]. Manning and co-workers enrolled carriers of BRCA1 mutation, with a tumor-nipple distance higher than 1 cm [22]. Patients with a big size of the bosom, mammary ptosis and smokers were excluded. Also, Yao and co-workers observed patients with BRCA1 (125 patients) and BRCA2 mutation (76 patients) [23]. Crowe and co-workers evaluated 110 patients, excluding tumors bigger than 3,5 cm or people with clinical involvement in the axillary node, centrally placed tumors and inflammatory mammary carcinoma, as well as those with neoplastic involvement of the nipple and those subjected to pre-surgery chemotherapy [25, 28]. Petit and Veronesi evaluated the results of 773 NSMs performed on 749 patients from 2002 to 2007; they excluded 98 cases because they did not respect the requested standards [26]. The inclusion criteria were BC at least 1 cm outside the margins of the areola, absence of nipple retraction, bloody discharge and/or micro-calcifications in the areolar zone. The remaining articles did not include the analysis of the characteristics of the patients but the decision of submitting patients to NSM procedure was carefully evaluated and indicated to preserve patients' health and safety.

II Surgical Technique

Different surgical techniques were evaluated. Dull used three different incisions: on a total of 197 NSM of his series, 27 have been conducted with a peri-areolar approach, 71 through lateral incision and 99 using an incision in the infra-mammary groove [19]. There were no significant differences on post-surgery complications. Moreover, in 106 (53,8%) patients underwent to tissue-expander reconstructive technique, while 91 patients (46,2%) underwent a direct reconstruction implant. There were

no differences in the complication rates between the two groups of patients, 16,9% and 17,6% respectively. Also, Manning *et al.* performed reconstruction with tissue-expander in 80/89 patients, confirming the USA trend to prefer the expander reconstruction [22, 38]. In Voltura *et al.*, the incision, for all the 51 NSM observed, was the lateral one [24]. Voltura and Crowe did not report the related rates, while, in a previous work, Crowe differentiated the choice of the incision: in surgical prophylaxis procedures, an oblique incision in the external upper quadrant was performed, while in NSM for carcinoma, a lateral incision was realized [25, 28]. These results are comparable to previous investigations; in a retrospective review based on 500 NSM, the complication rate was 21,1% in circumareolar incision cases and 8,5% in infra-mammary incision [39]. In a meta-analysis of 48 studies published between 1970 and 2013, the nipple necrosis rate was similar in both the groups: the circumareolar incision produced a rate of 17,81%, while the lateral and infra-mammary incisions had a necrosis rate of 8,83 and 9,09% respectively [40]. The infra-mammary incision appears to be the most reliable in terms of future complications.

III Most Encountered Complications

The most encountered complications in the 12 selected studies were tissue necrosis, followed by infections, although each study reported different percentages (Table 2). Radovanovic analysed early and late post-surgery complications in 64 procedures (14.51%) [18]. 22/26 ischaemic complications received a conservative treatment, and 4 patients requested the surgical removal of the necrotic skin. 11 patients (2,5%) needed the prosthesis explants. 68 patients (15,6%) developed remote metastasis and 53 (12,2%) deceased during the follow-up period of time. The smoking habit affected the good trend of the treatment: smokers developed complications more than no-smokers [19]. 4 smoker patients in Dull's series developed bilateral complications for infections and nipple necrosis. The remaining studies shown complications rate ranging between 12-18%, consistent with the studies available in literature.

IV Patients Satisfaction

Most studies didn't report on aesthetic results. The only ones examining the cosmetic results and patient's satisfaction were the studies conducted by Petit, Veronesi *et al.* and the one conducted by Voltura *et al.* [24, 26]. In the first paper, the cosmetic results were evaluated with a survey, with a rating from 1 to 10 and 159 patients were examined. The overall result of patients' satisfaction for symmetry, coloration and sensibility of NAC was 8/10. No patients regretted to have undergone a reconstructive surgery and 91,5% agreed that the mutilation was reduced after preserving the NAC. In addition, 93% of the women referred that the conservation of the nipple helped the psychological facing of the disease, and only 1,6% expressed total dissatisfaction. In Voltura and co-workers series, only 36 patients out of 38 submitted to NSM participated to the survey: 22/36 (61,1%) thought that the cosmetic results obtained were 'excellent', 10/36 (27,8%) evaluated as 'good' the results obtained, while 2 patients (5,5%) were not satisfied of the result and have estimated that the cosmetic look was poor. The overall satisfaction of patients submitted to NSM was very high; but only 2 of the studies selected for allowed to perform analysis on this matter. Further scientific investigation are needed in order to expand the study.

V Oncologic Safety

The main endpoint of this review was to evaluate the effectiveness of the NSM in terms of oncologic safety and cosmetic results through the study of clinical cases and written reviews. The analysis revealed that the NSM procedures performed for prophylactic purpose on specific subjects highlighted absence of the involvement of the NAC; while low rates of tumor recurrences have been detected in all the studies. Out of 12 articles consulted, 1 was a study about prophylactic NSM procedures only, so it was not included in the analysis of tumor recurrences after treatment of the mammary carcinoma [17]. The data have been included in the (Table 3).

Table 3: Number of removal of the nipple-areola compound (NAC) and related percentages.

Reference	Nr of removal NAC /NSM	% tumoral recurrences
Grobmyer <i>et al.</i> [17]	/	/
Radovanovic <i>et al.</i> [18]	24/441	5,4
Dull <i>et al.</i> [19]	1/73	1,4
Shimo <i>et al.</i> [20]	10/425	2,3
Moo <i>et al.</i> [21]	1/368	0,3
Manning <i>et al.</i> [22]	8/177	4,5
Yao <i>et al.</i> [23]	3/51	5,9
Voltura <i>et al.</i> [24]	2/34	5,9
Crowe <i>et al.</i> [25]	9/86	10,5
Petit <i>et al.</i> [26]	2/773	0,3
Sacchini <i>et al.</i> [27]	0	0
Crowe <i>et al.</i> [28]	6/37	16,2

Inside the cohorts of cases of breast cancer, the different phases of the disease and the duration of the follow-ups challenged the analysis; the lowest percentages in particular, were very likely influenced by the short follow-up periods, even if a follow-up of about 28 months was proven to be the period at highest risk of local recurrence [41]. Nevertheless, the analysis showed a percentage of tumor recurrences chargeable to the NAC of less than 17%; finally, it seems that the NSM is a feasible procedure with acceptable rates of local recurrences without compromising the short-term oncologic safety.

Conclusion

According to the collected data, NSM does not seem to increase the risk of developing breast cancer; even if the evaluated follow-ups do not allow to verify the long-term action. The NSM procedure seems to be particularly suitable as a prophylactic surgical option on carefully selected patients at high risk. The scientific research should expand the studies with further clinical cases; but, at the moment, the low risk of local recurrences chargeable to the NAC strengthens the oncologic safety of the procedure. The NAC conservation allows to obtain excellent aesthetic results, helping the psychological facing aspect of the disease, but a multi-disciplinary preventive approach is mandatory to explain the risks and the surgical complications related to the procedure.

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Ethical Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing Interests

None.

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