

Grisotti flap reconstruction: on the edge of breast conserving surgery

Mamoplastia com retalho Grisotti: no limite da cirurgia conservadora da mama

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Abstract

Overview and aims: Breast tumors that invade or are proximal to the nipple-areolar complex (NAC) have been classically treated with mastectomy. As an alternative, on the edge of breast conserving surgery, these cases may be approached using central lumpectomy and immediate reconstruction with Grisotti flap. The aim of this study was to determine the involved margins rate and locoregional and systemic relapse rates in patients that underwent this surgical technique.

Study Design: Retrospective observational descriptive study.

Population: Women that underwent central lumpectomy and Grisotti flap reconstruction in our center, during a 4-year period.

Methods: We reviewed clinical charts on patients' data including: diagnosis, indication for surgery, pathological findings, adjuvant treatments and relapse. Descriptive and bivariate analysis was performed.

Results: A total of 45 women were enrolled in the study. From these, 82.2% had invasive breast cancer, and the others had in situ disease. For characterization of tumor proximity to NAC, all patients were evaluated using Magnetic Resonance Imaging. All women underwent central lumpectomy with NAC excision, followed by Grisotti flap reconstruction. From these, 68.9% also underwent contralateral symmetrization on the same operating time. Also, in 80% we were able to perform sentinel lymph node biopsy and in 20% axillary lymphadenectomy was done. Median surgery duration was 71 minutes and median in-hospital stays was 1 day. In two cases, positive margins were present and reintervention was necessary. Considering other cancer treatments, 8.9% underwent neoadjuvant chemotherapy, 48.9% adjuvant chemotherapy, 93.3% radiotherapy and 88.9% hormonal therapy. For a median follow-up time of 31 months, we report one case of locoregional relapse and one case of systemic relapse.

Conclusions: Central lumpectomy combined with immediate Grisotti flap reconstruction is a good alternative for centrally located breast tumors. We report low positive margins rates (4.4%) and low relapse rates (2.3% for locoregional and 2.3% for systemic relapse).

Keywords: Breast cancer; Breast conserving surgery; Grisotti.

INTRODUCTION

Breast conserving surgery, when in combination with radiation, is proven to be safe and equivalent

to mastectomy in early-stage breast cancers, concerning overall survival and disease-free survival¹⁻³. However, centrally located breast tumors, that invade or are proximal to the nipple-areolar complex (NAC) have been classically treated with mastectomy. This relates to the fact that, in these cases, NAC resection is usually needed, because microscopic invasion of the NAC may reach 50% of them. Also, lumpectomy with NAC resection and simple closure is related to unsatisfactory cosmetic outcomes^{1,4-6}. Yet, these tumors can be alternatively treated with central lumpectomy and imme-

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diate reconstruction, using oncoplastic techniques, such as Grisotti flap reconstruction (adjacent skin flap to reconstruct a new areola)^{2,3,7,8}. This approach has been proven to be comparable to mastectomy in terms of adequate margins, local recurrence rates (under 8% at 5 year follow-up) and survival rates. Also, this surgical technique relates to great cosmetic results^{1,5,6,9}. Other diseases, such as Paget's disease of the nipple, where NAC needs to be excised, are also good candidates for this type of surgery¹⁰.

The primary objectives of this study were to determine involved margins rate and locoregional and systemic relapse rates in patients that underwent lumpectomy with concomitant Grisotti flap in the Breast Unit of the Surgical Department from Instituto Português de Oncologia de Lisboa Fernando Gentil (IPOLFG). We also conducted a descriptive analysis on patients and tumor characteristics.

METHODS

This is an observational retrospective descriptive study of patients who underwent lumpectomy and concomitant Grisotti flap reconstruction on the same operating time. Eligible patients for this study were those with breast cancer clinically proximal or invading the NAC or with Paget's disease of the nipple, that underwent the above-mentioned surgery between January 2015 and December 2018, in our center. Data was collected from their medical records.

Information that was obtained from medical records included: age, gender, pathology diagnosis, tumor biomarkers information, TNM staging, tumor location, indication for surgery, other surgical procedures performed at the same time (including information about axillary staging/treatment and contralateral symmetrization surgery), duration of surgery, neoadjuvant or/and adjuvant treatments, surgical complications, follow-up duration, locoregional relapse and systemic relapse information. Indication for surgery, as well as neoadjuvant and/or adjuvant treatments were given case by case, after a multidisciplinary decision.

The surgical technique that was performed was the same as described by Galimberti et al. in 1993⁷. The incision lines were previously marked during surgical preparation: a circle outline of the NAC and another smaller circle just below, surrounded by a comma-shaped line. We began the surgery with deepithelialization of this marked external area, sparing the skin that

would substitute the areola. Then, a circular periareolar cutaneous incision was done, continuing through the breast tissue until the fascia of the large pectoral muscle, in order to remove the tumor with safe margins. Extemporaneous histopathological examination of the tumor was always performed. Surgical clips were placed to mark the area where the tumor was removed. Then, we created a skin-glandular flap from the lower quadrant of the breast adjacent to the removed tissue. This flap was rotated upwards in order to fill the central defect created by the tumor excision. Suturing was done by layers. Contralateral symmetrization of the breast was mostly performed using an inverted-T shaped or short scar mammoplasty. This decision was made considering the size of the patient's breast compared to the tumor size and also after discussion between surgeon and patient. These surgeries were all performed by the same team of experienced oncological breast surgeons from our center.

Concerning sentinel lymph node biopsy (SLNB), a dual technique, with two concomitant tracers, was used: subareolar injection of the radioisotope Technetium-99m sulfur colloid previously to surgery and another subareolar injection of blue dye previous to surgical incisions.

Follow-up time was defined as the time interval between surgery day and the last clinical observation of the patient, until September 2019. Also, time interval until locoregional and/or systemic relapse was calculated on the same fashion. Information about disease relapse also included which organ or system was affected.

International ethical standards were used on the development of this study. Data was analyzed using Statistical Package for the Social Sciences (IBM SPSS Statistics 23.0 version), with descriptive and bivariate analyses. Concerning bivariate analysis, independent-samples T-test was used. Reported p-values are two-tailed, with a p=0.05 indicating statistical significance. Categorical variables are presented as frequencies and percentages and continuous variables as medians and interquartile range. Normal distribution was checked using Shapiro-Wilk or Skewness and Kurtosis.

RESULTS

A total of 45 patients, all of them women, were eligible and included in the study. All of them underwent central lumpectomy and immediate reconstruction



FIGURE 1. Central lumpectomy with immediate reconstruction using Grisotti flap technique, with subsequent nipple-areolar complex tattoo. (Photos kindly provided by Dr. João Vargas-Moniz)

with a Grisotti flap, such as exemplified on Figure 1.

These patients had a median age at time of surgery of 61.6 years-old (Interquartile range (IQR) 54-68 years-old). Table I shows some descriptive characteristics of these patients. The majority of them (82.2%) had a pre-surgical diagnosis of invasive breast carcinoma of no special type (NST), located centrally on the breast, more specifically in a retro areolar location. Five patients had ductal carcinoma *in situ* (DCIS) and there were three patients with Paget's disease of the nipple. Immunohistochemistry of the tumor was performed for all patients and this information is also present on Table I.

All patients were submitted to a breast Magnetic Resonance Imaging (MRI) during their diagnostical evaluation, in order to obtain information about local extent and contralateral disease, and also to investi-

gate the tumor proximity to CAM, which was the indication for surgery in 91.1% of them. Only one patient had anatomopathological confirmation of CAM invasion previous to surgery.

Local and systemic staging of breast cancer was performed in every patient, using TNM staging system. Almost all of them had a tumor size under 5 cm (T1 in 43.2% and T2 in 51.4%). There were no patients presenting with tumor extending to the chest wall or skin. Considering axillary staging, 27.0% of patients were classified as N1, and the others (73.0%) had no clinical or radiological suspicion of lymph node involvement. None of the 45 women had evidence of distant metastasis.

Descriptive statistics of the variables concerning the surgery is presented on Table II. Median operating time was 72.9 minutes (IQR 50-95 minutes). All patients,

TABLE I. DESCRIPTIVE STATISTICS CONCERNING PATIENTS AND THEIR DISEASE

Variable	Median	IQR
Age (years)	61.6	54-68
Variable	n	%
Comorbidities		
None	20	44.4%
Cardiovascular	18	40.0%
Endocrine	6	13.3%
Osteoarticular	5	11.1%
Bronchopulmonary	3	6.7%
Other oncological diseases	4	8.9%
Benign breast disease	1	2.2%
Others	5	11.1%
Menopause status		
Premenopausal	5	11.1%
Postmenopausal	40	88.9%
Diagnosis by breast lesion biopsy		
Invasive carcinoma, NST	37	82.2%
DCIS	5	11.1%
Paget's disease of the nipple	3	6.7%
Tumor estrogen receptors status*		
Positive	40	95.3%
Negative	2	4.7%
Tumor progesterone receptors status†		
Positive	33	89.2%
Negative	4	10.8%
Tumor ERBB2 expression†		
Positive	5	13.5%
Negative	32	86.4%
Tumor Ki-67 level†		
≤ 14%	14	37.8%
> 14%	23	62.2%
Molecular classification of the tumor†		
Luminal-A	14	37.8%
Luminal-B	16	43.3%
Luminal-B with HER-2 type	5	13.5%
Triple Negative	2	5.4%
Indication for surgery		
Centrally located tumor	42	93.3%
NAC proximity	41	
Presurgical pathological confirmation of NAC invasion	1	66.7%
Paget's disease of the nipple	3	
Staging (T)		
Tis	5	11.1%
T1	16	35.6%
T2	19	42.2%
T3	2	4.4%
Staging (N)		
N0	35	77.8%
N1	10	22.2%
Staging (M)		
M0	45	100%

*not performed in Paget's disease of the nipple; † only performed in invasive carcinomas

DCIS – Ductal Carcinoma in situ; IQR – Interquartile Range; NAC – Nipple-Areolar Complex; NST – No Special Type

TABLE II. DESCRIPTIVE STATISTICS CONCERNING THE SURGERY

Variable		Median	IQR
Surgical duration (minutes)		72.9	50-95
In-hospital stay (days)		1	1-2
Variable		n	%
Axillary surgery on the same time		36	80.0%
SLNB		9	20.0%
Lymphadenectomy			
Contralateral symmetrization			
Yes		31	68.9%
No		14	31.1%
Surgical margins status			
Positive		2	4.4%
Negative		43	95.6%
Surgical complications			
Surgical wound dehiscence		1	2.2%

IQR – Interquartile Range; SLNB – Sentinel Lymph Node Biopsy

including those with *in situ* disease, had axillary staging or treatment performed during surgery: those with no clinical suspicious adenopathies (80.0%) underwent SLNB and those with proven axillary disease (20.0%) were selected for complete axillary lymphadenectomy (AL). From the total of patients that underwent SLNB, no one needed reoperation to complete AL. Contralateral symmetrization of the healthy breast was performed in 68.9% of patients, considering their desire for this aesthetic complementary procedure. There were no differences in operating time length between women that underwent contralateral symmetrization and women that did not undergo this complementary procedure (73.1 minutes versus 67.2 minutes; p=0.854). The median in-hospital stay was one day (IQR 1-2 days).

Tumor margins were evaluated by a pathologist, primarily in an extemporaneous histopathological examination performed on the operating room. Then, definitive pathological evaluation and report were done. All patients had presumed intraoperative negative margins. However, after definitive examination, two patients (4.4%) with positive margins for tumor presence were identified. These patients were then reevaluated and proposed for simple mastectomy with immediate breast reconstruction, that they agreed to undergo.

As for surgical complications, we had only one case of surgical wound dehiscence that needed reintervention

for closure two weeks after the primary surgery (Clavien-Dindo IIIb).

Four patients with invasive breast cancer underwent neoadjuvant chemotherapy (NACT) before the decision for surgery: two cases concerned triple negative tumors and the other two cases were purposed for NACT because of tumor size. In all cases, tumor size was reduced but no complete pathological responses were seen. Data regarding neoadjuvant and adjuvant treatments is described on Table III. Adjuvant chemotherapy was given to 22 patients, regarding tumor characteristics, staging and individual comorbidities. All patients except one, including *in situ* disease, underwent locoregional radiotherapy (RT). This patient did not receive RT because she refused. Patients with positive estrogen and/or progesterone receptors were candidates for hormonal therapy, but one patient refused this adjuvant treatment. Premenopausal women (n=11) received Tamoxifen and postmenopausal women (n=29) were given Letrozole.

These patients were then followed by the surgeon that had done their surgical procedure, and also by their oncologist if NACT or adjuvant chemotherapy was previously done. Only one patient was lost to follow-up because she changed country residency. Medical appointments were scheduled each six months and mammogram was performed on an annual basis. Median follow-up time was 31 months (IQR 18-43

TABLE III. NEOADJUVANT AND/OR ADJUVANT TREATMENTS

Variable	n	%
Neoadjuvant chemotherapy	4	8.9%
Adjuvant chemotherapy	22	48.9%
Radiotherapy	42	93.3%
Hormonal therapy	40	88.9%
Tamoxifen	11	
Letrozole	29	

months). During this time, there was only one case of locoregional disease relapse (2.3%) to report, in a patient that had DCIS that relapsed on the same breast, 30 months after surgery. This patient refused RT and hormonal therapy as adjuvant treatments during primary disease. She underwent simple mastectomy for treatment of the relapsed disease. There was also one patient that developed a systemic relapse during follow-up (2.3%), specifically a femur osteoblastic metastasis, detected 32 months after treatment.

DISCUSSION

Breast conserving surgery is challenging in centrally located tumors, which occur in five to 20% of patients⁴. Mastectomy has been classically performed in this cases, because NAC excision is commonly needed for adequate tumor margins and cosmetic outcomes with central lumpectomy and NAC excision are usually poor^{1,5,6}. Thus, alternative breast conserving surgeries need to be considered. Grisotti flap technique involves central tumor resection along with NAC, with advancement and rotation of a dermoglandular flap from the same breast. This creates a new NAC and offers volume replacement⁸.

Even in these centrally located tumors, lumpectomy combined with radiotherapy seems to be no different from simple mastectomy in terms of survival⁹. In this study we report a locoregional relapse rate of 2.3% and a systemic relapse rate of 2.3%, for a median follow-up time of 31 months.

In our study, the majority of patients had an invasive breast cancer (82.2%). Estrogen and/or progesterone receptors were commonly positive. Although we only had one patient with presurgical pathological confirmation of NAC invasion, we performed lumpectomy with Grisotti flap in other 44 women with cen-

trally located tumors. This is consistent with the literature, because it is proven that NAC may be infiltrated with microscopic tumor in up to 50% of tumors that are up to two centimeters distant from the NAC⁴. Breast conserving surgery and Grisotti flap can also be done in women with other centrally located breast diseases¹⁰. We operated on some women with DCIS and Paget's disease of the nipple.

The majority of women in our study were postmenopausal women (88.9%), which can explain the relatively high percentage of patients with other comorbidities. However, these characteristics did not alter our surgical indication, when the patient desired a breast conserving surgery. Also, we consider that the short in-hospital stay, with a median of 1 day reported by us, is an advantage when compared to other surgical procedures, such as mastectomy associated with more complex reconstruction techniques.

Almost all the tumors that we operated on had a T staging of T1 or T2. In larger tumors, even with reconstruction, the cosmetic outcome is not always acceptable and involved margins are frequent. Patients with small retroareolar tumors are the best candidates for Grisotti flap, which is supported by Wagner, et al⁹. However, in our study, there were two patients with T3 staging that underwent lumpectomy and Grisotti flap. These women underwent NACT, in order to downsize the tumor and allow the surgeon to perform an optimal breast conserving surgery. In our view, this strategy is advantageous in patients with a great discrepancy between tumor and breast size, because it permits a more conservative and less mutilating surgery. This treatment option should be considered in more cases in the future, with a careful joint evaluation between surgeons and oncologists.

Apart from tumor size, ideal candidates for Grisotti flap are the ones that have large breast volume and ptotic breasts, because this allows better cosmetic out-

comes, even with larger breast resections^{4,6}, although we did not have access to this variable in our study. However, all women who decided to have contralateral symmetrization (68.9%) underwent an inverted T-shape procedure, which only makes sense if the patient has large breasts and wants to reduce them. For patients with very small breasts, we proposed mastectomy with other reconstruction techniques. For the rest of the patients, we routinely proposed breast symmetrization, if patient agreed. Wagner, et al. consider that contralateral symmetrization should be offered to these women but that this is time consuming and complications may be doubled⁹. However, we did not find any differences in operating times between women who underwent and did not undergo breast symmetrization (73.1 minutes versus 67.2 minutes; p=0.854). Also, we only report one case of wound dehiscence as surgical complications, with resolution after reoperation. We did not encounter any cases of flap necrosis or steatonecrosis, that are regularly reported on the literature⁴.

We report only two cases of positive margins (4.4%). There are several studies concerning margin status in breast conserving surgeries, but few report specific rates for central lumpectomy and Grisotti technique. Also, the number of patients enrolled in every study is relatively small. However, our positive margins rate seems similar or even lower than those reported in the literature. Most authors report 3.1-13.1% of cases with positive margins with this surgery^{5,9,11}. Yet, other studies report higher rates, especially related to DCIS, in which up to 25% may have positive margins, as mentioned by Wagner, et al⁹. We consider that our low positive margins rate is related to the extemporaneous exam that is always performed intraoperatively and also because we have experienced pathologists in breast cancer. We decided to reoperate and perform a simple mastectomy with immediate reconstruction to those two women who had positive margins.

In patients who underwent Grisotti flap, adjuvant treatments should not be any different from other breast tumors. All women should receive local radiotherapy in order to comprise with international recommendations after breast conserving surgery. We only had one patient who refused this treatment. This was our single case of locoregional relapse during follow-up time (2.3%). This woman had a DCIS and refused any adjuvant treatments, including radiotherapy and hormonal therapy. She had a relapse on the same breast approximately 30 months after surgery

and this time she underwent a simple mastectomy with immediate reconstruction. In all our patients, indication for other adjuvant treatments, such as adjuvant chemotherapy and hormonal therapy, was decided in multidisciplinary meetings.

We report a 2.3% locoregional relapse rate during our follow-up time. Moustafa, et al. did not report any relapsed cases, but the mean follow-up time was short (only 12 months)⁵. Other studies report locoregional relapses in up to 9% of operated patients, for a follow-up time of 6 to 76 months^{7,11,12}. Relapses not only relate to invasive breast tumors, but also with DCIS^{9,11}, which has happened in the case reported in our study. Regarding other tumor characteristics, Simmons, et al. state that location and size of the tumor are not significant predictors of local relapse¹¹.

We only reported one case of systemic relapse (2.3%), specifically in a woman who developed a femur osteoblastic metastasis 30 months after surgery. At the time of first diagnosis, this patient had an invasive carcinoma NST, triple negative, staged T2N1. She underwent NACT, adjuvant chemotherapy and radiotherapy. In a study by Wagner, et al. the only patient that developed distant metastasis (3% rate) had also bone metastasis, which was diagnosed 21 months after surgery. No information regarding characterization of the tumor is available⁹. Simmons, et al. also report only one patient with systemic relapse (3.1% rate) and this patient had positive margins in the histopathological examination of the surgical specimen, which differs from our patient¹¹. Again, although information specifically related to this technique is scarce, other studies report distant metastasis in 0-14% of patients, for a mean follow-up time up to 76 months, which is in accordance with our findings^{5,7,9,11,12}.

We did not compare locoregional and systemic relapse rates between central lumpectomy and mastectomy. However, Simmons, et al. concluded, in a retrospective study of 99 patients, that the type of surgery did not influence the relapse rates. After a median follow-up time of two and a half years, local recurrence was found in 6.3% of patients who underwent central lumpectomy compared to 4.5% in mastectomy patients, and systemic metastasis were found in 3% and 3.1% of cases, respectively¹¹. However, no prospective or randomized studies exists on this matter.

Limitations of this study include those inherent to retrospective studies, such as misclassification bias and missing data on the clinical charts. Our number of patients was limited, considering that the indication for

this surgery is very specific. Also, we did not evaluate patients' satisfaction or need for repeated cosmetic surgeries, which are important long-term indicators in breast conserving surgery. Still, we consider that our study has also some strengths. Our reported outcomes are well defined and we had a relatively long time of follow-up when compared with other studies.

In conclusion, central lumpectomy combined with immediate reconstruction such as Grisotti flap is a good alternative for centrally located breast tumors, instead of classical mastectomy. We report low positive margins rates (4.4%) and also low relapse rates (2.3% of locoregional relapse and 2.3% of systemic relapse). This surgery is not long to perform, requires a minimal hospital in-stay and has low surgical complications (we report a 2.2% of surgical complications, specifically wound dehiscence). We consider that immediate contralateral symmetrization should also be offered on the same operating time. However, there are very few studies concerning this subject. More prospective comparative studies with larger number of patients are required to define this surgery as a standard of care for women with centrally located breast tumors.

CONFLICTS OF INTEREST:

There are no conflicts of interest to report.

CONTRIBUTION OF EACH AUTHOR:

Mariana Ormonde: data collection; statistical analysis; writing of the manuscript

Francisco Cabral: data collection; statistical analysis

Catarina R. Santos: study design; statistical analysis; writing and review of the manuscript

Cristina Costa: writing and review of the manuscript

João Vargas Moniz: study design; data collection; writing and review of the manuscript

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RECEBIDO EM: 01/03/2020

ACEITE PARA PUBLICAÇÃO: 06/06/2020