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Feasibility of oncoplastic techniques in the surgical management of locally advanced breast cancer

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ABSTRACT

Background: Locally advanced breast cancer (LABC) is still common in developing countries. The association between neoadjuvant chemotherapy (NC) and oncoplastic surgery (OS) might provide an oncological treatment with satisfactory aesthetic results.
Purpose: The goal was to demonstrate if oncoplastic surgical techniques can be utilized to treat LABC which was submitted to neoadjuvant chemotherapy.
Methods: This prospective clinical trial included breast cancer patients, clinical stage III, who underwent established NC regimen. All patients underwent preoperative planning to control the tumor size and to define the surgical technique. A detailed analysis of the pathological specimen was performed.
Results: 50 patients were assessed and surgically treated. Tumor size ranged from 3.0 to 14.0 cm (median 6.5 cm). Pathologic response was rated as stable, progressive, partial response, and complete response in 10%, 8%, 80% and 2% of the cases, respectively. Seventeen (34%) patients were submitted to OS. No patient had positive margins. Skin involvement was presented in 36% of pathologic specimen.
Conclusions: Oncoplastic surgical techniques for selected patients decrease the rates of radical surgery despite of large tumors. (www.clinicaltrials.gov, NCT00820690).

1. Introduction

The incidence of locally advanced breast cancer (LABC) remains high[1] and requires special attention in developing countries. Non-metastatic LABC comprises tumors greater than 5 cm in diameter or that involve skin or chest wall.[2]

Historically, LABC was treated by radical surgery.[3] Progression of studies over time favored systemic therapy along with locoregional treatment.

The use of neoadjuvant chemotherapy (NC) allows the early initiation of systemic therapy, delivery of drugs through intact vasculature, in vivo assessment of response to therapy, and the possibility of breast-conserving surgery in a selected number of patients. On the other hand, its disadvantages are delayed local treatment, potential drug resistance, poorer response in large tumors, and the possibility of higher surgical risk.[4]

Over time, surgical techniques have advanced to the point where breast-conserving therapy (BCT) has become the standard form of treatment for early stage breast carcinomas.[5,6] By the early 90's Audretsch[7] suggested the use of plastic surgery techniques for the immediate breast cancer treatment. Conceptually, this approach referred to as "oncoplastic surgery", aims at providing safe oncologic treatment through careful pre-operative planning and the incorporation of plastic surgery techniques in order to obtain good oncologic control. Moreover, oncoplastic surgery (OS) very often offers improved overall aesthetic outcomes and favors the achievement of contralateral breast symmetry.[8,9]

In the same way, the mastectomy has changed and Toth & Lappert[10] described the technique of skin-sparing mastectomy (SSM) in association with the removal of malignant tumors. That enabled the maintenance of a large part of the skin and infra-mammary fold facilitating immediate breast reconstruction.[11]

Abbreviations: LABC, locally advanced breast cancer; NC, neoadjuvant chemotherapy; OS, oncoplastic surgery; BCT, breast conserving treatment; AP, anatomopathologic examination; DFS, disease free survival; SSM, skin-sparing mastectomy; PE, physical exam; MG, mammogram; US, breast ultrasound; MRI, magnetic resonance imaging.

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There is no consensus about the following treatment, moreover there are few studies regarding skin-sparing mastectomies and local advanced breast cancer.[12,13]

The purpose of this study was to demonstrate if oncoplastic surgical techniques can be utilized to treat LABC which was submitted to neoadjuvant chemotherapy. The focus was on the possibility of preserving breast shape, particularly using oncoplastic surgical techniques, including immediate breast reconstruction with implants after skin-sparing mastectomy. Therefore, a descriptive analysis of pathologic findings and surgical options was fundamental to the conclusions.

2. Patients and methods

This prospective clinical study was conducted between June/2008 and December/2009, including women with LABC, stage III, no clinical diffuse skin involvement, ECOG 0 or 1, and a confirmed diagnosis of infiltrating ductal or lobular carcinoma.

Exclusion criteria were pregnancy, primary or secondary inflammatory carcinomas, ulcerated tumors, atypical histology, and patient unavailability to undergo all exams.

2.1. Ethics

The study was approved by the local Committee of Research Ethics (135/2008 and 210/2009) and registered on www.clinicaltrials.gov, NCT00820690. Written informed consent was obtained from all subjects.

2.2. Clinical and radiological assessment

Staging was determined by exams. Diagnosis was confirmed by a previous biopsy. Preoperative physical exam (PE) tumor measurements were correlated with mammography (MG), breast ultrasound (US) and magnetic ressonance (MRI). Postoperatively pathologic findings were also correlated with PE, MG, US and MRI. Only the larger diameters were considered. Tumors were measured pre- and post-operatively using a caliper and Pixer Viewer® software version 3.315.R. Physical examination was considered as the gold standard for comparison with pre-chemotherapy radiologic exams as well as anatomopathologic examination (AP) for post-chemotherapy ones (Fig. 1).

Neoadjuvant chemotherapy, consisting of 4 cycles of doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 (4AC) followed by 4 cycles of paclitaxel 175 mg/m^2 (4T).

Pre-therapy, eligibility for any oncoplastic surgical technique to be used were assessed. After chemotherapy, these same aspects were reassessed. Assessments were mostly based on the relation between tumor size and breast volume.

Non-conserving surgeries consisted of radical and modified radical mastectomy. While in this study the oncoplastic surgical techniques included the use of periareolar, superior and inferior pedicle techniques, quadrantectomy with glandular remodeling, dermo-glandular flaps and immediate breast reconstruction with implant after skin-sparing mastectomies.

At the time of diagnostic biopsy, tumor borders were ink-marked on the patient's skin. Oncoplastic surgical treatment was chosen based on tumor size, breast volume, resection of the marked area, obtaining a surgical free margin, comorbidities, and patient desire. All patients underwent axillary lymph node dissection and adjuvant therapy, including radiotherapy assessment.

Patients were followed up from admission up to their last appointment. If a patient did not return for appointments in a period more than twice longer than expected, such individual was deemed lost to follow up.

2.3. Pathological assessment

Surgical specimens were identified according to their topography and spatial position (Fig. 2a). Perioperatively, an experienced pathologist assessed the surgical margins on frozen section (Fig. 2b). In-depth gross and microscopic examinations were performed. All specimens including the skin ink-marked areas of primary neoplasia were completely sectioned for microscopic examination so that residual tumor size could be measured even when it could not be well determined grossly (Fig. 2c). For anatomo-pathologic response assessment, tumoral as well as eventual fibrotic areas, presence of residual disease, macroscopic (residual nidus over small areas) and microscopic (residual scatter cells over original volume) disease foci were evaluated (Fig. 2d).

Final pathologic measurement was based on total tumor size, i.e., the sum of invasive plus non-invasive disease, if present. In cases of complete pathologic

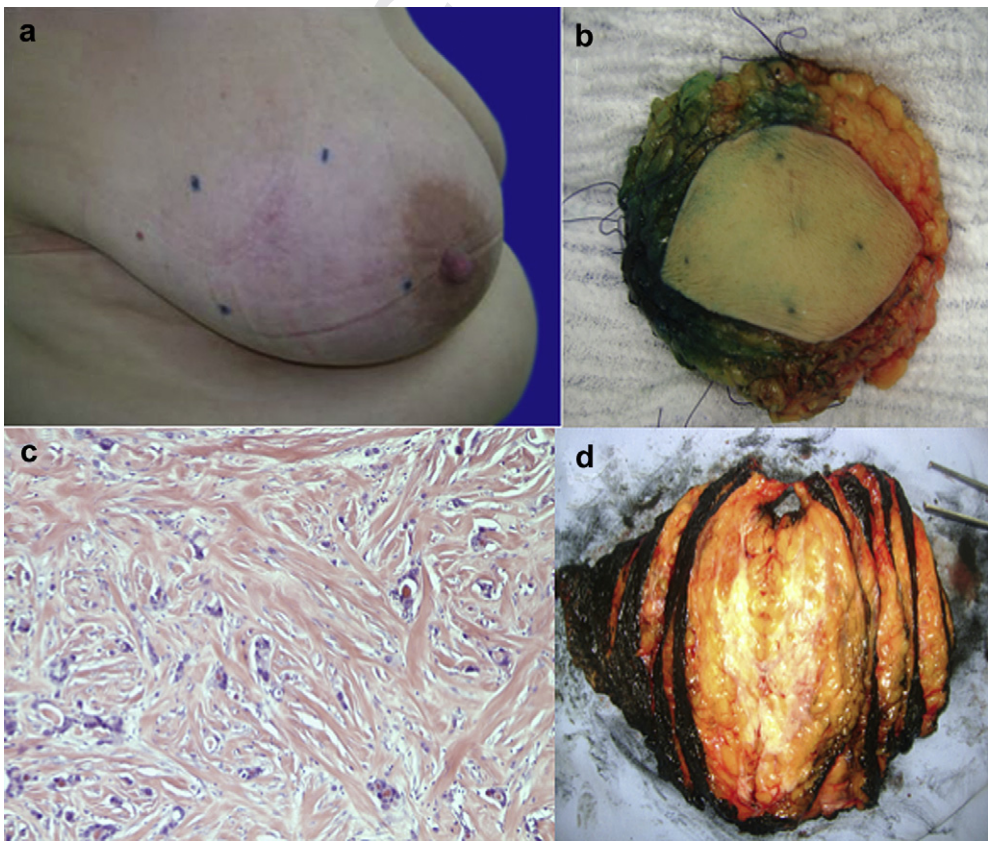

Fig. 1. Sequence of pathological exam: (a) Ink-marked tumor before neoadjuvant chemotherapy; (b). pathologic specimen; (c) gross assessment; (d) microscopic assessment: Multiple foci of residual single cells or small clusters in the midst of extensive fibrosis (100× – hematoxylin-eosin).

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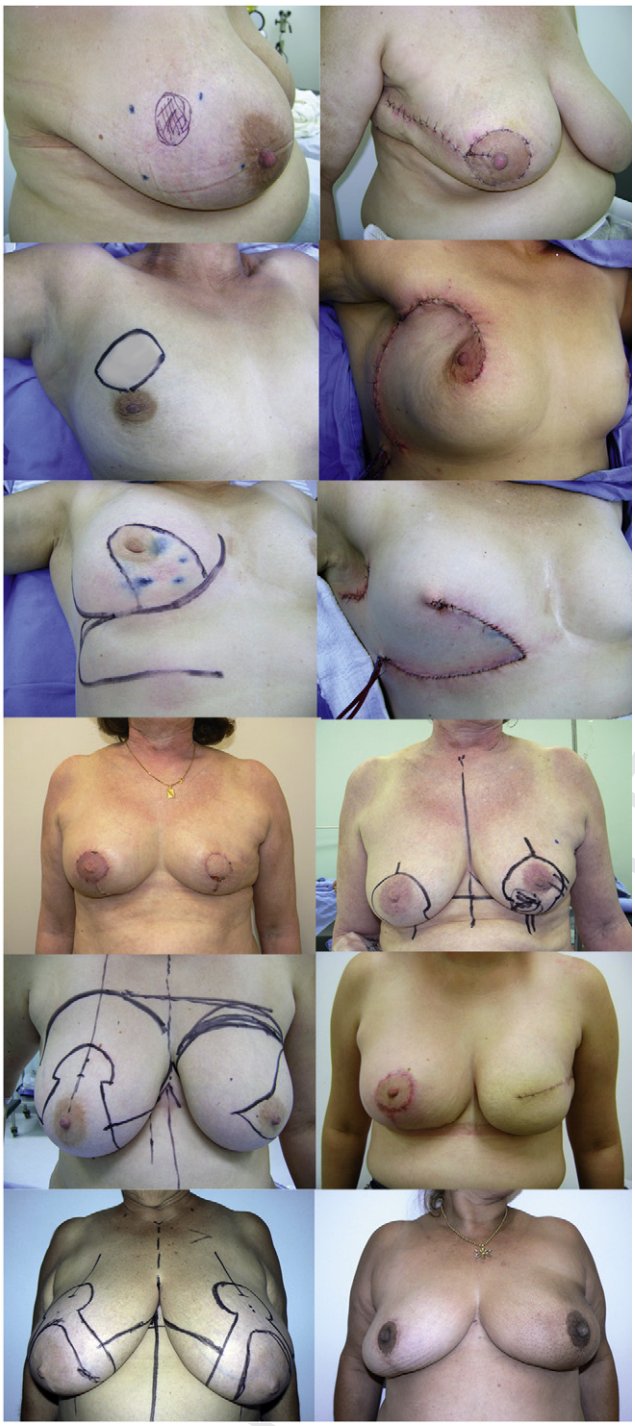

Fig. 2. Different techniques performed: (a) Quadrantectomy with glandular remodeling; (b and c) Locoregional rotational flap; (d) *Plug flap* associated to contralateral symmetrization; (e) Skin-sparing mastectomy using implant and contralateral symmetrization; (f) Left upper quadrantectomy using oncoplastic lower pedicle technique.

response associated with *in situ* residual carcinoma, total tumor distribution estimates were used. If the margins were free, conservative treatment was maintained. On the other hand, when margins were considered small on gross analysis, margin re-excision or classic mastectomy was performed.

2.4. Statistical analysis

A descriptive analysis of the results was carried out. The chi-squared test was performed to verify the relationship among variables and skin involvement. Then logistic regression was used to calculate the odds ratio and certify the results related to the skin involvement. Statistical analysis was performed using Statistical Package for Social Science – SPSS for Windows® version 17.0.

3. Results

Over 21 months, 50 patients were assessed and surgically treated. Patient median age was 45 years (21–65 years). The majority of the cases showed infiltrating ductal carcinoma (92%) while 8% had infiltrating lobular carcinomas (Table 1). Tumor size ranged from 3 to 14 cm (mean size = 6.7 cm, median size = 6.5 cm). Table 2 shows case distribution according to clinical stage (CS) III-TNM and tumor site.

Surgical planning was based on physical examination and imaging techniques prior and after chemotherapy, and also on post-chemotherapy response.

After chemotherapy 17 (34%) of patients were eligible to be operated and actually received some kind of oncoplastic surgical treatment (Table 3, Fig. 2). Of those, 5 (10%) underwent some kind of glandular remodeling for correction of acquired defect, 08 (16%) had skin-sparing mastectomy (SSM), 01 (2%) superior pedicle, and 2 (4%) inferior pedicle, and 1 (2%) underwent rotation of a dermo-glandular flap.

Classic mastectomy was performed in 66% of the patients, and Halsted radical mastectomy in only one case (2%).

The rates of complete clinical, radiologic, and pathological responses were 20% (in 10 patients), 6% (3 patients), and only 2% (1 patients), respectively. All patients showed tumor-negative margins. Table 3 shows the characteristics of the patients undergoing oncoplastic surgery, and examples are provided in Fig. 2. All women receiving conserving treatment had negative margins.

Pathologic responses were classified as stable, progressive, partial and complete in 10%, 8%, 80% and 2% of the cases, respectively. A great variety of pathologic responses was observed. Concentric decrease in tumor size was the most frequent finding (46%), followed by tumor microfragmentation (14%), and macro-fragmentation with multiple foci (12%) (Table 4).

Skin involvement was presented in 36% of pathologic specimen regardless previous clinical exam. The relation between tumor size and skin involvement was statistically significant. Comparing tumor size before ($p = 0.01$) and after ($p = 0.009$) the NC, the logistic regression showed that the previous measurement is a better predictor for skin involvement. The tumor size- > or = 6.5 cm before NC has showed approximately five times more chance of skin involvement, odds ratio = 4.964 (C.I. = 1.40–17.55).

4. Discussion

Neoadjuvant chemotherapy (NC) was introduced as a treatment for breast cancer in the 70 s. Since then, the rate of conserving surgeries has increased, even in LABC cases. Although objective responses to LABC systemic treatment ranging from 60% to 85% have been demonstrated in several studies,[14–16] there is still no consensus about breast conserving LABC treatment after NC.

The lack of uniform methods has led some authors[17,18] to associate LABC with poor prognosis. For some authors, the diversity of pathologic findings indicates the need for mastectomy.[15,19] However, the low recurrence rates reported in selected cases of T3 and T4 shows that these patients could have undergone conserving surgery.[20,21] Nonetheless, given that data on conserving treatment for T3 (>5 cm) and T4 tumors are still scarce, complete skin removal was performed in our cases of focal disease. In addition, whenever the extension of the skin edema was uncertain, classic mastectomy was carried out. The skin involvement stimulate a particular attention to this. 36% of involvement regardless the clinical examination and a better correlation with the tumor size

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Table 1
Profile of the tumors submitted to OS and observed in this series.

Case	Histologic type	ER	PgR	HER-2	Nuclear grade	Angio-lymphatic invasion	Intraductal carcinoma associated	Final AP tumor size(cm)	Number of dissecated lymph nodes	Number of positive lymph node
1	IDC	+	−	+++	III	No	No	1	22	0
2	IDC	−	−	+++	III	Missing	Missing	2	19	0
3	IDC	+	+	+++	II	No	No	1.5	26	3
4	IDC	+	+	+++	III	Missing	Missing	6	23	7
5	ILC	+	+	+++	I	No	Yes	5.5	20	2
6	IDC	+	+	+++	II	No	No	0.6	28	6
7	IDC	+	+	−	II	Yes	No	6.5	18	1
8	IDC	+	−	+++	III	No	No	3.5	6	0
9	IDC	+	+	−	III	No	No	6	7	0
10	IDC	+	+	+++	II	Yes	No	2.2	14	4
11	IDC	+	+	+++	III	No	No	1.5	21	15
12	IDC	+	+	−	III	No	No	8.3	22	0
13	IDC	+	−	−	III	Yes	Missing	0	27	0
14	IDC	−	+	−	II	No	No	4.4	1*	0
15	IDC	+	+	−	III	No	No	3	31	0
16	IDC	+	+	+++	II	No	No	1.2	21	0
17	IDC	−	−	−	III	No	No	4.2	24	0

IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; ER: estrogen receptor; PgR: progesterone receptor; * sentinel lymph node biopsy.

greater than 6.5 cm signalize for complete removal of the skin even after NC. This decision can affect the aesthetic result.

Poor aesthetic results were an impediment to BCT in LABC.[22] The integration of oncoplastic surgical techniques has allowed more extensive resections through alternative incisions that enable the dissection of larger breast volume with good cosmetic results.[7,8] Relatively simple oncoplastic surgical techniques can greatly improve cosmetic outcomes by reshaping the gland after quadrantectomy.[23,24]

This study aimed at associating NC response with oncoplastic surgical techniques in an attempt to provide safe surgical treatment for LABC. No prospective controlled trial has addressed this issue as suggested by Mathew et al.,[25] but these approaches can certainly be used to resect large-volume tumors, including skin. Regaño et al. treated 23 patients with oncoplastic surgery after NC.[26] Kaur et al.[27] demonstrated that oncoplastic techniques allowed removing a larger volume of breast tissue and obtaining wider margins in T1-T2 tumors. Furthermore Clough et al.[8] mentioned new incision options to resect larger tumors with oncologic safe margins.

According to some investigators, BCT should be indicated only when patients have resolution of any skin changes, absence of multifocal or multicentric disease, and residual tumor < 4 cm[28] or 5 cm.[20] However, studies addressing this issue are necessary.

Table 2
Case distribution according to clinical stage (CS) III- TNM and tumor site.

Variable	Category	*N* patients	(%)
CS III	IIIa	32	64
	IIIb	14	28
	IIIc	4	8
CS T-TNM	T2	1	2
	T3	33	66
	T4b	16	32
CS N-TNM	N0	2	4
	N1	35	70
	N2	10	20
	N3	3	6
Breast side	Left	27	54
	Right	20	40
	Bilateral	3	6
Topography	Outer UQ	15	30
	Central Q	10	20
	UpperQQ	9	18
	Medial LQ	4	8
	Lateral QQ	4	8
	Other	8	16
Total		50	100.0

Among our cases, oncoplastic surgeries were indicated when the pathology demonstrated concentric decrease in tumor volume (52.9%), tumor microfragmentation (17.6%), or complete response with tumor absence (5.9%). In these cases of complete pathologic response, clinical and radiologic responses were partial. LABC response to NC is probably induced by a process of tumor segmentation, and is associated with an increased incidence of multifocality and intraductal carcinomas.

Most usually, patients who receive NC have less breast tissue excised. Still, there is a lack of controlled studies assessing pathological response following the complete excision of the original tumor area. In our patients, total excision was made possible by ink-marking the tumor skin projection preoperatively as suggested by Mathieu et al.[29] In addition, imaging methods were also used to determine eligibility for surgery. It is noteworthy that skin tattooing permitted localizing the tumor area, which was completely removed, irrespective of the clinical-radiologic response. Thus, the quality of the measuring procedures and pathologic assessment was assured. The low rate of complete response obtained is due to a more thorough pathologic examination of the specimen regarding that we considered the entire volume of the tumor at pre-operative assessment.

Given that LABC requires the removal of extensive areas viewing oncologic safety, mastering oncoplastic surgical techniques are important to achieve optimal and safe results. Oncoplastic surgical techniques, in turn, certainly permit the excision of the entire preoperatively ink-marked tumor area regardless of tumor response. As they include the complete removal of the skin and parenchyma as well as any resulting lesions such as micro-fragmentation. The experience of the surgeons[30] was essential in the indication for oncoplastic surgery in 34% of our cases. Although

Table 3
Tumor characteristics in patients receiving oncoplastic techniques and type of surgery performed.

Anatomopathologic findings	No (%)
Concentric decrease	22 (44%)
Macrofragmentation with multiple macroscopic tumors	6 (12%)
Tumor microfragmentation	7 (14%)
Stable disease	5 (10%)
Macro and microfragmentation with *in situ* carcinoma	3 (6%)
in situ carcinoma	1 (2%)
Tumor absent	2 (4%)
Disease progression	4 (8%)
Total	50 (100.0%)

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Table 4
Macroscopic and microscopic anatomopathologic findings.

Case	CS-T TNM	Size pre-CT PE (cm)	CS-N TNM	Pre-CT assessment	CT AP response	Size post-CT PE (cm)	Size AP (cm)	Surgery type
1	T3	5.2	N1	Favorable breast/tumor	Tumor microfragmentation	0	1	Quadrantectomy/remodeling
2	T3	5.4	N1	Favorable breast/tumor	Tumor microfragmentation	0	2	Upper pedicle technique
3	T3	5.5	N1	Favorable breast/tumor	Macrofragmentation and microfragmentation with intraductal carcinoma	1.8	1.5	SSM[a]
4	T3	6	N1	Favorable breast/tumor	Stable	2.5	6	Lower pedicle technique
5	T3	6	N1	Favorable breast/tumor	Concentric decrease	2.5	5.5	SSM
6	T3	6	N1	Favorable breast/tumor	Concentric decrease	2	0.6	SSM
7	T3	6.5	N1	Favorable breast/tumor	Macrofragmentation with multiple tumors	4	6.5	SSM
8	T3	7	N1	Favorable breast/tumor	Concentric decrease	2.4	3.5	Quadrantectomy/remodeling
9	T3	7	N1	Favorable breast/tumor	Concentric decrease	3	6	SSM
10	T3	7	N1	Favorable breast/tumor	Concentric decrease	4.3	2.2	Quadrantectomy/remodeling
11	T3	7.8	N1	Favorable breast/tumor	Concentric decrease	5	1.5	Quadrantectomy/remodeling
12	T3	9	N2	Not eligible	Macrofragmentation and microfragmentation with intraductal carcinoma	3	8.3	Lower pedicle technique
13	T4b	3	N1	Favorable breast/tumor	Complete	1.8	0	Quadrantectomy/skin glandular flap
14	T4b	4	N0	Favorable breast/tumor	Concentric decrease	2.1	4.4	SSM
15	T4b	5.5	N2	Favorable breast/tumor	Tumor microfragmentation	2.7	3	SSM
16	T4b	5.5	N1	PT4 allowed BCT	Concentric decrease	3.5	1.2	Quadrantectomy/remodeling
17	T4b	6.5	N2	pT4 allowed BCT	Concentric decrease	3.5	4.2	SSM

[a] SSM: Skin-sparing mastectomy.

this subjective criterion cannot be expressed in numbers, it should certainly be taken into account.

Mainly for small breasts the first option could be associated with the concept of SSM and immediate breast reconstruction.[10] Often SSM involves subcutaneous mastectomy and/or contralateral mastopexy to achieve symmetrization, and therefore, has also been called oncoplastic mastectomy.[31] It provides excellent cosmetic outcome while being oncologically safe. Furthermore there is no consensus about the following radiotherapy treatment and there are few studies regarding skin sparing mastectomies and local advanced breast cancer.[12,13] Woosung et al. demonstrated that SSM after breast reconstruction is oncologically safe for LABC. There was no difference in local recurrence rates between SSM and conventional mastectomies. Only 56.3% of their cases received postoperative radiotherapy.[32]

The problems about the assessment tool depend on patient desire and surgeon experience. So the assessment can be imprecise and it can explain the decrease of indications after chemotherapy. All patients were thoroughly informed about the risk of complications, and poor aesthetic outcomes that could result from the association with radiotherapy.[33]

This study did not focus on the prognostic relationship among findings, but it clearly showed that the variety of pathologic responses seen indicate that the entire pre-chemotherapy tumor area should be removed, and that oncoplastic surgical techniques were a useful approach.

That being said, one might ask the following question: given that the present investigation aimed at removing the pre-chemotherapy tumor area, and plastic surgery techniques allow removing all the marked area with good cosmesis, why administer NC instead of removing the primary tumor? The answer is not quite simple. Despite all controversy regarding neoadjuvant and adjuvant therapies, primary therapy is known to enable assessment of in vivo tumor response, decrease the load of micrometastatic disease and reduce tumor size allowing its removal with safer margins,[34] as well as a better control of locoregional recurrence. Even though NC does not improve overall survival (OS) or disease-free survival (DFS),[25,35] it may offer significant psychological benefits[36,37] as well as the primary surgery. Recently Le Ray I et al. suggested that the use of neoadjuvant therapy in clinical practice should be carefully discussed before implementation to take into account the benefits and risks for the patient. Quality of life could be the cornerstone of this discussion.[38]

Therefore, careful consideration should be given to the use of conserving surgery, especially in LABC cases. Each case should be assessed individually combining clinical and imaging examinations which allows a good surgical planning to add oncoplastic surgical techniques to completely remove the pre-chemotherapy tumor.

5. Conclusions

The use of NC with oncoplastic surgical techniques for the treatment of selected LABC patients might be a good option to avoid radical surgery. It allows removing the entire area supposedly affected with safety and favorable cosmetic outcomes. A detailed pathologic analysis of a defined tumoral area improves the rates of findings. Follow-up data are essential to establish the oncologic and aesthetic efficacy of this treatment modality in the future.

Ethical approval

This paper mention an educational experience so it is not necessary for an Ethical Approval.

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Author contribution

AGZ Matthes and RAC Vieira: study design, data analysis and writing.

Others: data collection.

Conflict of interest

No conflict of interests.

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