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Review Article

Surgical Management of Locally Advanced Breast Cancer: Recommendations of the Brazilian Society of Surgical Oncology

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ABSTRACT

The Brazilian Society of Oncological Surgery organized a group of oncological surgeons to discuss surgical aspects associated with locally advanced breast carcinoma. This article reviews the indications, the different surgeries (especially those associated with thoracoabdominal or myocutaneous flaps), and associated complications. It discusses special conditions such as invasion of the chest wall and interscapular thoracic disarticulation. It makes recommendations based on the literature regarding clinical findings, tumor conditions, response to neoadjuvant therapy, choice of flaps in surgery, and tumor biology.

Introduction

In 2020, a group of breast studies was conducted within the Brazilian Society of Oncological Surgery. The mission was to seek a consensus regarding breast cancer surgery in Brazil. After discussions of potential topics, the group considered a frequent common in Brazil, i.e., a locally advanced mammary carcinoma (LABC), given its frequency and relevance in our environment. We observed the rarity of publications on the subject and chose to conduct a succinct review of the main surgical treatments performed by breast surgeons involved in treating LABC. The group pointed conditions related to this condition as the basis of the recommendations. A literature review was conducted, the text was organized and in the resectability and recommendations sections, points were discussed and organized in the form of a group consensus with the aim of generating recommendations for the surgeons involved in the treatment of patients with LABC.

In Brazil and other developing countries, LABC is a frequent problem that is influenced by limitations in its early diagnosis and treatment flow [1]. The treatment of LABC is not simple, and it involves discussions regarding neoadjuvant treatment, indications of resectability, mastectomy, and options for chest wall closure.

LABC usually presents as advanced breast cancer that is potentially curable with surgery, radiotherapy, and systemic therapy; however, some patients present with primarily inoperable tumors, even without metastatic disease, and other patients with metastatic LABC require palliative or hygienic surgery. There is no definition that encompasses all clinical findings, but there is a consensus that LABC includes extensive invasive disease with varying degrees of involvement of the skin and chest wall and/or profuse regional adenopathy [2-4]. LABC includes tumors larger than 5 cm (T3), tumors of any diameter with involvement of the skin or chest wall (T4) and/or extensive lymph node involvement (N2 or N3), and stages IIB and III can be considered [5].

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Inflammatory breast cancer (IBC) is a subtype of LABC, but it is usually studied separately due to its more severe biological behaviour.

In staging, chest, upper abdomen, and bone scintigraphy or PET-CT scans should be performed if available, although the latter is better for recognizing metastatic disease in this subgroup of patients [6]. In the presence of doubts regarding the potential metastatic disease, controls should be performed, and even then, some patients, even those with metastatic disease, will require hygienic surgery for local control due to ulceration, bleeding, or pain [7]. Breast evaluation most often involves mammography associated with ultrasound; for breast imaging, however, MRI can be considered for surgical planning after neoadjuvant chemotherapy because of high correlation with pathological results [8].

To increase resectability, neoadjuvant chemotherapy is the standard treatment for LABC and shows an overall survival rate equivalent to that of adjuvant treatment, with the advantage of increasing conservative treatment rates and the ability to select the patients with a better likelihood of survival, i.e., those who achieve a complete pathological response (CPR) [9, 10].

Many patients will obtain CPR, defined as the absence of residual tumor in the breast and lymph nodes, which is observed in 3-30% of cases and is considered the greatest predictor of disease-free and overall survival [9, 10]. The rates of CPR vary according to the subtype of disease and access to new drugs. Triple-negative and HER2 tumors have higher CPR rates; rates can be as high as 66% in HER2-positive tumors with double blocking [11-14]. At present, studies have shown increased survival in patients with triple-negative and HER2+ tumors without a complete pathological response who have access to adjuvant treatment with Xeloda (Create-X Trial) and TDM1 (Kathy Trial) [15, 16]. However, a percentage of patients will not respond to neoadjuvant treatment, and about 3% will present disease progression; therefore, it is necessary to be aware of surgical solutions for these patients. Similarly, neoadjuvant treatment should be monitored, and if disease progression occurs after two cycles of treatment, changes in therapy should be considered, and surgical treatment should be considered within a multidisciplinary context.

Surgery should be performed 3-4 weeks on average after the last application of chemotherapy, at which time the myelotoxicity of neoadjuvant chemotherapy has passed and spinal function has been reestablished, allowing safe conditions for surgical resection [17]. Complete resection is required, with free margins that meet the same criteria for free margins in initial tumors. Skin tattooing, metal clip placement clip, noting the area in the medical records, and resection of only the remaining area are discussed in the literature [18]. Additionally, the literature reflects the uncertainty regarding whether to resect the entire original tumor bed or only the residual tumor before systemic treatment; although there is a tendency toward oncological resection of the residual tumor area (and not the original tumor area), but there are no prospective and controlled studies validating this approach [19].

In LABC patients who respond to neoadjuvant chemotherapy, the omission of axillary lymphadenectomy, with the performance of sentinel lymph node research in good responders, has debatable value, although it can be performed in well-selected cases [20]. The presence of ulceration is associated with increased infectious phenomena, and many patients will have to undergo chemotherapy to increase resectability [21]. During surgery, steps should be taken to avoid infectious complications when resecting the lesion, such as covering the ulcerated area and providing therapeutic antibiotic therapy [22, 23]. To increase resectability in borderline situations, i.e., in cases of failure after neoadjuvant chemotherapy, some patients may undergo neoadjuvant radiotherapy [24, 25]. In patients with metastatic disease, the primary indication is based on the presence of ulceration, bleeding, or pain, with consideration of the molecular subtype, the presence of oligometastatic disease, and the metastasis site, or specific subgroups [7, 26]. A review of uncontrolled studies suggests a potential benefit of surgery, but this is not observed in prospective studies with initial randomization or the randomization of good responders [7, 26-30].

Resectability

In patients with LABC, surgical resection should promote local control, even in cases of metastatic disease. There is no sense in performing resection in cases of residual local disease, given the need for complementary treatment. Thus, when evaluating resection, surgical complications, potential morbidity, and associated mortality should be considered. Extensive soft tissue lesions will require myocutaneous or fasciocutaneous flaps for the closure of the defect, and lesions fixed to deep planes may indicate extension to the chest wall and the involvement of the rib cage. Thus, the main resectability criteria are as follows:

i. Adequate clinical condition for extensive surgery;
ii. Potential clinical benefit, determined by local control, with the aim of improving or palliating symptoms;
iii. Planned neoadjuvant sequencing strategies aimed at increasing resectability and adjuvant strategies aimed at increasing local control;
iv. Conditions for the resection of the entire lesion or primary closure of the area may require a team of professionals with knowledge of tumor resection, reconstruction of the skin defect, and/or chest wall reconstruction;
v. In the presence of extension to the axilla and extensive axillary skin resection, extensive flaps should be considered to allow arm mobility, eventually including the use of double flaps or microsurgical flaps;
vi. The presence of surgical complications is not an unresectability criterion in and of itself; however, the surgeon must have knowledge of multiple techniques to select the most appropriate flap and to intervene early in cases of surgical complications and tumors with adverse biological characteristics.

In contrast, tumors with the following criteria are considered unresectable (Figure 1):

i. Lesions with a large extension to the thoracic wall, for which closure of the skin defect would be impossible even with multiple myocutaneous flaps;
ii. Lesions with a large extension to bony parts, for which closure of the chest wall is not feasible;

iii. Lesions with direct involvement of the axillary nerve vasculature plexus, for which resection, even with interscapular thoracic disarticulation, has no curative purpose;

iv. Extensive lesions affecting resection areas that cannot be covered with double or microsurgical flaps;

v. Relative contraindications include tumors, even resectable ones, with aggressive tumor biology evidenced by rapid progression during previous chemotherapy; in such cases, a surgical complication could cause delays in subsequent therapy that allow an early local recurrence.

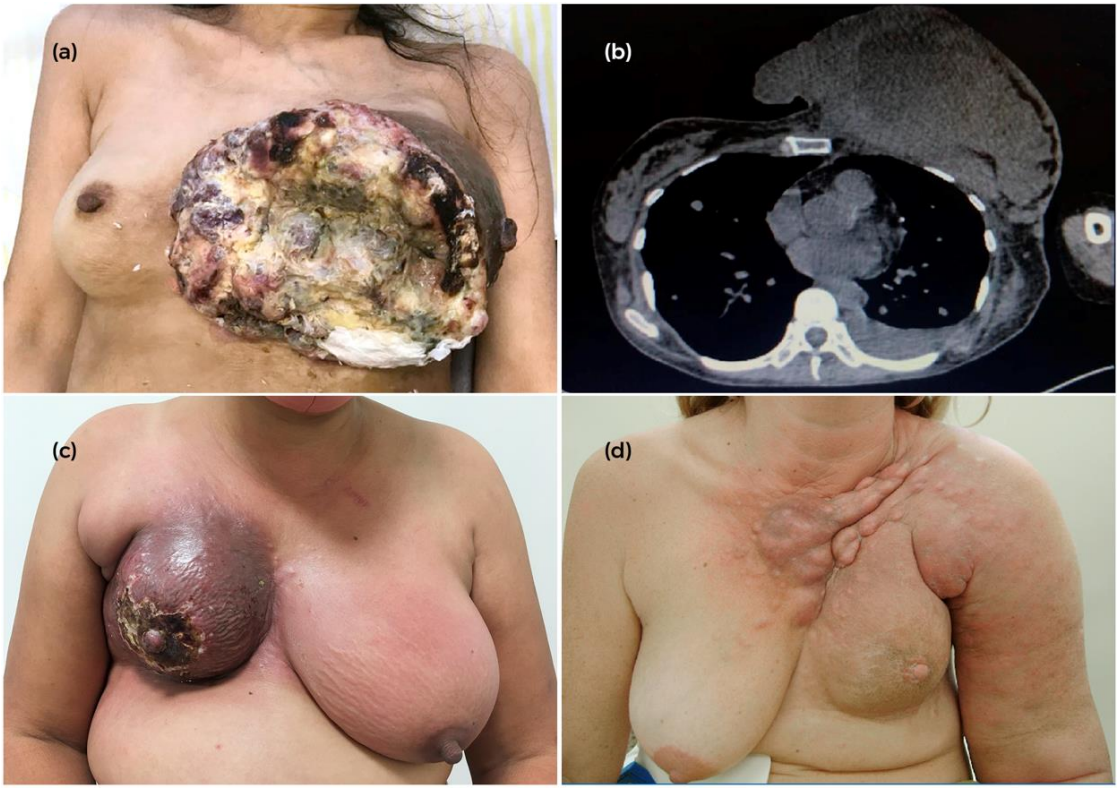

Figure 1: Conditions associated with unresectability. **a & b)** Extensive disease affecting soft tissues and extensive areas of the rib cage and sternum in a patient with pleural metastasis; **c)** bilateral disease with right lateral skin extension that creates a donor area for primary coverage; **d)** extension to the left upper limb and back.

Patchworks

A solution used in the past consisted of resecting the tumor and leaving a bloody area that can heal secondarily or with skin grafts [31]. It is advised to close all skin defects with flaps, although the association of skin grafts is reported in the literature [32, 33]. The main problem with skin grafts is that it increases the time for wound complete healing which makes, increasing the time to start another treatment [34].

The main types of flaps used to close tissue defects resulting from mastectomy for the treatment of locally advanced cancer are fasciocutaneous, dermofat, and myocutaneous [35-38]. In the absence of randomized studies in these repair methods, the choice of flap depends on the extent of tissue loss, the clinical condition of the patient, the need for concomitant chest wall resection based on the experience of the surgical team, and the material resources available [36].

Thoracoabdominal Flaps

Historically, these flaps were classified as dermofat and fasciocutaneous flaps, but this classification has been revised [36, 37]. These flaps are used to close small and medium defects. Their main advantage is the ease of use, but they can be associated with a higher rate of necrosis, greater than myocutaneous flaps. Lateral flaps have a lower rate of necrosis [36, 37].

Thoracoabdominal flaps are described in case series, are easy to perform, do not require the involvement of reconstructive surgeons, and have a higher rate of necrosis than myocutaneous flaps, with variations in the complication rate according to the type of flap [36]. Table 1 reviews previous group publications and update in literature related to the flaps for breast cancer, or VRAM flap in oncologic procedures [34, 36, 38-47]. The main complication is necrosis, with no separation according to the type of necrosis (tip necrosis or more extensive), the treatment performed (expectant or reapproach), the rate of reapproach in the operating room, or the time to the start of the next treatment; these issues should be addressed in future studies. We highlight a flap described and used for major defects, the ipsilateral, thoracoabdominal horizontal, dermofat flap (ITADE; Figure 2a), which allows the closure of areas of moderate extent where myocutaneous flaps would generally be used [36].

Table 1: Series with thoracoabdominal and myocutaenous flaps used in primary closure after mastectomy.

Flap/ Author	Number of cases	Cases with necrosis	Necrosis Rate
Thoracoabdominal Flap			
Deo (2018) [38]	72	8	11.1% total; 8.3% superficial; 2.7% Major
Min [34]	41	17	42.5% 4,9% extensive necrosis
Baroudi	34	10	29.4%
Buratani	30	0	0
Vieira/ ITADE [36]	23	9	34.8% tip necrosis 4.1% extensive necrosis
Deo (2003) [35]	22	2	9.1%
Das	20	1	5%
Persichetti	18	4	22.2%
Kubo/ Romboid [63]	14	2	14.3%
Park-TE (medial pedicle)	10	6	60.0%
Park-TA (lateral pedicle)	9	2	22.2%
Martela	8	0	0
Tai	5	1	20.0%
Lim	3	0	0
Myocutaneos Flap			
Le Boudec/ LD [42]	101	3	3%
Apffelstaedt/ LD [43]	83	14 (7 major)	16.8% 8,4% major
Salmon/ LD	40	2	5.0%
Munhoz/ LD	25	2	8.0%
Woo/ LD	12	0	0%
Amelung	12	4	25%
Micali/ LD	8	3	37.5%
Lee/ EOMF [40]	75	9	12.0%
Bogossian/ EOMF	20	1	5%
Gesson-Paute/ EOMF	9	0	0%
Cordoba/ EOMF	13	1	7.7%
Vieira/ MEOMF [39]	17	12	70.5%
Charanek/ VRAM [45]	55	2	3.6%
Lin/ TRAM [44]	16	1	6.3%
Mir/ TRAM-VRAM [41]*	60	8	13.3%
Mirza/ VRAM[46]**	58	10	17.2%
Daigeler/ VRAM[47]**	78	10	12.8%

Adapted from Vieira *et al.* [36]. New publications included [34, 38-43].

LD: Latissimus Dorsi; EOMF: External Oblique Myocutaneous Flap; MEOMF: Modified EOMF; ITADE: Ipsilateral Thoracoabdominal Dermofat flap. *Reconstruction for breast reconstruction for LABC; **Oncologic patients.

Myocutaneous Flaps

In the reconstruction of postmastectomy defects, there are several options, but basically, three flaps are generally used: the latissimus dorsi myocutaneous flap, the myocutaneous flap of the rectus abdominis, the myocutaneous flap of the oblique abdominal muscle, and potential combinations [2, 39, 40, 44, 48-50]. These flaps are used when the postmastectomy defect area is more extensive and can usually be performed by breast specialists, oncological surgeons and plastic surgeons; in general, they are associated with a lower rate of flap necrosis [36, 39]. Conversely, microsurgical flaps are a good option for the reconstruction of defects after mastectomy; however, they require a team with a high level of training in microsurgery [51]. A myocutaneous flap of the latissimus dorsi muscle (Figure 2b) can be used to close large defects after mastectomy for locally advanced breast cancer. It has a low rate of necrosis, and a large skin donation area can be used, but eventually, a second skin graft is need [2, 42, 43]. The limitation for its use is neoplastic infiltration of the vascular pedicle due to axillary disease.

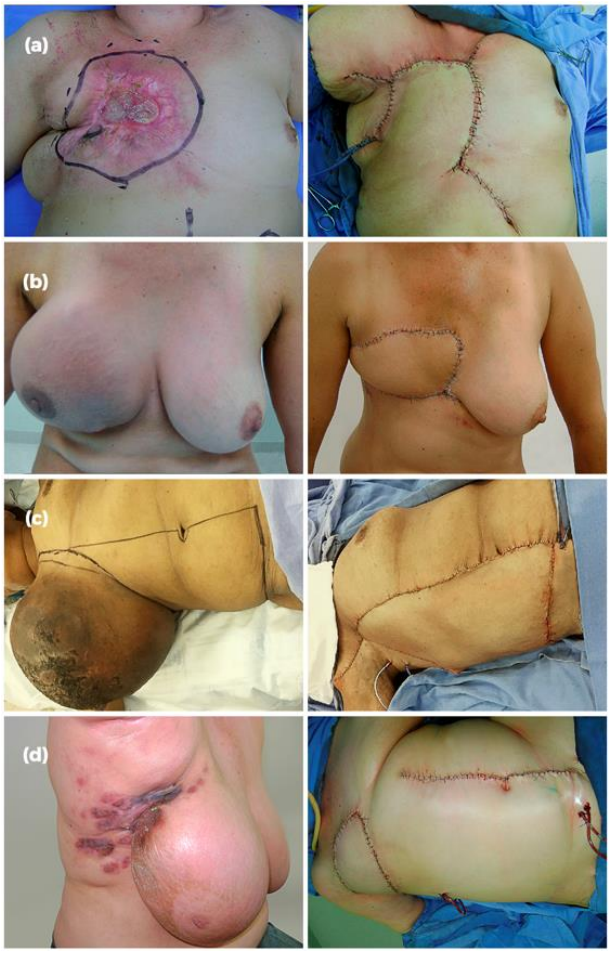

Figure 2: Flaps used for cutaneous synthesis after LABC mastectomy. **a)** ITADE flap; **b)** myocutaneous flap of the latissimus dorsi muscle; **c)** myocutaneous flap of the abdominal oblique muscle; **d)** transverse myocutaneous flap of the rectus abdominis muscle.

Myocutaneous flaps of the rectus abdominis muscle can be transverse (TRAM) or vertical (VRAM; Figure 2d). VRAM flaps is a versatile flap for reconstruction of oncology defects, with few series associated it with breast carcinoma reconstruction for LABC or closure of the chest wall [41, 45-47]. Evaluating series using this flap exclusively for primary closure for oncologic patients the VRAM rate of necrosis was 11.5%, although it was lower when used exclusively for breast cancer patients (3.6%) [45-47]. Comparing these flaps, TRAM offers better cosmetic results than VRAM flap, which may be considered after abdominoplasties [41-52]. These flaps require the involvement of trained surgeons and are associated with complications that impact the patient's quality of life: abdominal incisional hernia, navel necrosis, infection, flap necrosis, and abdominal wall fragility with bulging areas, even in the absence of incisional hernia [44, 48, 49].

The external oblique abdominal myocutaneous flap (EOMF; Figure 2c) have the advantages of fast execution and acceptable complication rates, and they do not require a change in the patient's position during surgery; however, they have a partial and tip necrosis [40]. One publication described a technical modification that allowed the resection of more extensive areas and although it was associated with high rates of necrosis, but the difference in relation to the classical surgery was the non-use of the anterior aponeurosis of abdominal rectus and the greater size of resection [39]. In cases of extensive resections in which the defect cannot be closed with a single flap, it may be necessary to combine flaps, for example, by combining a latissimus dorsi flap with a VRAM [50]. Although these situations are infrequent, if they are necessary, detailed planning should be performed by a team highly trained in all reconstruction techniques.

Reviewing breast cancer patients (Table 1), excluding possible double publication and publications used for general oncologic patients, the general rate of necrosis, for breast cancer patients, was lower in myocutaneous flaps (11.3%) than thoracoabdominal flaps (20.2%), as previously published [35, 36, 46, 47]. No difference was noted in relation to the rate of necrosis between latissimus dorsi (9.9%), classic EOMF (9.5%) and TRAM/VRAM (8.4%) flaps, although more studies are necessary to increase the global casuistry; all the studies were retrospectively carried out and a great variability was observed in relation to the necrosis rate by author.

Recommendations

The main problem affecting surgery involving flaps is the recovery time required before the next treatment (radiotherapy or chemotherapy) can take place, since many of these tumors show aggressive behaviour and

early local recurrence, even with free margins. Necrosis will increase the time until adjuvant therapy, increasing the risk of early recurrence. Thus, when choosing a flap, the potential for top necrosis, which can increase the time of local healing, should be evaluated, since extensive necrosis is an infrequent complication. Similarly, when evaluating the reconstruction of the chest wall, especially with the use of prosthetic materials, flaps with a low necrosis index should be considered, since necrosis can contribute to chest exposure and secondary infection [36].

The choice of flap should be based on tumor extension, the possibility of primary closure, local complications, and tumor biology, factors that determine the benefits of surgical treatment (Figure 3). Generally, in areas with small postmastectomy defects, the upper and lower subcutaneous cellular tissue is detached for closure. Conversely, in small- to medium-sized areas, the use of a thoracoabdominal flap is an option that should be considered according to the surgeon's experience. We advise avoiding skin grafts. Different types of thoracoabdominal flaps are described in the literature, and the surgeon should be aware of the different options (Table 1). Myocutaneous flaps have a lower rate of necrosis than thoracoabdominal flaps. The ITADE flap, despite having a higher rate of necrosis than other thoracoabdominal flaps, allows coverage of extensive areas without the use of myocutaneous flaps [36].

Figure 3: Necrosis. **a)** Tip necrosis; **b)** extensive, requiring surgery. Extensive tumor occupying the axillary cavity; **c)** preoperative; **d)** double latissimus dorsi and abdominal oblique flap; **e)** axillary dehiscence; **f)** early recurrence: bilateral tumor and double flap; **g)** ITADE on the right, latissimus dorsi flap on the left; **h)** dehiscence and early recurrence.

In cases of large defects, the options include myocutaneous flaps such as latissimus dorsi, oblique abdominal muscle, and rectus abdominis muscle flaps. The indications and contraindications of each, as well as the extent of the area to be covered, should be considered. The latissimus dorsi flap is the best because of its flexibility and low complication rate, but its use is limited by the size of the defect and invasion of the thoracodorsal pedicle. The decision to maintain the thoracodorsal pedicle when it is invaded should be based on the patient's clinical condition and curability criteria, even when secondary local radiotherapy will be performed [36].

VRAM and TRAM flaps provide an excellent donor area and can be considered in patients with a high body mass index. TRAM flaps are associated with a higher rate of necrosis, especially when they are monopediculated. The VRAM, which is minimally described in the literature, is a good flap with the disadvantage that it leaves an abdominal scar, a fact that is a background consideration in cases of advanced

tumors [45, 53]. Abdominal oblique muscle flaps allow the closure of large defects; when they are made, the anterior fascia of the rectus abdominis should be used, since studies that have used this tissue show a lower rate of necrosis. The literature presents the use of the anterior fascia of the rectum as an option, and a comparison of studies indicates that its use is associated with a lower rate of necrosis [39]. Despite the lack of prospective studies, we recommend the inclusion of the anterior fascia of the rectus abdominis as a good option.

In the presence of bilateral disease, each side is considered individually, and for closure, reverse abdominoplasty and the use of double flaps may be considered. As previously mentioned, a double flap can also be used when the initial plan proves to be ineffective for covering the area, when there is a need to use flaps without tension at the axillary level, and when the use of skin grafts is not desired. In cases of primary tumor or recurrence in the axillary cavity, the presence of a fold determines the need for more extensive flaps. In such cases, a latissimus dorsi flap is an acceptable option, but potential tumor infiltration of the flap and a microscopical residual disease in the pedicle, should be considered. A VRAM flap should be considered as a primary or second flap [36, 39, 53].

The very thin patient presents a challenge, given the limited donor skin available. In these cases, when a myocutaneous flap is considered, an oblique flap is not a good option [39]. Microsurgical flaps can be used given the presence of surgeons with experience with this technique; however, the rate of failure and partial or total loss of these flaps should be considered. Additionally, when considering concomitant chest wall resection, considerations should include comorbidities as well as pulmonary function, risk of associated infection (especially in the mediastinum), and potential curative nature. In terms of options for local coverage, flaps with a low necrosis index should be considered [54].

Special Conditions

In LABC, chest wall resection is not the rule. In general, the resection of these tumors occurs in selected cases, namely, patients with good clinical conditions and in situations of localized tumor disease, local recurrence, or single localized metastatic bone disease. In the evaluation of resection, complete resection of macroscopic disease (R0 resection) should be used to obtain free margins. When choosing the flap, viable flaps with low complication and necrosis rates should be considered, since in many cases, the chest wall will be replaced by synthetic mesh, where the presence of local complications can be disastrous [55]. The objective is to maintain thoracic stability and minimize dead space, allowing adequate coverage, shape, and function [56, 57].

When resection of the costal arches is necessary, the following considerations generally apply [58]: i) Resection of up to 3 ribs: no reconstruction of the chest wall itself, and a myocutaneous flap can cover the defect and isolate the pleural cavity from the subcutaneous tissue; ii) resection of 4 or more costal arches: in such cases, an unstable thorax may occur, and coverage with myocutaneous flaps may require the reestablishment of the chest wall with meshes, methyl methacrylate, and titanium metal rods. The mortality rate is up to 8.5% in patients who require extensive resections [59]. Another situation that should be discussed in LABC is interscapulothoracic disarticulation surgery. This surgery is usually used in cases of extensive breast tumors, axillary recurrence, brachial plexus infiltration, or sarcoma associated with lymphedema, in which the only curative situation is the loss of the upper limb [60, 61]. Palliative situations are also described in the literature, but their aim is hygienic control and improved quality of life [62].

Perspectives

The literature is open to the development and publication of new surgical techniques, but it is necessary to improve the knowledge regarding the described techniques, complications, and patient evolution. The differences observed in the literature may reflect a retrospective characteristic of the studies and the absence of rigid criteria for the measurement of the necrosis. Regarding the surgical treatment of LABC it is important to evaluate conditions related to the tumor, flap technique, postoperative complications, and generally, the literature focus on these conditions. But it is also important to evaluate conditions related to follow-up, as local recurrence (influenced by margin and molecular subtype); and patient conditions like the quality of life and the possibility of future breast reconstruction. Table 2 shows possible indicators to be reported in future studies.

Table 2: Important conditions to be evaluated associated to surgical management of LABC.

General	Category	Variables
Tumor	Tumor size	-
	Tumor condition	Primary, recurrence; breast, axillary cavum
	Size of resection	-
	Type of resection	R0, R1, R2
	Ulceration	Absent, present
	Time of surgery	Up front; after neoadjuvant therapy (chemotherapy +/- radiotherapy)
	Response to previous therapies	Stable disease; disease progression
	Intention to treat	Curative, palliative
	Metastasis	Absent; Oligometastatic; symptomatic
	Histology	Histology; molecular subtype
Flap technique	Classical description; variation	-
	Irrigation based	Thoracoabdominal or myocutaneous
	Thoracoabdominal	Irrigation based/ random; lateral, medial
	Myocutaneous	Type
	Skin grafts	Absent; association with flaps

	Size of the flap	-
	Time of the surgical procedure	-
	Hospitalization stay	-
	Antibiotics	-
Complication	Absent or present	
	Infection	Primary, secondary to necrosis
	Necrosis	Extension (tip, extensive)
		Depth (epidermolysis, total skin necrosis)
	Treatment of necrosis	Surgical revision, additional procedures: Expectant, local debridement, surgery with general anaesthesia
	Dehiscence	-
	Surgical healing time	Local control; beginning of the next adjuvant treatment
Patient	Patient	Age, BM, Smoking, Diabetes
	Postoperative survival	Comorbidities; Mortality (chest wall resection)
	Quality of life	-
	Secondary breast reconstruction	-
Follow up	Local recurrence	-
	Local free survival	-
	Overall survival	-

Conclusion

In the surgical indication for LABC, the patient's clinical condition, the tumor biology, the response to the established therapy, the presence of distant disease, the need for adjuvant therapy, local hygienic control, and the risk of necrosis should be considered. The pros and cons should be evaluated by the multidisciplinary team and discussed with the patient. The breast surgeon must have the knowledge of the different surgical options of choice for surgical treatment of LABC, a fact that will reflect in the resectability, or the necessity or not of another reconstructive surgeon.

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