



Current weaknesses of breast conserving strategies after neoadjuvant chemotherapy in breast cancer treatment

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Abstract: Locally advanced breast cancer (LABC) represents a worldwide major challenge, with a reported incidence reaching up to 90%. In such setting, current guidelines advise for neoadjuvant chemotherapy (NACT) as primary approach to provide effective systemic treatment while surgically down-staging the cancer at presentation. Despite advantages of NACT, ranging a reported locoregional response rate from 30% to 70%, several national surveys still describe higher mastectomy rates than expected. This phenomenon can be ascribed to radiology related factors, as the role of magnetic resonance imaging (MRI), despite having the highest correlation coefficient to final pathology, may still underestimate and overestimate tumor size, leading to surgical over and under treatment; surgeon related factors, as many breast surgeons routinely perform surgery based on pre-treatment characteristics rather than more appropriate post-treatment imaging and clinical results; patient related factors, as there is a well-documented tendency to prefer mastectomy instead of breast conservation therapy (BCT), in an attempt to reach better oncologic outcomes and hospital related factors, as there is too much variability between breast cancer centers, offering modern and minimally-invasive treatments and general hospitals, reporting a difficult access to advanced breast conserving strategies. In this context, the major part of this disinformation sequence is played by an important lacking of strong evidences, mostly regarding the oncologic outcomes of breast conserving surgery (BCS) and oncoplastic surgery (OS). Some recent high impact papers are reporting benefits of OS in LABC treatment, extending beyond improving cosmetic results, to the possibility of obtaining wider excisions with similar oncologic results as observed in patients submitted to classic BCS and mastectomy. Furthermore, what emerges from LABC literature is an imperative need of multidisciplinary breast centers worldwide diffusion, where breast-dedicated oncologists, radiologists and oncoplastic surgeons can offer patient-centered updated diagnostics, treatment protocols and surgical solutions, especially in a very delicate scenario, such as LABC treatment.

Keywords: Locally advanced breast cancer; neoadjuvant therapy; oncoplastic surgery; breast conserving surgery; mastectomy

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Introduction

In screened countries, the use of mammography and increased public awareness of breast cancer have resulted in women having smaller tumors and fewer involved nodes

at presentation, reducing cases of locally advanced primary diagnosis, intended as “large operable cases” at stage IIB–IIIA (T3N0–1) and “truly inoperable cases” (*Figure 1*), with involvement of supraclavicular or internal mammary nodal



Figure 1 Patient with locally advanced ductal carcinoma of the right breast determining a diffuse ulcerative and inflammatory clinical presentation. (A) Front view with diffuse peau d'orange and nipple areola complex ulceration; (B) left view; (C) magnetic resonance imaging, showing right breast 15-cm lesion, with skin involvement (arrows); (D) axillary lymph node involvement.

involvement (T4N2–3)/inflammatory breast cancer (IBC) (1).

Nevertheless, data emerging from National Cancer Database and the CONCORD high-resolution study reveal that approximately 8.5% of American and 4% of European patients still present with locally advanced breast cancer (LABC) (2); estimates that can reach up to 90% newly diagnosed breast cancers in low- to middle-income countries (3).

In such worldwide delicate setting, current guidelines advise for neoadjuvant chemotherapy (NACT) as primary treatment (4).

NACT achieves equivalent overall survival results, disease-free and distant disease recurrence that adjuvant systemic treatment (5-7) making the neoadjuvant approach a valid option, especially in breast cancer subtypes where the need for systemic therapy is clearly indicated, such as human epidermal growth factor receptor 2 (HER-2)-positive and triple negative breast cancers (TNBC) (8,9).

NACT rationale, is to offer effective systemic treatment while surgically down staging the cancer at presentation, potentially rendering operable patients who had been considered inoperable at the time of their diagnosis, as well as facilitating breast conserving surgery (BCS) when patients had initially needed mastectomy, with reported response rates ranging from 30% to 70% (10-15).

Besides the chance to pursue breast conservation, NACT also offers the potential advantage of gauging the sensitivity of the tumor to systemic therapy (16).

Moreover, pathological complete response to systemic therapy (no residual invasive disease in the breast and axilla regardless of the presence of residual *in situ* carcinoma) is a prognostic marker for long-term survival, especially in tumors with negative prognosis, such as TNBC disease (16,17-19).

Finally, in operable patients, NACT may offer the advantage over the adjuvant approach of anticipating

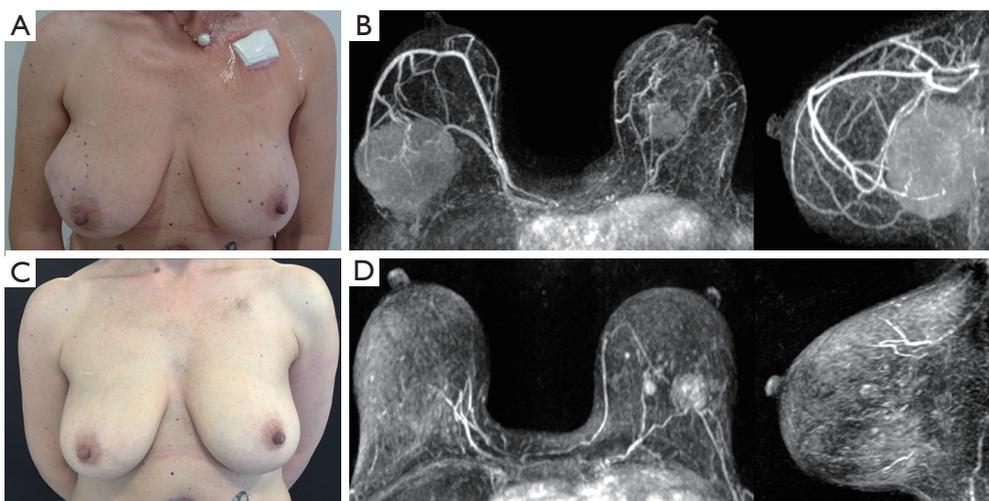


Figure 2 Clinical complete response to neoadjuvant chemotherapy. (A) Patient presenting with a massive T4 ductal carcinoma of the left breast with skin infiltration; (B) magnetic resonance reconstructions, confirming a 9-cm left breast malignant neoplasm, infiltrating pectoralis fascia and overlying skin; (C) clinical complete response; (D) magnetic resonance reconstructions, that confirmed a clinical complete response to neoadjuvant treatment.

administration of systemic treatment with a potential effect on systemic micrometastatic disease (16,18).

Despite these brilliant results of NACT (*Figure 2*), that can potentially lead to a significant decrease in mastectomy rates, several national surveys reported lower BCS than expected.

In 2012, the European Society of Mastology (EUSOMA) reported the results from the EusomaDB survey (a prospective European database), which integrates data from European breast units located in Germany, Switzerland, Belgium, Austria, and Italy, reporting a mastectomy rate of 25.1% (20).

But a wide between-facilities variation was recently evidenced by a French survey, with mastectomy rates between 15.0% and 45.7% (21).

In 2012, a United Kingdom retrospective study on hospital episode statistics (NHS records) showed that among breast cancer patients, 42.3% underwent mastectomy as a primary procedure (22).

In the USA, the multicenter Surveillance Epidemiology and End Results (SEER) study, which covered approximately 28% of the U.S. population, confirmed in 2010 a decreasing trend in mastectomies (23) but subsequent reports revealed higher rates (24,25) and in 2015, a nationwide study on 2.7 million patients, conducted by the American Cancer Society and the American College of Surgeons Commission on Cancer finally revealed a mastectomy rate of 35.5% (26).

The lack of increased rates of BCS may be related to several difficulties:

Radiology related factors

After NACT, magnetic resonance imaging (MRI) has been proposed to have a role in guiding breast cancer surgery by measuring the size of residual tumor and has been shown to have highest sensitivity for detecting residual disease (27).

Currently, the role of MRI, despite having this highest correlation co-efficient to final pathology, may still underestimate and overestimate residual tumor size, leading to surgical over and under treatment.

A recent metanalysis confirmed that both over- and under-estimation by MRI are possible, and observed limit of agreement (± 3.8 cm) shows that errors within that range, that would be crucial for the choice of treatment are still possible and must be carefully avoided (28) by MRI skilled radiologists.

Surgeon related factors

Boughey *et al.* reported that in patients with T2 or T3 tumors, NACT lead to significantly less resected tissue than adjuvant chemotherapy, observing no change in rates of re-excision and thus leading to the conclusion that it is not necessary to excise the entire pre-chemotherapy volume of tissue (29).

Nevertheless, many breast surgeons routinely perform surgery based on pre-treatment characteristics rather than more appropriate post-treatment imaging and clinical results. This commits patients to suboptimal cosmetic results or mastectomy.

Patient related factors

In his systematic review, Hamelinck *et al.* reported that 46% of breast cancer patients prefer mastectomy versus BCS, in an attempt to reach better oncologic outcomes (30).

This observation is a clear evidence that information between patient and clinicians is frequently lacking.

Hospital related factors

Lack of training in breast conserving procedures, such as oncoplastic surgery (OS) was identified in several studies worldwide, determining a high variability among specialized breast centers and general hospitals (31-33).

In Ontario, informal OS training opportunities exist; however, these are not well advertised or well known, leaving interested surgeons to seek out training in a piecemeal fashion (34).

In the United States, only 53% of recent breast surgical oncology fellowship graduates were comfortable performing oncoplastic breast surgery (35).

In their national French survey, Clough and colleagues reported a strong variability in implementation of Level 2 OS between surgeons (1.9–25.0%), with higher and significantly different rate of level 2 OS in dedicated cancer centers versus public practices (16.0% in dedicated cancer centers versus 7.6% in public hospitals) (21).

Factors related to lacking evidences in surgical breast conservation

Surgical management of breast cancer has undergone a continuous and dramatic evolution over the past 4 decades, trending away from radical procedures toward more breast-conserving techniques, that provide patients with greater aesthetic satisfaction (36).

BCS followed by radiotherapy was confirmed by many randomized studies and meta-analyses as an alternative to mastectomy, reaching similar prognostic results while preserving the shape of the breast.

The traditional approach to BCS consists of incision placement over the tumor, resection to clinically and/or

radiographically clear margins, and closure of skin without parenchymal closure, thus leaving a seroma cavity (37-40).

While this may provide adequate cosmesis in the immediate postoperative period, over time the seroma absorbs, leaving a breast contour deformity, which is exacerbated by adjuvant radiotherapy (41).

Factors known to contribute to poor cosmesis in BCS include high tumor volume to breast ratio, excision of >20% of breast volume, tumor location, breast ptosis, and large body habitus (42,43).

Given these conditions, poor cosmesis is verified in up to 40% of BCS patients and has been shown to significantly affect patients' quality of life and psychosocial outcomes (44-47).

In an attempt to optimize the balance between oncologic results and cosmetic outcomes, new surgical procedures that combine the principles of surgical oncology and plastic surgery have been introduced in recent years.

These new techniques called OS allow wider excisions with good oncologic outcomes, limiting the risk of a poor cosmesis (48-51) and further reducing mastectomy rates, thus improving patient's quality of life and self-esteem (*Figure 3*) (52,53).

Initial studies on OS focused primarily on cosmetic results. Only a few large-scale studies have evaluated survival, recurrence rates, and other measures of oncologic safety (54-59).

As a consequence, OS was firstly established as a good compromise between larger excisions and good cosmetic results, but limited evidence hampered OS to become the oncologic leading solution for breast conserving treatment of breast cancer.

Something started to change 3 years ago, when in 2014, Losken and colleagues published a meta-analysis that compared 24 OS papers (3,165 patients) versus 20 BCS papers (5,494 patients) reporting outcomes of both invasive and *in situ* breast cancer cases (60).

Their analysis evidenced a larger average tumor size in the OS group [2.7 cm in OS group versus 1.2 cm in breast conservation therapy (BCT) group] with a significant reduction in positive margin rate defined according to the American Society of Clinical Oncology (ASCO) and the American Society for Radiation Oncology (ASTRO) guidelines, as tumor cells at the cut edge of the surgical specimen (12% in OS group versus 21% in BCS group) (61,62).

With an average follow-up of 37.1 months (range, 12.0–74.0 months) in the OS group, versus 64.4 months (range, 30.0–240.0 months) in BCS group, the authors confirmed that OS lead to a significant reduction in local

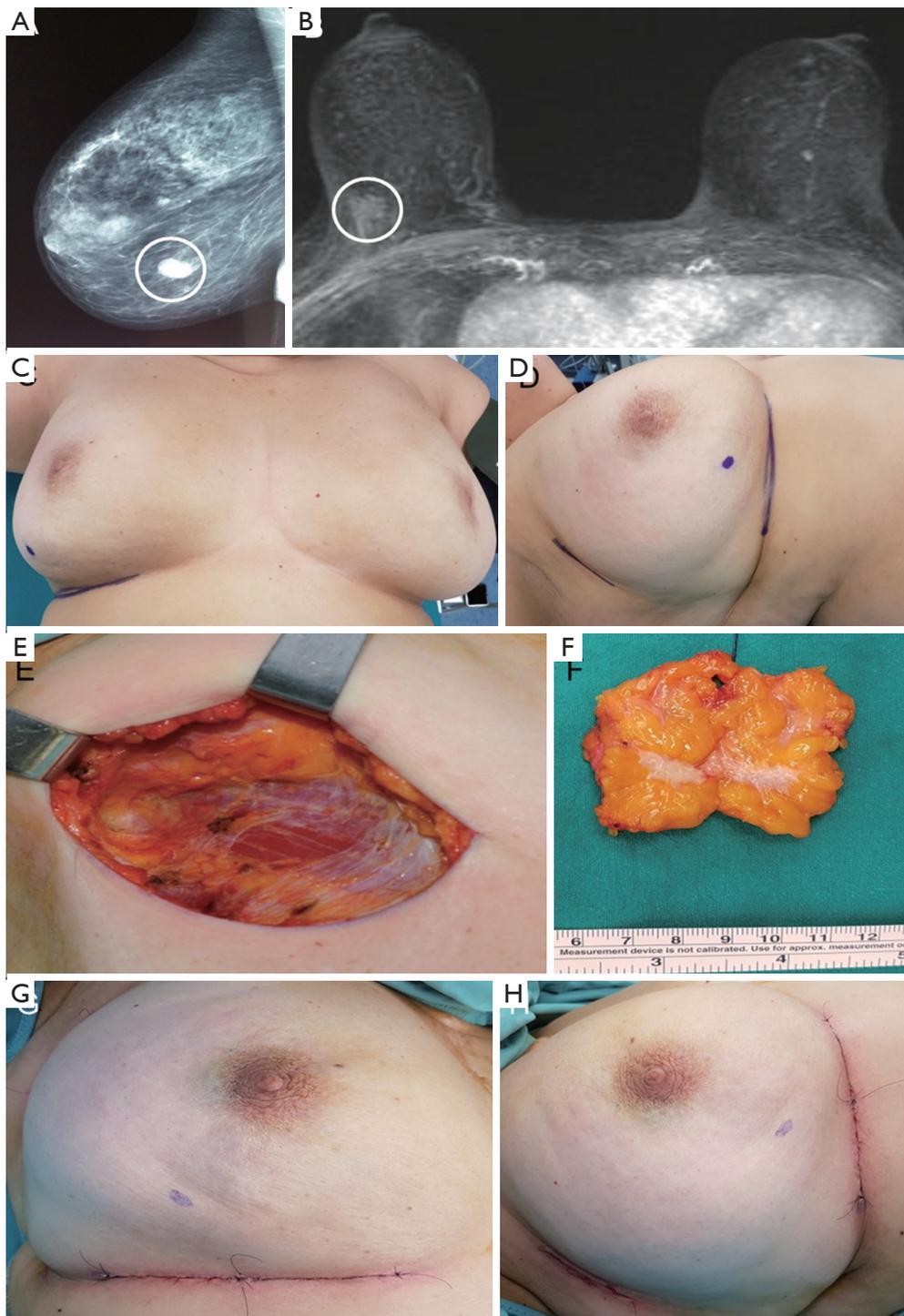


Figure 3 Oncoplastic inframammary fold approach of a lower outer right breast carcinoma. (A) Latero-lateral mammogram; (B) magnetic resonance reconstructions, confirming a 2.5-cm BIRADS4 right breast neoplasm; (C) preoperative assessment (front view); (D) preoperative assessment (lateral view); (E) outer external quadrantectomy with 20 % of glandular tissue excision; (F) surgical specimen; (G) postoperative cosmetic result (front view); (H) postoperative cosmetic result (lateral view).

recurrence rate (4.2% after OS versus 7.0% after BCS); with an overall cosmetic satisfaction of 90% in the OS group versus 80% in BCS group.

Recently, in their 2016 systematic review, De La Cruz and colleagues included 55 articles, collectively evaluating results on 6,011 patients treated for early-stage invasive breast cancer, with a mean tumor size of 23 mm (39.3% of T2 cases) and mean follow-up of 50.5 months (63).

Their analysis confirmed that OS enables surgeons to successfully remove greater volumes of mammary gland with wider surgical margins (thereby reducing positive margin, re-excision and secondary mastectomy rates), with excellent/good cosmetic outcomes 86% of cases.

The authors reported no statistically significant difference in the incidence of postoperative seromas, hematomas, infection, nipple necrosis and wound dehiscence among women undergoing OS and BCS and, concerning oncologic safety, no significant differences in overall survival, disease-free survival and local recurrence rate.

In patients with locally advanced breast cancer who received NACT, the evidences scenario is even more complex, as literature reporting the use of BCS and OS is limited and confounding.

Actually, reported results of breast conservation evidenced a discordance between recurrence rates of less than 10% (64,65) and studies that reported recurrence rates above 20% (66,67).

Recent evidences seem to refute initial data. In their 2017 metanalysis, Zhou and colleagues reviewed 2000–2015 literature selecting eight trials, with a total of 3,215 patients analyzed: 1,361 receiving BCS and 1,854 who underwent mastectomy (68). At 5 years follow-up, the prevalence of local recurrence was 9.2% in the BCS group, versus 8.3% in the mastectomy group and overall survival was significantly higher in the BCS group, confirming response to NACT a major prognostic factor.

Regarding the use of oncoplastic techniques in this setting, Mazouni *et al.* published in 2013 a case-control study of patients undergoing NACT, including 214 patients receiving BCS and 45 patients receiving OS (69).

At presentation, 25.8% were T3/T4 tumors and 44.8% had metastatic lymph node disease. Patients were initially treated with anthracycline, cyclophosphamide and 5-fluorouracil (5-FU) with or without docetaxel. Regarding surgery, the average excised tumor size was similar for both groups (40 mm) but the authors confirmed greater specimen volumes excised in patients undergoing OS. At a median follow-up of 46 months, local recurrence rate was

5% in BCS group versus 4% in OS group. No differences were observed regarding distant recurrence or survival.

Recently, Vieira *et al.* performed a matching case-control study, evaluating results of 78 patients with LABC who underwent NACT (doxorubicin-cyclophosphamide regimen followed by paclitaxel regimen). After completion of neoadjuvant treatment, 26 patients received OS, whereas 52 BCS. The authors reported an average size tumor of 5.25 cm (88.5% larger than 3 cm). The clinical and pathological group characteristics were similar, except the weight of surgical specimens and surgical margins, which were higher in OS group. At 67.1 months of follow-up, local recurrence was 11.5% in BCS group, versus 7.7% in OS group. The authors reported no difference in locoregional recurrence, overall survival and disease specific survival (70).

Conclusions

Recent literature demonstrates the benefits of OS, extending far beyond the mere reduction in poor cosmetic results, to the possibility of obtaining wider excisions with similar oncologic results observed in patients submitted to classic BCS and mastectomy. Future studies with longer follow-up and standardization of data are needed. Furthermore, what emerges from LABC literature is an imperative need of multidisciplinary breast centers worldwide diffusion, where breast-dedicated oncologists, radiologists and OS trained surgeons can offer patient-centered updated diagnostics, treatment protocols and surgical solutions, especially in a very delicate scenario, such as LABC treatment.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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