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New challenges in multimodal workout of locally advanced breast cancer

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ABSTRACT

The term “locally advanced breast cancer” (LABC) encompasses a heterogeneous group of breast neoplasms that represent an extremely variable percentage of newly diagnosed breast cancers (4–90%, depending of world regions). These cancers may have different clinical and biological characteristics that can be managed by primary surgery or neoadjuvant integrated treatments. In this paper we review the updated guidelines and discuss most recently reported evidence related to LABC multidisciplinary workout, in order to maximize results of combined systemic therapies, modern surgical procedures and radiotherapy.

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Introduction

The term locally advanced breast cancer (LABC) encompasses a heterogeneous group of breast neoplasms. In the last revision of the American Joint Committee on Cancer (AJCC) staging system, all of stage III disease is considered locally advanced, including cases with clinical stage IIB disease, such as primary tumor ≥ 5 cm and no nodal involvement (T3 N0); stage IIB–IIIA (T3 N0–1) considered as ‘large operable’ breast cancers and truly inoperable cases with involvement of supraclavicular or internal mammary nodal involvement (T4N2–3) and inflammatory breast cancer (IBC) featuring

marked neoangiogenesis, high grade, aneuploid features, hormone-receptor negative status, high S-phase fraction and p53 mutations and a severe prognosis (Fig. 1).^{1–3}

In screened populations, the use of mammography and increased public awareness of breast cancer have resulted in women having smaller tumors and fewer involved nodes at the time of initial presentation. As a matter of fact, data obtained from National Cancer Database and the CONCORD high-resolution study in Europe indicate that approximately 8.5% of American and 4% of European patients with breast cancer present with LABC.⁴

Nevertheless, LABC still remains an important and challenging therapeutical issue, especially in low- to middle-

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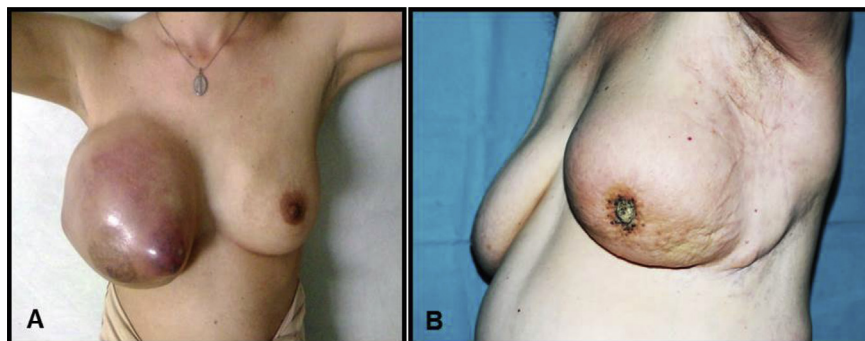


Fig. 1 – Inoperable LABC. (A) Patient with giant papillary carcinoma of the right breast determining a diffuse ulcerative and inflammatory clinical presentation (B) Massive inflammatory carcinoma of the left breast with diffuse «peau d'orange» and nipple areola complex ulceration.

income countries where its incidence can reach 90% of newly diagnosed breast cancers.⁵

This Review describes the current treatment options for the management of patients with LABC.

Clinical features

According to the 2016 National Comprehensive Cancer Network (NCCN) Guidelines, LABC can be stratified in operable LABC (clinical TNM stage T3, N1, M0) and inoperable LABC (clinical stage IIIA [except for T3, N1, M0], clinical stage IIIB or clinical stage IIIC).⁶

Diagnosis

In LABC workout, breast imaging is essential. Bilateral mammography and breast ultrasound (BU) should be performed as clinically warranted, as they can help to delineate the size and configuration of the primary breast tumor. Execution of Mammography determine the extent of any malignant microcalcifications that may indicate an extensive intraductal component,⁷ but may be inappropriate for patients with gross presentations of LABC (bleeding or fungating tumour), in which ultrasound is a valuable method in assessing tumor size and extent, before initiation of treatment.

In such setting, magnetic resonance imaging (MRI) is an important tool to integrate important information as axillary/internal mammary nodal status, pectoralis fascia/skin infiltration and real extent of breast cancer (infiltrative or in situ components) as well as in monitoring response to Neoadjuvant chemotherapy.^{8–10}

If standard imaging results equivocal or suspicious, fluorine 18 fluorodeoxyglucose – positron emission tomography computed tomography (FDG PET/CT) can be most helpful and its diagnostic power can be also used to detect regional node involvement as well as distant metastases in LABC including T3 N1 disease.^{11,12}

The diagnosis of LABC must be confirmed with core needle biopsy or fine needle biopsy. A core biopsy has the advantage of obtaining sufficient material to characterise the tumour (even on breast cancer, but also on suspected lymph nodes) in

terms of grade, hormone receptor status, proliferation index (Ki-67) and HER-2 status.

Furthermore, a genetic counseling is recommended if the patient is considered to be at high risk for hereditary breast cancer.¹³

Treatment

Operable LABC (clinical stage T3, N1, M0)

A subset of invasive breast cancers where the initial clinical and radiologic evaluation describe a disease to the breast and regional lymph nodes.

Were a reasonable initial surgical approach is likely to achieve pathologically negative margins and provide long-term local control, patients can be treated by means of breast conserving surgery (BCS) using oncoplastic procedures (OPP), that associating principles of surgical oncology with the best principles of reconstructive surgery have shown to optimize oncologic safety and cosmetic outcomes.^{14,15}

Conversely, candidates to primary mastectomy can be treated as nonoperable LABC patients, by means of neoadjuvant chemotherapy (NAC).

Even though NAC does not improve disease or overall survival, it does produce a shrinkage of the tumor in a variable percentage between 20% and 40% of patients, according to its histology (lobular or ductal carcinoma) and biological characteristics¹⁶ thus allowing BCS execution in cases that would have required a mastectomy (Fig. 2).^{17,18}

Before NAC, careful consideration should be given to the potential future need to identify the exact original tumor location if there is a complete clinical and radiological response. This is now performed routinely by inserting a radiopaque marker under mammographic, sonographic, or MRI guidance.^{19,20}

In cases of pCR, such marker placement allows the pathologist to scrutinize that particular area in search of residual tumor.

Inoperable LABC (clinical stage IIIA [except for T3, N1, M0], clinical stage IIIB or clinical stage IIIC)

The combination of systemic therapy, surgery and radiotherapy in inoperable LABC is mandatory, and although the

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