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Locally advanced breast cancer☆

Stefan Aebi [a, *], Per Karlsson [b], Irene L. Wapnir [c]

[a] Lucerne Cantonal Hospital and University of Bern, Cancer Center, Division of Medical Oncology, 6000, Lucerne 16, Switzerland
[b] Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden
[c] Stanford University, Stanford Cancer Institute, 875 Blake Wilbur Drive, Stanford, CA, 94305, USA

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ABSTRACT

Locally advanced breast cancer (LABC) is defined here as inoperable breast adenocarcinoma without distant metastases. Patients with LABC require a multidisciplinary approach. Given the risk of distant metastasis, staging exams are necessary. The incidence of LABC (stages IIIB and IIIC) has decreased in recent years. LABC has rarely been investigated separately: patients with LABC have participated both in clinical trials of palliative and of neoadjuvant therapy. Most trials did not analyze responses and long-term outcomes independently; thus, the treatment of patients with LABC is extrapolated from studies of patients with less or more advanced disease. Pathologic confirmation and molecular profiling are essential for the choice of neoadjuvant chemotherapy. Preoperative endocrine therapy may be considered in certain clinical situations; the addition of a CDK4/6 inhibitor is being investigated. HER2 positive LABCs are targeted with anti-HER2 agents combined with chemotherapy. PD-1 and PD-L1 antibodies in 'triple-negative' LABC are promising. Excellent responses to neoadjuvant therapy enable conservative surgery in many patients; however, inflammatory breast cancer may still indicate mastectomy. Postoperative radiotherapy is usually indicated. Target volumes include breast/chest wall, axillary, supraclavicular and internal mammary nodal basins. Preoperative radiation therapy can be useful in patients without response to systemic therapies. Palliative surgery for poor responders after neoadjuvant systemic and radiation therapy can be considered. Multidisciplinary teams can optimize local control and prevent relapses. However, modest improvement in survival was achieved between 2000 and 2014 underscoring the unmet need in patients with LABC who will benefit from specific research efforts in this disease entity.

Locally advanced breast cancer (LABC) is rare and represents about 5% of newly diagnosed breast cancers; in some less affluent countries however, LABC is present in a higher proportion of patients [37]. There is no universally agreed on definition of LABC. For this review, therefore, LABC is defined as breast cancer with no evidence of distant metastatic disease that cannot be reasonably resected surgically without prior systemic or radiation therapy; other definitions have included less advanced disease [38]. Biologically aggressive phenotypes of LABC include inflammatory breast cancer and other types of rapidly proliferating breast cancer; in contrast, LABC may also result from neglected less aggressive types of breast cancer representing the 'natural history' of untreated disease.

LABCs are also identified by the anatomic extent of disease, usually stage IIIB and IIIC, whereas some clinicians include patients with IIIA disease into the LABC definition. LABC includes inflammatory breast cancer, as defined by the AJCC or UICC staging systems. (Table 1).

In recent years, the proportion of LABC has declined in the United States (Fig. 1). In a population-based study from Sweden the proportion of breast cancer patient diagnosed with stage III disease declined from 15% between 1989 and 1993 to 12% between 2009 and 2013 and the 5-year excess mortality as compared to an age and period matched population decreased between these two periods by 48% [1]. While the explanation for the decline is speculative, it may be the result of increased public awareness and public health campaigns promoting early detection of breast cancer.

LABC can be classified as operable or inoperable disease.

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* Corresponding author.
E-mail addresses: stefan.aebi@onkologie.ch (S. Aebi), per.karlsson@oncology.gu.se (P. Karlsson), wapnir@stanford.edu (I.L. Wapnir).

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Table 1
AJCC Clinical stages IIIA, IIIB and IIIC (adapted from ([35])).

Stage	TNM	Explanations
IIIA	T0-3 N2 M0	Some clinicians consider N2 disease as locally advanced whereas T3 N1 is usually not considered as LABC
IIIB	T4 N0-2 M0	T4: Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); inflammatory carcinoma is classified as T4d
IIIC	Any T N3 M0	N3: Metastases in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement; or in ipsilateral internal mammary lymph node(s) with Level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement.

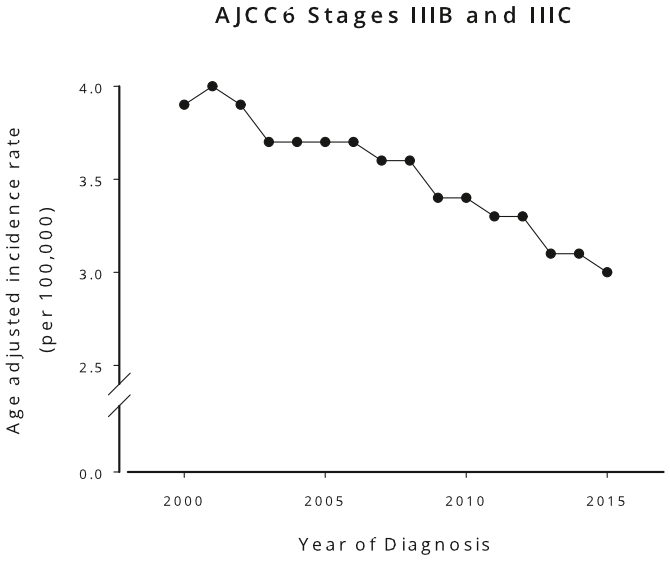

Fig. 1. Incidence of locally advanced breast cancer [36].

Whether or not a breast cancer is deemed resectable has changed over time as effective neoadjuvant systemic therapies have been adopted and extensive locoregional resections abandoned. While an unequivocal definition of irresectability does not exist, a few defining properties have gained widespread acceptance such as fixation of tumor to periosteum or intercostal muscles, impossibility to remove all gross disease, e.g., because of invasion of the brachial plexus, axillary vessels, ribs, or skin nodules tracking towards or beyond inframammary fold or sternum or “cancer en cuirasse”. Inflammatory breast cancer is considered as locally advanced disease.

Patients with apparent stage III disease have a sufficiently high incidence of simultaneous distant disease to warrant diagnostic imaging. With conventional staging procedures (chest x-ray, abdominal ultrasonography, and bone scan), the incidence of simultaneous metastases was >10% and up to 37% if chest and upper abdominal CT-scans were used [2]; [3]; [4]. Staging with ^{18}FDG-PET/CT is probably superior to conventional staging with a higher rate of detection of distant metastases. Migration of apparent stage III to stage IV disease was observed in 57 versus 44% of patients in a French study comparing ^{18}FDG-PET/CT with conventional CT based staging [5], and a Danish investigation found that staging with ^{18}FDG-PET/CT modified treatments substantially affecting 32% of radiation therapy, 23% of surgery, and 25% of oncological drug therapy recommendations [6]. Although a clinical benefit has not been demonstrated in a rigorous clinical trial, ^{18}FDG-PET/CT based staging is considered superior and standard where available for patients with LABC.

LABC has not been investigated as an entity of its own in randomized clinical trials in part because a subset of patients is eligible for neoadjuvant systemic therapy studies or, in other instances, may qualify for trials that combine inoperable local disease with stage IV breast cancer. Therefore, recommendations for diagnosis and treatment are extrapolated mainly from less advanced stages of breast cancer.

Patients with LABC have a potentially curable disease if local control is achieved. Thus, the patients need preoperative therapy with the aim of enabling surgery with clean resection margins. A generic workflow for the treatment of patients with LABC is shown in Fig. 2. Preoperative (neoadjuvant) systemic therapy is the standard approach to maximize response.

1. Preoperative systemic therapy

Chemotherapy is the conventional approach to patients with LABC, and the clinical trials of neoadjuvant systemic therapy included patients with LABC. The response to therapies containing both an anthracycline and a taxane is superior to anthracyclines only [7]; [8]; further, the addition of taxanes improves survival Early Breast Cancer Trialists' Collaborative Group, 2012. In patients with triple-negative breast cancer the addition of carboplatin to the taxane portion of a standard sequential anthracycline/taxane

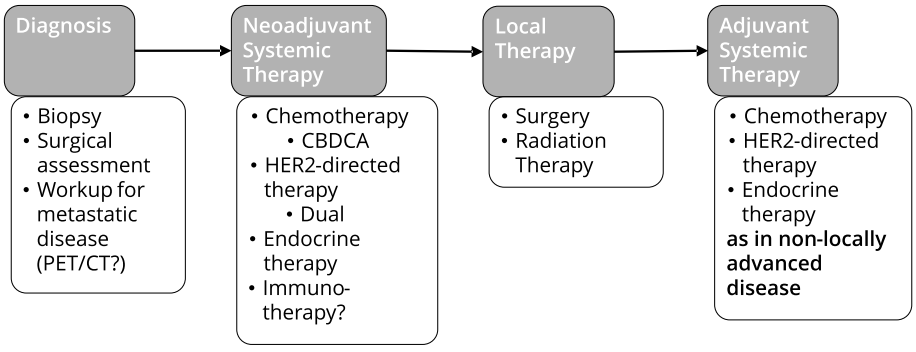

Fig. 2. Locally advanced breast cancer, general workflow.

regimen improved response in the randomized clinical trial CALGB 40603 [9]. Similar observations were reported in the German trial, GeparSexto [10]. Of note, the PARP inhibitor veliparib did not improve the probability of complete pathological response in triple-negative disease when added to a carboplatin and paclitaxel regimen [11]. In terms of complete response rate, albumin-bound paclitaxel was superior to solvent-based paclitaxel in the phase 3 clinical trial GeparSepto [12]; however, this observation was not confirmed in a similar European study [13].

HER2-directed treatments are standard for patients with HER2 positive breast cancer. Current evidence consistently shows that the addition of trastuzumab to chemotherapy improves the response and that dual inhibition of HER2 signaling by adding lapatinib [14] or pertuzumab [15] to trastuzumab further enhances the response and the rate of complete remissions. Thus, dual HER2 blockade should be used in the preoperative systemic therapy of HER2 positive LABC.

Neoadjuvant endocrine therapy is a therapeutic option for patients with highly endocrine responsive tumors; aromatase inhibitors are more effective than tamoxifen [16]; [17]. Fulvestrant was about as active as anastrozole in the neoadjuvant setting [18]. The action of endocrine agents is slow as compared to chemotherapy; therefore, the optimum duration of preoperative therapy is at least six months with frequent assessments of the response. Selected patients may expect response rates similar to chemotherapy with a comparable resectability even breast conserving surgery in many instances [19] . Inhibitors of CDK4 and CDK6 improve the response and the survival of patients with estrogen receptor positive, HER2 negative advanced breast cancer. Their preoperative use has been investigated in at least two trials. Both trials demonstrated that palbociclib and abemaciclib lead to a substantial reduction of the proliferative fraction as measured by Ki67 expression and a rate of partial or complete remission of about 50% Johnston, 2019; Hurvitz, 2020. Whether these intermediate endpoints are clinically reliable will remain to be seen on further follow-up. Nevertheless, a CDK4/6 inhibitor may be useful in selected patients to maximize response. In contrast, alpelisib, a selective inhibitor of PI3Kα failed to enhance the action of neoadjuvant endocrine therapy [20].

Immunotherapy with monoclonal antibodies targeting PD-1 and PD-L1 has the potential to advance the therapy of patients with triple negative LABC. Both pembrolizumab (KEYNOTE-522), and atezolizumab (IMpassion030), increased the rate of partial and complete response in combination with anthracycline and taxane containing neoadjuvant chemotherapy [21]; [22]. For instance, pembrolizumab increased the rate of complete remissions by 13.5%, and atezolizumab resulted in an increase by 17%; of note, these overall results are independent of the expression of PF-L1 in tumor cells or in tumor infiltrating immune cells, and they have not been analyzed by stage such that the effect of both drugs on LABC can only be guessed. At the time of writing, the magnitude of improvement of the response rate and the favorable event-free survival in KEYNOTE-522data [21] led regulatory agencies to approve the use of pembrolizumab for high-risk early triple negative breast cancer.

2. Preoperative radiation therapy

The standard use of radiation therapy for patients with LABC is in the adjuvant setting; comprehensive chest wall and nodal irradiation with target volumes including the breast, chest wall after mastectomy, supra- and infraclavicular nodal areas, internal mammary nodes, and any part of the axillary bed at risk with standard fractionation over 25–28 days and a cumulative dose of 45–50.4 Gy [23].

The experience with preoperative breast radiotherapy to improve resectability with tumor free margins is limited and poorly investigated. Neoadjuvant radiation therapy (45 Gy in 25 fractions followed by a 14 Gy boost) in combination with paclitaxel (30 mg/m2 three times weekly) was investigated in a phase II trial. The authors reported a pCR rate of 23% with better DFS and OS among patients with any pathological response [24].

An interesting registry study with 134 patients with stage IIIA and IIIB non-inflammatory breast cancer from Serbia has reported a response rate of 78% after treatment with 45 Gy in 15 fractions. The patients underwent mastectomy and axillary clearance 6 weeks later achieving a pathologic complete response rate in the breast of 15% and in axillary nodes of 7.5% [25]. Long-term follow up of a German series of 315 patients with LABC treated with neoadjuvant chemotherapy and radiotherapy reported better outcomes in patients with pCR and if the chemotherapy and radiotherapy were given concurrently [26]. Further, a randomized clinical trial from China comparing the sequencing of treatments for LABC indicated a possible benefit regarding both outcome and side effects with preoperative instead of postoperative radiotherapy [27].

In summary, preoperative radiation therapy has been sparsely studied in randomized trials. While breast radiotherapy may occasionally be useful as a single modality to achieve resectability, its combination with chemotherapy may be preferable given the high rates of occult metastatic disease prevalent in this population. Whether preoperative radiation therapy negatively impacts on surgical options for postmastectomy breast reconstruction needs to be evaluated. Given the advances of radiation and systemic therapies, it appears likely that the optimum use of preoperative radiation therapy deserves further investigation, for instance in patients with tumors refractory to systemic treatment.

3. Surgery

The goal of the surgical operation is to completely remove the primary tumor including locoregional disease and involved skin or muscles with direct extension of disease. Breast imaging, especially MRI, are useful guides to surgical planning after neoadjuvant treatments. While the traditional surgical approach was mastectomy, advances in systemic therapy have facilitated the downstaging of tumors making breast conserving surgery more common and safe [28] even for select patients with inflammatory carcinomas [29]; [30]. Mastectomy with immediate breast reconstruction, whether implant-based or autologous tissue are now routinely used for operable patients.

4. Adjuvant therapy

Patients with LABC should receive the same risk-adapted postoperative therapies as patients with less advanced disease. In general terms, the expression of estrogen and/or progesterone receptors mandates the adjuvant use of endocrine therapy, and patients with deleterious germline mutations of BRCA1 or BRCA2 qualify for adjuvant Olaparib Tutt, 2021. Patients who present with residual cancer after preoperative systemic therapy should receive post-neoadjuvant therapy such as trastuzumab-emtansine for HER2 positive [31] and capecitabine for triple negative breast cancer [32]. Most patients will receive postoperative radiotherapy encompassing the breast or chest wall and regional lymph nodes independent of their response to neoadjuvant therapy [33]. In the United States, NRG Oncology is conducting a randomized trial, NSABP B-51/RTOG 1304, of no radiation (except whole breast after lumpectomy) versus regional nodal and chest wall irradiation which includes patients with T3 N1 disease who are downstaged to node negative status after neoadjuvant chemotherapy [34]. Results

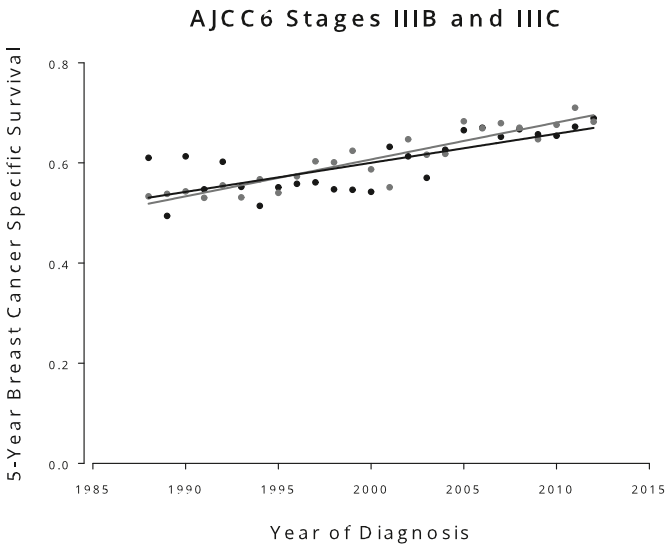

Fig. 3. Five year breast cancer specific survival of patients with Stage IIIB and IIIC breast cancer [36].

from such prospective studies while applying to large operable breast cancer will inform possible management strategies tailored to treatment response rather than just based on extent of disease at presentation.

5. Contemporary prognosis

For patients with LABC, the traditional prognostic and predictive factors might still be valid. A recent retrospective analysis of the SEER database including 36,500 patients with stage III breast cancer concluded that the breast cancer specific mortality was remarkably high and depended on stage (IIIA vs. IIIB vs. IIIC), expression of estrogen and progesterone receptors, histologic grade, nodal status, and race. The cumulative breast cancer specific mortality at 20 years from diagnosis varied between 43% in patients with estrogen receptor positive stage IIIA carcinomas to 69% in patients with stage IIIC hormone receptor negative breast cancer. Late relapses after 5 years varied by stage at presentation but was much higher in patients with hormone receptor positive disease (62–65%) than in those with hormone receptor negative disease (21–28%).

Advances in systemic and radiation therapy as well as in surgery in recent years are slowly improving the prognosis in patients with LABC as shown in Fig. 3 for the United States of America [36].

In conclusion, LABC, although rare, continues to present major challenges in terms of optimal treatments with modest improvement in mortality which remains unacceptably high. LABC should be a topic of research by itself, and it is necessary to distinguish biological phenotypes such as inflammatory breast cancer to enable specific therapeutic approaches. Multidisciplinary coordination for sequencing of treatments between surgeons, radiation and medical oncologists is a prerequisite for favorable outcomes of patients with aggressive breast cancers.

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Declaration of competing interest

The authors report no conflicts of interest related to this article.

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