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# MANAGEMENT OF NON-INFLAMMATORY LOCALLY ADVANCED BREAST CANCER: FOCUS ON SURGICAL APPROACHES

*A. Eroğlu*[1, *], *F. Aydin*[2]

[1]*Department of General Surgery & Surgical Oncology, Ankara University Medical School, Ankara 06260, Turkey*

[2]*Ankara University Medical School, Department of General Surgery, Ankara 06260, Turkey*

**In non-inflammatory locally advanced breast cancer, treatment typically includes neoadjuvant chemotherapy, surgery, and radiation therapy. Neoadjuvant chemotherapy allows *in vivo* assessment of primary tumor response to chemotherapy and is achieved the early control of micrometastatic disease. It also significantly improves surgical outcomes. Patients achieving pathologic complete response after neoadjuvant chemotherapy have a better survival. Tumor downsizing can make breast conserving therapy by allowing for smaller resections and improving cosmesis. Tumor downstaging with chemotherapy can allow breast conserving surgery in patients who are initially candidate for mastectomy. Sentinel lymph node biopsy is an appropriate alternative to routine staging axillary dissection for early-stage breast cancer patients with clinically negative axillary nodes. During the last years there have been a number of clinical studies on effectiveness and role of sentinel lymph node biopsy in patients receiving neoadjuvant chemotherapy. The use of sentinel lymph node biopsy is an alternative approach to axillary dissection in patients with neoadjuvant therapy. In conclusion, patients with locally advanced breast cancer are treated with neoadjuvant chemotherapy followed by breast conserving surgery with axillary dissection and radiation therapy as a part of the multimodality management.**

***Key Words*: locally advanced breast cancer, non-inflammatory breast cancer, surgery, treatment.**

## INTRODUCTION

Locally advanced breast cancer (LABC) refers to large operable (stage IIB, IIIA) or inoperable (stage IIIB, IIIC) tumors, including inflammatory breast cancer (IBC) [1–3]. Traditionally, the definition of LABC consists of patients with tumors > 5 cm, tumor with skin or chest wall involvement or fixed or matted axillary lymph node nodes. However, the definition of LABC nowadays has changed; some authors accept patients with stage IIB and large primary tumor (T3) without clinical adenopathy within the LABC domain [3].

LABC is defined by bulky primary chest wall tumors and/or extensive adenopathy. This includes T3 (> 5 cm) or T4 tumors (chest wall fixation or skin ulceration and/or satellitosis) and N2/N3 disease (axillary and/or internal mammary metastases) [2]. The sixth edition of the American Joint Committee on Cancer (AJCC) staging system includes isolated supraclavicular metastases in the stage III LABC category. LABC can be divided into operable and inoperable disease. Patients with diffuse breast edema or erythema, skin involvement, fixed tumor are generally accepted to be initially inoperable LABC. Besides, LABC including bulky T3 or T4 tumors of the breast or breast cancer associated with matted axillary or supraclavicular adenopathy is also defined as initially inoperable disease.

LABC occurs at diagnosis in approximately 20–25% of breast cancer patients worldwide [1, 4, 5]. Although significantly less, up to 10% of patients with breast cancer present with locally advanced or IBC in the Western world with implemented screening programs, LABC has been an important health problem in the developing countries.

## MULTIDISCIPLINARY APPROACHES

After the diagnosis of LABC the patient should undergo multidisciplinary review. The multidisciplinary team consists of surgical, medical and radiation oncologists, pathologist, radiologist, and plastic surgeon [2]. Local control and overall outcome have improved significantly with multimodal therapy. The prognosis of the patients with LABC is worse than patients with early breast cancer (EBC).

Neoadjuvant chemotherapy (NCT) also termed prospective, pre-operative, induction or primary chemotherapy has an important role in the several solid organ malignancies including breast cancer. Majority of LABC patients have occult distant micrometastases at the presentation, thus they are candidate for systemic therapy within the multidisciplinary approach [3]. NCT has become the standard care for LABC, since the early 1970's [4]. The first published study of primary systemic therapy in LABC was carried out by Hortobagyi et al. [6]. The authors showed that the multidisciplinary approach including preoperative induction chemotherapy, surgery, and radiation therapy to non-inflammatory stage III (both operable and inoperable) breast cancer rendered most patients

Received: February 22, 2013.
Correspondence: Fax: +90312 3191191
E-mail: aydaneroglu@hotmail.com

*Abbreviations used*: AJCC – American Joint Committee on Cancer; ALND – axillary lymph node dissection; BCS – breast conserving surgery; BCT – breast conserving treatment; DFS – disease-free survival; LRR – locoregional recurrence; EBC – early breast cancer; IBC – inflammatory breast cancer; LABC – locally advanced breast cancer; NCT – neoadjuvant chemotherapy; NSABP – National Surgical Adjuvant Breast and Bowel Project; EORTC – European Organization for Research and Treatment of Cancer; NI-LABC – non-inflammatory locally advanced breast cancer; OS – overall survival; SLNB – sentinel lymph node biopsy.

good prognosis and produced improved local and systemic control. The combined modality regimen resulted in an excellent local control rate superior to that recorded with surgery alone or radiotherapy alone. Their patients were treated with multiagents induction chemotherapy and then mastectomy with axillary dissection, and radiation therapy. Subsequently adjuvant chemotherapy was continued.

Progressive disease during NCT is very rare. The early detection of progression allows for discontinuation of ineffective regimens and conversion to other potentially beneficial treatments [7]. The patients with resistant disease to NCT should be excellent candidates to try alternative combined chemotherapy regimens. Despite the improved local and regional control in LABC patients, some of these patients developed distant metastases. Therefore more effective systemic treatment regimens will be needed to improve distant metastases-free and overall survival (OS) [6, 7].

## NEOADJUVANT SYSTEMIC THERAPY AND RESPONSE TO THE PRE-OPERATIVE THERAPY

NCT becomes the standard of care for patients with LABC. However, the optimal treatment of LABC remains undetermined. The most frequent local therapy in LABC remains a combination of surgery and radiotherapy [1]. Clinical and pathological characteristics influence the choice of local therapy type. Treatment of LABC has evolved within recent decades. For a long time, radical mastectomy remained the mainstay of treatment in LABC. Unfortunately, long-term outcomes were unsatisfactory. In patients with stage III breast cancer treated with induction chemotherapy followed by surgery, radiotherapy or a combination thereof, the risk of locoregional recurrence (LRR) is significantly low, in the range of 20%. Randomized trials and meta-analyses have demonstrated that local treatment following neoadjuvant therapy improves disease-free survival (DFS) and OS [1]. Moreover, the use of induction systemic therapy results in tumor downstaging and in selected LABC patients even allow for breast conserving surgery (BCS). Currently, a combination of induction systemic therapy with locoregional treatment including surgery and radiotherapy constitutes the standard of care in LABC since improving locoregional control is associated with better survival.

In general, LABC consists of a heterogeneous group of patients falling in AJCC stage III and the patients with LABC have poor prognosis [8]. However, the subgroups of patients with LABC who have complete response to NCT demonstrate a good prognosis than the patients with residual disease [9]. If there are no microscopic residual tumor at the primary tumor site and the axillary lymph nodes, it is categorized as pathological complete response (pCR). A partial response (PR) was defined as a decrease of tumor size 50% or more [9, 10].

The factors related to tumor response to NCT are multifactorial including multiple genes and proteins. Estimation of residual tumor volume after NCT is an important issue to subsequent surgical options. NCT induces cancer cells death by promoting apoptosis and cell necrosis. In some cases, the stromal component of tumor may persist and died and destroyed tumor cells can be replaced by scar tissue during NCT. Therefore this situation results in the misinterpretation of the residual tumor. Magnetic resonance imaging can distinguish between recurrence and fibrosis or scar tissue [11].

Tumor histology may play a role in breast conserving therapy (BCT) in LABC patients. Clinical and pathological responses to NCT are lower in lobular cancer compared with ductal cancer [12]. Currently, gene microarray profiling appears to promise in predicting response to NCT. Microarray investigations have shown a correlation between good response and gene changes during chemotherapy. Recently, DNA microarray analysis has been used to describe phenotype differences in gene expression patterns and molecular subtypes of breast cancer have been described. More recently, some studies have been shown the difference in both prognosis and response to chemotherapy amongst the subtypes [13–23]. Immunohistochemistry surrogates have been described that are validated against the original gene expression profiles. Nielson et al. demonstrated the identification of combinations of immunohistochemical markers closely matched the gene expression patterns [14]. Pusztai and coworkers suggested that the microarray technology and gene expression profiling are also being explored to optimize selection of neoadjuvant therapy [15].

Gene expression profiling may be useful in improving prediction of prognosis and treatment response. Hannemann et al. investigated gene expression profiles of the primary tumor to predict treatment response to NCT [16]. They found that response to NCT results in alterations in the gene expression. However, no gene expression profile predicting the response to NCT could be detected. In their pilot study, NCT causes major changes in gene expression in LABC patients responding to treatment, but no changes occur when the tumor does not respond to chemotherapy.

Gene expression profile is used for the classification of breast cancer and helps to distinguish prognostic subgroups. Some studies showed that gene expressing profiling predicts response to NCT [17, 18], however others did not find any relationship between gene expression and response to NCT. The different findings may depend on patient-associated factors like drug metabolism which cannot be measured using gene expression profile of the tumor [16].

Molecular subtypes have proven to be a powerful predictor of survival and distant recurrence [19]. The basal-like subtype derived less benefit in local control from postmastectomy radiation compared with other subtypes [20]. Nguyen et al. demonstrated that the

basal-like and HER2-enriched subtypes have a higher rate of in-breast recurrence than other subtypes [21]. Meyers et al. also reported that rates of LRR are significantly variable depending on molecular subtypes as determined by immunohistochemistry for estrogen receptor, progesterone receptor, and HER2 [22]. The basal-like subtype had a LRR rate of 14% compared with 4–5% for all other subtypes with most of these occurring in women who had undergone a mastectomy. Basal-like subtype is associated with the development of LRR after NCT. The development of LRR is predicated more by biology of tumor as evidences by molecular subtype, than by standard clinical and pathological risk factors.

Pre-operative systemic therapy is the treatment of choice for patients with LABC because of several advantages. Pre-operative therapy improves operability, sometimes allowing BCS to take place in patients with non-inflammatory LABC (NI-LABC). In a prospective study by Semiglazov et al., 235 patients with HER2-positive LABC or IBC were randomized to neoadjuvant trastuzumab plus chemotherapy or NCT alone [23]. The 228 patients received allocated treatment and were potentially eligible for surgery. All patients with IBC underwent mastectomy but some patients with LABC were treated with BCS. The addition of trastuzumab to NCT improved the OS and DFS. In addition, neoadjuvant trastuzumab plus chemotherapy enabled 23% of the patients to avoid mastectomy. In the prospective study, BCS was considered for patients with peripheral neoplasm measuring ⩽4cm in maximum diameter at diagnosis if a good cosmetic result is anticipated. BCS was also considered upon patient request. If patient has achieved an objective response to treatment (>50% reduction in tumor size) with no residual edema or peau d'orange, a good cosmetic result is expected. Their data suggest that trastuzumab-based neoadjuvant therapy improves operability and allows selected patients with LABC to avoid mastectomy. The authors also recommended that breast reconstructive with implants after mastectomy is discussed and agreed with the radiotherapist. Axillary lymph node dissection (ALND) was preferred up to the third level but dissection of the first two levels is acceptable. Nodal sampling or first level dissection is not considered adequate.

## CONTROVERSIES IN THE SURGICAL MANAGEMENT: BREAST CONSERVING SURGERY OVER MASTECTOMY AND RECONSTRUCTIONS

The radicalism of breast cancer surgery has decreased dramatically during the last century. Today Halsted mastectomy is very rarely indicated, only for tumor involving the pectoralis muscle. Mastectomy can be performed in case of the large tumor or multifocal disease or local recurrence after conservative treatment [24]. It is known that patients with NI-LABC often are managed with NCT as the initial treatment as opposed to surgery [13]. It is also recognized that BCS can be achieved and that these patients are not obligated to mastectomy. Currently, an increasing number of LABC patients undergo BCS after effective induction systemic therapy. The current NCCN guidelines suggest that the patients with T2 or T3 tumors are candidates for BCS with exception of size be considered for NCT.

More advanced clinical stage at presentation is associated with increased risk of LRR, therefore surgery and radiotherapy are recommended [1]. NCT improves respectability; approximately 80% of patients have significant primary tumor shrinkage, only 2–3% have signs of tumor progression [2]. Today optimal tumor control of LABC is achieved with neoadjuvant systemic therapy followed by surgery and radiotherapy. Postmastectomy irradiation for patients receiving NCT reduces the rate of LRR [25]. The postmastectomy radiation has also benefits for survival in patients with T3 tumors, stage III disease and ⩾ 4 positive lymph nodes after NCT. The radiation therapy should be considered for these patients regardless of the response of NCT. Irradiated patients have a lower rate of LRR [25].

The response to NCT has also associated with long-term outcome. Patients who have sufficient downstaging to allow BCT demonstrate better long-term outcome [13]. In contrast, patients who require mastectomy have higher risk of recurrent disease. The randomized and non-randomized trials have shown successful tumor downstaging after NCT. Patients with LABC who have clinical downstaging are candidate for BCT and the patients have the best long-term outcome.

Multidisciplinary trials such as the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18, B-27 and European Organization for Research and Treatment of Cancer (EORTC) trial 10902 have demonstrated that patients received NCT have DFS and OS rates similar to these of patients who are treated with surgery first followed by adjuvant systemic therapy [7, 10, 26–28]. According to the NSABP B-18 there were no differences between NCT and postoperative adjuvant chemotherapy arms in this respect; DFS was 55% *vs.* 53% and the OS was 69% *vs.* 70% respectively. According to this study the patient under 50 years old with receptor negative, node positive and tumor larger than 5 cm or partial remission after primary chemotherapy have significantly more relapse rates than patients who did not display the parameters. Although the randomized trials demonstrated that there were no significant difference in DFS or OS for patients who received either neoadjuvant or adjuvant chemotherapy, there was a significant increase in breast conversation therapy for patients with NCT. According to NSABP-18 trial, the BCT rate was 22% in the NCT group versus 8% in the adjuvant therapy group in patients with tumor > 5.1 cm. In addition, the patients with complete response after NCT had prolonged survival.

In EORTC trial 10902, 10-year OS was 66% and 65% in the postoperative and preoperative chemotherapy groups, respectively ($p > 0.05$) [10]. The 10-years DFS rates were as follows; 50% in the postoperative group,

48% in the preoperative group ($p > 0.05$). However, BCT rate was higher in the preoperative chemotherapy group than in the postoperative group (35% *vs.* 22%). NCT allows tumor downsizing in approximately 26% of patients. The long-term analysis showed that NCT increase BCT rate without increasing LRR rate.

In studies comparing preoperative to postoperative chemotherapy, no statistically significant differences were found in LRR. Although some studies have reported the higher rates of LRR after NCT, others have shown low rates of LRR in patients undergoing BCT after NCT [29]. Patient selection criteria are the major factor responsible for the variation in the rates of LRR. Chen et al. suggest that both pretreatment factors and residual pathological variables affect the rate of LRR for patients treated with BCT after NCT [29]. The authors concluded that BCT after NCT has a low rate of LRR in selected breast cancer patients, even those with T3 or T4 tumors. Residual tumor > 2 cm, multifocal residual disease, lymphovascular invasion and advanced lymph nodes involvement predict increased risk of LRR. T3 or T4 tumor is not associated with elevated rates of LRR and thus these tumors should not be considered a contraindication for BCS in the selected patients. If the patient has the following factors after NCT, BCS should not be performed: residual tumor > 5 cm, residual skin edema, direct skin involvement, chest-wall fixation, diffuse microcalcifications, multicentric disease, and contraindication to radiation therapy. If patient with locally advanced disease has less favorable response to NCT, the authors advocate for mastectomy with postmastectomy irradiation [29].

Prospective, randomized controlled trials have confirmed acceptable rates of local control among LABC patients undergoing BCS after neoadjuvant systemic therapy. BCS may be offered to selected patients after downstaging by NCT. Diffuse, suspicious microcalcifications or multiple lesions in different quadrants indicate multicentric disease and the situation is a contra-indication to BCS [2]. Several criteria for BCT following neoadjuvant systemic therapy have been adopted [2, 30]:

- Patient desires for breast preservation
- Absence of multicentric disease
- Resolution of skin edema
- Residual tumor size < 5 cm
- Absence of diffuse microcalcifications on mammogram
- Residual tumor mass amenable to a margin-negative lumpectomy resection

It is necessary to localize the tumor bed with a marker before administrating preoperative chemotherapy [10]. If BCS is planned, a microclip placed at the primary tumor is essential before the initiation of induction systemic therapy [2, 3, 10]. Before NCT the placement of metallic clips can facilitate later intraoperative evaluation of the tumor site. Breast conservation surgical techniques include the resection of any residual palpable abnormality in the initial tumor site. Mastectomy should be performed if diffuse foci of the residual tumor are present in the specimen. After BCT the surgeon should be leave the metallic clips within the resection cavity in order to facilitate radiation therapy planning [3]. Axillary dissection is performed for the following reasons; surgical removal of metastatic lymph nodes; the absolute number of metastatic nodes is an indicator of prognosis; the efficacy of novel agents on axillary response. In addition, clinical and radiologic assessment of axillary metastases is inaccurate.

Today depending on the development of chemotherapy regimens, it is possible to extend BCT to patients with LABC with a good outcome. NCT has also to potential to improve the cosmesis by decreasing the amount of breast tissue at the lumpectomy [4]. Although NCT is the standard of care for patients with LABC including IBC, it is becoming more common in early-stage of breast cancer. NCT has many potential advantages [7]. Firstly, NCT allows *in vivo* assessment of tumor response to therapy. Second, it allows the increased rate of BCT. Third, NCT can also positively impact cosmetic outcomes and can also reduce re-excision rates with BCT. On the other hand, the reasons of drawback of BCS in LABC are as follows: first, the development of local recurrence of breast cancer after BCS. Second, the patients with local recurrence may suffer psychological trauma from experiencing the recurrence. Third, local recurrence is also associated with an increased risk of developing distant metastases [4].

Patients with large tumors have become eligible for NCT to downsize the tumor and increase the possibility of BCS. In general, BCS can be performed in more than 50% of the patients with receiving NCT however others must undergo the mastectomy. Breast reconstruction is considered as part of the breast cancer treatment if a mastectomy is performed. When the nipple-areola complex is not preserved it is reconstructed in a second stage under local anesthesia [24].

Patients undergoing mastectomy should be informed about the immediate or delayed breast reconstruction as well as different reconstructions techniques, eventual complications or poor aesthetic results [24]. As mentioned below, today breast cancer is treated in the framework of a multidisciplinary team, including surgical, medical and radiation oncologists, pathologist, radiologist, plastic surgeon, psychologist and nurses. Immediate reconstruction requires a close collaboration between breast surgeons and plastic surgeons. LABC can be reconstructed after complete oncologic treatment. Expanders or implants are the most frequent technique used. In case of radiotherapy, a musculocutaneous flap is performed. The timing of the reconstruction is discussed. However, the general opinion is in favor of immediate reconstruction for non-invasive cancer and early-stage breast cancer. A delayed reconstruction is recommended in case of LABC [24].

Immediate reconstruction after mastectomy for patients with early-stage invasive breast cancer or ductal carcinoma *in-situ* is safe [31]. The oncologic safety and aesthetic results for skin-sparing mastectomy (SSM) and immediate breast reconstruction with a latissimus dorsi myocutaneous flap and saline breast prosthesis have already evaluated and concluded that the procedures might be an excellent alternative treatment to breast conservation for ductal carcinoma *in-situ* and early stage breast cancer. SSM minimizes deformity and improves cosmesis through preservation of the skin envelope of the breast. Chest wall skin is the most frequent site of local failure after mastectomy, therefore inadequate skin excision could results in an increased risk of local recurrence [31, 32].

There are many benefits and good results of immediate reconstruction in early stage breast cancer. Accordingly, this management has been also offered to patients with LABC at some centers. NCT demonstrates to reduce tumor size allowing preservation of the skin-envelope of the breast, which facilitates immediate reconstruction of the breast mound with autologous tissue [33].

The choice of the timing of reconstruction like immediate or delayed, should be considered to postmastectomy radiotherapy. Patients with LABC have traditionally not been eligible for skin-preserving mastectomy because of concerns about LRR of breast cancer and an inability to preserve the breast skin envelope for reconstruction after postmastectomy radiotherapy. The aesthetic outcomes of standard delayed breast reconstruction after radiotherapy in patients with LABC are satisfactory. Kronowitz et al. showed that skin-preserving mastectomy with a deflated tissue expander on the chest wall during postmastectomy radiotherapy does not increase LRR risk and that is associated with lower complication rates of definitve reconstruction in patients with LABC (stage IIB and stage III) [24].

The effect of NCT on surgical outcome is of particular concern in this patient group because any wound-healing complication might delay postoperative resumption of adjuvant treatment and may have a negative impact on patient prognosis [24, 32, 33]. Immediate breast reconstruction with implants is associated with more radiation related complications. Delayed reconstruction is therefore, usually preferred in LABC patients undergoing mastectomy. Delays in initiating post-chemotherapy or radiotherapy are associated with significant increases in adverse survival outcomes. Any wound-healing complications might delay postoperative adjuvant therapy and may have a negative impact on patient prognosis.

In a recent study, after NCT, the patients with LABC underwent mastectomy and immediate microvascular breast reconstruction including deep inferior epigastric perforator flap, transverse rectus abdominis musculocutanous flap, superior gluteal artery perforator flap, transverse musculocutaneous gracilis flap, or superficial inferior epigastric artery flap [32]. The control group consisted of the patients underwent mastectomy and immediate breast reconstructions without NCT. Immediate breast reconstruction for patients undergoing mastectomy offers numerous benefits compared with delayed reconstruction; the advantages are as follows: greater technical ease, better cosmetic results and decreased operative and recovery times. The study showed that immediate microvascular breast reconstruction with autologous tissue after NCT does not result in a higher complication rate compared with patients without NCT. In addition, the timely start of adjuvant therapy, even if complications occur did not delay.

## THE ROLE OF SENTINEL LYMPH NODE BIOPSY

It is known that axillary status is one of the most important prognostic variables in breast cancer. Lymph node status is a strong predictor of survival in early stage breast cancer. Axillary nodal status continues also to have prognostic value for LABC patients treated with NCT. Accurate assessment of axillary status provides the most important therapeutic management information as well as prognostic information. ALND is largely substituted by the sentinel lymph node biopsy (SLNB) in patients with early stage breast cancer (T1–2) and clinically negative lymph nodes. Intraoperative lymphatic mapping and SLNB are nowadays part of the standard management of patients with early stage breast cancer. However, feasibility and accuracy of sentinel node biopsy after NCT is controversial. Today SLNB biopsy has been routinely performed to smaller tumors as a staging and diagnostic procedure. Although SLNB is becoming the standard procedure in patients with early-stage breast cancer, this method has been considered in LABC [34, 35].

The appropriate use and optimal timing of SLNB in the setting NCT remains controversial. The issue of whether sentinel node staging should be performed before or after NCT is widely-debated NSABP B-27 study [36]. The largest series, NSABP B-27 in which 428 patients received NCT followed by SLNB and completion axillary dissection. In the study, the identification rate was 85% with false-negative rate of 11%. However, SLNB results have opted to perform the staging SLN biopsy prior to NCT. Nodal status is important in planning chemotherapy and for determining regional radiation benefit.

NCT downstages the involved axillary lymph nodes as well as primary tumor size (down-stage the axillary status in 30–40% of the patients with LABC) [35]. However, NCT has some adverse effects. Firstly, NCT results in the anatomical alteration of the lymphatic drainage, with lymphatic vessels disrupted by tumor, inflammation and fibrosis, or blocked by necrotic and apoptotic cells. Second, NCT can induce the non-uniform tumor regression in the axillary nodes. Several factors can alter the lymphatic drainage such as tumor cells infiltrating lymphatic vessels and NCT itself provokes fibrosis, necrosis and granulation tissue formation, and it can

produce a non-homogeneous disease regression, being more effective in the SLN than in other nodes. If NCT eradicates metastatic foci in SLN but not in non-SLN, false negative results will occur. The false negative result is an important problem in SLNB because it leads to incorrect lymph node staging and to inappropriate decision about adjuvant therapy.

Ozmen and coworkers evaluated the factors associated with sentinel lymph node identification, non-sentinel lymph node metastases and false-negative rates in patients with LABC after NCT [5]. In their study, the increased identification rate of SLN was found in smaller tumor after NCT. The situation might be due to the gradual infiltration of the lymphatic vessels by tumor cells which would prevent the penetration and the flow of the blue dye or isotope. Residual tumor size and nodal status before chemotherapy affect SLN identification accuracy. The involvement of non-SLN is associated with presence of multifocality or multicentric tumors, lymphovascular invasion, large residual tumor size.

Some authors have advocated SLNB before NCT. Papa et al. suggest that SLNB is performed prior to chemotherapy because of more accurate evaluation of axillary status, unaffected by any previous therapeutic intervention [37]. The authors showed that neoadjuvant therapy lowers the SLN identification rate and NCT also increases the false negative rate due to downstaging. This is possibly due to fibrosis within the axilla. NCT may interfere with the detection of metastases since chemotherapy induces histological changes such as fibrosis, fat necrosis, histiocytic accumulation, and granulation tissue formation. In light of this, the best timing for SLNB in patients planned for NCT is prior to neoadjuvant systemic therapy [37].

There are some advantages to performing SLN biopsy prior to systemic treatment. Firstly, it gives us the actual nodal staging at the diagnosis. Second, a negative SLN obviates the need for further axillary dissection and irradiation of the axilla is omitted. Third, NCT may affect SLN identification accuracy due to structural changes in lymphatic drainage. Accordingly, NCT may affect the identification rate and accuracy of lymphatic mapping. The axillary nodal status after NCT does not represent the pretreatment status, which is an important prognostic factor [37].

The candidates for SLNB before NCT are patients with large tumors and clinically negative nodes at the presentation. The disadvantage of SLNB before NCT is that patient with positive SLN is not able to avoid axillary surgery, even if NCT is eradicated the axillary disease. If the SLN is negative, the patient does not undergo ALND, thus the risk related to ALND can usually be avoided. SLNB is important to omit ALND in patients with negative SLN regardless of the timing of SLNB. On the other hand, there are several studies reporting SLNB after NCT but a few studies have evaluated SLNB before NCT [5, 8, 35, 38–42]. Several single-center experiences and meta-analyses have suggested the feasibility and accuracy of SLNB after NCT. However, further follow-up studies on patients with negative SLN after NCT who does not undergo ALND are required to establish the utility of SLNB after NCT.

SLNB is performed before NCT and then the patients with involved nodes should have axillary dissection after the completion of neoadjuvant therapy. The disadvantage of this approach is that the patients need to undergo at two surgical procedures; SLNB before NCT and then resection of the breast tumor with axillary surgery. Patients treated with NCT go on to routine level I and II axillary node dissection at the time of breast surgery [40]. On the other hand, the rate of SLN identification is significantly high in patients treated with SLNB before NCT [42]. In patients treated with SLNB before NCT, completion ALND for a positive SLN is performed at the time of definitive surgery after NCT. Axillary radiotherapy rather than ALND is a less morbid alternative for patient with clinically node-positive when SLN is negative after NCT. Accordingly, some authors recommend SLNB before NCT for clinically node-negative patients [37, 42].

SLNB can be also performed after NCT. The advantage of this approach is that axillary nodal status is successfully determined. After NCT, lymphatic mapping can not accurately demonstrate the nodal metastases because of excessive fibrosis of the lymphatics. It may be caused by an uneven effect of chemotherapy in patients with multiple positive nodes, so that the sentinel node is sterilized but residual disease persists in non-sentinel nodes. However, Newman et al. showed that SLNB after NCT is feasible with a SLN identification rate of 93% and false-negative rate of 8% [34]. Their results are comparable to reported rates in early-stage breast cancer. The use of radioactive isotope alone or in combination with blue dye is associated with a significantly higher rate of identification of the sentinel node. SLN identification rate is significantly better when the SLNB is performed before NCT. Failure to axillary lymphatic map was associated with clinically positive axillary at presentation and residual disease at ALND. Ozmen et al., Canavese et al., and Thomas et al. [5, 8, 35] showed that SLNB is feasible and safe procedure in LABC patients who become clinically node-negative after NCT.

One of the advantages of performing SLNB after NCT is that additional surgery is avoided, allowing for chemotherapy to start without delay. The axillary nodal status is down-staged by NCT, if tumor responds to NCT. Therefore NCT makes damage and alteration of lymphatic flow from the tumor tissue to the axillary nodes. Another advantage is that information regarding axillary nodal status after NCT is important. However, chemotherapy may damage and change the lymphatic drainage from tumors.

Finally, the optimal timing of SLNB is an important issue. Performing SLNB before NCT assures accurate assessment of initial axillary status, avoiding the possible negative effects of lymphatic scarring. However, performing SLNB after NCT allows to downstage nodal status in 20–30% of the patients [41].

Meta-analyses have showed that SLNB appears to be accurate technique for determining the need for axillary status in patients with clinically node-negative following preoperative chemotherapy [40, 41]. Besides, the meta-analyses have showed that pooled SLN identification rate and false-negative rate do not differ from the studies evaluating SLNB without NCT [41]. However, there is insufficient evidence to recommend SLNB as standard procedure following NCT. Clinical axillary status, response to chemotherapy, primary tumor size, and body mass index are associated with decreased SLN accuracy following NCT.

Patients with complete pathologic axillary response after NCT have significantly better prognosis. As well as primary tumor size, some authors have demonstrated that patients with initially axillary node-positive altered to node-negative by NCT (complete response) have significantly longer overall and DFS than patients with residual disease [9, 43]. Following NCT, SLNB as a therapeutic option in LABC patients who become clinically node negative is a promising approach that spares axillary dissection and its morbidity.

## CONCLUSION

NCT is used increasingly in the treatment of breast cancer for the following reasons; first, NCT allows more patients to be treated with BCS; second, it enables an *in vivo* evaluation of tumor sensitivity to the chemoterapeutic agents; third, tumor response to NCT serves as a predictor of favorable prognosis. NCT also is a key role for translational research. Tumor response to NCT appears to be a surrogate marker for the response of occult micrometastases. NCT increase the respectability rate of breast cancer and thus allows more patients to undergo BCS. BCT is a safe and effective alternative to mastectomy for selected patients after NCT. If the primary tumor is operable, but is not suitable for BCS, neoadjuvant therapy is an alternative approach [44].

SLNB is an accurate and safe method to assess axillary nodal status and it has replaced traditional axillary dissection as an initial staging procedure in early-stage, clinically node-negative breast cancer patients. The use of SLNB has been accepted as an alternative approach to axillary dissection in NI-LABC patients with neoadjuvant therapy. There is controversy about the appropriate timing of SLNB in patient with LABC receiving NCT. Preoperative chemotherapy yields reactive changes like fibrosis which can affect lymphatic drainage patterns, however, SLNB after NCT has been used as a safe approach.

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