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REVIEW

Breast conservation in locally advanced breast cancer in developing countries: Wise or waste

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Abstract
Breast conservation as an additional benefit was beyond the initial expectations of the investigators who pioneered neoadjuvant chemotherapy (NACT). In recent years an increasing number of patients with locally advanced breast cancer (LABC) are being treated with NACT, followed by breast conservation surgery with axillary dissection and radiation as a part of the multimodality management. Breast conservation has not been the standard of care for women with LABC, owing to concerns of increased chances of local recurrence, and possible survival disadvantage and psychological trauma from experiencing a recurrence of malignancy.

LABC is still a common form of presentation of breast cancer in developing countries. Strict adherence to treatment protocols and regular follow-ups for years may not be practical for a large majority of patients hailing from the regions most affected by LABC. Defaulters often thus have a heavy price to pay.

Hence lies the importance of carefully selecting LABC patients for a breast conservation approach from others that would have a higher risk of locoregional recurrence. Can we extrapolate the lessons learnt in early breast cancer to LABC and offer selected patients with LABC breast conservation therapy? Would the local control and survival results with conservative therapy be comparable to those obtained using mastectomy, or does the increased tumor burden in LABC necessitate ablative surgery in all women? This review aims to address these important questions.

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Contents

Neoadjuvant chemotherapy in locally advanced breast cancer

Locally advanced breast cancer (LABC) represents a heterogeneous group of tumors ranging from slow growing neoplasms to rapidly proliferating and aggressive ones. Patients with these cancers include those with operable disease at presentation (American Joint Committee on Cancer (AJCC) clinical TNM (Tumor Node Metastasis) stage T3N0, T3N1M0), inoperable disease at presentation (AJCC clinical stage IIIA (except T3N1M0), IIIB or IIIC) that includes inflammatory breast cancer (AJCC clinical stage T4d, Any N, M0) [1]. LABC represents only 2—5% of all breast cancers in the United States compared to 50—70% in India [2,3]. Despite this fact only very few studies from the developing nations have published their data on breast conservation in LABC. Thus most of the current understanding on the said subject is derived from single institution's experience and trials conducted across the world.

Since its initial use in the early 1970s, neoadjuvant chemotherapy (NACT) has become the standard of care for management of LABC and is increasingly being used for treatment of early-stage breast cancer [4]. It is presumed to have several advantages such as it can downsize large tumors, thus allowing breast conserving surgery in patients' so desiring, it provides in vivo information on tumor response to a specific chemotherapeutic agent, and probably helps in achieving longer disease-free survival (DFS) and overall survival (OS) [5]. In general, majority of patients achieve clinical response rates (60—90%) to NACT [6]. Complete pathologic remissions are however noted in only 3—30% of patients in most trials [7]. Although a few patients experience mixed responses (response in the primary tumor and no response in the lymph nodes and vice versa) for most patients' response is similar in all sites of tumor involvement. Pathological complete responses (pCR), now defined as no invasive or noninvasive tumor in the breast and axillary tissues removed at time of surgery, seem to be the most powerful predictor of outcome in terms of survival [8,9]. However, it should be remembered that patients with pathologic complete response can still experience disease recurrence. Results from several clinical trials reveal that pathologic positive node status after NACT is strongly associated with inferior OS and DFS compared with negative node status [10—13].

Evolution of the concept of breast conservation following neoadjuvant chemotherapy

Encouraged by the success of NACT in downstaging large breast tumors, efforts were directed to find out if NACT was in any way better than adjuvant chemotherapy in terms of DFS and OS.

Seven important randomized trials (National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 (Fisher et al.; Wolmark et al.) [14,15], NSABP B-27 (Bear et al.) [6,10], Mauriac et al. [16], Scholl et al. [17], European Organization for Research and Treatment of Cancer (EORTC) 10902 (van der Hage et al.) [18], Petrov Institute (Semiglazov et al.) [19], and from Royal Marsden (Powles et al.) [20]) have evaluated patients with breast cancer, comparing chemotherapy given either in the preoperative or the postoperative setting. There are difficulties in interpretation because of the variety of different chemotherapy regimens and also wide spectrum of disease stage and trial design. The trials however clearly demonstrate that administration of NACT results in a higher rate of breast conservation when compared to patients receiving chemotherapy in the adjuvant setting. Despite the success of tumor downstaging with NACT, published randomized trials (NSABP B-18 [14,15], NSABP B-27 [6,10], EORTC 10902 (van deer Hage et al.) [18], Petrov Institute (Semiglazov et al.) [19], and from Royal Marsden (Powles et al.) [20]) have so far failed to demonstrate a consistent survival advantage over postoperative chemotherapy.

NSABP B-18, a large randomized neoadjuvant clinical trial comparing the efficacy of neoadjuvant with adjuvant chemotherapy, randomized 1523 patients with operable stages I—IIIA breast cancers (13% had T3 tumor) into two groups, stratified by age, clinical tumor size and clinical nodal status to receive either preoperative or postoperative administration of four cycles of adriamycin and cyclophosphamide (AC) [14]. The specific aims of this trial were to determine whether NACT more effectively prolongs DFS and OS than the same chemotherapy given postoperatively, evaluate the response of the primary tumor to NACT and correlate the response with DFS and OS and to determine whether NACT, by reducing the size of the primary tumor, permits more conservative surgery and decreases the frequency of ipsilateral breast tumor recurrences (IBTR). The first group of patients underwent a total mastectomy plus axillary dissection or a lumpectomy plus axillary dissection followed by four cycles of AC. The second group of patients received four cycles of AC followed by a total mastectomy or lumpectomy within 4 weeks of the fourth course of chemotherapy, when blood counts allowed.

The results showed that there were no differences in DFS and OS for patients who received either neoadjuvant or adjuvant chemotherapy. However, patients who achieved pCR after NACT had prolonged DFS and OS compared with all other groups [14,15]. In addition, there was a significant increase in breast conservation therapy (BCT) for the NACT arm (68% vs. 60%) and a lesser likelihood of residual positive axillary lymph nodes (41% vs. 57%). With a median follow-up of 72 months, the local recurrence rates were 7.9% and 5.8% (no statistical significant difference) following BCT in the pre and the post operative chemotherapy arms, respectively. The NSABP investigators also reported that IBTR were some what higher in the particular subset of lumpectomy patients that were downstaged to become BCT eligible in comparison with the BCT patients who were BCT candidates at presentation (15.9% vs. 9.9%). It was further noted that this increase occurred mainly in patients who were under 50 years of age.

A subset analysis after 9 years of follow-up revealed that women less than 50 years of age seemed to show greater survival benefit (DFS and OS) to NACT (55% vs. 46% and 71% vs. 65% respectively). In contrast, patients over 50 years seemed to benefit more from postoperative chemotherapy. The reason for this remains speculative and requires confirmation. Moreover, patients with pCR continued to show superior OS and DFS (85% and 75%, respectively) compared with patients with residual invasive tumors (73% and 58%, respectively) [15]. Therefore, it is reasonable to attempt to increase the pCR in the hope that it will translate into an increase in patient survival.

The NSABP B-27 has reported a phase III randomized trial, the single largest NACT study to date, of operable breast cancer (45% had >4 cm) to evaluate whether sequencing docetaxel to neoadjuvant AC prolongs DFS and OS [6,10]. A total of 2411 patients were randomized into three treatment arms (1) 4 cycles of preoperative AC, (2) 4 cycles of preoperative AC followed by 4 cycles of docetaxel, and (3) 4 cycles of preoperative AC followed by 4 cycles of postoperative docetaxel. The pCR rate was 19% in the neoadjuvant combination therapy plus docetaxel arm compared with 9% in the combination therapy alone arm ($p < 0.01$). Despite an increased pCR, no significant difference in DFS or OS was seen with addition of docetaxel, and no difference in survival was observed in patients who received either neoadjuvant or adjuvant docetaxel. The lack of added benefit with docetaxel may be partly explained by the fact that tamoxifen was given concurrently with chemotherapy and thus, could have reduced the efficacy of chemotherapy. This factor may be critical in light of the results of the Intergroup trial 0100 [21], showing clearly that concomitant chemotherapy—tamoxifen—is significantly detrimental as opposed to sequential use of both therapies ($p = 0.045$). It has been estimated that the concomitant use of both therapies could decrease relative efficacy of chemotherapy by up to 50%. Moreover, another limitation of this trial was that majority of the patients (55%) had small tumors ($T < 4$ cm), a context in which the differential impact on pCR induced by NACT could be more difficult to demonstrate. However, pCR was significantly associated with improved OS regardless of treatment (hazard ratio $= 0.33$; $p < 0.0001$) [6].

Several trials were conducted on large operable and LABC patients selected for BCT by the type of response to chemotherapy. These trials have provided useful clinical information but did not address the relative efficacy of preoperative versus postoperative chemotherapy on DFS and OS, unlike the trials discussed previously.

(1) In 1990 Jacquillat et al. [22] reported results from a prospective trial of 250 patients with breast cancer (86 had stage IIA, 51 IIB, 36 IIIA, 58 IIIB) who were enrolled on a protocol combining neoadjuvant and consolidative therapy with vinblastine, thiotepa, methotrexate, and 5-fluorouracil, with or without doxorubicin, and radiation therapy as exclusive locoregional treatment. Surgery was used only as salvage therapy after locoregional relapse. Patients were stratified into four therapeutic options according to tumor size and clinical lymph node status. Overall breast conservation rate was 94%. A local relapse rate of 13% was noted. They found a good to excellent cosmetic result in 73% of patients and a fair result in 27%. Tumor response was the main predictive factor for DFS. A total of 58 patients (23%) had T4 disease, including inflammatory breast carcinoma. Of these patients, 35 (60%) had a complete clinical response after NACT. At a median follow-up time of 62 months, the locoregional recurrence rate in patients with T4 disease was 19%, and the 5-year DFS and OS rates were 52% and 58%, respectively.

(2) In 1994 Schwartz et al. [23] from Jefferson Medical College reported a series of 189 patients with LABC (stage IIB and III); results were compared between the two groups of responders, one who had undergone mastectomy (103, 64%) before 1983 and the other in whom a selected few had undergone breast conservation (55, 36%). They reported an 85% response to NACT, a DFS (77% vs. 56%) and 5-year OS (80% vs. 67%) favoring the breast conservation arm. Responders to NACT had a longer DFS (61%) and OS (69%). Ten percent mastectomy specimens had no in situ or invasive carcinoma and 7% had only in situ cancer.

(3) In 1995 Veronesi et al. [24] reported their experience from Milan in assessing the feasibility of breast

conservation in 226 patients with tumors >3 cm in diameter treated with NACT. In 90% of cases, size reduction was sufficient to justify breast conservation, including 20 of 29 patients with tumors >5 cm. Twelve local recurrences occurred among the 203 patients treated with breast conservation (5.9%) and 5 among the 23 treated with mastectomy (21.7%). They found evidence of multifocal disease in 37(16%) of 227 quadrantectomy specimens after NACT, and further explained that this pattern was more prevalent in larger tumors, ''probably because these tumors had not been destroyed uniformly by chemotherapy''. They cautioned that careful attention to surgical technique was essential to the successful application of NACT to breast conservation. These details include tattooing points on the skin for inclusion of the region of the initial tumor prior to chemotherapy, careful assessment of the mammographic zone of involvement before chemotherapy, resection of all associated microcalcifications, and meticulous histopathologic assessment of margins not only around residual cancer but the zone of regression.

(4) In a subsequent study in1997 Touboul et al. [25] reported their results of 147 (with large T > 3 cm and LABC) patients treated with four courses of NACT (doxorubicin, vincristine, cyclophosphamide, and 5-fluorouracil) followed by preoperative radiation therapy (45 Gy to the breast and nodal basins) and a fifth course of chemotherapy. Three different locoregional approaches were used, depending on tumor characteristics and tumor response. Surgery (total mastectomy with axillary dissection in 52 patients and wide local excision and axillary dissection in 47 patients) was reserved for patients who had clinically evident residual disease. Forty-eight patients with pCR received radiation boost only. After completion of local therapy, all patients received a sixth course of chemotherapy and were maintained on a non-anthracycline-based chemotherapy regimen. This study included 36 patients (24%) with T4 disease, including inflammatory breast carcinoma. Of these patients, 19 (53%) were able to have BCT. Of the 95 patients in the overall cohort who had BCT, 10-year locoregional failure occurred in 23% of those who had BCT and radiation therapy, 20% in radiation alone arm compared to 6% in the mastectomy arm ($p = 0.85$). The locoregional recurrence rate in patients with T4 disease who had breast conserving surgery was not reported. Local treatment was not found to influence the 10-year OS rates (OS was 66%). However, local failure significantly reduced OS ($p < 0.0001$).

(5) The University of Michigan (Merajver et al.) [26] reported results of a phase II trial in 1997 which sought to maximize breast conservation rates in 89 patients with LABC (44 had T4 tumors) following a prolonged course of chemo-hormonal therapy and a biopsy driven local therapy. All complete responders were irradiated, where as those with residual disease received mastectomy and irradiation. It was observed that a complete clinical response did not correlate to a pCR (61% vs. 28%). A 14% local failure rate was seen in the pathological complete responders who compared well with the group that received mastectomy and radiation (13%). It was however noted that there was a 27 week treatment time delay to local therapy, which probably accounted for a higher incidence of local failure.

(6) In 1998 Bonadonna et al. [27] reported on 161 patients with tumors >3 cm in a study from Milan. All patients received NACT and BCT was done (59% of patients) if the tumor had shrunk to <3 cm followed by postoperative irradiation. Only one local failure was reported after 12 months of follow-up (an IBTR of 7%).

(7) In 1998 Clark et al. [28] utilized aggressive multimodality therapy which was given over a relatively short duration of time (target treatment time 27–32 weeks) which they referred to as dose intense and dose dense NACT to 34 patients with predominantly T3/T4, N0–N2, M0 tumors consisting of 90 mg/m^2 of doxorubicin every 21 days × 4, appropriate surgery (a local excision if sufficiently downstaged or mastectomy if not),a high dose cyclophosphamide (CMF) every 2 weeks × 4,and radiation therapy. Fifteen out of 34 patients (44%) underwent breast conservation surgery, with only one locoregional failure on a median follow-up of 30 months. The actuarial 3-year DFS and OS were 77% and 87% respectively. Cosmetic results were good to excellent in 80% of patients. They concluded by stating that with the above regimen a subset of patients of LABC can preserve their breast with acceptable cosmesis without compromising local control or survival.

(8) In 2002 Cance et al. [29] reported a cohort of 62 patients with LABC (82% stage III, 17 had T4 disease) treated between 1992 and 1998 with a dose intensive and time intensive treatment regimen consisting of neoadjuvant doxorubicin, followed by surgery (BCT if sufficiently downstaged), followed by non-cross-resistant cyclophosphamide, methotrexate, 5-fluorouracil, followed by radiation therapy, with a total treatment time of 32–35 weeks. They reported an 84% clinical response rate (15% pCR). Overall 28 patients achieved significant downstaging to undergo BCT and it included 22 (45%) of 49 patients with non-inflammatory LABC. This group of patients had a 14% long-term local recurrence rate, even with a significant number of inflammatory cancers. Notably despite the large and locally extensive nature of the primary tumors in this study, IBTR occurred in only two patients with conserved breasts. The 5-year OS for the cohort was 76% and for those who underwent BCT was 96%. Based on these data they hypothesized that the best outcome can be achieved by treating patients with best clinical response.

(9) In 2003 McIntosh et al. [30] from the Aberdeen group presented a series of 166 patients with LABC (T2 > 4 cm, T3, T4, or N2) treated with NACT cyclophosphamide, vincristine, Adriamycin, prednisolone (CVAP) and then appropriate surgery (breast conservation or a mastectomy) followed by radiotherapy. They reported a clinical response rate of 75% (21% complete (15% pCR) and 54% partial). 25% of the patients went in for a conservation surgery. With a median follow-up of 14 months they reported a median survival of 27 months, a 2% local recurrence in the breast conservation group where as a 7% local recurrence rate in the mastectomy group. A total of 36 patients (22%) with T4 disease were included in this study, and 6 of these (17%) had a complete clinical response. The overall locoregional recurrence rate in patients with T4 tumors was 16%. The authors found that residual disease in the axillary lymph nodes was a predictor of local disease recurrence.

Recently (in 2004) Shenet al. [31] from the MD Anderson Cancer Center reported their findings on 33 patients with

stage IIIB or IIIC breast cancer who completed treatment consisting of four cycles of NACT, lumpectomy, radiation therapy, and consolidative chemotherapy between 1987 and 1999. Initial median tumor size was 7 cm. All patients had skin involvement, defined as erythema, skin edema, direct skin invasion, ulceration, or peau d'orange. Following chemotherapy, median pathologic tumor size was 2 cm. Complete resolution of skin changes occurred in 29 patients (88%). At median follow-up time of 91 months in surviving patients, 26 patients (79%) were alive without evidence of disease. The 5-year DFS was 70%, and the 5-year OS was 78%. The actuarial IBTR was 6% at 5 years. The authors concluded that mastectomy is not mandatory for all patients with breast cancer who present with skin involvement.

Moreover, besides converting patients from mastectomy candidates to candidates for BCT, the use of NACT has the potential to improve the cosmetic result by decreasing the amount of breast tissue that needs to be removed at the time of lumpectomy. This endpoint is subjective and difficult to quantify and requires an accurate assessment of the patterns of primary tumor shrinkage and of the amount of residual disease in the breast after NACT. In addition there are still several gray areas in literature (discussed in brief below) regarding tumor bed localization in patients with pCR following NACT, the number of NACT cycles to be administered and the best locoregional treatment option for post NACT LABC patients without compromising their long-term DFS and OS. Again everything has to be weighed carefully so that the decision taken is not only safe and practical but also cost-effective for patients from lower socioeconomic strata hailing from the developing countries.

Issues needing special attention regarding breast conservation in LABC

Assessment of feasibility for breast conservative surgery

Accurate assessment of the extent of the primary tumor in the breast before, during, and after NACT is critical. Post NACT criteria for selecting patients for BCT remain the same as for BCT without NACT (Table 1) [32].

Precise measurement clinically is difficult and subject to considerable interobserver variation. The predictive accuracy of pCR by an ultrasound of the breast has been studied at the Royal Marsden. Of 52 patients, 31 (60%) achieved complete clinical response but in only 5 of these was the post NACT ultrasound normal. In the rest residual mass or diffuse echogenic tissue was seen although 10 such patients actually had pCR [33]. Vallone et al. [34] described their experience with contrast enhanced Color Doppler assessment of response to NACT in 50 LABC (T3, T4) patients. The authors reported that the contrast increased the sensitivity and improved the diagnostic precision, thus allowing for a better image of the vessels, and was able to pick up residual vascularity in 9 patients (indicating active residual tumor) in whom the basic Color Doppler examination demonstrated substantial avascularity.

Although mammography is generally superior to clinical examination in predicting clinical complete response [35], it is not very accurate in predicting pCR [36]. Moreover it is a costly investigation and may not be universally available in most developing countries. A study conducted to pathologically assess the response of 38 LABC patients to NACT revealed that when the residual tumors in the mastectomy specimens were measured, mapped, and compared to the pretreatment and preoperative clinical and mammographic findings, both were found inadequate for the selection of candidates for breast conservation [37].

Table 1 Criteria for selecting patients with locally advanced breast cancer for breast conserving therapy after primary chemotherapy [32].

1	Solitary primary tumor 4 cm or less in size, or two primary tumors within a sphere of less than 4 cm
2	Absence of multiple scattered calcifications in the breast
3	No skin involvement
4	Tumor: breast size ratio small enough for a good cosmetic result
5	Clinically node negative, or with small, mobile, low axillary nodes
6	Absence of extensive involvement within the breast or dermis
7	No contraindication for radiotherapy (i.e. collagen vascular disease, etc.)

Magnetic resonance imaging (MRI) before and after NACT can identify two distinct patterns of tumor shrinkage (concentric and dendritic) [38], and thus can be useful in identifying appropriate candidates for BCT after NACT [39]. However, an important caveat of MRI is its lower specificity. Irregularity of architectural distortion and persistence of microcalcifications makes accurate measurement of response to NACT difficult at times. Thus, if multicentric lesions are present on the original and/or post-chemotherapy MRI, consideration should be given to obtaining histologic confirmation of these lesions before deciding to proceed with mastectomy. Indeed more studies are needed to establish the role of MRI in surgical planning of patients who are receiving NACT [40].

A study from Korea [41] evaluated the predictive value of [^{18}F]fluorodeoxyglucose positron emission tomography (FDG PET) for the pathological response of breast cancer after completion of NACT in 50 patients with newly diagnosed, non-inflammatory large or LABC. The authors concluded that results indicate a possible predictive value of FDG PET for the assessment of post NACT pathological response of primary breast cancer. However, FDG PET is a highly specialized investigation that is only available in selected cancer centers and again out of reach of a large majority of our patients with LABC.

Other simple, safe, economical and effective methods especially in the context of countries with limited resources include tattooing the entire tumor extent or putting the biopsy scar at the epicenter of the tumor. The latter is practiced regularly at one of the cancer centers in India [42]. Lannin et al. [43] recently described a method in 34 patients with breast cancer where the edges of the tumor were tattooed prior to NACT, allowing all tissue initially involved with tumor to be resected following the

chemotherapy. Of the 22 patients who have so far undergone lumpectomy, 77% had residual pathologic evidence of tumor, but the margins were negative in 91%. The authors thus concluded that this method is simple and practical.

Another interesting technique of tattooing breast cancer has been reported by Mathieu et al. [44]. The authors injected a suspension of micronized charcoal at a defined granulometry and a concentration of 10% at the time of the initial biopsy before NACT in 109 patients with large breast tumors. The charcoal was well tolerated and was detected in 94% of the 91 patients who underwent conservative treatment after 3—4 cycles of NACT. The charcoal was seen in the nodule or at the periphery in the surgical specimen without any acute inflammatory reaction or diffusion.

A study from India recently reported use of sterile silver wire markers placed at all tumor margins percutaneously under local anesthesia in 40 LABC patients before NACT [45]. Though the authors claim their procedure to be inexpensive (compared to titanium clips that are costly) and without significant pain or discomfort due to silver wires, the technique does however require needle localization often under mammographic vision while allowing accurate determination of the pre- and post-NACT tumor size and margins. In addition the migration of silver wires is certainly a possibility during the course of the treatment.

Localizing tumor bed in complete response to NACT

At times patients achieve a complete clinical response and radiological response to NACT. Breast conservative surgery in such patients might prove to be difficult unless the primary tumor area had been marked previously. For a patient who is about to receive NACT it is therefore important to mark the exact tumor location by any of the various techniques discussed in the previous few paragraphs under mammographic or sonographic guidance especially in patients with dense breasts [42—47]. This can be performed either at the time of the initial core biopsy or subsequently when there is clinical evidence of response. Marker placement is crucial in cases of pathologic complete response because it guides the surgical identification and excision of the tumor bed area and facilitates the pathologist's search for residual tumor.

Number of NACT cycles

A great heterogeneity is seen in patient responses with regard to number of cycles for maximum tumor reduction. In most studies, a fixed number of cycles (three to four cycles) of NACT are administered. However some patients require as many as five or more cycles to achieve maximum response. Many studies have delivered initial, neoadjuvant chemotherapy in a flexible manner, to best clinical response with or without one or two additional cycles of chemotherapy [14,48]. The optimal method of chemotherapy delivery remains uncertain. This assumes importance if conservative surgery is the prime aim of administering NACT to a patient. Moreover, several retrospective studies have shown that post NACT residual tumor burden has direct impact on locoregional control and survival [49]. The optimum schedule as of now is subject to results from various randomized clinical trials.

Drawbacks of breast conservative surgery in LABC

Increased locoregional recurrence

Information is sparse regarding the outcome of breast conservation following NACT in LABC. Breast conservation has not been the standard of care for women with LABC, owing to concerns that downsized tumors might leave a field of satellite nodules rather than shrink concentrically, that the surgeon may lose a window of opportunity to obtain durable locoregional control of the disease. The development of local recurrence of breast cancer after BCT negates one of the most important benefits of breast conservation, namely that patients may require subsequent mastectomy to achieve local control of disease. In addition, it is possible that these patients may also suffer psychological trauma from experiencing a recurrence of malignancy. Local recurrence of the disease has been shown to be associated with an increased incidence of developing distant disease, which is detectable either at the same time or shortly afterwards.

The clinically relevant question that remained unanswered by various trials involving NACT was which of these patients would do well with a breast conservation approach and which others would have a higher risk of locoregional recurrence. Studies evaluating local recurrence after NACT and BCT have shown conflicting results. Three large, randomized, prospective controlled trials comparing preoperative and postoperative chemotherapy have not demonstrated a difference in local recurrence (Wolmark et al. [15], van der Hage et al. [18], and Makris et al. [50]). Single institution studies have reported low local recurrences, 2.5—10% [27,29,30,51]. Several treatment factors may have impacted local recurrence rates in these trials, including the width of negative margins, the use of tamoxifen in women older than 50 years, the use of radiotherapy only as BCT, and inconsistent use of an RT boost to the lumpectomy site. With careful attention to all these details, local recurrence rates should be low in these patients too.

The use of only radiotherapy after pCR as BCT needs attention as the literature is a little controversial about it at this moment. In a French study by Touboul et al. [25] (discussed above), 48/147 patients with pCR underwent only radiotherapy boost to the tumor bed whereas 47 patients with residual disease underwent wide local excision followed by two courses of chemotherapy and radiotherapy too. The 5-year OS was 81% in patients with wide local excision + radiotherapy while it was 65% in the radiotherapy alone group. Similarly recently Clouth et al. [52] reported their findings on 101 patients with LABC treated with NACT. Only multiple core biopsies and axillary clearance followed by irradiation was performed on patients with pCR. Two of 20 patients with pCR developed local recurrence after a mean follow-up of 33.5 months. The authors then decided to change their treatment protocol to include pretreatment marking and subsequent surgical excision in these groups of patients.

It is prudent to discuss the results of the NSABP B-18 [14,15] trial in this context. There was no difference in

locoregional recurrence rates in the chemotherapy-first group of the trial when compared with women undergoing adjuvant chemotherapy. The breast cancer recurrence rate was however increased in those who were candidates for mastectomy at diagnosis compared with those who were candidates for breast conservation before the NACT (15.7% vs. 9.9%, respectively; $p = 0.04$).

This led many to be reluctant about BCT as a safe possibility following NACT in patients with advanced disease. These findings can be explained by several issues. First, this subset consisted of predominantly of T3 tumors and as local recurrence is one of the underlying features of tumor biology, it would be expected that the more advanced lesions might have increased local recurrence rates regardless of surgery type and treatment sequence. Also, radiation boost doses were not consistently used in the lumpectomy patients, and tamoxifen was used only in patients over 50 years. Both the above interventions and a more aggressive approach to margin control might have influenced local recurrence rates in the downstaged tumors.

On the contrary, van der Hage et al. [18] found no difference in locoregional recurrence rates between patients who converted to BCT after NACT compared with those eligible for BCT before chemotherapy in their trial.

Chen et al at the MD Anderson Cancer Center [53] evaluated the outcome of 340 patients with stage II or III disease who were carefully selected for BCT following NACT. Selection criteria included no postsurgery residual malignant calcifications, no residual T4 breast skin abnormalities, achievement of negative surgical margins, and no multicentric disease. In this series, the 5-year and 10-year breast recurrence rates were excellent (only 5% and 10%, respectively). Factors associated with breast cancer recurrence and locoregional recurrence were identified to further refine selection criteria and the following four factors were found to have adverse effects: clinical N2 or N3 disease, lymphovascular space invasion in the primary tumor biopsy, a multifocal or break-up pattern of residual disease, and residual disease greater than 2 cm. It is important to note that many of these same features are also associated with higher locoregional recurrence rates after mastectomy and radiation. Clinical T stage did not correlate with breast cancer recurrence, but when T3 or T4 tumors responded to chemotherapy by breaking up and leaving a multifocal pattern of residual disease, the breast cancer recurrence rate was 20% [53]. The authors then developed a prognostic index using the four adverse factors. The presence of zero to two of these factors was associated with low rates of locoregional recurrences but the few patients with three of the factors had high rates of recurrence and may be better served by undergoing a completion mastectomy [54].

As already outlined in Table 1 factors increasing the risk of local recurrence and therefore contraindications of breast conservation surgery in LABC patients include persistent skin edema, residual tumor >5 cm, and extensive intramammary lymphatic invasion. Vishwambharan et al. [55] carried out simulation lumpectomy to achieve 1–2 cm clearance from tumor on the mastectomy specimens of 30 patients with LABC whose tumors reduced with NACT to at least 5 cm. Tumors with postchemotherapy size >3 cm were margin positive in 13/24 (54%) compared to tumors size 3 cm (1/6; 17%). Tumors in the subareolar location had significantly higher incidence of residual tumor in the nipple areola complex ($p = 0.04$). The authors concluded that margin positivity can be reduced by removing the nipple areola complex in subareolar tumors and by limiting breast conservation to tumors with post-chemotherapy size <3 cm [55].

Few authors have suggested a very wide local excision that includes the whole original tumor-bearing area with or without immediate reconstruction (e.g. latissimus dorsi myocutaneous flap) to ensure negative margins especially in post-NACT LABC patients [45,56]. Aggarwal et al. [45] reported that if post-NACT margins are used to guide the wide local excision, 35% patients would have infiltrated margins compared to only 5% if excision is wide of the marked pre-NACT margins.

However, the general consensus during surgery for BCT is that the tissue resected must include all residual palpable and radiographic abnormalities. Not all the initial tumor volume needs to be excised, though pathological negative margins remain essential.

Histology may also play a role in BCT feasibility. Few studies have demonstrated that clinical and pathological responses are lower in lobular carcinomas when compared to ductal carcinomas [57–59].

Some patients are not candidates for BCT even with an excellent response to NACT. These include women with inflammatory breast cancers, extensive microcalcifications throughout the breast, patients unwilling to undergo radiation therapy, or coexisting medical condition that may increase radiation injury such as autoimmune connective tissue disease. In spite of good local control, distant metastases occur frequently in LABC patients. For example, despite good local control, 32% developed distant metastases after 30 months of follow-up as shown in one study following a very wide local excision for post NACT tumor [56].

Need of adequate infrastructure

The importance of timely chemotherapy and radiotherapy cannot be emphasized enough in the treatment of LABC, in particular if BCT is attempted. Health care inequalities exist in most developing countries such as ours. The hospitals range from highly specialized superspecialty institutions with well-trained staff in major cities to Primary Health Centers on the periphery with minimal staff and health care facilities [3]. As a result of this inappropriate concentration of comprehensive cancer centers to metropolitan cities, only a fraction of total cancer patients can access these services. It is therefore not unusual to find suboptimal treatment of cancer in the rural and semi-urban regions of India [60]. Various studies on breast cancer published from India reflect the disease profile and treatment characteristics unique to the urban rich and the middle-class patients. The breast cancer profile at community level is largely unrepresented.

The availability of radiotherapy units in developing countries is often below the World Health Organization (WHO) recommendations (<0.4 Radiotherapy units/million population) and hence is a major issue of concern. Only 20–25% of patients in developing countries that need

radiotherapy can access it today [61]. As noted by an advisory group (PAHO-WHO-IAEA-UNIDO, 1995), ''approximately 2300 megavoltage teletherapy units are currently installed in developing countries, primarily cobalt-60 units. It should be noted that the developed countries (North America, Western Europe, Australasia and Japan) have about 15% of the world population; 80% (3565/4253) of all electron accelerators and over 30% (630/2025) of all cobalt machines'' [62]. As many as 22 African and Asian countries have no service of radiotherapy at all. In Africa in 2002, the actual supply of megavoltage radiotherapy machines (cobalt or linear accelerator) was only 155, 18% of the estimated need. In the Asia—Pacific region, nearly 4 million cases of cancer arose in 2002. In 12 countries with available data, 1147 megavoltage machines were available for an estimated demand of nearly 4000 megavoltage machines. Eastern Europe and Latin America showed similar shortages [63]. Unfortunately, lack of trained staff results in underutilization or inappropriate utilization of even the existing scarce radiotherapy facilities in many countries. In addition, machine down-time is high in many developing country institutions due to lack of preventive maintenance [61].

India, for example, has only 363 teletherapy units and 70 linear accelerators catering for a population of over 1 billion [64]. According to the WHO bulletin update, India needs another 1000 units to meet its future demands. Moreover, all these are located in major urban centers far from remote villages and towns where the majority of our patients come from. The cancer centers are often overloaded and result in treatment delays. Patients, most without any insurance cover, are thus forced to spend a handful of resources and result in frequent dropouts. The outcome of such patients can only be imagined. It may be mentioned that even in developed counties like the USA there are underserved regions, where the nearest facilities—for radiation oncology for example—are situated far away from the patient's location. The UK still has substantial problems in delivering a satisfactory radiotherapy service nationwide. As an illustration of this, delay to treatment for radiotherapy for women with early breast cancer is lengthening rather than shortening in some parts of the country, extending to many weeks in some departments [63]. Hence, tackling cancer problems in developing countries could be also useful for the very developed countries!

Surgery is the key prognostic factor in the treatment of breast cancer. Meticulous surgery with proper evaluation of the excised specimen by a pathologist specializing in breast cancer is necessary for a good patient outcome. Several studies in the literature emphasize the fact that as NACT becomes the mainstream of management for LABC, pathologists are required to recognize treatment-induced changes. Moll et al. [65] found an increase in nuclear atypia of tumor cells as the most prominent histologic change following NACT in 51% of their 61 patients with LABC (stage III). Nuclear atypia was frequently accompanied by tumor cell enlargement (in 49% of the cases). Most commonly, a tumor with relatively small cells presented with large epithelioid apocrine features after NACT. In 6 cases (13%), the mitotic rate decreased significantly, while in 12 cases (26%) the mitotic rate increased after NACT. Elston histograde remained unchanged in 70% of the cases but increased in 17% and decreased in 13%, mainly due to changes in mitotic rates. Extensive tumor cell vacuolization, a common change seen after radiotherapy, was a minor finding but was seen focally. The adjacent normal breast tissue showed lobular atrophy with hyalinization and minimal epithelial atypia of lobules and ducts. The authors concluded that changes in residual tumor and normal breast are common following systemic cytotoxic therapy [56].

Another study by Rajan et al. [66] from the MD Anderson Cancer Center revealed that residual tumor size following NACT in LABC patients is influenced by variable pathologic changes that occur within the tumor bed. Chemotherapy-induced fibrous stromal involution is reported to occur in up to 67% of tumors and can result in clinical and macroscopic overestimation of residual tumor size. In their study the greatest reduction was observed in the cellularity of residual primary tumors that measured <1 cm (pathologic T1a (pT1a) and pT1b tumors), but changes in cellularity varied in the pT1, pT2, and pT3 residual tumor categories. The authors stressed upon the need for the development of new histologic approaches for pathologic and clinical assessment particularly for tumors in which less than pathologic complete response is achieved [57].

Similar is the role of a radiologist who along with the clinician will help in selecting patients for BCT after NACT and also in detecting a recurrent cancer during follow-up screening. It is pertinent the multidisciplinary team should include a radiation oncologist and a medical oncologist. Thus an adequate infrastructure is the basic necessity when undertaking such procedures.

Patient awareness

A well-informed patient with a fair socioeconomic background who understands the nature of the treatment may be good candidate for BCT following NACT. Most patients hailing from the developing country such as ours with a LABC often find it difficult to stick to stringent radiotherapy and chemotherapy protocols and long-term follow-up. In a yet unpublished study, we analyzed the response of our operable LABC patients to a simple questionnaire regarding their willingness for NACT. At the counseling for selection/choice of treatment, women were explained the options for therapy and breast conservation.

Surprisingly of 50 patients, only 10 wanted to undergo NACT. The rest, 40 (80%) wanted to opt first for surgical removal of their breast cancer. Thirty-five (70%) patients were not interested in BCT at all. It appears that women and their spouse respond favoring mastectomy in the majority, believing that once cancer has developed that breast is no good to them and they fear that the disease may reappear later. Excessive fear for radiotherapy and chemotherapy is not widespread but women who have seen a friend or relative undergoing these treatments with their complications do request to avoid these modalities and refusal for BCT is one way to achieve this. There is another dimension to refusal of radiotherapy and chemotherapy: the cost of the adjuvant treatment. The total cost burden of radiotherapy in our area comes approximately to US$300 and that of chemotherapy ranges from $600 for FAC/FEC $\times$ 6 cycles regimens to $12,000 for Taxotere-based

regimens. Though the requirement of both was discussed, many (70%) opted for management to avoid this if possible. Both these modalities are not free of cost in India except in a very few hospitals.

A large number of our patients are unable to reach the cancer center due to various problems as outlined previously. They often seek treatment locally in their small towns and villages. We evaluated the data of some 58 such patients visiting our center after primary treatment elsewhere [60]. Only 14 had undergone a BCT with documented negative margins. Twenty-two patients had no histopathology report of their lumpectomy specimen and had presented to us after developing recurrence. Nonetheless the two major cancer centers in India have reported favorable results of BCT in LABC patients [65,66]. The first study reported on 664 patients with LABC, 28.3% (188) of whom were treated with post-NACT BCT [67]. The lumpectomy margins were positive in 8.5% patients with a gross positive rate of 2.3%. The 3-year DFS was 8% after BCT and 10.7% after mastectomy. The authors concluded that BCT is technically feasible and safe in post-NACT LABC patients. But here it is important to note that the two groups, i.e. BCT vs. mastectomy, are strictly not comparable. Only patients who were sufficiently downstaged by NACT could undergo BCT and the rest were treated with mastectomy. The number of LABC patients included in the other published study from India was too small to reach to any conclusion (of 102 patients who underwent BCT, only 12 had LABC) [68]. The figures clearly indicate the need for more studies on the subject from the countries with limited resources where LABC still remains a major problem.

Conclusion

Breast conservation is indeed a wise and an attractive option in patients with early breast cancer. With the development of active chemotherapy regimens it is now possible to extend BCT to some patients with LABC, with a fairly good outcome. By identifying patients at high likelihood of having negative axillary nodes, sentinel lymph node biopsy alone (or even no axillary surgery) may become appropriate options in the future. But it would be wise to limit such procedures to selected patients keen for breast conservation that are backed by a sufficient support system, so that at the end of the day it is the patient who benefits the most and the efforts put in do not go to waste.

Conflict of interest statement

The authors have no conflict of interest.

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