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Original Article

Breast conservation and sentinel lymph node biopsy after neoadjuvant systemic therapy

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Introduction

Two large prospective randomized trials demonstrated that primary chemotherapy (PC) does not improve prognosis of patients with breast cancer unless a pathological complete response (pCR) is achieved.[1,2] Despite this, the field of preoperative treatment of breast cancer remains very attractive for two main reasons: firstly because it represents a unique opportunity to evaluate response to treatment in vivo and secondly because by reducing tumor size conservative surgery can also be applied to women who would otherwise be candidates for mastectomy.[3] However, several authors have reported high local recurrence rates in patients who underwent BCS after PC[4–9] and therefore the surgical community has been hesitant to fully embrace the conservative approach after chemotherapy. Conservation of the breast after PC carries some pitfalls and differs from conventional conservative surgery performed in chemo-naïve patients. The desired goal of reducing tumor size makes identification of the original tumor size difficult especially when a major response is obtained. Moreover, large tumors at presentation might not be uniformly destroyed by chemotherapy[3] and the cut margins might lie at a site where probably the tumor was grossly located and there may remain the possibility of microscopic persistence of viable tumor cells.

Breast conservation surgery after primary chemotherapy

In the proceedings of the Neoadjuvant Chemotherapy Consensus Conference it was stated that the first indication for primary chemotherapy in operable breast cancer was reduction of tumor extent to enhance the possibility of breast-conserving surgery. However, some concern was raised regarding the reported higher rate of local recurrence.[10]

In fact, in the NSABP B-18 trial,[11] after 9 years of follow up the rate of IBTR was slightly higher in patients treated with conservative surgery after primary chemotherapy with respect to those patients who underwent lumpectomy and postoperative chemotherapy, without reaching statistical significance (10.7% vs 7.6%, p = 0.12). A marginally statistical significance was reported in the rate of IBTR found in patients converted to lumpectomy after PC compared to those who received lumpectomy as originally planned (15.9% vs 9.9%, p = 0.04). This difference was no longer statistically significant after controlling for patient age and initial clinical tumor size.

In the EORTC 10902 trial[2] no difference in loco-regional recurrence was found in patients who received preoperative chemotherapy compared to postoperative adjuvant treatment. However, patients who were planned to undergo mastectomy but underwent breast-conserving therapy because of tumor downstaging did worse in terms of overall survival (HR, 2.53; 95% CI, 1.02–6.25) compared to patients who were initially planned to receive conservative surgery and were treated accordingly. The authors concluded that these findings supported the assumption that radical conservative surgery, especially after downstaging, may be more difficult because of the fact that tumor-free margins are more difficult to assess after PC.

Conservative surgery after PC is difficult and a higher local reappearance rate makes sense. In fact, in this scenario large tumors might undergo a honeycombed and not concentric shrinkage and viable tumor foci may remain some distance away from the central tumor site.[3] Moreover, macroscopic evaluation of margins represents a challenge even for the experienced surgeon and intra-operative frozen section of margins is not completely reliable. The sum of these considerations might lead to an incomplete excision of the tumor and to a subsequent higher risk of developing IBTR. From

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Table 1
Practical recommendations

Some considerations have to be done for the proper management of patients undergoing PC or for the patients who achieved a sufficient response to allow breast conservation:
1. prior to starting PC, histological diagnosis needs to be provided in order to confirm the presence of invasive carcinoma and to have biologic features of the tumor. In case of a highly responsive cancer the expected probability of pCR is low[12] and the indication to PC should be rediscussed,
2. patients with multicentric breast cancer should not be considered candidates for PC,
3. tumor site must be marked before starting PC or during chemotherapy in case of major response,
4. provide localization of the residual tumor if it is not any longer palpable at the end of PC,
5. macroscopic evaluation of the specimen during the operation along with the pathologist is recommended to ensure adequacy of the resection,
6. all suspicious microcalcifications have to be excised and the adequacy of the resection has to be verified with x-ray of the specimen.

this standpoint, it is mandatory to mark the tumor bed to ensure an adequate resection. We routinely use skin-tattooing which is a simple and not expensive method, but insertion of a radio-opaque clip might be helpful especially in those patients who experience a complete clinical response. Table 1 summarizes the practical recommendations for patients undergoing PC.

In our Institute we tried to evaluate the issue of the impact of surgical margins on outcome.[13] We considered 309 patients with T2–T3 breast cancer candidates to mastectomy who underwent PC. Conservative surgery was carried out on 195 patients (63.1%). Only four patients required a new operation for extensively positive margins (defined as tumor cells at the inked margin or close proximity of both in situ and invasive component) whereas 24 had focally positive margins and were not re-excised. The possibility of having positive margins did not correlate with the response (p-value = 0.44) even if a lower percentage of positive margins can be observed in patients with a pCR which was defined as absence of invasive cancer in the breast. This supports the assumption that the tumor shrinkage is often not concentric, and thus unpredictable. In the 24 patients who had focally positive margins or a close proximity, radiotherapy was considered adequate after a thorough case by case discussion was done taking into account the preference of the patient and the desire of breast conservation. The local recurrence rate of 6.6% after 41 months in patients treated with conservative surgery after PC was acceptably low, and consistent with the data from the NSABP B-18 trial. As expected from data in chemo-naïve patients[14] the status of margins significantly increased the IBTR rate (13.3%, p = 0.05), but did not exert an impact in terms of overall survival after a limited follow up. Nevertheless, some caveats might be raised. In fact, our analysis has some limitations such as the small number of patients of positive margins especially if compared to patients with negative margins (24 vs. 171) and the relatively short follow up.

We concluded that in the presence of a focally positive margin, the acceptably low rate of IBTR, the absence of impact on overall survival and the desire for breast conservation all have to be taken into account when discussing treatment options with the patient and need to be balanced against other factors which might increase the risk of IBTR. We believe that these are interesting data to discuss with the patients.

In the paper by Chen et al. (14) the variables that positively correlated with IBTR and local-regional recurrence after breast conservation following PC were: clinical N2–N3 disease at presentation, residual tumor larger than 2 cm, a multifocal pattern of residual disease, and lymphovascular space invasion in the specimen. In this paper, margin status was not associated with an increased rate of loco-regional recurrence, possibly because of the low number of patients with positive margins (4%). It also should be pointed out that the authors were unable to retrospectively determine the percentage of patients eligible for BCS at presentation, whereas all our patients were candidates for mastectomy. In the same paper, T stage at diagnosis, when not combined with other unfavourable factors, did not predict IBTR when each T stage was analysed independently, and when T1–T2 were compared to T3–T4 or when T4 was compared to other clinical T stages.[15]

Patients with clinical T4 disease at presentation were excluded from our analysis since the vast majority of these patients were treated with mastectomy regardless of the response, but we agree with Chen et al.[15] that these are important data for discussing conservative surgery even in those patients with clinical T4 stage at presentation as long as appropriate selection criteria are used.

Sentinel node biopsy after primary chemotherapy

Earlier papers on SLNB after primary chemotherapy (PC) reported that the false negative rate of SLNB was higher in patients who had received PC than in those who had not.[16–19] More recent and larger studies have demonstrated that, with increasing experience, the identification and false-negative rates of SLNB are similar to those reported in the absence of PC.[20–23] The largest paper published on this topic, reports the experience collected within the National Surgical Adjuvant Breast and Bowel Project multicentric trial B-27,[24] in which after neoadjuvant chemotherapy 428 patients underwent lymphatic mapping. Success rate for the identification and removal of a sentinel node was 84.8%. Success rate increased significantly with the use of radioisotope (87.6% to 88.9%) versus with the use of lymphazurin alone (78.1%, p = 0.03). Of the 343 patients who had SLNB and axillary dissection, the SLNs were positive in 125 patients and were the only positive nodes in 70 patients (56.0%). Of the 218 patients with negative SLNs, non-sentinel nodes were positive in 15 (false negative rate, 10.7%, 15 of 140 patients). There were non-significant differences in false-negative rate according to clinical patient and tumor characteristics, method of lymphatic mapping or tumor response to chemotherapy. The authors concluded that the results were comparable to those obtained in multicentric studies evaluating SLNB before systemic therapy and that the sentinel node concept is applicable also following neoadjuvant chemotherapy.

A meta-analysis concerning sentinel lymph node biopsy after preoperative chemotherapy has been published[25] including twenty-one papers for a total of 1273 patients. Selected papers had to meet two criteria. First, patients had to have had operable breast cancer and to have undergone SLNB after preoperative chemotherapy and, second, patients had to have undergone subsequent axillary lymph node dissection. The identification rate (IR) ranged from 72% to 100%, with a pooled estimate of 90%. The sensitivity of SLNB ranged from 67% to 100%, with a pooled estimate of 88%. These results are comparable to those obtained from multicenter studies evaluating SNB before systemic therapy and suggest that sentinel node biopsy is applicable following neo-adjuvant chemotherapy.

Therefore, in women with a clinically negative axilla before the start of PC, SLNB might be considered after the completion of medical treatment if no progression has occurred. In patients with suspicious axillary nodes at presentation which have been

Table 2
Advantages of performing SNB before and after chemotherapy[a]

SLNB before chemotherapy:

- Provides accurate assessment of initial axillary lymph node involvement
- May affect decisions concerning whether to use radiation after mastectomy or whether to use radiation to treat the regional lymphatics
- May affect systemic treatment decisions, if a particular systemic regimen would only be used for patients with positive lymph nodes (an uncommon situation in typical candidates for preoperative chemotherapy)
- False-negative rates are more clearly established for patients treated with sentinel lymph node surgery before chemotherapy

SLNB after chemotherapy:

- Eliminates the need for doing two surgical procedures
- More comprehensive assessment of the ability of the preoperative chemotherapy to achieve a pathologic complete response
- Takes advantage of the down-staging effect of preoperative chemotherapy and as a result may decrease the number of patients that require an axillary lymph node dissection
- Does not delay administration of preoperative chemotherapy

[a] Adapted from TA Buchholz et al.[26]

"downstaged" to N0 by medical treatment, SLNB might also be considered an option in the hands of surgeons with extensive experience in this procedure. SLNB is obviously not recommended for patients whose axillary nodes remain clinically suspicious after PC. PET scan might be a useful tool to properly select those patients in which SLNB can be performed, even though this still represents a matter of research.

Some considerations might be added regarding the opportunity to gain pathological information on the nodal status before starting preoperative treatment. The pros and cons of performing SLNB before and after chemotherapy were discussed by Buchholz et al.[26] and are summarized in Table 2. Axillary status before PC provides prognostic information that could be missed following PC, and therefore it might be considered to perform axillary staging before PC in the event of a clinically negative axilla. Afterwards, if the node(s) were negative, axillary dissection (AD) following PC could be avoided, whereas in the case of a positive SLN, AD would be part of the surgical plan after medical treatment. This approach might also overcome the concern regarding the debated lower identification rate and sensitivity of SLNB after PC.[27] On the other hand, it is conceivable that the prognostic value of axillary staging following PC is even higher, since it already mirrors response to treatment. Moreover, performing SLNB before PC would lead to complete AD in all patients with positive SLNs, and therefore to the use of AD in a higher fraction of patients, given that PC may "sterilise" axillary node metastases in about 20% of patients.[28] At the moment, in our institute we prefer to perform SLNB in selected patients after PC rather than before.

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