De-Escalation of Surgical Treatment after Neoadjuvant Chemotherapy in Breast Cancer Patients

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Breast cancer is a major health problem with millions of new cases detected every year. Progress in early diagnosis and management modalities has significantly enhanced patient outcomes. Among these, neoadjuvant chemotherapy (NAC), also known as primary chemotherapy, has emerged as a valuable tool in the multidisciplinary treatment of locally advanced and operable breast tumours [1].

Despite several clinical trials demonstrating comparable disease-free and overall survival between systemic therapy administered pre- or post-surgery, the use of NAC is growing due to its ability to provide various advantages such as [2]:

- Disease downstaging and surgical de-escalation: One of the significant benefits of NAC is the potential for tumour downstaging. By reducing the size of the cancer, NAC may transform patients eligible for mastectomy into candidates for conservative treatment [3]. Moreover, primary chemotherapy can decrease the amount of tissue removed in patients with sizable neoplasms who are already suitable for breast-conserving surgery (BCS) allowing enhanced aesthetic results. Additionally, another surgical benefit is the axillary downstaging enabling the avoidance of lymph nodes dissection in carefully selected patients and minimizing surgical complications.

- Assessment of treatment response: NAC enables early monitoring of the response to drugs, thereby providing the opportunity to switch therapies if a patient does not adequately respond.

- Tailored treatment approach: The response to NAC can help to tailor subsequent treatment strategies, including the type of adjuvant therapy optimizing the patient’s overall treatment plan.

- Early systemic treatment of micrometastatic disease: NAC has the potential to address systemic spread of the disease prior to surgery.

The most common indications for primary chemotherapy in operable breast cancer include: high tumour-to-breast volume ratio; metastatic disease involving the lymph nodes; and cancers with particular biological characteristics (triple negative and human epidermal growth factor receptor (HER2) positive tumours; poorly differentiated luminal B tumours with high Ki 67). Patients with triple-negative and HER2-positive breast cancers are more likely to achieve a pathological complete response (pCR) following NAC making them ideal candidates for this treatment approach [4,5].

As the efficacy of NAC has improved and a significant proportion of patients achieve pCR, there has been growing interest in surgical de-escalation after NAC. The potential benefits of adopting a de-escalated surgical approach post-NAC are [6]:

- Improved cosmetic outcomes: The use of less extensive surgical procedures can result in more satisfactory aesthetic results and better quality of life for cancer survivors without compromising oncological outcomes; the psychological and cosmetic benefits of less invasive surgical procedures significantly improve the overall well-being and satisfaction of patients.

- Reduced morbidity: Reduced surgical interventions lead to decreased rates of complications such as wound infections, seromas, lymphedema, and shoulder dysfunction.

- Faster recovery: Less extensive surgery typically results in a shorter hospital stay and faster overall recovery allowing breast cancer patients to resume their normal activities sooner.

- Cost-Effectiveness: De-escalation of surgery can lead to significant cost savings for healthcare systems in terms of hospitalization, surgical procedures, post-operative care and rehabilitation.

1. De-Escalation of Breast Surgery

The optimal surgical approach for breast cancer following NAC should consider factors such as multicentricity, gland volume, tumour dimensions, the potential for obtaining clear surgical margins and the patient’s preferences.

However, secondary to NAC there has been a shift towards a more conservative surgical approach that involves the removal of the cancer and an adequate margin of surrounding normal tissue while preserving as much of the breast as possible [7].

Surgical de-escalation using BCS can be performed in the presence of a favorable disease response to NAC. A substantial decrease in tumour size after NAC is crucial for successful BCS. Nevertheless, conservative surgery must
ensure complete removal of the cancer with clear surgical margins, achieve an optimal aesthetic result and minimize the excision of healthy breast tissue.

Optimal surgical margins are defined as “no tumour on the ink” [8]. It is essential to avoid tumour-involved margins as they significantly increase the risk of local recurrence (LR) and often require further treatment such as re-excision or even mastectomy. In cases where tumours are not well-defined or have a scattered distribution, achieving clear margins can be challenging.

To perform optimal surgical de-escalation with BCS while sparing as much glandular tissue as possible, it is necessary to follow some mandatory recommendations such as [9]:

- Careful staging before NAC with ultrasonography, mammography and magnetic resonance imaging.
- Positioning clips prior to NAC to identify the cancer site and pathologic axillary lymph nodes.
- Adequate restaging after NAC with radiological preoperative identification of tumour residue and/or clips particularly after an optimal response to therapy.
- Application of oncoplastic techniques to achieve extensive resections and minimize the risk of LR without compromising the aesthetic outcomes.
- Identification of the lesion and study of margin adequacy using both radiologic and pathologic intraoperative evaluations.

Mastectomy after NAC must be performed if BCS cannot guarantee adequate surgical margins and satisfactory cosmetic results. Indications for mastectomy include multicentric or extensive cancers, unfavorable breast-tumor volume ratio, tumour-involved margins after re-excisions, inability to undergo adjuvant radiotherapy following BCS, and patient preference.

However, when a mastectomy is required, a surgical de-escalation can be carried out through more conservative techniques like nipple-sparing, skin-sparing or skin-reducing mastectomies combined with immediate breast reconstruction [10].

Furthermore, some recent trials are evaluating in the neoadjuvant setting whether breast surgery can be omitted and replaced by radiotherapy for highly selected patients with pCR verified by an image-guided vacuum-assisted core needle biopsy [11,12].

2. De-Escalation of Axillary Surgery

The increasing efficacy of NAC is also leading to a gradual de-escalation of axillary surgery. Several studies have shown excellent pCR rates in lymph nodes after NAC, ranging from 50–60%, particularly in HER2-positive and triple-negative cancers.

Thanks to downstaging, the less invasive sentinel lymph node biopsy (SLB) can be used for axillary staging, thereby avoiding the potential complications of axillary dissection such as seromas, hematomas, paresthesias, lymphedema and shoulder impairment [13–15].

When using SLB for surgical de-escalation after NAC, minimal false negative rates (<10%) and high identification rates (>90%) comparable to traditional surgery are mandatory to optimize oncological results [15].

SLB is always considered a safe and effective procedure when performed in patients with clinically negative lymph nodes at presentation (cN0) and after NAC (ycN0) [14,15].

Recently, surgical de-escalation with SLB has also been endorsed in patients with initially positive lymph nodes (cN+) that convert to negative after NAC (ycN0) as long as some necessary tasks are performed to optimize false negative and identification rates, such as [15]:

- Accurate staging of the axilla by clinical exam, ultrasonography and magnetic resonance imaging pre-NAC.
- Positioning of clips within the pathological axillary nodes at the time of needle biopsy prior to chemotherapy.
- Restaging of the axilla with an accurate assessment of nodes post-NAC.
- Localization of clipped nodes by specific techniques with magnetic seeds or radioactive seeds.
- Utilization of a dual-tracer technique combining radiocolloid and blue dye for the identification of sentinel nodes.
- Application of the technique known as “Target Axillary Dissection” which involves the removal of a minimum of 3 sentinel nodes including the those previously marked with clips.
- Control of the complete removal of clipped nodes by intraoperative radiologic assessment.

Currently, axillary dissection in the neoadjuvant setting remains indicated in patients with pathologic lymph nodes before surgery (ypN+) and in patients with positive sentinel nodes (ypN0i+[sn]) including isolated tumour cells (ypN0i+[sn]) and micrometastases (ypN1mic[sn]) [13–15].

Ongoing studies such as ALLIANCE A011202 and NEONOD2 are also evaluating the possibility of further surgical de-escalation replacing axillary dissection with radiotherapy in selected patients with pathologic sentinel nodes after NAC [6].

3. Conclusions

The de-escalation of surgery is a viable and effective strategy for selected breast cancer patients in the neoadjuvant setting (Fig. 1).

It offers the advantages of improved aesthetic outcomes, better quality of life and reduced morbidity without compromising oncologic results.

The decision to de-escalate should be carefully evaluated for each patient considering the response to NAC, tumour biology and patient preferences.

A collaborative decision-making involving a multidisciplinary team is mandatory to identify the most appropriate candidates, choice the best de-escalation approach and ensure successful outcome.

Ongoing research on artificial intelligence, radiomics, genomic profiling and tumour biomarkers are mandatory to better predict response to NAC and improve surgical de-escalation even to the point of eliminating the need for the scalpel.

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