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Review

De-escalation of Axillary Surgery in the Neoadjuvant Chemotherapy (NACT) Setting for Breast Cancer: Is it Oncologically Safe?

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Abstract. *Background/Aim: The treatment of breast cancer has progressed considerably over the years, with a significant de-escalation from radical mastectomies to the current paradigm of breast conserving surgery (BCS) and neoadjuvant chemotherapy (NACT). We aimed to appraise the literature regarding the feasibility of de-escalation of treatment of axillary disease in the context of NACT. Materials and Methods: We appraised studies and guidelines published regarding this topic and discussed them in this mini-review. Results and Conclusion: The SNB following NACT is oncologically safe in patients with clinically node negative disease and in patients with biopsy proven axillary node involvement at presentation provided that the dual technique is used and the clipped pathological node is harvested.*

The treatment of breast cancer has come a long way since the days of Halsted and Patey (1, 2), with a consistent trend towards de-escalation from radical procedures towards the current norm of breast conserving surgery and neoadjuvant chemotherapy (NACT) (3). Whilst this historic trend has been well-recognised in the context of oncological resection, de-escalation in the treatment of axillary disease has been less uniform. Whilst the previous orthodoxy of complete axillary lymph node dissection (cALND) has given way to a more conservative approach determined by sentinel node status, the road ahead with regards to treatment of axillary disease in breast cancer has been subject to much debate. One plank of this debate has been the management of the axilla after NACT. In this mini-review, we endeavour to appraise the current literature regarding this subject and hopefully draw clinically relevant conclusions.

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Current Evidence Outside NACT

There is a level I evidence from randomised controlled trials that not removing all axillary lymph nodes containing metastasis does not compromise overall survival (OS). In the recently reported Z011 trial, there was no statistically significant difference in clinical outcomes between patients randomised to cALND following a positive sentinel node biopsy and those randomised to observation only. A 27.3% of patients undergoing cALND had macro-metastasis. Since the two groups were matched and are the result of randomisation, then a similar proportion of patients who underwent observation only would have metastatic disease in the axillary lymph nodes (4). Both groups had radiation therapy (RT) to the breast, which would have included the lower axilla to a variable degree and RT was considered as one possible explanation for this similar clinical outcome. However, this does not alter the fact that cALND to remove all positive lymph-nodes did not translate into a clinical outcome benefit.

Further evidence to support this observation can be derived from the initial sentinel node biopsy trials where patients were randomised to sentinel node biopsy (SNB) only if the sentinel node was negative for malignancy or axillary node dissection if the sentinel node biopsy was positive for malignancy. It is well recognised that the SNB procedure is associated with a false negative rate (FNR) in the region of 10%, and therefore those patients randomised to observation only following a false negative SNB would have axillary lymph nodes containing metastatic disease, however, this did not compromise their overall or disease-free survival (DFS).

In the first such randomised trials, the recurrence and mortality events were in fact lower in the SNB group compared with the cALND group, although this difference was not statistically significant (5, 6).

The ALMANAC trial confirmed that the omission of complete axillary dissection when the SNB is negative results in less morbidity and greater quality of life in addition to cost-effectiveness (7).

The trial also confirmed the results from earlier studies that there was no difference in the incidence of recurrence between the SNB group and the cALND group. The equivalence in oncological outcome was also confirmed in the B 32 randomised controlled trial (8).

Therefore, there is clear evidence that the omission of surgical removal of non-sentinel nodes containing small volume disease does not compromise OS. This is consistent with the notion that invasive breast cancer is usually a systemic disease at initial diagnosis (9). This concept has been recently supported further by the findings of genomic profiling and circulating tumour cells and tumour DNA in the peripheral blood (10).

Since then de-escalation of axillary surgery has expanded worldwide on the basis that the SNB is a staging procedure and provided that adjuvant systemic therapy and radiation therapy are used appropriately according to tumour biology, then additional axillary surgery would not improve OS.

Regional Node Irradiation as the Only Therapy After Positive SNB

Furthermore, regional node irradiation (RNI) without cALND did not increase the risk of axillary failure in selected patients with early-stage invasive breast cancer (cT ≤3 cm, cN0) and pN1(sn). In this randomised trial, 38.5% of those assigned to the cALND group had further lymph-node involvement and therefore, a similar number was expected in the RNI group (11).

Similar results were observed in the AMAROS trial where the incidence of additional involved lymph-nodes in the axillary node dissection group was 33%. Although the OS was similar in both groups, however, the initial recurrence was higher in the RNI group without compromising overall survival. Furthermore, the incidence of lymphoedema was significantly lower in the RNI group (12).

Is the SNB a Valid Alternative to cALND in the Context of NACT?

cN0 breast cancer. Encouraged by the evidence discussed above, de-escalation of axillary surgery was expanded to the neoadjuvant setting. A recent meta-analysis of 16 studies including approximately 1,500 patients, confirmed that the SNB is technically feasible and sufficiently accurate for staging the axilla in initially clinically node-negative (cN0) breast cancer after NACT (13). The authors calculated a pooled identification rate of 96% and false negative rate of 6% (95% confidence interval=3-8%). The oncological safety of the SNB in this setting derived further support from clinical outcome analysis after adequate clinical follow up. In a retrospective analysis of cN0, T1-T3 patients who underwent SNB after NACT (n=575) or first-line surgery (n=3,171), nodal recurrence was 1.2% in the NACT group, with no difference in disease-free or overall survival between groups. The FNR was 5.9% (11). The incidence of axillary recurrence following a negative SNB after NACT was reported to be as low as 0.24% in patients with cN0 disease (14).

Therefore, the SNB has become the standard of care after NACT in patients with cN0 disease despite the fact that a small percentage of patients would have undetected residual disease in non-sentinel nodes thus, potentially raising the possibility of adjuvant systemic under-treatment in patients with HER2 positive and triple negative breast cancer (TNBC) where residual disease can be used to guide the use of further adjuvant systemic therapy, such as capecitabine for TNBC (15) and TD-M1 for HER2 positive disease (16). However, the risk of omitting adjuvant chemotherapy in patients undergoing initial breast cancer surgery including SNB is similar since the FNR is less than 10%. Nevertheless, no compromise of oncological outcome was demonstrated in this setting.

cN1 breast cancer. We have recently reported through a meta-analysis, that in patients (n=3398) presenting with biopsy proven axillary lymph-node involvement and undergoing NACT, the SNB is a valid alternative to cALND with a FNR of 13% and identification rate of 91% (17). Subgroups analysis showed that the FNR can be decreased to less than 10% by identifying three or more SLNs, adding patent blue dye in a dual-mapping technique, marking the metastatic lymph node with a clip before NACT and then removing it, and using immunohistochemistry (17-19). The inclusion/addition of the clipped node to the SNB can achieve an FNR of as low as 2% (17, 20). For patients with initially involved nodes, with negative SNB after NACT, no lympho-vascular invasion and a remaining breast tumour size up to 5 mm, the risk of a positive cALND was reported to be 3.7%, regardless of the number of SLNs removed (15).

Tailoring adjuvant systemic therapy following NACT does not only depend upon the axillary node status, but also on the presence of residual disease in the breast. In a recent analysis of 30,821 patients with cT1/cT2 N0/N1 breast cancer treated with NACT and surgical resection, the incidence of nodal positivity in the presence of breast pathological complete response (pCR) was found to be 30.5% for ER+/HER2-ve, 14.1% for TNBC and 12.4% for

HER2+ve disease (21). The B arm of the Sentina trial (in press) will show that only 1.2% of TNBC patients and 0.5% of HER2 positive patients had residual axillary disease in case of a breast pCR. For patients with ER+/HER2-ve disease, the residual disease pathology is very unlikely to alter adjuvant treatment, which would consist usually of optimal endocrine therapy.

Assuming an FNR of 10% implies that the risk of omitting adjuvant TD-M1 in patients with HER2 positive disease achieving breast pCR would be 1.24%, and the risk of omitting adjuvant capecitabine in patients with TNBC achieving breast pCR would be 1.4%. For TNBC, the absolute overall survival benefit of adjuvant capecitabine is 5.6% (16). For HER2 positive disease, the absolute benefit of adjuvant TD-M1 in terms of DFS as a surrogate marker of OS was reported to be 5.4% (19).

These figures indicate that the probability of compromising OS or distant DFS is approximately 1 in 2,000 if complete axillary dissection is omitted. However, this probability would be lower with an FNR below 10%. Since including the clipped node in axillary staging post NACT is becoming standard practice, the probability of oncological compromise would be around 1 in 10,000 assuming an FNR of 2% (20). Such a low risk does not justify a more invasive surgery that has been demonstrated to increase morbidity and cost and compromise patient quality of life. The recent advent of wireless localisation systems has facilitated accurate marking and localisation of the biopsy proven lymph-node by deploying the marker at the time of biopsy (22).

Conclusion

The SNB following NACT is oncologically safe in patients with clinically node negative breast cancer and in patients with biopsy proven axillary node involvement at initial presentation provided that the dual technique is used and the clipped pathological node is harvested.

Conflicts of Interest

The Authors do not have any conflicts of interest to declare in relation to this article.

Authors' Contributions

KM drafted the initial manuscript. UW performed the literature searches and completed the final draft of the manuscript.

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