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De-escalating Surgery Among Patients with HER2 + and Triple Negative Breast Cancer

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Abstract

Purpose of Review De-escalation of surgery has been central in the evolution of multidisciplinary management of breast cancer. Advances in oncology and increasing use of neoadjuvant chemotherapy (NACT) have opened opportunities for further surgical de-escalation especially for HER2 + and triple negative (TN) disease. The aim of this review is to discuss the recent data on de-escalation of surgery as well as the future directions.

Recent Findings Patients with TN and HER2 + breast cancer with excellent response to NACT would be the ideal candidates for surgical de-escalation. Post-NACT image-guided biopsy, potentially combined with machine learning algorithms, may accurately identify patients achieving pathologic complete response that would be eligible for clinical trials assessing safety of omission of breast and axillary surgery.

Summary Multidisciplinary research is required to further support results of preliminary studies. Current data point towards a future when even less or no surgery may be required for exceptional responders.

Keywords Surgical de-escalation · Breast surgery · Triple negative · HER2 positive · Breast cancer

Introduction

Breast cancer management has evolved significantly over the past decades towards less aggressive, tailored treatments. From the seminal clinical trials led by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Milan Groups establishing the role of breast conserving surgery [1, 2], to the adoption of sentinel lymph node biopsy (SLNB) for the staging of the axilla [3, 4], and the omission of axillary lymph node dissection (ALND) in selected patients even in the presence of low burden axillary disease [5, 6], de-escalation of surgery has played central role within this paradigm shift.

Multidisciplinary working, advances in radiotherapy and especially in systemic therapy, and its use in the neoadjuvant setting have been pivotal in the successful implementation of surgical de-escalation. Within this context of modern multidisciplinary management of breast cancer, the use of neoadjuvant chemotherapy (NACT) is increasing [7]. Historically, NACT was used for advanced disease stage at presentation, to convert inoperable cancers to operable. However, the observed increase in NACT utilization has been greatest in patients with triple negative (TN) and human epidermal growth factor receptor 2 (HER2) positive cancers [8]. In these subgroups, NACT is now considered standard of care even in early, operable disease as it may provide significant prognostic information to allow tailored adjuvant treatment decision-making [9•, 10•]. In addition, a significant proportion of patients with these breast cancer subtypes may get an excellent tumor response to NACT. Advances in chemotherapy, targeted therapies, and the introduction of immunotherapy have resulted in pathologic complete response (pCR)

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rates exceeding 60% [11–14]. This has created an opportunity for further surgical de-escalation in patients with TN and HER2 positive breast cancer.

De-escalation of Breast Surgery

The idea to de-escalate surgery in patients treated with NACT is not new. Historically, there have been attempts to omit surgery, but these led to high rates of loco-regional recurrence (LRR) [15]. However, these early studies were performed more than 20 years ago, in an era when multidisciplinary management of breast cancer was not as developed. In addition, the observed LRR for both patients treated with surgery and those who only had radiotherapy would be considered high for modern standards. It is also important to note that in these studies, clinical examination was the only modality used to assess response to NACT and patient selection and treatment was not based on breast cancer subtype.

Despite these caveats and limitations, omission of surgery may not result in worse oncological outcomes. In an early study by Ring et al. [16], patients who achieved a complete clinical response to NACT did not have surgery and went straight to radiotherapy. This group had higher LRR compared to patients treated with surgery, although not statistically significant, but there was no difference in disease-free survival (DFS) and overall survival (OS). In a more recent study looking into data from the National Cancer Database, there was no difference in OS between patients with complete clinical response who did not have surgery and those who underwent surgery and were found to have pCR. In the same study, no OS differences were observed in patients receiving radiotherapy but no surgery and patients undergoing both surgery and radiotherapy [17]. Another retrospective study showed that omission of surgery in patients with complete clinical response to NACT was not associated with worse DFS and OS [18]. These findings highlight that surgical de-escalation in the breast may be feasible especially in patients who are most likely to be excellent responders to NACT.

In this context, breast cancer subtype is of paramount importance for patient selection. Patients with TN and HER2 positive disease have been shown to get the highest rates of pCR [11–14, 19]. However, even if pCR is not achieved, a proportion of patients will have low residual disease burden potentially allowing sufficient local control with radiotherapy only. This approach could be paralleled to the management of patients with occult breast primary, when surgery has not been shown to confer OS benefit compared to radiotherapy [20].

Based on these observations, patients with TN and HER2 positive breast cancers, demonstrating excellent response to NACT would be the ideal candidates for surgical de-escalation. The challenge is how these excellent responders can be accurately identified prior to surgery. Published data has consistently shown that imaging modalities alone cannot reliably predict pCR [15]. However, image-guided breast biopsy has demonstrated promising accuracy to identify residual disease. Several international groups have been working on the assessment of image-guided biopsy as a tool to select exceptional responders. However, the reported results are conflicting.

The German group in one of the first reports in the field showed that image-guided vacuum assisted biopsy (VAB) was associated with a false negative rate (FNR) for residual disease of 28.6% and 16.7% for TN and HER2 positive cancers respectively. However, when the VAB was considered representative (presence of tumor or tumor bed in histopathological examination), the performance of the technique improved with a FNR of 4.8% for the whole cohort [21]. Similar results were reported in the prospective, multi-center RESPONDER trial. Subgroup analysis for TN and HER2 positive cancers showed a FNR of 17% and 25% respectively. However, when a large bore VAB needle (7G) was used, no residual cancers were missed (FNR 0%) [22•]. On recent further analysis of the same data, age and presence of DCIS were found to be associated with the FNR. In a selected sub-cohort of patients with unicentric disease, not associated with DCIS and a representative VAB, the FNR was 2.9% [23].

The group from South Korea has demonstrated that post-NACT image-guided biopsy was associated with a FNR ranging from 25 to 40% for core biopsy and VAB respectively. Specifically in patients with TN or HER2 positive cancer, the negative predictive value (NPV) of image-guided biopsy ranged between 83.3 and 87.5%. However, in selected patients having at least 5 cores and very good response on magnetic resonance imaging (MRI), the FNR was 0% [24].

In the UK, post-NACT image-guided biopsy has been used by groups at Birmingham and The Royal Marsden Hospital. The NOSTRA PRELIM study using ultrasound-guided core biopsy correctly identified residual disease in 80% of patients [25]. A retrospective analysis from the Royal Marsden Hospital showed that image-guided VAB was associated with a FNR of 0% for TN and 25% for HER2 positive breast cancer [26]. Following these results, a standardized assessment protocol was adopted. This included patients with TN or HER2 positive, unifocal breast cancer, with residual imaging abnormality ≤ 2 cm who had a VAB to sample at least 90% of the breast residuum. The preliminary results of this prospective cohort demonstrated a FNR of 9.1% [27] while further ongoing analysis (anecdotal) has shown a FNR of 5%.

The group at MD Anderson Cancer Center assessed the use of image-guided breast biopsy in a prospective feasibility clinical trial including only patients with TN and HER2

positive disease. The combination of fine needle aspiration (FNA) and a median of 12, 9G needle VAB cores resulted in a FNR of 5% [28•].

However, there are also studies that have reported negative results. The MICRA study from the Netherlands used ultrasound-guided core biopsy in patients with MRI radiologic complete response or residual enhancement measuring up to 2 cm. The patients had a maximum of 8 14G cores and this was associated with an overall FNR of 37%. Specifically for TN cancers, the FNR was 55% and for HER2 positive ranged between 29 and 71% for hormone receptor (HR) positive/HER2 positive and HR negative/HER2 positive disease respectively [29]. It should be noted that although breast MRI was utilized, the actual biopsy procedure was done in the operating room directed by intraoperative ultrasound which is not optimal for image-guided biopsy. These findings may be, to a certain extent, also explained by the use of non-VAB 14G needle for the core biopsy which yields significantly less tissue and therefore may result in inadequate sampling of the breast residuum/tumor bed thus missing residual disease.

Finally, the study from the NRG group in the USA showed a similarly high FNR of approximately 50%. Specifically for TN cancer, the FNR was 63.6% and for HER2 positive disease 40% [30]. However, the full report including the actual selection of patients for unicentric disease, tumor size, number of VAB cores removed, use of appropriate image guidance, and removal of the initial biopsy clip, in the study, is not yet available. These are critical parameters necessary for super selectivity in this emerging field of eliminating surgery after NACT.

Careful patient selection and the image-guided biopsy modality used may play an important role in the accuracy of this diagnostic approach. A study from Memorial Sloan Kettering assessed the use of MRI-guided VAB in patients with radiologic complete response and showed that 7–12 9 G vacuum cores resulted in FNR ranging from 14 to 25%. This was depending on the definition used for pCR. If this was defined as no residual disease including invasive cancer and DCIS, the FNR was 25%, while when pCR was defined as no residual invasive disease, the FNR was 14.2% [31]. An analysis from MD Anderson Cancer Center showed that stereo-guided compared to ultrasound-guided VAB was associated with the ability to retrieve more cores and had a higher positive predictive value for residual disease, therefore recommending this modality as the preferred method for identification of patients with pCR for trials testing the safety of omission of surgery [32].

A multi-center pooled analysis of patient level data reported an overall FNR of image-guided breast biopsy of 18.7% across all tumor subtypes and biopsy techniques. However, exploratory subgroup analysis showed that use of a standardized protocol to retrieve ≥ 6 representative VABs of a residual imaging abnormality measuring ≤ 2 cm, could reliably predict residual TN or HER2 positive cancer with a FNR of 4.2% [33•].

Recently, the use of a machine learning algorithm to analyze patient, imaging, tumor, and VAB characteristics has shown excellent results to identify pCR with a FNR of 0% [34•, 35•] suggesting that this "intelligent VAB" may be an additional tool in the diagnostic armamentarium to reliably identify patients with TN and HER2 positive breast cancer that would be suitable for surgical de-escalation. However, the wider applicability of this modality in the everyday clinical practice is yet to be determined.

Although the aforementioned results on the use of post-NACT image-guided breast biopsy are encouraging, there may be some skepticism around omission of surgery and the potential implications of missing any residual disease. Especially for patients with TN and HER2 positive breast cancer, this could potentially affect adjuvant treatment decision-making and the use or not of capecitabine [10•] or trastuzumab emtansine [9•] respectively. It should be noted though that low volume residual disease in the breast may still be missed even with surgery. Especially since modern practice has moved away from removing the original footprint of the disease towards a more "risk-adapted" approach [36] to resect the area of the residual imaging abnormality or the area around the pre-NACT inserted marker clip in case of radiologic complete response. When performing post-NACT image-guided biopsy, appropriate patient selection, image guidance, adequate sampling of the breast residuum and meticulous and extensive processing, and histopathological examination of the specimens are of paramount importance to reduce the risk of not identifying residual disease.

Elimination of surgery in excellent responders, as demonstrated by pCR on post-NACT image-guided biopsy, is currently being tested in a clinical trial at MD Anderson Cancer Center (NCT02945579) [37]. Preliminary analysis of the results, presented at the American Society of Breast Surgeons 23rd Annual Meeting (2022), showed an early ipsilateral breast recurrence-free survival of 100%. Outside the context of clinical trial, a small cohort of patients at the Royal Marsden Hospital ($n = 8$) with excellent response to NACT and pCR on post-treatment image-guided biopsy decided not to undergo surgery and proceed to radiotherapy, while continuing systemic therapy as indicated as per standard of care. At a median follow-up of 32.5 months, there are no LR recurrences [38].

De-escalation of Axillary Surgery

Axillary surgery has been the topic of extensive research for more than 50 years. Its role as a therapeutic procedure had already been challenged since the NSABP-B04 trial [39].

This showed no difference in oncological outcomes in the group of patients not having axillary surgery leading to the hypothesis that leaving positive nodes behind might not have an impact on oncological outcomes, especially in the modern era of multidisciplinary management of breast cancer with the routine use of systemic therapies with or without radiotherapy.

With the increasing use of NACT, especially for TN and HER2 positive breast cancer, further de-escalation of axillary surgery in these patients should be considered. There is increasing data supporting de-escalation from ALND to SLNB and targeted axillary dissection (TAD) for clinically node positive (cN+) patients converting to clinically node negative (cN0) after NACT. Following the seminal clinical trials showing feasibility of SLNB if ≥ 3 lymph nodes are removed, with an associated FNR < 10% [40–43], clipping of the biopsy proven metastatic axillary lymph node and TAD has further supported the shift away from ALND for these patients. Targeted axillary dissection has been shown to be associated with a FNR between 2 and 4.3% [44•, 45, 46, 47•] and is now included as recommendation in the National Comprehensive Cancer Network (NCCN) and American Society of Clinical Oncology (ASCO) guidelines [48, 49]. If patients are found to have positive axillary lymph nodes on SLNB/TAD, the standard of care is to proceed with ALND. However, this might be avoided, depending on the results of the ongoing ALLIANCE A011202 clinical trial (NCT01901094) [50] looking into axillary radiotherapy instead of ALND for the management of residual disease on SLNB.

The next important question is whether there is scope for further surgical de-escalation in patients who are cN0 at diagnosis and receive NACT. There is data showing that especially in patients with TN and HER2 positive cancers, which are the subtypes with the highest pCR rates, those who were cN0 at diagnosis and achieved a pCR in the breast had a very low risk of nodal disease. In the study by Tadros et al., among patients with TN and HER2 positive breast cancer who achieved a pCR in the breast no disease was identified in the axillary lymph nodes [51]. Similar results of low risk of nodal positivity have also been shown in other reports [52, 53]. In the largest of these studies by Barron et al., using the National Cancer Database and analyzing data from over 13,000 patients, the risk of nodal disease in patients with TN and HER2 positive cancer achieving pCR in the breast was 1.6% [54•]. This risk is very low, and similar to the FNR of SLNB. It is therefore important to consider if SLNB can be omitted in patients with these cancer subtypes if they get breast pCR.

A number of studies are being set up to assess the safety of omitting SLNB in patients with TN and HER2 positive breast cancer treated with NACT. The EUBREAST-01 is a prospective, single-arm study of patients with complete radiological response on NACT, who will undergo breast surgery and if pCR is confirmed they will not have axillary surgery [55]. Another prospective, single-arm trial (NCT04225858) is being set up in the Netherlands, omitting SLNB in patients with TN and HER2 positive breast cancer who achieve complete radiological response on post-NACT MRI [56]. Finally, as mentioned above, utilizing post-NACT image-guided VAB to select exceptional responders to NACT, an ongoing clinical trial at the MD Anderson Cancer Center is investigating the safety of elimination of breast and axillary surgery and the preliminary analysis has shown promising results (NCT02945579) [37].

Conclusions

Surgical de-escalation has been central in the multidisciplinary management of breast cancer, towards tailored, less aggressive treatments. Improved understanding of the importance of tumor biology and increasing use of NACT in combination with advances in medical and radiation oncology have opened new, exciting opportunities to further de-escalate breast and axillary surgery in patients with TN and HER2 positive breast cancer. Multidisciplinary research in this field is pointing towards a future when even less or no surgery may be required for exceptional responders.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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