

## Review

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### De-Escalation of Breast Cancer Surgery Following Neoadjuvant Systemic Therapy

Wazir and Mokbel. De-escalation of breast cancer surgery following neoadjuvant systemic therapy

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**Simple Summary:** The treatment of breast cancer has seen significant advances, with patients achieving better survival whilst undergoing less onerous treatments. We shall discuss recent and ongoing trials regarding the de-escalation strategies of breast cancer surgery following neoadjuvant systemic therapy, and ponder the implications for current practice and future developments.

**Running Title:** Wazir & Mokbel. De-escalation of breast cancer surgery...

#### Abstract:

**Introduction:** Breast cancer treatment has seen many advances in recent decades, lessening the morbidity to patients, while improving outcomes. Central to these gains have been the introduction of breast conserving surgery and neoadjuvant systemic therapy (NST). There is a considerable interest in further de-escalation of the treatment of breast cancer, which is being studied in several ongoing randomised trials. **Methodology & Results:** We aim to appraise the current literature regarding the various aspects of de-escalation of surgical treatment of breast cancer after NST, and attempt to prognosticate the future course of breast oncotherapy.

**Keywords:** breast cancer; neo-adjuvant therapy; de-escalation

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## 1. Introduction

Currently, over 20% of patients with early breast cancer are treated with neoadjuvant systemic therapy (NST) and has been increasing over the years (1). Initially, the reason offering NST was downstaging locally advanced tumours to facilitate breast conserving surgery (BCS). However, its role has expanded to include other aims such as *in vivo* drug sensitivity testing and provision of critical prognostic information that can guide and tailor adjuvant treatment for residual disease. The use of adjuvant systemic therapy in patients with residual disease following NST for triple negative breast cancer (TNBC) or HER2 positive breast cancer has been shown to improve overall survival (2, 3).

Furthermore, advances in NST protocols have increased the rates of observed pathological complete response (pCR). Examples of such refinements in current NST protocols include carboplatin for TNBC (4), the addition of pertuzumab to trastuzumab for HER2 positive breast cancer (5) and, more recently the addition of immunotherapy for TNBC (6).

In addition to the marked improvements in pCR rates, there is a growing body of evidence from randomised controlled trials (RCTs) that omission of surgery for minimal residual disease in the axilla outside the NST does not compromise oncological outcome. Two randomised trials have demonstrated that omission of complete axillary lymph node dissection (ALND) when the sentinel lymph node biopsy (SLNB) is positive for malignancy does not compromise the overall survival. The American College of Surgeons Oncology Group (ACSOG) Z0011 trial in which patients with clinically negative breast cancer with 1-2 positive sentinel lymph nodes achieved equivalent overall (OS) and disease-free survival (DFS) comparable to those undergoing ALND (7).

In the AMAROS trial, patients with positive SLNB undergoing axillary radiation therapy had a similar OS to those undergoing ALND (8). The axillary local recurrence rate was slightly higher in the radiation group and incidence of lymphedema was higher in the ALND arm. The SLNB procedure is known to have a recognised false negative rate (FNR) in patients with cN0 disease (up to 10%). However, the various RCTs comparing the SLNB and ALND in patients with a clinically node-negative breast cancer has shown equivalent oncological outcomes (9). These observations have inspired research into the potential for de-escalating breast cancer surgery following NST. In view of the limited evidence regarding surgery de-escalation after neoadjuvant endocrine therapy, neoadjuvant chemotherapy +/- immunotherapy will be the focus of this article.

## 2. Predictors of pCR

Patients with TNBC or HER2 positive disease are known to have the highest rates of pCR in the breast (10). Other predictors of high pCR include high tumour grade and high proliferation index. Hormone sensitive lobular breast cancer is known to achieve the lowest rate of pCR. Axillary pCR seems to be higher than that of the breast, however breast pCR is the best predictor of pCR (11).

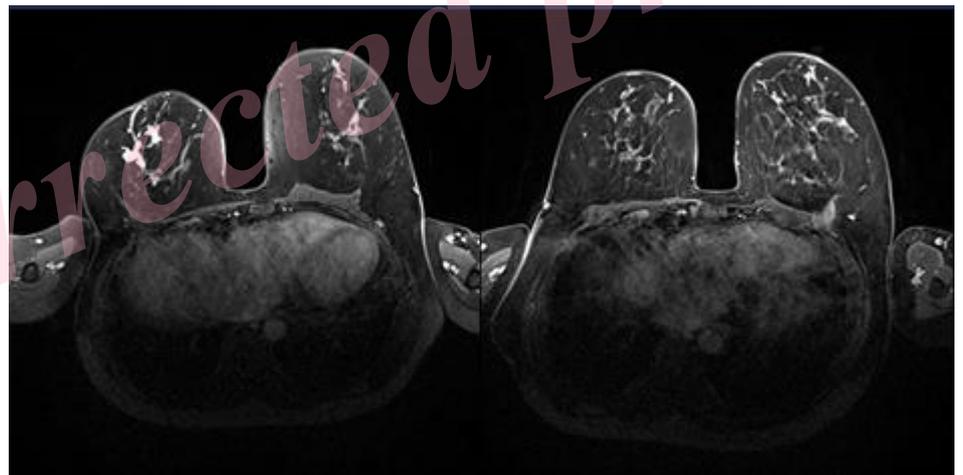
Patients with triple-negative or HER2 positive breast cancer who achieve pCR in the breast would be excellent candidates for de-escalation of breast cancer surgery. Therefore, it is critical that imaging modalities accurately predict pCR so that de-escalation of breast cancer surgery can be accurately planned. However, it should be noted that breast cancer patients who have a partial or complete response in imaging, as well as pCR, are also candidates for de-escalation in surgery.

We have recently reviewed the evidence regarding the potential role of PET in the assessment of axillary disease and concluded that 18FDG-PET/CT has a low sensitivity but high specificity for ALN disease. Therefore, ultrasound-guided biopsy could be considered in a positive CT/PET. Modest accuracy prohibits the use of 18FDG-PET/CT alone in axillary staging. Prospective research using standardised protocols and quantitative cut-off points is warranted (12).

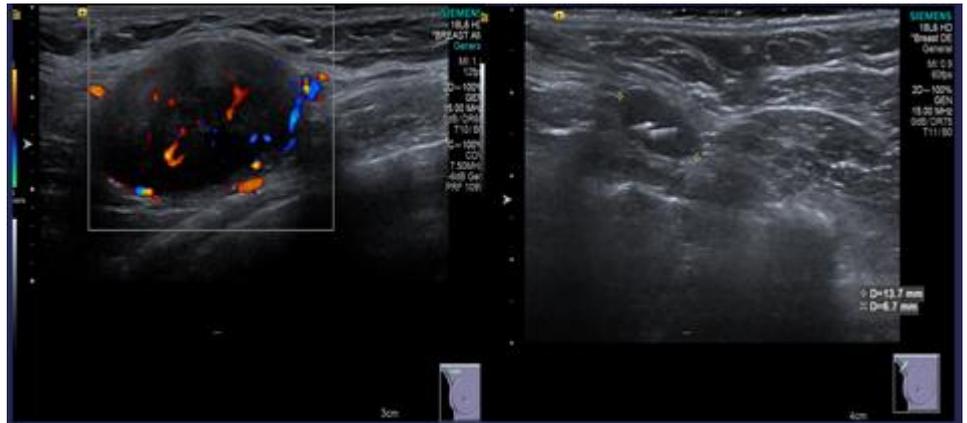
Moreover, the diagnostic performance of non-invasive imaging including PET and MRI for assessment of axillary response after NST in clinically node-positive breast cancer was the focus of a recent systematic review and meta-analysis. The authors concluded that the diagnostic performance of current non-invasive imaging modalities is too limited to accurately assess axillary response after NST in clinically node-positive breast cancer patients (13).

Breast magnetic resonance imaging (MRI) seems to be the most accurate modality for predicting pCR of the primary tumour (Figure 1) and has received the highest rating (rated 9) by the American College of Radiologists (14, 15). A recent meta-analysis as demonstrated that contrast enhanced breast MRI has performed well in predicting pCR of the primary tumour with a pooled sensitivity of 80% and specificity 84% (16).

Ultrasonography (rated 8) represents the second-best modality for monitoring the primary tumour response in the breast and is valuable in countries with limited MRI resources. In relation to monitoring the nodal response in patients with initially node-positive breast cancer ultrasonography seems to be the gold standard (Figure 2) (15).



**Figure 1.** MRI demonstrating clinical complete response (cCR) of recurrent node positive TNBC in the right breast to NST that included Carboplatin and Pembroluzimab in a 50 year old woman (left: before NST; right: after NST). The patient achieved pCR.



**Figure 2.** Ultrasound scan of the right axilla demonstrating a pathological lymph node (cT0N1M0 TNBC) with an increased blood flow (left: before NST) that has responded well to NST (right: after NST). The Savi Scout reflector to facilitate targeted axillary dissection (TAD) is seen within the lymph node (right)

### 3. Clinically node-negative breast cancer (cN0)

SLNB following NST in patients with clinically node-negative (cN0) breast cancer has been shown to be equivalent to SLNB prior to treatment. A recent meta-analysis (17) reported an identification rate of 96% and a false negative rate (FNR) of 6% in post-NST SLNB. There was no significant difference in OS or DFS thus confirming the oncological safety of this approach (18, 19).

Furthermore, the SLNB performed post-NST is more likely to be negative, thus down-staging axillary disease and reducing the rate of ALND. In view of the clear evidence regarding the efficacy of this approach, the SLNB after NST has become the gold standard in patients with clinically node-negative breast cancer undergoing NST as reflected by its incorporation into international guidelines (20). A prospective cancer registry study in Germany recorded that almost 100% of breast cancer patients underwent complete ALND 2008. However, the number of patients undergoing this radical approach of surgery has declined sharply to almost 24.4% in 2016 (21).

Barron *et al.* reported that in clinically node-negative, triple-negative or HER2 positive breast cancer who achieve pCR in the breast following NST the incidence of residual nodal disease was less than 2% (22). The authors reported a nodal pCR of 98.4% in such patients when analysing data spanning more than 4,000 patients in the National Cancer Database. The incidence of positive SLNB was found to be 1.6% which is significantly below the FNR of SLNB in patients undergoing upfront surgery for cN0 breast cancer outside the NST setting. This finding has raised the question whether the SLNB can be safely omitted in this selected group of patients (cN0 triple-negative or HER2 positive breast cancer) who achieve complete clinical response (cCR) in the breast as determined by MRI. This is the basis of a new clinical trial that has just commenced recruitment (23).

### 4. Clinically node-positive breast cancer (cN1-2) and NST

In a previous study, we demonstrated that SLNB alone in patients with initially biopsy proven lymph node involvement undergoing neoadjuvant chemotherapy had a FNR of 13% which is above the gold standard target of 10%.(24). However, the FNR was reduced if a minimum of three lymph nodes were harvested including the marked biopsy-proven lymph

node, in addition to the use of immunohistochemistry (IHC) and the dual tracer technique in sentinel node mapping (24).

More recently, we have conducted a pooled analysis of published studies which has shown that harvesting the biopsy proven lymph node that is marked prior to NST is associated with an acceptably low FNR of 6.2% with a successful retrieval rate of 90% (25).

There are currently no RCTs confirming oncological safety of omitting ALND for ypN0 disease following NST in patients presenting initially with cN1. However, a recent large European study demonstrated that there was no difference in OS or DFS between patients presenting cN1-2 disease who were rendered SLNB negative and patients presenting with cN0. The rate of axillary recurrence was reported to be 1.8% in the former and 1.6% in the latter [26]. In this study that included 688 patients. ALND was not performed when the post-NST SLNB was negative. However, some patients received radiation therapy. Furthermore, we have estimated that in the worst-case scenario the probability of compromising OS would be in the region of 1 in 4000 for a FNR of 5% in this setting [27].

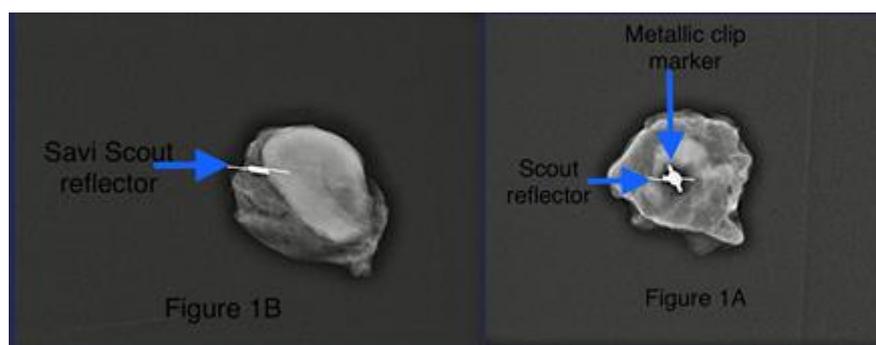
### **5. Targeted axillary dissection (TAD)**

Targeted axillary dissection (TAD) refers to the combination of SLNB and marked lymph node biopsy (MLNB), in which lymph nodes are identified and marked radiologically prior the operation and excised during surgery. This has been shown to result in a FNR of 5.2% according to our recent pooled analysis (25). It is worth highlighting however, that the degree of overlap between the SLNB and MLNB is approximately 75% (26). If histological examination of TAD reveals no evidence of residual disease, then a complete ALND and its associated morbidities could be avoided, thus enhancing quality of life. However, if residual disease is identified in the TAD specimen, then escalation of the treatment in the form of surgery (ALND) or radiation therapy is indicated. This approach of treatment escalation should be considered even if the residual disease is minimal such as micro metastases or isolated tumour cells (ITCs) for which ALND is not indicated in patients who did not receive NST (27).

This escalation of axillary treatment is important in view of the fact that increased residual disease burden has been associated with worsening overall survival with the 5-year survival being reported as 88.9% for ypN0 compared with 77.6% for ypN1 and 82% for ypN0 (i+) and 79.5% for ypN1 (mi) N2 (28).

TAD is traditionally performed by deploying a marker clip within the biopsy proven lymph node at the time of diagnosis and subsequent localisation by inserting a guidewire under ultrasound control on the day of surgery. In this context, the hydrogel marker (HydroMark) seems to be the best marker in view of the excellent visibility on ultrasonography and sufficiently long half-life (25).

Wire-free techniques have been recently introduced whereby the marker that can be localised by an external detection system is deployed at the time of lymph node biopsy so that a second localisation procedure can be avoided (25). These techniques that allow decoupling of radiology and surgery schedules include the use of radioactive iodine seeds, ferromagnetic seeds (MagSeed; Endomag, London, United Kingdom), radio frequency identification tag (LOCALIZER, Hologic Inc., Santa Carla CA, USA) and infrared reflector combined with radar (SAVI SCOUT, Merit Medical, Aliso Viejo, CA, USA) (25) (Figure 3).



**Figure 3.** TAD guided by SAVI SCOUT. TAD: Targeted axillary dissection.

The use of radioactive iodine seeds, also known as MARI technique (Marking the Axillary lymph node with Radioactive Iodine seeds), has been curtailed by the extensive regulatory and administrative requirements due to radiation handling. Unlike magnetic seeds and radiofrequency tags, the SAVI SCOUT system generates minimal MRI-void signals and therefore it can be deployed at the time of biopsy in both the primary tumour and the biopsy-proven lymph node (29).

The optimal management strategy of the axilla in patients with cN1 who achieve a cCR in the axilla (ycN0) is the focus of ongoing AXSANA trial (30). This prospective study is not randomised and includes oncological outcome in its primary endpoints.

#### **6. Can breast lumpectomy be safely omitted?**

In patients with occult breast cancer, radiation therapy to the breast has been demonstrated to achieve an OS similar to total mastectomy (31), implying that omission of surgical excision of the occult primary tumour in the breast may not have a detrimental oncological impact. Surgical resection of the primary tumour was not mandatory in some of the trials that compared neoadjuvant and adjuvant chemotherapy. When considering the trials which allowed the omission of primary breast cancer surgery, there is evidence that the distant disease-free survival and OS were not compromised when primary breast cancer surgery is omitted. However, there was a higher incidence of local recurrence (32). A similar observation was reported in a study by Ring *et al.* (33) where the omission of lumpectomy after NST was associated with a higher risk of local recurrence without a compromise of OS. However, when the ultrasound response was taken into consideration, the local recurrence rate declined from 33% to 8% at five years. These observations raised the possibility of eliminating breast lumpectomy after NST. In order to achieve the optimal outcome, it is logical to consider this form of de-escalation in patients who are most likely to be excellent responders (33).

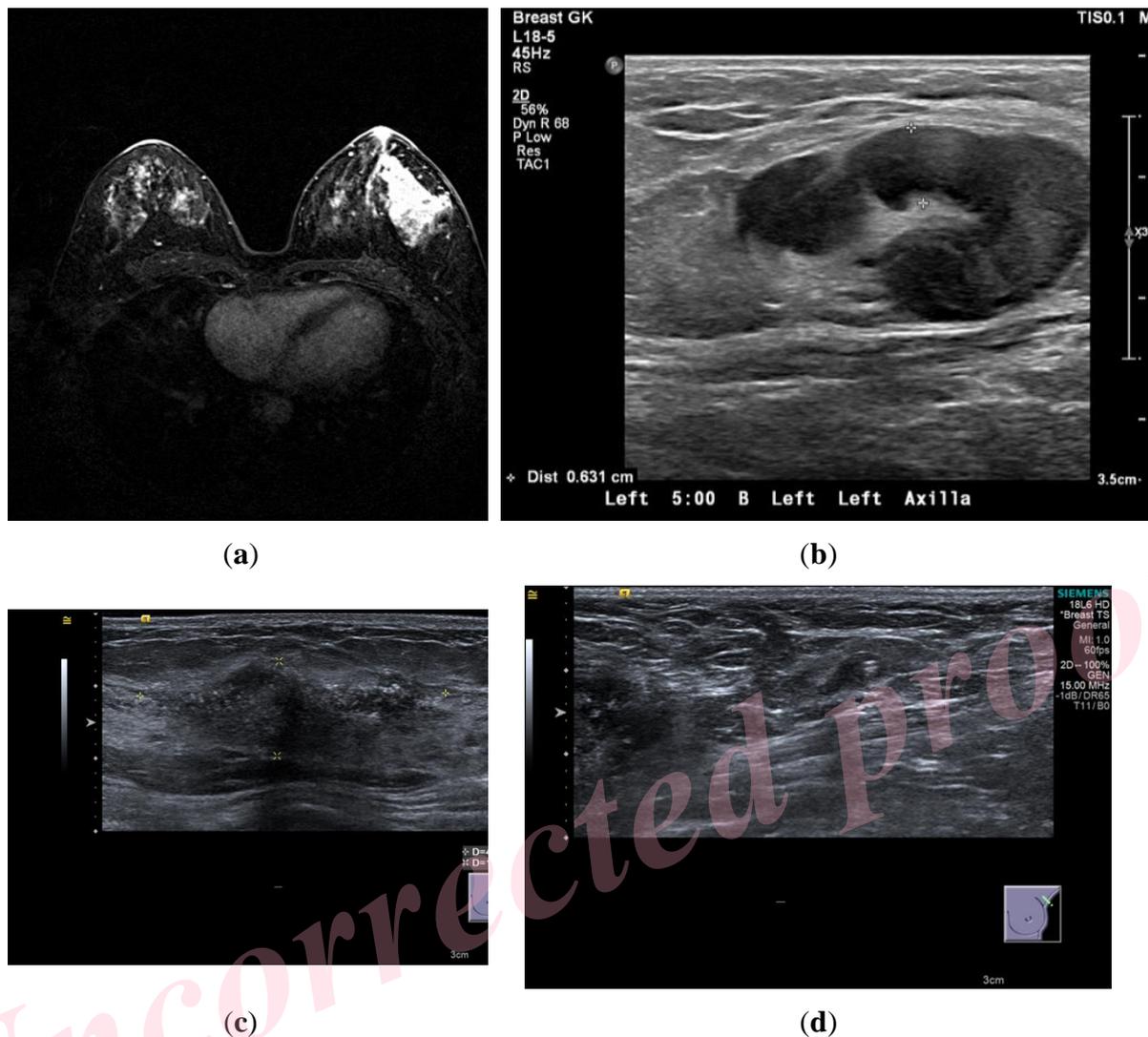
In this context the molecular subtype plays an important role in patient selection with patients diagnosed with TNBC or HER2 positive disease representing the best candidates. Furthermore, complete radiological response of the primary tumour as assessed by MRI would be another important factor to consider in patient selection. For this approach to be effective we should be able to reliably verify pCR without surgery. A meta-analysis of studies evaluating the accuracy of imaging-guided core-biopsy has demonstrated a FNR of 28% which is significantly above the acceptable target of 10%. However, specificity was as expected to be high at 99% (34). When considering patients with triple-negative or HER2 positive breast cancer who achieve a complete or partial response on breast imaging the accuracy improves to 98% with a FNR of 5% with the use of vacuum assisted core biopsy (9-gauge) obtaining 12 cores in addition to fine needle aspiration cytology (35).

These encouraging results have inspired the NCT 02945579 trial at MD Anderson which has almost completed accrual. In addition to assessing DFS and OS, the trial included quality of life and cost-effectiveness as part of its primary end points. The use of biomarkers of response such tumour infiltrating lymphocytes (TILs) (36) and circulating tumour DNA (ctDNA) should be included in future studies as a strategy of monitoring response to treatment and predicting pCR. There is a growing body of evidence that ctDNA reflects residual disease burden and disappearance of this marker in the peripheral blood during NST correlates with pCR and an excellent prognosis (37).

### **7. De-escalation of NST**

Achieving pCR following NST is associated with significantly better DFS and OS, particularly for triple-negative and HER2+ breast cancer (38). Adjuvant chemotherapy in patients who achieved pCR does not seem to improve outcomes (39). This raises the possibility of de-escalating NST especially in patients with ER-HER2+ breast cancer who are very likely to attain pCR with pertuzumab, trastuzumab, paclitaxel, and carboplatin thus avoiding the more toxic anthracyclines (40). Patients with cN0-2 disease who achieve cCR as determined by MRI and ultrasound can be selected for surgery after a shorter course of NST to verify pCR and avoid the anthracycline phase of treatment (Figure 4).

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**Figure 4.** This 45-year-old lady presented with ER-HER2+ T3N1M0 breast cancer. She received 12 weeks of weekly paclitaxel and carboplatin and 3 weekly trastuzumab and pertuzumab followed by surgery that confirmed pCR.: (a) MRI prior to treatment demonstrating the large primary tumour; (b) ultrasound scan of the axilla prior to treatment demonstrating the pathological lymph-node; (c) Ultrasound scan of the breast after NST showing non-specific textural change; (d) Ultrasound scan of the left axilla after NST showing a normal giraffe note containing the Savi Scout reflector within it that was subsequently used to guide TAD.

## 8. Conclusions:

We know that a certain proportion of but not all patients with cCR after NST has pCR and pN0. Patients with triple-negative or HER2 positive breast cancer who achieve a complete clinical response after NST as determined by breast MRI and/or ultrasound represent excellent candidates for de-escalation of breast cancer surgery. Patients with the cN1-2 disease before NST and had cN0 after NST can undergo TAD as an alternative to complete ALND if pCR is achieved. TAD has been recently facilitated by the advent of novel wire-free and radiation free technologies

The elimination of lumpectomy following an excellent response to NST remains the subject of ongoing clinical trials and is likely to become the new standard of care in selected patients in the future.

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**Compliance with ethical standards*****Ethical approval***

Not applicable

***Informed consent***

Patients provided consent for anonymised specimen radiographs to be used.

***Conflicts of interests***

KM has received honoraria for providing academic and clinical advisory to Merit Medical. UW declared no conflict of interest.

**Contribution of authors**

KM initiated the project. UW completed the literature review and drafted the final manuscript.

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