

Axillary strategies in breast cancer

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Impact paragraph

In the past decades, breast cancer treatment has evolved extensively. Until the mid-twentieth century, patients underwent a radical mastectomy according to the Halsted approach, which included the excision of the pectoral muscles and axillary lymph nodes. Through advancements in research, better understanding of breast cancer biology, and improved treatments, leading to improved survival, we have entered the current era. The primary aim now is to de-escalate treatment while maintaining oncologic safety and improving morbidity outcomes, thereby enhancing quality of life (QoL). In modern breast surgery, options include mastectomy (i.e., removal of the breast) and breast-conserving surgery (BCS), which can be complemented by reconstructive or oncoplastic surgery, respectively. Regarding the axilla, ongoing efforts are being made to de-escalate axillary staging and treatment strategies in both node-negative (cN0) and node-positive (cN+) breast cancer. The aim of this thesis was to pave the way for more consensus-based axillary strategies in both cN0 and cN+ breast cancer.

Axillary strategies in cN0 breast cancer - primary surgery

In cN0 disease, axillary lymph node dissection (ALND) has long been replaced by sentinel lymph node biopsy (SLNB). Even in case of limited sentinel lymph node (SLN) involvement, it is safe to omit completion axillary treatment in patients treated with BCS. It is expected that an incidental dose to the axilla provided by whole breast radiotherapy (RT) following BCS results in a low axillary recurrence rate. Since chest wall RT is not routinely performed after mastectomy, we evaluated the oncologic safety of omitting completion axillary treatment in mastectomy patients with limited SLN involvement.

The results showed a low number of regional recurrences, indicating that there is room for refraining from completion axillary treatment in selected patients. Patients were selected for omission of completion axillary treatment based not only on tumour characteristics (e.g., micrometastatic disease) but also based on factors such as age and overall health. While awaiting ongoing randomized controlled trials that include patients with macrometastatic SLN involvement, these results can already be used in clinical practice when deciding on axillary treatment. Moreover, it emphasizes the importance of considering overall health when making treatment decisions, with shared decision-making being an important part of the process. These results are of great importance for clinicians as well as patients and should be incorporated into breast cancer guidelines.

Neoadjuvant systemic therapy

Neoadjuvant systemic therapy (NST) has presented several opportunities. It allows for assessment of in vivo disease response to systemic therapy, and can downsize local disease. Initially inoperable local disease can become operable, and in cases of operable

local disease, BCS is more often feasible. NST can also downstage nodal disease. In both the primary tumour and in the lymph nodes, it can even lead to a pathological complete response (pCR), which is associated with improved prognosis. However, the use of NST has also introduced uncertainties regarding staging and treatment after NST.

Axillary strategies in cN0 breast cancer - neoadjuvant systemic therapy

In cN0 breast cancer, it was unclear whether results of trials investigating axillary strategies in patients with SLN involvement in the primary surgery setting could be extrapolated to patients with SLN involvement after NST (i.e., ypN+). We assessed the prognostic significance of ypN+ in cN0 disease.

The results revealed that patients with cN0ypN+ had a statistically significant worse 5-year overall survival compared to patients with cN0 with nodal pCR (i.e., ypN0). These results highlight the importance of studies evaluating axillary strategies in the NST setting, and will hopefully raise awareness during multidisciplinary meetings, as these patients can have chemotherapy-resistant or even progressive disease, and therefore may need additional treatment. These findings are of great importance for both clinicians and patients.

Axillary strategies in cN+ breast cancer

In patients with cN+ disease, NST also had implications for clinical practice. While the ALND was replaced by the SLNB in case of cN0 disease decades ago, it remained common practice in cN+ disease for quite some time. However, due to NST, it became possible to achieve ypN0. Therefore, less invasive axillary staging procedures were implemented to provide response-guided treatment, and to omit the ALND in case of ypN0: SLNB, excision of a marked lymph node (e.g., MARI-procedure), and targeted axillary dissection (TAD) (e.g., RISAS-procedure).

Targeted axillary dissection

Given its superior diagnostic accuracy, targeted axillary dissection (TAD) seems the preferred option for axillary staging. We performed a systematic review on TAD techniques.

We discussed the benefits and drawbacks of each definitive marker, and evaluated the timing of definitive marker placement. We emphasized that the two-step procedure can negatively affect the ability to identify the marked lymph node, and thus the importance of assessing the identification rate of the marked lymph node at imaging after NST, and not just at surgery. The findings are therefore very relevant for researchers when conducting future studies. In clinical practice, together with additional information (e.g., costs, logistics), these results are also relevant for clinicians, as they can help determine

the most appropriate TAD technique for their hospital. Furthermore, it enables clinicians to inform patients about the benefits and drawbacks of the TAD techniques.

Response-guided treatment

NST did not only affect surgical strategies, but also locoregional RT strategies, as locoregional RT guidelines were originally based on studies in the primary surgery setting. We investigated the oncologic safety of de-escalated locoregional RT according to a predefined consensus-based study guideline in patients with cT1-2N1 breast cancer.

The results suggested that locoregional RT can be omitted in selected patients in whom ALND is performed (i.e., no chest wall RT and no regional RT in case of ypN0, and no regional RT in case of ypN1 (1-3 positive nodes)). The study guideline has laid a good foundation for response-guided RT, and can thus contribute to treatment decisions in clinical practice. The results are relevant for clinicians, especially in countries where ALND is still often performed. As the study guideline requires fine-tuning, such as taking into account breast cancer molecular subtype, the results are also important for researchers. Moreover, since results were difficult to interpret when ALND was omitted, this highlighted the need for more evidence concerning response-guided treatment based on less invasive axillary staging procedure. It also emphasized the importance of informing patients about the current knowledge gaps.

Meanwhile, in clinical practice, ALND was being omitted (or replaced by RT), sometimes even in case of ypN+. With a wide variety of axillary staging and treatment strategies being performed in the Netherlands, it was made possible to conduct a nationwide registry study to assess these strategies. The Dutch multicentre MINIMAX study was therefore initiated. The 5-year oncologic safety outcomes of the retrospective cohort are yet to be analysed. The 1-year QoL outcomes are expected half 2024.

Hence, within a short period of time, this study will provide more insight into the outcomes of currently performed axillary strategies, for both ypN0 and ypN+ disease, also taking into account factors such as breast cancer molecular subtype and the extent of residual disease (if applicable). The results need to be awaited. In the future, if found clinically relevant, the results on oncologic safety and impact on QoL will be implemented into breast cancer guidelines, to be used for decision-making in multidisciplinary meetings. The results will be relevant for both the clinician and the patient, as it will enhance shared decision-making based on more evidence regarding oncologic safety and impact on QoL of the different axillary strategies. Lastly, the results can also be relevant for researchers, as they may aid to the development of prediction models in which both oncologic safety outcomes and patient-reported QoL outcomes are incorporated.

To gain insight into practice variation in the Netherlands, we conducted a survey among the local principal investigators of the hospitals participating in the MINIMAX study. *It has provided an overview of the nationwide variety in less invasive axillary staging procedures, reasons to directly perform an ALND after NST, and response-guided treatment strategies, including indications for completion ALND and/or RT. These results are important for raising awareness about these variations in clinical practice, not only among clinicians but also among patients. Furthermore, it emphasizes the importance of including patients in studies such as the MINIMAX. In addition, we found that some hospitals define the cN-status not based on anatomical extent (according to the AJCC), but on the number of suspicious lymph nodes before NST (e.g., 1-3 is cN1, and ≥ 4 is cN2). We hope that these results will lead to the cN-status primarily being defined according to the AJCC in all hospitals (with the number of suspicious nodes in parentheses if also wanting to provide this information, e.g., cN1(4)). Not doing so can particularly lead to unreliable data when conducting research. Therefore, outcomes of this survey are not only important in clinical practice, but also in research.*

In both cN0 and cN+ disease, having ypN+ disease can be chemotherapy-resistant or even progressive disease. We assessed the prognostic significance of nodal status before and after NST.

We found that patients with ypN+ have decreased overall survival, most apparent in HR-HER2+ and triple negative disease. This indicates that especially these patients can benefit from additional treatment, such as TDM-1 or capecitabine, as was demonstrated by the KATHERINE and CREATE-X trials, respectively. Hence, restaging after NST is of utmost importance. It is especially relevant that clinicians consider these results when deciding on type of staging procedure.

Quality of life

When optimizing treatment, impact on QoL should be taken into account. We performed a systematic review to assess the relationship between personality traits and QoL in breast cancer patients.

We found that personality affects QoL, with the effect being most apparent between personality traits “optimism” and “trait anxiety” and the psychosocial QoL domains. These results are highly relevant for researchers, as personality should be considered when evaluating impact on QoL of breast cancer treatment. This is done in the MINIMAX study, and will help interpret the patient-reported QoL outcomes. Moreover, both clinicians and patients should be aware of these results, as personality can have a substantial impact on patient’s well-being during and after treatment.