MINImal vs. MAXimal Invasive Axillary Staging and Treatment After Neoadjuvant Systemic Therapy in Node Positive Breast Cancer: Protocol of a Dutch Multicenter Registry Study (MINIMAX)

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Abstract

In node positive breast cancer patients who are treated with neoadjuvant systemic therapy, axillary staging and treatment is still a topic of debate. This multicenter study will contribute to evidence-based guidelines with regard to the oncologic safety and impact on quality of life of less vs. more invasive axillary staging and treatment strategies.

Background: Node positive breast cancer (cN+) patients with an axillary pathologic complete response after neoadjuvant systemic therapy (NST) are not expected to benefit from axillary lymph node dissection (ALND). Therefore, less invasive axillary staging procedures have been introduced to establish response-guided treatment. However, evidence is lacking with regard to their oncologic safety and impact on quality of life (QoL). We hypothesize that if response-guided treatment is given, less invasive staging procedures are non inferior to standard ALND in terms of oncologic safety, and superior to standard ALND in terms of QoL. Patients and Methods: MINIMAX is a Dutch multicenter registry study that includes patients with cN1-3M0 unilateral invasive breast cancer, who receive NST, followed by axillary staging and treatment according to local protocols. In a retrospective registry of ±4000 patients, the primary endpoint is oncologic safety at 5 and 10 years (disease-free, breast-cancer-specific and overall survival, and axillary recurrence rate). In a prospective multicenter registry, the primary endpoints are QoL at 1 and 5 years, and we aim to verify the 5-year oncologic safety. With an estimated 5-year disease-free survival of 72.5% and anticipated loss to follow-up of 10%, a sample size of 549 is needed to have 80% power to detect non-inferiority (with a 10% margin) of less invasive staging.

Abbreviations: ALND, axillary lymph node dissection; ARR, axillary recurrence rate; BCSS, breast-cancer-specific survival; cN0, node negative breast cancer; cN+1, node positive breast cancer; DFS, disease-free survival; FNR, false negative rate; ICCHOM, The International Consortium for Health Outcomes Measurement; IKNL, The Netherlands Comprehensive Cancer Organization; MARI, marking the axillary lymph node with radioactive iodine; NEO-FFI, Neuroticism Extraversion Openness Five Factor Inventory; NCR, The Netherlands Cancer Registry; NPV, negative predictive value; OS, overall survival; pCR, pathologic complete response; PROMs, patient reported outcome measures; RISAS, radioactive Iodine Seed localization in the Axilla in axillary node positive breast cancer combined with dual tracer Sentinel node procedure following neoadjuvant chemotherapy; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; STAM-trait, Spielberger State-Trait Anxiety Inventory; TAD, targeted axillary lymph node dissection; TNM, TNM classification; T, primary tumour; N, regional lymph nodes; M, distant metastases.

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A list of participating centres and their local principal investigators is provided in Appendix A.

MINIimal vs. MAXimal Invasive Axillary Staging and Treatment

**Introduction**

In the past decades, there has been a trend towards de-escalating axillary surgery in breast cancer patients who undergo primary surgery. Following landmark trials such as NSABP B-32, sentinel lymph node biopsy (SLNB) has replaced axillary lymph node dissection (ALND) in node negative (cN0) patients, on account of their equivalent survival and regional control, and the superiority of SLNB in terms of post-surgical morbidity outcomes.\(^1\)\(^-\)\(^3\) Even in the case of a positive SLNB (limited to two positive nodes), it is safe to omit ALND when breast conserving therapy is performed and adjuvant treatment is given.\(^4\)\(^-\)\(^6\)

In node positive (cN+) patients who receive neoadjuvant systemic therapy (NST), staging and treatment of the axilla remains an area of controversy. NST results in an axillary pathologic complete response (axillary-pCR) in at least a third of cN+ patients\(^7\)\(^-\)\(^12\); depending on breast cancer molecular subtype, axillary-pCR rates can be as high as 74%.\(^13\) It is hypothesized that patients with an axillary-pCR do not benefit from ALND, since axillary-pCR is associated with an improved survival.\(^14\)\(^-\)\(^17\) As a result, less invasive axillary staging procedures have been introduced to enable response-guided treatment, thereby omitting standard ALND. Examples of these less invasive staging procedures are SLNB, Marking Axillary lymph nodes with Radioactive Iodine seeds (MARI-procedure), and Targeted Axillary Dissection (TAD, a combination of SNLB and excision of a marked metastatic lymph node).\(^16\)\(^-\)\(^20\)

While these less invasive staging procedures are expected to diminish morbidity, each procedure risks leaving behind chemotherapy-resistant disease. Several studies have shown that SLNB is associated with unacceptably high false negative rates (FNRs), and a negative predictive value (NPV) that does not exceed 86%. This means that residual disease resistant to systemic therapy is missed in 1 in 6 patients with tumor-free SLN+.\(^9\)\(^-\)\(^11\)\(^,\)\(^13\)\(^,\)\(^17\)\(^,\)\(^20\)\(^-\)\(^21\) Donker et al developed the MARI-procedure, which resulted in a FNR of 7%, and a comparable NPV of 83%.\(^16\)\(^,\)\(^22\) The accuracy of TAD appears higher, yet evidence is limited to a few small cohort studies.\(^19\)\(^,\)\(^23\)\(^-\)\(^25\) Preliminary results of the RISAS trial (combining MARI-procedure and SLNB) presented at SABCS 2020 seem to confirm the accuracy of TAD in a large multicenter cohort.\(^26\) Final results of the RISAS trial and trials such as GANEAX3 (NCT03630913) have to be awaited to determine the most accurate procedure.\(^27\)\(^,\)\(^27\)

While the less invasive axillary staging procedures are being implemented in daily practice, ALND is more frequently replaced by axillary radiotherapy.\(^28\)\(^-\)\(^30\) However, there is only little evidence that it is safe to omit standard ALND in cN+ patients undergoing NST, in terms of survival and recurrence rates.\(^31\)

Furthermore, it is unknown how this trend affects quality of life (QoL), the importance of which has grown as the survival and recurrence rates of breast cancer improve. Hence, studies are urgently required that adequately compare the less and more invasive axillary staging and treatment procedures in terms of oncologic safety and impact on QoL. Four randomized controlled trials are currently comparing axillary treatment strategies in cN+ patients undergoing NST, with disease-free survival as primary endpoint (ATNEC: NCT04109079; NSABP-B51: NCT01872975; TAXIS: NCT03513614; Alliance A011202: NCT01901094). These trials have some limitations. It will be some years before the first trial results are expected, while prompt assessment of oncologic safety is required. With the ongoing trend towards less invasive strategies, it may also become progressively difficult to motivate patients to participate in these trials. Furthermore, three of four trials only include patients with cN1 disease. Patients with cN2-3 disease can also achieve an axillary-pCR, which implies that an ALND may not be necessary. Moreover, they have an indication for locoregional radiotherapy and thus an increased risk of developing morbidity when this is combined with ALND.\(^3\)\(^-\)\(^3\)\(^2\)

In the Netherlands, axillary staging and treatment strategies in cN+ patients treated with NST vary widely between institutions.\(^28\) Consequently, a retro- and prospective registry of cN1-3M0 patients can be assembled, that allows for comparison between less and more invasive strategies. The observational MINIMAX study will offer insight into the oncologic safety and impact on QoL of response guided-treatment based on the outcome of less vs. more invasive axillary staging procedures in cN+ patients treated with NST, and therefore will contribute to evidence-based practice. In the event that less invasive strategies and standard ALND both have benefits and drawbacks, the study results will be most valuable for shared decision-making and personalized treatment.

**Main Study Objectives**

The primary objectives are 1) to compare the oncologic safety at 5 and 10 years, in terms of disease-free survival (DFS), breast-cancer-specific survival (BCSS), overall survival (OS), and axillary recurrence rate (ARR), and 2) to assess the impact on QoL at 1 and 5 years, of the less and more invasive axillary staging and treatment procedures in cN+ breast cancer patients treated with NST.

**Patients and Methods**

**Study Design**

MINIMAX is a Dutch multicenter registry study that includes cN1-3M0 unilateral invasive breast cancer patients, who receive

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**Keywords:** Breast cancer, Node positive, Axillary surgery, Axillary lymph node dissection, Sentinel lymph node biopsy, MARI-procedure, Targeted axillary dissection

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NST, followed by axillary staging and treatment according to local protocols. It comprises a retrospective registry, and a prospective multicenter registry. In both parts of the study, clinical data will be collected from patients’ medical files by specially trained data managers of the Netherlands Comprehensive Cancer Organization (IKNL), and databases will be based on the Netherlands Cancer Registry (NCR). They will partly consist of regular NCR data, such as patient characteristics, baseline tumor characteristics (based on pathology and imaging), data on systemic therapy, and type of surgery of the breast and axilla (ie, SLNB, excision of a marked metastatic lymph node, TAD, and/or ALND). In addition, data will be collected on imaging strategies (ie, ultrasound, MRI and/or PET-CT) to evaluate nodal status (before, during, and after NST), specifications of axillary surgery (eg, number of lymph nodes excised) and pathology outcomes, radiotherapy target volumes, doses and fractionation, and follow-up in terms of survival and recurrence.

In the retrospective registry, clinical data will be analyzed of approximately 4,000 patients, who were diagnosed with CN+ breast cancer between 2014 and 2017, to determine oncologic safety at 5 and 10 years. Five-year oncologic safety will be available in 2023.

In the prospective multicenter registry, to evaluate impact on QoL, Patient Reported Outcome Measures (PROMs) will be provided at baseline (ie, time of diagnosis), and 1 and 5 years after diagnosis. Therefore, written informed consent will be obtained. Moreover, we aim to verify the 5-year oncologic safety. The first results will be available by the end of 2023. Thirty-five centers will participate in this study. A list of participating centers and their local principal investigators is provided in Appendix A. The study was approved by the Institutional Review Board of the Netherlands Cancer Institute – Antoni van Leeuwenhoek (IRB 20-003) and by the local ethics committees of the participating centers. The MINIMAX study is registered at ClinicalTrials.gov (NCT04486495).

**Study Population**

Women are eligible for this study if they are \( \geq 18 \) years with unilateral invasive breast cancer and cN1-3 with at least one pathologically proven axillary lymph node metastasis, who are treated with NST (chemotherapy ± immunotherapy), followed by surgery of the breast and the axilla. Exclusion criteria are neoadjuvant endocrine therapy, distant metastases (also in case of oligometastatic disease), previous surgery (including SLNB prior to NST) or radiotherapy of the ipsilateral axilla, history of invasive breast cancer, and other malignancies except for basal/squamous cell skin cancer and in situ carcinoma of the cervix or breast (unless surgery or radiotherapy of the ipsilateral axilla has been performed).

**Quality of Life - Prospective Multicenter Study**

**Patient Reported Outcome Measures (PROMs)**

PROMs can be used to quantify QoL at several time points, with the purpose of giving feedback to the individual patient at the outpatient clinic, improving individual health care as well as shared decision-making.\(^{33,34}\) Therefore, PROMs have a leading role in the Standard Set for Breast Cancer, which was developed by a multidisciplinary international working group in collaboration with the International Consortium for Health Outcomes Measurement (ICHOM). For this study, a validated Dutch version of the generic EORTC QLQ-C30, and the breast cancer specific EORTC QLQ-BR23 and BREAST-Q will be used, as proposed by ICHOM,\(^{35}\) along with the generic EQ-5D-5L. Together, these PROMs will evaluate various domains of the patients’ QoL, such as global health status, physical functioning, treatment-related morbidity (eg, pain or other complaints of the breast and arm), body image, and psychosocial and sexual wellbeing. The PROMs will be provided at baseline (ie, time of diagnosis), and 1 and 5 years after diagnosis. To attain a proper baseline, the first PROMs need to be completed before NST starts. The coordinating investigator will send and then collect the PROMS, a process facilitated by a secure platform built by two software programs, LimeSurvey and GemsTracker. PROMs will be available both online and paper-based.

**Spielberger State-Trait Anxiety Inventory (STAI-trait) & Neuroticism Extraversion Openness Five Factor Inventory (NEO-FFI)**

Studies have shown that personality traits, such as anxiety, can affect QoL.\(^{36,37}\) A Dutch validated short version of the STAI-trait and NEO-FFI will be used to assess whether personality traits influence the QoL outcome.\(^{38}\) These questionnaires will be provided at baseline (ie, time of diagnosis).

**Statistics**

**Endpoints**

In the retrospective study, DFS, BCSS, OS, and ARR will be assessed at 5 and 10 years for various invasive axillary staging and treatment procedures separately using the Kaplan-Meier method.

DFS is defined as the time interval between the date of diagnosis and the date of any invasive locoregional or distant recurrence, contralateral breast cancer, second primary invasive non-breast cancer, or death from any cause, whichever comes first, measured in days. Patients who are still alive without an event are censored at the date of last follow-up. BCSS and OS are defined as the time interval between the date of diagnosis and the date of death from the disease or from any cause, respectively, measured in days. Patients who are still alive are censored at the date of last follow-up. ARR is defined as tumor recurrence or as a residual tumor that becomes clinically apparent in the ipsilateral axilla (pathologically proven).

In the prospective multicenter study, 5-year oncologic safety will be defined in the same manner. Impact on QoL will be assessed at 1 and 5 years.

**Sample Size**

In the retrospective study, the estimated sample size is 4000 patients, who were diagnosed with cN+ breast cancer between 2014 and 2017. Preliminary analyses have shown that in the Netherlands the ratio of women who received less invasive axillary staging compared to standard ALND is about 1 to 1. In the prospective multicenter study, to test the hypothesis that less invasive axillary
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staging is non-inferior to standard ALND in terms of oncologic safety, we aim to analyze the data of 494 women. When assuming a 5-year DFS of 72.5%, we should have 80% power to exclude a non-inferiority margin of 10%, and thus the lower bound of the 95% confidence interval of DFS should not be less than 62.5%. In our registry, the anticipated loss to follow-up rate is 10%, and therefore we intend to include 549 patients. Based on analysis of NCR data, we expect to reach our calculated sample size within two years.

Regarding our second important outcome measure, impact on QoL, we expect a loss to follow-up rate of 20-30%, which would be in line with other QoL-studies. With 30% loss to follow-up, we would still have 80% power to detect a standardized mean difference in impact on QoL with Cohen’s d of 0.3.

Planned Analysis

In both studies, to assess oncologic safety with cohort data, we will compare Kaplan-Meier estimates derived using propensity score weighting. The propensity score is the probability of an individual to receive ALND conditional on observed baseline covariates. Conditional on this score, both groups’ baseline characteristics are expected to be similar, as would be expected in a randomized clinical trial. To enable an individual’s propensity score to be calculated if baseline data is missing, we will use stochastic regression imputation to complete the data before estimating the propensity score. This process will be performed for DFS, BCSS, OS, and ARR. The difference will be compared to the predefined non-inferiority limit of 10% using the upper bound of the 95% confidence interval of the difference. If necessary, a competing risk model will be used. Using Kaplan-Meier estimates and both univariable and multivariable Cox proportional hazards regression, we will evaluate the influence of nodal status (cN1-3 and ypN0-3) and breast cancer subtype on the oncologic safety outcomes. Finally, univariable and multivariable Cox proportional hazards regression will be used to identify risk factors for regional recurrence.

In the prospective multicenter study, the one-way ANOVA will be used to compare parametric continuous variables (PROMs) between less and more invasive axillary surgery groups, all in relation to baseline levels. In case of evidence of differences, we will perform post-hoc between-group testing adjusted for multiple testing using the bonferroni correction. To evaluate possible differences adequately both statistical significance and clinical significance need to be addressed.

Discussion

Nowadays, substantial axillary-pCR rates are achieved in cN+ patients treated with NST. It is hypothesized that ALND can be safely omitted in cN+ patients who achieve an axillary-pCR. As a result, less invasive axillary staging procedures are being implemented globally to establish response-guided treatment. This has led to a decrease in (completion) ALND, not only in the Netherlands (99% in 2006, to 53% in 2016), but also in other countries, and this trend seems to coincide with an increased use of adjuvant axillary radiotherapy. Interestingly, ALND is being omitted in both patients with axillary-pCR, and those with residual disease. However, it is unclear whether omitting ALND or replacing ALND by radiotherapy in cN+ patients treated with NST is safe with regard to long-term prognosis.

Since omitting standard ALND is accompanied by the risk of leaving behind chemotherapy-resistant residual disease, this may result in undertreatment of the axilla. Moreover, adjuvant systemic treatment in case of residual disease can result in improved prognosis (eg, capcitabine in HER2-negative patients, and TDM-1 in HER2-positive patients). Therefore, it is of great importance that residual axillary disease is detected, and thus, in order to provide appropriate adjuvant treatment, the less invasive axillary staging procedure that replaces standard ALND has to be highly accurate.

While there is a search for the most accurate staging procedure, other issues need to be addressed. The question remains whether less invasive axillary staging is appropriate for all cN+ patients treated with NST, or if standard ALND should be applied in selected cN+ patients. This has resulted in differences regarding patient selection in accuracy studies. For instance, all cN+ patients were included in the MARI trial, yet the RISAS trial did not include cN3a and cN3c patients, and the trials Z1071, SN-FNAC and SENTINA did not include cN3 patients at all. However, patients with extensive axillary involvement can achieve an axillary-pCR as well, in which case standard ALND is debatable. Moreover, cN3 patients already have an indication for locoregional radiotherapy, which can be an extra argument for omitting ALND.

Pathology outcomes of the less invasive staging procedures serve to guide adjuvant axillary treatment plans (ie, no further treatment vs. completion ALND and/or radiotherapy). In case of an axillary pCR, identified by less invasive staging procedures, completion ALND or radiotherapy may not be deemed necessary. In the event that less invasive staging procedures identify residual disease, adjuvant axillary treatment is indicated. In these cases, it is unclear whether completion ALND with or without radiotherapy is required, or if radiotherapy alone is sufficient. The AMAROS trial showed no significant difference in survival and recurrence rates between ALND or radiotherapy in cN0 patients with a positive SLNB who were treated with primary surgery and adjuvant systemic therapy. However, these results cannot be extrapolated to cN+ patients treated in the neoadjuvant setting, with potentially chemotherapy-resistant residual disease. Moreover, it is unclear if decision-making with regard to adjuvant axillary treatment plans can be based solely on the pathology outcomes of the less invasive axillary staging procedures, since the impact of a false negative result is unknown. Furthermore, tumor biology (ie, grade, lympho-vascular invasion, molecular subtype) may be a reason to apply adjuvant axillary treatment regardless of an axillary-pCR. Other factors such as the extent of lymph node involvement prior to NST (eg, cN1-3, according to the AJCC staging system, or having <4 or ≥4 suspicious nodes, as proposed in the MARI protocol), response on imaging after NST, and the extent of residual disease (isolated tumor cells vs. micro- or macrometastases) are also taken into account to determine the extent of axillary staging and treatment strategies.

All these uncertainties have resulted in an undesired variety of axillary staging and treatment strategies depending on local prefer-
ences. Some centers already have adopted less invasive axillary staging procedures, while other centers still perform standard ALND. Evidence in terms of oncologic safety is needed to determine the appropriate strategy for patients with axillary-pCR, as well as for patients with residual axillary disease. Since QoL is of utmost importance for shared decision-making, as it can affect patient preferences for specific strategies, this also has to be taken into account. The MINIMAX study is designed to answer both of these needs. Since a randomized controlled trial is no longer feasible in the Netherlands, due to less invasive strategies being the preferred policy in many hospitals, an observational study design is the favored option. The MINIMAX study is expected to offer insight into the oncologic safety and impact on QoL of the various invasive axillary staging and treatment procedures in cN1-3M0 breast cancer patients treated with NST. The retrospective cohort study will focus on oncologic safety, while the prospective multicenter study will assess impact on QoL, and validate the oncologic safety analysis. The results will contribute to developing uniform evidence-based guidelines. If less and more invasive strategies appear to have both risks and benefits, then these findings will be highly valuable for shared decision-making and personalized treatment.

**Clinical Practice Points**

Nowadays, most node positive breast cancer patients are treated with neoadjuvant systemic therapy. Patients with a pathologic complete response of the axillary lymph nodes are not expected to benefit from axillary lymph node dissection. Therefore, less invasive axillary staging procedures have been introduced to establish response-guided treatment, hereby omitting standard axillary lymph node dissection. While there is a search for the most accurate less invasive axillary staging procedure, there is a need for evidence to support the assumed oncologic safety and superior quality of life of response-guided treatment based on these procedures. In the meantime, less invasive axillary staging procedures are already implemented globally. This multicenter registry study of node positive patients treated with neoadjuvant systemic therapy will contribute to the development of evidence-based guidelines. In the event that less invasive axillary staging procedures and standard axillary lymph node dissection both have risks and benefits, the study results will be most valuable for shared decision-making and personalized treatment.

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**Disclosure**

The authors have stated that they have no conflicts of interest.

**Appendix**

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