Risk of Positive Sentinel Lymph Node After Neoadjuvant Systemic Therapy in Clinically Node-Negative Breast Cancer: Implications for Postmastectomy Radiation Therapy and Immediate Breast Reconstruction

S. Samiei, MD, B. N. van Kaathoven, BSc, L. Boersma, MD, PhD, R. W. Y. Granzier, MD, S. Siesling, MD, PhD, S. M. E. Engelen, MD, PhD, L. de Munck, MSc, S. M. J. van Kuijk, PhD, R. R. J. W. van der Hulst, MD, PhD, M. B. I. Lobbes, MD, PhD, M. L. Smidt, MD, PhD, and T. J. A. van Nijnatten, MD, PhD

1Department of Surgery, Maastricht University Medical Center+, Maastricht, The Netherlands; 2Department of Radiology and Nuclear Medicine, Maastricht University Medical Center+, Maastricht, The Netherlands; 3GROW – School for Oncology and Developmental Biology, Maastricht University Medical Center+, Maastricht, The Netherlands; 4Department of Radiation Oncology, Maastricht University Medical Center+ (MAASTRO Clinic), Maastricht, The Netherlands; 5Department of Research, Netherlands Comprehensive Cancer Organization, Utrecht, The Netherlands; 6Department of Health Technology and Services Research, Technical Medical Center, University of Twente, Enschede, The Netherlands; 7Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center+, Maastricht, The Netherlands; 8Department of Plastic, Reconstructive, and Hand Surgery, Maastricht University Medical Center+, Maastricht, The Netherlands

ABSTRACT

Background. Residual axillary lymph node involvement after neoadjuvant systemic therapy (NST) is the determining factor for postmastectomy radiation therapy (PMRT). Preoperative identification of patients needing PMRT is essential to enable shared decision-making when choosing the optimal timing of breast reconstruction. We determined the risk of positive sentinel lymph node (SLN) after NST in clinically node-negative (cN0) breast cancer.

Methods. All cT1-3N0 patients treated with NST followed by mastectomy and SLNB between 2010 and 2016 were identified from the Netherlands Cancer Registry. Rate of positive SLN for different breast cancer subtypes was determined. Logistic regression analysis was performed to determine correlated clinicopathological variables with positive SLN.

Results. In total 788 patients were included, of whom 25.0% (197/788) had positive SLN. cT1-3N0 ER+HER2−, cT1-3N0 ER−HER2+, and cT1-2N0 triple-negative patients had the lowest rate of positive SLN: 7.2–11.5%, 0–6.3%, and 2.9–6.2%, respectively. cT1-3N0 ER+HER2− and cT3N0 triple-negative patients had the highest rate of positive SLN: 23.8–41.7% and 30.4%, respectively. Multivariable regression analysis showed that cT2 (odds ratio [OR] 1.93; 95% confidence interval [CI] 1.01–3.96), cT3 (OR 2.56; 95% CI 1.30–5.38), grade 3 (OR 0.44; 95% CI 0.21–0.91), and ER+HER2− subtype (OR 3.94; 95% CI 1.77–8.74) were correlated with positive SLN.

Conclusions. In cT1-3N0 ER+HER2+, cT1-3N0 ER−HER2+, and cT1-2N0 triple-negative patients treated with NST, immediate reconstruction can be considered an acceptable option due to low risk of positive SLN. In cT1-3N0 ER+HER2− and cT3N0 triple-negative patients treated with NST, risks and benefits of immediate reconstruction should be discussed with patients due to the relatively high risk of positive SLN.
Neoadjuvant systemic therapy (NST) has become a more common approach for early-stage breast cancer. NST targets both systemic and locoregional disease sites and can lead to pathologic down-staging. The increasing use of NST has affected the locoregional treatment decisions, including the surgical management of the breast and axillary lymph nodes, and the indications for postmastectomy radiation therapy (PMRT).1–3

Previous randomized, clinical trials have reported that PMRT is associated with a lower locoregional recurrence rate (LRR), and improved disease-free survival and overall survival.4–6 The indication for PMRT is not only dependent on the clinical disease stage and patient characteristics, but also on the final pathological disease stage after NST.7,8 According to the current guidelines, residual axillary lymph node involvement after NST is the most determining factor for the indication of PMRT independent of other risk factors.9,10 However, axillary lymph node involvement after NST is difficult to predict.

In parallel, breast reconstruction has become an important aspect of breast cancer treatment. Rates of reconstruction at the time of mastectomy (i.e., immediate breast reconstruction) have increased considerably over the past decades.11–13 This is important given that immediate breast reconstruction not only benefits the quality of life and reduces the adverse psychosocial consequences, but it is also preferred by most patients.14–18 If PMRT is indicated in women with immediate breast reconstruction, PMRT can adversely affect the aesthetic outcome of the reconstructed breast and increase the complication risks depending on the type of breast reconstruction.19–21 Preoperative identification of patients who do need PMRT is essential to enable adequate shared decision-making when choosing the optimal timing of breast reconstruction.

Therefore, the purpose of this study was to determine the overall risk of a positive sentinel lymph node (SLN) after NST in cT1-3N0 breast cancer patients and for the different breast cancer subtypes to support preoperative shared decision-making.

METHODS

This study was approved by the Privacy Review Board of the Netherlands Cancer Registry (NCR), managed by the Netherlands Comprehensive Cancer Organization (IKNL). All cT1-3N0 breast cancer patients who had undergone NST (chemotherapy with or without trastuzumab) with subsequent mastectomy and sentinel lymph node biopsy (SLNB), from January 2010 through December 2016, were identified from the NCR.

On-site trained registrars of NCR collect data from patients’ medical records from all hospitals in the Netherlands. Data were collected on age, tumor characteristics (clinical TNM stage and the pathological TNM stage after NST, tumor histology, tumor grade, and receptor status), and treatment regimens (systemic therapy, breast and axillary surgery, radiation therapy, and immediate breast reconstruction). The axillary nodal status was determined before NST administration by ultrasound. Patients were considered cN0 if ultrasound showed no suspicious lymph nodes or in the case of negative tissue sampling. The pathologic examination of the SLN was performed according to the national guidelines.22,23 The SLN was sliced on at least three levels with 250-μm spacing and stained with hematoxylin and eosin (H&E). In the case of H&E-negative SLN, immunohistochemistry was performed. The SLN outcome was considered positive in the case of micro- and/or macrometastases.24 In the case of isolated tumor cells, the SLN outcome was considered negative.

The ER (Estrogen Receptor) and HER2 (Human Epidermal growth factor Receptor 2) status were determined by immunohistochemistry. Immunohistochemistry testing of ER and HER2 was in accordance with the Dutch national guidelines.22,23 The method of scoring for ER status was based on the percentage of tumor cells with nuclear staining. ER was classified as positive if the percentage was ≥10%. The scoring of HER2 status was based on the membranous staining of invasive tumor cells. The scoring system is categorized according to coloration in 0 (<10% tumor cells stain), 1+ (>10% tumor cells stain with weakly intensity), 2+ (>10% tumor cells stain with moderate intensity), or 3+ (>30% tumor cells stain with strong intensity). The coloration scores 0 and 1+ were classified as negative, and the score 3+ was classified as positive. In the case of a 2+ equivocal score, fluorescent in situ hybridization (FISH) was performed and the outcome of FISH overruled.

According to the Dutch national guidelines of 2008 and 2012, the indication for systemic therapy was based on age, tumor size, grade, and receptor status.22,23 Chemotherapy was recommended for: (1) N0 patients ≤35 years (except grade 1 tumors of ≤1.0 cm); (2) N0 patients ≥35 years with tumors 1.1–2.0 cm and grade 2, or tumors ≥2.0 cm; (3) N0 patients with HER2+ tumors ≥0.5 cm. These guidelines recommended the following chemotherapy regimens: 6 cycles of TAC (docetaxel, doxorubicin, and cyclophosphamide), or 3 cycles of FEC (fluorouracil, epirubicin, and cyclophosphamide), or 4 cycles of AC (doxorubicin and cyclophosphamide) followed by 12 cycles of paclitaxel or 4 cycles of docetaxel. In addition, HER2+ patients were
also treated with trastuzumab for a total of 1 year. No additional HER2-targeted therapy was advised between 2010 and 2016.

Descriptive analyses were performed to evaluate the overall rate of a positive SLN and for the different breast cancer subtypes for cT1-3N0 patients. Patients were stratified into four subtypes with ER-positive(+)HER2+, ER-negative(−)HER2+, ER+HER2−, and triple-negative patients. The PR (Progestosterone Receptor) was not included in the determination of the ER+HER2+, ER−HER2+, and ER+HER2− subtypes. Univariable logistic regression analysis was applied to determine the association of patient and/or tumor characteristics with a positive SLN. Multivariable logistic regression analysis was used to adjust for potential confounders. Odds ratios (ORs) with 95% confidence interval (CI) were presented. A two-sided p value < 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 25, IBM, Armonk, New York, NY).

RESULTS

A total of 1914 patients were diagnosed with cT1-3N0 breast cancer between January 2010 and December 2016 in the Netherlands and treated with NST followed by mastectomy and SLNB. Patients were excluded if the SLNB had been performed before NST (n = 782). Other exclusion criteria were the unknown date of SLNB or NST (n = 259), unknown SLNB outcome (n = 33), neoadjuvant endocrine therapy (n = 30), unknown breast cancer subtype (n = 13), and distant metastases at primary breast cancer diagnosis or within 91 days after surgery (n = 9). A total of 788 patients (median age, 48 [range, 18–78] years) were included for final analyses, of whom 106 (13.5%) had macrometastases. The overall rate of a positive SLN for the cT1-3N0 patients was 25.0% (197/788). The rate of a positive SLN per subtype was 10.4% (11/106) for the cT1-3N0 ER+HER2+, 3.7% (2/54) for the cT1-3N0 ER−HER2+, 35.9% (170/474) for the cT1-3N0 ER+HER2+, and 9.1% (14/154) for the cT1-3N0 triple-negative patients. Table 2 shows the SLN outcome for the different breast cancer subtypes.

In the ER+HER2+ subgroup, 7.2% (2/28) of the cT1N0 patients had a positive SLN, 11.5% of the cT2N0 (6/52), and 11.5% (3/26) of the cT3N0 patients. Of these patients with a positive SLN, 27.3% (3/11) had micrometastases, and 72.7% (8/11) had macrometastases. In these ER+HER2+ patients, 86.8% (92/106) had received neoadjuvant trastuzumab.

In the ER−HER2+ subgroup, the cT1N0 and cT3N0 patients had no positive SLN, and 6.3% (2/32) of the cT2N0 patients had a positive SLN. Both cT2N0 patients with a positive SLN had micrometastases. Neoadjuvant trastuzumab was administered in 92.6% (50/54) of these ER−HER2+ patients.

In the ER+HER2− subgroup, 23.8% (20/84) of the cT1N0 patients had a positive SLN, 36.6% (90/246) of the cT2N0, and 41.7% (60/144) of the cT3N0 patients. Of these patients with a positive SLN, 34.7% (59/170) had micrometastases and 65.3% (111/170) had macrometastases.

In the triple-negative subgroup, the rate of a positive SLN for cT1N0 and cT2N0 patients was respectively 2.9% (1/34) and 6.2% (6/97). This increased up to 30.4% (7/23) for the cT3N0 patients. Micrometastases were found in 35.7% (5/14) of the SLN positive patients and 64.3% (9/14) had macrometastases.

Clinical T1-3N0 ER+HER2+, cT1-3N0 ER−HER2+, and cT1-2N0 triple-negative patients had the lowest rate of a positive SLN: 7.2–11.5%, 0–6.3%, and 2.9–6.2%, respectively. Clinical T1-3N0 ER+HER2− and cT3N0 triple-negative patients had the highest rate of a positive SLN: 23.8–41.7% and 30.4%, respectively (Table 2).

The univariable analysis showed that age ≥ 40 years (OR 1.65, 95% CI 1.07–2.53, p = 0.022), cT2 stage (OR 1.77, 95% CI 1.09–2.94, p = 0.021), cT3 stage (OR 2.78, 95% CI 1.64–4.72, p < 0.001), lobular histology (OR 1.77, 95% CI 1.20–2.62, p = 0.004), and ER+HER2− subtype (OR 4.83, 95% CI 2.52–9.27, p < 0.001) were associated with higher odds of a positive SLN. Tumor grade 2 (OR 0.57, 95% CI 0.33–0.98, p = 0.043) and tumor grade 3 (OR 0.21, 95% CI 0.11–0.40, p < 0.001) were associated with lower odds of a positive SLN. After adjustment for confounders, the multivariable analysis showed that cT2 stage (OR 1.93, 95% CI 1.01–3.69, p = 0.047), cT3 stage (OR 2.73, 95% CI 1.34–5.54, p = 0.006), and ER+HER2− subtype (OR 3.82, 95% CI 1.72–8.84, p = 0.001) were correlated with higher odds of a positive SLN. Grade 3 (OR 0.44, 95% CI 0.21–0.91, p = 0.026) remained correlated with lower odds of a positive SLN. Table 3 shows the univariable and multivariable logistic regression analysis for the outcome of positive SLN after NST.
DISCUSSION

In this study, nationwide data were used to report on the risk of a positive SLN in cT1-3N0 breast cancer patients, who had undergone NST followed by mastectomy and SLNB, regarding the need for PMRT and therefore the timing of breast reconstruction (immediate or delayed). We found that cT2 stage, cT3 stage, and ER+/HER2− subtype were correlated with higher odds of a positive SLN after NST. Grade 3 was correlated with lower odds of a positive SLN after NST. The lowest risk of a positive SLN was in the ER−HER2− subtype (3.7%), whereas the highest risk of a positive SLN was in the ER+HER2− subtype (35.7%).
At present, there are no results of randomized trials addressing the role of PMRT following NST. The pooled analysis of National Surgical Breast and Bowel Project (NSABP) B-18 and B-27, and several retrospective studies have addressed the advantages of PMRT after NST.\(^2,3,7,8,25\) Available studies showed that age \(\leq 40\) years, triple-negative subtype, grade 3 tumors, lymphovascular invasion, and advanced clinical and pathological stage are high-risk features associated with LRR and should require PMRT after NST. Residual axillary lymph node involvement after NST is, in particular, an important prognostic factor for LRR and the most determining factor for the indication of PMRT independent of the risk factors.\(^9,26,27\) In our study, independent clinicopathological variables have been assessed that are correlated with a positive SLN after NST. The correlation between cT2 stage, cT3 stage, and ER+HER2− subtype with higher odds of a positive SLN after NST is supported by previous research.\(^27–29\) Both clinical tumor size and tumor subtype are independent predictors of pathologic complete response (pCR). We also showed that patients with larger breast tumors and ER+HER2− subtype have the lowest axillary lymph node response to NST. On the other hand, we demonstrated that tumor grade 3 is an independent predictor correlated with lower odds of a positive SLN after NST. This is in line with previous research given that high-grade tumors are associated with higher rates of axillary pCR.\(^30–33\)

The increasing use of NST and the inability to predict the axillary lymph node status after NST have raised questions regarding the patients who do need PMRT and increased the complexity of immediate breast reconstruction planning. Immediate breast reconstruction reduces the number of surgical procedures and has a better aesthetic outcome due to decreased scarring and preservation of the breast skin envelope.\(^34–37\) However, there can be potential reconstruction-related complications with performing an immediate breast reconstruction in patients that unexpectedly require additional PMRT after NST.\(^38,39\) The type of reconstruction (i.e., implant vs. autologous) can affect the complication risks in the setting of radiation therapy. PMRT in the setting of implants can adversely affect the aesthetic outcome and is associated with an increased risk of complications, such as capsular contraction and implant failure.\(^19,40,41\) Existing data on autologous reconstruction and PMRT found an increased odds of fat necrosis and volume loss, but acceptable results with regard to complications.\(^21,41–45\)

### TABLE 3 Logistic regression analysis for the outcome of positive SLN after NST

|                     | Univariable analysis | Multivariable analysis |
|---------------------|----------------------|------------------------|
|                     | OR 95% CI            | p value                | OR 95% CI            | p value                |
| **Age (year)**      |                      |                        |                       |
| \(\leq 40\)         | 1 [reference]        | 1 [reference]          |                       |
| > 40                | 1.65 1.07–2.53       | \(p = 0.022\)          | 1.13 0.63–2.04        | 0.668                  |
| **Clinical tumor stage** |                    |                        |                       |
| T1                  | 1 [reference]        | 1 [reference]          |                       |
| T2                  | 1.77 1.09–2.94       | \(p = 0.021\)          | 1.93 1.01–3.69        | 0.047                  |
| T3                  | 2.78 1.64–4.72       | \(p < 0.001\)          | 2.73 1.34–5.54        | 0.006                  |
| **Tumor histology** |                      |                        |                       |
| Ductal              | 1 [reference]        | 1 [reference]          |                       |
| Lobular             | 1.77 1.20–2.62       | \(p = 0.004\)          | 0.69 0.39–1.23        | 0.211                  |
| Other               | 1.49 0.89–2.50       | \(p = 0.130\)          | 1.51 0.74–3.06        | 0.254                  |
| **Tumor grade**     |                      |                        |                       |
| 1                   | 1 [reference]        | 1 [reference]          |                       |
| 2                   | 0.57 0.33–0.98       | \(p = 0.043\)          | 0.66 0.38–1.16        | 0.151                  |
| 3                   | 0.21 0.11–0.40       | \(p < 0.001\)          | 0.44 0.21–0.91        | 0.026                  |
| **Tumor subtype**   |                      |                        |                       |
| ER+HER2+            | 1 [reference]        | 1 [reference]          |                       |
| ER−HER2+            | 0.33 0.07–1.56       | \(p = 0.162\)          | 0.20 0.02–1.68        | 0.138                  |
| ER+HER2−            | 4.83 2.52–9.27       | \(p < 0.001\)          | 3.82 1.72–8.48        | \(p = 0.001\)          |
| Triple negative     | 0.86 0.38–1.98       | \(p = 0.730\)          | 0.96 0.35–2.62        | \(p = 0.932\)          |

SLN sentinel lymph node, NST neoadjuvant systemic therapy, OR odds ratio, CI confidence interval, ER Estrogen receptor, HER2 Human Epidermal growth factor Receptor 2, Triple-negative negative for ER, PR, and HER2
PMRT should be determined before surgery to diminish the risks of unexpected indication for PMRT and preserve patient satisfaction.

Clinical decision-making regarding the need for PMRT and immediate breast reconstruction requires a multidisciplinary approach and careful patient counseling. The results in this study indicate that cT1-3N0 ER+HER2− and cT3N0 triple-negative patients treated with NST have a high-risk of a positive SLN. For these patients, SLNB as a separate procedure preceding to reconstruction can be considered to provide information about the pathologic axillary lymph nodes prior to definitive surgery. If the SLN is positive, the breast reconstruction can then be delayed, or a tissue expander can be placed to preserve the breast skin envelope. Data about the axillary lymph nodes prior to a mastectomy can improve the surgical plan for breast reconstruction by incorporating the need for PMRT in surgical decision-making. If PMRT is required, these patients should be well informed throughout the entire decision-making process about the possibility of unfavorable outcomes due to irradiation and contribute to the sequence of breast reconstruction and PMRT.

It has not been fully elucidated whether micrometastases in the axillary lymph nodes after NST should be counted as an indicator for treatment with PMRT. Limited data are available on micrometastases and the LRR rate. In the Mamtani et al. study, 352 T1–T2 breast cancer patients were included, who had undergone primary mastectomy with isolated tumor cells or micrometastases in the axillary lymph nodes. Of these patients, 95% received adjuvant systemic therapy. The LRR rate without PMRT was 2.8% after 6 years and no LRR occurred among the patients who had received PMRT. There was no significant difference in LRR rate for patients treated with or without PMRT. A limitation is that these results only apply to patients treated with adjuvant rather than neoadjuvant systemic therapy so that the resistance or response to NST is not taken into account. In a study by van Nijnatten et al., disease-free survival (DFS) and overall survival (OS) of clinically node-positive patients treated with NST and subsequent axillary lymph node dissection were compared between three groups: axillary pCR (ypN0), isolated tumor cells or micrometastases, and macrometastases. They showed that DFS and OS are not significantly different between patients with axillary pCR and isolated tumor cells or micrometastases, but is significantly lower for patients with macrometastases. In our study, micrometastases were considered as node positive according to the current guidelines. Micrometastases were detected in 35.0% (69/197) of the positive SLNs. If only macrometastases were considered as node positive, the positive SLN outcome for all subtypes would be considerably lower. For the cT1-3N0 ER+HER2+ patients, this would even mean that none of the patients had a positive SLN and therefore no indication for PMRT. Further data are needed on whether PMRT is indicated in cN0 patients treated in the neoadjuvant setting with chemoresistant disease.

A strength of this study is the nationwide character of the data including general, academic, and cancer centers, and thus all patients in the Netherlands. Also, the large patient population gave us the opportunity to divide patients into subgroups and therefore the ability to determine the risk of a positive SLN for the different breast cancer subtypes. This study also has certain limitations, such as its retrospective design which made it impossible to retrieve missing data on tumor grade or subtype, date of SLNB or NST, and SLNB outcome. Furthermore, based on the available data it was not possible to determine whether a full course of chemotherapy regimen was completed. Lastly, the lymphovascular invasion was not available in the NCR database and could therefore not be included in the analyses.

CONCLUSIONS

In conclusion, these results showed that in cT1-3N0 ER+HER2+, cT1-3N0 ER−HER2+, and cT1-2N0 triple-negative patients treated with NST, immediate breast reconstruction can be considered an acceptable option due to the low risk of a positive SLN and therefore a decreased likelihood of PMRT. However, in cT1-3N0 ER+HER2− and cT3N0 triple-negative patients treated with NST, the risks and benefits of immediate breast reconstruction should be discussed with these patients due to the relatively high risk of a positive SLN and therefore an increased likelihood of PMRT. In these high-risk patients with a desire for immediate breast reconstruction, an SLNB after NST can be performed before breast surgery to determine the need for PMRT and discuss the potential complications of PMRT thoroughly with the patient in the case of a positive SLN prior to the reconstruction. For both situations, this study provides data for adequate shared decision-making.

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