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COMMENTARY

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Omission of axillary lymph node dissection after neoadjuvant chemotherapy for clinically node-positive breast cancer: How can we select patients?

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One of the benefits of neoadjuvant chemotherapy (NAC) for breast cancer patients is downstaging the axilla.[1,2]

Axillary lymph node metastases can be marked for localization and removing after NAC. Axillary lymph node dissection (ALND) can therefore be reserved for patients who remain pathologically lymph node positive after NAC. However, also in these patients, it occurs regularly that no additional positive lymph nodes are found.

We investigated the incidence of remaining positive lymph nodes in the completion ALND following the finding of a tumor-positive marked lymph node after NAC. We tried to identify risk factors for additional positive lymph nodes at ALND, with the ultimate goal to predict in which of these patients an ALND might be omitted.

We conducted a retrospective chart review selecting patients with invasive breast cancer with lymph node involvement detected by ultrasound of the axilla and pathologically confirmed. Positive lymph nodes were marked with an iodine seed (MARI procedure)[3] or with a radio-opaque marker.[4] Screening for distant metastases was negative.

These patients were treated with NAC, followed by a lumpectomy or mastectomy and resection of the marked lymph node. Only in case of a positive marked lymph node, a completion ALND was performed.

In this study, we searched for potential risk factors for additional positive lymph nodes in the ALND.

We investigated the following variables, known to be prognostic factors for lymph node metastases: clinical and pathological tumor and nodal stage, hormone receptor status, HER2 status, Bloom & Richardson grade, clinical and pathological response to NAC, number of positive nodes at presentation, presence of vascular invasion, presence of extranodal growth in the excised marked lymph node, size of metastasis of the marked lymph node. The other investigated items were age at diagnosis, tumor type, and additional negative lymph nodes next to the marked lymph node.

IBM SPSS Statistics 22 was used for statistical testing. Nonparametric tests were used. Pearson's chi-square test and Fisher's exact test were used to determine the significance of a possible association with the presence of additional positive lymph nodes in the ALND. A multivariate analysis was performed using variables significantly associated with the presence of additional positive lymph nodes in the ALND, and odds ratios were calculated. All statistical analyses were two-sided. Significance was assigned at $P < .05$.

Sixty-nine patients were included. They were diagnosed with cT1-4 N1-3 M0 breast cancer (eighth edition of the TNM

TABLE 1 Significant characteristics and bivariate association with the extent of nodal metastasis in the ALND

Variables	Number of patients (n = 69), n (%)	No additional positive lymph nodes in ALND (n = 37), n (%)	Additional positive lymph nodes in ALND (n = 32), n (%)	*P* value
Number of positive LN before NAC				
1	30 (42.4)	23 (77.0)	7 (23.0)	.005
2	10 (13.6)	5 (50.0)	5 (50.0)	
3	11 (16.7)	3 (27.3)	8 (72.7)	
>3	18 (27.3)	6 (33.3)	12 (66.7)	
ypT stage				
ypT0 or ypTis	7 (10.1)	5 (71.4)	2 (28.6)	.040
ypT1	25 (36.2)	15 (60.0)	10 (40.0)	
ypT2	24 (34.8)	15 (62.5)	9 (37.5)	
ypT3	10 (14.5)	2 (20.0)	8 (80.0)	
ypT4	3 (4.4)	0	3 (100.0)	

Abbreviations: ALND, axillary lymph node dissection; LN, lymph nodes; NAC, neoadjuvant chemotherapy.

classification) from March 2012 until October 2018. Thirty-two patients (46%) had positive lymph nodes in the completion ALND.

The chance of a positive ALND increased with an increase in number of positive lymph nodes on imaging previous to NAC (P = .005) (Table 1). Patients with a higher pathologic tumor stage (ypT stage) had a higher chance of additional positive lymph nodes in the ALND (P = .040) (Table 1). In the group of seven patients with stage ypT0 or ypTis, three patients had only one positive lymph node prior to NAC. All three had no additional positive lymph nodes in the ALND.

Two variables were independent predictors for additional positive lymph nodes in ALNDs. The number of affected nodes before NAC had a significant association, with an odds ratio (OR) of 5.9 (95% CI 2.0-17.1, P = .001). There was also a significant association with additional positive lymph nodes in ALNDs in patients who were diagnosed with ypT3 or ypT4 breast cancer, OR 9.2 (95% CI 1.8-45.4, P = .002) .

In the neoadjuvant setting, predictors of additional positive axillary lymph nodes after NAC are not well known.

No trials have yet been published to investigate whether omitting ALND is oncologically safe after NAC in patients with a positive marked lymph node before treatment. However, Koolen et al proposed an algorithm and made a distinction between one to three and four or more FDG-avid lymph nodes before NAC.[5] According to our study, the risk of additional pathological lymph nodes in the ALND was 50% for patients with 2 involved lymph nodes before NAC and 73% for patients with 3 involved nodes upfront. However, only a minority of the patients in our study underwent PDG-PET/CT imaging.

Currently, there are two studies on axillary treatment after NAC in patients with clinically positive lymph nodes. These are the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-51/ RTOG Radiation Therapy Oncology Group (RTOG) 1304 trial (NCT01872975; clinicaltrials.gov) and the Alliance A11202 study (NCT01901094).

The limitations of this study were inherent to the retrospective design, the low number of patients, and the methods of determining the number of positive lymph nodes before NAC lacked uniformity. In the future, it would be desirable to document the number of pathologically enlarged lymph nodes in imaging reports. Alternatively, PET-CT can be used to estimate the number of affected lymph nodes.

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