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ORIGINAL ARTICLE – BREAST ONCOLOGY

Heterogeneous Responses of Axillary Lymph Node Metastases to Neoadjuvant Chemotherapy are Common and Depend on Breast Cancer Subtype

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ABSTRACT

Background. The objective of this study was to analyze heterogeneous responses of axillary lymph node metastasis to neoadjuvant chemotherapy and to determine to what extent they differ between tumor subtypes (TN, HER2+, HR+/HER2−).

Methods. This retrospective, monocenter study included 72 consecutive, histologically node-positive breast cancers (cT1–4 cN1–3 cM0) diagnosed in the period from January 2015 to December 2016, who had received axillary lymph node dissection following neoadjuvant chemotherapy. All individual lymph node specimens were re-evaluated for the presence of tumor cells and chemotherapy effects to assess their response to neoadjuvant chemotherapy on an individual lymph node level according to the Sataloff classification.

Results. Heterogeneous axillary responses to neoadjuvant chemotherapy occurred in 47.2% of the included 72 patients. The partial response rate was significantly higher in HR+/HER2− tumors (74.2%) than in TN (28.6%) and HER2+ tumors (25.0%) ($p < 0.001$). The presence of at least one negative, completely responding lymph node in the axillary lymph node dissection specimen had a false-negative rate of 48.8% in predicting ypN0. It dropped below 10% if at least four completely responding negative lymph nodes were identified.

Conclusions. Our study shows that axillary heterogeneous response rates differ significantly between tumor subtypes.

With axillary pathological complete response (pN-CR) rates in invasive breast cancer reaching up to 65% under modern systemic treatment regimens, post-neoadjuvant axillary lymph node status is a powerful prognostic indicator.[1,2] It determines both overall and disease-free survival of patients receiving neoadjuvant chemotherapy (NACT), regardless of primary tumor response.[3,4]

While the ypN status is widely used to guide therapeutic decisions,[5] available data allows us to assume that the removal of noncancerous lymph nodes will not improve outcomes but could increase morbidity.[6] Furthermore, the ACOSOG Z0011 and the AMAROS trials have shown in the adjuvant setting that even leaving positive lymph nodes behind did neither significantly impact survival, nor nodal recurrence rates in patients receiving adjuvant radiotherapy.[7–9]

These results, which suggest that lymph node removal during axillary staging should primarily be used as a diagnostic tool instead of a therapeutic measure aiming to improve survival, have resulted in efforts to decrease the invasiveness in patients receiving neoadjuvant chemotherapy as well. The former standard for axillary staging after NACT in cN+ patients, axillary lymph node dissection (ALND), is associated with significant postoperative morbidity and possibly represents an overtreatment

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especially for converters to a negative lymph node status.[6,10] Therefore, efforts have been made to cut the aggressiveness of the procedure to reduce the associated morbidity.

Sentinel lymph node biopsy (SLNB) represents a less invasive alternative to ALND but has an increased false-negative rate (FNR) of 12.6–14.2% after NACT.[6,7,11] Uneven eradication of axillary lymph node metastasis due to reactive fibrosis and tumor debris altering the lymphatic drainage pattern has been suspected as a reason for the higher FNR of staging procedures after NACT.[12] However, this FNR has been reported to decrease to 9.1% if nuclear tracer and blue dye techniques are combined and if at least three sentinel nodes (SLNs) are removed during SLNB.[7] The clipping of a biopsy-proven metastatic lymph node, which is removed after NACT with or without a simultaneous sentinel lymph node biopsy, may decrease the FNR below 5% after NACT in initially cN+ patients.[13,14]

The purpose of this study was to describe the frequency and details of heterogeneous nodal tumor responses to NACT by examining each lymph node individually for tumor cells and signs of treatment effects and to compare the resulting nodal partial (pN-PR) and nodal mixed response (pN-MR) rates between tumor subtypes (TN, HER2+, HR+/HER2−). Our goal was to examine whether the identification of completely responding negative lymph nodes (LN-A) in the specimen of axillary dissection correlates with the odds of a pathological complete response of the entire nodal basin (ypN0).

METHODS

We included 72 consecutive female patients with primary invasive breast cancer and positive nodal status (cT1–4 cN1–3 cM0) diagnosed between January 2015 and December 2016 at our institution who underwent ALND after NACT.

Diagnostic Procedures, Neoadjuvant Therapy and Surgical Management

All patients received clinical routine, guideline-adherent diagnostic and therapeutic procedures, including radiotherapy, NACT regimens and adjuvant systemic treatment, according to current national and international guidelines.[15,16] The completion of the entire anthracycline- and taxane-based NACT regimen was an inclusion criterion. All included patients had breast-conserving surgery and therefore received adjuvant breast radiation with an intraoperative boost and radiotherapy of the regional lymphatic pathways. Axillary radiation was performed for all patients with ≥ 4 metastatic lymph nodes (> (y)cN2). As per standard protocol, for hormone receptor-positive patients, adjuvant endocrine therapy was administered with Tamoxifen or an aromatase inhibitor. For HER2-positive patients, Trastuzumab was added to the standard anthracycline-taxane chemotherapy regimen and then continued for 1 year total. Bisphosphonates were given at the beginning of the adjuvant therapy depending on the results of a guideline conforming risk assessment.

Tumors were classified as either hormone-receptor positive/HER2-negative (HR+/HER2−), HER2-positive (HER2+), or triple-negative (TN; estrogen-receptor negative, progesterone-receptor negative and HER2-negative). The initial clinical nodal status (cN1–3) prior to NACT was determined by axillary ultrasound and subsequently confirmed histologically.

ALND was performed after the completion of NACT in all patients. As histologic signs of tumor remission or therapeutic effect (defined as intranodular fibrosis and/or a foamy histiocytic infiltrate obliterating the nodal architecture and/or the presence of hemosiderin laden macrophages) in post-neoadjuvant axillary dissection specimen have been proven to be reliable indicators of prior nodal metastasis, these signs of tumor remission allowed us to identify former tumor involvement even in negative (ypN0) lymph nodes retrospectively and thereby to determine the exact number of completely or partially responding lymph nodes.[17]

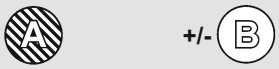
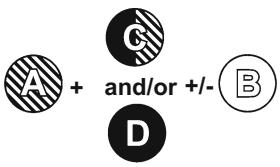
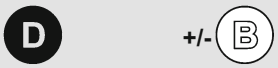
Pathological Lymph Node Evaluation and Definitions

Lymph nodes in the ALND specimens were serially sectioned and processed according to AGO guidelines.[18] Immunohistochemistry was performed only in cases, where the presence of residual tumor cells in resected lymph nodes could otherwise not be excluded. Each axillary lymph node was re-evaluated separately and assigned to one of four groups according to the presence or absence of regressive changes and/or metastases following the Sataloff classification.[19] Isolated tumor cells (ypN0(i+)) were interpreted as tumor involvement which led to the respective lymph node being classified as positive (ypN+). The response pattern of the entire axilla was categorized on the basis of individual lymph node reaction to NACT (Table 1):

- Nodal pathological complete response (pN-CR = ypN0)
- Nodal partial response (pN-PR)
- Nodal mixed response (pN-MR): A subgroup of pN-PR.
- Nodal stable disease (pN-SD)

pN-PR was defined as the heterogeneous response of axillary lymph node metastases to NACT. pN-MR, a

TABLE 1 Classification of the global axillary response to neoadjuvant chemotherapy

Global axillary response pattern	Definition	Individual lymph nodes contained in axilla
Nodal pathological complete response (pN-CR = ypN0)	Absence of any invasive tumor cells (including isolated tumor cells) with evidence of treatment effect	 LN-A (+/- LN-B)
Nodal partial response (pN-PR)	Lymph node metastasis responding to a variable extent to NACT	 Different combinations of LN-A and/or LN-C and/or LN-D (+/- LN-B)
Nodal mixed response (pN-MR)	Lymph node metastasis with no and/or partial response to NACT with presence of pathologically complete responding lymph nodes	 LN-A + LN-C and/or LN-D (+/- LN-B)
Nodal stable disease (pN-SD)	Lymph node metastasis without evidence of tumor regression	 LN-D (+/- LN-B)

* LN-A  Lymph node without tumor cells and with evidence of therapeutic effect

LN-B  Lymph node without tumor cells and without evidence of therapeutic effect

LN-C  Lymph node with tumor cells and with evidence of therapeutic effect

LN-D  Lymph node with tumor cells and without evidence of therapeutic effect

subgroup of pN-PR, was defined as the simultaneous presence of pathologically complete responding lymph node metastasis/es and lymph node metastasis/es with partial ± nonresponse (Table 1). In accordance with recent studies, a breast pCR was defined as the absence of vital invasive and non-invasive tumor cells in the breast (ypT0).[20]

In order to examine whether the presence of negative, completely responding lymph nodes (LN-A) in the axillary lymph node dissection specimen was associated with a complete response of all metastases in the entire axilla (ypN0), the false-negative rate was calculated by interpreting the presence of at least one, two, three, four, or five LN-A nodes as a negative test result.

Statistical Analysis

Because this was an explorative analysis, the resulting p values were not adjusted for multiplicity and thus have no confirmatory value. p values < 0.05 were regarded as statistically significant.

Reported rates and diagnostic measures were reported with standard deviation and/or corresponding 95% exact binomial confidence intervals (95% CI) in square brackets. Comparisons between subgroups were performed using Chi square tests for categorical data and using analysis of variance (ANOVA) for continuous data. All statistical analyses were performed using SPSS Statistics software version 24.0.

RESULTS

Patient Characteristics

Table 2 summarizes the characteristics of the study cohort. The median age of the 72 patients included in the analysis was 55 years at time of diagnosis. The mean tumor size was 33 mm (SD 18). Thirty-one (43%) patients had HR+/HER2− lesions, 20 (28%) had HER2+ lesions (of which 8 were estrogen receptor-positive and 12 estrogen receptor-negative), and 21 (29%) had TN disease. A total of seven patients had invasive-lobular carcinoma (9.7%), of which one tumor respectively was HER2+ and TN and five were HR+/HER2− tumors. The included tumors were classified as grade 2 (44.4%) and grade 3 (55.6%). There were no significant differences in age, size of the primary tumor, invasive tumor type, cT and cN stage based on tumor subtype. All included patients were clinically node positive according to axillary imaging (cN+), which was histologically confirmed.

A median of 13 lymph nodes was removed by ALND with no difference in the number of removed lymph nodes among different tumor subtypes. Of all 905 removed lymph nodes, the majority (530/905, 58.6% [55.3%; 61.7%]) were LN-B nodes (lymph nodes without tumor cells and without evidence of therapeutic effect, i.e., lymph nodes without metastases before and after NACT). In the 41 cases with residual axillary disease, containing all patients with a nodal partial response (pN-PR) or nodal stable disease (pN-SD), the percentages of positive lymph nodes was significantly different between tumor subtypes ($p < 0.001$). Affected HR+/HER2− axillae showed significantly more positive LN-C and LN-D nodes than TN axillae (43.3% [38.5%; 48.4%] vs. 25.2% [18.5%; 33.3%]; $p < 0.001$).

A pathologic complete response (pCR), defined as the absence of residual invasive or noninvasive tumor cells in both the primary breast tumor and in the axilla (ypT0 + ypN0), was achieved in 25 of 72 patients (34.7% [23.9%; 46.9%]) (Table 3). The pCR rate was different between the subgroups ($p < 0.001$): HR+/HER2− tumors showed the lowest pCR rate with 4 of 31 patients achieving a pCR (12.9% [3.6%; 29.8%]), TN tumors showed a pCR rate of 38.1% (8/21; [18.1%; 61.6%]) and HER2+ tumors had the highest pCR rate (13/20, 65.0% [40.8%; 84.6%]). Furthermore, in the HER2+ subgroup, all 8 estrogen-receptor negative (ER-) patients achieved a pCR (100.0% [67.6%; 100.0%], while the pCR rate of HER2+ ER+ patients reached 41.7% [19.3%; 68.1%] (5/12).

Of the 27 patients with ypT0 status post-NACT, 92.6% [75.7%; 99.1%] also converted to node-negative (ypN0), whereas only 13.3% [5.1%; 26.8%] of the 45 ypT+ patients achieved a nodal CR (ypN0).

TABLE 2 Study cohort

Variable	(%)
No. of patients	72
Age (year)	
Median	55
Minimum	32
Maximum	78
Size of primary tumor (mm)	
Mean	33
Standard deviation	18
Invasive tumor type	
Invasive-ductal	64 (88.9)
Invasive-lobular	7 (9.7)
Other	1 (1.4)
Tumor subtype	
Triple negative	21 (29.2)
HER2+	20 (27.8)
HR+/HER2−	31 (43.1)
cT	
cT1	11 (15.3)
cT2	33 (45.8)
cT3	14 (19.4)
cT4	14 (19.4)
cN	
cN1	63 (87.5)
cN2	6 (8.3)
cN3	3 (4.2)
Grading	
2	32 (44.4)
3	40 (55.6)
ALND	72 (100.0)
No. of LNs removed	
Median	13
Percentile 25	9
Percentile 75	16
No. of pos. LNs	
Median	1
Percentile 25	0
Percentile 75	5
% of pos. LNs	
Mean	20.2
ypT	
ypT0	27 (37.5)
ypT+	45 (62.3)
ypN	
ypN0	31 (43.1)
ypN+ (including ypN0(i+))	41 (56.9)

Absolute values with percentage share of the total number of patients given in round brackets

TN triple-negative, *HER2+* HER2-positive, *HR+/HER2−* hormone receptor-positive/HER2-negative, *ALND* axillary lymphonodectomy, *LNs* lymph nodes

TABLE 3 Nodal pathological response to neoadjuvant chemotherapy compared between different subtypes of breast cancer

	Gesamt	TN	HER2+	HR+/HER2-	*P*
No. Patients	72	21	20	31	
pCR, No. (%)	25 (34.7)	8 (38.1)	13 (65.0)	4 (12.9)	< .001***
95% CI (%)	[23.9; 46.9]	[18.1; 61.6]	[40.8; 84.6]	[3.6; 29.8]	
pN-CR, No. (%)	31 (43.1)	12 (57.1)	14 (70.0)	5 (16.1)	< .001***
95% CI (%)	[31.4; 55.3]	[34.0; 78.2]	[45.7; 88.1]	[5.5; 33.7]	
pN-PR, No. (%)	34 (47.2)	6 (28.6)	5 (25.0)	23 (74.2)	< .001***
95% CI (%)	[35.7; 58.7]	[11.3; 52.2]	[8.7; 49.1]	[55.4; 88.1]	
pN-MR, No. (%)	20 (27.8)	5 (23.8)	3 (15.0)	12 (38.7)	.162
95% CI (%)	[17.9; 39.6]	[8.2; 47.2]	[3.2; 37.9]	[21.9; 57.8]	
pN-SD, No. (%)	7 (9.7)	3 (14.3)	1 (5.0)	3 (9.7)	.665
95% CI (%)	[4.0; 19.0]	[3.1; 36.3]	[0.1; 24.9]	[2.0; 25.8]	
		pN-CR**, pN-PR**, pCR*			
			pN-CR***, pN-PR***, pCR***		

Absolute values with percentages given in round brackets and 95% confidence intervals of the percentage in square brackets. The *p* value is indicated in the rightmost column with brackets below additionally showing significant differences between the subgroups

pCR pathological complete response rate (ypN0 + ypT0), *pN-CR* nodal pathological complete response rate (ypN0), *pN-PR* nodal parial response rate, *pN-MR* nodal mixed response rate, *pN-SD* nodal stable disease rate, *TN* triple-negative, *HER2+* HER2 positive; *HR+/HER2−* hormone receptor positive/HER2-negative, *CI* confidence interval

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

Nodal Complete Response, Partial Response, Mixed Response, and Stable Disease Rates

An axillary complete response (pN-CR) was observed in 31 of 72 patients (43.1% [31.4%; 55.3%]) (Table 3). The axillary pN-CR rate was different between tumor subgroups ($p < 0.001$) with HER2+ tumors showing the highest pN-CR rate (14/20, 70.0% [45.7; 88.1%]), whereas HR+/HER2− tumors had the lowest pN-CR rate (5/31, 16.1% [5.5%; 33.7%]) (Table 3). In axillary pN-CR patients, 33.8% of lymph nodes showed evidence of tumor regression, and the remaining 66.2% were negative without observed treatment effect after NACT, i.e., lymph nodes without metastases before and after NACT.

Axillary partial responses (pN-PR), defined as a heterogeneous lymph node response to NACT, were seen in 34 of 72 patients (47.2% [35.7%; 58.7%]). Mixed responses (pN-MR), where pathologically complete responding lymph nodes (LN-A) were found next to metastatic lymph nodes with no and/or partial response to NACT (LN-D and/or LN-C), occurred in 20 of these 34 patients. The partial response rate was significantly higher in HR+/HER2− tumors (74.2% [55.4; 88.1%]) than in TN (28.6%, [11.3%; 52.2%) and HER2+ tumors (25.0% [8.7%; 49.1%]) ($p < 0.001$; Table 3).

After NACT, the axillae of seven patients remained positive and showed no evidence of treatment effect in the axilla resulting in a stable disease rate (pN-SD) of 9.7% [4.0%; 19.0%]) that did not differ between the subgroups (Table 3).

Within the HER2+ subgroup, we found a significantly different nodal response pattern between the 12 estrogen

receptor-positive and the 8 estrogen-receptor negative patients. While 100.0% [67.6%; 100.0%] (8/8) of the 8 estrogen-receptor-negative (ER-) patients achieved a nodal complete response (ypN0), the corresponding pN-CR rate for the 12 included HER2+ and estrogen receptor-positive (ER+) patients was 50.0% [25.4%; 74.6%] (6/12), with 41.7% [19.3%; 68.1%] (5/12) of ER+ patients showing a nodal partial response (pN-PR) and 8.3% [1.5%; 35.4%] (1/12) presenting with nodal stable disease (pN-SD).

Seven of the included patients (9.7%) had invasive-lobular carcinoma, and none of those lobular tumors achieved a nodal complete response (pN-CR) or pCR, whereas this subgroup showed a partial response rate (pN-PR) of 85.7% [48.7%; 97.4%] (6/7) and a stable disease rate (pN-SD) of 14.3% [26%; 51.3%] (1/7). Although the majority of those patients had HR+/HER2− disease, we found that omitting these invasive-lobular patients from the analysis did not have a major effect on the significance levels of the results shown above. The pCR ($p = 0.001$), pN-CR ($p < 0.001$), and pN-PR ($p = 0.002$**) rates are still significantly different between TN, HER2+, and HR+/HER2− subtypes if only the 65 invasive-ductal carcinomas are taken into consideration.

Correlation Between the Number of Completely Responding LN-A Nodes and Axillary Nodal Complete Response (ypN0)

The presence of at least one negative, completely responding lymph node (LN-A) in the axillary lymph node dissection specimen had a false-negative rate of 48.8% [34.3%; 63.5%] (20/41) in predicting a complete response of the entire axilla (ypN0) (Table 4). The false-negative rate decreased with an increasing number of removed LN-A nodes and dropped below 10% if at least four negative LN-A nodes were identified (FNR = 9.8% [3.9%; 22.5%], 4/41; Table 4).

TABLE 4 False-negative rate (FNR) for the exclusion of axillary metastatic disease (ypN0) according to the number of removed LN-A nodes

No. LN-A-LNs	FNR (%) 95% CI (%)
≥ 1	48.8 [34.3; 63.5]
≥ 2	36.6 [23.6; 51.9]
≥ 3	12.2 [5.3; 25.5]
≥ 4	9.8 [3.9; 22.5]
≥ 5	9.8 [3.9; 22.5]

All values are specified as percentages with 95% confidence intervals in square brackets

LN-A-LNs lymph nodes without tumor cells and with evidence of therapeutic effect, *FNR* false-negative rate, *CI* confidence interval

DISCUSSION

In this study, we assessed the frequency of a heterogeneous response of axillary lymph node metastasis to neoadjuvant chemotherapy and compared the resulting nodal partial (pN-PR) and nodal mixed response (pN-MR) rates vary between tumor subtypes (TN, HER2+, HR+/HER2−).

Although some prior studies have suggested that tumor remission depends mainly on tumor biology, which should be identical for axillary metastases originating from the same primary breast tumor, heterogeneous axillary responses (pN-PR) occurred in nearly half of the examined axillae (34/72; 47.2% [35.7%; 58.7%]).[21] The odds of these partial axillary responses furthermore differed significantly between tumor subtypes. We found that partial axillary responses occurred significantly more frequently in HR+/HER2− tumors than in TN and HER2+ subtypes. Within the HER2+ subgroup, all estrogen-receptor negative patients achieved a nodal complete response with consequently no axillary partial responses occurring in this group.

A significant influence of the tumor subtype on the axillary nodal response to NACT has previously only been shown for pCR rates (with pCR being defined as ypT0 and ypN0) and axillary complete response rates (pN-CR), which have been shown to be significantly higher in HER2+ and TN tumors than in HR+/HER2− tumors.[22–24] This observation was confirmed in our study as the pCR and pN-CR rate were five and four times higher respectively in HER2+ than in HR+/HER2− tumours ($p < 0.001$).

A previous study reporting on regression patterns after NACT in the primary breast tumor and in ALND and/or SLNB specimen reported a heterogeneous nodal response rate of 23.5%, which is in keeping with our findings, but found no significant association between molecular subtypes and the homogeneity of regression in lymph nodes, although heterogeneity of nodal responses was more frequent in Luminal A/B than in HER2+ and TN subtypes.[25]

Our finding that tumor biology also influences the odds of a heterogeneous axillary response seems to be of special interest considering recent efforts to decrease the invasiveness of post-neoadjuvant axillary staging in a time where new post-neoadjuvant treatment regimens are

becoming available for non-pCR patients. Axillary staging after NACT is particularly important in initially node-positive (cN+) patients, because post-neoadjuvant axillary lymph node status is one of the strongest prognostic factors to guide further treatment and because high nodal conversion rates of around 40% reaching up to 65% in HER2+ tumors have been shown in recent studies as well as in our own analysis.[7,26,27]

In summary, in the setting of NACT, the failure to identify metastatic lymph nodes may potentially entail missing crucial information for post-neoadjuvant treatment plans, while the resection of non-metastatic lymph nodes may aggravate morbidity.[6,10] Therefore, post-neoadjuvant SLNB has been proposed as an alternative in order to decrease the invasiveness of the staging procedure. Recent studies found a FNR of 12–14% for post-neoadjuvant SLNB.[7,28] While a general consensus on axillary management in the post-neoadjuvant setting has not yet been reached, increased use of SLNB and decreased use of ALND have been reported in cN1 breast cancer patients treated with NACT at some institutions.[29] Furthermore, the recent AMAROS study and the ACOSOG trial have shown that in a defined subgroup of patients with minimal residual disease (1–2 positive sentinel lymph nodes, T1/2) after NACT, a completion ALND might be safely replaced by axillary radiotherapy or even omitted without compromising axillary control.[7–9] These results emphasize the importance of an exact post-neoadjuvant axillary staging in order to accurately distinguish patients with minimal or no residual disease from those in need of additional axillary surgery.

In this context, our results showing a higher rate of nodal partial responses (pN-PR) in HR+/HER2− subtypes suggest that a surgically removed negative lymph node might be less representative of the whole axilla's response to NACT in HR+/HER2− than in HER2+ and TN tumors. This could explain the significantly higher FNR of post-neoadjuvant SLNB in luminal (HR+/HER2−) than in nonluminal (HR-) tumors that has been described in the literature[28] and could help to guide patient selection for the omission of ALND after NACT.

Although the influence of a higher FNR on survival and locoregional and systemic recurrence rates has not yet been thoroughly examined, different procedures have been developed to lower the FNR of post-neoadjuvant axillary staging. Axillary lymph node sampling (ALNS), the non-directional removal of 3–6 palpable axillary lymph nodes, is widely practiced instead of SLNB as a less invasive alternative to ALND[30,31] as the combination of SLNB and ALNS reportedly has a significantly lower false-negative rate than SLNB alone (3.6% vs. 14.3%).[32,33] This technique is based on the assumption that the removal of additional, randomly selected lymph nodes allows a better detection of residual axillary disease and thereby lowers the FNR of post-neoadjuvant staging.

Conversely, new targeted approaches aiming to remove a few selected lymph nodes whose reaction to NACT is thought to be representative of the entire axilla's response, have been proposed. Such new procedures are the Targeted Axillary Dissection (TAD) and MARI (Marking the Axilla with Radioactive Iodine seeds), where a metastatic lymph node is marked before the start of NACT and located and removed with or without the SLNs after NACT. If the clipped node alone (and no additional SLN) is evaluated post-NACT, TAD and MARI have a reported FNR of 4% and 7% respectively, while the identification rate for the clipped node reaches 94% and 97%.[13,14] Because pre-neoadjuvant axillary staging currently relies heavily on axillary ultrasound, which has been shown to provide at best a moderate diagnostic accuracy, the advent of these new targeted procedures may entail priorization of the sensitivity of the pretherapeutic staging to be able to identify, biopsy, and mark all suspicious lymph nodes before NACT.[34] This in turn might lead to an overtreatment of the cN+ group.

Our results suggest that the undirected random sampling of lymph nodes following NACT does not reliably predict the nodal status of the entire nodal basin, even if they show signs of complete disease regression. Conversely, in targeted procedures, such as SLNB, TAD, and MARI, the excised lymph nodes are specifically chosen for analysis due to their sentinel function in the lymphatic system or due to their size or abnormal appearance on ultrasound prior to neoadjuvant chemotherapy. These methods seem to provide far lower false-negative rates.[13,14] This allows us to hypothesize that the lymph nodes removed by SLNB, TAD, and MARI might be more representative of the entire axilla's reaction to NACT. The currently ongoing RISAS trial might confirm this hypothesis. The purpose of this trial is to validate the RISAS procedure (Radioactive Iodine Seed localization in the Axilla with the Sentinel node procedure), a combination of the MARI procedure with a sentinel lymph node biopsy. If this targeted axillary staging technique proves to be accurate, it could replace post-neoadjuvant ALND in the assessment of the axillary response to NACT.[35]

While our study is a monocenter series of consecutive node positive breast cancer patients receiving NACT in a 2-year period, the limited number of cases, of which 9.7% were lobular carcinomas, with even smaller groups for the subgroup analyses, still precludes definitive conclusions. Because of the high pCR rate of 43%, only the remaining 41 patients were available for the detailed analysis of heterogeneous axillary partial responses. However, the clearly observed higher partial response rate together with

a lower complete response rate in HR+/HER2− tumors compared with HR-negative tumors seems to be conclusive.

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DISCLOSURE None.

ETHICAL STANDARD The study was approved by the ethics committee of the University of Heidelberg (reference number: S-241/2017). All procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments.

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