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Tailored axillary surgery in patients with clinically node-positive breast cancer: Pre-planned feasibility substudy of TAXIS (OPBC-03, SAKK 23/16, IBCSG 57-18, ABCSG-53, GBG 101)[☆]



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ABSTRACT

Aim: We developed tailored axillary surgery (TAS) to reduce the axillary tumor volume in patients with clinically node-positive breast cancer to the point where radiotherapy can control it. The aim of this study was to quantify the extent of tumor load reduction achieved by TAS.

Methods: International multicenter prospective study embedded in a randomized trial. TAS is a novel pragmatic concept for axillary surgery de-escalation that combines palpation-guided removal of suspicious nodes with the sentinel procedure and, optionally, imaging-guided localization. Pre-specified study endpoints quantified surgical extent and reduction of tumor load.

Results: A total of 296 patients were included at 28 sites in four European countries, 125 (42.2%) of whom underwent neoadjuvant chemotherapy (NACT) and 71 (24.0%) achieved nodal pathologic complete response. Axillary metastases were detectable only by imaging in 145 (49.0%) patients. They were palpable in 151 (51.0%) patients, of whom 63 underwent NACT and 21 had residual palpable disease after NACT. TAS removed the biopsied and clipped node in 279 (94.3%) patients. In 225 patients with nodal disease at the time of surgery, TAS removed a median of five (IQR 3–7) nodes, two (IQR 1–4) of which were positive. Of these 225 patients, 100 underwent ALND after TAS, which removed a median of 14 (IQR 10–17) additional nodes and revealed additional positive nodes in 70/100 (70%) of patients. False-negative rate of TAS in patients who underwent subsequent ALND was 2.6%.

Conclusions: TAS selectively reduced the tumor load in the axilla and remained much less radical than ALND.

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1. Introduction

Over the last decade, axillary surgery has been de-escalated in selected clinically node-negative patients with positive sentinel lymph nodes (SLNs) [1–6]. In recent years, this trend also involved clinically node-positive patients with nodal pathologic complete response (pCR) after neoadjuvant chemotherapy (NACT) [7-12]. Axillary lymph node dissection (ALND) remains standard of care in the upfront surgery setting in most patients with palpable nodal disease. Patients with non-palpable axillary disease detected by preoperative imaging were eligible for the axillary surgery deescalation landmark trials ACOSOG Z0011 and EORTC-AMAROS [1,2]. However, a series of observational studies consistently showed that patients with imaging-detected and biopsy-confirmed metastases have a higher burden of nodal involvement than patients with SLN-detected metastases, thereby questioning the routine omission of ALND in these patients [13–19]. Moreover, ALND is indicated in most patients with residual disease after NACT [20]

We developed a novel approach called tailored axillary surgery (TAS) for patients with clinically node-positive breast cancer during upfront surgery and after NACT. The concept of TAS is to turn a clinically positive axilla into clinically negative primarily by palpation-guided selective removal of obvious nodal disease,

thereby tailoring the extent of axillary surgery to the extent of axillary disease. The concept also includes the sentinel lymph node (SLN) procedure to reduce the volume of microscopic disease. The aim of TAS is to decrease the tumor load in the axilla to the point where adjuvant regional nodal irradiation (RNI) can control it. The ongoing international TAXIS trial (SAKK 23/16/IBCSG 57-18/ABCSG-53/GBG 101; ClinicalTrials.gov Identifier: NCT03513614, see supplementary protocol) [21] will determine if TAS in combination with RNI is oncologically non-inferior and associated with improved quality of life (QoL) compared to ALND. Most surgeons consider it impossible to determine positive lymph nodes by clinical palpation alone, particularly in the neoadjuvant setting. Therefore, we pre-specified the present subproject during early stage of patient accrual in TAXIS [21] to study the difference in surgical extent between TAS and ALND and to quantify the extent of tumor load reduction by TAS.

2. Materials and methods

2.1. Study design and patient population

This was an international multicenter prospective study embedded in the randomized TAXIS [21] trial. Patients with clinically node-positive breast cancer were included, defined as nodal



Fig. 1. The concept of tailored axillary surgery (TAS).

disease detected by palpation or imaging at the time of initial diagnosis. Histologic or cytologic confirmation of breast cancer was required both in primary tumor and lymph node. Patients were included in both the upfront surgery setting and in case of residual nodal disease after NACT. Patients with stage IV, cN3c or cN2b breast cancer, contralateral or other tumor malignancy within 3 years, prior axillary surgery (except SLN) or prior axillary radiotherapy were considered ineligible. The patient population included the first 200 consecutive TAXIS patients and all patients (n = 96) that were screening failures during the same period due to a) absence of clip in specimen radiography, b) palpable disease left behind in the axilla after TAS, c) failure to identify the SLN, and d) nodal pCR after NACT (see appendices, page 30, Figure A1: Prespecified prospective study population embedded in TAXIS trial). These 296 patients were treated between August 07, 2018, and April 02, 2020.

The TAXIS trial and the present prospective substudy were approved by the local ethics committees and were performed in accordance with the requirements of the national regulatory authorities. Written informed consent was obtained from all patients.

2.2. Surgical management

The initially sampled and histologically or cytologically positive node was marked with a clip. TAS was defined by palpation-guided selective removal of presumed nodal disease in combination with the SLN procedure, while the sequence of the individual steps was left to the surgeon's discretion. Imaging-guided localization of the clipped node and other suspicious nodes to facilitate surgical removal is conceptually encouraged in TAS, but not mandatory (Fig. 1).

TAS was designed to turn a clinically node-positive axilla into clinically negative by removing all palpably obvious disease. Microscopic tumor volume is further reduced in the axilla by identifying and removing all lymph nodes with tracer uptake. We acknowledged that TAS cannot reflect a procedure as standardized as ALND, because it was designed to de-escalate axillary surgery in a personalized fashion. Therefore, we expected that the pragmatic concept of TAS will result in inter-surgeon variability. This substudy was pre-specified to evaluate the translation of this concept into practice.

The SLN technique was left to the discretion of the operating surgeon, while dual mapping was recommended. ALND primarily cleared levels I and II. A full level III dissection was carried out only when there was gross nodal disease detected by palpation or imaging.

2.3. Pathologic and radiologic evaluation

Pathologic evaluation was not centralized and performed according to the lymph node processing protocol at the local pathology department. Nodal pathologic complete response was defined as absence of any nodal disease after NACT, including isolated tumor cells, which, however, were classified as ypN0 (i+) according to TNM staging in the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, eighth edition [22]. Specimen radiography was performed on all removed lymph nodes to document removal of the clip during surgery. Systemic radiologic staging was performed within two months before registration. Repeat staging after NACT was optional. Residual suspicious lymph nodes detected by imaging performed for radiotherapy treatment planning or re-staging before the end of adjuvant treatment neither demanded nor prohibited take back surgery for completion ALND or selective removal of these nodes or an additional radiotherapy boost.

3. Aims

The primary aim of the present study was to quantify the extent of residual disease after TAS. Therefore, we registered a) number of positive nodes removed by TAS, b) number of positive nodes removed by ALND after TAS, c) number of negative nodes removed by TAS, d) number of negative nodes removed by ALND after TAS, e) number of failed identification and removal of SLNs, f) number of patients taken back for surgery before start of radiotherapy for residual disease suspected by imaging, and g) number of patients receiving an extra radiation boost for residual disease suspected by imaging before end of adjuvant treatment. The following performance characteristics were added post-hoc: False-negative rate (FNR) was calculated as the number of patients with negative nodes during TAS who were found to have positive nodes by subsequent ALND, divided by the total number of patients with positive nodes detected by ALND and/or TAS. Negative predictive value (NPV) was defined as the number of true negative cases for TAS, divided by the total number of all pathologically negative cases detected by TAS. Diagnostic accuracy (DA) was defined as the number of true positive plus the number of true negative cases, divided by all cases.

3.1. Statistical analysis

This analysis includes the first 200 TAXIS patients as well as the 96 patients pre-registered but not randomized in TAXIS during this time period. Continuous endpoints were summarized using median and interquartile range (IQR). Categorical endpoints were summarized using frequency counts and percentages and compared between subgroups of interest using Fisher's exact test. Two-tailed tests with a significance level of 0.05 were used. No adjustment was made for multiple testing and all analyses are considered exploratory. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

4. Results

A total of 296 patients with a median age of 57 years (range: 25–88 years) were included at 28 breast centers in Switzerland, Hungary, Germany and Austria (Table 1).

At time of initial diagnosis, lymph node metastases were palpable in 151 (51.0%) and detectable only by imaging in 145 (49.0%) patients (Fig. 2 and appendices, page 31, Table A1: Patient and tumor characteristics by palpable versus non-palpable nodal disease).

According to the preferences of the treating physicians and institutions, 125 (42.2%) underwent NACT, of whom 71 (24.0%) achieved nodal pCR. The median age of patients who underwent NACT was 50 years (interquartile range [IQR] 44–58) compared to 61 years (IQR 50–73) in the upfront surgery setting (p < 0.001). In addition, patients undergoing NACT had higher clinical nodal stage at initial diagnosis, more Her-2 positive and triple negative disease, and higher tumor grade (all p < 0.001, Table 2).

TAS successfully removed the clipped node in 279 (94.3%) patients. The clipped node corresponded to a node with SLN tracer uptake in 197 (66.6%) of patients. It was localized under imagingguidance in 183 (61.8%) and was considered palpably obviously suspicious by surgeons in 139 (47%). In the entire patient population that included patients with nodal pCR, the median number of lymph nodes removed by TAS was four (IQR 3–7), one (IQR 0–3) of which was positive (see appendices, page 33, Table A2: Characteristics of tailored axillary surgery and axillary lymph node dissection). Surgeons estimated to have removed and labeled a median of 2 (IQR 1–3) nodes with SLN tracer uptake that corresponded to a median of 3 (IQR 2–4) nodes when counted by the pathologists, one of which was positive (IQR 0–2). Presumed palpable disease could not be removed by TAS in two (0.7%) patients. Three patients (1.0%) had no tracer uptake in palpable and non-palpable nodes.

FNR of TAS in patients who underwent subsequent ALND was 1.8%, NPV was 95.5%, and DA was 98.3%. Clip removal rate, FNR, NPV and DA for the overall cohort and by upfront surgery versus NACT are shown in Table 3.

In 225 patients with nodal disease at the time of surgery -in case of upfront surgery or residual disease after NACT- TAS removed a median of five (IQR 3–7) nodes, two (IQR 1–4) of which were positive. Two [IQR 1–3] of these nodes were considered palpably

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Table 1

Patient and tumor characteristics.

Variable	No. (%)
No. of patients	296 (100.0%)
Age, years	
Median (IQR)	57 (46, 68.5)
Age, years	
\leq 50	112 (37.8%)
>50	184 (62.2%)
No	170 (57 4%)
Ves	170 (37.4%)
Unknown	1 (0.3%)
Nodal pCR rate after neoadjuvant therapy	71 (24.0%)
Type of breast surgery	. ,
Breast conserving	179 (60.5%)
Mastectomy + - reconstruction	116 (39.2)
None ^a	1 (0.3%)
Tumor size at initial diagnosis, mm	20 (20 40)
Median (IQR)	28 (20, 40)
	1 (0.3%)
T1	67 (22.6%)
T2	189 (63.9%)
T3	28 (9.5%)
T4	9 (3.0%)
Tis (DCIS)	1 (0.3%)
Tx	1 (0.3%)
Clinical N stage at initial diagnosis	105 (10 000)
NI by palpation	137 (46.3%)
N1 Dy IIIIagilig N2/3	130 (43.9%)
Postoperative N stage	23 (1.0%)
pN0	5 (1.7%)
pN1mi	0 (0.0%)
pN1	102 (34.5%)
pN2	39 (13.2%)
pN3	20 (6.8%)
ypN0	71 (24.0%)
yphu(IIC)	2(0.7%)
ypN1 ypN2	40 (15.5%) 9 (3.0%)
vpN3	2 (0.7%)
Histology	_ ()
Invasive ductal	223 (75.3%)
Lobular	27 (9.1%)
Other	46 (15.5%)
Receptor status at initial diagnosis	
HR+/Her2-	187 (63.2%)
HK+/Her2+	42 (14.2%)
HR-/Her2-	10 (J.4%) 35 (11.8%)
Missing/unknown	16 (5 4%)
LVI	10 (0110)
Yes	147 (49.7%)
No	138 (46.6%)
Missing/unknown	11 (3.7%)
Modified Bloom-Richardson score	
l u	11 (3.7%)
	162 (54.7%)
m Missing/unknown	110 (39.2%) 7 (2 <i>4</i> %)
	· (2.7/0)

Abbreviations: IQR, interquartile range; pCR, pathologic complete response; NST, no special type; LVI, lymphovascular invasion.

^a Primary tumor was inoperable and surgical treatment consisted exclusively of axillary surgery.

obviously suspicious by surgeons. Three [IQR 2–4] of these nodes were radioactive and/or blue. Of 100 patients with confirmed nodal disease at the time of surgery who underwent ALND following TAS in the TAXIS trial, only 6 (6%) underwent axillary radiation. A median number of 14 (IQR 10–17) additional lymph nodes were removed by ALND and a median of 1.5 (IQR 0–5.5) were positive.



Fig. 2. Study population by palpable versus non-palpable axillary disease.

Additional positive nodes were removed in a total of 70 (70%) patients. Of 100 patients with confirmed nodal disease at the time of surgery who underwent TAS without ALND in the TAXIS trial, 93 (93%) underwent axillary radiation. No patient underwent axillary redo surgery and two patients received a radiation boost for residual suspicious findings in the axilla on imaging before the end of adjuvant treatment.

Imaging-guided localization was attempted in 257 patients (86.8%) and was successful in 242 (81.8%). Various types of clips and imaging-guided localization techniques were used (Table 4).

There was no significant difference in the rate of clip removal by use of imaging-guided localization (94.6% (243/257) with vs. 92.3% (36/39; p = 0.47) without), but a trend toward lower rate of clip removal after NACT (91.2% (114/125) with vs. 96.5% (164/170) without NACT (p = 0.075). There was a trend toward a lower median number of lymph nodes removed during TAS when imaging-guided localization was performed (4 [IQR 3–7] vs 6 [IQR 4–7]; p = 0.09). Type of clip was not associated with successful surgical removal of the clipped node in patients with nodal disease at the time of surgery (p = 0.197) and in patients with nodal pCR (p = 0.875; appendices, page 35, table A3: Successful surgical removal of clipped node by type of clip).

5. Discussion

The study showed that TAS removed the clipped node in 94.3% of patients and that TAS was much less radical than ALND in terms of the number of nodes removed. After omission of ALND after TAS, only two patients received an extra radiotherapy boost and no patient underwent axillary redo surgery for suspected residual disease. More than half of patients underwent upfront surgery, 85% of whom had estrogen receptor positive and Her-2 negative disease, which reflects current clinical practice at the 28 participating sites from four European countries.

TAS is not a novel surgical procedure, but a new concept that combines several surgical techniques to achieve tumor load reduction in a population of patients where ALND is still standard care. The individual steps, however, are either identical or related to known procedures. Targeted removal of palpable lymph nodes, for example, is inspired by a procedure called axillary node sampling [23,24]. During TAS, however, palpation is used to identify clearly abnormal nodes, with the limitations described above. The SLN procedure was defined in line with previous landmark studies in patients with biopsy-proven node-positive breast cancer [7,25]. While palpably suspicious findings are mostly not encountered during a SLN procedure outside of this experimental setting-because they are considered one of its contraindications when detected before surgery-they are routinely expected and targeted during TAS. Another difference to standard SLN techniques refers to the localization of the clipped node with use of modern-day imaging.

Patients in TAXIS are at the far end of the risk spectrum of nodepositive breast cancer with the highest stages ever studied in axillary surgery de-escalation trials. It was not surprising that ALND removed additional positive nodes in 70% of patients after TAS. While all of these patients received axillary radiation to levels I-IV and mostly also to the internal mammary chain, it is important to wait for the results of TAXIS to confirm oncologic safety before replacing ALND by TAS in clinical practice. In Z0011, 27% of patients had additional positive nodes removed by ALND in the control group. Most patients in the SLN only group did not develop regional recurrence [2,3,26], even though available data on radiation fields suggest that many of them did not receive directed nodal irradiation [27]. Results were similar in EORTC AMAROS, where additional lymph nodes metastases were found in 33% of patients who underwent ALND [1]. Contemporary findings in patients with lymph nodes detected by either physical exam or imaging and treated with surgery first showed that more than 40% of breast cancer patients with clinically positive nodes had minimal nodal disease (pN1) at surgery [28]. Finally, even the old landmark trial NSABP B-04 showed no significant differences in disease-free and overall survival in women with palpable nodal disease among those who

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Table 2

Patient and tumor characteristics by use of neoadjuvant chemotherapy versus upfront surgery.

Variable	Neoadjuva (N = 125)	int therapy	Upfront Sur	rgery (N = 166)	p-value
	n	(%)	n	(%)	
Node positivity (categorized)					0.89
Node-positivity detected by imaging and non-palpable (62	(49.6%)	81	(48.8%)	
Node-positivity palpable (cN1-3)	63	(50.4%)	85	(51.2%)	
Clinical N stage at initial diagnosis		. ,		. ,	0.001
N1 by imaging	56	(44.8%)	78	(47.0%)	
N1 by palpation	51	(40.8%)	83	(50.0%)	
N2/3	18	(14.4%)	5	(3.0%)	
Clinical T stage					0.36
cTO	1	(0.8%)	0	(0.0%)	
cT1b	6	(4.8%)	5	(3.0%)	
cT1c	25	(20.0%)	30	(18.1%)	
cT2	74	(59.2%)	112	(67.5%)	
cT3	16	(12.8%)	11	(6.6%)	
cT4a	1	(0.8%)	0	(0.0%)	
cT4b	2	(1.6%)	5	(3.0%)	
cT4c	0	(0.0%)	1	(0.6%)	
cTis (DCIS)	0	(0.0%)	1	(0.6%)	
cTx	0	(0.0%)	1	(0.6%)	
Postoperative N stage					<.001
pN0	0	(0.0%)	5	(3.0%)	
pN1	0	(0.0%)	102	(61.4%)	
pN2	0	(0.0%)	39	(23.5%)	
pN3	0	(0.0%)	20	(12.0%)	
ypN0	71	(56.8%)	0	(0.0%)	
ypN0 (i+)	2	(1.6%)	0	(0.0%)	
ypN1	42	(33.6%)	0	(0.0%)	
ypN2	8	(6.4%)	0	(0.0%)	
ypN3	2	(1.6%)	0	(0.0%)	
Tumor type					0.07
Invasive ductal	96	(76.8%)	123	(74.1%)	
Invasive lobular	6	(4.8%)	20	(12.0%)	
Other	23	(18.4%)	23	(13.9%)	
Tumor receptor subtype					<.001
HR+/HER2+	33	(26.4%)	8	(4.8%)	
HR+/HER2-	44	(35.2%)	141	(84.9%)	
HR-/HER2+	13	(10.4%)	2	(1.2%)	
HR-/HER2-	30	(24.0%)	5	(3.0%)	
Missing	5	(4.0%)	9	(5.4%)	
Unknown	0	(0.0%)	1	(0.6%)	
Tumor grade	_		_		<.001
G1	3	(2.4%)	8	(4.8%)	
G2	51	(40.8%)	107	(64.5%)	
G3	65	(52.0%)	50	(30.1%)	
Unknown	6	(4.8%)	1	(0.6%)	

Note: Five patients who received neoadjuvant therapy other than chemotherapy are not shown here.

Table 3

Clip removal rate, FNR, NPV and DA for the overall cohort and by upfront surgery versus NACT.

				_
Clip removal rate 94.3% 96.4% 91.2% FNR 1.8% 2.4% 0% NPV 95.5% 92.3% 100% DA 08.2% 97.6% 100%	Clip removal rate S FNR 1 NPV S DA S	e 94.3% 96.4% 1.8% 2.4% 95.5% 92.3%	91.2% 0% 100%	

had the axilla irradiated as compared with those who had the lymph nodes removed [29]. These findings make us believe that outcomes will be favorable in the TAXIS trial.

In the present study, 51% of patients had palpable metastases at diagnosis and 57.4% underwent upfront surgery. Accordingly, the

clipped node was considered to be palpably suspicious during surgery in almost half of patients (47%). While use of imagingguided localization was associated with a trend toward less lymph nodes removed (p = 0.09), it did not improve the high detection rate of the clipped node by TAS. These are fundamental differences to the use of the SLN procedure or targeted axillary dissection (TAD) as diagnostic staging procedures to determine nodal pCR after NACT [7–12,30]. Such contemporary diagnostic concepts foresee further surgery when residual disease is found in the nodes. In addition, they are usually applied in the absence of palpably suspicious findings and TAD by definition requires imaging-guided localization. A recent prospective registry study of patients undergoing neoadjuvant systemic therapy at 50 German centers validated the performance of TAD in general, but showed that the clipped node is missed in a significant number of patients [31]. On a global scale, the SLN procedure is the most commonly

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Table 4

Marking	f of	sami	pled	node	with	clip	and	imagin	g-guid	led	localiz	ation
	, •••	Juni	o re a	moue		- P					o camb.	

Variabla	Nia (9/)
Variable	NO. (%)
Imaging modality used to clip the node	N = 296
Ultrasound	293 (99.0%)
Type of clip used to mark the positive node	N = 296
Direct magseed	16 (5.4%)
Direct radioactive seed	1 (0.3%)
Nitinol ring marker (nickel titanium alloy)	91 (30.7%)
Titanium or stainless steel marker with gel	92 (31.1%)
Titanium or stainless steel marker without gel	88 (29.7%)
Imaging-guided localization of the clipped node: attempted	N = 296
Yes	257 (86.8%)
No	39 (13.2%)
Imaging-guided localization of the clipped node: successful	N = 257
Yes	242 (94.2%)
Unsure	7 (2.7%)
No	8 (3.1%)
Reason for failure	N = 257
Clip not visible	6 (2.3%)
Wire missed target	2 (0.8%)
Localization performed before surgery	185/257
	(72.0%)
Imaging modality used to localize the clipped node (before	
surgery)	100 (07 20)
Ultrasound	180 (97.3%)
Computed tomography	2(1.1%)
Type of localization used (before surgery)	- (0 - 00)
Magseed	5 (2.7%)
ROLL	52 (28.1%)
Radioactive seed	21 (11.4%)
Tattoo	4 (2.2%)
Wire	93 (50.3%)
Other	10 (5.4%)
Localization performed during surgery:	72/257 (28.0%)
Type of localization used (during surgery)	N = 72
Tattoo	2 (2.8%)
Wire	43 (59.7%)
Ultrasound alone	21 (29.2%)
Other	6 (8.3%)

performed procedure to determine nodal pCR and omit ALND in this setting, with several recent observational studies supporting its oncologic safety [32–35]. Importantly, nodal pCR is not known at the time of surgery in many clinically node-positive breast cancer patients undergoing NACT, since modern day imaging is not capable of reliably detecting or excluding residual disease after NACT [36]. From a technical (as opposed to conceptual) point of view, therapeutic TAS can eventually turn out to be similar to diagnostic TAD in the subset of TAXIS patients with no palpably suspicious nodes when NACT is used and imaging to localize the clipped node. Therefore, it is reassuring to see the low FNR of 1.8% for TAS, which was comparable to the results from prospective studies on TAD [31,37].

In the neoadjuvant setting, Alliance A011202 (ClinicalTrials.gov Identifier: NCT01901094) overlaps with TAXIS in the patient population with palpable axillary disease that turns into a clinically negative axilla with residual disease in the SLN. A recent retrospective analysis of the National Cancer Database observed inferior survival associated with the omission of ALND in patients with residual nodal disease following NACT [38]. Nevertheless, accrual is high in both trials, implying limited skepticism among investigators in the US and in Europe to include patients into a trial where half of patients with residual disease do not undergo ALND. In fact, the 2021 St. Gallen consensus conference revealed substantial disagreement among experts when asked about the omission of ALND in the setting of micrometastatic residual disease [39]. Importantly, TAXIS also includes patients whose axillary disease remains palpable after NACT, which accounted for 7% of patients overall and to exactly one third (21 of 63) of patients with upfront palpable disease undergoing NACT (Fig. 2).

This study has several limitations, mainly due to the pragmatic concept of TAS. Firstly, we refrained from pre-defining and collecting enough variables to accurately assess the relative contribution of the individual steps of TAS to the reduction of tumor load in the axilla, which, in turn, makes it impossible to know if palpation-, SLN tracer-, or imaging-guided removal of nodes was most effective. For the same reason, we were not able to assess differences in number of removed nodes with SLN tracer uptake by use of single versus dual agent mapping. Secondly, while the resulting heterogeneity of the patient population will facilitate applicability and generalizability of the results, it complicates statistical analysis and interpretation due to numerous stratification factors and preplanned subgroup analyses.

6. Conclusions

In summary, TAS was feasible with removal of the sampled node, the SLNs and all palpably obvious disease in the vast majority of the 296 patients, with no further improvement by imagingguided localization. TAS selectively removed positive lymph nodes and remained much less radical than ALND, but subsequent ALND removed additional positive nodes in 70% of patients after TAS. The ongoing TAXIS trial will determine whether axillary treatment by TAS and radiotherapy is oncologically non-inferior and associated with improved QoL compared to ALND in patients with clinically node-positive breast cancer.

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All other authors declare no competing interests relevant to this manuscript.

Appendix



Fig. A.1Pre-specified prospective study population embedded in TAXIS trial.

Table A.1

Patient and tumor characteristics by palpable versus non-palpable nodal disease

No. of patients: 151 145 Median (UQR) 55 (45-69) 57 (47-67) Age year 62 (41.15) 50 (34.53) >50 89 (88.95) 95 (65.53) Neoadjuvant chemotherapy 87 (57.66) 83 (57.23) No 87 (57.66) 83 (57.23) Yes 63 (41.72) 62 (42.83) Unknown 10 (073) 0 (003) Nodal pCF rate after neoadjuvant therapy 36 (23.85) 35 (24.15) Type of broats surgery 87 (37.75) 59 (40.73) Breast conserving 93 (61.65) 86 (59.33) Mastectomy - reconstruction 57 (27.75) 59 (40.73) None* 100.73) 100.73) Tar 37 (24.53) 30 (20.73) Ta 15 (9.93) 13 (9.05) Ta 15 (9.93) 13 (9.05) Ta 16 (2.85) 5 (3.43) Ta 16 (9.93) 16 (9.23) Ta 10 (0.73) 0 (0.03) Ta 10 (0.73) 0 (0.03) Ta	Variable	Palpable nodal disease No. (%)	Non-palpable nodal disease No. (%)
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"presst conserving" 91 (61.6%) 86 (59.3%) Mastectomy + = reconstruction 57 (37.7%) 59 (40.7%) None* 1 (0.7%) 28 (21-40) Tumor size at initial diagnosis, mm 0 (0.0%) 1 (0.7%) Th 37 (24.5%) 30 (20.7%) T1 37 (24.5%) 30 (20.7%) T2 39 (61.6%) 96 (66.2%) T3 15 (9.9%) 13 (9.0%) T4 4 (26.5%) 5 (3.4%) T5 (DCIS) 1 (0.7%) 0 (0.0%) Tx 1 (0.7%) 0 (0.0%) Tx 0 (0.0%) 13 (9.9%) Tx 1 (0.7%) 0 (0.0%) Tx 1 (0.7%) 1 (0.0%) <td< td=""><td>Type of breast surgery</td><td></td><td> ()</td></td<>	Type of breast surgery		()
Mater 57 (37.7%) 59 (40.7%) None* 1 (0.7%) ************************************	Breast conserving	93 (61.6%)	86 (59.3%)
None* 1 (0.72) Tumor size initial diagnosis mm 28.5 (20-40) 28 (21-40) Clinical T stage at initial diagnosis 0 0.00%) 10.07%) T1 0.00%) 0.027%) 0.027%) T2 93 (61.6%) 0.96 (66.2%) 0.00%) T3 15 (9.9%) 13 (9.0%) 13 (9.0%) T4 42 (26%) 5 (3.4%) 0.00%) Tx 10.07%) 0 (0.0%) 0.00%) Tx 10.07%) 0 (0.0%) 0.00%) Tx 0 (0.0%) 13 (9.0.3%) 0.00%) Tx 10.07%) 0 (0.0%) 0.00%) Tx 10.07%) 0 (0.0%) 0.00%) Tx 10.07%) 0 (0.0%) 0.00%) N2/3 0 (0.0%) 0 (0.0%) 0.00%) PN1 5 (3.64%) 47 (32.4%) pN1 5 (6.64%) 5 (3.4%) pN1 5 (6.64%) 5 (3.4%) pN1 5 (6.64%) 5 (3.4%) pN1 2 (14.68%)	Mastectomy + - reconstruction	57 (37.7%)	59 (40.7%)
Tumo size at initial diagnosis, mm 28 (21–40) Median (10R) 28 (20–40) To 1000) 10.73) T1 37 (24.5%) 96 (66.2%) T2 93 (61.6%) 96 (66.2%) T3 15 (9.9%) 13 (9.0%) 96 (66.2%) T4 4 (2.6%) 0 (0.0%) 0 (0.0%) Ts (DCIS) 10.77%) 0 (0.0%) 0 (0.0%) Tx 1007%) 0 (0.0%) 0 (0.0%) Tk stage at initial diagnosis (0.0%) 0 (0.0%) 0 (0.0%) Tk stage at initial diagnosis (0.0%) 0 (0.0%) 0 (0.0%) N1 by inagning 0 (0.0%) 13 (69.3.8%) 0 (0.0%) Postoperative N stage (0.0%) 0 (0.0%) 0 (0.0%) pN1 mi 0 (0.0%) 0 (0.0%) 0 (0.0%) pN2 12 (9.9%) 2 (1.4 (6.8)) 0 (0.0%) pN4 2 (2.6%) 2 (4.1 (6.8)) 0 (0.0%) ypN0 36 (23.28%) 35 (24.1 %) 0 (0.0%) ypN1 2 (1.4 (6.8)) <t< td=""><td>None*</td><td>1 (0.7%)</td><td></td></t<>	None*	1 (0.7%)	
Median (1QR) 28 (20-40) 28 (21-40) Clinical T stage at initial diagnosis 0(0.0%) 1 (0.7%) TI 37 (24/53) 30 (20.7%) T2 93 (61.6%) 96 (66.2%) T3 15 (9.9%) 13 (90.0%) T4 4 (2.6%) 5 (3.4%) T5 (DCIS) 1 (0.7%) 0 (0.0%) Tk 1 (0.7%) 0 (0.0%) N2/3 0 (0.0%) 9 (62.8) PN1 0 (0.0%) 0 (0.0%) pN1 0 (0.0%) 0 (0.0%) pN1 0 (0.0%) 0 (0.0%) pN2 1 (1.5%) 0 (0.0%) pN1 2 (2.16.3%) 2 (1.4%) pN1 2 (2.16.3%) <td>Tumor size at initial diagnosis, mm</td> <td></td> <td></td>	Tumor size at initial diagnosis, mm		
To 0003) 10.7%) To 37 (24.5%) 30 (20.7%) T2 33 (6.6%) 96 (66.2%) T3 15 (9.9%) 13 (9.0%) T4 4 (2.6%) 5 (3.4%) Ts (DCIS) 10 (0.7%) 0 (0.0%) Tx 10 (0.7%) 0 (0.0%) Tx 10 (0.7%) 0 (0.0%) Tx 0 (0.0%) 16 (9.3.8%) N1 by imaging 0 (0.0%) 16 (9.3.8%) N2/3 0 (0.0%) 0 (0.0%) Postoperative N stage (0.0%) 0 (0.0%) PNI 5 (36.4%) 47 (32.4%) pN2 12 (9.9%) 2 (1.4%) pN3 12 (7.9%) 8 (5.5%) ypN0 36 (23.8%) 35 (24.1%) ypN1 22 (14.6%) 24 (16.6%) ypN1 22 (14.6%) 24 (16.6%) ypN2 4 (2.6%) 24 (16.6%) ypN3 20 (1.3%) 9 (6.2%) Doular 18 (11.9%) 9 (6.2%) Doular <td< td=""><td>Median (IQR)</td><td>28.5 (20-40)</td><td>28 (21-40)</td></td<>	Median (IQR)	28.5 (20-40)	28 (21-40)
T0 0 (0.0%) 1 (0.7%) T1 37 (24.53) 30 (20.7%) T2 93 (61.6%) 96 (66.2%) T3 15 (99%) 13 (00%) T4 4 (2.6%) 5 (3.4%) Ts (DCIS) 1 (0.7%) 0 (0.0%) Tx 1 (0.7%) 0 (0.0%) N1 by plaption 3 (2.0%) 2 (1.4%) pN1 3 (2.0%) 2 (1.4%) pN1 0 (0.0%) 0 (0.0%) pN2 15 (9.9%) 2 (1.6%) pN3 12 (7.9%) 8 (5.5%) ypN0 2 (1.4%) 2 (1.6%) ypN1 2 (1.4%) 2 (1.6%) ypN2 4 (2.6%) 2 (3.4%) ypN3 2 (1.3%) 0 (0.0%)	Clinical T stage at initial diagnosis		
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12 95 (11.63) 96 (06.24) T3 15 (29.32) 13 (9.08) T4 4 (2.63) 5 (3.43) Ts (DCS) 1 (0.73) 0 (0.03) Tx 1 (0.72) 0 (0.03) Clinical N stage at initial diagnosis 0 (0.02) 136 (93.83) N1 by palpation 137 (90.7%) 0 (0.02) N2/3 14 (9.33) 9 (6.23) Postoperative N stage (1.43) 9 (6.23) PN1 5 (56.43) 47 (32.43) pN1 5 (56.43) 47 (32.43) pN2 15 (9.93) 24 (16.63) pN3 12 (7.93) 8 (5.53) ypN0 36 (23.83) 35 (24.13) ypN1 22 (14.63) 24 (16.63) ypN2 2 (133) 0 (0.03) ypN3 9 (12.83) 2 (3.43) ypN3 9 (12.83) 9 (6.23) thet/Her2+ 19 (12.63) 27 (18.63) HR+/Her2+ 9 (6.03) 14 (15.53) thet/Her2+ 9 (6.03) 9 (6.23) thistology 11 (1.75.3) 9 (6.23)		37 (24.5%)	30 (20.7%)
13 13 (39.5) 13 (39.5) 13 (39.5) 14 4 (2.6%) 5 (3.4%) 1s (DCIS) 1 (0.7%) 0 (0.0%) Tx 1 (0.7%) 0 (0.0%) N by palation 137 (90.7%) 0 (0.0%) N by imaging 0 (0.0%) 136 (93.8%) N2/3 14 (9.3%) 9 (62.8) Postoperative N stage 21 (4.4%) 0 (0.0%) pN0 3 (2.0%) 2 (1.4%) pN1 min 0 (0.0%) 0 (0.0%) pN1 55 (36.4%) 47 (32.4%) pN2 15 (9.9%) 24 (16.6%) pN3 12 (7.9%) 8 (5.5%) ypN0 36 (23.3%) 35 (24.1%) ypN1 22 (14.6%) 24 (16.6%) ypN2 4 (2.6%) 24 (16.6%) ypN3 21 (13%) 0 (0.0%) ypN4 13 (19.9%) 26 (24.1%) ypN3 19 (12.6%) 27 (18.6%) ypN3 21 (13%) 9 (62.3%) Histology 11 (4 (75.5%) 10 (0.0%) Histology 19 (12.6%) 27 (18.6%) <t< td=""><td>12</td><td>93 (61.6%)</td><td>96 (66.2%)</td></t<>	12	93 (61.6%)	96 (66.2%)
IF (CLS) 1 (0.7%) 0 (0.0%) Tx 1 (0.7%) 0 (0.0%) Tx 1 (0.7%) 0 (0.0%) N by palpation 137 (90.7%) 0 (0.0%) N by palpation 136 (93.8%) 9(5.2%) Postoperative N stage 9 (62.2%) 9(5.2%) PN0 3 (2.0%) 0 (0.0%) 0 (0.0%) pN1 0 (0.0%) 0 (0.0%) 0 (0.0%) pN1 55 (36.4%) 47 (32.4%) pN2 15 (9.9.%) 24 (16.6%) pN3 12 (7.9%) 8 (5.5%) ypN0(TTC) 2 (1.3%) 0 (0.0%) ypN1 22 (14.6%) 24 (16.6%) ypN2 4 (2.6%) 5 (3.4%) ypN3 2 (1.3%) 0 (0.0%) Histology 1 1 1 Invasive ductal 14 (75.5%) 109 (75.2%) Lobular 19 (12.6%) 27 (18.6%) Receptor status at initial diagnosis 1 1 HR /Her2- 18 (11.9%) 9 (6.2%) <t< td=""><td>13 T4</td><td>15 (9.9%)</td><td>13 (9.0%) 5 (2.4%)</td></t<>	13 T4	15 (9.9%)	13 (9.0%) 5 (2.4%)
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Clinical N stage at initial diagnosis 137 (90.7%) 0 (0.0%) NI by plaption 137 (90.7%) 0 (0.0%) NI by imaging 0 (0.0%) 136 (93.8%) NZ/3 14 (9.3%) 9 (6.2%) Postoperative N stage 2 (1.4%) pN1 min 0 (0.0%) 0 (0.0%) pN1 min 0 (0.0%) 0 (0.0%) pN2 15 (9.9%) 24 (16.6%) pN3 12 (7.9%) 8 (5.5%) ypN0(TCr) 2 (1.4%) 0 (0.0%) ypN1 26 (24.8%) 24 (16.6%) ypN1 26 (24.8%) 24 (16.6%) ypN1 22 (14.6%) 24 (16.6%) ypN1 22 (14.6%) 24 (16.6%) ypN2 4 (2.6%) 5 (3.4%) ypN3 2 (1.4%) 9 (6.2%) listology 114 (75.5%) 109 (75.2%) lobular 19 (12.6%) 27 (18.6%) Receptor status at initial diagnosis 91 (60.3%) 9 (66.2%) HR+/Her2- 19 (60.3%) 24 (16.6%) HR-/Her2-	Tx	1 (0.7%)	0 (0.0%)
N1 by plation 137 (90.7%) 0 (0.0%) N1 by maging 0 (0.0%) 136 (93.8%) N2/3 14 (9.3%) 9 (62.8%) Postoperative N stage 2 (1.4%) pN1 min 0 (0.0%) 0 (0.0%) pN1 min 0 (0.0%) 0 (0.0%) pN1 55 (36.4%) 47 (32.4%) pN2 15 (9.9%) 24 (16.6%) pN3 12 (7.9%) 8 (5.5%) ypN0 36 (22.8%) 35 (24.1%) ypN0 36 (22.8%) 35 (24.1%) ypN0(TC) 21 (1.4%) 24 (16.6%) ypN1 22 (14.6%) 24 (16.6%) ypN1 22 (14.6%) 24 (16.6%) ypN1 22 (14.6%) 24 (16.6%) ypN2 4 (26.2%) 5 (3.4%) ypN3 21 (1.3%) 0 (0.0%) ibtology 114 (75.5%) 109 (75.2%) cbular 19 (12.6%) 27 (18.6%) dcc2x) 10 (2.6%) 9 (62.2%) Other 19 (16.0%) 9 (62.2%) HR+/Her	Clinical N stage at initial diagnosis	1 (0.7%)	0 (0.0%)
NI by imaging 0 (0.0%) 136 (93.8%) N2/3 14 (9.3%) 9 (6.2%) Postoperative N stage pN0 3 (2.0%) 2 (1.4%) pN1mi 0 (0.0%) 0 (0.0%) pN1mi 0 (0.0%) 0 (0.0%) pN1 55 (36.4%) 47 (32.4%) pN2 15 (9.9%) 24 (16.6%) pN3 12 (7.9%) 8 (55.5%) ypN0 36 (23.8%) 35 (24.1%) ypN1 22 (14.6%) 24 (16.6%) ypN0(ITC) 2 (1.3%) 0 (0.0%) ypN1 22 (14.6%) 24 (16.6%) ypN3 2 (1.3%) 0 (0.0%) ypN3 2 (1.4%) 24 (16.6%) ypN3 19 (12.6%) 27 (18.6%) Histology 19 (12.6%) 27 (18.6%) Receptor status at initial diagnosis 6 (66.2%) RR+/Her2- 19 (60.3%) 9 (6.2%) HR+/Her2- 9 (60.8) 9 (6.2%) MK+/Her2+ 7 (46.5%) 9	N1 by palpation	137 (90.7%)	0 (0.0%)
N2/3 14 (9.3%) 9 (6.2%) Postoperative N stage	N1 by imaging	0 (0.0%)	136 (93.8%)
Postoperative N stage pN0 3 (2.%) 2 (1.4%) pN1 0 (0.0%) 0 (0.0%) pN1 55 (36.4%) 47 (32.4%) pN2 15 (9.9%) 24 (16.6%) pN3 12 (7.9%) 8 (5.5%) ypN0 36 (23.8%) 35 (24.1%) ypN0 2 (14.6%) 24 (16.6%) ypN1 2 (14.6%) 24 (16.6%) ypN1 2 (14.6%) 24 (16.6%) ypN1 2 (14.6%) 2 (4.1%) ypN2 4 (2.6%) 5 (3.4%) ypN3 2 (1.1%) 0 (0.0%) ypN3 2 (12.6%) 27 (18.6%) Wosting Learch 19 (12.6%) 27 (18.6%) Receptor status at initial diagnosis # # HR+/Her2- 9 (60.3%) 9 (62.2%) HR+/Her2+ 7 (4.6%) 9 (62.2%) HR+/Her2+ 7 (4.6%) 9 (62.2%) HR+/Her2+ 7 (4.6%) 9 (62.2%) HR-/Her2+ 7 (4.6%) 77 (53.1%) No 61 (40.4%)	N2/3	14 (9.3%)	9 (6.2%)
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pN1mi 0 (0.0%) 0 (0.0%) pN1 55 (36.4%) 47 (32.4%) pN2 15 (9.9%) 24 (16.6%) pN3 12 (7.9%) 8 (5.5%) ypN0 36 (23.8%) 35 (24.1%) ypN0(TCC) 2 (1.3%) 0 (0.0%) ypN1 22 (14.6%) 24 (16.6%) ypN1 22 (14.6%) 3 (3.4%) ypN2 4 (2.6%) 5 (3.4%) ypN3 2 (1.3%) 0 (0.0%) Histology 114 (75.5%) 109 (75.2%) Lobular 19 (12.6%) 27 (18.6%) Other 19 (12.6%) 27 (18.6%) Receptor status at initial diagnosis # # HR+/Her2+ 18 (11.9%) 24 (16.6%) HR+/Her2+ 18 (11.9%) 26 (66.2%) HR+/Her2+ 18 (11.9%) 24 (16.6%) HR+/Her2+ 18 (11.9%) 24 (16.6%) HR+/Her2+ 18 (11.9%) 26 (16.2%) HR+/Her2+ 18 (11.9%) 24 (16.6%) VI Go(0.8) 7	pN0	3 (2.0%)	2 (1.4%)
pN1 55 (36.4%) 47 (32.4%) pN2 15 (9.9%) 24 (16.6%) pN3 12 (7.9%) 8 (5.5%) ypN0 36 (23.8%) 35 (24.1%) ypN0(TC) 2 (1.3%) 0 (0.0%) ypN1 22 (14.6%) 24 (16.6%) ypN2 4 (2.6%) 5 (3.4%) ypN3 2 (1.3%) 0 (0.0%) Histology 1 109 (75.2%) Invasive ductal 114 (75.5%) 109 (75.2%) Lobular 18 (11.9%) 9 (6.2%) Other 19 (12.6%) 27 (18.6%) Receptor status at initial diagnosis # # HR+/Her2- 91 (60.3%) 96 (66.2%) HR+/Her2- 91 (60.3%) 96 (66.2%) HR+/Her2- 91 (60.3%) 96 (66.2%) Missing/unknown 9 (6.0%) 7 (4.6%) VI 7 5 (3.3%) 6 (4.1%) Vo 6 (17.2%) 9 (6.2%) 10 Missing/unknown 9 (6.0%) 7 (4.3%) 6 (2.4%)	pN1mi	0 (0.0%)	0 (0.0%)
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ypN1 $22 (14.0 \%)$ $24 (16.0 \%)$ ypN2 $4 (2.6\%)$ $5 (3.4\%)$ ypN3 $2 (1.3\%)$ $0 (0.0\%)$ Histology $114 (75.5\%)$ $109 (75.2\%)$ Lobular $114 (75.5\%)$ $109 (75.2\%)$ Other $19 (12.6\%)$ $27 (18.6\%)$ Receptor status at initial diagnosis $21 (1.0\%)$ HR+/Her2- $91 (60.3\%)$ $96 (66.2\%)$ HR+/Her2+ $18 (11.9\%)$ $24 (16.6\%)$ HR+/Her2+ $18 (11.9\%)$ $24 (16.6\%)$ HR+/Her2+ $26 (17.2\%)$ $9 (6.2\%)$ Missing/unknown $9 (6.0\%)$ $7 (4.8\%)$ LVI Yes $85 (56.3\%)$ $62 (42.8\%)$ No $61 (40.4\%)$ $77 (53.1\%)$ Modified Bloom-Richardson score I I I $5 (3.3\%)$ $6 (4.1\%)$ II $80 (53.0\%)$ $82 (56.6\%)$ III $60 (39.7\%)$ $56 (38.6\%)$ Missing/unknown $6 (4.0\%)$ $1 (0.7\%)$	ypN0(IIC)	2 (1.3%)	0(0.0%)
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$\begin{array}{cccc} HR + /Her2- & 91 (60.3\%) & 96 (66.2\%) \\ HR + /Her2+ & 18 (11.9\%) & 24 (16.6\%) \\ HR - /Her2+ & 7 (4.6\%) & 9 (6.2\%) \\ HR - /Her2- & 26 (17.2\%) & 9 (6.2\%) \\ Missing/unknown & 26 (0\%) & 7 (4.8\%) \\ LVI & & & & & & & & \\ Yes & 85 (56.3\%) & 62 (42.8\%) \\ No & 61 (40.4\%) & 77 (53.1\%) \\ Missing/unknown & 5 (3.3\%) & 6 (4.1\%) \\ Modified Bloom-Richardson score & & & & & & \\ I & 5 (3.3\%) & 6 (4.1\%) \\ II & 80 (53.0\%) & 82 (56.6\%) \\ III & 60 (39.7\%) & 56 (38.6\%) \\ Missing/unknown & 6 (4.0\%) & 1 (0.7\%) \\ \end{array}$	Receptor status at initial diagnosis		
$\begin{array}{cccc} HR+/Her2+ & 18 (11.9\%) & 24 (16.6\%) \\ HR-/Her2+ & 7 (4.6\%) & 9 (6.2\%) \\ HR-/Her2- & 26 (17.2\%) & 9 (6.2\%) \\ Missing/unknown & 26 (0.0\%) & 7 (4.8\%) \\ LVI & & & & & & & & & \\ Yes & 85 (56.3\%) & 62 (42.8\%) \\ No & 61 (40.4\%) & 77 (53.1\%) \\ Missing/unknown & 5 (3.3\%) & 6 (4.1\%) \\ Modified Bloom-Richardson score & & & & & & \\ I & 5 (3.3\%) & 6 (4.1\%) \\ II & 80 (53.0\%) & 82 (56.6\%) \\ III & 60 (39.7\%) & 56 (38.6\%) \\ Missing/unknown & 6 (4.0\%) & 1 (0.7\%) \\ \end{array}$	HR+/Her2-	91 (60.3%)	96 (66.2%)
HR-/Her2+ $7 (4.6\%)$ $9 (6.2\%)$ HR-/Her2- $26 (17.2\%)$ $9 (6.2\%)$ Missing/unknown $9 (6.0\%)$ $7 (4.8\%)$ LVI $7 (4.6\%)$ $7 (4.6\%)$ Yes $85 (56.3\%)$ $62 (42.8\%)$ No $61 (40.4\%)$ $77 (53.1\%)$ Missing/unknown $5 (3.3\%)$ $6 (4.1\%)$ Modified Bloom-Richardson score 1 I $5 (3.3\%)$ $6 (4.1\%)$ II $80 (53.0\%)$ $82 (56.6\%)$ III $60 (39.7\%)$ $56 (38.6\%)$ Missing/unknown $6 (4.0\%)$ $1 (0.7\%)$	HR+/Her2+	18 (11.9%)	24 (16.6%)
HR-/Her2- 26 (17.2%) 9 (6.2%) Missing/unknown 9 (6.0%) 7 (4.8%) LVI 7 (53.1%) Yes 85 (56.3%) 62 (42.8%) No 61 (40.4%) 77 (53.1%) Missing/unknown 5 (3.3%) 6 (4.1%) Modified Bloom-Richardson score I 5 (3.3%) 6 (4.1%) III 80 (53.0%) 82 (56.6%) Missing/unknown 60 (39.7%) 56 (38.6%)	HR-/Her2+	7 (4.6%)	9 (6.2%)
Missing/unknown 9 (6.0%) 7 (4.8%) LVI	HR-/Her2-	26 (17.2%)	9 (6.2%)
LVI Yes 85 (56.3%) 62 (42.8%) No 61 (40.4%) 77 (53.1%) Missing/unknown 5 (3.3%) 6 (4.1%) Modified Bloom-Richardson score 7 7 I 5 (3.3%) 6 (4.1%) III 80 (53.0%) 82 (56.6%) III 60 (39.7%) 56 (38.6%) Missing/unknown 6 (4.0%) 1 (0.7%)	Missing/unknown	9 (6.0%)	7 (4.8%)
Yes 85 (56.3%) 62 (42.8%) No 61 (40.4%) 77 (53.1%) Missing/unknown 5 (3.3%) 6 (4.1%) Modified Bloom-Richardson score 5 (3.3%) 6 (4.1%) I 5 (3.3%) 6 (4.1%) II 80 (53.0%) 82 (56.6%) III 60 (39.7%) 56 (38.6%) Missing/unknown 6 (4.0%) 1 (0.7%)	LVI		(12,0%)
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Missing/unknown 5 (3.3%) 6 (4.1%) Modified Bloom-Richardson score 6 6 I 5 (3.3%) 6 (4.1%) II 80 (53.0%) 82 (56.6%) III 60 (39.7%) 56 (38.6%) Missing/unknown 6 (4.0%) 1 (0.7%)	INU Missing/unknown	01 (40.4%) 5 (3 3%)	//(33.1%) 6(4.1%)
I 5 (3.3%) 6 (4.1%) II 80 (53.0%) 82 (56.6%) III 60 (39.7%) 56 (38.6%) Missing/unknown 6 (4.0%) 1 (0.7%)	Modified Bloom-Richardson score	J (J.J/0)	U (4.1%)
II 80 (53.0%) 82 (56.6%) III 60 (39.7%) 56 (38.6%) Missing/unknown 6 (4.0%) 1 (0.7%)		5 (3 3%)	6 (4 1%)
III 60 (39.7%) 56 (38.6%) Missing/unknown 6 (4.0%) 1 (0.7%)	П	80 (53 0%)	82 (56 6%)
Missing/unknown 6 (4.0%) 1 (0.7%)	III	60 (39.7%)	56 (38.6%)
	Missing/unknown	6 (4.0%)	1 (0.7%)

*Primary tumor was inoperable and surgical treatment consisted exclusively of axillary surgery.

Table A.2

Characteristics of tailored axillary surgery and axillary lymph node dissection

	$\begin{array}{l} \text{Upfront Sur} \\ \text{N} = 166 \end{array}$	gery	Neoadjuvant Chemotherapy $N = 125$				
Variable			Residual No (N = 54)	dal disease	Nodal Patho Complete R $(N = 71)$	ologic esponse	
TAS (n = 291*)	Median	(IQR)	Median	(IQR)	Median	(IQR)	
Total number of nodes removed by TAS	5	(3, 7)	4	(3, 5)	4	(2, 6)	
Number of sentinel nodes	3	(2, 4)	2	(1, 4)	3	(2, 4)	
Number of palpably suspicious nodes	2	(1, 4)	1	(0, 2)	1	(0, 2)	
Number of positive ^a nodes	2	(1, 4)	1	(1, 2)	0	(0, 0)	
Number of negative nodes	2	(1, 4)	2	(1, 4)	4	(3, 5)	
	n	(%)	n	(%)	n	(%)	
Largest sentinel node metastasis							
Isolated tumor cells	0	(0.0%)	1	(1.9%)	0	(0.0%)	
Micro	4	(2.5%)	10	(18.5%)	0	(0.0%)	
Macro	130	(78.3%)	36	(66.7%)	0	(0.0%)	
NA (no positive sentinels)	22	(13.3%)	5	(9.3%)	71	(100.0%)	
Unknown	10	(6.0%)	2	(3.7%)	0	(0.0%)	
Largest non-sentinel node metastasis							
Isolated tumor cells	0	(0.0%)	1	(1.9%)	0	(0.0%)	
Micro	6	(3.6%)	2	(3.7%)	0	(0.0%)	
Macro	54	(32.5%)	8	(14.8%)	0	(0.0%)	
NA (no positive non-sentinels)	96	(57.8%)	43	(79.6%)	71	(100.0%)	
Unknown	10	(6.0%)	0	(0.0%)	0	(0.0%)	
ALND $(n = 123)^{**}$	Median	(IQR)	Median	(IQR)	Median	(IQR)	
Number of additional lymph nodes removed by ALND	14	(9, 18)	14	(10, 16)	12.5	(8.5, 23)	
Number of additional positive ^a lymph nodes removed by ALND	2	(0,6)	1	(0, 3)	0	(0, 0)	
	n	(%)	n	(%)	n	(%)	
Number of patients with additional positive ^a nodes removed by ALND							
No additional positive nodes	25	(29.1%)	10	(40.0%)	8	(100.0%)	
One additional positive node	17	(19.8%)	5	(20.0%)	0	(0.0%)	
Two additional positive nodes	6	(7.0%)	2	(8.0%)	0	(0.0%)	
Three additional positive nodes	6	(7.0%)	2	(8.0%)	0	(0.0%)	
Four additional positive nodes	6	(7.0%)	2	(8.0%)	0	(0.0%)	
>four additional positive nodes	26	(30.2%)	4	(16.0%)	0	(0.0%)	

Abbreviations: IQR, interquartile range; TAS, tailored axillary surgery; ALND, axillary lymph node dissection; NA, not applicable.

^a Nodes with isolated tumor cells are counted as positive.

* Five patients who received neoadjuvant therapy other than chemotherapy are not shown here.

** Two patients who received neoadjuvant therapy other than chemotherapy are not shown here.

TABLE A.3

Successful surgical removal of clipped node by type of clip

	Type of Clip					
	Direct Magseed	Direct Seed	Ring Marker	Marker With Gel	Marker Without Gel	P-Value ^b
Confirmed nodal disease at the time of surgery $(n = 219)$	N = 14	N = 3	N = 58	N = 69	N = 75	0.197
Clip surgically removed ^a	13 (92.9%)	3 (100.0%)	55 (94.8%)	64 (92.8%)	74 (98.7%)	
Clip not removed	1 (7.1%)	0 (0.0%)	3 (5.2%)	5 (7.2%)	1 (1.3%)	
Nodal pathologic complete response (n = 71)	N = 2	N = 0	N = 33	N = 23	N = 13	0.875
Clip surgically removed ^a	2 (100.0%)	0 (0.0%2)	30 (90.9%)	20 (87.0%)	12 (92.3%)	
Clip not removed	0 (0.0%)	0 (0.0%)	3 (9.1%)	3 (13.0%)	1 (7.7%)	

^a As documented by specimen radiography.

^b Fisher's exact test, excluding the categories "direct magseed" and "direct seed" due to small sample size.

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