

Axillary surgery in node-positive breast cancer[☆]

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ABSTRACT

Long-term follow-up data from multicenter phase III non-inferiority trials confirmed the safety of omission of axillary dissection in selected patients with clinically node-negative, sentinel node-positive breast cancer. Several ongoing trials investigate extended eligibility of the Z0011 protocol in the adjuvant setting. De-escalation of axillary surgery in patients with clinically node-positive breast cancer is currently limited to the neoadjuvant setting, where the sentinel procedure is used to determine nodal pathological complete response. Targeted axillary dissection lowers the false-negative rate of the sentinel procedure, which, however, is consistently associated with a very low risk of axillary recurrence in several recent single-center series. Axillary dissection remains standard care in patients with residual disease after neoadjuvant chemotherapy while the results of Alliance A011202 are pending. The TAXIS trial investigates the role of tailored axillary surgery in patients with clinically node-positive breast cancer, a novel concept designed to selectively remove positive nodes in the adjuvant and neoadjuvant setting.

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1. Summary

The evolution of axillary surgery is characterized by surgical de-escalation. Radical axillary lymph node dissection (ALND) was performed as standard in patients with breast cancer for almost a century. Since the identification of the sentinel nodes in the 90s, ALND was performed for clinically node-positive breast cancer and whenever cancer was found in the sentinel nodes. Today, we have learned from clinical trials that we can omit ALND in many patients with positive sentinel nodes [1,2]. In a situation with positive sentinel nodes and a high risk of recurrence, axillary radiation is increasingly preferred over ALND [3,4]. In the future, we will have to answer the question if we can omit the sentinel procedure in patients with negative ultrasound [5–8]. We will also have to answer the question if we can omit ALND in all patients with positive sentinel nodes, even if there are additional risk factors [9–11]. Finally, we will have to find ways to omit ALND in clinically node-positive breast cancer with residual disease after neoadjuvant

chemotherapy (NACT) (NCT01901094) and in the upfront surgery setting [12]. Current concepts use limited axillary surgery procedures, such as the sentinel procedure, to determine if the nodes are clear after NACT without removing them all [13,14].

2. Current indications for axillary dissection

Long-term follow-up data of several large phase III non-inferiority trials, randomizing clinically node-negative patients with positive sentinel nodes into one group with axillary dissection, compared to no axilla-specific treatment, have been published. Both the ACOSOG Z0011 and the IBCSG 23–01 trials found extremely low rates (<2%) of axillary recurrence, showing that many of these patients do not need axilla-specific treatment [1,2]. ALND is still considered standard practice in clinically node-positive breast cancer in the upfront surgery setting, in patients with residual nodal disease after NACT and in locally advanced breast cancer (cT3–4, inflammatory breast cancer, >2 positive sentinel nodes, gross extranodal disease). ALND is also indicated in sentinel node-positive patients with macrometastases undergoing mastectomy, but only if the positive sentinel node per se does not indicate postmastectomy radiotherapy (PMRT) or if irradiation does

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Table 1
Current indications for axillary lymph node dissection.

Clinical setting	Type of surgery	Nodal status	Primary axillary surgery procedure	Indication for ALND
After NACT		cN0	SLNB	Any residual disease ^a
		cN1 → cN0	SLNB (>2 neg. SLN) or TAD	Any residual disease ^a , <3 negative SLN ^b
		cN1 → cN1	ALND	
Upfront surgery	BCS +WBR	cN0	SLNB ^c	≥ 3 positive SLN, cT3-4
		cN1	ALND	
	Mastectomy	cN0	SLNB	SLN-macrometastasis if no PMRT is planned
		cN1 or inflammatory breast cancer	ALND	

NACT = neoadjuvant chemotherapy; SLNB = sentinel lymph node biopsy; SLN = sentinel lymph node; TAD = Targeted axillary dissection; ALND = axillary lymph node dissection; BCS = breast conserving surgery; WBR = whole breast radiotherapy; PMRT = postmastectomy radiotherapy.

^a Some centers omit ALND in case of isolated tumor cells.

^b Some centers omit ALND when <3 negative SLN are removed.

^c In case of 1 or 2 metastases with additional risk factors (e.g., microscopic extracapsular tumor extension, lymphovascular invasion), nodal irradiation can be considered.

not include the lymph nodes (Table 1). If PMRT is performed and includes the axilla, sentinel node-positive patients do not require ALND, as radiation will suffice [3]. This has been demonstrated by the EORTC AMAROS trial, where the promising 10-year follow-up data were presented at the San Antonio Breast Cancer Symposium 2018, while full publication is pending [15]. In this trial, clinically node-negative, sentinel node-positive patients (n = 1425, of whom 17% underwent mastectomy) were randomized into a control group with ALND compared to axillary irradiation as experimental treatment. At a median follow-up of 10 years, axillary recurrence occurred in 0.9% in the ALND group vs. 1.8% in the irradiation group. Even though non-inferiority could not be proven statistically, from a clinical point of view looking at the very low rates of axillary recurrence, clinical non-inferiority was demonstrated. Therefore, in cases where treatment of the axilla is planned for patients within this population, irradiation can be an alternative to ALND. Patient selection for axillary radiation versus observation in this situation is a field of ongoing controversy.

3. Can Z0011 eligibility be broadened?

Because of the limitations of the ACOSOG Z0011 study, a series of randomized trials were initiated to validate the findings of Z0011 after the first results were published. In the meantime, however, the protocol has been validated by prospective observational studies and practice has been changed accordingly in many countries [16,17]. Therefore, the randomized trials adjusted their focus to patients that were excluded from Z0011. In the ERC/IPC 2012-001 SERC trial from France, they included 1855 patients at 53 sites according to Z0011 from 2012 to 2018 and started to select Z0011 non-eligible patients in August 2018 [9]. In the SENOMAC trial from Sweden, several countries started to focus on patients undergoing mastectomy [10]. All of these axillary surgery de-escalation studies encountered methodological challenges, primarily due to a lack of power based on lower than expected rates of events or accrual [1–3,9,10,15].

4. Clinically node-positive breast cancer

Clinically node-positive patients are commonly defined by the occurrence of palpable disease at the time of diagnosis. Non-palpable disease detected solely on imaging can be considered clinically node-positive or imaging node-positive and refers to a frequent subpopulation in clinical practice where preoperative ultrasound or MRI is routinely used. Both groups are often jointly categorized as biopsy-proven node-positive breast cancer, as pathologic confirmation of malignancy is recommended [18]. Most of these patients still undergo ALND in the upfront surgery setting

and in the event of residual nodal disease after NACT. The use of non-invasive imaging after NACT cannot replace axillary surgery. In a meta-analysis looking at how reliable imaging is in determining nodal pathological complete response (pCR), the outcome of 2380 patients in 13 studies with non-invasive imaging after NACT was compared with axillary surgery [19]. The study showed an axillary pCR of 39.5% (941/2380). Sensitivity for ultrasound, MRI, or PET-CT was far away from being reliable in terms of assessing accurate axillary response after NACT (65%, 60%, resp. 38%). At this point, microscopic analysis of at least a few nodes after NACT is needed to determine pCR in the lymph nodes, which de-escalated axillary surgery in current practice. A meta-analysis of 20 studies including 2217 patients investigated the false-negative rate (FNR) of the sentinel node procedure in biopsy-proven clinically node-positive patients with clinically node-negative sentinel lymph nodes after NACT undergoing back-up ALND [13]. The FNR was 22%; however, the FNR decreased to 8% when at least three negative nodes were removed and double tracing was used. The MARI procedure selectively marked and removed the sampled node with a radioactive seed, which showed a FNR of 7%. With the combination of the two techniques, selective localization and removal of the clipped node together with the sentinel procedure, the lowest FNR of 2–4% can be achieved [13]. This combination is called targeted axillary dissection (TAD). The prospective SenTa registry study included 473 patients with clipped nodes at 50 German centers. It showed that the clipped lymph node and sentinel node were identical in 64.8% and the detection rate of the clipped lymph node after NACT was 86.9% [14]. This means that the clip was left behind in 13% of patients, which can become problematic from a medical-legal aspect in case of regional recurrence. However, in terms of the FNR, performance was well with a FNR of 7.2% for the removal of just the localized node and a FNR of 4.3% when TAD was performed (Table 2).

The sentinel node procedure after NACT in clinically node-positive patients who turned clinically node-negative after NACT

Table 2
De-escalating axillary surgery in clinically node-positive breast cancer undergoing NACT [13,14].

Procedure	n (patients)	Identification rate	FNR
SLNB	2002	89%	Overall: 17% <3 SNL: 22% ≥3 SNL: 8%
MARI	95	97%	7%
TAD (seed)	120	100%	2–4%
TAD (no seed)	473	86.6%	4.3%

SLNB = sentinel lymph node biopsy; SNL = sentinel lymph node; FNR = false-negative rate; NACT = neoadjuvant chemotherapy; MARI = marking the axillary positive lymph node with an iodine seed, TAD = targeted axillary dissection.

Table 3
De-escalated axillary surgery procedure in clinically node positive-breast cancer. Axillary recurrence in node-negative patients after NACT [20–23].

First author	n (patients)	SLNB (median no.)	Double tracer	Irradiation	Axillary recurrence (absolute no.)	Median follow-up (y)
Wong	102	4	Yes	71%	0	3
Kahler-Ribeiro-Fontana	123	2	No (only ⁹⁹ Tc)	42%	2	9.2
Damin	38	2	Yes	87%	1	4.7
Piltin	139	3	NA	78%	1	2.8

is the most commonly performed procedure today. For a long time, the importance of the FNR was unclear, since leaving chemo-resistant cancer in the nodes may increase axillary recurrence compared to the adjuvant setting. A retrospective single-center study from Canada investigated 102 patients in this setting [20]. Of these, 71% had regional irradiation and a medium of 4 negative sentinel nodes were removed. There was not a single case of axillary recurrence at a median follow-up of three years. However, since the authors insisted on having several negative nodes, the expected FNR was low and in combination with the broad use of axillary irradiation, these results were expected. On the other hand, a series from Milan also reported only two axillary recurrences at a very long median follow up of 9.2 years in 123 patients [21]. Importantly, they used only single tracer (⁹⁹Tc), resulting in 74% of patients with less than 3 negative sentinel nodes, and the majority of patients did not get regional irradiation. Hence, the expected FNR was much higher, and yet, the vast majority of patients did not show recurrence. Similar results were confirmed in two retrospective studies from Brazil and the Mayo Clinic with removal of a median of 2 and 3 negative sentinel nodes, respectively, and very low rate of recurrence [22,23]. These results confirmed that the sentinel procedure is a valid treatment option in these patients (Table 3).

5. Ongoing clinical trials in clinically node-positive breast cancer

ALND is the standard procedure when residual disease after NACT is detected in the sentinel nodes. The ongoing Alliance A011202 trial is randomizing this patient population into ALND

compared to axillary radiation in the context of extended regional nodal irradiation (NCT01901094). Accrual is almost completed and the primary endpoint analysis is expected in a few years. Until then, the omission of ALND should be considered experimental in most of these patients. An analysis from the National Cancer Database looked at patients with up to 3 lymph nodes with residual disease and compared the sentinel procedure (defined as removal of ≤4 lymph nodes) with radiation (n = 304) versus ALND with radiation (n = 1313) [24]. Patients without ALND showed worse overall survival (71% vs. 77% at 5 years). Even though there is always selection bias in such studies—patients with more co-morbidities were spared ALND and the difference in outcome was due to the comorbidity and not the omission of the ALND—these results call for caution and confirmation by randomized trials. Interestingly, however, the authors found subgroups, primarily luminal tumors with only one lymph node metastasis, where the omission of ALND did not decrease survival.

The European phase III randomized controlled TAXIS trial investigates the role of a novel concept called tailored axillary surgery (TAS) in patients with clinically node positive breast cancer in the neoadjuvant and the upfront surgery setting (NCT03513614). Accrual is running as estimated, with over 400 patients already randomized of the total planned sample size of 1500 (Fig. 1). TAS removes all palpably clearly suspicious lymph nodes together with the sentinel lymph nodes, whereas imaging-guided localization of the clipped node is optional. Main purpose of TAS is to reduce the tumor load in the axilla to the point where axillary irradiation can control it. Therefore, in a randomized manner, TAS with axillary irradiation is compared to standard ALND in the context of extended regional nodal irradiation. This non-inferiority trial

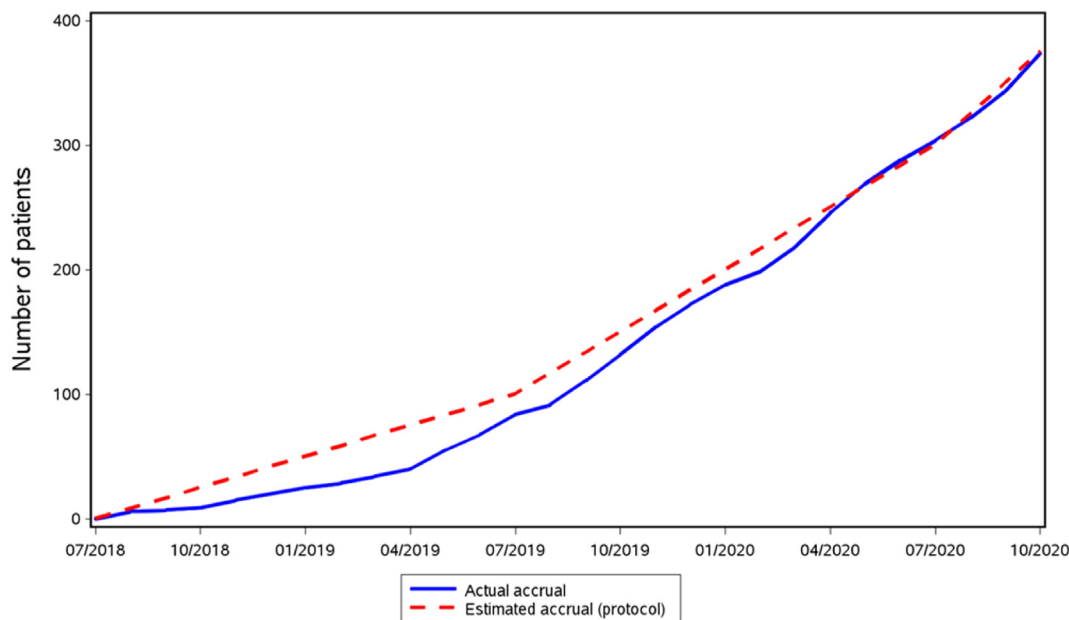


Fig. 1. Accrual of the TAXIS trial. The dotted line is the estimated accrual, the blue line is the actual accrual.

investigates disease-free survival as primary endpoint and quality of life as most important secondary endpoint. Completion of accrual is expected in 2024 and analysis of the primary endpoint to be published in 2030.

Declaration of competing interest

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