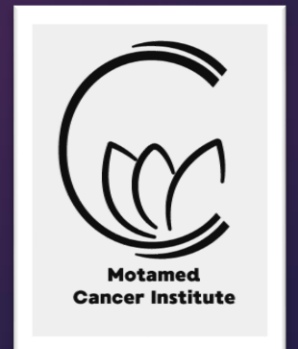


به نام خداوند جان و خرد

Review of SLNB and new techniques

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The Z0011 study (ACOSOG group)

- ▶ Patients with **T1-2** lesions, breast-conserving surgery (**BCS**), whole breast radiotherapy (**WBRT**) and had **1 to 2 positive sentinel nodes** (micro or macroscopic disease).
- ▶ 446 cases were randomized to SLNB-only and 445 cases to completion ALND.
- ▶ Median follow-up of **6.3 years**:
- ▶ no statistically significant differences in **local recurrence** ($p = 0.11$), regional recurrence ($p = 0.45$), disease-free survival ($p = 0.14$), and overall survival ($p = 0.25$) between the two groups

Recent update of the Z0011 / 2016-2017

- ▶ Median follow-up of **9.25 years** confirms positive results on locoregional disease control.
- ▶ The **cumulative incidence of regional recurrences** at 10 years in the ipsilateral axilla was similar in both arms with **(0.5%)** in the ALND group compared with **(1.5%)** patients in the SLNB-only group ($p = 0.28$).
- ▶ **Ten-year** locoregional recurrence was **6.2%** with ALND and **5.3%** with SLNB-only ($p = 0.36$).
- ▶ **SLN was the only site of metastasis in 73%** of cases in the ALND group.
- ▶ After multivariable analyses adjusted for treatment arm; **hormone receptor** status, pathologic **tumor size** and **tumor grade** were associated with locoregional recurrences

Recent update of the Z0011 / 2016-2017

- ▶ The 10-year OS was 86.3% in the SLND-only group and 83.6% in the ALND group (Non-inferiority $p = 0.02$).
- ▶ The 10-year DFS was 80.2% in the SLND-only group and 78.2% in the ALND group ($p = 0.32$)
- ▶ The first phase of trial was closed with 891 cases before reaching the planned accrual size of 1900 patients), and limited follow-up (6.3 years), because the event rate was much lower than anticipated in both arms

updated reports with longer median follow-up of 9.25 and 9.3 years, respectively, have confirmed its findings

The AMAROS Trial

- ▶ (After Mapping of the Axilla: Radiotherapy Or Surgery?) trial from the EORTC selected patients with **similar criteria to Z011, but also included cases operated with mastectomy.**
- ▶ Patients were randomized to completion ALND (744) or axillary radiotherapy (681).
- ▶ After a median **follow-up of 10 years**, there were no significant differences in 10-year axillary recurrence, **10y-DMFS** (Distant metastasis-free survival) and **10y-OS** between the two groups.
- ▶ **More second primaries** were observed after axillary radiotherapy: 75/681 contralateral breast) as compared to ALND: 57/744 (11 contralateral breast) ($p = 0.035$).
- ▶ The 5 year report showed a statistically significant difference in the 5-year incidence of measured **arm lymphedema**, with 13% after ALND and 5% in the radiotherapy group ($p = 0.0009$)
- ▶ Approximately 80% of lesions were < 2 cm with a resulting **82% of cases being treated with BCS** and approximately 18% with mastectomy in both arms

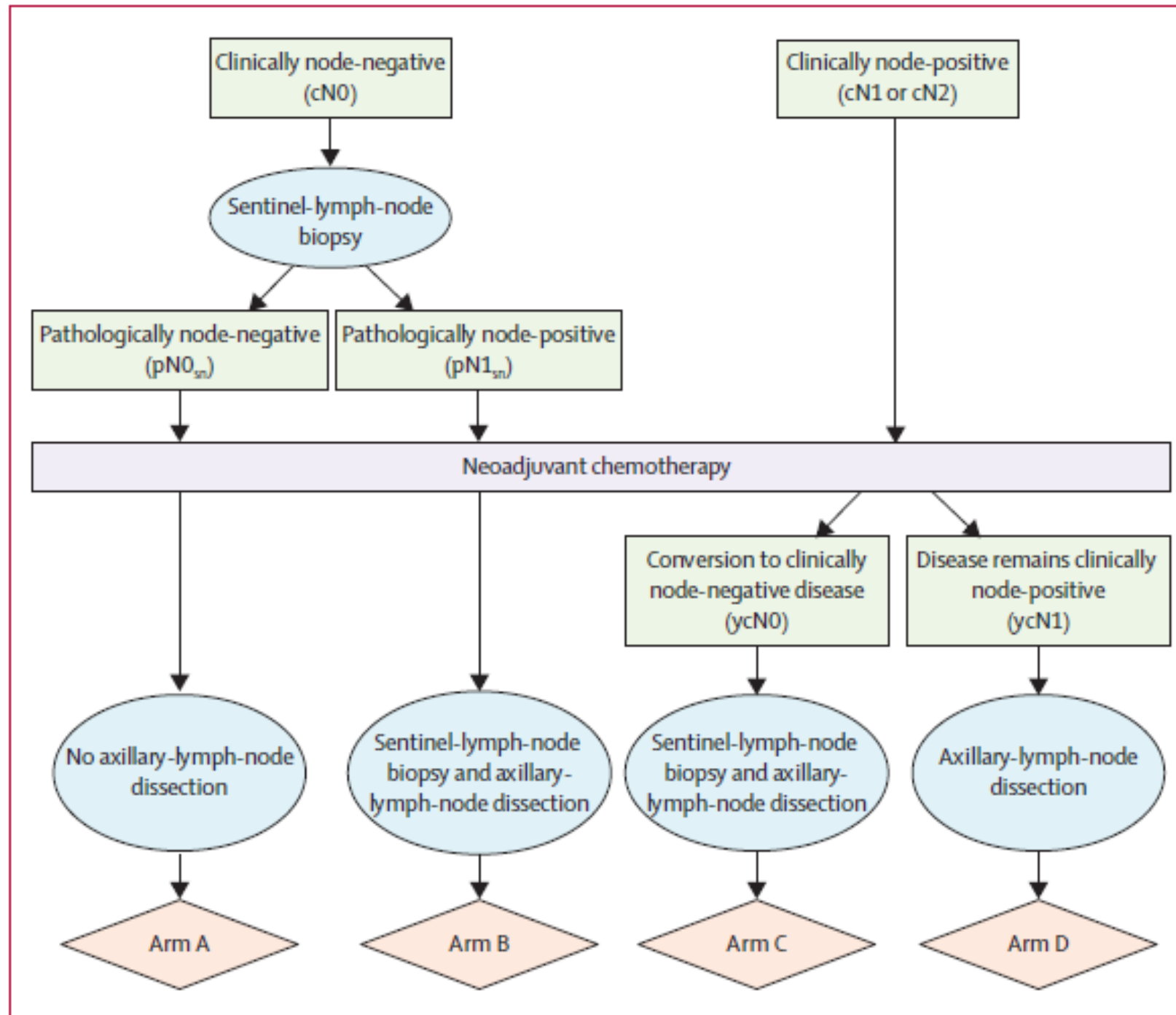
Ongoing or recently closed European trials on management of the axilla in patients with operable invasive breast cancer.

Study	Design	Start- End
SOUND (Sentinel node vs. Observation after axillary UltrasouND)	cT1 cN0, for BCS +WBRT randomized to No axillary surgery vs. SLNB	Mar 2012-June 2017
POSNOC (POSitive Sentinel NOde: adjuvant therapy alone versus adjuvant therapy plus Clearance or axillary radiotherapy) UK	cT1-2 cN0 with 1-2 (+)SLNs (macrometastasis only), for BCS or Mastectomy randomized to No ALND vs. ALND or ax-RT	Jan 2014-Dec 2023
INSEMA (Intergroup Sentinel Mamma)	cT1-2 cN0, for BCS + WBRT randomized to No axillary surgery vs.SLNB (1:4 allocation) a second randomization of cases with 1-3 positive SLNs to either no further surgery or completion ALND 1:1 (macrometastasis only) Outcome: DFS-Non-inferiority	Sep 2015-Sep 2024
BOOG 2013-07 (The value of completion axillary treatment in sentinel node positive breast cancer patients undergoing a mastectomy) Netherlands	cT1-2 cN0 with 1-3 (+)SLNs (microb or macrometastasis), for Mastectomy randomized to No ALND vs. ALND or ax-RT	Jun 2014-Jun 2027
SENOMAC (Omission of Axillary Clearance in Breast Cancer Patients with Sentinel Node Macrometastases) Sweden	cT1-3 cN0 with 1-2 (+)SLNs (macrometastasis only), including also patients prior to neoadjuvant chemo, for BCS or Mastectomy randomized to No ALND vs. ALND	Jan 2015-Jan 2022
TAXIS (Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer) non-inferiority, randomized controlled trial (RCT) 34 study sites from four different countries	patients with a clinically biopsy-proven positive axilla BCS + WBRT or Mastectomy +chest wall RT randomized to TAS + ALND +Regional node RT vs. TAS+ Regional +Ax-RT Aim: TAS and axillary radiotherapy (RT) is non-inferior to axillary lymph node dissection (ALND) in terms of DFS of breast cancer patients with positive nodes at first presentation in the era of effective systemic therapy and extended regional nodal irradiation.	Aug 2018-Mar 2029
Alliance A011202 USA:	cT1-3cN1 (S)LN+ after NACT ALND+ extended regional nodal irradiation vs. axillary radiotherapy + extended regional nodal irradiation	Feb 2014 Jan 2024

Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA) Trial:

- ▶ **four-arm**, prospective, **multicentre cohort** study undertaken at 103 institutions in Germany and Austria
- ▶ Of 1737 patients who received treatment, 1022 women underwent sentinel-lymph-node biopsy before neoadjuvant chemotherapy (arms A and B), with a detection rate of **99·1%**
- ▶ In patients who had a **second sentinel-lymph-node biopsy** procedure after neoadjuvant chemotherapy (arm B), the detection rate was 60·8% and the false-negative rate was 51·6%
- ▶ In patients who converted after neoadjuvant chemotherapy from cN+ to ycN0 (arm C), the **IR** was **80·1%** and **FNR** was **14·2%**.
- ▶ The FNR = 24·3% for one node 18·5% for two sentinel nodes removed (arm C).

Sentina Trial Design



Sentinel Lymph Node Surgery after Neoadjuvant Chemotherapy in Patients With Node-Positive Breast Cancer: The American College of Surgeons Oncology Group (ACOSOG) Z1071 Clinical Trial

- ▶ women with clinical T0–4 N1–2, M0 breast cancer who received Neoadjuvant chemotherapy.
- ▶ Following chemotherapy, patients underwent both SLN surgery and ALND.
- ▶ SLN surgery using **both blue dye and a radiolabeled colloid** mapping agent was encouraged.
- ▶ **IR= 93%**
- ▶ **FNR of 12.6%**
- ▶ Only one SLN was excised in 78 patients (12.0%). Of the remaining 525 patients with 2 or more SLNs removed, a **pathological complete nodal response of 41.0%**.
- ▶ Given this FNR threshold, changes in **approach** and **patient selection** that result in greater sensitivity would be necessary to support the use of SLN surgery as an alternative to ALND

Feasibility and reliability of sentinel lymph node biopsy after neoadjuvant chemotherapy in breast cancer patients with positive axillary nodes at initial diagnosis: An up-to date **meta-analysis** of 3,578 patients “2021”

- ▶ In the **SENTINA** and the **ACOSOG Z1071** trials, FNRs were 12% and 14% respectively, and thus higher than the arbitrarily chosen but widely accepted cut-off value of 10%
- ▶ A total of **3578** participants (mean 133 per study, range: 26-637) in **27 trials** were identified for inclusion in this met analysis from 2004 to 2020.
- ▶ **FNR** of SLNB = **3 % to 36 %**. A pooled estimate of **15 %**
- ▶ **23 % with one SLN** removed, **16 %** with two SLNs dissected, and **7 % with the removal of no less than three SLNs**.
- ▶ cN- patients following NACT (**6 %, 7 %**) or early-stage BC without NACT (**7.3 %**)
- ▶ In subgroup analysis, the application of **dual mapping** could clearly decrease the FNR. The FNR was significantly high in the **luminal types**, and it declined with combination method (CEUS+Bd)
- ▶ **IR** = 72 % to 100 %. The combined estimate = **91 %**,
- ▶ it is below the rate recorded for **node-negative BC patients post-NACT (96 %, 94 %)** and **cN- patients without NACT (95 %)**

Post-NACT SLNB

IR= 72- 100% (The pooled IR=91%)

FNR=3 % to 36 %

FNR for a single tracer was 17 % , Dual tracer was 10 %

stages N 1, N2 , and N3 , the combined FNR were 14 % , 10 % and 6 %

Luminal A, 24 %; Luminal B, 29 %, Her-2 overexpression, 7 % , triple negative breast cancer, 11 %

one SLN = 23 % , Two SLN=16 % , no less than three SLNs= 7 %

National and international guidelines on axillary surgical staging in initially node-positive patients receiving neoadjuvant therapy.

- ▶ many questions regarding the marking technique, i.e., the optimal time for marker placement, the number of marked nodes. the optimal number of SLNs to be excised remain unanswered.

Table 2. National and international guidelines on axillary surgical staging in initially node-positive patients receiving neoadjuvant therapy.

National/International:	Staging Recommendation for cN+ → ycN0 Patients	Level of Evidence/Grade of Recommendation	
European Society for Medical Oncology (ESMO) [10]	Sentinel lymph node biopsy (SLNB) can be an option, as long as additional recommendations are followed (e.g., dual tracer, clipping/marking of positive nodes, minimum of three sentinel nodes removed)	III, B	Ann. Oncol. 2019,30, 1674
National Comprehensive Cancer Network (NCCN) [9]	Consider SLNB. Relatively high false-negative rate (FNR) (>10%) can be improved by marking biopsied lymph nodes to document their removal, using dual tracer, and by removing more than 2 sentinel nodes	2B	Version 1.2021—15 January 2021
American Society of Breast Surgeons [13]	If SLNB after neoadjuvant therapy is attempted, dual tracer should be used. If a SLN and/or the clipped node (if clipped) is not identified, an Axillary lymph node dissection (ALND) is recommended	Not provided	accessed on 27 March 2021
Finland [14]	ALND		
Germany (S3 guideline) [15]	ALND		

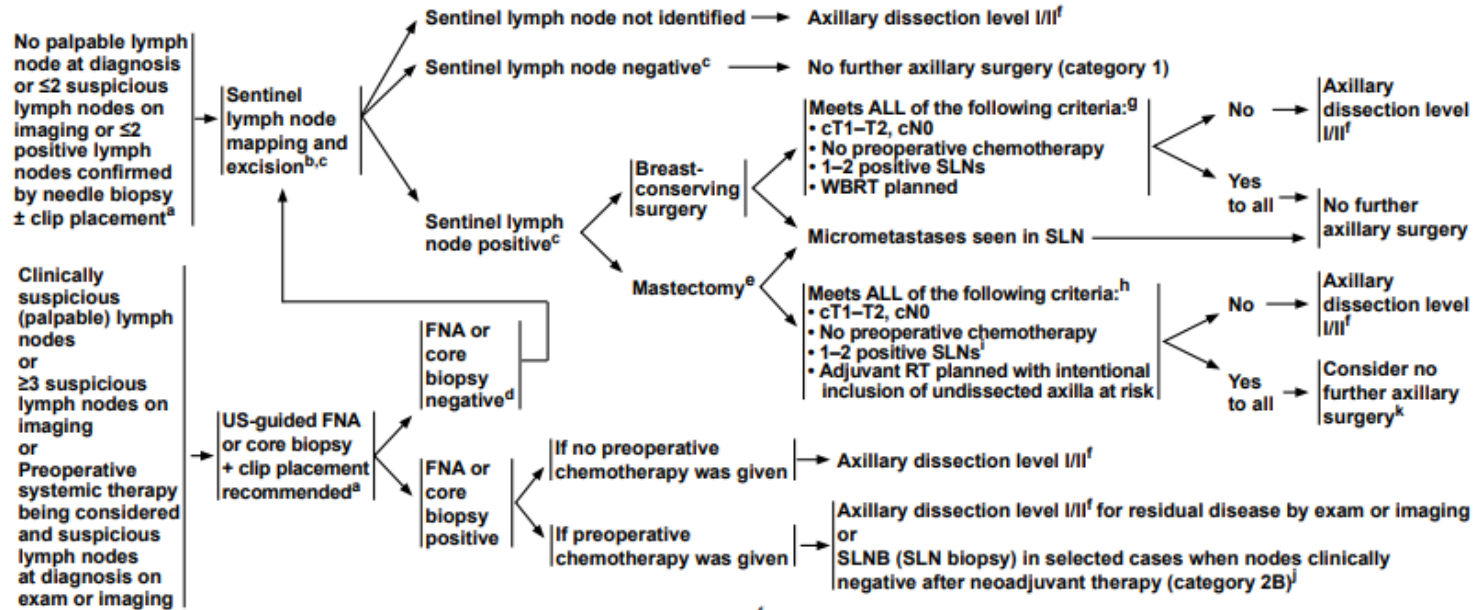


National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022 Invasive Breast Cancer

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CONSIDERATIONS FOR SURGICAL AXILLARY STAGING



^a If a positive lymph node is clipped at biopsy, every effort should be made to remove the clipped node at the time of surgery.
^b SLN mapping injections may be peritumoral, subareolar, or subdermal.
^c Sentinel node involvement is defined by multilevel node sectioning with hematoxylin and eosin (H&E) staining. Cytokeratin immunohistochemistry (IHC) may be used for equivocal cases on H&E. Routine cytokeratin IHC to define node involvement is not recommended in clinical decision-making.
^d If clinically negative axilla before chemotherapy and then have a positive

^f See [Axillary Lymph Node Staging \(BINV-E\)](#).
^g ACOSOG Z0011: Giuliano AE, et al. JAMA. 2017 Sep 12;318(10):918-926.
^h EORTC AMAROS: Donker M, et al. Lancet Oncol. 2014;15(12):1303-10; Rutgers E, et al. Cancer Research. 2019;79(4 Supplement):GS4-01-GS04-01.
ⁱ Limited data exist for ≥3 positive SLNs.
^j Among patients shown to be N+ prior to preoperative systemic therapy, SLNB has a >10% false-negative rate when performed after preoperative systemic therapy. This rate can be improved by marking biopsied lymph nodes to document their removal, using dual tracer, and by removing ≥3 sentinel nodes (targeted axillary

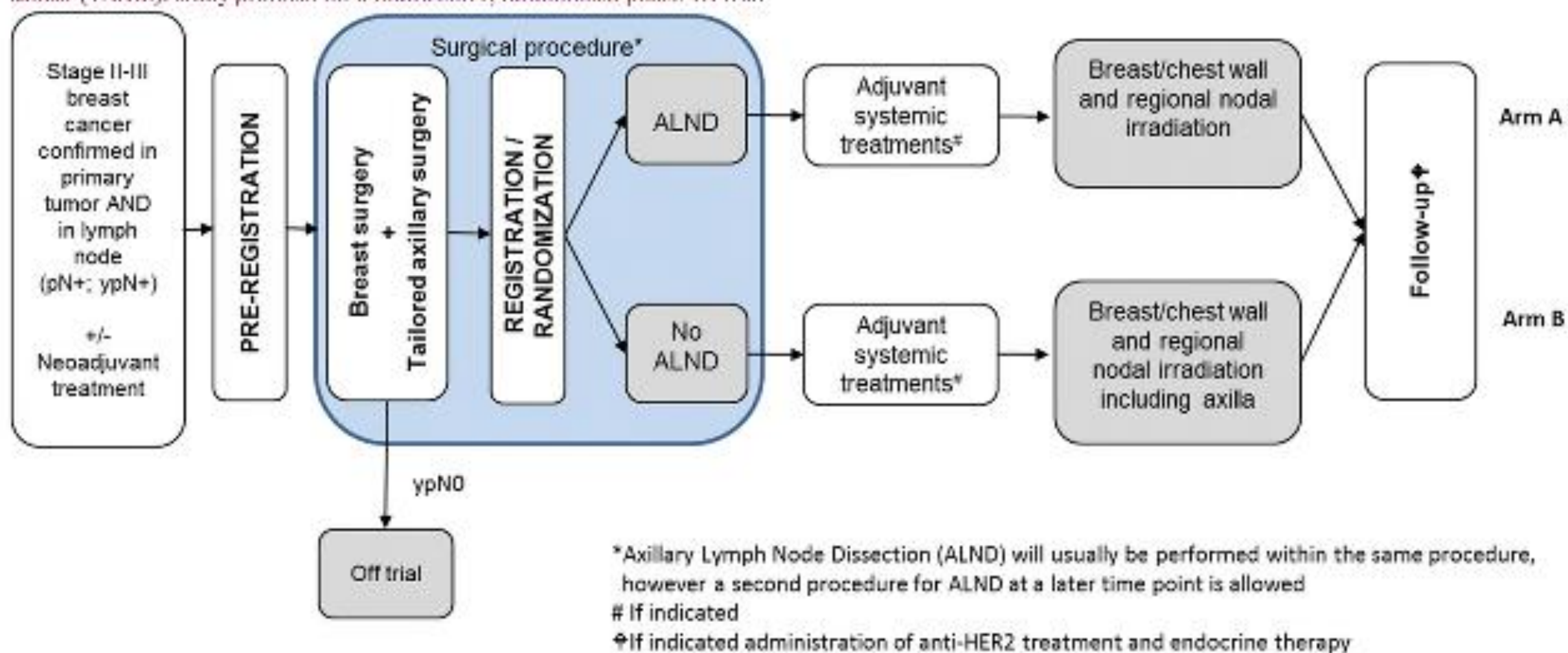
Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS)

- ▶ **International, multicenter**, phase-III, **non-inferiority**, randomized controlled trial (RCT), including **34** study sites from **four** different countries. (Switzerland, Austria, Italy, Hungary).
- ▶ To randomize **1500** patients to either receive TAS followed by ALND and regional nodal irradiation excluding the dissected axilla, or receive TAS followed by regional nodal irradiation including the full axilla.
- ▶ Inclusion criteria:
 - ❖ **Node-positivity detected by imaging** (iN+) and confirmed by pathology
 - ❖ **detected by palpation** (cN1–2) and confirmed by pathology
 - ❖ Node-positivity initially detected by imaging (negative on palpation) and **residual disease intraoperatively confirmed** by pathology (in SLN or non-SLN during surgery) in case of neoadjuvant treatment
 - ❖ Node-positivity initially detected by palpation and residual disease **intraoperatively confirmed by pathology** in case of neoadjuvant treatment
 - ❖ Eligible for primary ALND or SLN procedure with frozen section and either (1) newly diagnosed or (2) isolated in-breast recurrence or second ipsilateral breast cancer (at least 5 years disease free and no prior axillary surgery or loco-regional RT)
 - ❖ **Most suspicious axillary lymph node clipped**

Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS)

- ▶ **AIM: treatment with TAS and axillary radiotherapy is non-inferior to ALND in terms of disease-free survival of clinically node-positive breast cancer patients in the era of effective systemic therapy and extended regional nodal irradiation.**
- ▶ **SLN procedure in combination with the selective removal of all palpable disease and documentation of the removal of the initially biopsy-proven and clipped lymph node (TAD) by specimen radiography.**
- ▶ If **the clip is not documented** in the specimen radiography, the patient is excluded and undergoes ALND.
- ▶ The SLN procedure should preferably be performed by **dual mapping**
- ▶ In addition to the removal of the sentinel nodes, all **palpably suspicious nodes**, defined as either hardened or irregular or very large or a combination, are removed. Levels I–III by palpation is mandatory
- ▶ residual suspicious lymph nodes detected by imaging before the end of adjuvant treatment does neither demand nor prohibit take-back surgery for completion ALND or selective removal of these nodes or an additional RT boost.

TAXIS trial flow chart



Axillary surgical staging techniques: The most important definitions

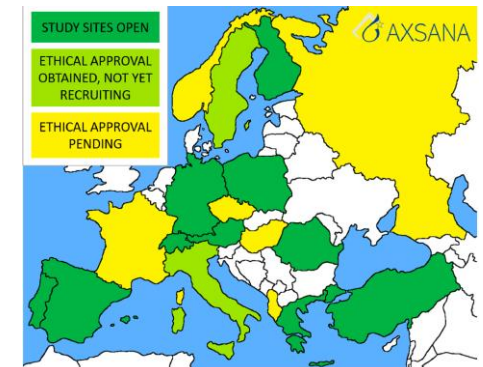
Axillary lymph node dissection (ALND)	Systematic removal of lymph nodes from the axilla, usually level I and II, sometimes including also level III
Sentinel lymph node biopsy (SLNB)	Identification and removal of the sentinel lymph node, usually using radioactive tracer (Technetium-99) or blue dye
Targeted lymph node biopsy (TLNB)	Selective removal of metastatic lymph node(s) marked before neoadjuvant therapy
Targeted axillary dissection (TAD)	Combination of TLNB and SLNB
tailored axillary surgery (TAS)	removal of detectable positive nodes

Possible options for marking and localizing suspicious lymph nodes prior to start of neoadjuvant chemotherapy

Marking	Localization, Advantages	
Clip placement	Preoperative imaging-guided wire localization Intraoperative ultrasound Preoperative placement of a radioactive /magnetic seed, radar marker, or ink into the clipped area (mostly ultrasound-guided)	Largest amount of data Reliable radiographic visibility No radioactivity involved Relatively low cost
Radioactive seed	Intraoperative localization using gamma probe	requires complex radiation safety procedures Signal reduction over time High cost, Allergic reactions sometimes
Magnetic seed	Intraoperative localization using magnetic probe No preoperative wire localization necessary, No radioactivity involved, Transcutaneous localization before skin incision possible	Very limited data Concerns regarding use in patients with pacemakers and implantable defibrillators Standard metal surgical tools should not be used during measurement Allergic reactions rare MRI artifacts High cost Localization in deep tissue may result in weaker signal (recommended depth max. 3.5 cm)
Carbon suspension (Tattooing)	Spot is the first and only non-India ink Food and Drug Administration-approved product It is a sterile, nontoxic, suspension containing No preoperative wire localization necessary No radioactivity involved Low cost	the inability to see the tattooed node at the time of surgery, causing more dissection Marking cannot be localized without surgical exploration of the axilla Possible ink migration Possible skin discoloration In case blue dye is used for SLNB, the ink colors must differ
Radar reflector localization (RRL)		
Radiofrequency identification devices (RFID tags)		

The AXSANA Study: Which Axillary Strategy Is Optimal in the cN+ycN0 Setting?

- ▶ The European Breast Cancer Research Association of Surgical Trialists (**EUBREAST**) has initiated AXSANA (AXillary Surgery After NeoAdjuvant Treatment), a multinational **prospective cohort study** which enrolls cN+ patients undergoing NACT who convert to ycN0.
- ▶ The **aim** of AXSANA is to assess the impact of different surgical staging procedures in the axilla on the **oncologic outcome(5-y DFS, 3-y Ax recurrence)** and on **health-related quality of life**.
 - Possible options for marking and localizing suspicious lymph nodes prior to start of neoadjuvant chemotherapy
 - Which Marking and localization methods for target lymph node?????
 - How Many Nodes Should Be Marked?
 - When Should Lymph Nodes Be Marked?
 - What to Do in Case of a "Lost Marker"?
 - Is TAD Safe for All Patients? TNBC, HER2 overexpressed
 - Beyond Surgical Therapy: Which Fields Should Be Irradiated after TAD?
- ▶ AXSANA is open for all countries provided that patients receive treatment according to current international standards (<http://axsana.eubreast.com>, accessed on 27 March 2021).



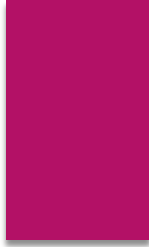
technologies in sentinel node identification

SLN identification technique	General description		Detection Rate (%)	FN Rate (%)
Technetium-99m (99mTc)- 99mTc-sulphur colloid 99mTc-nanocolloid 99mTc-labelled antimony trisulphide 99mTc calcium phytate	very small nanoparticles (<10 nm) are best suited for lymphoscintigraphy or rapid SLND, whereas large particles (>100 nm) display longer retention in the first encountered lymph node and are therefore better suited for SLNB.	Handling of isotopes the injection is done preoperatively	96.5	2.6
Blue Dye methylene blue (MB), isosulphan blue, patent blue V	the location of the injection can be peritumoral, intratumoral, intradermal around the tumour, areolar, and above tumour subdermally	The major problem with blue dyes is the risk of Anaphylaxis MB was reported to have a lower risk of allergic reactions but displayed other side effects, skin necrosis and induration with associated pain, pulmonary oedema, or serotonin syndrome Isosulphan and patent blue have been reported to produce a higher rate of adverse reactions	86.8	18.4
99mTc tilmanocept (Lymphoseek)	dextran based tracer an improved lymphatic uptake, high SLNs retention, rapid injection site clearance and low distal node accumulation translating to accurately improved detection and greater proportion of positive nodes among node-positive patients reduce unnecessary excision of healthy nodes	The radiation dose and exposure to the patient and medical staff are significantly decreased compared to the conventional albumin-based nanocolloid due to smaller effective dose and shorter clearance half-life		

technologies in sentinel node identification

<p>Indocyanine Green Fluorescence (ICG)</p>	<p>fluorescent dye with the absorption and fluorescence spectrum nearinfrared region (NIR).</p> <p>injected either retroareolarly or periareolarly (subdermal or intradermal)</p> <p>high-sensitivity camera in real-time</p> <p>lower cost, fewer adverse effects</p> <p>quick transcutaneous real-time visualization (within several minutes), facilitating the localization of the incision</p>	<p>tendency to identify a larger number of SLNs which is most likely due to the low molecular weight and fast diffusion of ICG through the lymphatics</p> <p>difficulty with ICG fluorescence detection for lymph nodes more than 1 cm below the skin, need for operating theatre lights to be turned off during fluorescence navigation,</p>	<p>97.9</p>	<p>0.6</p>
<p>Superparamagnetic Iron Oxide SPIO</p>	<p>injection of the Sienna (Endomagnetics Ltd, Cambridge, United Kingdom) intravenously or interstitially by the surgeon,</p> <p>The SLN traced using SPIO can be detected using a handheld magnetometer (Sentimag; Endomagnetics stay</p> <p>in the tissue for a prolonged period</p> <p>no problems with toxicity in clinical use or safe waste disposal</p> <p>does not need special handling procedures and scheduling with a nuclear medicine department</p>		<p>97.4</p>	<p>4</p>

technologies in sentinel node identification



<p>Contrast-Enhanced Ultrasound Using Microbubbles CEUS</p>	<p>using intradermal sulfur hexafluoride microbubbles with a mean bubble size of approximately 2.5 mm (range, 1-10 mm), the ultrasound apparatus is readily available in most medical units; the procedure is easy and fast, the contrast agent is cheap, safe, and easily accessible as a complementary preoperative technique</p>	<p>the learning curve for CEUS is relatively long and image interpretation is highly subjective</p>	<p>92.8</p>	<p>10.5</p>
<p>Combination of multiple techniques preoperative CT lymphography (CTLG)+ intraoperative fluorescence navigation+ intraoperative one-step nucleic acid amplification (OSNA)</p>	<p>identification rate was 100 %.</p>			

the dual technique has proven to be clinically effective and is recommended to achieve significantly lower FNR even in challenging conditions such as limited surgeons' experience, or neoadjuvant therapy, prior surgery, poor uptake of the radiotracer, and in obese patients

technologies in breast cancer sentinel node biopsy

Table 2 Pooled estimates of detection rate and false-negative rate for each method

	Detection rate (%)	False-negative rate (%)
ICG	97.9 (96.9, 98.9)	0.6 (−0.3, 1.5)
SPIO	97.4 (96.3, 98.6)	4.0 (1.9, 6.1)
CEUS	92.8 (86.7, 98.8)	10.5 (1.7, 19.4)
Tc	96.5 (95.2, 97.9)	2.6 (0.7, 4.6)
Tc/BD	96.7 (94.3, 99.1)	5.5 (0.9, 10.2)
BD	86.8 (82.7, 91.0)	18.4 (11.9, 24.9)

