AXSANA

(AXillary Surgery After NeoAdjuvant Treatment)

-EUBREAST 3-

A prospective multicenter cohort study to evaluate different surgical methods of axillary staging (sentinel lymph node biopsy, targeted axillary dissection, axillary dissection) in clinically node-positive breast cancer patients treated with neoadjuvant chemotherapy

Study protocol

Clinical Trials.gov
NCT 04373655

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Glossary and Abbreviations

ACOSOG	American College of Surgeons Oncology Group
AGO	German Working Group Gynecological Oncology (Arbeitsgemeinschaft Gynäkologische Onkologie)
ALND	axillary lymph node dissection
cN0	initial clinical node status negative
cN+	initial clinical node status positive
CRF	Case Report Form
DFS	disease-free survival
FNR	false-negative rate
iDFS	invasive disease-free survival
NCCN	National Comprehensive Cancer Network
NACT	neoadjuvant chemotherapy
OS	overall survival
pCR	pathological complete remission
pN0	pathological node status negative
pN+	pathological node status positive
post-NACT	status after neoadjuvant chemotherapy
SLN	sentinel lymph node
SLNB	sentinel lymph node biopsy
TLN	target lymph node = suspicious lymph node that has been marked
TLNB	target lymph node biopsy = targeted removal of the marked target node
TAD	targeted axillary dissection = TLNB + SLNB
ycN0	clinical node status after neoadjuvant chemotherapy negative
ycN+	clinical node status after neoadjuvant chemotherapy positive
ypN+	pathological node status after neoadjuvant chemotherapy negative
ypN0	pathological node status after neoadjuvant chemotherapy positive

Introduction / Rationale

For many decades, axillary lymph node dissection (ALND) has been considered standard of care in breast cancer (BC) patients. The procedure aimed at assessing the pN status (diagnostic / staging) to guide adjuvant therapy decisions as well as ensuring adequate locoregional control (therapeutic). However, ALND is associated with high morbidity and may therefore lead to reduced quality of life in BC patients (1).

In women undergoing primary surgery, ALND as a staging tool has been replaced by the less invasive sentinel lymph node biopsy (SLNB) without compromising the disease-free or overall survival (DFS, OS). Since then, the therapeutic benefit of ALND in patients with clinically occult metastasis in the sentinel lymph node (SLN) has been challenged as well. According to the current national and international guidelines (e.g. ESMO, NCCN, German S3 guideline and AGO recommendations) completion ALND can be safely omitted in selected patients with 1-2 positive sentinel lymph nodes (2,3,4,5).

The feasibility and safety of the SLNB after neoadjuvant chemotherapy (NACT) has been controversially discussed, particularly regarding women who initially presented with positive lymph nodes (cN+) and converted to ycN0 following NACT. In these patients, two large prospective multicenter trials reported a false-negative rate (FNR) of 12 and 14%, respectively (6,7), thus exceeding the generally accepted (albeit arbitrarily chosen) cutoff of 10%. The clinical relevance of an FNR > 10% and its impact on oncological endpoints (DFS, OS) remains unclear. For this reason, numerous national guidelines still recommend ALND in these patients (3,4).

Possible ways to further reduce the FNR in cN+ patients have been extensively discussed in the recent years. In 2016, Caudle et al. reported on a novel surgical approach (TAD = targeted axillary dissection) that consists of inserting a marking (e.g. a clip or a radioactive tracer) into the metastatic lymph node before NACT. In patients in whom the marked lymph node (target lymph node = TLN) and the sentinel node had been successfully removed, the FNR was as low as 1.4% (8). These retrospectively analyzed data from a prospective register support the hypothesis that TAD can improve the relatively low success rates of SLNB and reduce the long-term morbidity of patients undergoing axillary surgery in the neoadjuvant setting.

The optimization of systemic treatment strategies has led to an increase in pathological complete remission (pCR) rates over the last years. pCR rates of up to 70% have been reached in subgroups (9). Conversion to negative lymph node status in patients receiving neoadjuvant

therapy who were initially diagnosed with nodal involvement can be observed in up to 50% of patients (7,10). Therefore, the number of patients undergoing ALND despite negative lymph nodes after NACT is increasing.

Various forms of axillary staging surgery after NACT are currently in use internationally with the aim to ensure oncological safety and to avoid over-therapy (ALND, TAD, SLNB). The choice of the appropriate technique generally depends on the recommendations issued by national panels/associations and surgeons.

According to an analysis of 12,965 women from the U.S. American National Cancer Database, the percentage of patients receiving SLNB alone in this setting increased between 2012 and 2015 from 22.8% to 42.2%. At the same time the number of removed nodes increased as well (> 2 nodes in 63.8% of cases), although the number of detectable sentinel nodes in previous large studies did not exceed two (11). These data show a lack of standardization in this patient subgroup. The surgical approach depends mostly on the personal preferences of the surgeon.

Although the use of TAD in clinical routine is increasing, data from prospective studies are still limited.

Hartmann et al. evaluated the identification rate of the TLN in a prospective single-center feasibility study including 30 patients (12). The TLN could be identified on ultrasound in 25 out of 30 patients (83.3%). In 9 out of 30 (30%) women clip removal could not be confirmed on radiography. The authors concluded that clip marking of the TLN is not a suitable technique for clinical routine due to low visibility and identification rate of the clipped node after NACT.

Siso et al. examined 46 patients undergoing clip marking of the biopsied TLN (13). In 2 out of 46 (4.3%) patients the clip could not be identified preoperatively. In 44 out of 46 patients the TLN was detected on ultrasound and removed. The false negative rate was 4.1%.

Several validating studies are still ongoing. The following studies aim at evaluating the reproducibility of TAD and the feasibility of different marking techniques (carbonic ink, clip, radioactive seed) (14):

Study	**Country**	**Marking technique**
RISAS (NCT 02800317)	The Netherlands	Radioactive seed
SENTA (NCT 03012307)	Germany	Clip
TATTOO (DRKS 00013169)	Germany/Sweden	Carbonic ink

GANEA 3 (NCT 01221688)	France	Clip

Several issues regarding currently used axillary staging techniques remain yet to be clarified. Based on the unclear evidence, the guideline recommendations for the cN+ → ycN0 patients differ strongly. The current ESMO guidelines state that (1) SLNB may be carried out in selected cases, and, if negative, further axillary surgery may be avoided and (2) the FNR of SLNB alone can be improved by marking the biopsied positive node(s) to verify the removal. In Germany, the S3 guideline (last version: 2019) recommends ALND in patients with initial nodal involvement. In contrast, the German Working Group Gynecological Oncology (AGO) changed their recommendations in 2019 and endorsed TAD as technique of choice for this patient subgroup. In several European countries (Sweden, Norway, Finland) ALND is still considered standard of care for these patients. In others, such as Italy, most patients receive SLNB alone without marking and removing the target lymph node. In the current NCCN guidelines the TAD is considered an optional technique. A prospective analysis comparing different techniques regarding feasibility, safety, morbidity and surgical effort is urgently needed. Due to high complexity and discordant recommendations, a randomized trial comparing different techniques is hardly feasible and therefore would not clarify currently open issues within a reasonable timeframe.

Based on the lack of sufficient evidence and discrepancies between different national and institutional standards, the EUBREAST study group (www.eubreast.com) decided to initiate a prospective cohort study as an international project that aims at comparatively evaluating data on axillary staging after NACT.

Study design

International prospective cohort study

Study aims

Primary study aims:

- Evaluation of the 5-year invasive disease-free survival (iDFS) in cN+ → ycN0 patients treated with different axillary staging techniques (ALND, TAD, SLNB, TLNB)

- Evaluation of the 3-year axillary recurrence rate in cN+ → ycN0 patients treated with different axillary staging techniques (ALND, TAD, SLNB, TLNB)
- Evaluation of quality of life and arm morbidity in patients treated with different axillary staging techniques

Secondary study aims:

- Evaluation of the feasibility of different forms of axillary staging techniques regarding:
    - Detection rate of the SLNB
    - Detection rate of the TLN
    - Detection rate of the SLN + TLN
- Evaluation of the success rate of nodal staging using different axillary staging techniques
- Evaluation of the number of removed lymph nodes using different axillary staging techniques and their correlation to complications, arm morbidity and quality of life
- Evaluation of the operating time as a surrogate parameter for surgical resources
- Evaluation of the rate of patients with positive nodes according to the technique used (as a surrogate parameter for the FNR)
- Evaluation of factors (marking technique) associated with successful detection of the TLN
- Evaluation of the impact of experience of centers on the success rates of TAD
- Evaluation of surgical standards of care in different European countries
- Evaluation of treatment decisions in case of ypN+ status following NACT (ALND vs. radiation therapy)
- Evaluation of iDFS in patients with ypN+ status who received ALND or radiation therapy or both
- Analysis of factors contributing to a decreased quality of life and subjective symptoms of arm morbidity, i.e. baseline quality of life and sense of coherence, extent of axillary surgery and other locoregional and systemic therapies received
- Evaluation of economic resources required for different forms of axillary staging techniques (material costs, operative time etc.)

Inclusion and exclusion criteria

Inclusion criteria

- Signed informed consent form
- Primary invasive breast cancer (confirmed by core biopsy)
- cN+ (confirmed by core biopsy/fine needle aspiration or presence of highly suspicious axillary node[s] on imaging)
- In case a minimally invasive biopsy of axillary lymph node(s) has been performed and yielded a negative or inconclusive result, patients may be included if the final classification after imaging-pathology-correlation is cN+
- cT1-cT4c
- Scheduled for neoadjuvant systemic therapy
- Female / male patients ≥ 18 years old

Exclusion criteria

- Distant metastasis
- Recurrent breast cancer
- Inflammatory breast cancer
- Extramammary breast cancer
- Bilateral breast cancer
- History of invasive breast cancer, DCIS or any other invasive cancer
- Confirmed or suspected supraclavicular lymph node metastasis
- Confirmed or suspected parasternal lymph node metastasis
- Axillary surgery before NACT (e.g. SLNB or nodal sampling)
- Pregnancy
- Less than 4 cycles of NACT administered
- Patients not suitable for surgical treatment

Registration and therapy

All patients with histologically confirmed invasive breast cancer and suspicious ipsilateral axillary lymph node(s) on ultrasound and/or clinical examination should be informed about the possible participation in the AXSANA study. The inclusion and exclusion criteria are verified by the investigator and written informed consent is obtained from the patient. The pretherapeutic evaluation of the suspicious node is conducted using core biopsy or fine needle aspiration.

Surgical treatment, pathological assessment and postoperative locoregional and systemic therapy should be conducted according to institutional and national standards. Since the AXSANA study in a non-interventional trial, the study sites do not deviate from their own institutional protocol at any timepoint.

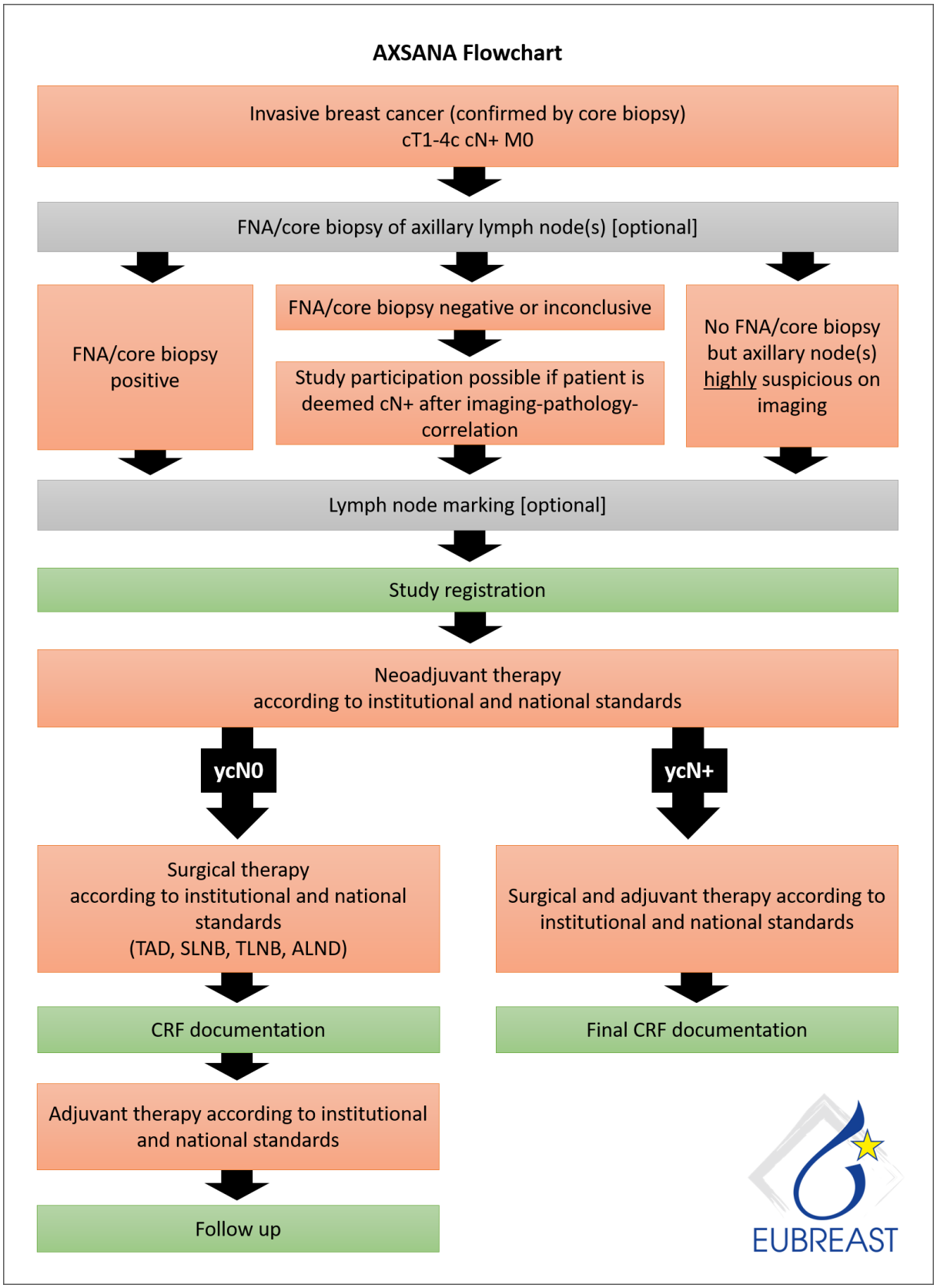
Tissue from the axilla must be clearly identified as SLN, TLN or non-SLN. In case the SLN and the TLN are the same node, this must be documented.

The follow up on patient status is conducted yearly during the first 5 years after surgery. The follow up on arm morbidity and quality of life is conducted at baseline (i.e. between 4 weeks before surgery and the day of surgery) and after 1, 3 and 5 years.

Evaluation of the quality of life

The quality of life is to be evaluated using standardized forms that are included in the CRF:

- EORTC QLQ-C 30
- EORTC QLQ BR 23
- Lymph ICF
- Sense of coherence (SoC)
- Three questions concerning training activity and smoking


AXSANA Flowchart
Invasive breast cancer (confirmed by core biopsy)
cT1-4c cN+ M0
FNA/core biopsy of axillary lymph node(s) [optional]
FNA/core biopsy positive
FNA/core biopsy negative or inconclusive
Study participation possible if patient is deemed cN+ after imaging-pathology-correlation
No FNA/core biopsy but axillary node(s) highly suspicious on imaging
Lymph node marking [optional]
Study registration
Neoadjuvant therapy
according to institutional and national standards
ycN0
ycN+
Surgical therapy
according to institutional and national standards
(TAD, SLNB, TLNB, ALND)
Surgical and adjuvant therapy according to institutional and national standards
CRF documentation
Final CRF documentation
Adjuvant therapy according to institutional and national standards
Follow up
EUBREAST

Data management and analysis

Data management and analysis are conducted by the EUBREAST study group and its affiliates. All patients who fulfill inclusion criteria should be recorded in the study identification list that remains at the study site. For further analysis pseudonymized data are either filled in the CRF by the study site and forwarded to EUBREAST e.V. for inclusion in the electronic database or transmitted directly by the study site via eCRF. Are the data insufficient for evaluation of predefined study aims, the center will be requested to provide further pseudonymized surgical and pathological details.

Statistical considerations

The analysis will be conducted using descriptive statistics.

Funding

The study will be supported by the AGO-B (study group of the German Working Group Gynecological Oncology), the AWOgyn (the German Working Group for Reconstructive Surgery in Oncology-Gynecology) and a grant from the Claudia von Schilling Foundation for Breast Cancer Research. Further grants may be applied for.

Target accrual

Unlimited

Study duration

Primary study endpoint: 10 years (5 years of enrollment and 5 years follow up)
Secondary study endpoints: non-definable

Amendments

Amendment 1 (26.10.2020)	Inclusion criteria: • "cN+ (confirmed by core biopsy or fine needle aspiration)" changed to: "cN+ (confirmed by core biopsy/fine needle aspiration or presence of highly suspicious axillary node[s] on imaging)" • Added: "In case a minimally invasive biopsy of axillary lymph node(s) has been performed and yielded a negative or inconclusive result, patients may be included if the final classification after imaging-pathology-correlation is cN+" • „cT1-3" changed to „cT1-cT4c" The following exclusion criteria have been added: • Bilateral breast cancer • History of invasive breast cancer, DCIS or any other invasive cancer • Confirmed or suspected supraclavicular lymph node metastasis • Confirmed or suspected parasternal lymph node metastasis • Axillary surgery before NACT (e.g. SLNB or nodal sampling) Evaluation of the quality of life: "Three questions concerning training activity and smoking" added AXSANA Flowchart changed according to new inclusion and exclusion criteria Funding: "Further grants may be applied for" added Target accrual added Study duration added
Amendment 2 (09.07.2023)	Duration of study changed Number of cases changed Details of the study administration updated

Protocol Change Log

Version	Changes
5.3	Protocol Change Log added (previously a separate document) Study administration updated
5.2	Amendment 09.07.23 (there is no version 5.1 – skipped to keep numbering as in the German version)
5.0.15	Head of National Steering Committee of Hong Kong added
5.0.14	Head of National Steering Committee of Bulgaria added
5.0.13	Head of National Steering Committee of Belgium added
5.0.12	Head of National Steering Committee of Thailand added and affiliation of Head of Steering Committee of Germany updated
5.0.11	Head of National Steering Committee of Mexico, United Kingdom and Slovenia added; affiliation of Organizing Committee member updated
5.0.10	Head of National Steering Committee of Israel added
5.0.9	Head of National Steering Committee of Peru added
5.0.8	Head of National Steering Committee of Azerbaijan added
5.0.7	Head of National Steering Committee of Albania added
5.0.6	Heads of National Steering Committee of India and Czech Republic added
5.0.5	Timepoint of baseline QoL evaluation specified
5.0.4	International Steering Committee and International Steering Board defined Statistician added
5.0.3	Head of National Steering Committee of France corrected Organizing Committee added
5.0.2	Head of National Steering Committee of Finland and Norway added
5.0.1	Head of National Steering Committee of Turkey added
5.0	Amendment 26.10.20
4.6.5	Address of Dr. Isabel Rubio corrected
4.6.4	Head of National Steering Committee of Romania added Denmark removed (not participating)
4.6.3	Follow up intervals corrected (old: year 1, 3, 5; new and CRF-conform: yearly in the first 5 years)

4.6.2	Head of National Steering Committee of Portugal added
4.6.1	Head of National Steering Committee of Switzerland added
previous versions	redactional changes only

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