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Omission of axillary sentinel lymph node biopsy in early invasive breast cancer

Toralf Reimer *

Department of Obstetrics and Gynecology, University of Rostock, Südring 81, 18059, Rostock, Germany

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ABSTRACT

Local treatment of the axilla in clinically node-negative (cN0) early breast cancer patients with routine sentinel lymph node biopsy (SLNB) is debated after publication of ACOSOG Z0011 data in 2010. Currently, prospective randomized surgical trials investigating the omission of SLNB in upfront breast-conserving surgery (BCS) and in the neoadjuvant setting, respectively. Several prospective randomized trials (SOUND, INSEMA, BOOG 2013–08, and NAUTILUS) with axillary observation alone versus SLNB in cN0 patients and primary BCS have primary objectives to evaluate oncologic safety when omitting SLNB. The Italian SOUND trial was the earliest to open in 2012 and has completed accrual in 2017. First oncologic outcome data are expected soon for SOUND and at the end of 2024 for INSEMA. Improvements in systemic treatments for breast cancer have increased the rates of pathologic complete response (pCR) in patients receiving neoadjuvant systemic therapy (NAST), offering the opportunity to de-escalate surgery in patients who have a pCR. Two prospective single-arm trials (EUBREAST-01, ASICS) include only patients with the highest likelihood of having a pCR after NAST (triple-negative or HER2-positive breast cancer) and type of surgery will be defined according to the response to NAST rather than on the classical T and N status. The ongoing trials will hopefully help us to understand whether we might take the best therapeutic decisions without the pathologic evaluation of nodal status.

1. Introduction

Axillary nodal status has long been regarded as the most important prognostic factor together with tumor size and was used for guidance of postoperative systemic and radiotherapy. With the growing understanding of tumor biology, at least systemic treatment is now indicated and targeted according to intrinsic subtypes.

The publication of ACOSOG Z0011 trial outcomes [1,2] opened a decade of de-escalation trials for axillary surgery in early breast cancer. After ASCO presentation at the meeting in 2010 and publication of the survival data with a median follow-up of 6.3 years the decision-making process of national funding institutions and ethics commissions changed significantly for submitted randomized trial designs using the omission of SLNB as experimental arm. The Italian SOUND trial [3] was the earliest to open in 2012 and has completed accrual in 2017.

1.1. Upfront surgery: guideline recommendations

Axillary SLNB should be considered as standard procedure for axillary staging of early breast cancer for clinically node-negative (cN0) patients age <70 years without significant competing comorbidities. According to current Ontario Health (Cancer Care Ontario) and ASCO guideline the SLNB is not required for patients ≥70 years with T1cN0 invasive breast cancer, that is hormone receptor-positive and HER2-negative [4]. This is based on the Choosing Wisely statement released by the Society of Surgical Oncology [5]. Importantly, this recommendation is open for patients with breast-conserving surgery (BCS) and mastectomy, respectively. If omission of SLNB is an option, interdisciplinary discussion regarding postoperative radiotherapy and/or hormonal treatment should be considered before surgery.

This recommendation for omission of SLNB in patients ≥70 years with low-risk breast cancer is supported indirectly by the CALGB 9343 trial [6]. Although this trial was focused on the role of breast irradiation in patients age ≥70 years who received tamoxifen after lumpectomy for early breast cancer, nearly two thirds of the patients had no axillary staging procedure. Published long-term follow-up has demonstrated low rates of in-breast recurrence and low rates of axillary recurrence. Among those who did not undergo axillary intervention, there were no axillary

* The University of Rostock, Department of Obstetrics and Gynecology, 18059, Rostock, Suedring 81, Germany.
E-mail address: toralf.reimer@med.uni-rostock.de.

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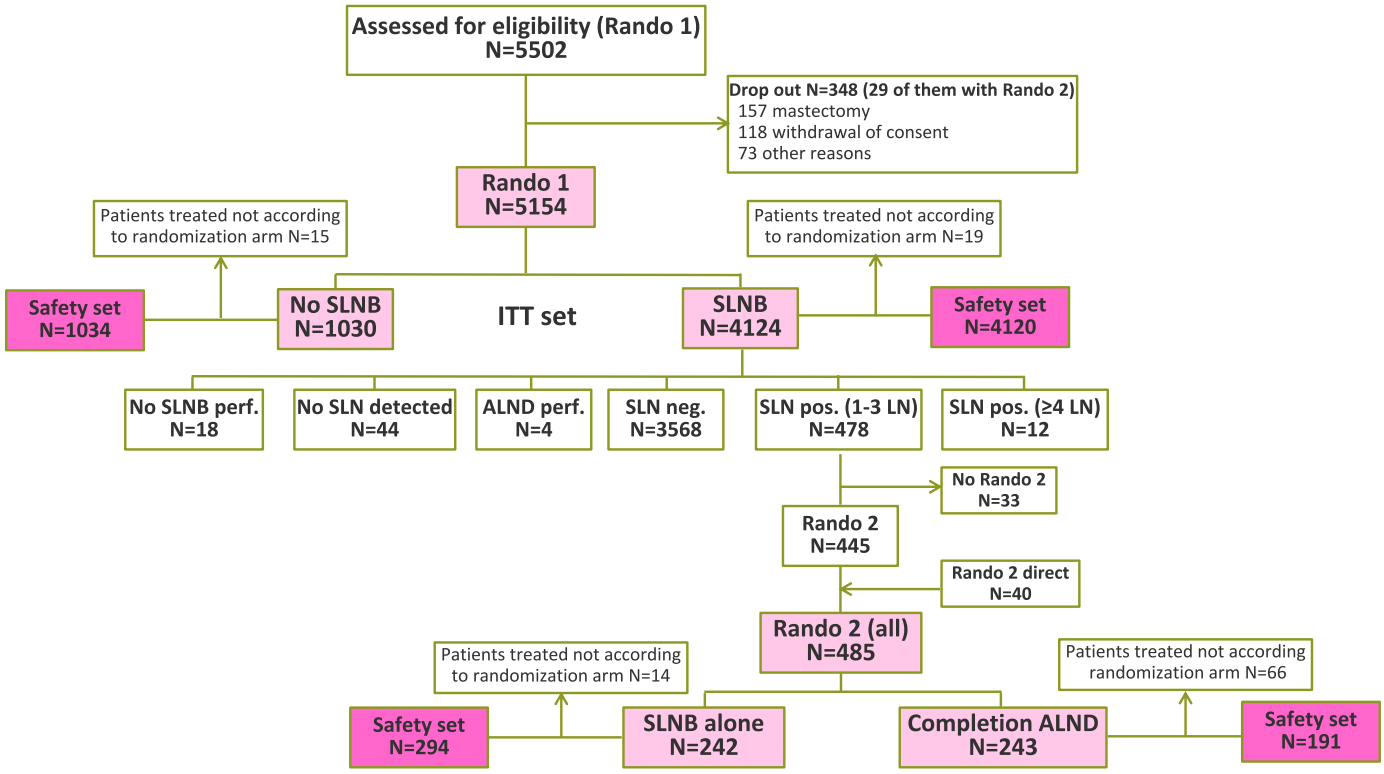

Fig. 1. CONSORT diagram of fully recruited INSEMA trial [15]. Abbreviations: SLNB = sentinel lymph node biopsy; ITT = intention-to-treat; perf. = performed; SLN = sentinel lymph node; ALND = axillary lymph node dissection; neg. = negative; pos. = positive; LN = lymph node.

recurrences in the tamoxifen plus radiation therapy group (N = 195); there were six of 200 in the tamoxifen alone group.

The NCCN Guidelines for breast cancer (current version 4.2022) released over the last years the following statement [7]: In the absence of definitive data demonstrating superior survival, the performance of axillary staging may be considered optional in patients who have particularly favorable tumors, patients for whom the selection of adjuvant systemic and/or radiotherapy is unlikely to be affected, the elderly, or those with serious comorbid conditions.

The German AGO Breast Committee also permits the omission of SLNB in elderly patients with cN0 status under certain conditions (≥70 years, comorbidity, pT1, hormone receptor-positive, HER2-negative). In this scenario, the indication for SLNB is rated +/− [8]. The final decision should be made individually and in the context with postoperative radiotherapy planning. The omission of radiotherapy after BCS in Germany is only an option for patients with pathologically proven N0 (pN0) status.

1.2. *Upfront surgery: ongoing clinical trials*

There are several ongoing prospective randomized trials investigating the omission of axillary SLNB in cN0 patients with early breast cancer and upfront surgery. A comprehensive overview about three European (SOUND, INSEMA, and BOOG 13–08) and an Asian (NAUTILUS) adjuvant surgical trials were recently published in *The Breast* by Hersh and King [9]. Additionally, the SOAPET trial (China) was designed as single-arm study more focussing on preoperative axillary assessment.

Importantly, all discussed trials are restricted to BCS, but they are not limited to the elderly population or to a distinct intrinsic subtype, respectively. Currently, there is no prospective randomized trial registered investigating the need of SLNB versus no axillary intervention in cN0 patients with early-stage, invasive breast cancer undergoing primary mastectomy.

It is assumed that reduced axillary intervention leads to improved quality of life (QoL). Because QoL considerations are the primary motivation for abandoning SLNB, there is a need for randomized trials with QoL as a defined primary endpoint [10]. However, all ongoing trials evaluating the omission of SLNB have survival endpoints as primary outcome. First oncological outcome data are expected soon for SOUND and at the end of 2024 for INSEMA.

The three European trials were designed to compare SLNB versus observation when physical examination and axillary ultrasound (AUS) are negative in patients with BCS. The Italian SOUND (NCT02167490), German/Austrian INSEMA (Intergroup Sentinel Mamma; NCT02466737), and Dutch BOOG 2013–08 (NCT02271828) trials focus on omission of SLNB with different inclusion criteria [11].

The SOUND trial is a prospective randomized multicentric study, designed by the European Institute of Oncology (EIO) of Milan. Eligibility and exclusion criteria were published by Gentilini and Veronesi [3,12]. Briefly, cT1N0 patients treated with BCS underwent an AUS in order to rule out evident or suspicious nodal involvement. Patients with either negative AUS or negative fine-needle aspiration (FNA) were randomized to two groups: SLNB (+ axillary lymph node dissection [ALND] in all cases with SLN macrometastases) versus no axillary surgery. The mandatory completion ALND is a critical point with respect to the ACOSOG Z0011 data [1,2]. The primary endpoint is distant disease-free survival (DDFS) with the assumption to obtain reliable results in a shorter period of time compared to overall survival. Overall, 1560 women (780 per arm) were required to establish whether the observation group did not have worse outcome than the SLNB group, accepting a maximum tolerable 5-year DDFS of 94% [3]. The first patient was included in January 2012; recruitment closed after 1464 patients in June 2017.

Previous data regarding side effects or impact on physical function and symptoms were published for the SOUND trial. Gentilini et al. reported the first 180 recruited SOUND patients using the QuickDASH (Disability Arm and Shoulder) questionnaire for the assessment of the

physical function of the upper limb as a secondary outcome. Patients who underwent SLNB had a higher score of disability in the early postoperative period (one week after surgery) compared to patients with no SLNB. After 6 and 12 months, both groups' scores decreased to values similar to baseline. Patients with completion ALND (N = 5) had a persistently higher rate of disability over the entire follow-up period [13].

The goal of the ongoing German/Austrian INSEMA study is to show that a reduced extent of axillary surgery is not inferior with regard to invasive disease-free survival (IDFS) outcome compared to the standard arm in early-stage breast cancer patients. In this trial, patients with breast cancer ≤5 cm (T1/T2), node-negative axilla (clinically and/or per imaging), planned BCS, and age ≥18 years were recruited [14]. Patients were first randomized to either no axillary surgery or SLNB in a 1:4 allocation. Patients with SLNB and pN+(sn) status were secondly randomized (1:1 ratio) to either SLNB alone or completion ALND in the case of <4 involved nodes (1–3 macrometastases). Due to the unequal-sample-size design for the primary outcome (Rando 1), the total number of patients amounts to 5505.

INSEMA enrolled patients between September 2015 and April 2019 in 142 German and nine Austrian study sites (Fig. 1). The median age at diagnosis was 62.0 years. Most patients presented with low-risk breast carcinoma (78.6% pT1 stage, 98.5% hormone receptor-positivity, 3.6% HER2-positivity, and 3.6% G3 tumors). The majority (73.3%) had an invasive carcinoma of no special type (72.7% in SLNB versus 75.8% in no SLNB arm), and 87.1% had Ki-67 values ≤ 20% [15].

Due to the frequent use of protocol-prohibited nodal fields in the ACOSOG Z0011 trial [16], a preplanned central quality assurance review process for radiotherapy planning was included in the INSEMA protocol, and the associated findings were published in 2020 [17]. Assuming ≥80% of prescribed breast dose as the optimal dose for curative radiation of low-volume disease in axillary lymph nodes, at least 50% of reviewed INSEMA patients received an adequate dose in axillary level I, even with contemporary 3D techniques. Dose coverage was much less in levels II and III, and far below therapeutically relevant doses. No differences between treatment arms were observed. In addition to the SOUND trial, INSEMA aims to clarify certain problems of ACOSOG Z0011: distribution of axillary isodoses with standard whole-breast irradiation and ignoring of SLNB with micrometastases for second randomization.

Patient-reported outcomes (PROs) as a secondary endpoint were reported for the complete INSEMA population at the San Antonio Breast Cancer Symposium 2021 as oral presentation. PROs were assessed for patients with no axillary surgery, SLNB alone, and ALND. QoL questionnaire EORTC QLQ-C30 and its breast cancer module (BR23) were used at baseline (pre-surgery) and 1, 3, 6, 12, and 18 months after surgery. There were significant differences for the BRBS (breast symptoms) and BRAS (arm symptoms) scores favoring the no SLNB group in all post-baseline assessments. Patients in the SLNB group showed significantly and clinically relevantly higher scores for BRAS (differences in mean values ≥ 5.0 points at all times), including pain, arm swelling, and impaired mobility in all postoperative visits, with the highest difference at one month after surgery. Scoring of the QLQ-C30 questionnaire revealed no relevant differences between the treatment groups, although some comparisons were statistically significant [15].

The Dutch BOOG 2013–08 trial is a non-inferiority randomized controlled multicenter trial. Women with cN0 T1-2 invasive breast cancer undergoing BCS will be randomized to SLNB versus no SLNB. In the case of SLNB and involved nodes, additional treatment is provided according to local guidelines. In contrast to SOUND and INSEMA, patients with neoadjuvant chemotherapy are included as well. The primary endpoint is the regional recurrence rate after 5 years; the estimated sample size is 1644 patients [18]. The sample size was adjusted in September 2021 to N = 1730 due to 5% rate of protocol violations. The full recruitment of the trial was reported in January 2022 on the BOOG study center website [19].

All European trials do require negative axillary imaging, predominantly with AUS. The Chinese SOAPET trial is a two phase study designed as single-arm assignment with a target number of N = 1528. In the first stage, the negative predictive value is evaluated in patients with negative preoperative axillary assessment, including axillary PET (mSUV <0.27) and routine imaging examinations (physical examination, AUS, MR imaging). In the second stage, SLNB will be spared in the patients with negative preoperative axillary assessment [20].

Finally, the NAUTILUS trial (Korea) is comparable to the first randomization of INSEMA trial with a 1:1 allocation between treatment arms (SLNB versus no axillary intervention). AUS is mandatory before surgery with predefined imaging criteria for inclusion [21]. A total of 1734 patients are needed, considering a 5% non-inferiority margin, 5% significance level, 80% statistical power, and 10% drop-out rate [22].

1.3. Neoadjuvant setting

Patient with an indication for neoadjuvant systemic therapy (NAST) and initially cN0 status should not undergo axillary intervention (SLNB, core needle biopsy, or FNA) before NAST. For post-NAST ycN0 patients, the performance of SLNB is recommended as current standard procedure (German AGO recommendation ++) [8]. A German-wide NOGGO MONITOR 24 survey demonstrated that nearly all surgeons (N = 116) accepted this approach for daily practice [23]. In cN0 patients, study-level meta-analyses involving >6000 patients report sentinel node identification rates of 90–96% and false-negative rates of 6–12% [24], results slightly inferior to those seen in upfront surgical setting.

Improvements in systemic treatments for breast cancer have increased the rates of pathologic complete response (pCR) in patients receiving NAST, offering the opportunity to de-escalate surgery in patients who have a pCR. Two ongoing European trials (EUBREAST-01, ASICS) include only patients with the highest likelihood of having a pCR after NAST (triple-negative or HER2-positive breast cancer) and type of surgery will be defined according to the response to NAST rather than on the classical T and N status.

Background for this approach are published data of retrospective cancer registry analyses. A MD Anderson study showed that breast pCR after NAST correlated with nodal pCR after NAST. This study included 290 patients with triple-negative (TNBC)/HER2-positive breast cancer with T1-2 cN0/iN0 disease. Of the 116 patients (40.4%) who had a breast pCR, none (0.0%) had evidence of axillary lymph node metastases after NAST. Among 237 patients with biopsy-proven pre-treatment N1 disease, 89.6% of patients with a breast pCR had no evidence of axillary metastases after NAST, while 57.5% of patients without a breast pCR had residual axillary metastases [25].

Rates of breast and nodal pCR with NAST differ with tumor subtypes and are higher in TNBC or HER2-positive tumors when compared to hormone receptor-positive/HER2-negative disease [26]. An analysis of the Netherlands Cancer Institute (N = 298 with initially cN0 status before NAST) confirmed the MD Anderson study [27]. In general, the SLNB-positive rate was low among TNBC/HER2-positive subtypes (3.1%); and was extremely low (0.0%) in cases with pCR in the breast (N = 98).

Barron et al. extended the retrospective evaluation of nodal positivity rates in cN0 patients with HER2-positive (N = 3062) and TNBC (N = 2315) with a breast pCR after NAST using the National Cancer Database [28]. In patients with cN0 HER2-positive disease or TNBC with breast pCR, the nodal positivity rate was 1.6% for both subtypes. Rates of ypN-positivity were higher in patients with cN0 and residual disease in the breast after NAST (16.9% for HER2-positive and 12.6% for TNBC). Among patients with initially cN1 and HER2-positive disease, 43.3% achieved breast pCR with 12.4% of those being ypN-positive. Corresponding data for cN1 TNBC were 37.3% for achieving breast pCR and 14.1% for being ypN-positive.

Identical rates for ypN-positivity in initially cN0 patients with breast pCR after NAST (1.6% for ER+/HER2+, 0.0% for ER-/HER2+, and 1.5%

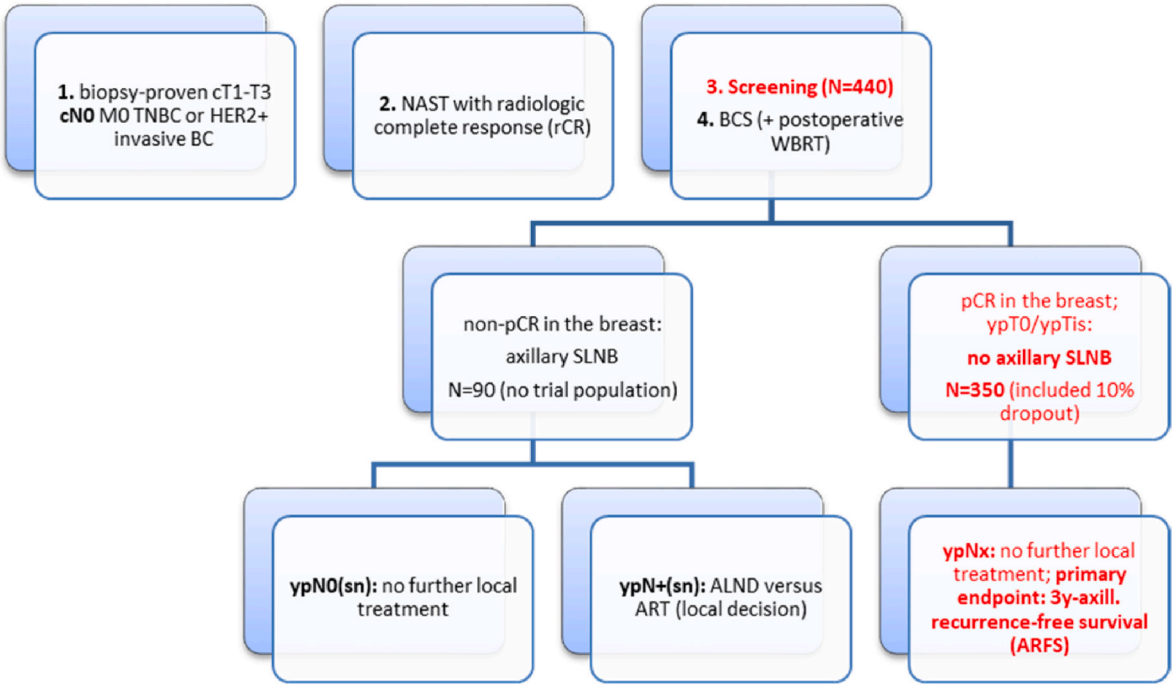

Fig. 2. Flow chart of the EUBREAST-01 (GBG104) trial according protocol amendment#2. Abbreviations: TNBC = triple-negative breast cancer (ER <10%/PgR <10%/HER2-negative); BC = breast cancer; NAST = neoadjuvant systemic therapy; BCS = breast-conserving surgery; WBRT = whole-breast radiotherapy; SLNB = sentinel lymph node biopsy; pCR = pathologic complete response; cALND = completion axillary lymph node dissection; ART = axillary radiotherapy; ER = estrogen receptor; PgR = progesterone receptor.

for TNBC subtype) were reported by Samiei et al. using data from the Netherlands Cancer Registry [29]. The odds of ypN0 was decreased in case of clinical T3 stage (OR 0.59), cN1 (OR 0.03), and ER-positive/HER2-negative subtype (OR 0.30). Taken together, in patients with cN0 HER2-positive disease or TNBC with breast pCR, the nodal positivity rate was less than 2%, which supports consideration of omission of axillary surgery in this subset of patients.

Whether the safe determination of breast pCR will be possible in future through minimally invasive methods using vacuum-assisted core biopsy (VACB) remains to be seen. Recently, Kuerer et al. published a small single-arm phase 2 trial with complete elimination of open breast surgery in exceptional responders to NAST [30]. The omission of axillary and breast surgery in highly selected patients with an image-guided VACB-determined breast pCR in TNBC and HER2-positive disease seems feasible. At a median follow-up of 26.4 months, no ipsilateral breast tumor recurrence occurred in these 23 patients with initially cN0 status.

EUBREAST-01 (NCT04101851) is a prospective non-randomized, single-arm surgical trial for patients with initially cN0 status and HER2-positive disease or TNBC with breast pCR (ypT0 or ypTis). After radiologic complete remission (rCR) at the end of NAST all patients will be treated with lumpectomy (BCS) alone without any axillary surgery. Approximately 80% of these patients will be assigned to the single study arm (no axillary SLNB) due to breast pCR at the final pathology (target number N = 350). The trial will be closed for recruitment in December 2023 at the latest. The flow chart of EUBREAST-01 trial according protocol amendment#2 is shown in Fig. 2. A randomized design is not useful due to expected extremely low axillary recurrence rates after 3 and 5 years for the experimental arm. The measure of success is a 3-year axillary recurrence-free survival rate (primary outcome) of at least 98.5%. In case of a two-arm randomized setting the risk for underpowered testing because of low number of events will be considerably high [31].

The Dutch ASICS trial (NCT04225858) is single-arm trial open to both BCS and mastectomy patients in which SLNB will be omitted in HER2-positive or TNBC patients with a radiographic complete response on MR imaging after NAST. The cN0 status will be confirmed with physical examination, AUS and axillary PET. The primary endpoint is 5-year rate of axillary recurrence; an axillary recurrence rate of <6% at 5 years will be considered acceptable [9].

2. Conclusions

Currently, axillary surgery for breast cancer is a staging procedure that does not seem to influence breast cancer mortality, since the risk of developing metastasis depends mainly on the biologic behavior of the primary tumor (seed-and-soil model) [32]. Postsurgical therapy should therefore be based on biologic tumor characteristics rather than nodal involvement. However, some recommendations are still influenced by nodal status.

- the indication for regional node irradiation in ≥pN2a disease,
- the decision of adding chemotherapy to endocrine treatment in luminal B tumors,
- the type and duration of endocrine treatment in hormone receptor-positive disease,
- the adjuvant indication for dual anti-HER2 therapy,
- the postneo-/adjuvant indication for abemaciclib considering monarchE data, and
- the postneoadjuvant indication for olaparib in patients with gBRCA mutation.

At the moment, it is still unclear what level of information is needed to properly treat our patients. The ongoing trials will hopefully help us to understand whether we might take the best decisions without the pathologic evaluation of nodal status. Improved staging power of imaging modalities is further desired in light of the low sensitivity of AUS. The discussed upfront surgical trials cannot provide all the answers; for example, it remains unclear whether patients without SLNB can be offered partial breast irradiation alone in low-risk situations (allowed

option in SOUND) and whether SLNB can also be avoided in patients with stage T1-2 tumors who have a mastectomy indication.

Declaration of competing interest

The author has no competing interests to declare.

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