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The influence of breast cancer subtypes on axillary ultrasound accuracy: A retrospective single center analysis of 583 women

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ABSTRACT

Introduction: Axillary ultrasound staging (AUS) is an important tool to guide clinical decisions in breast cancer therapy, especially regarding axillary surgery but also radiation therapy. It is unknown whether biological subtypes influence axillary staging using ultrasound (AUS).
Method: This is a retrospective single center analysis. All patients with breast cancer, a preoperative axillary ultrasound and a complete surgical axillary staging were included between 1999 and 2014, except patients with neoadjuvant chemotherapy (NACT). The results of the AUS were compared with final pathological results. Biological subtypes were identified by immunohistochemistry.
Results: 583 women were included in the study. Sensitivity, Specificity, positive and negative predictive value for AUS were 39%, 96%, 91% and 83%. While sensitivity was significantly lower in Luminal A and B patients (25.0%; 39.8%) as compared to non Luminal breast cancer patients (TN 68.8%; Her2+ 71.4%; $p = 0.0032$), there were no significant differences between the groups with respect to specificity, PPV and NPV.
Conclusion: Solely regarding sensitivity of AUS, our study could show significant differences between biological subtypes of breast cancer with lower sensitivity in Luminal patients. While PPV was excellent, standing for a low overtreatment rate using AUS for clinical decision making, sensitivity was poor overall, comparable to the results of other studies.

Introduction

Axillary ultrasound (AUS) in breast cancer patients is an important tool to guide treatment decisions. Sentinel lymph node biopsy (SNB) is the standard technique to determine axillary lymph node status [1,2]. However recent publications changed the management of axillary surgery enhancing the need for an excellent axillary staging method before surgery.

Neoadjuvant chemotherapy (NACT) has been increasingly used especially in Europe which results in several unresolved issues.

The use of sentinel node biopsy (SNB) after NACT has been extensively investigated and prospective trials indicate that only patients with a clear negative axillary status after NACT may safely undergo SNB [3]. Moreover radiation oncologists guide their treatment decision using the axillary status before NACT, and treatment response is therefore not taken into account. Thus there is an urgent need for a pre- and post-neoadjuvant axillary staging method with high sensitivity and an excellent positive predictive value (PPV) to avoid over-as well as undertreatment.

In addition, retrospective data suggest that patients with a favourable tumorbiology and a clearly negative axillary staging might omit axillary surgery at all [4,5]. There are some prospective

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trials ongoing for patients with clinically node negative breast cancer randomising between sentinel biopsy versus no axillary surgery. In this respect the need for an accurate preoperative staging method with excellent specificity and negative predictive value (NPV) for the axilla is important in order not to undertreat patients in the future.

While clinical axillary staging by palpation is extremely unaccurate [6,7], AUS may provide more relevant information. Recently the largest analysis regarding accuracy of AUS demonstrated a 60% sensitivity with an 80% PPV and a 90% specificity with a 75% NPV [8]. This means that AUS did not find 40% of axillary lymph node metastases while the number of negative lymph nodes beside an abnormal ultrasound remained high at 20%. The number of pathologic lymph nodes in patients with a normal AUS was 25%. While specificity was acceptable above 90%, the NPV was quite low (<80%) and so AUS should not be used to select patients not needing surgical axillary staging outside clinical trials so far. These data are in line with other publications and demonstrate that AUS alone is not accurate enough for axillary staging [9,10].

The description of breast cancer intrinsic subtypes changed the management of breast cancer within the last 10 years. There are differences in the burden of lymph node metastases regarding subtypes with the highest rate in Her2-positive disease and the lowest in Luminal A disease [11]. In this respect our study aim was to determine whether immunohistochemically determined breast cancer subtypes differed regarding sensitivity, specifity, PPV and NPV of AUS performed before surgery. Moreover we aimed to evaluate the value of AUS for radio-oncologic decision guidance after neoadjuvant therapy and to define a subgroup which may not need axillary surgery at all based on a high specifity and NPV by preoperative AUS.

Material and methods

The study was evaluated and accepted by the local ethical committee. A prospective database with clinical data of all patients was reviewed and analysed. Missing data were retrospectively looked up from electronic charts in the hospital database (SAP®).

Inclusion and exclusion criteria

All patients with invasive breast cancer of any age diagnosed and treated between 1999 and 2014 at the Breast Health Center, Hospital of the Sisters of Charity, Linz Austria with preoperative AUS were included, except patients with NACT. Patients with a bilateral breast cancer and bilateral AUS were counted as two cases. All patients had either SNB with or without axillary lymph node dissection (ALND) or immediate ALND.

Axillary ultrasound diagnosis

AUS was performed by 3 board-certified (EUSOMA) breast radiologists within one week prior to surgery. Criteria generally used at our institution to define a suspicious node include cortical thickness >3 mm, cortical nodule, displacement or loss of the hilum, architectural distortion, or round shape. Node size >10 mm is considered abnormal but is generally not used as sole criterion to define a suspicious node. Results of the AUS were either suspicious, normal or unclear. Biopsy of all suspicious nodes had not been common praxis in our institution as a routine.

Axillary surgery

In case of suspicious lymphe nodes in AUS, an conventional ALND has been carried out, otherwise we performed sentinel node biopsy. We used Lymphoscintigraphy in order to detect the sentinel node. 22 MBq Tc 99m (Nanoscan 0,2 ml) was injected into the breast periareolar at four locations either 1h or the day before surgery. 20 min after application, images were acquired using.

SPECT/CT to visualize the number and location of sentinel nodes. A gamma probe with or without prior injection of blue dye (Bleu Patent V Guerbet) was used to detect the sentinel node in the operation room. All Tc containing and/or blue sentinel nodes were removed until the rest of the axilla had a gamma count of less than 10% of the highest count [12].

The sentinel lymph node(s) were sent to the pathological department for frozen section analysis (see section pathological examination). In cases of one or more macrometastasis ALND was followed in all cases until 2012. Thereafter some clinically and biologically low risk patients had no further ALND while macrometastases with extracapsular extensions were usually followed by ALND. Their data are currently prospectively stored within an Austrian registry (ABCSG33 = Austrian Breast and Colorectal Cancer Group). Detection of micrometastasis was not followed by ALND [13].

Pathological examination

For frozen section analysis, very small lymph nodes (<5 mm) were analysed unsliced, small lymph nodes (5 mm – 1 cm) were bisected, lymph nodes > 1 cm were sliced at 2–3 mm intervals. The remaining frozen tissue was fixed in formalin, embedded in paraffin, sliced at 200 μm intervals and stained with H&E. Additional CK-immunostaining was performed on every second slide.

In order to define breast cancer subgroups we used immunohistochemical differences based on the recent St. Gallen consensus conference [14]. The following definitions were used:

Luminal A (estrogen receptor >10% and progesterone receptor >10% and KI67 ≤ 20 and G1 or 2 and Her2-negative) Luminal B (estrogen receptor >10% and one of the following: progesterone receptor <10%, G3 or KI67 > 20%), basal-like (estrogen receptor and progesterone receptor <10% and Her2-negative), Her2-enriched (patients with Her2-positive disease including luminal type Her2 positive breast cancer; either immunhistochemical +++ staining or ++ and ISH amplified >2,0 ratio).

Over- and undertreatment based on AUS

AUS staging before neoadjuvant therapy for radio-oncologic decision making

Neoadjuvant therapy reduces the number of lymph node metastases by 40% [15-17]. Thus there are several patients having lymph node metastases before but not after neoadjuvant therapy. In these cases there are no data whether radiation therapists should treat the periaxillary lymphatic tissue including supraclavicular fields. European guidelines are in favor of treating these fields [18-20], however, it is necessary to have a proper staging system before neoadjuvant treatment. Although in our study we did not include patients with NACT, we tried to calculate potential over- and undertreatment if AUS is used for pre-therapeutic staging of the axilla using sensitivity, specifity, NPV and PPV data from our analysis as we assumed that the results of these patients do not differ from those with NACT (regarding AUS before NACT obviously):Overtreatment was defined as rate of cN1-pN0 patients. Undertreatment was defined as rate of cN0-pN1 + cNX-pN1 patients.

AUS before surgery for decision regarding surgical axillary staging

In general there are around 60% of breast cancer patients with a negative axillary sentinel lymph node depending on tumor biology. These patients are overtreated by using sentinel lymph node

biopsy. We calculated the risk of over- and undertreatment using our evaluated sensitivity, specifity, PPV and NPV for AUS if used for preoperative decision making regarding performing a sentinel node biopsy or not. Overtreatment was defined as rate of cN1-pN0 plus cNX-pN0 patients. Undertreatment was defined as rate of cN0-pN1 patients.

Statistical analysis

Categorical variables are described with absolute frequencies and percentages. Age as continuous and normally distributed variables was described by mean and standard deviation (SD). Sensitivity was defined as the proportion of AUS positive or AUS and clinical examination positive patients among all patients with macrometastases. Unclear and negative AUS were considered as false negative. Specificity was defined as the proportion of AUS negative or AUS and clinical examination negative patients among all patients without macrometastases. Unclear and positive AUS were considered as false positive. Positive predictive values (PPV) were calculated as the proportion of patients with macrometastases among all AUS positive or AUS and clinical examination positive patients. Negative predictive values (NPV) were calculated as the proportion of patients without macrometastases among all AUS negative or AUS and clinical examination negative patients. Confidence intervals (CI) for percentages were calculated according to the method of Wilson. Differences in sensitivities, specificities, PPV and NPV among subgroups was tested by exact chi-square tests at a two sided significance level of 5%.

Results

Demographics

Table 1 demonstrates the demographic data of all analysed patients. 583 patients with breast cancer diagnosed and surgically treated between 1999 and 2014 and not receiving NACT had AUS at our breast health center. There were 229 Luminal A, 277 Luminal B, 52 triple-negative and 19 Her2-positive breast cancers. 6 patients were unclassified due to missing immunohistochemical data. (It had been 4 LumA, 46 LumB, 38 TN and 14 Her2-enriched patients we had to exclude because of NACT.)

Sensitivity, specifity, PPV, NPV in all patients

Table 2 shows that out of the 158 patients with macrometastases 62 had a clearly positive AUS (**sensitivity 39.2%**; 95% CI: 31.9%–47.0%). In 85 patients the AUS was clearly negative (**61% false negative**) and in 11 patients with macrometastases the AUS result was unclear.

Out of the 425 patients without macrometastases 407 had a clear negative AUS (**specificity 95.8%**, 95% CI: 93.4%–97.3%). Only 6 patients were diagnosed by AUS as positive (**4% false positive**) and in 12 patients without macrometastases AUS result was unclear.

Out of the 68 patients with clearly positive AUS 62 patients had macrometastases, resulting in a **PPV of 91.2%** (95% CI: 82.1%–

Table 2
Positive (PPV) negative (NPV) predictive value false negative rate (FNR) and false positive rate (FPR).

ALL n = 583	%	
Sensitivity	39	158 SNB+
+clinic	18	62 AUS+
Specificity	96	425 SNB-
+clinic	95	407 AUS-
PPV	91	68 AUS+
+clinic	97	62 SNB+
NPV	83	492 AUS-
+clinic	85	407 SNB-
FNR	61	158 SNB+ 85 AUS- AUS unclear 11
FPR	4	425 SNB- 6 AUS+ AUS unclear 12

Table 1
Demographic data (BCT = breast conserving therapy, MX = mastectomy, SNB = sentinel node biopsy, ALND = axilla dissection).

	ALL n = 583	all in subgroups	Luminal A	Luminal B	tripple negative	her2 enriched	others
n	583	577 *(99.0%)*	229 *(39.3%)*	277 *(47.5%)*	52 *(8.9%)*	19 *(3.3%)*	6 *(1.0%)*
Age (mean ± SD)	62.8(±12.3)	62.8(±12.3)	61.9 (±11.7)	62.5 (±12.9)	67.7 (±10.8)	63.2 (±13.0)	52.7(±12.6)
pT1a	17	15 *(8.8%)*	8 *(4.7%)*	4 *(2.3%)*	0	3 *(1.8%)*	2 *(1.2%)*
pT1b	134	134 *(100%)*	68 *(50.7%)*	52 *(38.8%)*	9 *(6.7%)*	5 *(3.7%)*	0
pT1c	250	250 *(100%)*	97 *(38.8%)*	129 *(51.6%)*	19 *(7.6%)*	5 *(2%)*	0
pT1mic	4	0	0	0	0	0	4 (100%)
pT2	133	133 *(100%)*	42 *(31.6%)*	64 *(48.1%)*	21 *(15.8%)*	6 *(4.5%)*	0
pT3	27	27 *(100%)*	10 *(37.0%)*	16 *(59.3%)*	1 *(3.7%)*	0	0
pT4b	17	17 *(100%)*	4 *(23.5%)*	11 *(64.7%)*	2 *(11.8%)*	0	0
pTx	1	1 *(100%)*	0	1 *(100%)*	0	0	0
pN0	356	350 *(98.3%)*	152 *(42.7%)*	158 *(44.4%)*	31 *(8.7%)*	9 *(2.5%)*	6 *(1.7%)*
pN0(i+)	22	22 *(100%)*	8 *(36.4%)*	13 *(59.1%)*	1 *(4.5%)*	0	0
pn1a	116	116 *(100%)*	41 *(35.3%)*	61 *(52.6%)*	8 *(6.9%)*	6 *(5.2%)*	0
pN1mi	47	47 *(100%)*	17 *(36.2%)*	23 *(48.9%)*	4 *(8.5%)*	3 *(6.4%)*	0
pN2	0	1 *(100%)*	0	1 (100%)	0	0	0
pN2a	29	29 *(100%)*	7 *(24.1%)*	16 *(55.2%)*	6 *(20.7%)*	0	0
pN3	12	12 *(100%)*	4 *(33.3%)*	5 *(41.7%)*	2 *(16.7%)*	1 *(8.3%)*	0
BCT	445	442 *(99.3%)*	189 *(42.5%)*	203 *(45.6%)*	39 *(8.8%)*	11 *(2.5%)*	3 *(0.7%)*
MX	137	134 *(97.8%)*	40 *(29.2%)*	73 *(54.5%)*	13 *(9.7%)*	8 *(6.0%)*	3 *(2.2%)*
missing	1	1 *(100%)*	0	1 *(100%)*	0	0	0
SNB	435	429 *(98.6%)*	183 *(42.1%)*	201 *(46.2%)*	34 *(7.8%)*	11 *(2.5%)*	6 *(1.4%)*
ALND	147	147 *(100%)*	46 *(31.3%)*	76 *(51.7%)*	17 *(11.6%)*	8 *(5.4%)*	0
missing	1	1 *(100%)*	0	0	1 *(100%)*	0	0

95.9%). Out of the 492 patients with clearly negative AUS 407 patients had no macrometastases, resulting in a **NPV of 82.7%** (95% CI: 79.1%-85.8%). From the 23 patients with unclear AUS, 11 patients (47.8%) had macrometastases and 12 patients (52.2%) had no macrometastases.

As only 28 patients had a positive clinical examination out of the 62 patients with macrometastases and positive AUS, sensitivity due to positive AUS and clinical examination was reduced to 17.7%.However 402 of the 407 patients with negative AUS also had a negative clinical assessment and therefore specitivity was slightly enhanced to 94.6%. From the 29 patients with both AUS and clinical examination positive 28 patients actually had marcometastases resulting in an increased PPV of 96.5%. Of the 479 patients with both AUS and clinical examination negative 402 patients actually had no macrometastases, NPV remains nearly unchanged with 83.9%.

Sensitivity, specifity, PPV, NPV according to subgroups

As shown in Fig. 1 Luminal patients had a worse **sensitivity** (Lum A 25.0% (13 out of 52 patients); Lum B 39.8% (33 out of 83 patients)) compared to non Luminal breast cancer patients (TN 68.7% (11 out of 16 patients), Her2+ 71.4% (5 out of 7 patients) $p = 0.0032$.

There was no significant difference found regarding **specifity** (96.6% (171 out of 177) for Luminal A; 94.3% (183 out of 194 patients) for Luminal B; 97.2% (35 out of 36) for TN and 100% (12 out of 12 patients) for Her2+; $p = 0.6065$) and **PPV** (92.9% (13 out of 14 patients)for LuminalA; 89.2% (33 out of 37 patients)for LuminalB; 91.7% (11 out of 12 patients)for TN and 100% (5 out of 5 patients) for Her2+ $p = 1.0000$).

NPV was highest in TN and Her2+ patients (TN 89.7% with 35 out of 39 patients, Her2+ 85.7% with 12 out of 14 patients), whereas Luminal A and Luminal B had a lower NPV (82.6% (171 out of 207 patients); 81.0% (183 out of 226 patients) even if it was of no statistical significance either ($p = 0.5983$) as shown in Fig. 1.

Over- and undertreatment based on AUS

AUS staging before neoadjuvant therapy for radio-oncologic decision making

Table 3 shows that AUS is a very useful tool for clinical decision making. Overtreatment using AUS for radio-oncologic decisions would have been below 2% in all subgroups and also undertreatment appears to be acceptable in TN and Her2+ patients with 10%, however about 17% of Luminal patients would have been undertreated.

AUS before surgery for decision regarding indication for surgical axillary staging

Table 3 shows further that AUS is only of little benefit for luminal patients regarding the indication, whether axillary sentinel staging is necessary or not. 16% of Luminal patients would have been undertreated. However, for triple-negative and Her2-positive tumors, AUS may be useful for deciding whether surgical axillary staging is necessary or not, since undertreatment would be around 10%. The number of overtreated patients would have been negligibly small in all subgroups.

Discussion

AUS is getting more important with the increased use of neoadjuvant therapy, omission of ALND in cases of only one or two macrometastases [21-23] and perhaps in the near future omission of any surgical axillary staging in clinically and radiologically nodal negative patients.

Recent studies demonstrate that AUS has unsatisfactory sensitivity, specifity, PPV and NPV in this respect.

This retrospective single center analysis of 583 patients is the first study, analysing the impact of breast cancer subtypes on the accuracy of axillary ultrasound (AUS).

In general our data analysing all patients irrespective of biological subgroups are in line with other publications showing, however, an even poor sensitivity (39%) for AUS in detecting lymph

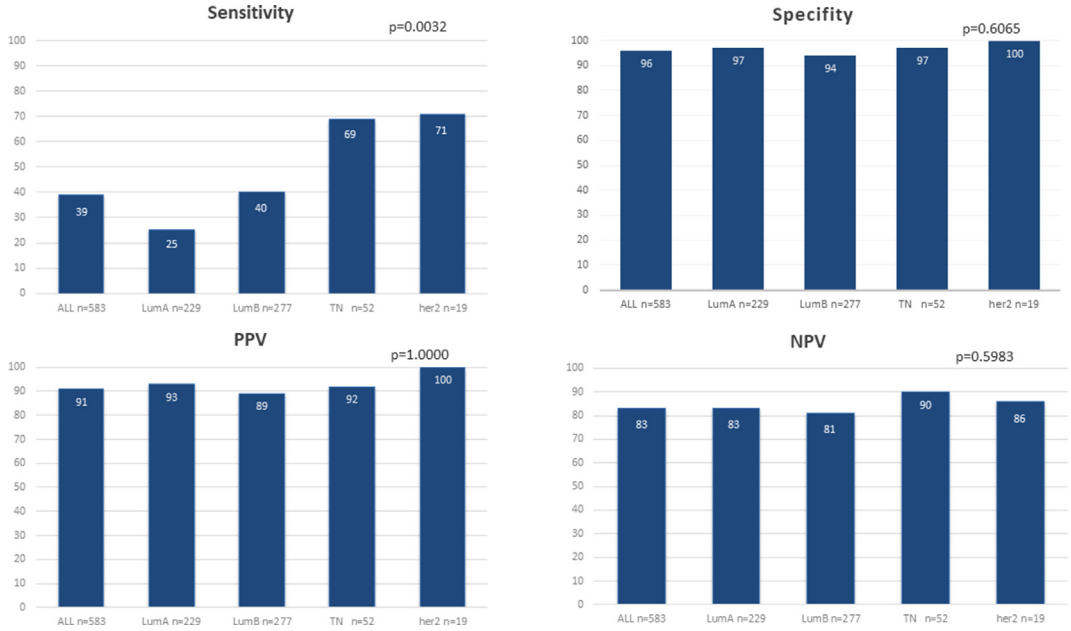

Fig. 1. Sensitivity, positive predictive value (PPV), specifity and negative predictive value (NPV) of axillary ultrasound according to immunohistochemical subgroups (Lum A = Luminal A breast cancer, LumB = Luminal B BC, TN = tripple negative BC, her2 = her2 positive BC).

Table 3
Patients who might have been over- or undertreated if AUS (axillary ultrasound) was used for clinical decision guidance.
NACT = neoadjuvant chemotherapy; Lum = luminal; TN = tripple negative; her2: her2 enriched.
Formular:
Undertreatment for AUS regarding lymphatic RT in cN1/NACT = cN0/pN1 + cNX/pN1
Overtreatment for AUS regarding lymphatic RT in cN1/NACT = cN1/pN0
Undertreatment for AUS cN0 and no surgical axillary staging = cN0/pN1
Overtreatment for AUS cN0 and no surgical axillary staging = cN1/pN0 + cNX/pN0

radiooncologic treatment guidance after NACT by pretherapeutic AUS					
	all	LumA	LumB	TN	her2
undertreatment	16.5%	17.0%	18.0%	9.6%	10.5%
overtreatment	1.0%	0.4%	1.4%	1.9%	0%
axillary surgical staging in AUS cN0 patients					
	all	LumA	LumB	TN	her2
undertreatment	14.6%	15.7%	15.5%	7.7%	10.5%
overtreatment	3.1%	2.6%	4.0%	1.9%	0%

node negative disease but an excellent specifity (96%) in identifying lymph node positive disease with a PPV of 91% and a NPV of 83%. In that respect, additional clinical assessment does not bring us any further. While PPV increases up to 97%, sensitivity even drops below 20% and therefore the number of potentially undertreated patients is still rising (Table 2). This goes in line with the impact of lymphe node biopsy as we have seen im many studies [24,25]. Considering the inhomogenitiy of our own data in this respect, resulting from different biopsy methods over the years and a high percentage of patients with biopsy before NACT, we did not analyse these findings in our study for lack of significance.

After dividing patients into tumor-specific subgroups using immunohistochemistry, we were able to detect a significant difference in accuracy of AUS comparing these subgroups only with regard to sensitivity which was significantly worse in Luminal breast cancer showing values of 25% (LumA) and 40%(LumB) while non-Luminal breast cancer had sensitivity values of 70%. NPV was also worse in Luminal breast cancer patients compared with non-Luminal patients, however this did not reach statistical significance. Thus there would be a higher risk of undertreating Luminal breast cancer patients when using AUS instead of surgical staging for guiding clinical decisions.

So, if radiation therapy guidance after neoadjuvant therapy [26] and surgery would be solely based on pre-neoadjuvant AUS, 18% of the Luminal breast cancer patients would be undertreated compared with 10% of non-Luminal patients (Table 3). From 506 Luminal A and B breast cancer patients in this study 455 were either cN0 or cNX and from those 89 had pN1 status. Those would have been undertreated by pre-neoadjuvant chemotherapy AUS-guided radiation therapy. Similarly if patients with an AUS cN0 staging would omit axillary sentinel staging, 16% of Luminal A and B breast cancer patients would have been undertreated (from 506 Luminal A and B patients, 79 out of 433 AUS cN0 patients had pN1 status), while only 8–10% of non-Luminal patients would not have undergone the necessary procedure of surgical axillary staging.

On the other hand, the analysis of our data showed excellent specificity and PPV in all subgroups which means that overtreatment is not an issue for us - neither for radiation therapy nor for surgical axillary staging - if we make our decisions on the basis of AUS. Table 3 shows overtreatment percentages lower than 3% which may also have some importance regarding immediate reconstruction, as postmastectomy radiation therapy is indicated in lymph node positive disease. In this respect implant-based immediate reconstruction should be avoided in these patients due to the high morbidity rates of radiated protheses [27-29].

We conclude that, especially in Non-Luminal breast cancer patients, AUS is a suitable method for guiding loco-regional treatment decisions. This is all the more important as these women make up the majority of neoadjuvant treated patients. It must be noted, however, that the number of TN and Her2-enriched patients has been quite small in our study just because of the exclusion of patients with NACT. Considering that sensitivity is quite low notably in Luminal breast cancer patients, here AUS alone is not accurate enough to avoid surgical axillary staging.

Our patient number was too small to establish sonography as a good predictive tool for more than 2 positive lymph nodes. This would have been helpful in identifying patients not needing axillary lymph node dissection in cases of 1 or 2 macrometastases within the sentinel lymph nodes.

The strength of our study is that ultrasound was exceptionally performed by 3 EUSOMA-certified breast radiologists. Data were collected over several years prospectively in our databank by a single data manager specifically responsible for the breast center data. All patients had axillary ultrasound within this period at our breast center. A possible bias is the retrospective nature of our study and the small number of her2-enriched and TN patients.

Declarations of interest

None.

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