GYNECOLOGIC ONCOLOGY

Preoperative morphological diagnosis of axillary lymph nodes in a breast center consultation service: evaluation of fine-needle aspiration and core biopsy techniques

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Abstract

Purpose Preoperative routine examination of axillary lymph nodes (ALN) in breast cancer patients is carried out physically and by ultrasound imaging; unsuspicious nodes will lead to a sentinel node (SN) procedure, suspicious ones require axillary dissection (AD). Pre-operative biopsy techniques like fine needle aspiration (FNA) or core biopsy (CB) may reduce the number of false "suspicious" cases and prevent overtreatment. We evaluated the effectiveness of both biopsy techniques.

Materials and methods After physical and ultrasound examination 241 suspicious ALNs were found in 214 patients. Ultrasound-guided FNA and/or CB procedures were chosen randomly, resulting in 138 FNA and 86 CB. In 17 further events both FNA and CB were employed. The samples were examined in our Cytology lab or in the Pathology Department and the findings correlated with post-operative histological lymph node reports. Patients with histologically proven breast cancer underwent sentinel node biopsy, cytologically or histologically positive FNA/CB-findings prompted ALN dissection.

Results Out of 155 FNA samples 34 were not representative (21.9%), 89 showed no tumor cells (57.4%), 30 showed positive tumor cells (19.4%), leaving two missing. All 103 CB showed representative material, positive in 62 (60.2%) and negative in 41 (39.8%) cases. Correlation with histological reports revealed a statistically non-significant advantage for CB over FNA regarding total accuracy (92.9% vs. 78.3%) and sensitivity (92% vs. 73.7%).

Conclusions Preoperative CB and alternative FNA are valuable complementary methods of predicting ALN involvement in breast cancer patients and may spare the patient unnecessary ALN dissection.

Keywords Breast cancer · Axillary lymph node · Morphology · Core biopsy · Fine needle aspiration

Background

Breast cancer (BC) is the most frequent female cancer disease. In Germany, approximately 70,000 new cases are reported every year, and another 6.500 cases of breast carcinoma in situ are discovered [1]. Substantial efforts have been made during the last 20 years to improve health care for BC by developing and improving diagnostic and therapeutic guidelines, certifying breast cancer centers, and establishing a mammography-screening program [2]. Through these measures the relative incidence of "early" breast cancer has increased, advanced cases have been observed less frequently over the past two decades [3].

Based on the rationale that BC is not only a regional, but also a systemic disease, the extent of surgical strategies has been minimized. Both breast conserving operations and the sentinel node concept aim at reducing surgical trauma for the patient and maintaining optimized oncological safety [4, 5].

When a patient is presented to a certified breast cancer center (CBCC) with a suspicious palpable mass or a suspicious lesion discovered in mammography, it has become routine to carefully record the patient's history, examine breast and armpit by inspection and palpation (I&P) and carry out an additional linear-array ultrasound (US) of the

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breast and the axilla [6]. Additionally, color-coded Doppler and/or elastography techniques may be helpful [7].

A palpable mass will be core-biopsied under US control, non-palpable lesions by X-ray-guided stereotactic mammotome procedure, leaving a titanium clip within the lesion center. The specimen is delivered to the pathologist's, and tumor morphology, grading and prognostic factors like hormone receptors, epithelial growth factor antigen (her2neu) and proliferation marker ki67 (mib1) can be analyzed and reported, if breast cancer is proven [8].

If the axillary lymph nodes (ALN) are reported to be found unsuspicious by physical and US examination, the tumor board has to decide between neo-adjuvant chemotherapy (NACT) or primary surgery. As soon as NACT is recommended, sentinel node (SN) biopsy may be done before onset of NACT, eventually joined by a port implantation. The optimal timing of SN, whether it is to precede or follow NACT, is still under controversial discussion (Classe) [9]; (Kuehn) [10]. If ALN is regarded as suspicious the extirpation will be postponed until NACT has been completed [11].

Primary surgery on the other hand will be done with SN sampling if ALN is unsuspicious, and with axillary dissection (AD), if there are signs that the nodes are affected by a tumor [11]. However, if only physical and US examination are carried out, involvement of ALN may be overestimated, so that AD may be mistakenly indicated [12].

In order to reduce mistaken indications it is necessary to ensure a preoperative assessment of a possible pathological ALN involvement. This may be achieved by core biopsy (CB), if the suspicious ALN is in a free topographic position in the armpit [6]. CB of ALN can be taken together with the preoperative tumor biopsy. US-guided CB should harvest enough material to provide a reliable pathological screening, if the focused node is not in close neighborhood to vulnerable armpit vessels and/or nerves. But in many situations the investigator will refrain from CB jet puncture because she/he needs to ponder a morbidity risk. Under these circumstances fine-needle aspiration (FNA) of lymph node material may be considered instead of CB [13]. The investigator's balanced decision between both CB and FNA reflects her/his care of the patient's safety in clinical routine. The aim of this study is to evaluate the accuracy of CB and FNA techniques in order to improve preoperative advice and decision making for the patient's sake.

Patients and methods

A retrospective observation study was conducted analyzing the records of 250 patients. The patients were seen in our CBCC within a time span of 33 months after presentation on an outpatient schedule either for health care reasons (e.g. after mammography screening) or during follow-up after BC treatment. All patients who had undergone core biopsy (CB) or fine needle aspiration (FNA) of suspicious ALN were included. Choice of CB or FNA techniques was at the investigator's disposition taking into account the particular topographic anatomy of the patient's armpit structures.

After ascertaining the patient's medical history and physical examination of breast and axilla, imaging of ALN was achieved by a Hitachi Type HI VISION Preirus® ultrasound transducer. The patient lies in supine position with 120° elevated arms and slight elbow joint flexion, her hands raised above her head. US examination followed a standardized routine from lateral to medial in sagittal transducer position, and afterwards from cranial to caudal in transversal position. US findings were categorized as "normal", "changed, but not suspicious" and "suspicious". ALN was regarded as "suspicious" according to published morphological features, derived out of in vitro studies [14]. We attempted to translate these results in vivo by evaluating ultrasound examinations of ALN mainly in respect of cortical features, then echogenicity and measuring the sizes and length/width-ratios. Intra- and perinodal vessels were marked by Doppler ultrasound [15].

Core biopsy was facilitated by a small skin incision after disinfection and local anesthesia, and a 12-gauge-needle was placed US-guided in front of the target lymph node. At least three 10–15 mm long specimens were obtained using a BARD Magnum Core High Speed Biopsy System® (C.R. Bard, Inc., Covington (GA) USA). Tissue was fixed in formalin and sent to the Pathology Department. Classical staining was done to prove malignancy, eventually followed by immunohistochemical investigations. CB involves a considerable bleeding risk, and therefore anticoagulant therapy should be suspended 1 week before the intervention.

If the target lymph node was situated in close proximity to vulnerable structures, FNA was preferred in order to avoid vessel or nerve lesions. FNA involves a very low bleeding risk so that in most cases anticoagulant therapy may be sustained. With this method local anesthetics or skin incision are not necessary. A 20-gauge needle can be guided by ultrasound into the target lymph node, and tissue is harvested by vacuum aspiration in a fan-shaped movement, facilitated by a syringe provided with a handle. The tissue is spread onto a microscopy slide, fixed and sent to the Cytology lab. Cytological findings were classified according to the European Guidelines for Quality Control of Breast Cancer Screening and Diagnosis [16]. Evaluation was carried out in close cooperation with the Department of Pathology.

Morphological examination delivered information about possible tumor involvement, and—if desired after malignancy has been proven—about grading, estrogen- and progesterone-receptor content, amount of her2-neu-antigen and proliferation marker ki67. In general, morphological characterization was either "negative" (unsuspicious cells)

or "positive" (proof of malignant cells) or "inadequate material".

CB and FNA procedures were documented in a separate CBCC biopsy record book.

For all patients with proven breast (or non-breast) cancer, full medical history and diagnostic records were presented in the interdisciplinary tumor board. Therapeutic strategies e.g. neo-adjuvant therapy (NACT) or primary surgery, surgical extent and approach, chemo-(immuno-)therapy following study protocols or guidelines, radiation therapy and endocrine maintenance protocols were discussed and scheduled. Each patient was given thorough advice and signed an informed consent. Patients with proven lymph node metastasis were scheduled for AD, the extent (steinthal level I, II or III) depending on intra-operative clinical findings. Patients without suspicious or not histologically proven lymph node metastasis were assigned for SN biopsy.

Patient case history and therapeutic data were collected, adding cytology and/or pre- and post-operative histology findings employing the hospital's documentation system SAP R/3 IS-H/i.s.h.med® (Siemens/SAP). Documentation and data analysis were carried out using the table calculation program Microsoft Office Excel 2003® and 2010®.

In order to evaluate the particular quality of CB and FNA in the context of preoperative morphological diagnosis, prevalence, sensitivity and specificity were extracted and calculated. The BAYES formula was used to calculate positive and negative predictive values. The quotient of correct test results by all tests yields total accuracy.

Results

Total sample

250 consecutive samples were gathered between 2009-12-14 and 2012-09-17 from 221 patients. Twenty-seven patients had two, and another two patients had three punctures. Nine of the 250 samples had to be excluded because the punctured lymph nodes were not located in the armpit. Thereby the sample size was reduced to 241 samples out of 214 patients and will be reported hereafter. The mean age of the patients was 57.6 years, ranging from 29 to 92 years. 239 patients were female and two male. Inspection and palpation of the armpit revealed 152 (63.1%) normal findings, 79 (32.8%) were classified as suspicious, and another 10 (4.1%) had insufficient reports. Using ultrasound 218 cases were classified as suspicious (90.4%). Unsuspicious but changed nodes were seen 15 times (6.2%), five times (2.1%) they were found unsuspicious. Three times (1.2%) the ultrasound report was missing (see Table 1).

155 FNA and 103 CB were taken; 17 patients had both FNA and CB. 156 health care patients were explored due to

Table 1 Characteristics of the total study sample ($n=241$)

	Physical exam.	US
Negative	152 (63.1%)	5 (2.1%)
Unsuspiciuos changed	0	15 (6.2%)
Positive	79 (32.8%)	218 (90.4%)
N.A.	10 (4.1%)	3 (1.2%)

Physical exam. physical examination findings, *US* ultrasound findings, N.A. not available

either suspicious physical or US findings. Twenty-three of them were proven healthy according to lymph node morphology. In 133 cases a pathological diagnosis was found with 19 benign and 114 malign diseases.

FNA group

155 FNA tests were carried out on patients with a mean age of 57.9 years. 94 (60.6%) health care patients had 71 (75.5%) histologically proven primary breast carcinoma, 11 (11.7%) had benign breast diseases, and in 12 cases the histology of an in-breast mass was not suspicious. Among 60 patients in a follow-up situation there were 16 (26.7%) with histologically proven local recurrences and a second primary carcinoma. Forty-three patients were without pathological breast findings. Cytological lymph node examinations yielded 89 (57.4%) tumor cell free samples, 13 of them contained hardly any lymph node tissue. 30 (19.4%) slides showed obvious tumor cells; 34 (21.9%) samples were classified as non-representative. Following FNA, 16 patients underwent an additional preoperative core biopsy. Seven patients had a sampling of preoperatively wire-marked single lymph nodes. Thirty-five patients had subsequent SN biopsy, with 15 cases of consecutive AD, and 31 patients had a primary AD. Seventy-six patients had no consecutive armpit operation mostly due to benign morphological findings, and six of these because of a palliative situation in which surgery was contraindicated. After completion of all diagnostic and surgical procedures 65 patients in the FNA group were free of cancer. In 89 patients malign disease was diagnosed including 84 breast carcinoma (BC). Five patients had malign diagnosis of a non-breast-cancer: non-small-cell lung cancer (NSCLC), chronic lymphatic leukemia (CLL), malign melanoma (MM), and two carcinoma of unknown primary (CUP). With the exception of CUP all non-breast-cancer diagnoses were known before FNA.

CB group

103 patients with a mean age of 57.3 years had CB of suspicious lymph nodes, 70 (68%) presenting themselves for health care reasons and 33 (32%) in a follow-up to breast

cancer. In the health care group 50 (48.5%) malign diseases were verified by histology, 49 of them BC and one CUP-syndrome. In eight patients (7.8%) benign diseases were found, and the remaining 45 patients were disease-free. Fifteen patients (45.4%) in the follow-up group showed histological evidence of ipsilateral recurrent disease, another two (6%) were diagnosed as suffering from contralateral breast cancer. Sixteen patients were found relapse-free. All CB samples showed adequate material, so that none of the probes had to be rejected. In 62 (60%) cases the lymph node tissue was classified as malign, leaving 41 (40%) benign results. As mentioned above, in the CB group additionally 17 FNA in 16 patients were carried out, one of them had two FNA. After complete diagnosis 68 patients had an indication for further surgical/histological investigation of ALN. Eight times a SN biopsy was carried out, and five of these patients had a secondary AD due to malign SN. Forty-three patients had a primary AD, and in three cases wire-marked single lymph nodes were removed. Unfortunately, in four cases there is a lack of data on surgical procedures in the armpit. And ten patients were in impaired state of health so that they were classified as requiring palliative treatment, further surgical procedures being contraindicated. The synopsis of all diagnostic and surgical procedures and their histological evaluation revealed 73 patients (70.8%) with proven malignancies. Sixty-eight had BC or recurrent BC, and five non-breast-cancer diagnosis: we registered one patient with a Hodgkin- and one with non-Hodgkin-lymphoma, one B cell-lymphoma, one Ewing-sarcoma, and one CUP-syndrome.

Breast cancer group

Invasive breast cancer

In 137 patients with a mean age of 56.4 years, breast cancer was diagnosed after histological examination. 101 (73.7%) patients had primary carcinoma and 33 (24.1%) had primary metastasis. Three patients (2.2%) had incomplete reports about metastasis status. 44 (32.1%) were clinically classified as cN0, 71 (51.8%) as cN+, and in 22 cases (16.1%) no information was available on nodal status. Because the tumor stage and prognostic factors are not relevant to the study's target, they are not detailed. Thirty patients received neoadjuvant chemotherapy (NACT: chemotherapy ± targeted anti-Her2 therapy) and ten patients achieved complete remission after NACT (ypT0). The histological examination of ALN in BC patients was positive in 67 cases (48.9%), three of them were classified as micrometastases. In 44 cases (32.1%), ALN was found to be free of tumor cells, 13 of them with previous NACT. Surgical armpit exploration was contraindicated in 22 patients (16.1%), mainly due to poor general condition or distant metastases. In four patients (2.9%), the pathologist did not find lymph node material.

These cases were classified as not available (see Table 2). In addition, three patients with ductal carcinoma in situ (DCIS) had FNA. All of these were cytologically negative, which was confirmed by the subsequent SN examination. These patients are included in the evaluation.

Fine needle aspiration of axillary lymph nodes in breast cancer patients

Out of 140 patients with BC (137 invasive and three DCIS) 84 underwent FNA. In 17 cases (20.2%) slides did not show representative material, 37 contained no tumor cells (44% negative), 28 (33.3%) were positive, and for two slides the cytology report was missing. Afterwards diagnostic and therapeutic procedures followed, depending on clinical findings and the cytology report to clarify ALN tumor involvement as mentioned above. Comparing FNA results with corresponding histological findings after surgery, the prevalence of lymph node metastases was calculated as 46.1% (30/65). In three cases micrometastasis was found. Out of 37 patients with negative ALN cytology four had additional CB, and these four plus another 28 were explored surgically. Seventeen times the SN procedure yielded unsuspicious healthy nodes, four patients required secondary AD due to positive nodes. Six patients had primary AD, one had single wire-marked lymph node extirpation, whereas in six patients bad general health caused us to abstain from further surgical procedures. The histology of the removed lymph nodes after negative FNA is summed up in Table 3a.

Eight patients with FNA had primary NACT. False-negative rates (FNR) for FNA in BC patients could be calculated as 9.5% (8/84). For representative samples only, FNR was 12.3% (8/65), FNR correlated to histology 16% (8/50). Reducing FNR to the negative FNA group resulted in 21.6% (8/37), and with respect to histology correlation 28.6% (8/28). Twenty-eight pathological cytology findings after FNA caused the following 22 surgical procedures: six additional CB, one SN with following AD, three with extirpation of wire-marked lymph nodes, and 18 with primary AD. Six times consecutively indicated AD were omitted for reasons given above. Each CB after positive FNA confirmed

Table 2 Characteristics of the breast cancer patients ($n = 137$)

	M	cN	pN	NACT
Negative	101 (73.7%)	44 (32.1%)	44 (32.1%)	107 (73%)
No ALN surgery			22 (16.1%)	
Positive	33 (24.1%)	71 (51.8%)	67 (48.9%)	30 (27%)
N.A.	3 (2.2%)	22 (16.1%)	4 (2.9%)	0

M metastatic status, *cN* clinical nodal status, *pN* pathological nodal status, *NACT* neoadjuvant chemotherapy, *ALN* axillary lymph nodes, *N.A.* not available

Table 3 Histology results after FNA according to surgical method and NACT ($n = 82$)

	Number treated	Negative	Positive	Wire-marked	NACT
(a) FNA negative: 37					
Core biopsy (CB)	4	4	0	0	–
Sentinel node (SN)	17	17	0	2	3
SN + AD	4	0	4	0	0
Axillary dissection (AD)	6	3	3	0	2
Single lymph node	1	0	1	1	1
Unavailable	3				1
No intervention	6				1
(b) FNA positive: 28					
Core biopsy (CB)	6	0	6	0	–
SN + AD	1	0	1	0	0
Axillary dissection (AD)	18	4	14	2	5
Single lymph node	3	2	1	2	1
Unavailable	2				2
No intervention	4				0
(c) FNA unrepresentative: 17					
Sentinel node (SN)	3	3	0	0	0
SN + AD	9	3	6	1	1
Axillary dissection (AD)	3	3	0	0	1
No intervention	2				0

FNA fine-needle aspiration, *CB* core biopsy, *SN* sentinel node, *AD* axillary dissection, *NACT* neoadjuvant chemotherapy

the previous FNA result. Histology results after positive FNA are shown in Table 3b.

Eight patients in this group had previously been given NACT. False-positive cases were found six times. Omitting histology reports invalidated by previous NACT, the false-positive rate (FPR) was calculated as 2.5% (2/80), and taking only histology-correlated results FPR aggregated to 4.3% (2/46). For patients with non-assessable cytology further armpit diagnosis and therapy was of course mandatory. Histology after unrepresentative FNA samples is given in Table 3c. Two patients in this group had already NACT. Lymph nodes were found negative in nine and positive in six patients.

Core biopsy of axillary lymph nodes in breast cancer patients

Sixty-eight patients had CB of ALN, which was classified as negative in 11 and as positive in 57 cases. Postoperative histology examination found 35 exclusively macrometastatic lymph nodes and 18 tumor-free ALN. In 15 cases surgical procedures were not carried out due to the reasons mentioned above, or information was missing. The prevalence of positive lymph nodes was determined as 66% (35/53). Negative CB was followed by four additional FNA, which were negative as well. Five patients were scheduled to SN procedure, and for two of them an additional AD was necessary. One patient was operated with AD after wire-marking of an US-suspicious LN, another had several wire-marked LN taken, three times the surgical document was missing and the last patient did not undergo surgery due to distant metastasis (see Table 4a). Three patients in the CB negative group had prior NACT. Postoperative correlation to the lymph node histology revealed two positive nodes, one after SN and subsequent AD, the other after primary AD. Positive CB results were found in 57 patients and seven of these had additional FNA. As may be seen in Table 4b, 25 patients were treated by NACT. SN was scheduled for three patients, one affording consecutive AD due to positive SN. Two SN procedures revealed negative nodes as well as 11 out of 42 primary AD. Thirty-one patients had positive nodes after primary AD, and another one after single LN removal. Nine patients had no surgical procedure due to bad general health or distant metastasis.

False-negative rate (FNR) of CB in BC patients was 2.9% (2/68); correlation to surgical proven LN resulted in a FNR of 3.8% (2/53). Excluding compromised findings after NACT and re-operation of one clinically suspicious but surgically negative patient resulted in a FNR of 1.8% (1/57), or FNR = 2.4% (1/42), if only cases with histological confirmation were taken into account.

Table 4 Histology results after CB according to surgical method and NACT (n = 68)

	Number treated	Negative	Positive	Wire-marked	NACT
(a) CB negative: 11					
FNA	4	4	0	0	0
Sentinel node (SN)	3	3	0	1	1
SN + AD	2	1	1	0	0
Axillary dissection (AD)	1	0	1	1	0
Single lymph node	1	1	0	1	1
Unavailable	3				1
No intervention	1				0
(b) CB positive: 57					
FNA	7	0	6	0	3
Sentinel + AD	3	2	1	0	3
AD	42	11	31	1	19
Single lymph node	1	0	1	1	0
Unavailable	1				0
No intervention	9				0

FNA fine-needle aspiration, *CB* core biopsy, *SN* sentinel node, *AD* axillary dissection, *NACT* neoadjuvant chemotherapy

Sensitivity, specificity, positive (PPV) and negative predictive value (NPV)

Counting all patients who underwent any surgical procedure to evaluate ALN status, FNA achieved a sensitivity of 66.7% and a specificity of 76.9%. Four patients showed complete remission of ALN after NACT and should be excluded from our calculation, which then results in a sensitivity of 66.7% and a specificity of 90.9%. Being aware of impairment of ALN status by prior NACT in general, adjusted FNA sensitivity (omitting NACT patients) was calculated as 73.7% with a confidence interval (95%) of 44.7–84.4%. The same consideration applied to adjusted specificity results of 89.5% (CI 95% from 70.8 to 98.9%).

Using BAYES theorem to compute the positive predictive value (PPV) of FNA in the BC group, based on a group-specific prevalence of 46.1% (see above), PPV was determined as 71.1% for the total group; calculation of the negative predictive value (NPV) of FNA for the total group amounts to 73%. The above mentioned considerations regarding complete remission of ALN formerly involved and now in remission after NACT yields PPV = 87.9% and NPV = 73.2%, given a 50% prevalence of histology proven ALN. Excluding all patients after NACT will change adjusted PPV to 88% and NPV to 76.7%. The overall result of fine-needle aspiration accuracy of all representative slides amounted to 72% (36/50) and adjusted FNA accuracy (without NACT cases) to 78.3% (36/46).

The same calculation was done regarding core biopsy in breast cancer patients, based on a prevalence of 66% ALN metastasis. Including one secondary proven lymph node metastasis as mentioned above, the sensitivity of US-guided CB was 94.4% and the specificity 29.4%. Excluding 11 patients with complete remission of ALN after NACT, specificity attained 83.3% (CI 95% from 35.9 to 99.6%) and sensitivity was calculated as 94.4% (CI 95% from 81.3 to 99.3%). And finally, omitting all NACT patients, adjusted sensitivity and specificity parameters were 92% and 75% respectively.

Core biopsy reached a PPV of 72.2% and a NPV of 73% in our breast cancer patients. Leaving out patients with complete remission after NACT prevalence of ALN metastasis was 83.3%, and PPV and NPV were computed as 96.6% and 74.9% respectively. Exclusion of the NACT group as a whole led to a prevalence of 82.8%, changing adjusted PPV to 94.7% and NPV to 66.1%.

Total accuracy of CB was 73.6% (39/53) and this value grew after exclusion of NACT-patients to an adjusted accuracy of 92.9% (39/42). Suspicious ALN examined both by FNA and CB (7.1%: 10/140) had identical cytology and histology findings.

We were able to use a set of 60 patient data to compare the sensitivity of both FNA and CB. The calculation of confidence intervals for the sensitivity difference between FNA and CB procedures, takes into account the number of patients without complete remission after NACT.

Table 5 Confidence intervals for the sensitivity difference of FNA and CB

Estimated value for sensitivity-difference CB > FNA: $\Delta \hat{p}$ = 27.8%			
Confidence level $P = 1 - \alpha$	Two-sided		
95.0%	7.5%	$\leq p \geq$	48.1%
99.0%	1.1%	$\leq p \geq$	54.4%
99.9%	− 6.3%	$\leq p \geq$	61.8%

As is documented in Table 5, this difference is delta = 27.8% with a 95% confidence interval from 7.5 to 48.1%.

Non-breast cancer group

The total sample population included 101 patients with a mean age of 56.8 years without proven breast cancer. After completing the whole diagnostic procedure ten patients with non-breast cancer were found, 90 cases did not show any sign of malign disease, and in one patient the histology report was missing.

FNA in non-breast cancer

In this group 71 FNA were carried out, of which, 52 qualified cytological negative, two positive and 17 not representative. Three cytological negative patients had a confirmation by CB and one patient had a wire-marked lymph node extirpation. All histology reports confirmed the absence of tumor cells. Two patients with positive cytological findings had subsequent surgery with a single LN extirpation and one AD. Histology reports were positive in both cases, revealing one non-small-cell lung carcinoma and a B cell-lymphoma. Two patients without representative slides had an additional CB, and in three a surgical exploration followed (SN > AD, primary AD and single LN extirpation). Histology reports were negative in all five cases.

CB in non-breast cancer

Thirty-five patients in this group underwent CB, and histology was negative in 30 cases (as well as cytology in five additional FNA). None of these patients had additional surgical procedures. One out of five patients with positive CB findings had a single LN removed because no primary tumor could be found. Definite LN histology was positive and compatible to a LN metastasis of Ewing's sarcoma. The other four patients had a CUP-syndrome with hepatic and lymph node metastasis. Further, one Hodgkin, one non-Hodgkin and one B-cell lymphoma were diagnosed.

Discussion

The ALN status is still the most important prognostic factor in breast cancer [17–19]. Over the past two decades, widespread investigation has aimed at minimizing surgical measures in exploring ALN. In this context the SN concept was developed [4, 11] with the result that AD can be omitted, if SN is histologically proven to be without metastasis.

Two extensive randomized trials, the ACOSOG study Z0011 [20] and the IBCSG 23-01 trial [21], compared AD vs. none, if one or two SN were involved. No differences in clinical outcome were found if appropriate tangential-field radiotherapy was given after surgery. Almost the same holds true of the EORTC 10981-22023 AMAROS–study [22]. In this study very few events of ALN recurrence were reported, and only a few more in the case of patients receiving only radiotherapy, but a much longer period of observation is needed to produce relevant outcome data. Admittedly the radiotherapy group had considerably fewer side effects e.g. in terms of post-therapeutic lymphedema. These findings led to guideline recommendations [1] that a complete AD is not necessary in limited SN involvement.

Considering the growing number of patients who begin their individual treatment process with NACT, the timing of the SN procedure was questioned. An early study with a comparatively low sample size of 195 patients [9] suggested that the result of SN analysis after NACT might be equivalent to a preoperative examination. The SENTINA-study [10] evaluated 1737 patients, 1022 of whom had previously undergone SN analysis; the other 715 patients had received NACT. Results of this big four-armed study were summarized as follows: "Sentinel-lymph-node biopsy is a reliable diagnostic method before neoadjuvant chemotherapy. After systemic treatment or early sentinel-lymph-node biopsy, the procedure has a lower detection rate and a higher false-negative rate compared with sentinel-lymph-node biopsy done before neoadjuvant chemotherapy. These limitations should be considered if biopsy is planned after neoadjuvant chemotherapy."

After all the question of obligatory SN or ALN surgery has not finally been answered and remains open to further discussion. That makes it all the more important to know as much as possible about the tumor types of ALN before recommending some type of axilla surgery to the individual patient. If the morphology of ALN could be precisely described before the operation, surgery of ALN could be avoided or minimized to the sentinel-node procedure for patients with negative morphological findings. In the case of patients with proven metastasis of ALN straightforward AD would be recommended and multiple operations would be unnecessary.

Our study reflects these open questions of an improved preoperative diagnosis of ALN. We planned a sample size of 250 patients but had to exclude nine after reviewing patients' records (see above). 241 cases were regarded as sufficiently representative to evaluate FNA and CB in addition to physical and ultrasound examination. The number of FNA and CB samples collected in our study provides reasonable information compared to other unicentric studies (see Table 5). Data collection was done retrospectively and covers an accrual time of 33 months in between 2009 and 2012. The mean age of our patients was calculated as 57.6 years which is in accordance with most of the comparable studies in literature, as is the distribution of 239 female (99.2%) and two male patients (0.8%). 137 patients had histologically proven breast cancer, and in 67 cases metastatic lymph nodes were found after pathological examination, including three micrometastases.

A considerable group of 30 patients underwent NACT and 10 patients reached complete remission after NACT (ypT0). Comparable to many of the literature data, these patients had to be separated evaluating FNA and CB. As has been stressed by Hieken et al. [23], a great number of positive lymph nodes will experience complete remission by NACT, and post-operative correlation of preoperative morphological findings to the definite ALN histology will not be possible. Therefore the statistical values of the diagnostic methods need to be adjusted to the number of patients without preoperative NACT.

It should be taken into account that this study has been carried out parallel to a lot of meanwhile published scientific research on similar topics which will need to be discussed below. Current guidelines [1, 8, 24] in part include insights from these investigations.

It is well known that physical examination of ALN is probably mistaken in one-third of the patients [19]. In most of the false-negative cases lymph nodes are not palpable in axillary fat tissue, or are underestimated when occurring during the course of an inflammatory disease. The addition of ultrasound (US) examination may compensate the deficits of clinical assessment [25, 26], but a sensitivity of 42–56% and a specificity of 70–90% reported in literature [27] is heterogeneous and not convincing [14]. False-negative correlation to histology is merely due to overestimation of enlarged lymph nodes in benign diseases e.g. hyperplasia or inflammation [6]. Apart from other reasons this may be also due to different morphological types of breast cancer like lobular carcinoma [28, 29].

In our study, 71 breast cancer patients were classified cN+ (histological proof in $n = 67$). In contrast to many other reports in literature this means a slight clinical overestimation. As the study was triggered by suspicious or questionable ultrasound findings we have to admit a remarkable overestimation of 218 suspicious out of 241 total cases, a number which is three times as high as the number of histologically proven lymph node metastases.

According to the limited diagnostic success of physical examination and axillary ultrasound further diagnostic tools were added such as FNA or CB.

Historically FNA was incorporated into the so-called triple-diagnosis of breast tumors consisting of physical examination, mammography and cytology, and it yielded excellent sensitivity and specificity results [30–33]. FNA was mainly applied to palpable masses and had its limitations in occult lesions [34].

After the introduction of CB into the diagnosis of palpable tumors and mammography-guided vacuum-assisted biopsies of occult lesions [35], the use of FNA in breast cancer diagnosis decreased and is no longer recommended [1].

Surprisingly, FNA experienced a renaissance when morphological diagnosis of ALN was warranted. Most authors argue that less risk of damage to neighboring vulnerable structures favors the use of FNA [6]. Restrictions of the method may be caused by ALN size, operator skills, and access to a qualified Cytology lab [27]. Quite a number of studies report on clinical findings, US examination of the axilla and FNA to predict the possible tumor involvement of ALN. Sample sizes of studies with histologically proven ALN after FNA are moderate ($n = 85–137$) [27, 36, 37]. All these studies have in common that the combination of clinical examination, US and FNA produces high specificity figures of 96–100%, but sensitivity keeps low and comparatively high false-negative rates (FNR) are reported. Most probably sensitivity is directly correlated to primary tumor size [38, 39]. The biggest study on this topic [40] confirms the findings of the smaller studies and reports a FNR of 31% out of 323 proven ALN metastasis. The authors analyzed possible predictors of FNR by univariate and multivariate regression analysis and identified age < 60 years, breast tumor size > 20 mm and a positive progesterone-receptor as independent factors. Finally Houssami et al. [41] presented a meta-analysis of 21 studies based on 4941 patients, which elucidated the value of US-guided FNA for the morphological characterization of US-suspicious ALN (see Table 5).

In our study we found 34 samples out of 155 FNA samples (21.9%) without representative material. The problem of unsuccessful punctures reflects the all-day routine work of a breast cancer center which has to integrate young learning residents with lack of experience into the breast center team. Desirable improvement of puncture skills is hampered by individual learning curves. Correlation of cytological reports after FNA with post-operative histology findings rendered an FNR of 28.6%, an adjusted sensitivity of 73.7%, a specificity of 89.5%, a positive predictive value (PPV) of 88% and a negative predictive value (NPV) of 76.7%.

As already mentioned, CB has become the method of choice for preoperative morphological examination of

Table 6 Comparison of literature data for statistical quality criteria of fine-needle aspiration (FNA) and core biopsy (CB)

Author	Leenders	Houssami-meta	Solon	Ahn	Rautiainen	Gannot	Own data
Year	2011	2014	2012	2013	2013	2014	
FNA							
Number	320	2805		48	66	70	155
FNR	31%	25%					28.6%
Sensitivity	57.6%	79.6%		73%	72.5%	76.1%	73.7%
Specificity	99.3%	98.3%		100%	100%		89.5%
PPV	99.1%	100%			100%		88%
NPV	63.4%	67.4%			81.7%		76.7%
Accuracy	75.3%						78.3%
CB							
Number			121	48	66	70	103
FNR							2.4%
Sensitivity			96.5%	77%	**88.2%***	**89.9%***	**92%***
Specificity			100%	100%	100%		75%
PPV			100%		100%		94.7%
NPV			63.6%		91.2%		66.1%
Accuracy			96.7%				**92.9%***

FNR false-negative rate, *PPV* positive predictive value, *NPV* negative predictive value

*CB significant better compared with FNA

palpable tumors and non-palpable lesions of the breast [35]. CB yields a bigger sample size and larger volumes of tissue; microcalcification may be detected by sample radiography and prognostic factors are easier to detect and to quantify compared to cytology specimens. These advantages make it reasonable to transfer the method to gain material from ALNs as well. A couple of studies have covered the addition of CB to clinical examination and axillary US with restricted sample sizes [42–47]. Sample sizes were $n = 21$–210 in terms of US-suspicious ALN. The biggest study of Solon et al. reported sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of CB of 96.5% (110 of114), 100% (7 of 7), 100% (110 of 110), 63.6% (7 of 11), and 96.7% (117 of 121), respectively. No false-positive results were found. Nevertheless only 110 out of 210 ALN metastases could be detected pre-operatively, which was in part caused by non-suspicious US, and in other cases was due to inconvenient topographic position close to vessels, the thoracic wall or the skin.

In our study all of 103 core biopsies showed representative material, with histologically positive in 62 (60.2%) and negative results in 41 (39.8%) cases. A remarkably low rate of false-negative results was found (FNR = 2.4%). Correlation with post-operative histological ALN reports revealed an adjusted statistically non-significant advantage for CB over FNA regarding total accuracy (92.9% vs. 78.3%) and sensitivity (92% vs. 73.7%). Specificity (75% vs. 89.5%), positive (PPV: 94.7% vs. 88%) and negative predictive value (NPV: 66.1% vs. 76.7%) did not differ significantly either.

A comparison of our data with literature reports is given in Table 6.

A couple of studies compared the values of FNA and CB for preoperative morphological assessment of ALN. Ahn et al. [12] estimate the significance of both methods to be equal. Rautiainen et al. [48] appraise CB as the preferable tool. Ganott et al. [49] find CB better than FNA, but recommend FNA in addition. Obviously the value of both methods improves according to tumor and ALN size [6]. Nevertheless it has to be kept in mind that fine-needle aspiration and core biopsy of axillary lymph-nodes may render false-negative results [50].

Conclusion

The results of our study are in accordance with data from studies using both FNA and CB methods for morphological analysis of ALN (Table 6). In our opinion it is pointless to question the best of both methods. Each of them possesses advantages and disadvantages. Regarding sampling efficiency, sensitivity, sample size and volume, CB is superior to FNA. But many of the ALN which are difficult and/or dangerous to puncture by CB may safely be investigated by the FNA method. We recommend using CB if possible and adding FNA as a complementary method if CB cannot be applied.

Due to the fact that ultrasound may overestimate suspicious ALN, CB or—if CB seems too dangerous or technically not applicable—FNA should be introduced into the

preoperative diagnosis of breast cancer. If the morphological assessment of the punctured lymph node is unsuspicious the patient may be scheduled for SN biopsy. As false-positive results are unlikely, patients with morphologically proven ALN may be scheduled for AD if ultrasound or other imaging methods indicate the possibility of larger ALN involvement.

This also holds true for patients after NACT when the extent of axillary surgery has to be determined. Schwentner et al. [51] concluded after reevaluation of the SENTINA-trial (Kühn): "The diagnostic accuracy of ultrasound and palpation following NST (= NACT) is unacceptably low and additional tools for evaluation of the axillary lymph node status following NST are urgently needed." Our recommendations exactly meet these requirements.

It remains a matter of investigation whether patients scheduled for NACT could be spared a primary SN biopsy in case of negative CB/FNA-gained ALN morphology. In the light of the rationale that patients with limited ALN involvement do not need further AD, those patients could be randomly assigned to a study on secondary SN procedure after NACT or in-breast surgery only.

Compliance with ethical standards

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