Diagnostic value of preoperative axillary lymph node ultrasound assessment in patients with breast cancer qualified for sentinel lymph node biopsy

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Abstract

Introduction: Sentinel lymph node biopsy (SLNB) is a standard procedure in the therapeutic management of patients with non-advanced breast cancer.

Aim: To analyse the utility of ultrasound scan (USS) examination in the process of patient qualification for SLNB and to estimate the optimal time to perform USS in the clinical preoperational assessment of axillary lymph nodes.

Material and methods: A prospective analysis of 702 patients with invasive breast cancer treated with SLNB between 7.03.2012 and 27.05.2013 was performed. The patients were divided into three groups: I (USS < 8 weeks before SLNB), II (USS > 8 weeks before SLNB and another one on the day before SLNB) and III (USS > 8 weeks before SLNB without perioperative USS). In these patients the percentage of metastases in the sentinel lymph node and the clinical factors influencing the diagnostic value of preoperative ultrasound scan were assessed.

Results: Metastatic lesions in sentinel lymph nodes were found in 154 (21.9%) patients. The highest percentage of metastases was noted in patients operated on in the second and third month from the beginning of preoperative diagnostics. None of the factors tested (size of the original tumour, histological malignancy grading, kind of preoperative diagnostics, Ki-67 value, biological type of the tumour, age) had a statistically significant influence on the diagnostic value of perioperative USS examination in the analysed time span.

Conclusions: The lowest percentage of metastases in the sentinel lymph node was noted in the patients qualified for SLNB who had the ultrasound performed directly before the surgical procedure (not more than 4 weeks before the surgery).

Key words: breast cancer, sentinel lymph node biopsy, qualification for treatment, perioperative ultrasound testing.

Introduction

Sentinel lymph nodes are the first lymph nodes on the route by which the lymph is transported from the area of the tumour. The assessment of metastatic lesions in sentinel lymph nodes plays a crucial role in determining the degree of histological malignancy of cancer, particularly with reference to malignant melanoma and breast cancer patients, since it directly influences the prognosis and the choice of the surgical treatment regimen [1]. The procedure of sentinel
lymph node biopsy (SLNB) is a standard procedure in the diagnostic and therapeutic management in patients with no suspicious axillary lymph nodes (cN0 patients) [2–5]. Sentinel lymph node biopsy using blue dye and radioisotopes is a method of choice allowing one to identify the sentinel lymph nodes [1]. Despite the demographic prognoses about the increasing number of breast cancer patients, thanks to ongoing national programmes of early breast cancer detection, it can be assumed that the increase will concern, in the first place, cases of locally advanced disease. Early diagnosis of the disease will allow patients to be qualified for breast and axillary lymph node conserving treatment [6–8]. Therefore, it is vital to properly plan the necessary treatment procedure for each patient.

The introduction of any new surgical procedure is connected with the phenomenon of the learning curve, relevant to all new technical treatment. Along with the technical details of the procedure, it may also be related to the gradual extension of recommendations regarding the use of the procedure. In the case of SLNB in breast cancer patients, the initially accepted constraints concerning the maximum tumour size (the largest diameter not exceeding 3 cm) may change as the experience in the use of this method is enhanced. Sentinel lymph node biopsy use in patients with larger tumours (T2 > 3 cm and T3) or with multiple tumours may result in the growth of the global percentage of metastases detected in the sentinel lymph node – from 12.5% to 23.3% [9]. This emphasises the importance of proper preoperative diagnostics, particularly with reference to minimising the number of false negative results of the procedure administered.

Axilla assessment reduced only to physical examination before SLNB may result in high risk of error. This concerns, in particular, a high risk of false negative results estimated at the level of 53% of all cases [10, 11]. Therefore, it is essential to complete and objectify the results of physical examination by means of imaging methods.

Standard ultrasound scan (USS) is a method of choice in lymph node diagnoses; at present, more and more frequently there are also ultrasound scans performed with the use of contrast (contrast-enhanced ultrasound – CEUS). A contrast agent is administered subcutaneously or intravenously around the malignant tumour and, after a local massage, the contrast material is detected by lymph vessels and eventually reaches the sentinel lymph node, which can be detected in a low mechanical index ultrasound scan. Contrast substances which are used can be solutions of 25% albumin and hydroxyethyl starch [1]. Preoperative ultrasound examination of the axilla with the subsequent biopsy performed under ultrasound control is a method of moderate sensitivity; it enables detection of about 50% of metastases in axillary lymph nodes before a surgical procedure. This method can be used as a method of qualification for axillary lymphadenectomy and allows unnecessary SLNB to be avoided [12]. In the analysis of Mainiero et al. it was found that fine-needle biopsy was the most useful method of preoperative procedure diagnosing axillary lymph nodes in patients with breast tumour over 2 cm large or suspicious lymph nodes in an ultrasound scan [13]. Vacuum-assisted core biopsy (VAB) guided by ultrasound is a minimally invasive method of diagnosing focal breast lesions and as an alternative to open surgical biopsy should be a standard and the method of choice in diagnosing breast tumours [14]. The use of conventional imaging such as mammography and USG examination in women at high risk for breast cancer may not bring optimal results in many cases. All women with a 20% or greater lifetime risk of developing breast cancer should undergo annual magnetic resonance mammography as a diagnostic adjunct to USS and mammography [15].

**Aim**

The aim of the study was to analyse the diagnostic value of ultrasound examination in the process of patient qualification for SLNB. It was also attempted to establish an optimal moment for performing ultrasound examination in the preoperative assessment of axillary lymph node status.

**Material and methods**

Our analysis is a prospective study of 702 patients diagnosed with locally advanced breast cancer (701 women and 1 man) who underwent SLNB in the period from 7.03.2012 to 27.05.2013 in the Department of Breast Cancer and Reconstructive Surgery in the Oncology Centre in Bydgoszcz. The age of patients was 23 to 89 years (mean age – 58.1 ±10.7 years).

Patients with invasive locally advanced breast cancer were qualified for the group analysed. An additional inclusion criterion was absence of clinically suspicious axillary lymph nodes on the side of the tu-
mourn which were assessed both palpably in physical examination and in the first ultrasound scan; both of these methods were used to qualify patients for surgical treatment conserving axillary lymph nodes – SLNB.

Depending on the time span between the first ultrasound and the SLNB procedure in the analysed clinical material, the three following groups were determined: group I of 353 patients (preoperative ultrasound performed up to 8 weeks before SLNB), group II of 172 patients (ultrasound performed more than 8 weeks before SLNB with a follow-up ultrasound test on the day preceding the surgery performed by the same radiologist), and group III of 177 patients (ultrasound more than 8 weeks before SLNB without a follow-up ultrasound scan). The allocation of patients to groups II and III was organised on a random basis, and the patients in each group were allocated proportionally.

For the whole group analysed in the study, the correlation was assessed between the time span mentioned above (estimated from the first ultrasound examination to qualification for SLNB) and the percentage of metastases in sentinel lymph nodes (univariate analysis). An analysis was also performed of the influence of some clinical factors on the diagnostic value of preoperative ultrasound verification of the axillary lymph node status (multi-dimensional analysis, in time function). In the statistical analysis the following elements were taken into consideration: the diameter of the tumour (T feature assessed at baseline ultrasound), histological grading (G), the kind of preoperative diagnostics of the tumour (fine-needle aspiration biopsy, core needle biopsy, surgical biopsy), mitotic index Ki-67 value (ranges 0–14%, 15–30%, 30–45%, > 45%), biological type (according to St Gallen 2011) and the age of patients (< 40 years old, 40–60 years old, > 60 years old) [2]. For the sake of the statistical analysis, the time between the baseline ultrasound and the SLNB procedure was divided into monthly periods.

In the case of the group II patients, the clinical value of an ultrasound scan performed on the day preceding SLNB was also verified in a detailed analysis of the follow-up ultrasound tests of axillary lymph node status. In the conclusions, the histopathology report from SLNB was taken into consideration (the percentage of metastatic lesions). The ultrasound sensitivity was calculated as the quotient of true positive results and the sum of true positive (TP) and false negative (FN) results: TP/TP + FN, specificity of the study – as a quotient of the true negative and the sum of true negative (TN) and false positive (FP) results: TN/TN + FP. Positive predictive value (PPV) was calculated as a quotient of the true positive and the sum of true positive and false negative results: TP/TP + FP; and negative predictive (NPV) was calculated as the quotient of true negative results and the sum of true negative and false positive test results: TN/TN + FN.

**Results**

Metastases in the sentinel lymph node were found in 154 patients (21.9% of all patients included in the study). The proportion was different in each group of patients (Table I); however, the differences

| Clinical data                        | Group I n (%) | Group II n (%) | Group III n (%) | All n (%) |
|--------------------------------------|---------------|----------------|-----------------|-----------|
| General patient number               | 353           | 172            | 177             | 702       |
| Metastases in sentinel lymph node    | 86 (24.4)     | 32 (18.6)      | 36 (20.3)       | 154 (21.9)|
| Original tumour size (USS) – cT:    |               |                |                 |           |
| T1a                                  | 5 (1.4)       | 14 (8.1)       | 5 (2.8)         | 24 (3.4)  |
| T1b                                  | 60 (17.0)     | 44 (25.6)      | 62 (35.0)       | 166 (23.6)|
| T1c                                  | 182 (51.6)    | 87 (50.6)      | 74 (41.8)       | 343 (48.9)|
| T2                                   | 99 (28.0)     | 22 (12.8)      | 28 (15.8)       | 149 (21.2)|
| T3                                   | 1 (0.3)       | 0 (0)          | 1 (0.6)         | 2 (0.3)   |
| No data                              | 6 (1.7)       | 5 (2.9)        | 7 (4.0)         | 18 (2.6)  |
between the groups regarding tumour size assessed in the baseline ultrasound made it impossible to draw precise conclusions at this stage of statistical analysis. In some cases the original tumour was not detected in an ultrasound (18 patients who underwent mammotomic stereotactic biopsy before SLNB).

The analysis of how the length of the period preceding the SLNB procedure (counted from the baseline ultrasound scan) influenced the percentage of metastatic lesions showed the highest value of the latter in those patients who had SLNB performed in the second and third month after the start of the preoperative diagnostics. Both in the case of an ultrasound scan performed 5 to 8 weeks before SLNB and of the test performed 9 to 12 weeks before SLNB, the percentage of diagnosed metastases in surgically removed lymph nodes (26.2% and 22.4% respectively) was higher than the mean value for the whole group of patients (21.9%). The results are shown in Table II. The differences were not statistically significant.

Tumour size (assessed in the baseline ultrasound scan), its histological malignancy grade, the kind of preoperative diagnostics of the original tumour, value of mitotic index Ki-67, biological type or age did not have any statistically significant influence on the differences in the value of preoperative ultrasound verification, in particular with reference to the identified time brackets (Table III).

In order to present the differences with reference to the percentage of metastases in the sentinel lymph node, we compared the results having divided the period in which the baseline ultrasound was performed into two time brackets. It was discovered that the highest diagnostic value was demonstrated by the assessment of local axillary status performed up to four weeks before a surgical procedure. Although the differences were not statistically significant, the results are shown in Table IV.

### Discussion

In order to perform the analysis described here, the imaging method was chosen as the one most frequently used in the preoperative diagnostics of non-advanced breast cancer patients being prepared for sentinel lymph node biopsy. Among currently available methods of local control of axilla, an ultrasound scan is the most available, the cheapest, and repeatable method allowing one to objectify the obtained results. The lowest percentage of lymph node metastases was noted when the baseline ultrasound was performed in the period directly preceding SLNB (not more than 4 weeks before the surgery). In the later period, with the increase of the percentage of false negative results of axillary lymph node status, the observed diagnostic value of the test decreased.

The main aim of the study was to determine when the preoperative diagnostic scheme used in patients qualified for SLNB (involving palpable examination and ultrasound testing) becomes the procedure based only on the palpable examination before the surgery.

The assessment of clinical value of preoperative ultrasound examination was also performed by Perhavce et al., who analysed a group of 470 breast cancer patients qualified for SLNB. The general percentage of metastases detected after SLNB was 43% (202/470). With reference to the patients who were diagnosed in ultrasound examination before the surgery, the percentage was lower – 39% (101/213); in patients who were diagnosed only by means of physical examination, the figure was 47% (10/213; p-value = 0.092). A lower percentage of macrometastases in the removed sentinel lymph nodes (44% vs. 66%; p = 0.002) was noted in patients who were diagnosed in ultrasound examination. Additionally, the metastatic lesions were smaller (mean size 5.4 mm vs. 6.8 mm; p-value = 0.027). According to the authors, ultrasound examination has a higher diagnostic value in assessing the preoperative axillary lymph node status (false negative result in 39% of patients tested). Up to 47% of patients, despite the absence of palpably suspicious axillary lymph node metastases...
Table III. Influence of some clinical factors on diagnostic value of ultrasonographic assessment of axillary lymph node status

| Clinical data analysed | Time from performing the baseline ultrasound preceding SLNB and percentage of sentinel lymph node metastases – number of patients – n (%) |
|------------------------|---------------------------------------------------------------------------------------------------------------|
|                        | Up to 4 weeks | 5 to 8 weeks | 9 to 12 weeks | 13 to 16 weeks | Over 16 weeks |
| Original tumour size:   |               |               |               |               |               |
| T1a                    | 1 (0)         | 4 (0)         | 6 (0)         | 5 (0)         | 8 (0)         |
| T1b                    | 14 (7.1)      | 46 (28.3)     | 40 (15.0)     | 26 (11.5)     | 40 (20.0)     |
| T1c                    | 47 (23.4)     | 135 (22.2)    | 82 (24.4)     | 40 (15.0)     | 39 (15.4)     |
| T2                     | 26 (19.2)     | 73 (35.6)     | 21 (38.1)     | 19 (33.3)     | 11 (36.4)     |
| T3                     | –             | 1 (0)         | –             | –             | 1 (0)         |
| No data                | 2 (0)         | 4 (0)         | 3 (0)         | 3 (0)         | 6 (16.7)      |
| Age [years]:           |               |               |               |               |               |
| Up to 40               | 6 (33.3)      | 18 (33.3)     | 8 (12.5)      | 5 (20.0)      | 3 (66.7)      |
| 40 to 60               | 54 (22.2)     | 138 (29.7)    | 78 (17.9)     | 40 (20.0)     | 48 (18.8)     |
| Over 60                | 30 (10.0)     | 107 (20.6)    | 66 (28.8)     | 47 (12.8)     | 54 (14.8)     |
| Histological malignancy grading: |           |               |               |               |               |
| G1                     | 5 (0)         | 9 (0)         | 9 (11.1)      | 3 (0)         | 12 (8.3)      |
| G2                     | 62 (21.0)     | 189 (26.5)    | 105 (21.9)    | 69 (20.3)     | 189 (26.5)    |
| G3                     | 23 (17.4)     | 60 (31.7)     | 30 (30.0)     | 15 (6.7)      | 13 (30.8)     |
| No data                | –             | 5 (0)         | 8 (12.5)      | 5 (0)         | 4 (0)         |
| Preoperative diagnostics: |           |               |               |               |               |
| FNAB                   | 40 (20.0)     | 130 (25.4)    | 59 (18.6)     | 23 (13.0)     | 18 (22.2)     |
| CNB/VAB                | 35 (20.0)     | 112 (26.8)    | 67 (29.9)     | 41 (14.6)     | 24 (16.7)     |
| Surgical biopsy        | 15 (13.3)     | 21 (28.6)     | 26 (11.5)     | 28 (21.4)     | 63 (17.5)     |
| Ki-67 value [%]:       |               |               |               |               |               |
| 0–14                   | 23 (8.7)      | 65 (20.0)     | 54 (20.4)     | 25 (24.0)     | 38 (21.1)     |
| 15–30                  | 28 (14.3)     | 77 (33.8)     | 42 (19.0)     | 31 (19.4)     | 35 (11.4)     |
| 30–45                  | 8 (50.0)      | 21 (19.0)     | 8 (62.5)      | 2 (50.0)      | 4 (75.0)      |
| Over 45                | 4 (0)         | 29 (41.4)     | 12 (33.3)     | 1 (0)         | 4 (0)         |
| No data                | 27 (25.9)     | 71 (19.7)     | 36 (16.7)     | 33 (6.1)      | 24 (16.7)     |
| Biological type of breast cancer: |           |               |               |               |               |
| Luminal A              | 23 (8.7)      | 63 (19.0)     | 54 (20.4)     | 25 (24.0)     | 38 (21.1)     |
| Luminal B1             | 39 (20.5)     | 117 (29.9)    | 54 (22.2)     | 30 (20.0)     | 43 (16.3)     |
| Luminal B2             | 3 (33.3)      | 24 (25.0)     | 13 (38.5)     | 9 (22.2)      | 3 (100)       |
| HER2 positive          | 2 (0)         | 13 (30.8)     | 9 (22.2)      | 5 (20.0)      | 5 (20.0)      |
| Triple negative        | 14 (14.3)     | 33 (30.3)     | 13 (15.4)     | 11 (0)        | 4 (0)         |
| No data                | 9 (44.4)      | 13 (15.4)     | 9 (22.2)      | 12 (0)        | 12 (0)        |

FNAB – Fine-needle aspiration biopsy, CNB/VAB – core needle biopsy/vacuum-assisted biopsy, G – histological malignancy grading, HER2 – expression/amplification of HER2 receptor.
Table IV. Diagnostic value of baseline ultrasound in assessment of axillary lymph node status – analysis in two independent time brackets

| Clinical data analysed | USS testing up to 4 weeks before SLNB | USS testing more than 4 weeks before the SLNB | Value of p |
|------------------------|----------------------------------------|---------------------------------------------|-------------|
|                        | Number of patients | Percentage of metastases | Number of patients | Percentage of metastases |               |
| Original tumour size:  |                          |                              |                          |                              |               |
| T1a                    | 1                       | 0                            | 23                      | 0                            | –            |
| T1b                    | 14                      | 7.1                          | 152                     | 19.7                         | 0.249        |
| T1c                    | 47                      | 23.4                         | 296                     | 20.9                         | 0.703        |
| T2                     | 26                      | 19.2                         | 123                     | 35.8                         | 0.104        |
| T3                     | –                       | –                            | 2                       | 0                            | –            |
| Age [years]:           |                          |                              |                          |                              |               |
| Up to 40               | 6                       | 33.3                         | 34                      | 29.4                         | 0.897        |
| 40 to 60               | 54                      | 22.2                         | 304                     | 23.7                         | 0.406        |
| Over 60                | 30                      | 10.0                         | 274                     | 20.1                         | 0.183        |
| Histological malignancy grading: |          |                              |                          |                              |               |
| G1                     | 5                       | 0                            | 33                      | 6.1                          | –            |
| G2                     | 62                      | 21.0                         | 439                     | 23.0                         | 0.720        |
| G3                     | 23                      | 17.4                         | 118                     | 28.0                         | 0.293        |
| Preoperative diagnostics: |                    |                              |                          |                              |               |
| FNAB                   | 40                      | 20.0                         | 230                     | 22.2                         | 0.783        |
| CNB/VAB                | 35                      | 20.0                         | 244                     | 24.6                         | 0.732        |
| Surgical biopsy        | 15                      | 13.3                         | 138                     | 18.8                         | 0.665        |
| Ki-67 value [%]:       |                          |                              |                          |                              |               |
| 0–14                   | 23                      | 8.7                          | 182                     | 20.9                         | 0.053        |
| 15–30                  | 28                      | 14.3                         | 185                     | 23.8                         | 0.049        |
| 30–45                  | 8                       | 50.0                         | 35                      | 37.1                         | 0.257        |
| Over 45                | 4                       | 0                            | 46                      | 34.8                         | 0.330        |
| Biological type:       |                          |                              |                          |                              |               |
| Luminal A              | 23                      | 8.7                          | 180                     | 20.6                         | 0.175        |
| Luminal B1             | 39                      | 20.5                         | 244                     | 24.6                         | 0.581        |
| Luminal B2             | 3                       | 33.3                         | 49                      | 32.7                         | 1.0          |
| HER2 positive          | 2                       | 0                            | 32                      | 25.0                         | 0.602        |
| Triple negative        | 14                      | 14.3                         | 61                      | 19.7                         | 0.643        |

FNAB – Fine-needle aspiration biopsy, CNB/VAB – core needle biopsy/vacuum-assisted biopsy, G – histological malignancy grading, HER2 – expression/amplification of HER2 receptor.
In our group the results were much more favourable. With reference to the diagnostic value of ultrasound axilla examination preceding the excision of the sentinel lymph node, despite the absence of pathology in the test in 21.9% of patients, metastases in sentinel lymph nodes were detected (false negative ultrasound examination result). Ultrasound examinations performed directly before SLNB showed, in 14.4% of cases, a result opposite to the one which was presented in the pathology report.

The unsatisfactory reliability of pre-surgery assessment of lymph nodes in ultrasound examinations was commented on by Diepstraten et al. [17]. In the meta-analysis of 31 selected works from between 1999 and 2012 (including 9 prospective studies), clinical material of the overall number of 9212 patients was assessed. In the conclusions it was stated that in up to 25% of patients the correct ultrasound assessment preceding SLNB was a false negative result. The authors of this analysis also noted the high value of ultrasound examination, which allows one to detect metastases in axillary lymph nodes before surgery. Despite the absence of suspicious lymph nodes in patients with breast cancer preparing for SLNB, additional use of ultrasound assessment (combined with fine-needle aspiration biopsy of visible suspicious lymph nodes) allowed metastases in axilla to be detected in 50% of cases.

With reference to our clinical material, the suggested proportion was slightly lower. Nevertheless, histopathological verification confirmed the presence of metastases in 42.3% of patients with suspicious axillary lymph nodes detected in ultrasound examination (performed just before the surgery). The high diagnostic value of ultrasound assessment of axillary lymph nodes was confirmed by the authors of SOUND (Sentinel node vs. Observation after axillary UltraSouND), a prospective study launched in the European Institute of Oncology in Milan [18]. Its aim was to compare the treatment outcomes of 1560 patients with invasive breast cancer qualified for sentinel lymph node biopsy. Inclusion criteria are: tumour size (up to 2 cm in diameter), degree of invasiveness, planned breast-conserving treatment, and normal result of the preoperative ultrasound assessment of axilla (or presence of a single lymph node successfully verified in preoperative fine-needle aspiration biopsy).

In half of the patients tested, SLNB was performed, and in the remaining patients conservative treatment was used (without surgical procedures regarding the axillary lymph node system). The expected outcome of the study is the absence of statistically significant differences regarding the comparison of remote treatment results in both groups of patients.

In the group tested, the obtained preoperative sensitivity of ultrasound examination in detecting metastases present in the sentinel lymph node was 34.4%. Thus, it is considerably lower than the results published by Ciatto et al. and many other authors – 70–96%. In accordance with the same notifications, specificity of ultrasound assessment ranges from 50% to 73% (up to even 100% – in cases of an ultrasound scan being complemented by fine-needle aspiration biopsy of suspicious lymph nodes) [19–21]. The value obtained in our study at the level of 89.3% does not differ from the ones quoted above.

Low sensitivity of $[^{18}F]-2$-fluoro-2-deoxy-D-glucose positron emission tomography (FDG PET) examination in detecting metastases in lymph nodes makes SLNB an obligatory method to be used in cases of negative test results. A considerably high positive predictive value of FDG PET examination makes it a good selective method for patients who, after neoadjuvant chemotherapy, qualify for axillary lymph node dissection, without SLNB. However, this requires further study on larger groups of patients [22].

**Conclusions**

Ultrasound assessment of the axillary lymph node status in patients with breast cancer who qualify for sentinel lymph node biopsy is an examination method of high specificity (89.3%) and equally high predictive value of the negative test result (85.6%). Thereby, on the basis of an ultrasound scan it is possible to select patients in whom it is unlikely to detect metastases in lymph nodes in the excision procedure during SLNB.

The lowest proportion of metastases in the sentinel lymph node was found in patients who, while being qualified for SLNB, had an ultrasound scan performed shortly (not more than 4 weeks) before the surgery. The observations made refer to both univariate analysis (the percentage of metastases in respective time periods) and multidimensional analysis (the percentage of metastases depending
on the chosen clinical agent, assessed in the time dimension).

Conflict of interest
The authors declare no conflict of interest.

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