

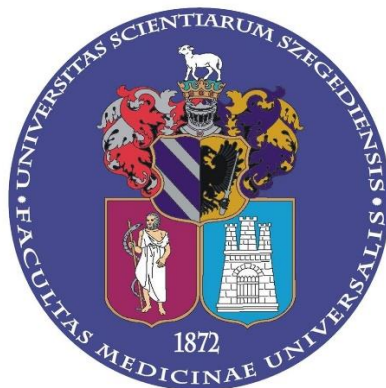
UNIVERSITY OF SZEGED FACULTY OF MEDICINE
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**THE SIGNIFICANCE OF AXILLARY TREATMENT IN
THE COMPLEX THERAPY FOR PATIENTS WITH
BREAST CANCER**

Ph.D. Thesis

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1. INTRODUCTION

Complex treatment of patients with breast cancer, including surgical treatment, has significantly changed over the past 100 years. Due to the development in diagnostics, a better understanding of the biological characteristics of tumours and the expansion of treatment options in oncology, super-radical resection surgery – applied initially – has been replaced by increasingly less invasive interventions, and the aim to conserve the breast became generally accepted.

Axillary lymph node dissection used to constitute an integral part of the onco-surgical treatment of breast cancer. In the past 25 years, there have also been significant changes in the diagnostics and treatment of the axilla. Due to the introduction of sentinel lymph node biopsy (SLNB) in 1993, axillary block dissection (ABD), which is characterised by a significant morbidity rate, became safely avoidable in a significant proportion of patients. Similarly, staging, thus complex oncology treatment of breast cancer also became significantly more accurate. The introduction of SLNB also brought about the intraoperative assessment of the sentinel lymph node, which reduced the number of surgeries in two sittings, and, therefore, patient burden and surgery costs.

Initially, if preoperative assessment was negative, but intraoperative or final histological examination found a metastasis in the sentinel lymph node, axillary block dissection was considered necessary. Clinical studies later showed that performing SLNB is sufficient even in the presence of a lymph node containing a micrometastasis or an isolated tumour cell (e.g. International Breast Cancer Study Group (IBCSG) 23-01, Agència d'Avaluació de Tecnologia i Recerca Mèdiques (AATRM) 048/13/2000).^{9,10} Milestone findings of the Z0011 study of the American College of Surgeons Oncology Group (ACOSOG) showed that axillary block dissection is not necessary even in the presence of up to 2 positive lymph nodes containing macrometastases, if this complies with the inclusion criteria of the study. The findings of study of the European Organization for Research and Treatment of Cancer (EORTC), titled After Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS) show that even in patients who underwent mastectomy and have a sentinel lymph node that is proven to be metastatic, axillary block dissection is avoidable, and axillary irradiation and close follow-up is sufficient.

Currently accepted international guidelines in breast cancer recommend axillary block dissection, if preoperative assessments confirm axillary metastasis, and the patient undergoes surgery with or without prior neoadjuvant therapy.

Multiple studies show that targeted axillary irradiation is a therapeutic alternative to axillary block dissection. Patients increasingly and rightfully demand a better understanding of treatment alternatives and more control over which one to choose. The reduction in the indication of axillary block dissection and appearance of irradiation as a therapeutic alternative, and also participation of patients in therapeutic decision-making warranted the rethinking of the application of intraoperative lymph node diagnostics and imprint cytology.

However, patients where preoperative assessment already confirms axillary lymph node metastasis constitute a separate treatment group. In these cases, axillary block dissection continues to be the surgical recommendation. Axillary ultrasound plays a fundamental role in screening axillary metastasis, and a positive scan necessitates aspiration cytology. The sensitivity of axillary ultrasound ranges from 25 to 71%, depending on the immunohistochemical status of the tumour. Combined with fine-needle aspiration cytology (FNAC), its sensitivity increases to 70–80%.

In cases with a positive lymph node by aspiration cytology, a proportion of patients receive systemic neoadjuvant therapy. Multinational results indicate that in these cases, a significant proportion of patients experience complete axillary pathologic regression.

Similarly, it is also known that in a certain proportion of patients, only the sentinel lymph node contains a metastasis. An American study published in 2017 confirmed that if the primary tumour is ≤ 2 cm as measured by breast ultrasound, aspiration cytology confirms ≤ 1 positive axillary lymph node, and the patient does not receive neoadjuvant therapy, ABD is not necessarily justified, and SLNB is recommended instead.

2. AIMS

2.1 First study

Introduced 20 years ago, lymph node biopsy significantly reduced the number of radical surgical interventions – axillary block dissections – in the treatment of early breast cancer. In the meantime, intraoperative processing of sentinel lymph nodes became increasingly widespread, as its use helped avoid surgery in two sittings.

Over the past years, surgical treatment of the axilla, primarily in terms of the necessity of axillary block dissections, has considerably changed. Results of several prospective studies indicate that ABD is not warranted for sentinel lymph nodes containing positive, isolated tumour cells (ITC, ≤ 0.2 mm), and micrometastases (≤ 2 mm), and adjuvant therapy is sufficient (systemic therapy, whole-breast irradiation). Based on the ACOSOG Z0011 study published in 2011, axillary block dissection is not necessary even in T1 or T2 breast cancer, following wide local excision, or sentinel lymph node biopsy showing no more than 1 or 2 macrometastases in sentinel lymph nodes.

All these factors warranted the rethinking of the application of routine imprint cytology. In this work, we retrospectively looked at the findings of imprint cytology assessments performed in our institute and also analysed these in the context of the new international guidelines in axillary treatment.

2.2 Second study

In the second study, we looked for correlations between axillary ultrasound and clinicopathological factors, which help us predict the presence and severity of axillary metastasis in order to decide in advance – in light of the results of preoperative assessments – the cases in which axillary block dissection can be avoided.

Our investigation aimed to find correlations between pre- and intraoperative assessments and clinicopathological factors, which allows us to assess not only the presence of axillary metastasis, but also its severity (mild or severe). Our additional goal was to decide in advance – based on pre- and intraoperative assessments – which cases require axillary block dissection and which cases necessitate sentinel lymph node biopsy only.

3. PATIENTS AND METHODS

3.1 Patients

The study involved the retrospective analysis of the pre-, intra- and postoperative data of 2671 cases involving surgery due to early invasive breast cancer at the Department of Surgery, Faculty of Medicine, University of Szeged between 1 January 2007 and 31 December 2017. Mandatory parts of the complex breast assessment included physical examination, ultrasonography and mammography. If a suspicious, metastatic axillary lymph node was noticed during axillary ultrasound, aspiration cytology was always performed. If aspiration cytology confirmed the presence of a metastasis, a certain portion of patients also received systemic neoadjuvant therapy.

In our first study, we looked at the sensitivity and specificity of the imprint cytology of the sentinel lymph node from 1168 patients who underwent surgery due to invasive breast cancer between 1 May 2008 and 31 December 2014. In addition, we retrospectively analysed the method in the context of the ACOSOG Z0011 study, accepted international guidelines and consensus conference guidelines.

In the second study, we looked at the pre- and postoperative data of 2671 cases involving surgery due to early invasive breast cancer between 1 January 2007 and 31 December 2017. We looked for correlations between preoperative axillary assessments and clinicopathological factors, which allowed us to predict not only the presence of axillary metastasis, but also its severity (mild or severe).

3.2 Surgery technique

3.2.1 Surgical treatment

In the surgical treatment of invasive breast tumours, our aim in general is to achieve oncologically adequate – tumour free – resection edges. Our goal was to provide locoregional tumour control and precise locoregional staging. With the aesthetic outcome also taken into consideration, breast-conserving surgery was performed whenever possible.

Sentinel lymph nodes were removed with the double tracer method published by Albertini in 1996. ROLL (radio-guided occult lesion localisation) and dual labelling were used to localise breast tumours and the sentinel lymph node. At least 4 hours before the surgery, isotope (^{99m}Tc) labelled human colloidal albumin was administered into the lesion, which was followed by lymphoscintigraphy to determine the projection of the sentinel lymph node and that of the lymphatic drainage. As a first step during surgery, Patentblau dye was administered around the areola, and then manual gamma probe was used to remove the tumour and the sentinel lymph node during the same procedure approximately 10 minutes later.

3.2.2 Technique of imprint cytology

The cut surface of the fresh sample prepared from a lymph node (250 μm slices) was pressed on a slide, and then an impression smear was prepared. The resulting imprint cut surfaces were fixed in 95% ethanol for 5–6 seconds, and the samples were evaluated after hematoxylin eosin staining.

3.2.3 Indication of axillary blockdissection

In the first study (between 2008 and 2014), in agreement with the Hungarian guidelines in force, we performed ABD if either the preoperative assessments (ultrasound-guided FNAC/core biopsy), or intraoperative imprint cytology, or the final pathologic examination of the sentinel lymph node confirmed lymph node metastasis.

Later, from 2014, imprint cytology was no longer used, and, in agreement with the guideline changes, if metastasis (macrometastasis) is found in > 2 SLN and/or the patient does not meet the inclusion criteria of the Z-0011 study. ABD is also performed in cases with mastectomy and SLNB, if no postoperative radiation therapy is planned, and SLN (even one lymph node) contains a macrometastasis. If ultrasound-guided FNAC/core biopsy or SLNB prior to neoadjuvant (primary

systemic) therapy, or SLNP performed after neoadjuvant (primary systemic) therapy confirms lymph node metastasis, ABD is performed in these cases also.

Neoadjuvant therapy was administered in accordance with the current international practice, primarily to be able to remove tumours that were originally found to be oncologically inoperable, and to be able to perform breast conserving surgery instead of mastectomy. Indication of neoadjuvant therapy is established from the cT2 and cN0 or c/pN1 status, and from the cT1–4/cTx N2 status (the latter: unknown primary breast tumour). Regular physical and imaging examinations were performed to evaluate the efficacy of therapy, and in cases where there was a possibility for breast conserving therapy, clip labelling of the tumour was also performed at the beginning of the therapy.

3.3 Statics

IBM SPSS Statistics v22 program was used for statistical analysis in our study. Continuous variables were presented as mean and standard deviation, categorical variables were presented as case number and percentages. Chi square test followed by logistic regression were used to evaluate cumulative effect of the variables on the axillary status. The difference was considered to be statistically significant in cases where $p < 0.05$.

4. RESULTS

4.1. Is intraoperative touch imprint cytology indicated in the surgical treatment of early breast cancers?

In our Department, TIC was performed in 1168 cases for invasive breast tumor during the period under examination. The average age of the patients was 58.63 (25–88) years. TIC was positive in 202 cases in 17.29% (202/1168) of the cases. A total of 2101 lymph nodes were sent for imprint cytology, which is an average of 1.8 (1–6) lymph nodes per patient, and 348 were confirmed positive with final histological processing of the sample.

During a final histological examination of the samples, metastasis was found in 149 additional previously (intraoperatively) negative sentinel lymph nodes (false negative cases: 149/1168 [12.75%]), and metastasis was not confirmed in three cases found to be positive with imprint cytology (false positive cases: 3/149 [0.25%]). The sensitivity of the imprint cytology was 57.18%, with a specificity of 99.63%.

A total of 204 axillary block dissections were performed in one session, and then 80 block dissections were performed on a separate occasion. In 64 cases, an ABD was not performed, as the patient had not given his consent for the intervention, the patient had chosen adjuvant chemotherapy, or the oncoteam had not recommended additional surgery due to the presence of micrometastasis (Table 1).

Table 1. Imprint cytology results (1 May 2008–31 Dec 2014)

	Total:	%
Number of patients:	1168	100
Imprint cytology results:		
intraoperative (positive)	202	17.3
intraoperative (negative)	966	82.7
false negative	149	12.76
false positive	3	0.24
Number of positive final histological examinations:	348	29.79
Number of negative final histological examinations:	820	70.21
Type of surgery:		
excision	883	75.6
mastectomy	285	24.4
Average number of SLNBs:	1.8	
ABDs	284	24.32
in one session	204	17.47
supplementary	80	6.85

At that point, patients meeting the inclusion criteria for the Z0011 study and seven patients that could not be classified in this group were excluded from the positive cases by intraoperative examination, metastasis smaller than 2 mm was confirmed in these cases (ITC, micrometastasis), and then the sensitivity and specificity of the method were recalculated.

After screening, 76 positive, two false positive, 149 false negative and 966 negative cases were found in the repeated imprint cytology group. Sensitivity was 34.23%, and specificity was 99.76%. Axillary block dissection was performed in 284 cases, but, based on the new guidelines, only 105 cases were indicated. 179 cases, that is, 15.32% of the cases, were performed unnecessarily (Table 2).

Table 2: Results modified in accordance with the criteria

	Imprint (all cases)	Cases meeting Z0011 criteria	Cases not meeting Z0011 criteria but involving micrometastasis	Results recalculated
Number of patients	1168	117	7	1168
Imprint				
Positive	202	117	7	78
Negative	966	0	0	966
Final histology				
Positive	348	116	7	225
False positive	3	1	0	2
False negative	149	0	0	149

As the results were processed, the average size of the metastases and the distribution of micro- and macrometastases in false negative and positive cases were examined as well. In positive cases, the average size of the micrometastases was 1.52 mm, while that of the macrometastases was 8.33 mm. The average size of the micrometastases was 1.1 mm, while that of the macrometastases was 4.79 mm in the false negative group. Therefore, it can be concluded that imprint cytology cannot be considered a sensitive intervention for surgeries on smaller metastases.

4.2. Is axillary lymph node dissection necessary for positive preoperative aspiration cytology lymph node results?

In our second study, we analysed the data of 2671 patients who underwent surgery due to malignant breast cancer at the Department of Surgery of University of Szeged between 1 January 2007 and 31 December 2017. Preoperative examinations (axillary ultrasound, aspiration cytology sampling) confirmed axillary metastasis in 190 cases, where axillary block dissection was performed after neoadjuvant treatment. In our study, we compared the clinicopathological findings (histological, immunohistochemical status, tumour location, pre- and postoperative tumour size, number of positive tumours observed, lymph node size as described by ultrasound, neoadjuvant treatment) with lymph node status (N0-1 or N2-3, Z1 or Z2 – cases with a maximum of two or more metastatic lymph nodes), sorting patients into either the group that received or the group that did not receive neoadjuvant treatment, and we looked into which perioperative examination finding allows us to predict the presence of a lymph node with a maximum of 2 or 3 metastases in the axilla.

Pre- and postoperative data of 2671 cases where surgery was performed due to early invasive breast tumour were evaluated in the Department of Surgery, Faculty of Medicine, University of Szeged between 1 January 2007 and 31 December 2017.

The average age of the patients was 59.73 years (25–93). In 260 cases, axillary ultrasound suggested a metastatic lymph node; therefore, aspiration cytology sampling was performed, and in 190 cases (average age: 60.31 years, 29–89), pathology reports suggested metastasis. In these cases, ALND was performed. The average number of lymph nodes removed was 13.49.

False positive results were found in 22 (16.8%) of the 131 aspiration cytology examinations in patients not receiving neoadjuvant therapy. Based on the final histological examination of the axillary lymph nodes, 76 (58%) patients were confirmed to be stage N0-1 and 55 (42%) patients were stage N2-3. No significant correlation was found between the preoperatively examinable clinicopathological parameters and the axillary lymph node status for patients not receiving neoadjuvant therapy.

Neoadjuvant therapy was administered in 59 cases, and in 23 (39%) of these cases, complete axillary pathological remission was confirmed. Based on the final histological examination of the axillary lymph nodes, 40 (68%) patients were stage in N0-1, and 19 (32%) patients were in stage N2-3.

The results of the histological examinations, the immunohistochemistry status, the location of the tumour, and the number of the positive lymph nodes detected by the ultrasound examination showed no correlation with the final histological status of the lymph node. If preoperative ultrasound examinations find that the primary breast tumour is ≤ 20 mm ($p = 0.002$) or the positive lymph node is ≤ 15 mm ($p = 0.04$), the status of the axillary lymph nodes will likely be stage N0-1; therefore, a maximum of 3 positive axillary lymph nodes are present (Table 3).

Table 3. Relation of preoperative imaging results to final lymph node disease burden in patients receiving neoadjuvant therapy - Chi square test.

Neoadj.	N0-1 (n=40)	N2-3 (n=19)	p value
Tumour size on imaging	n=40	n=19	0.002
≤ 20 mm	28 (70%)	5 (26.32%)	
> 20 mm	12 (30%)	14 (73.68%)	
Tumour size on imaging (TNBC)	n=16	n=7	< 0.001
≤ 20 mm	14 (87.5%)	0 (0%)	
> 20 mm	2 (12.5%)	7 (100%)	
Lymph node size on imaging	n=31	n=13	0.04
≤ 15 mm	20 (64.51%)	4 (30.77%)	
> 15 mm	11 (35.49%)	9 (69.23%)	
Lymph node size on imaging (TNBC)	n=12	n=6	0.737
≤ 15 mm	5 (41.67%)	3 (50%)	
> 15 mm	7 (58.33%)	3 (50%)	
Tumour ≤ 20 mm and lymph node ≤ 15 mm	n=20	n=4	0.01
Number of abnormal lymph nodes on axillary ultrasound	n=40	n=19	0.161
1	38 (95%)	15 (78.95%)	
> 1	2 (5%)	4 (21.05%)	

We examined the likelihood of stage N0-1 in the presence of two preoperative factors: ≤ 20 mm tumour size as measured by ultrasound and a ≤ 15 mm size of the lymph node considered to be metastatic. In the patient group not receiving neoadjuvant therapy ($p = 0.948$), this could not be confirmed, but in patients receiving neoadjuvant therapy, the likelihood of maximum 3 metastatic lymph nodes is very high ($p = 0.01$).

Logistic regression was used to examine which variables are predictive of the axillary status. Using the omnibus test, we found that the independent variables in the model are more related to the dependent variable than we would expect due to chance ($p < 0.001$). We were able to confirm that the size of the tumour (Exp (B) = 1.050, 95% CI = 1.016–1.085, $p = 0.004$) is predictive of the axillary status. The resulting model was statistically significant ($\chi^2 = 18.806$, $df = 3$, $p < 0.001$). Using the model, the proportion of cases categorized correctly was 69.4% (overall percentage), which leads to a more precise result compared to categorizing by chance (55.4%).

Cases with maximum 2 (Z1) and 3 or more lymph nodes (Z2) were compared with the examinable preoperative factors in patients grouped by receiving or not receiving neoadjuvant therapy. In patients not receiving neoadjuvant therapy, the size of the breast tumour, the axillary status, clinicopathological characteristics of the tumour showed no correlation with the final histological status of the axilla. In patients receiving neoadjuvant therapy, the possibility of maximum 2 metastatic lymph nodes is very high if the size of the tumour is ≤ 20 mm ($p = 0.008$) based on the ultrasound examination. The joint presence of two preoperatively examinable factors – ≤ 20 mm tumour size confirmed by ultrasound and a ≤ 15 mm size of the lymph node considered to be metastatic – increased the possibility of maximum 2 positive lymph nodes only in patients receiving neoadjuvant therapy ($p = 0.728$ vs. $p = 0.017$). The final lymph node status of the axilla showed no connection with other clinicopathological characteristics (Table 4).

Table 4: Relation of preoperative tumour and lymph node size to final lymph node disease burden in patients not receiving neoadjuvant therapy - Chi square test.

Neoadj. 0	N0–1 (n=76)	N2–3 (n=55)	p value
Tumour size on imaging	n=76	n=55	0.703
≤ 20 mm	44 (57.9%)	30 (54.5%)	
> 20 mm	32 (42.1%)	25 (45.5%)	
Lymph node size on imaging	n=68	n=48	0.979
≤ 15 mm	31 (45.6%)	22 (45.8%)	
> 15 mm	37 (54.4%)	26 (54.2%)	

5. DISCUSSION

In the past 100 years we have seen an enormous development in the surgical treatment of breast cancer, and this is especially true for axillary surgery. The previously mandatory axillary block dissection, the removal of stage 1 or stage 2 axillary lymph nodes has been replaced by sentinel lymph node biopsy, and the indications for ABD have become considerably limited. Besides local tumour control, the fundamental aim of axillary surgery is to obtain accurate information about the involvement of the axilla in cancer, which is crucially important in the future therapy and prognosis of the cancer.

The introduction of sentinel lymph node biopsy in patients with breast cancer was initiated in 1991. Blue dye mapping of lymphatic drainage in breast cancer was first performed by Giuliano . Administration of radiolabelled colloids for intraoperative detection of the sentinel lymph node using a gamma-ray detection probe was introduced later. Preoperative lymphoscintigraphy enabled the accurate determination of the location and number of sentinel lymph nodes. Different methods based on these two techniques are now applied all around the world. Its significance lies in the fact that it considerably reduced the development of lymphoedema – the infamous side effect of axillary procedures – compared to block dissection. In addition to sentinel lymph node biopsy, preoperative ultrasound and aspiration cytology sampling are the most commonly used and studied examinations used for the detection of axillary metastases in newly diagnosed breast cancer. Axillary ultrasound was first used in combination with aspiration cytology sampling for the diagnosis of axillary lymph nodes suspected of containing metastases in 1997. Aspiration cytology is more commonly used, as it is quick, less painful for the patient, and also cost effective. Its disadvantage is that a negative finding does not rule out malignancy, but a positive finding is considered valid.

a) Is intraoperative touch imprint cytology indicated in the surgical treatment of early breast cancers?

In the meantime, intraoperative processing of sentinel lymph nodes became increasingly widespread, as its use helped avoid surgery in two sittings thereby reducing patient burden and surgery costs.

Intraoperative histological examinations include imprint cytology, frozen section histology and a nucleic acid amplification study. The specificity and sensitivity of these examinations are similar. The sensitivity of the nucleic acid amplification study is 76.9–98.2%, and that of frozen section

histology and imprint cytology varies between 68.49 and 98.81%. The specificity of all three methods is considered almost 100%.

Studies and guidelines published in the past 10 years (ACOSOG Z0011, NCCN Guidelines, St. Gallen Consensus Conference, German-Austrian-Swiss Consensus Conference, IBCSG 23-01) in cases that are in compliance with certain criteria (including isolated tumour cells, micrometastasis and in cases of a sentinel lymph node containing no more than two macrometastases, the patient undergoes breast-conserving surgery and receives systemic oncological treatment and whole-breast irradiation), consider axillary block dissection avoidable, as this does not pose a risk in terms of overall survival or local recurrence. Similarly, the indication of ABD is reduced by clinical studies supporting the fact that axillary radiation is an alternative treatment option to surgery, but it is associated with lower morbidity (as in the OTOASOR and AMAROS trials). Axillary radiotherapy does not pose an increased risk to survival and locally recurring cancer, and the incidence of lymphedema that is primarily responsible for morbidity is significantly decreased as well. According to the AMAROS study, lymphedema occurred in 23% of the cases five years after axillary block dissection, while this was 11% in patients treated with axillary radiation. Another important factor is that in the case of axillary block dissection performed for positive imprint cytology, the patient is unable to participate in the therapeutic decision and choose from among therapeutic options.

These factors suggest a reconsideration of the routine use of imprint cytology. Based on our results, the sensitivity of imprint cytology is 57.18%, its specificity is 99.63%, and these values are consistent with international data. (The sensitivity of imprint cytology varies between 68.49 and 98.81%, with a specificity of approximately 100%). With regard to metastasis sizes and distribution, imprint cytology is less suited to detecting metastases of 2 mm or smaller, with 84.15% of micrometastases remaining undetected, but 70.3% of macrometastases can be detected with this method.

However, according to the latest guidelines, the sensitivity of imprint cytology (based on cases with therapeutic consequences) is only 34.23% (with unchanged specificity). This sensitivity value is so low that the usability of this method is questionable. ABD was only indicated in 9% of the patients in the period under examination (105/1168). However, based on the new guidelines, supplementary lymph node dissection was performed “unnecessarily” in 15.32% of the patients (179/1168). It is not insignificant that imprint cytology increased surgical costs and the duration of surgery unnecessarily in a large percentage of the patients (91%).

First study shows that axillary block dissection is only necessary in the treatment of the axillary region in an increasingly smaller group of patients (9%), and this percentage will further decrease with more extensive use of alternative axillary radiotherapy.

Based on our results, imprint cytology of the sentinel lymph node(s) in patients operated on for malignant breast cancer has no confirmed benefits based on the current guidelines, and its routine use is not indicated. According to the latest international guidelines, intraoperative examination of the sentinel lymph node(s) may be indicated in the case of mastectomy (when postoperative radiotherapy is not planned) and after neoadjuvant therapy, as ABD is still indicated in these cases.

b) Is axillary lymph node dissection necessary for positive preoperative aspiration cytology lymph node results?

Nowadays, the effort to further limit the indication area of ALND accompanied by significant morbidity is completely reasonable. One way to do this is to preoperatively screen patients only at N1 stage axillary status. Based on several international guidelines (National Comprehensive Cancer Network [NCCN], St. Gallen consensus conference, ESO-ESMO international consensus conference, Hungarian Breast Cancer Consensus Conference), in cases characterised by the presence of axillary lymph nodes considered to be negative by preoperative examinations, sentinel lymph node biopsy should be performed, and with axillary lymph nodes considered to be positive, aspiration cytology or core biopsy should be performed. Several research groups have studied which factors detected or examined during the preoperative period (imaging studies, histological finding, immunohistochemistry status, location of the tumour etc.) may be suitable to determine whether sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND) should be performed during the surgery with certainty even before the surgery in cases with positive axillary ultrasound and positive aspiration cytology. In the post-Z0011 period of the treatment of breast tumours, not only the presence of an axillary metastasis is examined, but positive cases are also differentiated as mild (N1 lymph node status, 1 to 3 positive lymph nodes) and severe (N2 lymph node status, 4 or more positive lymph nodes) axillary metastases. Lim et al. have confirmed that if the patient meets the criteria of the Z0011 study, and the axillary ultrasound detects 3 or more positive lymph nodes, it is very likely that there are multiple positive lymph nodes in the axilla; therefore, axillary lymph node dissection cannot be avoided. This result has also been confirmed by the study of Liu et al., which found that ALND may be avoided if patients meet the criteria of the Z0011 study, and the axillary ultrasound examination confirms only one suspected metastatic lymph node. If – based on ultrasound examination – two lymph nodes are considered to be

metastatic, histological sampling and axillary lymph node dissection are recommended (the latter subject to positive histology findings). The study of Liang et al. highlights the importance of preoperative histological examination; the authors have shown that in cases where axillary lymph nodes are found to be positive with fine needle aspiration cytology, the patient is more likely to have more than 3 metastatic lymph nodes in the axilla, compared to cases where the sentinel lymph node biopsy confirms 1 to 2 metastatic lymph nodes.

In our study, we examined which combination of preoperative parameters would allow axillary lymph node dissection to be avoided, if axillary lymph node involvement is confirmed preoperatively. Data of 2671 cases were analysed: axillary ultrasound was performed in all cases, a metastatic lymph node was found in 260 cases, from which aspiration cytology was also performed. The examination confirmed metastasis in 190 cases. In these cases, based on the guidelines of previous consensus conferences, axillary lymph node dissection was performed as the primary surgery both in patients receiving neoadjuvant therapy and in patients not receiving neoadjuvant therapy. We also examined which of these clinicopathological characteristics could eliminate the need for this radical surgical intervention. Based on our results, the severity of the involvement of the axillary region in the tumour process could not be clearly predicted preoperatively with the clinicopathological characteristics of the tumour in patients not receiving neoadjuvant therapy (N0-1 vs. N2-3). In contrast, a study conducted in the United States of America and published in 2017 confirmed that primary ALND is not necessary and SLNB is recommended if the preoperative breast ultrasound confirmed a 2-cm or smaller primary tumour in the breast, maximum one positive lymph node is confirmed with aspiration cytology, and the patient does not receive neoadjuvant therapy. In their retrospective study conducted in the United Kingdom, Lloyd et al. also found that patients are very likely to have maximum 2 or less axillary lymph nodes with macrometastasis if the preoperative ultrasound confirmed a 20-mm or smaller primary tumour, histology of this tumour confirmed invasive ductal or lobular carcinoma, and breast conserving surgery was performed. Therefore, in these cases, ALND represents overtreatment. Differences between our study findings and international literature are presumably due to the differences observed in the clinicopathological characteristics of the tumours.

Based on our study we claim that N0-1 lymph node status in patients not receiving neoadjuvant therapy cannot be safely determined by preoperative examinations, while the lymph node status of patients receiving neoadjuvant chemotherapy can be predicted with great certainty based on the results of the preoperative ultrasound examination. If the patients also receive neoadjuvant therapy, it can be predicted with high probability whether the disease is in stage N0-1 or not, and whether

axillary lymph node dissection can be avoided or not based on the preoperative size of the tumour (≤ 20 mm, $p = 0.002$) and the preoperative size of the lymph node (≤ 15 mm, $p = 0.04$).

In patients with breast tumours, lymph node status of the axilla has a key role in planning the local and systemic therapy. If there is a metastatic lymph node in the axilla, a significant proportion of patients receive neoadjuvant systemic therapy, which resolves the axillary metastatic process in approximately 40% of the cases. Following neoadjuvant therapy, the standard surgical procedure in these patients was axillary lymph node dissection even in cases with complete pathological remission. Several studies have addressed the question of sentinel lymph node biopsy and repeated biopsy after neoadjuvant therapy (for example: SENTINA). In the ACOSOG Z1071 study, the rate of false negative sentinel lymph node biopsies was close to 10% false negative (12.6%), and this value further decreased with the removal of the lymph node indicated with a marker (metal clip) during axillary core biopsy. During the surgical intervention, the sentinel lymph node is already detected using the classical dual tracer method (technetium 99m-labelled human colloidal albumin and blue dye). With this technique (targeted axillary dissection, TAD) the rate of false negative sentinel lymph nodes decreased to approximately 2%. Pilewski et al. analysed data from 425 patients and studied to what extent preoperative imaging studies influence the lymph node status of the axilla. If the examinations suggested the presence of a metastatic lymph node, and the patient met the criteria of the Z0011 study, axillary lymph node dissection could have been avoided in 71% of the cases. If aspiration cytology was positive, ALND was unnecessary in 45%. Our analyses confirmed the same result. Following neoadjuvant therapy, maximum 3, and maximum 2 positive lymph nodes were confirmed with the final histology in two-thirds (40/59, 68%), and in over 50% (34/59, 57%) of the cases, respectively; therefore, axillary lymph node dissection could have been avoided. A Spanish study published in 2018 also investigated whether axillary lymph node dissection should be performed after neoadjuvant therapy in cases where an axillary lymph node is considered to be positive with aspiration cytology. In cases showing a significant presence of the Her2 receptor and low expression of the oestrogen receptor, there is a high chance that complete pathological remission occurs, and in these cases, ALND was not recommended.

In a meta-analysis published in 2016, data from 3398 patients were reviewed, and the authors aimed to see whether axillary lymph node dissection is necessary after neoadjuvant therapy in lymph node positive breast tumour cases. According to the analysis, the recommended treatment strategy at present is axillary lymph node dissection. However, optimizing preoperative examinations and screening the patient population may help to achieve a more precise preoperative evaluation of the axillary lymph node status. In the future, performing SLN with dual tracer

method, labelling the positive axillary lymph node in advance with a metal clip or with a radiopharmaceutical containing iodine, followed by the removal of the labelled lymph node may decrease the number of axillary lymph node dissections. Based on the analysis, HER2 positive and triple negative cases by immunochemistry require further studies. A study published in 2017 showed that the efficacy of neoadjuvant therapy did not differ in these cases, but further studies are recommended in these cases as well. Our study also showed, in patients with triple negative breast cancer (TNBC) who receive neoadjuvant therapy, if the size of the tumour is ≤ 20 mm, the axillary lymph node status is N0-1 in 87.5% of the patients. The same result was found in a study performed in 2016; ALND could be avoided after neoadjuvant therapy in 48% of the patients, especially in case of HER2 receptor positive and triple receptor negative cases. The study supported performing sentinel lymph node biopsy in patients with breast tumour receiving neoadjuvant therapy and with multiple axillary lymph node metastases as well. To support the results, longer studies are required. The retrospective study of Pilewski, which processed data from 1944 patients confirms this result; the study concluded that if patients receive neoadjuvant therapy followed by mastectomy, and the receptor status is HER2 positive and triple receptor negative, ALND could most likely have been avoided. Low oestrogen, and increased Her2 receptor and Ki67 expression results in higher numbers of pathological regression. Axillary block dissection is not recommended in these cases.

In an ideal situation, preoperative axillary examination not only identifies the positive lymph nodes, but also helps in selecting the proper treatment plan, and as a result, patients may receive individualized medical care. In accordance with our results, detecting the suspicious lymph nodes with axillary ultrasound examination may predict the stage of the disease; therefore, we consider the complete examination of the axilla important in excluding potential lymph node metastases. With patients under check-up examinations due to an invasive breast tumour, the preoperative size of the tumour, the size of the lymph node in case of positive aspiration cytology can be used to identify patients with stage N0-1 lymph nodes. Our results confirm that in patients receiving neoadjuvant therapy, in addition to the preoperative size of the tumour (≤ 20 mm, $p = 0.002$), the preoperative size of the lymph node (≤ 15 mm, $p = 0.04$) may also be used to predict that the stage of the disease is N0-1. In neoadjuvant therapy, labelling the suspectedly positive lymph nodes – with metal clips, for example – followed by the surgical removal of the affected lymph node, then the administration of adjuvant, targeted radiotherapy and close follow-up may be adequate treatment for the patient.

6. CONCLUSIONS:

- 1) Our findings indicate that imprint cytology assessment of sentinel lymph nodes offers no justifiable benefit in the context of current guidelines; thus, its routine use is no longer reasonable in the surgical treatment of early breast cancer. Based on the latest international guidelines, intraoperative assessment of sentinel lymph nodes is indicated in mastectomy (when no postoperative irradiation is planned) and after neoadjuvant therapy, as in these cases, ABD is still recommended.

- 2) In cases with positive preoperative axillary ultrasound and aspiration cytology, if the breast tumour is ≤ 20 mm, and the patient receives neoadjuvant therapy, the axilla is most probably in stage N0-1. In these cases, marking the positive lymph node, and removal of this involved lymph node during surgery, as well as targeted adjuvant radiotherapy and close monitoring is an adequate treatment alternative to ABD.

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LIST OF PAPERS

THIS DOCTORAL THESIS IS BASED ON THE FOLLOWING PUBLICATIONS:

- I. **Horváth, Z** ; Paszt, A ; Simonka, Z ; Látos, M ; Oláh, V ; Nagyszegi, D ; Kaizer, L ; Fejes, Z ; Hamar, S ; Csörgő, E ; Ormándi K ; Lázár M ; Lázár G. Is intraoperative touch imprint cytology indicated in the surgical treatment of early breast cancers? EUROPEAN JOURNAL OF SURGICAL ONCOLOGY 43 : 7 pp. 1252-1257. , 6 p. (2017) IF: 3,83
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