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Impact of Size of the Tumour, Persistence of Estrogen Receptors, Progesterone Receptors, HER2Neu Receptors and Ki67 Values on Positivity of Axillary Lymph Nodes in Patients with Early Breast Cancer with Clinically Negative Axillary Examination

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Abstract

AIM: The study aimed to identify factors that influence the positivity of axillary lymph nodes in patients with early breast cancer and clinically negative axillary lymph nodes, who were subjected for modified radical mastectomy and axillary lymphadenectomy.

MATERIAL AND METHODS: This study included 81 surgically treated, early breast cancer patients during the period from 08-2015 to 05-2017. All the cases have been analysed by standard histological analysis including macroscopic and microscopic examination by routine H&E staining. For determination of molecular receptors, immunostaining by PT LINK immunoperoxidase has been done for HER2neu, ER, PR, p53 and Ki67.

RESULTS: Patients age ranged between 31-73 years, an average of 56.86 years. The mean size of a primary tumour in the surgically treated patient was 20.33 ± 6.0 mm. Axillary dissection revealed from 5 to 32 lymph nodes, with an average of 14. Metastases have been found in 1 to 7 lymph nodes, with an average 0.7. Only 26 (32.1%) of the patients showed metastases in the axillary lymph nodes. The univariant regression analysis showed that the size of a tumour and presence of HER2neu receptors on cancer cells influence the positivity of the axillary lymph nodes. The presence of the estrogen receptors, progesterone receptors have no influence on the positivity for metastatic deposits of lymph nodes. Multivariant model and logistic regression analysis as significant independent factors or predictors of positivity of the axillary lymph nodes are influenced by the tumour size only.

CONCLUSION: Our study showed that the metastatic involvement of the axillary lymph nodes is mainly influenced by the size of a tumour and presence of HER2neu receptors in the univariant analysis. This point to the important influence of positivity of the axillary lymph nodes but, in multi-variant regressive analysis the lymph node status correlates with the tumour size only.

Introduction

Axillary status (involvement of lymph nodes in axilla with a metastatic tumour from primary breast cancer) together with the size of a primary breast tumour is the main factors that define the stage of breast cancer but also predict prognosis of the breast cancer [1].

Introducing procedure – detection of sentinel node and biopsy, is a minimally invasive procedure that determines first drainage lymph node in the axillar pit [2]. Examination of this lymph node at the same

surgical intervention gives us information about the status of this lymph node but also gives us information about other lymph nodes in the axilla. We suppose that if the sentinel lymph node is negative (not involved with metastases), we suppose that all other lymph nodes in the axillary pit is negative and is not necessary to do lymphadenectomy. Knowing the status of the axillary lymph nodes is very important, for the planning further therapeutic procedure.

The study aimed to analyse which factors that influence the positivity of axillary lymph nodes, with a point to tumour size, expression of estrogen, progesterone and HER2neu receptors on tumour cell surface, values of Ki67, in patients with early breast cancer and clinically negative axillary lymph nodes.

Material and Methods

In the prospective study were analyse 81 surgically treated patients with early breast cancer during 08.2015-05.2017 year, with clinically negative axilla, at which were done a radical surgical intervention of the breast with complete axillary lymphadenectomy. All the cases have been analyzed by standard histological analysis including macroscopic and microscopic analysis of standard H&E staining. For determining of molecular receptors immunostaining by PT, LINK immunoperoxidase has been done for HER2neu, ER, PR, p53 and Ki67.

Statistical analysis was done with statistical program Statistica 7.

Results

Patients age ranged between 31-73 years, an average of 56.86. The stages of the primary breast cancer in our patients are given in Table 1. The biggest frequency was found for stage IIA (41.97%), stage IA (29.63%), and for stage IIB (23.46%). We found stage IIA in 2.47%, the stage 0 in1.23%, and stage IB in 2.23%. We did not find any cases in stages IIIB and IIIC.

Table 1: Stages of the primary breast cancer in our patients

Variable	Total (No = 81) (100.00%)
Stage	
0	1 (1.23%)
IA	24 (29.63%)
IB	1 (1.23%)
IIA	34 (41.97%)
IIB	19 (23.46%)
IIIA	2 (2.47%)
IIIB	0 (0.00%)
IIIC	0 (0.00%)

Characteristics of the primary breast cancer in our patients are shown in Table 2. There were not found statically significant differences between axilla positive and axilla negative patients for tumour size, location, and histology. Nuclear grade was significantly diferent in the patients with axillary negative patients, where patients with G1 were (10.91%) and with G3 were (1.82%) in comparison with the positive axillary patients, where patients with G1 were (0%), and with G3 were (11.54%), ($p < 0.044$). The mean size of a primary tumour in the surgically treated patient was 20.33 $\pm$ 6.0 mm. On dissection from the axillary pits, there were taken out 5 to 32 lymph nodes, an average of 14.0. Metastases have been found in 1 to 7 lymph nodes, an average 0.7. In 32.1% of the patients have been found metastases in the axillary lymph nodes (Table 2).

Table 2: Characteristics of the primary breast cancer in our patients

Variable	Axilla positive (N = 26) (32.1%)	Axilla negative (N = 55) (67.9%)	Total (N = 81) (100.00%)	P
Tumor size				
Tis	0 (0.00%)	1 (1.82%)	1 (8.40%)	
T1a	0 (0.00%)	3 (5.45%)	3 (3.70%)	
T1b	0 (0.00%)	8 (14.54%)	8 (9.87%)	0.540
T1c	5 (19.23%)	16 (29.09%)	21 (25.92%)	
T2	21 (80.76%)	27 (49.09%)	48 (59.25%)	
Location				
Central	5 (19.23%)	10 (18.18%)	15 (18.52%)	
Inner	4 (15.38%)	9 (16.36%)	13 (16.05%)	0.991
Lateral	17 (65.38%)	36 (65.45%)	53 (65.43%)	
Histology				
Ductal	21 (80.77%)	46 (83.64%)	67 (82.72%)	
Lobular	3 (11.54%)	4 (7.28%)	7 (8.64%)	0.807
Other	2 (7.69%)	5 (9.09%)	7 (8.64%)	
Nuclear grade				
1	0 (0.00%)	6 (10.91%)	6 (7.41%)	
2	23 (88.46%)	48 (87.27%)	71 (87.65%)	0.044*
3	3 (11.54%)	1 (1.82%)	4 (4.94%)	

*, Statistically significant differences; N = number.

The univariant regression analysis showed that the size of a tumour ($p = 0.022$) and presence of HER2neu receptors on cancer cell ($p = 0.037$) influence on the positivity of the axillary lymph nodes.

Table 3: Characteristics of receptors in the primary breast cancer in our patients

Variable	Axilla positive (N=26) (32.1%)	Axilla negative (N = 55) (67.9%)	Total (N = 81) (100.00%)	P
Estrogen receptors				
Positive	22 (84.61%)	45 (87.82%)	67 (82.71%)	0.755
Negative	4 (15.38%)	10 (18.18%)	14 (17.28%)	
Progesterone receptors				
Positive	18 (69.23%)	41 (74.54%)	59 (72.84%)	0.615
Negative	8 (30.77%)	14 (25.45%)	22 (27.16%)	
Her 2neu receptors				
Positive	13 (50.00%)	21 (38.18%)	34 (41.97%)	0.314
Negative	13 (50.00%)	34 (61.82%)	47 (58.02%)	
P53				
Positive	11 (42.31%)	26 (47.27%)	37 (45.68%)	0.675
Negative	15 (57.69%)	29 (52.73%)	44 (54.32%)	
LVI				
Positive	15 (57.69%)	5 (9.09%)	20 (24.69%)	< 0.001*
Negative	11 (42.31%)	50 (90.91%)	61 (75.31%)	
Ki67				
< 20	11 (42.31%)	24 (43.64%)	35 (43.21%)	0.910
> 20	15 (57.69%)	31 (56.36%)	46 (56.79%)	

*, Statistically significant differences; N = number.

Characteristics of the receptors in the patients with primary breast cancer are shown in Table 3. The presence of the estrogen receptors, progesterone

receptors showed that they do not have influence on the positivity for metastatic deposits in axillary lymph nodes, except the frequency of LVI positive patients (57.69%) in positive axillary patients in comparison with axillary negative patients (9.09%), ($p < 0.001$) (Table 3).

Multivariant model and logistic regression analysis as significant independent factors or predictors of positivity of the axillary lymph nodes are influenced by the tumour size only ($p = 0.014$).

Discussion

Axilar lymphadenectomy gives us parameters for the axillar status, but at the same time is the therapeutic procedure. On the other hand, axillar lymphadenectomy was followed with many unlike features and complications like as sensation in the arm, reduction of the arm mobility and lymphedema [3]. Use the thesis of the Fisher and Veronesi that breast cancer is the systemic disease at the moment of the diagnosis it, and needs to be treated as a systemic disease with drugs that work in the whole body (chemotherapeutic, antihormonal therapy, immunotherapy) [4, 5]. So axillar status is a first diagnostic tool, and in many instances especially if it is not involved with metastatic disease, which is in 40-70% not involved, it is not necessary to done axillar lymphadenectomy [6].

Prediction of axillary status can be used to predict whole axillar status, predict sentinel node and predict nonsentinel node status if sentinel node is positive [7-10].

Many authors use many standard methods for prediction of the axillar status, as clinical examination, mammography, ultrasonography, but also introduce new methods like ultrasound guide biopsy, CT, NMRI, Pet-CT, SPET-CT, contrast examinations, but in any case they see enlarged lymph nodes, but is impossible to guarantee that all this are metastatic changed (low sensitivity) [11-14]. Use of these methods is possible only to lower rate of falls negative results [15].

In last period we done lot investigations how different factors influent to positivity of axillary lymph nodes, on different groups of patients (patients with early breast cancer, patients with early breast cancer and clinically negative axilla, all surgically treated patients with breast cancer, patients with advanced breast cancer) and in last period we examined how size of tumor, persistence of estrogen receptors, progesterone receptors, HER 2 new receptors and Ki67 values influent to chance of dispersion of the disease in the axilla. Interesting is the fact that in the same institution in the same period, but on different groups of patients according to the stage of the disease were analysed the factors that can predict positivity of axilla. We find that in the whole group where patients with early but also with advantage stage were an as important factor for appearing metastases in axilla were the persistence of lymphovascular invasion and bigger values of Ki67 that were not important in groups with only early breast cancer. The possibility is that with the advantage of the stage are appearing aggressive factors in a tumour that after that influence on spreading the tumour cells in lymph nodes in axilla [16, 17].

Introduction of SLND detection, especially if are used both type of detection, as vital blue due (methylene blue) and radioisotope Technician with colloid particles (radiocoloid) at the end of the last century, give us very successful tool for detection SLND, which histological examination, give us successfully status of SLND but also status of whole axilla [16, 18-22].

In literature, there are many investigations for determination of factors that can predict positivity of axilla, SLND and NSLND if SLND is positive. Factors can be divided into few categories:

- Epidemiological (age, race, side, localisation);
- Clinical (palpability of a tumour, palpability of axillary lymph nodes, location);
- Pathological (histology of a tumour, differentiation of cells, neovascularisation of a tumour, vascular and lymphovascular invasion, extensive intraductal component, the persistence of receptors on the surface of the cells- estrogen, progesterone, Her-2 new, the persistence of p53 proteins, the persistence of factor of proliferation Ki67. Knowing these parameters is possible to determine subtype of breast cancer.);
- Biochemical (CEA, CA 15-3);
- Genetic (BRCA1, BRCA2, VEGFC, MIB1, CCR7, CXCR4) [23-59].

Many of the factors that were examined as a predictor of axillary status, is very well known, known is a biological way of action, and is very well known how is their action to the biology of a tumour, and how they work to spread the disease in the body. So estrogen receptors are on the surface of the cell. The connection of the estrogen and estrogen receptors activate many processes in the cell and favourite raising and dividing the cells, so favourite estrogen rising of a tumour. Giving the drugs that blockade estrogen receptors or drugs that blockade synthesis of the estrogen will stop rising of a tumour. The same situation is with persistence of HER-2 neu receptors. HER2 is a membrane tyrosine kinase and oncogene that is overexpressed and gene amplified in about 20% of breast cancers. When activated it provides the

cell with potent proliferative and anti-apoptosis signals, and it is the major driver of tumour development and progression of breast cancer. Over expression will activate many pathways in the cell, so the cells will raise and divide uncontrolled, so a tumour will raise and can't be under control. Giving the target drug – monoclonal antibody-Trastuzumab (Herceptin), will blockade this receptor, and the tumour will be under control. More, giving chemotherapeutics which interact with all cells which is divide fast; a tumour will be under control. Ki67 is a factor that shows the proliferative activity of the tumour cells. Ki67 is in correlation with S phase of cells and mitotic activity. Normal breast cell has a proliferative activity of 3% (3% of cells are in dividing stage). The Bigger activity of 20 % shows an aggressive tumour with bad prognosis and shorter survival [60-62].

Many investigators analyse many factors, how to allow or in combination can predict the status of the axillar lymph nodes, the status of SLND and in recent time status of NSLND. Postaci, Jiao, Jaime Jans, Ugras, Gangi, Pijnappel, Sawaki, Brenin, Chung, Chadha, Tan, Gajdos, Qiu, Ashturkar, Wu, Tseng, Ko, Li, Ngo, Yoo, Danko, Cabioglu, Capdet, Susini, Wasuthit are part of authors whose in last decade investigate which factors influent to positivity of axillar lymph node or positivity of sentinel node. They investigate all factors that can be investigated like epidemiological, clinical, histopathological, genetic, molecular. Mainly from all these studies dominantly main factors that can influent to positivity of axillar nodes are the size of a tumour, location, histology, grade of differentiation, lymphovascular invasion. But also in many of the investigations, other factors that can influence to positivity of axillar lymph nodes are referred: age, the persistence of estrogen, progesterone and Her two new receptors on the surface of the cells, a subtype of breast cancer, values of Ki67, multifocality, EIC and other. In only a few studies were referred VEGFC, MIB1, CEA, CA 15-3, CCR7, CXCR4 and others [23-46].

It is very interesting how some factors in some studies are important factors that predict axillar involvement with metastases, but in other studies, these factors are not important, and no influence to axillar involvement. For example in studies of Jiao, Pijnappel, Sawaki, Gangi, Qiu one of the essential factors that predict axillar involvement is the persistence of hormonal receptors and HER 2 receptors on the tumour cell, much more is well defined that Luminal and Her enriched tumours lymph nodes are more often involved with metastatic disease. On the other hand, triple negative tumours rarely have involvement of lymph nodes with metastatic disease, never less than this type shows early distant metastasis and worse prognosis. But in many others, studies show that persistence of hormone receptors, HER 2 receptors on the surface of tumour cells, does not influence involvement of axillary lymph nodes with metastases. So it is interesting why the same factor in one study is the main factor, and in other study is not important [24, 27-29, 35].

In our study, the univariant regression analysis showed that the size of a tumour and presence of HER2 neu receptors on the surface of cancer cell influence on the positivity of the axillary lymph nodes. The presence of the estrogen receptors and progesterone receptors showed that they do not have an influence on the positivity for metastatic deposits in axillary lymph nodes. Multivariant model and logistic regression analysis as significant independent factors or predictors of positivity of the axillary lymph nodes are influenced by the tumour size only. It is necessary as a minimum to done detection and biopsy of the sentinel node, which is further histology examined. With detecting status of the sentinel node, we can safely predict the status of other lymph nodes in the axilla.

In conclusion, our study showed that the involving of the axillary lymph nodes is mainly influenced by the size of a tumour and presence of HER2neu receptors in the univariant analysis points the important influence of positivity in the axillary lymph nodes but the only size of a tumour in the multivariate regressive analysis.

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