

## PROGNOSTIC FACTORS ON THE POSITIVITY FOR METASTASES OF THE AXILLARY LYMPH NODES FROM PRIMARY BREAST CANCER

Borislav Kondov<sup>1</sup>, Goran Kondov<sup>1</sup>, Zoran Spirovski<sup>1</sup>, Zvonko Milenkovic<sup>2</sup>,  
Risto Colanceski<sup>1</sup>, Gordana Petrussevska<sup>3</sup>, Meri Pesevska<sup>4</sup>

<sup>1</sup> University Clinic for Thoracic and Vascular Surgery - Medical Faculty Skopje, R. Macedonia

<sup>2</sup> University Clinic for Infective Disease and Febrile Conditions - Medical Faculty Skopje, R. Macedonia

<sup>3</sup> Institute for Pathology - Medical Faculty Skopje, R. Macedonia

<sup>4</sup> University Clinic for Oncology and Radiotherapy- Medical Faculty Skopje R. Macedonia

**Corresponding Authors:** Borislav Kondov, University Clinic for Thoracic and Vascular Surgery, Skopje, Majka Tereza 17, 1000 Skopje, R Macedonia, tel.: 072 539 003, e-mail: b\_kondov@yahoo.com

### ABSTRACT

**Aim:** The aim of the study was to identify the impact of T stage, the presence of estrogen, progesterone, HER2neu receptors and the values of the Ki67 on the positivity for metastases of the axillary lymph nodes, from primary breast cancer.

**Material and methods:** 290 surgically treated patients for breast cancer were included in the study. All cases have been analyzed by standard histological analysis including microscopic analysis on standard H&E staining. For determining the molecular receptors - HER2neu, ER, PR, p53 and Ki67, immunostaining by PT LINK immunoperoxidase has been done.

**Results:** Patients age was ranged between 18-90 years, average of 57.6±11.9. The mean size of the primary tumor in the surgically treated patient was 30.27 + 18.3 mm. On dissection from the axillary pits 8 to 39 lymph nodes were taken out, an average of 13.81±5.56. Metastases have been found in 1 to 23 lymph nodes, an average 3.14±4.71. In 59% of the patients there have been found metastases in the axillary lymph nodes. The univariate regression analysis showed that the location, size of tumor, differentiation of the tumor, stage, the value of the Ki67 and presence of lymphovascular invasion influence on the positivity of the axillary lymph nodes. The presence of the estrogen receptors, progesterone receptors and HER2neu receptors showed that they do not have influence on the positivity for metastatic deposits in axillary lymph nodes. The multivariate model and the logistic regression analysis as independent significant factors or predictors of positivity of the axillary lymph nodes are influenced by the tumor size and the positive lymphovascular invasion.

**Conclusion:** Our study showed that the involving of the axillary lymph nodes is mainly influenced by the size of the tumor and the presence of lymphovascular invasion in the tumor. Ki67 determined proliferative index in the univariate analysis points the important influence of positivity in the axillary lymph nodes, but not in the multivariate regressive analysis.

**Key words:** breast cancer, axillar status, tumor size, T stage, estrogen receptors, progesterone receptors, HER2neu receptors, Ki67, lymphovascular invasion

### INTRODUCTION

Involvement of axillary lymph nodes with metastatic disease from primary breast cancer is the most significant prognostic factor of the disease. Some factors are well known to influence the prognosis of the disease and early appearance of the local and distant relapse.

The axillar status (involvement of lymph nodes in axilla with metastatic diseases from primary breast cancer) together with the size of the primary breast tumor are the main factors that determine the stage of breast cancer, but also predict the prognosis of the breast cancer disease (1). Up to now all information about the axillar status were taken from the examinations of the axillar lymph nodes that we take out

with the axillar lymphadenectomy. This is part of the surgical treatment of patients with breast cancer – radical mastectomy or breast conserving surgery followed with axillar lymphadenectomy.

Introducing the procedure - detection of the sentinel node and biopsy is minimally invasive procedure that determines the first drainage lymph node in the axillar pit (2). The 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 axilla.

Knowing the status of the axilla is very important, for the planning of the further therapeutic procedure.

### AIM

To analyze which factors have an influence on the positivity of the axillar lymph nodes, with point to tumor size, persistence of estrogen, progesterone and Her 2neu receptors on tumor cell surface, Ki67, at our patients.

### MATERIAL AND METHODS

290 surgically treated patients for breast cancer that have a complete history for all parameters were included in the study. All the cases have been analyzed with standard histological analysis including macroscopic and microscopic analysis on standard H&E staining. For determining the molecular receptors immunostaining with PT LINK immunoperoxidase has been done for HER2neu, ER, PR, p53 and Ki67.

We performed the statistical analyze with the statistical program Statistica 7.

### RESULTS

Patient's age ranged between 18-90 years, average of 57.6. The mean size of the primary tumor in the surgically treated patient was  $30.27 \pm 18.3$  mm. On dissection, 8 to 39 lymph nodes were taken from the axillary pits, an average of 13.81. Metastases have been found in 1 to 23 lymph nodes, an average 3.14. In 59% of the patients metastases in the axillary lymph nodes have been found.

The univariate regression analysis showed that the location, size of tumor, differentiation of the tumor, stage, the value of the Ki67 and presence of lymphovascular invasion influence on the positivity of the axillary lymph nodes. The presence of the estrogen receptors, progesterone receptors and

HER2neu receptors showed that they do not have influence on the positivity for metastatic deposits in the axillary lymph nodes. The multivariate model and the logistic regression analysis as independent significant factors or predictors of positivity of the axillary lymph nodes are influenced by the tumor size and the positive lymphovascular invasion. (Table 1.)

### DISCUSSION

Axillar lymphadenectomy gives us parameters for axillar status, but at same time it is a therapeutic procedure. On the other hand, axillar lymphadenectomy was followed with many unlike features and complications as sensation in the arm, reduction of the arm mobility and lymphedema (3). Using the thesis of Fisher and Veronesi, that breast cancer is the systemic disease at the moment of the diagnosis, so it needs to be treated as systemic disease with drugs that work in the whole body (chemotherapeutic, antihormonal therapy, immunotherapy) (4,5). So, the axillar status is the first diagnostic tool and in many instances, especially if it is not involved with metastatic disease, which is in 40-70%, it is not necessary to do an axillar lymphadenectomy. This situation will be more reliable with introducing mammographic screening, with detecting much smaller tumors and without involved lymph nodes in the axillar pit (6).

The prediction of the axillar status can be used to predict the whole axillar status, to predict the sentinel node and to predict the non-sentinel node status if the sentinel node is positive. In the last case it is possible to use prediction, and not to do axillar lymphadenectomy in case when the sentinel lymph node is positive, because in 40-50% cases the other lymph nodes is negative (7, 8, 9, 10).

Many authors use some standard methods for prediction of the axillar status, as clinical examination, mammography, ultrasonography, and also introduce new methods like ultrasound guide biopsy, CT, NMRI, Pet-CT, SPETCT, contrast examinations. In many cases they have detected enlarged lymph nodes, but it is impossible to guarantee that all this is metastatic changed (low sensitivity) (11, 12, 13, 14). With the use of these methods it is possible only to lower the rate of false negative results (15).

The introduction of the SLND detection, especially if both types of detection are used, as vital blue dye (methylene blue) and the radioisotope Technetium with colloid particles (radiocolloid) at the end of the last century give us very successful tool for the SLND detection, which histological examination gives us a successfully status of SLND, but also the status of the whole axilla. The successful rate

of SLND detection is 98% (74-99%), and the false negative rate is less than 5% (0-19%) (16, 17, 18, 19, 20). The false negative rate can be lower using the extirpated sentinel lymph node in the investigation and not only the histological examination of the frozen sections, but also the use of the immunohistochemical analyses with cytokeratin, or the use of OSNA (analyzing the amplification of the RNA copies of CA19)(16, 17, 21, 22, 23).

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

- Epidemiological (age, race, side, localization)
- Clinical (palpable tumor, palpable axillar lymph nodes, location of the tumor)
- Pathological (histology of tumor, differentiation of cells, neovascularization of the tumor, vascular and lymphovascular invasion, extensive intraductal component, persistence of the receptors on the surface of the cells – estrogen, progesterone, Her-2 new, persistence of p53 proteins, persistence of factor of proliferation Ki67. By knowing these parameters it is possible to determine the subtype of the breast cancer.
- Biochemical (CEA, CA 15-3)
- Genetic (BRCA 1, BRCA2, VEGFC, MIB1, CCR7, CXCR4 ) (24-60).

Some of these investigations can be provided to the material taken from the tumor before the surgical intervention with “core” biopsy, which is very important for planning further therapeutic steps (42).

As first prediction the axillar status gives us the possibility to introduce SLND biopsy as minimally invasive surgery, especially in the early stages, but also in some cases with well-defined tumors which are in the early stage, it is possible not to do lymphadenectomy. If we know the axillar status before the beginning of the treatment we can:

- plan to perform the SLND investigation at the early stages of breast cancer (T1 or T2 with clinically negative axilla), and if this node is negative not to further conduct the axillar lymphadenectomy. In the literature it is referred that SLND was indicated at 60-70% of patients with breast cancer, and at 60-70% of them will be with negative SLND, and it will be not necessary to perform the lymphadenectomy. This is the reality especially in regions where mammographic screening is done.

- plan not to perform SLND or ALND in rare cases, in different tumors, older patients, with very low chances for metastases in the lymph nodes.
- plan to use other therapeutic opportunities as systematic therapy or radiotherapy.

Many of the factors that were examined as predictors for axillar status are very well known. Also, there are known pathophysiological mechanisms of their action, and it is very well known how is their action to the biology of the tumor and how they work to spared the disease in the body. So, estrogen receptors are on the surface of the cell. The connection of the estrogen and the estrogen receptors activate many processes in the cell and favor the raising and the dividing the cells. So, estrogen favors the rising of the tumor. Giving the drugs that blockade the estrogen receptors or drugs that blockade the synthesis of the estrogen will stop the rise of the tumor. The same situation is with the 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 the tumor development and the progression of the breast cancer. The over expression will activate many pathways in the cell, so the cells will raise and divide uncontrolled, so the tumor will raise and will not be under control. Giving the target drug – monoclonal antibody - Trastuzumab (Herceptin) will block these receptors, and the tumor will be under control. Moreover, giving chemotherapeutics which interact with all the cells that divide fast; the tumor will be under control. Ki67 is a factor that shows the proliferative activity of the tumor cells. Ki67 is in correlation with the S phase of the cells and mitotic activity. Normal breast cell has a proliferative activity of 3% (3% of the cells are in dividing stage). A bigger activity of 20 % shows the aggressive tumor with bad prognosis and shorter survival (61, 62, 63).

Many investigators analyze many factors, how they enable, or in combination can predict the status of the axillar lymph nodes, the SLND status and in recent time the NSLND status. 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 that in the last decade investigated which factors influence the positivity of the axillar lymph node or the positivity of the sentinel node. They investigate all the factors that can be investigated like epidemiological, clinical, histo-



pathological, genetic, and molecular. Mainly, from all those studies the dominant factors that can influence the positivity of the axillar nodes are: the size of the tumor, location, histology, grade of differentiation, lymphovascular invasion. But, also in many investigations other factors that can influence the positivity of the axillar lymph nodes are referred: age, persistence of estrogen, progesterone and Her 2 neu receptors on the surface of the cells, subtype of breast cancer, the values of Ki67, multifocality, EIC and other. In only few studies VEGFC, MIB1, CEA, CA 15-3, CCR7, CXCR4 and others were referred (24-47).

In the studies of Jiao, Pijnappel, Sawaki, Gangi, Qiu one of the essential factors that predict the axillar involvement is the persistence of the hormonal receptors and Her 2 receptors on the tumor cell, moreover, it is well defined that Luminal and Her enriched the tumors lymph nodes are more often were involved in the metastatic disease. On the other hand, triple negative tumors rarely have involvement in the lymph nodes with metastatic disease, however, this type shows early distant metastasis and worse prognosis. But many others studies show that the persistence of the hormone receptors, Her 2 receptors on the surface of the tumor cells has no influence on the involvement of the axillar lymph nodes with metastases. So it is interesting which are the factors that influence the fact that the same factor in one study is the main factor, and in other study it is not an important one (25, 28, 29, 30, 36).

In our study the univariate regression analysis showed that the location, size of tumor, differentiation of the tumor, stage, the value of the Ki67 and the presence of the lymphovascular invasion influence the positivity of the axillary lymph nodes. The presence of the estrogen receptors, progesterone receptors and HER2 neu receptors showed that they do not have influence on the positivity for the metastatic deposits in the axillary lymph nodes. The multivariate model and the logistic regression analysis as independent significant factors or predictors of positivity of the axillary lymph nodes are influenced by the tumor size and the positive lymphovascular invasion.

The predicting of the NSLND positivity is important, and it is very current in the last years, because according to some investigations 30-40% of Z011 in the axillar pit are only sentinel node positive, so in these patients it is not necessary to do axillar lymphadenectomy (48).

For this reasons there were defined many nomograms for predicting status, where different factors from three to nine were incorporated, with various combinations. So now it is actual not to do the axillar lymphadenectomy also in patients with positive 1

or 2 sentinel lymph nodes in which the nomogram assists the prediction of the further progress of the disease in other lymph nodes in the axillar pit. These patients must be treated with systemic therapy and locally radiotherapy (48).

Factors that are included in many of the nomograms are: tumor size, tumor differentiations, lymphovascular invasion, number of positive SLND, number of negative SLND, size of metastasis in SLND, type of SLND detection, type of histological examination of SLND, number of CK19 determined with OSNA, Ki 67 and others (49- 60).

Most popular nomograms are:

- MSKCC that involves: size of tumor, differentiation of tumor-G, number of positive SLND, number of negative SLND, type of detection SLND, LVI, multimodality and positivity for estrogen receptors. This is the most frequently used, and one of the best for prediction.
- Stanford that involves: size of tumor, size of metastases in SLND, and LVI.
- Tenon that involves: size of tumor, ratio between positive and negative SLND, size of metastases in SLND.
- Bolster that involves: size of tumor, LVI, size of SLND metastases.
- Cambridge that involves: differentiation of tumor-G, ratio between SLND+ and SLND, size of SLND metastases.
- MDA that involves: size of SLND metastases, size of tumor, LVI, number of extracted SLND.
- Mayo that involves: age, size of SLND metastases, number of SLND positive, number of SLND negative, size of Tumor.
- Ljubljana that involves: size of metastases in SLND, number of SLND negative, number of SLND positive, size of tumor, LVI, ultrasound findings.

The investigation of the factors that involve NSLD are done by: Metini, Xiang, Miao, Nadem, Van der Hoven, Yao lung Kuo, Cordero, Pepeles, Gur, Gserini, Fredman, Gullen, Van la Para, Williams (49-60). Some of them test some nomograms in their patients and suggest which is the best for prediction. But no one can predict with 100% safety, status of axilla, or SLND in all patients, so it is necessary as minimum to do the detection and the biopsy of the sentinel node, which is further histology examined. By detecting the status of the sentinel node we can safely predict the status of other lymph nodes in axilla.

### CONCLUSION

Our study showed that the involving of the axillary lymph nodes is mainly influenced from the size of the tumor and the presence of lymphovascular

invasion in the tumor. Ki67 determined the proliferative index in the univariate analysis and points out the important influence on the positivity in the axillary lymph nodes but not in the multivariate regressive analysis.

**Table1.** Characteristics of the primary breast cancer in our patients

Variable	Axilla positive (no=171)	Axilla negative (no=119)	Total (no=290)	p
<b>Tumor size</b>				
Tis	3 (1,75%)	10 (8,40%)	13 (4,48%)	
T1a	22 (12,86%)	15 (12,60%)	37 (12,76%)	
T1b	5 (2,92%)	11 (9,24%)	16 (5,51%)	
T1c	21 (12,28%)	27 (22,68%)	48 (16,55%)	
T2	93 (54,38%)	50 (42,02%)	143 (49,31%)	
T3	13 (7,60%)	2 (1,68%)	15 (5,17%)	
T4	14 (8,19%)	4 (3,36%)	18 (6,19%)	1,0 ns
<b>Location</b>				
Central	39 (22,8%)	22 (18,49%)	61 (21,03%)	
Inner	19 (11,11%)	18 (15,12%)	37 (12,06%)	
Lateral	113 (66,08%)	79 (66,39%)	192 (66,91%)	0,79 ns
<b>Histology</b>				
Ductal	141 (82,46%)	96 (80,67%)	237 (81,44%)	
Lobular	18 (10,53%)	9 (7,56%)	27 (9,31%)	
Other	12 (7,02%)	14 (11,76%)	26 (8,97%)	0,86 ns
<b>Nuclear grade</b>				
1	3 (1,75%)	13 (10,92%)	16 (5,52%)	
2	115 (67,25%)	87 (73,11%)	202 (69,65%)	
3	53 (30,99%)	19 (15,96%)	72 (24,48%)	0,99 ns
<b>Estrogen receptors</b>				
Positive	130 (76,02%)	85 (71,43%)	215 (74,14%)	
Negative	41 (23,98%)	34 (28,57%)	75 (25,86%)	0,53 ns
<b>Progesteron receptors</b>				
Positive	139 (81,29%)	87 (73,11%)	226 (77,93%)	
Negative	32 (18,71%)	32 (18,71%)	64 (22,07%)	0,75 ns
<b>Her 2 new receptors</b>				
Positive	52 (30,41%)	38 (31,93%)	90 (31,03%)	
Negative	119 (69,59%)	81 (68,07%)	200 (68,97%)	0,37 ns
<b>P53</b>				
Positive	88 (51,46%)	43 (36,13%)	131 (45,18%)	
Negative	83 (48,54%)	76 (63,86%)	159 (54,82%)	0,92 ns
<b>LVI</b>				
Positive	99 (57,89%)	18 (15,13%)	117 (40,34%)	
Negative	72 (42,10%)	101 (84,87%)	173 (59,65%)	1,0 ns
<b>Ki67</b>				
< 20	58 (33,92%)	68 (57,14%)	126 (43,20%)	
> 20	113 (66,08%)	51 (42,86%)	164 (56,80%)	0,99 ns
<b>Stage</b>				
0			3 (1,03%)	
IA			43 (14,83%)	
IB			9 (3,10%)	
IIA			83 (28,62%)	
IIB			126 (43,45%)	
IIIA			43 (14,83%)	
IIIB			15 (5,17%)	
IIIC			34 (11,72)	

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## Резиме

### ПРОГНОСТИЧКИ ФАКТОРИ НА ПОЗИТИВИТЕТОТ ЗА МЕТАСТАЗИ НА АКСИЛАРНИТЕ ЛИМФНИ ЖАЗЛИ КАЈ ПРИМАРЕН КАРЦИНОМ НА ДОЈКА

**Борислав Кондов<sup>1</sup>, Горан Кондов<sup>1</sup>, Зоран Спировски<sup>1</sup>, Звонко Миленковиќ<sup>2</sup>, Ристо Чоланчески<sup>1</sup>, Гордана Петрушевска<sup>3</sup>, Мери Пешевска<sup>4</sup>**

<sup>1</sup> Универзитетска клиника за торакална и васкуларна хирургија  
- Медицински факултет Скопје, Р. Македонија

<sup>2</sup> Универзитетска клиника за инфективни болести и фебрилни состојби  
- Медицински факултет Скопје, Р. Македонија

<sup>3</sup> Институт за патологија  
- Медицински факултет Скопје, Р. Македонија

<sup>4</sup> Универзитетска клиника за онкологија и радиотерапија  
- Медицински факултет во Скопје, Р. Македонија.

## Апстракт

**Цел:** Целта на студијата беше да се одреди влијанието на Т-стадиумот, присуството на естроген, прогестерон, HER2neu рецептори и вредностите на Ki67 на позитивитетот за метастази во аксиларните лимфни жлезди кај примарен карцином на дојка.

**Материјал и методи:** Во студијата беа вклучени 290 хируршки третираны пациенти поради карцином на дојка. Сите случаи беа анализирани со стандардните хистолошки анализи, вклучувајќи микроскопска анализа со стандардно H&E-боење. За одредување на молекуларните рецептори – HER2neu, ER, PR, p53 и Ki67, беше применета обработка со RT LINK-имунопероксидаза.

**Резултати:** Пациентите беа на возраст од 18 до 90 години, просечно 57,56±11,9. Средната големина на примарниот тумор беше 30,27±18,3. Кај пациентите од пазувната јама беа извадени од 8 до 39 лимфни

јазли, просечно  $13,81 \pm 5,56$ . Зафатени со метастаски депозит беа од 1 до 23 јазли, просечно  $3,14 \pm 4,71$ . Позитивност на аксиларни лимфни јазли е детектирана кај 59%. Со униваријантна регресиска анализа беа издвоени следниве фактори, кои влијаат на позитивност на аксила: локација, големина на туморот, диференцираност на туморот, стадиум, вредност на Ки67 и лимфоваскуларна инвазија. Присуството на естрогени рецептори, прогестеронски рецептори и HER2neu рецептори покажа дека тие немаат влијание на позитивитетот за метастатските депозити во аксиларните лимфни јазли. Мултиваријантниот модел на логистичка регресиска анализа, како независни сигнификантни фактори, односно предиктори за позитивноста на лимфните јазли во пазувната јама, ги потврди големината на туморот и позитивната лимфоваскуларна инвазија на туморот.

**Заклучок:** Од иследувањата во нашата серија се утврди дека на позитивитетот на аксиларната јама влијание има големината на туморот и позитивната лимфоваскуларна инвазија на туморот. Факторот Ки67, кој ја презентира способноста за делба, биолошката агресивност на туморот, во униваријантната анализа укажува на значајно влијание за позитивитетот на аксиларните лимфни јазли.

**Клучни зборови:** малигном на дојка, аксиларен статус, големина на туморот, Т-стадиум, естрогени рецептори, прогестеронски рецептори, херцептински рецептори, Ки67, лимфоваскуларна инвазија