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FACTORS PREDICTING THE LIKELIHOOD OF NON-SENTINEL LYMPH NODE METASTASES IN BREAST CANCER PATIENTS WITH A POSITIVE SENTINEL LYMPH NODE: A SINGLE-CENTER STUDY

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Abstract

This study aims to determine and appraise the factors predicting the likelihood of non-sentinel lymph node metastases in breast cancer patients, in order to avoid unnecessary axillary lymphadenectomy.

A consecutive cohort study ascertained 133 patients with a detected sentinel lymph node, who met the inclusion criteria: early breast cancer (in T1, 2; N0 and M0 stage), tumor size of 5 cm or less and clinically negative axillary status.

The patients were then divided into three groups, according to the SLN and NSLN status (group 1 = SLN -; group 2 = SLN +, NSLN -; group 3 = SLN +; NSLN +). Number of patients was n=98; n=19 and n=16, respectively.

Aim of the study is to determine factors that can predict positivity of non-sentinel lymph nodes in condition when sentinel lymph nodes were positive.

According to the correlation matrix, Kolmogorov-Smirnov test, when comparing the negative and positive NSLNs in the group of positive SLNs, whether NSLN will be positive or not, depends on the tumor size, number of detected NSLNs and pT.

It also depends on the age, number of positive and negative SLNs, number of negative NSLNs, pN, G, stage, positivity of p53 and positivity of Her 2 new.

Longer follow-up studies of a larger group of patients are required to define the exact factors contributing to a positive NSLN when SLN is positive.

In our study the determined risk factors which contribute to the positivity of NSLNs were: age, number of identified and negative NSLNs, number of negative and positive SLNs, pN, G, stage of the disease, positivity of p53 and positivity of Her 2 new.

Keywords: lymphadenectomy, sentinel lymph node, non-sentinel lymph node, breast cancer, metastases, risk factors for positivity of SLND or NSLD.

Introduction

Axillary lymph node dissection (axillary lymphadenectomy) is a standard approach for breast cancer patients who are undergoing radical procedures. In the literature, it has been established that only 30-40% (40-60% at our clinic) of these patients have axillary lymph node metastasis [7,13,14].

According to this fact, 50% of the patients underwent avoidable lymphadenectomy. It follows that lymphadenectomy is of greater importance to determine the stage of the disease than to treat it [7,8].

Upon further analysis, it has been also confirmed that in 30-40% of the patients with a positive sentinel lymph node (SLN), the other non-sentinel lymph nodes (NSLN) were negative for metastatic deposits.

We came to the conclusion that in more than half of the patients with a positive SLN, unnecessary axillary lymphadenectomy was performed.

According to the literature, there are several epidemiological, clinical and anatomical, biochemical and genetic factors which determine whether SLNs will be positive.

Hence, this study aims to detect all the factors which affect the SLN to be positive and NSLN negative, and also the ones that influence NSLN to be positive, all in order to avoid needless axillary lymphadenectomy.

Materials and methods

A consecutive cohort study ascertained 133 patients with a detected sentinel lymph node, who met the inclusion criteria: early breast cancer (in T1, 2; N0 and M0 stage), tumor size of 5 cm or less and clinically negative axillary status.

SLNs were detected with administration of radio colloid and methylene blue injection and visualized by static gamma camera and hand-held gamma detector probe. In patients with a positive SLN detected, complete axillary lymphadenectomy was performed.

Determination of the factors that influence whether SLN will be positive or negative followed.

To accomplish this, patients were divided into 3 groups:

-group 1: patients with a negative SLN (n=98)

-group 2: patients with a positive SLN and negative NSLN (n=19)

-group 3: patients with a positive SLN and positive NSLN (n=16)

Results

At the Clinic for Thoracic and Vascular surgery in Skopje, North Macedonia, detection and biopsy of SLN were performed on 133 patients diagnosed with early breast cancer (table 1) and (table 2).

Table 1. Patients diagnosed with early breast cancer.

SLN status	Number of patients – n	Percentage
SLN -	98	73.7%
SLN +	35	26.3%
	133	100%
NSLN status when SLN is +		
SLN + NSLN -	19	54.3% (from 35) 14.3% (from 133)
SLN+ NSLN+	16	45.7% (from 35) 12% (from 133)

Table 2. Basic characteristic of the patients divided into groups.

		N **133**	**SLN -** **98**	**SLN +** **NSLN -** **19**	**SLN +** **NSLN +** **16**
Age		54,41	54,08	53,10	58
			$t_{2,3}$=0,31	ns $t_{3,4}$=-1,2	Ns
				$t_{2,4}$=-1,2 ns	
Age	<50	49 (36,84%)	39 (39,79%)	8 (42,10%)	2 (12,50%)
	51-74	77 (57,89%)	53 (51,94%)	11 (57,89%)	13 (81,25%)
	>75	7 (5,26%)	6 (6,12%)	0 (0%)	1 (6,25%)
				Hi^2	**P<0.01 s**
T	Mm	17,42	16,05	26,89	14,05
			$t_{2,3}$=-5	**$St_{3,4}$=6,12**	**S**
				$t_{2,4}$=0,66 ns	
T	T1	93 (69,92%)	76 (77,55%)	1 (5,26%)	16 (100%)
	T2	39 (29,32%)	21 (21,43%)	18 (94,74%)	0 (0%)
	T3,4	1 (0,75%)	1 (1,02%)	0 (0%)	0 (0%)
				Hi^2	**P<0.01 s**
Tumor type	Ductal	102 (76,69%)	72 (73,47%)	18 (94,73%)	13 (62,5%)
	Lobular	23 (16,54%)	20 (20,41%)	1 (5,2%)	1 (6,25%)
	Mixed	8 (6,01%)	6 (6,12%)	0 (0%)	2 (12,5%)
				Hi^2	**P<0.01 s**
G	1	15 (11,28%)	14 (14,28%)	0 (0%)	1 (6,25%)
	2	64 (48,12%)	47 (47,96%)	8 (42,10%)	9 (56,25%)
	3	54 (40,60%)	37 (37,75%)	11 (57,90%)	6 (37,50%)
				Hi^2	P=0,16 ns
SLN -	0-2	77 (57,89%)	49 (50%)	14 (73,68%)	14 (87,5%)
	>2	56 (42,11%)	49 (50%)	5 (26,32%)	2 (12,5%)
				Hi^2	P=0,016 s

SLN +	0-2	126 (94,73%)	98 (100%)	14 (73,68%)	14 (87,5%)
	>2	7 (5,27%)	0 (0%)	5 (26,32%)	2 (12,5%)
				Hi^2	**P<0.01 s**
Extranodal extension	-	132 (99,25%)	98 (100%)	19 (100%)	15 (93,75%)
	+	1 (0,75%)	0 (0%)	0 (0%)	1 (6,25%)
				Hi^2	P=0,06 ns
		133	**98**	**19**	**16**
ER	+	99 (74,43%)	79 (80,61%)	18 (94,74%)	2 (12,5%)
	-	34 (25,57%)	19 (19,39%)	1 (5.26%)	14 (87,5%)
				Hi^2	**P<0.01 s**
Her2	-	114 (85,71%)	85 (86,73%)	17 (89,43%)	12 (75%)
	+	19 (14,29%)	13 (13,27%)	2 (10,57%)	4 (25%)
				Hi^2	P=0,61 ns
Mutifocal	-	124 (93,23%)	93 (94,9%)	17 (89,47%)	14 (87,5%)
	+	9 (6,77%)	5 (5,1%)	2 (10,53%)	2 (12,5%)
				Hi^2	P=0,64 ns
LVI (limphovascular invasion)	-	115 (86,47%)	92 (93,88%)	15 (78.95%)	8 (50%)
	+	18 (13,53%)	6 (6,12%)	4 (21,05%)	8 (50%)
				Hi^2	**P<0.01 s**
SLN n		3.058	3.031	3.316	2.875
				$t_{2,3}$ ns	$t_{3,4}$ ns
SLN +		0.47	0	1.895	1.687
			$t_{2,3}$=-20	**S**$t_{3,4}$=-0,5	Ns
				$t_{2,4}$=12,6 s	
MS type	Macro MS	34 (25,56%)	0 (0%)	18 (94,7%)	16 (100%)
(Metastasis type)	Micro MS	1 (0,75%)	0 (0%)	1 (5,%)	0 (0%)
	Cells isolated	2 (1,5%)	2 (2%)	0 (0%)	0 (0%)
				Hi^2	**P<0.01 s**

The following table (table 3) shows subtype classification according to the presence or absence of estrogen receptors (ER), progesterone receptors (PR) and HER 2 receptors on the tumor cell surface, as well as dependence on the biological characteristics of the tumor, expressed through Ki -67 percentage score (the percentage of positively stained tumor cells among the total number of malignant cells assessed).

Table 3. Subtype classification according to the presence or absence of estrogen receptors (ER), progesterone receptors (PR) and HER 2 receptors on the tumor cell surface

	Luminal A	Luminal B	Luminal B with Her 2+	Her 2 enriched	Triple negative	
SLN -	47 (47,95%)	28 (28,57%)	9 (9,2%)	2 (2,04%)	12 (12,24%)	**98**
SLN + NSLN -	7 (36,84%)	11 (57,89%)	0 (0%)	1 (5,3%)	0 (0%)	**19**
SLN + NSLN +	5 (31,25%)	7 (43,75%)	3 (18,75%)	1 (6,25%)	0 (0%)	**16**
	59(44,36%)	**46(34,59%)**	**12(9,02%)**	**4(3,00%)**	**12(9,02%)**	**133**

Hi^2 P=0.012 s

According to the International Classification of Nuclear Determined subtypes of breast cancer, the following subtypes exist: Luminal A (ER + and / or PR +, HER2 negative, Ki-67 <14%), luminal B with HER2 negative (ER + and / or PR +, HER2 negative, Ki-67≥14%), luminal B with HER2-positive (ER + and / or PR +, HER2 +, any Ki-67), HER2-enriched (ER-, PR-, HER2 +), and basal-like (triple negative) (ER-, PR-, HER2 negative, CK5 / 6 + and / or EGFR +).

According to the correlation matrix, Kolmogorov-Smirnov test, when comparing the negative and positive NSLNs in the group of positive SLNs, whether NSLN will be positive or not, depends on the tumor size, number of detected positive NSLNs and pT.

It also depends on the age, number of positive and negative SLNs, number of negative NSLNs, pN,G, stage, positivity of p53 and positivity of Her 2 new.

Discussion

Numerous studies have explored and assessed the factors that influence the axillary status to be positive in breast cancer patients. The factors that are most commonly used in many nomograms are: tumor size and differentiation, presence of lymphovascular invasion, number of positive and negative SLNs, size of involved SLN, type of detection and histological assessment of the SLN, value of cytokeratin 19 (CK 19) identified with the use of OSNA, value of Ki-67 and other factors [1-6, 9-12, 15-22].

The most popular nomograms are:

-The MSKCC (Memorial Sloan Kettering Cancer Center nomogram), which lists the following factors: tumor size and differentiation, number of positive and negative SLNs, type of SLN detection, presence of lymphovascular invasion, presence of estrogen receptors and whether it is multifocal or not.

-The Stanford nomogram uses tumor size, size of involved SLN and lymphatic invasion.

-Tenon nomogram uses tumor size, size of involved SLN and the ratio between positive and negative SLNs.

-The Boston nomogram includes the tumor size, size of involved SLN and the presence of lymphovascular invasion.

-The Cambridge nomogram – tumor differentiation, ratio between identified and positive SNLs and the size of the recognized SLN

-MDA nomogram – number of identified and size of the SLN, the size of the tumor and the presence of lymphovascular invasion

-Mayo nomogram – size of the tumor, number of positive and negative SLNs and size of the metastatic lesion SLN

-Ljubljana nomogram predicting the likelihood of NSLN metastases in breast cancer patients includes the size of detected SLN, number of positive and negative SLNs, tumor size, presence of lymphovascular invasion and axillary ultrasound findings.

The fact that various studies have shown different factors for predicting the likelihood of NSLN metastases makes it clear that there are still no strongly determined variables that can safely predict the axillary status in order to avoid unnecessary axillary lymphadenectomy.

Knowing that in our study there was a low percentage of patients with NSLN positive status-12.03%, it is important to conduct research studies with a larger group of patients.

In terms of the SLN and NSLN positive status, we have established the following: it is more common in older age and in menopause in women, in tumors smaller in size, less common in ductal invasive tumors and more common in the ones that are mixed, more common in moderately differentiated tumors (intermediate grade – G2).

Also, these findings are more prevalent in tumors that are ER negative and HER 2 positive. There is a lower prevalence in Luminal A and higher in Luminal B genotype.

The incidence of lymphovascular invasion is significant and macro metastases are more common.

Conclusion

Longer follow-up studies of a larger group of patients are required to define the exact factors contributing to a positive NSLN when SLN is positive.

In our study the determined risk factors which contribute to the positivity of NSLNs were: age, number of identified and negative NSLNs, number of negative and positive SLNs, pN, G, stage of the disease, positivity of p53 and positivity of Her 2new.

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