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1. Physician Mastologist Universidad CES, Msc Epidemiology and Public Health VIU, Cancer Research Group IDC, Medellin, Colombia. ORCID: 0000-0001-9485-7483

Corresponding author:
Oscar Alejandro Bonilla Sepúlveda
♀ Calle 2 sur # 46-108 consultorio 1215 (Código postal 050021), Torre medica Salud Las Vegas, Medellín, Colombia
☎ 3235100605
✉ mastologia.bonilla@gmail.com

Usefulness of intraoperative sentinel node palpation in breast cancer: a cross-sectional study

Utilidad de la palpación intraoperatoria del ganglio centinela en el cáncer de mama: estudio transversal

Oscar Alejandro Bonilla Sepúlveda[1]

ABSTRACT

Objective: To determine the usefulness of intraoperative palpation and macroscopic characteristics of the sentinel lymph node in breast cancer in predicting its involvement on microscopic examination. **Methods:** Descriptive cross-sectional study with secondary analysis of a surgeon's personal registry between May 1, 2018, and October 31, 2020, at a referral center in Medellin, Colombia. Women with breast cancer without clinical axillary involvement taken to surgery for sentinel node biopsy were included. Demographic, clinical and paraclinical data were collected and analyzed using descriptive statistics. **Results:** Of 355 patients who underwent sentinel node biopsy for breast cancer, the sentinel node detection rate was 98.3 % (n= 347). A higher probability of being affected was found in patients who underwent mastectomy (ORa= 4.61; 95% CI: 1.07-19.81), when the consistency of the node was hard or semi-hard (ORa= 3.90; 95% CI: 2.00-7.62) and when the shape of the node was lobulated or irregular (ORa= 12.98; 95% CI: 2.10-80.19). In contrast, it was less likely to be affected when it had received neoadjuvant chemotherapy (ORa= 0.11; 95% CI: 0.02-0.57). **Conclusion:** The evaluation of macroscopic features during sentinel node technique for axillary staging can predict its involvement on microscopic examination.
Key words: Breast neoplasms, Sentinel lymph node

RESUMEN

Objetivo. Determinar la utilidad de la palpación intraoperatoria y las características macroscópicas del ganglio centinela en cáncer de mama en predecir su afectación en el examen microscópico. **Métodos.** Estudio descriptivo de corte transversal con análisis secundario del registro personal de un cirujano entre el 1 de mayo de 2018 y el 31 de octubre de 2020, en un centro de referencia en Medellín, Colombia. Se incluyeron mujeres con cáncer de mama sin afectación clínica axilar llevadas a cirugía para biopsia de ganglio centinela. Se recopilaron los datos demográficos, clínicos y paraclínicos que fueron analizados utilizando estadística descriptiva. **Resultados.** De 355 pacientes sometidas a biopsia de ganglio centinela por cáncer de mama, la tasa de detección de ganglio centinela fue del 98,3 % (n= 347). Se encontró mayor probabilidad de estar afectado en las pacientes a quienes se les realizaba una mastectomía (ORa= 4,61; IC95%: 1,07 a 19,81), cuando la consistencia del ganglio era dura o semidura (ORa= 3,90; IC 95%: 2,00 a 7,62) y cuando la forma del ganglio era lobulada o irregular (ORa= 12,98; IC 95%: 2,10 a 80,19). Por el contrario, era menos probable que estuviera afectado cuando había recibido quimioterapia neoadyuvante (ORa= 0,11; IC 95%: 0,02 a 0,57). **Conclusión.** La evaluación de las características macroscópicas durante la técnica del ganglio centinela para la estadificación axilar puede predecir su afectación en el examen microscópico.
Palabras clave. Neoplasias de la mama, Ganglio linfático centinela

INTRODUCTION

According to Globocan, in 2020 there were 2,261,419 new cases of breast cancer worldwide[1]. In Colombia, for the same year, the incidence was 15,509 cases, occupying the first place for cancer in women with 25.7 %[2]. This makes breast cancer a matter of public health interest, due to the increase in incidence and associated mortality[3].

The axillary nodes receive the lymphatic drainage of the breast and are affected by metastatic tumor deposits from the primary tumor, this being one of the most important prognostic factors. The traditional treatment has been axillary lymphadenectomy of levels 1 and 2, being

considered the most accurate method for evaluation and control of regional tumor dissemination[4].

Giuliano et al.[5], in 1990, described sentinel node biopsy, based on the fact that tumor cells migrate in an orderly manner through the lymphatic tracts. Therefore, the sentinel node is the first to be affected by metastasis, being able to predict the involvement of other nodes in the lymphatic chain and being a less invasive method with less associated morbidity.

Clinically palpable axillary lymph nodes are considered a sign of regional metastasis and represent a contraindication for performing sentinel node biopsy[6]. Clinical examination of the axilla by palpation is inaccurate, even when performed by an experienced surgeon. In the studies of Lang et al.[7] and Voogd et al.[8], when the axilla was considered to be unaffected, it was affected in 44 % and 34 % of cases, respectively. Intraoperative palpation of the axilla and sentinel node or other suspicious nodes can predict possible involvement and reduce the false negative rate[9].

The aim of the present study was to describe the intraoperative morphological characteristics of the sentinel lymph node during its biopsy for breast cancer, the sociodemographic characteristics of the patients and to determine the correlation with the microscopic study, in a reference center in Medellin, Colombia.

METHODS

A descriptive cross-sectional study was developed in women with breast cancer taken to surgery with sentinel node biopsy attended in a referral center in Medellín, Colombia, between May 1, 2018 and October 31, 2020, through secondary sources of information settled in the personal record of a surgeon.

Patients with histological diagnosis of infiltrating breast carcinoma without axillary clinical involvement by physical examination and ultrasound and taken to surgery for sentinel node biopsy were identified. Patients with incomplete clinical history or with data loss greater than 10 % were excluded and, in the case that the axilla was clinically affected and confirmed with biopsy and in the metastatic stage, consecutive sequential sampling was performed. We obtained 355 records that met the inclusion criteria.

During all sentinel lymph node biopsy procedures, the surgeon evaluated the macroscopic characteristics of the sentinel lymph node intraoperatively and ex vivo. The variables of clinical interest were defined and dichotomized as follows: 1) Size: smaller than 2 cm (normal) vs larger than 2 cm (abnormal); 2) Consistency: soft (normal) vs hard or semi-hard (abnormal); 3) Shape: reniform or oval (normal) vs lobulated or irregular (abnormal); 4) Capsule: smooth (normal) vs irregular (abnormal); 5) Adhesion: non-adherent (normal) vs adherent (abnormal); 6) Perinodal fat: no inflammatory changes (normal) vs with inflammatory changes (abnormal).

The following variables were measured: age, insurance, occupation, residence, histologic type and grade, tumor, node and metastasis (TNM) staging, estrogen and progesterone receptors, human epidermal growth factor receptor 2 (HER2), ki67 antigen, type of breast surgery, sentinel node technique, number of resected and affected sentinel nodes, laterality, axillary level, axillary emptying, size, shape, consistency, adherence and perinodal involvement of the sentinel node.

After standardization of the research protocol, the information was collected, tabulated and verified by the researcher in a database in Excel® format. Descriptive analysis of the sociodemographic and clinical variables was performed. Absolute frequencies and percentages, mean and standard deviation were calculated, according to the nature and distribution of the variables. Normal distribution was validated using the Shapiro Wilk goodness-of-fit test. Bivariate analysis was performed with the chi2 test to establish the association between sentinel node involvement and the independent variables of clinical interest. For hypothesis testing, a confidence interval of 95% and a significance level of 5% was established.

The association between the presence or absence of lymph node involvement and suspicious macroscopic morphologic findings was estimated by means of the crude odds ratio (OR), assessing the magnitude of the association with its respective confidence interval. The latter was evaluated by means of an explanatory

multivariate logistic regression model with the enter method, constructed with the variables that were significant in the bivariate analysis, and those that met the Hosmer Lemeshow criterion ($p < 0.25$) in the univariate analysis. SPSS statistics software version 23 was used.

Regarding ethical aspects, the present study is considered a risk-free study, according to the classification set forth in Article 11 of Resolution No. 008430 of 1993 (issued by the Colombian Ministry of Health), and complies with international standards, the Declaration of Helsinki and the ethical guidelines for biomedical research prepared by the Council for International Organizations of Medical Sciences -CIOMS.

Results

During the 30-month period, 554 axillary surgeries, 355 sentinel node biopsies (66 %) and 199 lymphadenectomies (34 %) were performed in the referral center. The mean age of the patients was 60.2 years (SD 12.6), the most frequent his-

tological type was ductal (80.7 %, n=285), and according to TNM classification 47.3 % (n=168) corresponded to stage I, being the most frequent. Table 1 shows the sociodemographic characteristics, histology, classification, TNM stage and immunohistochemistry.

The most frequent type of surgery was quadrantectomy in 58 % (n=206); radio-guided sentinel node technique was performed in 97.9 % (n=337) of the cases, with a detection rate of 98 % (n= 348). Intraoperative evaluation of the axilla consisting of palpation of all sentinel nodes showed that the most frequent size found was less than 1 cm (80.6 %, n= 289); only 2 % (n= 7) were larger than 2 cm. Lobular and irregular shape were found in 5.9 % and 0.6 %, respectively, while consistency as a marker of lymph node involvement in the hard and semi-hard category was present in 24 % (Table 2).

The cut-off values for sensitivity, specificity and predictive values for each morphological feature of the sentinel lymph node are shown in Table 3.

Table 1. Sociodemographic characteristics, histology, classification, TNM stage and immunohistochemistry.

Variable	(n=355) Frequency (%)	Variable	(n=355) Frequency (%)
Social Security		**Employment**	
Contributory	261 (73.9)	Housewife	217 (61.1)
Subsidized	87 (24.5)	Pensioners	55 (15.5)
		Employees	43 (12.1)
Residence		**Histological type**	
Medellín	161 (45.6)	Ductal	287 (80.8)
Antioquia	114 (32.1)	Lobular	24 (6.8)
Other departments	71 (20)	Other types	23 (6.5)
		In situ	21 (5.9)
Histological grade		**Tumor size in pathology (cm)**	
I	61 (17.2)	Mean	2.6
II	174 (49)	Standard deviation	2.8
III	116 (32.7)	Minimum - Maximum	0.1 - 25
No data	4 (1.1)		
Disease stage		**Estrogen receptors**	
0	17 (4.8)	Positive	296 (83.3)
I	168 (47.3)	Negative	57 (16)
II	141 (39.7)	No data	2 (0.5)
III	29 (8.2)		
Progesterone receptors		**HER2 Receptor**	
Positive	256 (72.1)	0 / 1+	268 (84)
Negative	97 (27.3)	2+	7 (2)
No data	2 (0.5)	3+	44 (12.5)
		No data	36 (10.1)
ki67 proliferation index		**Saint Gallen intrinsic subtype**	**(n= 320)**
> 20	189 (53.3)	Luminal A	108 (33.8)
< 20	132 (37.2)	Luminal B HER -	139 (43.4)
No data	34 (9.5)	Luminal B HER +	25 (7.8)
		HER enriched	14 (4.4)
		Triple negative	34 (9.6)

Table 2. Surgical and sentinel node characteristics.

Surgery type	(n=355) Frequency (%)	Laterality	n & Frequency
Quadrantectomy	206 (58)	Right	195 (54.9)
Mastectomy	149 (42)	Left	157 (44.2)
		Bilateral	3 (0.8)
Number of nodes		**Sentinel lymph node involvement**	
Mean	1.9	Not affected	268 (75.5)
Standard deviation	1.28	Affected	80 (22.5)
Minimum - Maximum	1 - 9	No data	7 (2)
Freezing		**Axillary emptying**	
No	167 (47)	No	297 (83.7)
Yes	182 (51.3)	Yes	58 (16.3)
No data	6 (1.7)		
Size	**(n= 349)**	**Shape**	**(n= 349)**
Less than 1 cm	286 (80.6)	Reniform/oval	326 (91.5)
1-2 cm	56 (15.8)	Lobular	21 (5.9)
Larger than 2 cm	7 (2)	Irregular	2 (0.6)
Consistency	**(n= 349)**		
Soft	264 (74.4)	Capsule	(n= 349)
Semi-hard	39 (11)	Smooth	331 (93.2)
Hard	46 (13)	Irregular	18 (5.1)

Table 3. Sensitivity, specificity, predictive values of intraoperative sentinel lymph node characteristics.

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Hard consistency	57.5	85.4	54.1	12.9
Size > 2 cm	5	98.9	57.1	77.8
Inflammatory perinodal fat	22.5	97.8	75	80.8
Irregular shape	27.5	99.2	91.7	82.1
Irregular capsule	18.7	99	83.3	80.3
Adherence	26.2	97.4	75	81.5

In the bivariate analysis significant statistical differences were found for the macroscopic characteristics evaluated, together with other variables of clinical interest, which were introduced in the multivariate analysis, finding that there is a greater probability that the sentinel lymph node was affected in patients who underwent mastectomy (aOR= 1.07-19.81), when the consistency of the node was hard or semi-hard (aOR= 3.90; 95% CI: 2.00-7.62) and when the shape of the node was lobulated or irregular (aOR= 12.98; 95% CI: 2.10-80.19). In contrast, it was less likely to be affected when the patient had received neo-adjuvant chemotherapy (aOR= 0.11; 95% CI: 0.02 to 0.57) (Table 4).

Discussion

Radioisotope sentinel node biopsy is a widely accepted and reliable surgical method for nodal staging of breast cancer, included in the American Society of Clinical Oncology clinical practice guideline published in 2017[6]. Intraoperative sentinel node evaluation can identify and select patients requiring lymphadenectomy and avoid a second surgical procedure.

In the study by Carmon et al.[10], which included 290 patients, 30.7 % (n= 89) had sentinel node involvement; the mean number of sentinel nodes removed was 2.6, similar to the present study where 23.1 % (n = 80) had sentinel nodes involved, and an average of 1.9 nodes were removed.

In the study by Krag et al.[11], using a 99mTc-labeled sulfur colloid, the intraoperative identification of the sentinel lymph node was 82%; in the present study a detection rate of 98% was found. Despite the obvious advantages of this technique, the possibility of false negative results is the main limitation, which may be caused by lymphatic blockage of the sentinel node and uptake in neighboring nodes; it is advisable to try to improve the detection rate[12].

TABLE 4. BIVARIATE AND MULTIVARIATE ANALYSIS FOR SENTINEL LYMPH NODE INVOLVEMENT.

Variable	Raw OR	95% CI	p	OR adjusted	95% CI	p
Mastectomy/Quadrantectomy	1.49	1.16 - 91	0.003	4.61	1.07 - 19.81	0.04
Irregular capsule	16.7	4.97 - 56.4	0.000	1.07	0.16 - 7.10	0.93
Inflammatory perinodal fat	10	4.11 - 24.37	0.000	1.49	0.31 - 7.09	0.61
Adherent lymph node	10	4.43 - 22.77	0.000	1.36	0.32 - 5.78	0.66
Freezing	1.4	1.15 - 1.71	0.002	1.76	0.25 - 12.08	0.56
Hard ganglion consistency	3.95	2.79 - 5.58	0.000	3.90	2.00 - 7.62	0.000
Size > 2 cm vs < 2 cm	4.46	1.02 - 19.54	0.03	0.62	0.54 - 7.26	0.70
Lobulated or irregular vs. round lymph node shape	36.85	8.85 - 153.34	0.000	12.98	2.10 - 80.19	0.006
Positive progesterone receptors	1.21	1.07 - 1.37	0.01	1.93	0.42 - 8.82	0.39
Positive estrogen receptors	1.17	1.08 - 1.26	0.003	1.89	0.65 - 7.82	0.99
Pre-operative chemotherapy	0.36	0.17 - 0.79	0.000	0.11	0.02 - 0.57	0.009

OR=odds ratio. 95% CI=95% confidence interval. p=value.

Infiltrated sentinel nodes generally increase in size and firmness. In this way they can be detected by intraoperative palpation, even when there is no uptake by the radiopharmaceutical[13]. For this reason, removal of suspicious palpable lymph nodes (increased in size and consistency) has been recommended, with no demonstrated increased consumption of time or resources[10,14].

In the study by Serrano et al.[13], intraoperative palpation identified when axillary nodes were affected in 10% (n= 5/50), reducing the occurrence of false negatives. On the other hand, the study by Pluta et al.[14] in a group of 34 patients identified 6% of affected lymph nodes that were not detected in the lymphoscintigraphy. And Martin et al.[15], with the same strategy managed to reduce the false negative rate from 12% to 4%.

In intraoperative palpation of the axilla, Carmon et al.[10] found that 7 cases were suspected of being affected, and in the microscopic study this was confirmed in 5 cases, which made it possible to identify 71% of the affected lymph nodes. In the present study, intraoperative palpation made it possible to identify 57.5%, with a specificity of 85.4%, and false negatives were 12.9% when the lymph node was hard.

In the study of Serrano et al.[13], out of a total of 168 patients 19 % (n= 32) had suspicious nodes (hard and enlarged); out of a total of 50 nodes evaluated, 5 nodes (10 %) were affected by tumor. In the present study, out of a total of 355 patients studied 85 (23.9 %) had hard sentinel lymph nodes, of which 46 (57.5 %) were affected by metastases.

It is noteworthy that in the present study 57.3 % had suspicious adenopathies (hard lymph nodes) and microscopic confirmation of carcinoma involvement, and that on physical examination of the axilla all were classified as N0, which implies that axillary palpation is imprecise and presents difficulties in the evaluation of the deep axillary planes. On the other hand, 45.9 % of the cases had suspicious intraoperative features, but were not affected after microscopic study. This high percentage is possibly associated with reactive or inflammatory changes post biopsy. It is important to perform an ultrasound evaluation to objectify these adenopathies and thus differentiate those suspicious lymph nodes that require a biopsy to confirm the presence of neoplastic infiltration[16].

As strengths of the study, it is the first in the Latin American literature that explores the usefulness of intraoperative palpation and analyzes different morphological findings in sentinel lymph node biopsy in breast cancer. As limitations, it is found that the evaluation of the nodes by palpation requires experience, which makes its reproducibility difficult.

In conclusion, the evaluation of macroscopic characteristics during the sentinel lymph node technique for axillary staging can predict its involvement in the microscopic examination.

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