

Predictive factors of axillary metastasis in patients with breast cancer and positive sentinel lymph node biopsy

Fatores preditivos de metástases axilares em pacientes com câncer de mama e biópsia de linfonodo sentinela positivo

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ABSTRACT

Objective: to evaluate the risk factors for the presence of non-sentinel axillary metastatic disease in patients with breast cancer and positive sentinel node biopsy. **Methods:** retrospective cross-sectional study of women with breast cancer operated at the Cancer Institute of Ceará between 2002 and 2012 and submitted to sentinel lymph node biopsy. **Results:** Among 946 breast cancer patients, 331 underwent sentinel lymph node biopsy, which was positive in 83. These patients underwent axillary lymphadenectomy and 39 (46%) had metastases in other axillary lymph nodes. The variables that were significant for additional axillary disease included Ki67>14 ($p=0.043$), angiolymphatic invasion ($p=0.01$) and tumor size ($p=0.027$). No association was observed with estrogen, progesterone, tumor grade and Her-2 receptors. **Discussion:** the presence of angiolymphatic invasion and tumor size have also been related to additional axillary metastasis in other studies. In addition to these variables, the same predictive effect was observed when we evaluated Ki67. The validation of these results may allow the customization of breast cancer treatment, which may reduce its morbidity. **Conclusion:** angiolymphatic invasion, tumor size (T3/T4) and Ki67>14 were factors predictive of axillary metastasis involvement in addition to the sentinel lymph node.

Keywords: Breast neoplasms. Sentinel lymph node biopsy. Axilla.

INTRODUCTION

Breast cancer is the second most frequent tumor in world population and the most common in women. According to the National Institute of Cancer in Brazil (INCA), in 2014 there were 57,120 new cases¹. Modern treatment of breast cancer began in the beginning of the past century by Halsted surgery consisting of breast removal, and removal of major and minor pectoral muscles, and axillary lymphadenectomy (AL). However, local and distant relapse were frequent².

Traditionally, AL was the regional treatment choice for breast cancer, even with clinical negative axillary lymph nodes. Axillar staging is essential for choosing adjuvant treatment and regional control of the disease, but edema and articular dysfunction caused by treatment may harm quality of life³. For that, in 1971, it was started the *National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04* study, in order to determine if less extensive surgeries

would be as efficient as radical mastectomy. In the long term, it was not observed increase of global survival with axillary dissection⁴.

Sentinel lymph node hypothesis (SL) was proposed to stage axillary lymph nodes with lower morbidity, by biopsy of sentinel lymph node (SLB), the first to drain the breast^{5,6}. New studies of NSABP such as B32 concluded that axillary lymphadenectomy in patients with SL negative did not change disease-free survival, mortality or local recurrence, even with negative rates close to 10%. This lymph node status would be a good predictor of the presence of metastasis at other axillary lymph nodes, and it would be necessary axillary lymphadenectomy in patients with negative SLB. However, most women with positive SLB did not have additional axillary disease^{7,8}.

ACOSOG Z0011 work evaluated, in a randomized manner, 891 patients submitted to AL or only follow up after positive SLB. There was no statistical difference between loco-regional and distant relapse rates in both groups⁹.

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The objective of this study was to verify the existence of association among several studied variables and the axillary lymph node involvement in patients with breast cancer with positive SLB.

METHODS

This is a cross-sectional study that used secondary data obtained in the charts of women with breast cancer treated surgically at the Cancer Institute of Ceará (CIC) from 2002 to 2012, in cases where SL were studied. Other inclusion criteria included histology compatible with invasive ductal carcinoma in patients treated integrally at CIC. The exclusion criteria included failure to identify SL, absence of information at the charts, patients submitted to neoadjuvant therapy and surgery in patients with relapse.

SLB was performed by intradermic injection of 0.8 ml of Technetium-99m fitec radiopharmaceutical agent, using 29.6 MBq (0.8 mCi), around the areola, in four cardinal points of the breast. SL was localized with gamma radiation detection probe. After removal, it was cut in 2 mm longitudinal slices in its higher axis and all were submitted to histologic exam, without immune-histochemical staining.

It was studied the following independent variables: staging (T), tumor angio-lymphatic invasion (ALI), tumor grade (TG), estrogen receptors (ER), progesterone receptors (PR), over-expression of c-erbB-2 (HER-2) and Ki-67.

Data was analyzed by *Statistical Package for Social Science (SPSS)* for Windows, version 21.0. For characterization of results, it was used absolute frequency (N) and relative frequency (%), average, median. For association analysis among categorical variables it was used the Chi-square test. For frequencies lower than 5 or with small size, the test was replaced by the exact Fisher test when appropriate. Correct values of "p" were obtained by chi-square distribution, when applicable, excluding cases categorized as "ignored", "unknown", or "not available" from each studied variable. A significance level of 5% was used.

RESULTS

Target population of 946 patients, after verification of inclusion criteria, was reduced to 652 women with invasive ductal carcinoma (IDC), and 331 (50.77) were studied by SLB, that was positive in 87 (26.28%) and negative in 244 (73.72%). Four patients with positive SLB were not submitted to axillary lymphadenectomy. The remaining 83 presented the following results: 39 (46%) showed local lymph node metastasis other than SL (Figure 1). 71% of patients with T3/T4 tumor had residual lymph node disease (10/14) and those with T1/T2 had residual disease in 42% (29/69).

The only independent variables that were predictive of non-sentinel axillary lymph node metastasis in the presence of positive SLB were Ki-67 > 14, a marker associated to cellular proliferation, with cut point of 14 ($p=0.043$), tumor size (T) ($p=0.027$) and angio-lymphatic invasion (ALI) ($p=0.01$) (Table 1).

DISCUSSION

The extension of surgical treatment for breast cancer (primary or with lymphatic invasion) is diminishing over the years. Several studies, in particular NSABP, that was started 45 years ago, showed that smaller surgeries may be as efficient as radical surgeries. This study provided theoretical reference for proposal of other researches that evaluated the role of axillary status, until the age of SL⁴.

NSABP study B32 had an important impact on validation of sentinel lymph node study. 5611 patients with invasive breast cancer were evaluated and randomized, following negative biopsy of sentinel lymph node, for axillary dissection or observation. It was verified axillary relapse in 0.4% of patients submitted to SLB and axillary surgery and in 0.7% of those that, after SLB, were only observed, with a 10% of negative rate (17% when only one sentinel lymph node was identified). Therefore, a negative SLB does not correspond

to absence of additional axillary disease, but this residual disease did not impact on global survival or loco-regional relapse^{7,8}.

As reliability of the method improved, it was then questioned the need of axillary surgery

even in patients with positive SLB, since in 50% of patients only SL is affected. Our study showed the same results as that of Giuliano *et al.*¹⁰ in 1997: 54% of lymphadenectomies after positive SLB did not show any metastatic axillary lymph nodes. That is,

Table 1. Risk factor for axillary metastasis in patients with positive SLB.

Evaluated Risk Factors		Patients with positive lymph nodes	Patients with negative lymph nodes	Total	p
Tumor grade	Grades 1 and 2	35	33	68	0.398
	Grade 3	7	6	13	
	Not informed	2	0	2	
	Total	44	39	83	
RE	Positive	33	33	66	0.426
	Negative	10	6	16	
	Not informed	1	0	1	
	Total	44	39	83	
RP	Positive	29	27	56	0.945
	Negative	11	9	20	
	Not informed	4	3	7	
	Total	44	39	83	
Tumor size	T1 and T2	33	28	61	0.027
	T3 and T4	4	10	14	
	Not informed	7	1	8	
	Total	44	39	83	
HER-2	Positive	7	3	10	0.478
	Negative	33	31	64	
	Not informed	4	5	9	
	Total	44	39	83	
KI-67	< or = 14	5	10	15	0.043
	>14	8	12	20	
	Not informed	31	17	48	
	Total	44	39	83	
Lymph vascular invasion	Positive	16	27	43	0.01
	Negative	21	10	31	
	Not informed	7	2	9	
	Total	44	39	83	

axillary surgery was unnecessary in more than 50% of patients.

With that in mind, new clinical studies were proposed to verify which variables could predict the occurrence of axillary lymph node metastasis and that could be used to avoid axillary surgery in patients with positive SL. Z0011 study showed that patients with T1/T2 lesion and negative axillary lymph nodes and with up to two positive SL, referred to adjuvant systemic therapy, did no benefit from axillary surgery, even with 27% of residual disease in the SL arm. These patients had the same survival free of the disease, same mortality and lower morbidity (edema, numbness of arm and quality of life) when compared to patients submitted to axillary surgery⁹. In our study, reinforcing the results of Z0011, T staging, T1/T2 versus T3/T4 could help decide which women should be submitted to further axillary surgery.

In the AMAROS study, there was no significant difference of AL efficiency and axillary radiotherapy, even in the presence of residual disease of 33%¹¹. In the present study, residual axillary disease was identified in 46% of patients. It is important to stress that Z0011 and AMAROS studies excluded T3 and T4 patients and that, in our work, this group of patients represented 16.8% of studied women, with additional rate of axillary disease of 71%.

In order to search for new accurate tools to indicate the probability of the presence of non-sentinel metastatic lymph nodes, some centers such as MD Anderson Cancer Center, developed a nomogram to evaluate the non-sentinel lymph node status in the presence of positive SLB. It was used the size of primary tumor, histology, presence of ALI, number of total and affected lymph nodes, size of metastasis and extracapsular extension¹². ALI and size of tumor were coincident with our work. On the other hand, Ki67 that was not used in the nomogram, was significant for residual axillary disease in our study.

Another nomogram developed by Memorial Sloan Kettering Cancer Center (MSKCC) included the following significant variables: tumor size, lymph-

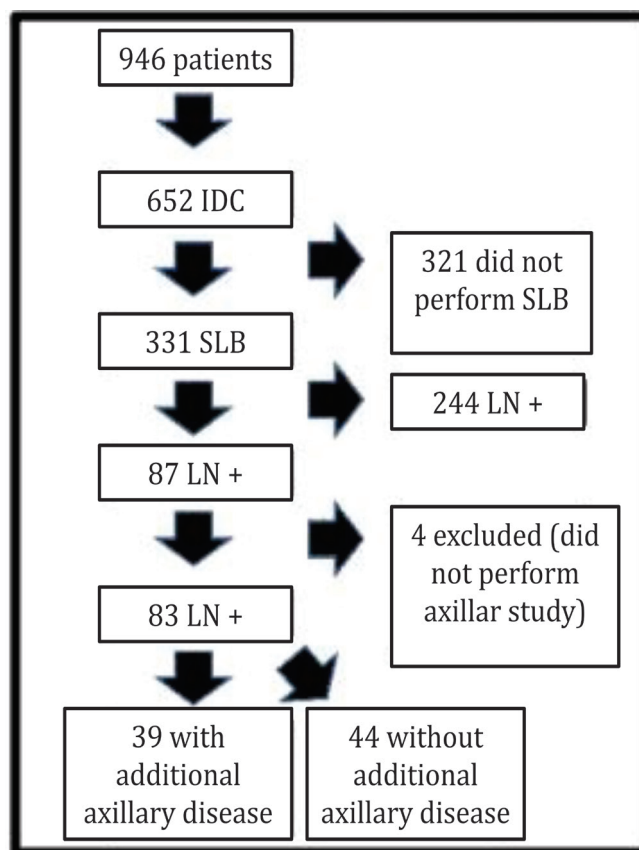


Figure 1. Patients with breast cancer evaluated in this study.

IDC= invasive ductal carcinoma; SLB= sentinel lymph node biopsy; LN+= lymph node positive; LN-= lymph node negative.

vascular invasion, detection method and number of positive and negative lymph nodes^{13,14}. Again, ALI and tumor size were important as in our work. But Ki67 and HER-2 were not studied as in MD Anderson nomogram.

AMAROS work and posteriorly MA-20¹⁵ presented a conflict regarding the extension of radiotherapy treatment of drainage chains¹⁶. In those studies, patients were submitted to specific treatment of arm pit, supra-clavicular fossa and internal mammary chains (MA-20), while Z0011 used radiotherapy only in tangent fields, in most women. Possibly, in some patients, mainly those with higher risk of residual disease, they could benefit from wider nodal irradiation, while others did not need such treatment. Evaluation of predictive factors for lymph node involvement could also have a role in the decision making. During the last congress in San Antonio, it was suggested the use of nomograms to help decide about the treatment¹⁷.

We conclude that, patients with T3/T4 tumors presented a very high risk of additional axillary involvement when SL is positive. Risk factor for the presence of metastatic lymph nodes, apart from sentinel biopsy, were: tumor size, presence of LAI and KI-67>14. When these variables are considered as predictive for axillary involvement,

the treatment may be customized, maintaining oncologic safety and reducing the morbidity of surgery. These factors may help mastologists and radiotherapists to propose an adequate local treatment¹⁷. And these data may be used in the future to propose a correct nomogram for Brazilian scenario.

R E S U M O

Objetivo: avaliar os fatores de risco para presença de doença metastática axilar não sentinela em pacientes com câncer de mama e biópsia do linfonodo sentinela positiva. **Métodos:** estudo transversal, retrospectivo, de mulheres com câncer mamário operadas no Instituto do Câncer do Ceará, entre os anos de 2002 e 2012 e submetidas à biópsia de linfonodo sentinela. **Resultados:** de 946 pacientes com câncer de mama, 331 foram submetidas à biópsia de linfonodo sentinela, que foi positiva em 83. Estas foram submetidas à linfadenectomia axilar e 39 (46%) apresentaram metástases em outros linfonodos axilares. As variáveis que foram significantes para doença axilar adicional foram Ki67>14 ($p=0,043$), presença de invasão angiolinfática ($p=0,01$) e tamanho tumoral ($p=0,027$). Não foi observado associação com receptores de estrogênio, progesterona, grau tumoral e Her-2. **Discussão:** a presença de invasão angiolinfática e tamanho tumoral também já foram relacionados à metástase axilar adicional em outros estudos. Além destas variáveis observou-se o mesmo efeito preditivo quando avaliamos o Ki67. A validação destes resultados poderá permitir a customização do tratamento do câncer de mama, podendo reduzir sua morbidade. **Conclusão:** invasão angiolinfática, tamanho tumoral (T3/T4) e Ki67>14 foram fatores preditivos de acometimento de metástase axilar além do linfonodo sentinela.

Descritores: Neoplasias da Mama. Biópsia de Linfonodo Sentinela. Axila.

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