

## CORRELATION BETWEEN HISTOPATHOLOGICAL DIAGNOSIS AND THE INTRAOPERATIVE FREEZING METHOD OF SENTINEL LYMPH NODE IN BREAST CANCER

---

### *Maria Eduarda Sperandio Bonfante*

Doctor graduated by: Centro Universitário do Espírito Santo (UNESC-ES). Resident in Otorhinolaryngology at: Hospital Federal da Lagoa (HFL-ES).

### *Danielle Ramos Vasconcelos*

Médica egressa do Centro Universitário do Espírito Santo (UNESC-ES).

### *Lucas Cardoso Gobbi*

Doctor graduated by: Centro Universitário do Espírito Santo (UNESC-ES). Resident in Gynecology and Obstetrics at: Hospital Maternidade São José (HMSJ-ES)

### *Clarissa Carlini Frossard*

Doctor graduated by: Universidade Federal do Espírito Santo (UFES). Specialist in Basic Surgery by: Hospital e Maternidade São José (HMSJ-ES).

### *Raney Matos dos Anjos*

Doctor graduated from: Centro Universitário do Espírito Santo (UNESC). Basic Surgical Specialist by: Hospital e Maternidade São José (HMSJ-ES). Vascular Surgery Resident at: Hospital e Maternidade São José (HMSJ-ES).

All content in this magazine is licensed under a Creative Commons Attribution License. Attribution-Non-Commercial-Non-Derivatives 4.0 International (CC BY-NC-ND 4.0).



**Luciano Antonio Rodrigues**

PhD in Health Sciences, Nurse, Lead Researcher of the Territory, Health and Society Research Group, Professor of Health Courses at: Centro Universitário do Espírito Santo (UNESC-ES).

**Abstract:** The study of the sentinel lymph node using the intraoperative freezing method has proven to be an important ally in the management of patients with breast cancer, as it identifies the need for radical axillary lymph nodeectomy, a complex surgery associated with high rates of morbidity, in addition to a worse prognosis. Subsequently, the sentinel lymph nodes are reevaluated using the histopathological method to definitively confirm the presence or absence of metastasis. Given this assumption, the study aims to correlate the result of the freezing method with the histopathological report, aiming to define the sensitivity and specificity of the freezing section when compared to the gold standard diagnosis. This was a qualiquantitative, descriptive study, using secondary cross-sectional data from one year. The sample consisted of 93 female patients, over 18 years old, diagnosed with breast cancer, who underwent the lymph node freezing method at this service. The study was approved by the Human Research Ethics Committee, substantiated opinion no. 4,976,455 of September 15, 2021. All data analyzed showed that patients with breast cancer underwent the sentinel intraoperative freezing method. lymph node. The average age at diagnosis was 56 years, with a range from 32 to 85 years. 20.4% of patients had a palpable lymph node in the physical examination at the first consultation and 35 patients had metastasis, corresponding to 37.6% of the sample, with lymph node metastasis was detected in 32 of these patients. Bone, liver, lung and even brain metastases were also identified, all with a poor prognosis. Staging of breast cancer, using the TNM as a parameter, 24 patients were classified as IA, 30 as IIA and 19 as IIB. Only 4 patients had distant metastasis, and were therefore classified as stage. IV. The remaining metastases were from lymph nodes close to the original tumor. Regarding the intraoperative

sentinel lymph node freezing test compared with the histopathological method, 19 true positive results (20.4%) and 14 false negative results (15.1%) were observed, which gives the freezing test a sensitivity of 57% for this sample and specificity of 100%, that is, all positive results from the frozen section test were confirmed by histopathology, but there was a high rate of false negatives ( $p < 0.05$ ). Of the 14 false-negative results for metastasis in the frozen section test, 5 were due to micrometastasis (35.7%). All patients diagnosed with micrometastasis presented a false negative test. The data analyzed in this sample corroborates the relevance that there is a correlation between the result of the freezing method and the histopathological report between the presence of micrometastases and false negative results in this type of tumor. However, there was no statistical significance between histological subtype, immunohistochemistry and false negative results. It was observed that the lobular subtype has a worse prognosis than the Invasive ductal subtype due to its greater relationship with metastases and more advanced staging. It was possible to observe the impact that the frozen section test has on the choice of the type of surgery, almost all patients with a positive frozen section test had surgical treatment complemented with radical lymphadenectomy, while patients with a negative frozen section underwent quadrantectomy or even mastectomy without lymph node emptying, less invasive surgeries.

**Keywords:** Breast neoplasms; Lymphatic Metastasis; False negatives; Frozen tissue sections; Radical axillary lymphodectmonia.

## INTRODUCTION

After non-melanoma skin cancer, the most common malignant tumor among women, in Brazil and around the world, is breast carcinoma. Injuries in the early stages are

potentially curable if treated appropriately, and early diagnosis and breast-conserving surgery result in a good survival rate. For this purpose, different diagnostic strategies have become essential in the appropriate management of these patients (MAHADEVAPPA et al., 2017).

For many years, radical axillary lymph nodeectomy was a fundamental part of the surgical treatment of breast cancer. However, with early diagnosis, it was observed that this procedure was not always necessary. In many cases, there was no evidence of lymph node involvement, not justifying surgery with such a high morbidity rate (VIEIRA et al., 2012).

Therefore, several clinical trials were developed with the aim of determining the survival of patients treated with axillary dissection or with more conservative measures. A major study published in the Journal of the American Medical Association (JAMA) evaluated this effect on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis. The result was that patients with invasive T1 or T2 tumors, without palpable axillary adenopathy and 1 or 2 sentinel lymph nodes with metastases, treated with more conservative isolated sentinel lymph node dissection surgery had a survival similar to those treated with complementary axillary lymph node dissection, with survival rates of 86.3% and 83.6%, respectively (GIULIANO et al., 2017).

Therefore, the concept of sentinel lymph node has become extremely important for the management of these patients, as these lymph nodes receive lymphatic drainage from the region where the tumor is located, being the first to receive metastases. Sentinel lymph node biopsy can reliably predict axillary status in breast cancer, which is the main prognostic factor. In recent years, the use of the sentinel lymph node frozen section has accurately selected patients who require radical axillary

lymph nodeectomy associated with adjuvant therapy and those who can undergo more conservative treatment (VIEIRA et al., 2012). They also state that the evaluation of the sentinel lymph node is carried out intraoperatively. These lymph nodes.

They are removed and evaluated by pathologists using the aforementioned freezing technique, in which it is possible to quickly define whether there is lymph node involvement or not, helping the surgeon to make decisions. The problem with this technique is the occurrence of false negatives when compared to the gold standard diagnosis, which is histopathological evaluation and more recent studies, this rate has varied from 4.7 to 16.7%.

However, some studies demonstrate more controversial and unfavorable results. False-negative rates in a study carried out in South Korea ranged from 9% to 59%. This large variation may have several explanations, such as failures in the freezing process that affected the permanent analysis and the neoplastic characteristics themselves (JUNG et al., 2020). In some studies, the sentinel lymph node frozen section has low sensitivity and high false-negative rates in detecting micrometastases (YOON et al., 2019; WEISER et al., 2000; LOMBARDI et al., 2018). In others, the benefit of routine intraoperative frozen section analysis tends to increase with tumor size, and therefore routine analysis may not be indicated in patients with small breast cancer (WEISER et al., 2000; FRANCISSSEN, 2013; WADA et al., 2004). These specific data are not yet consolidated in the literature, and, therefore, more studies must be carried out.

The freezing sections, therefore, guide more assertive and individualized decision-making for each patient. However, a false-negative result may result in a worsening of the prognosis by making a second, even more invasive surgical approach necessary, which

creates stress, delays the start of adjuvant treatment and increases costs. In this sense, this study aims to correlate the result of the freezing method with the histopathological report, aiming to define the sensitivity and specificity of the freezing section when compared to the gold standard diagnosis.

## MATERIALS AND METHODS

This was a descriptive, cross-sectional, qualitative study, using secondary data from patient records from a regional philanthropic hospital that is a reference for oncological surgeries in the northwest region of Espírito Santo, Brazil. The sample consisted of 93 female patients, over 18 years old, diagnosed with breast cancer, who underwent the freezing method in this service.

The study was approved by the Human Research Ethics Committee, substantiated opinion number: 4,976,455 of September 15, 2021. The analysis of the medical records took place over the course of one year (2022) and, in order to consolidate the participants' information, research, a thorough evaluation of their medical records was carried out in order to correlate the result of the freezing method with the histopathological report, aiming to define the sensitivity and specificity of freezing when compared to the gold standard diagnosis. In addition, the characteristics of the neoplasm were evaluated, such as current age group and age at diagnosis, presence of clinical lymph node, presence of metastasis, staging, how the diagnosis was given, treatment performed, immunohistochemistry, histological subtype, treatment progress, result of frozen section, histopathological result and type of surgery performed, with the purpose of establishing relationships between the presence of false-negatives and factors intrinsic to the tumor.

Statistical interference, compilation, tabulations and data crossing were developed

based on Pearson's chi-square data analysis method, using the SPSS Statistics 22.0 software, considering a percentage for validation of significance of  $p < 0.05$ .

## RESULTS AND DISCUSSION

Of the 93 medical records analyzed of patients with breast cancer who underwent the intraoperative sentinel lymph node freezing method, the average age at diagnosis was 56 years, with a range from 32 to 85 years.

Other variables analyzed demonstrated the following results: 20.4% of patients had a palpable lymph node on physical examination at the first consultation and 35 patients presented metastasis, corresponding to 37.6% of the sample, with lymph node metastasis being detected in 32 of these patients. Bone, liver, lung and even brain metastases were also identified, all with a poor prognosis.

Regarding the staging of breast cancer, using the TNM as a parameter, 24 patients were classified as IA, 30 as IIA and 19 as IIB. Only 4 patients had distant metastasis, and were therefore classified as stage

### THE REMAINING METASTASES WERE FROM LYMPH NODES CLOSE TO THE ORIGINAL TUMOR.

In the semiological evaluation, 50.5% of patients were diagnosed when they presented some local symptom, such as breast pain, perception of a lump, papillary effusion or changes in the skin of the breast. As for the other patients, 41.9% were diagnosed through screening mammography and only 6.5% through breast self-examination.

Immunohistochemistry is extremely important for defining treatment and patient prognosis and must be requested in all cases. 51.6% had positive estrogen and progesterone receptors, having a better prognosis due to the good response to hormone therapy.

21.6% of patients expressed positive HER2, which represents a more guarded prognosis. However, the subtype with the worst prognosis and least responsive to therapy is triple negative, with hormone receptors and negative HER2, which represented 15.1% of the sample. In these cases, the use of hormone therapy is not indicated.

The most common histological subtype found in the sample was Invasive ductal, with 86% representation, followed by lobular (9.7%) and other rarer subtypes, such as mixed ductal-lobular carcinoma (2.2%) and mucinous carcinoma (two%).

Regarding the frozen section test, 20.4% of the results were positive for sentinel lymph node metastasis intraoperatively, while confirmation by the histopathological method revealed that 35.5% of the lymph nodes evaluated were actually positive.

The treatment instituted varied according to the staging, immunohistochemical markers, histological subtype and individualities of the patients. 57% received complete treatment, requiring chemotherapy, radiotherapy and hormone therapy in addition to surgery. 12.9% of patients did not undergo hormone therapy due to the absence of hormone receptors in the tumor and two patients abandoned treatment after surgery.

All patients in the study underwent some surgical intervention, 58.1% corresponding to quadrantectomy surgery, which has the lowest degree of invasion among existing proposals, and 6.5% underwent mastectomy. Radical lymphadenectomy was performed in 29% of patients, always associated with quadrantectomy or mastectomy. Furthermore, 6.5% of patients underwent reoperation to expand surgical margins.

As it is a cross-sectional and retrospective study that analyzed patients who began diagnostic investigation in the last two years, 78.5% are still undergoing treatment, the



majority on hormone therapy, with an average duration of 5 years. Only 6.5% have already completed treatment and are currently only undergoing follow-up to screen for recurrence, 11.8% of recently diagnosed patients are still having their therapeutic plan evaluated and 2.2% are undergoing palliative treatment.

In the evaluation process, the intraoperative sentinel lymph node freezing test was compared to the histopathological method, which is the gold standard for diagnosing lymph node involvement by breast neoplasia. In this sample, 19 true positive results (20.4%) and 14 false negative results (15.1%) were observed, which gives the freezing test a sensitivity of 57% for this sample and a specificity of 100%, or In other words, all positive results from the frozen section test were confirmed by histopathology, but there was a high rate of false negatives ( $p < 0.05$ ). Of the 14 false-negative results for metastasis in the frozen section test, 5 were due to micrometastasis (35.7%). All patients diagnosed with micrometastasis presented a false negative test.

As it can be seen in the table above, the false negatives in this study occurred mainly in patients with lymph node micrometastases, initial staging and in younger women (average age of 53 years). However, there was no statistical significance in the correlation between the histological subtype and immunohistochemistry with the results of the frozen section test ( $p = 0.43$ ), which makes it possible to state that the false negative results did not occur due to such tumor characteristics.

Furthermore, the freezing test had a positive predictive value of 100%, which means that all positive results were confirmed true by the gold standard test, and a negative predictive value of 81%, which corresponds to the proportion of patients undergoing the test who presented positive results.

reliable negative. The accuracy of the test, which corresponds to true positives and true negatives, was 84%.

For the statistical analysis of metastases, lymph node (N) and distant (M) metastases were considered. It was observed in the sample that the histological subtype most related to metastases was lobular (32.3%), while invasive ductal carcinoma, although with an extremely more significant numerical prevalence, was responsible for only 5.4% of metastases. It is therefore correlated that the lobular subtype is more invasive and has a worse prognosis than the most common subtype, which is invasive ductal carcinoma ( $p < 0.05$ ).

Another fact that corroborates the justification is the type of surgical treatment chosen. Of the patients with the invasive ductal subtype, 49.5% underwent quadrantectomy alone and only 4.2% required radical lymphadenectomy. As for invasive lobular, 23.7% of patients underwent radical lymphadenectomy ( $p < 0.05$ ).

Regarding metastases and the freezing test of the 37.6% patients with metastasis, 19.4% had a positive freezing result, while 18.3% had a negative freezing result.

This result is directly associated with the low freezing sensitivity (57% sensitivity).

On the other hand, of the 62.4% patients without metastasis, only 1.1% presented a positive frozen section test, this being a carrier of distant metastasis, while the remaining 61.3% presented a truly negative test, corroborating to demonstrate that the test has high specificity (specificity of approximately 100%).

There was also statistical significance in relation to the type of treatment chosen and surgery performed ( $p < 0.05$ ). A total of 57% of patients underwent quadrantectomy only and in the sample, 38.6% received complete clinical treatment, with chemotherapy, radiotherapy and hormone therapy. Furthermore, of the

Age	Metastasis	Staging	IHC	Histopathological
51	Lymph node micrometastasis	T2N1M0	PR, ER and HER2 positive	Invasive ductal
37	Sentinel lymph node	Não classificado	Positive PR and RE	Invasive ductal
38	Sentinel lymph node	T2N1M0	PR, ER and HER2 positive	Invasive ductal
66	Sentinel lymph node	T2N1M0	Positive PR and RE	Invasive ductal
59	Sentinel lymph node	T4N2M0	positive RE	Invasive ductal
40	Lymph node and lung	T1N1M1	PR, ER and HER2 positive	Mixed invasive carcinoma
61	Sentinel lymph node	T3N1M0	PR, ER and HER2 positive	Invasive ductal
49	Lymph node micrometastasis	T1N1M0	Positive PR and RE	Invasive ductal
40	Lymph node micrometastasis	T2N1M0	Positive PR and RE	Invasive ductal
59	Sentinel lymph node	T2N1M0	Positive PR and RE	Invasive lobular
84	Sentinel lymph node	T1N1M0	PR, ER and HER2 positive	Invasive ductal
48	Lymph node micrometastasis	T1N1M0	Positive PR and RE	Invasive ductal
62	Lymph node micrometastasis	T1N1M0	Positive PR and RE	Invasive ductal
51	Lymph node	T1N2M0	Positive PR and RE	Invasive ductal

TABLE 1: Characteristics of tumors with false negative results in the frozen section test

Source: Generated from the aforementioned study.

		Histopathological			
Diagnostic Methods		Positive %	Negative %	Total	
Freezing	Positive	Count	19	0	19
		% within freezing (1 or 2)	100	0,0	100,0
		% within Histopathological (1 or 2))	57,6	0,0	20,4
		% of Total	20,4	0,0	20,4
	Negative	Adjusted ResidualCount	6,6	-6,6	
			14	60	74
		% within freezing (1 or 2)	18,9	81,1	100,0
		% within Histopathological (1 or 2)	42,4	100,0	79,6
	% of total	15,1	64,5	79,6	
	Residual adjusted	-6,6	6,6		
Total	Count	33	60	93	
	% within freezing (1 or 2)	35,5	64,5	100,0	
	% within Histopathological (1 or 2)	100,0	100,0	100,0	
	% of total	35,5	64,5	100,0	

TABLE 2: Correlation between histopathological diagnosis and the method of intraoperative sentinel lymph node freezing in breast cancer.

Source: Generated from the aforementioned study.

			Histopathological Subtype		Total
			Lobular	Invasive	
Metastasis	Positive	Count	30	5	35
		% within Metastasis	85,7	14,3%	100,0
		% within Histopathological (1 or 2)	90,9	8,3%	37,6
		% of total	32,3	5,4%	37,6
		Adjusted Residual	7,9	-7,9	
	Negative	Count	3	55	58
		% within Metastasis	5,2	94,8	100,0
		% within Histopathological (1 or 2)	9,1	91,7	62,4
		% of Total	3,2	59,1	62,4
		Adjusted Residual	-7,9	7,9	
Total	Count	33	60	93	
	% within Metastasis	35,5	64,5	100,0	
	% within Histopathological (1 or 2)	100,0	100,0	100,0	
	% of total	35,5	64,5%	100,0	

TABLE 3: Correlation between histological subtypes and the presence of metastasis

Source: Generated from the aforementioned study.

Diagnostic Methods			Freezing		Total
			Positive %	Negative %	
Metastasis	Positive	Count	18	17	35
		% within Metastasis	51,4	48,6	100,0
		% within freezing (1 or 2)	94,7	23,0	37,6
		% of total	19,4	18,3	37,6
		Adjusted Residual	5,8	-5,8	
	Negative	Count	1	57	58
		% within Metastasis	1,7	98,3	100,0
		% within freezing (1 or 2)	5,3	77,0	62,4
		% of Total	1,1	61,3	62,4
		Adjusted Residual	-5,8	5,8	
Total	Count	19	74	93	
	% within Metastasis	20,4	79,6	100,0	
	% within Freezing (1 or 2)	100,0	100,0	100,0	
	% of total	20,4	79,6	100,0	

TABLE 4: Correlation between the frozen section test and the presence of metastasis

Source: Generated from the aforementioned study.



20.4% patients with a positive intraoperative frozen section test, 19.4% also underwent radicallymphadenectomy, which demonstrates how much influence the test offers on surgical therapeutic decisions. Of the 79.6% of patients with negative frozen section, only 8.7% underwent radical lymphadenectomy, and 57% underwent surgery quadrantectomy. Therefore, it is possible to state that positive freezing is associated with a more invasive surgical treatment, while negative freezing is associated with a more conservative surgical treatment.

## CONCLUSION

The research results show that, from the users' perspective, Primary Health Care in the Columbia neighborhood presented a

low degree of service orientation in relation to PHC attributes. Despite the impossibility of generalizing the results to the entire municipality of Colatina, these results can guide health professionals and local and national managers in the search for strategies to strengthen PHC.

It is recommended that more evaluative studies be carried out in which other agents are included, such as Family Health Strategy professionals, so that, from a new perspective, a comparison can be made between the two views, identifying the main needs of this population and suggest proposals for joint interventions that are more appropriate to the reality experienced by the user.

## REFERENCES

- FRAGOMENI ALMEIDA, Renata; PORTELA COELHO, Guilherme. Avaliação histopatológica do Sentinel lymph node no câncer de mama [S. l.], 7 abr. 2012.
- FRANCISSEN, Claire *et al.* Evaluation of the benefit of routine intraoperative frozen section analysis of sentinel lymph nodes in breast cancer. **International Scholarly Research Notices Oncology**, v. 2013, p. 1-5, 2013.
- GIULIANO, Armando E. *et al.* Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) randomized clinical trial. **Journal of the American Medical Association (JAMA)**; Chicago, v. 318, n. 10, p. 918-926, 2017.
- JUNG, Sung Mi *et al.* Is the intraoperative frozen section analysis of sentinel lymph nodes necessary in clinically negative node breast cancer?. **Annals of Surgical Treatment and Research**; Korea, v. 99, n. 5, p. 251, 2020.
- LOMBARDI A, Nigri G *et al.* Role of frozen section in sentinel lymph node biopsy for breast cancer in the era of the ACOSOG Z0011 and IBCSG 23-10 trials. **The Surgeon**; Edinburgh, v.16, n.4, pg. 232-236, 2018.
- MAHADEVAPPA, Asha *et al.* Intra-operative diagnosis of breast lesions by imprint cytology and frozen section with histopathological correlation. **Journal of clinical and diagnostic research: JCDR**; India, v. 11, n. 3, pg. 1-6, 2017.
- VIEIRA, Carlos S. *et al.* Falso-negativo no exame de congelação do sentinel lymph node em câncer de mama. **Revista Brasileira de Mastologia**; Rio de Janeiro, v. 22, n. 2, p. 51-56, 2012.
- WADA, Noriaki *et al.* Evaluation of intraoperative frozen section diagnosis of sentinel lymph nodes in breast cancer. **Japanese Journal of Clinical Oncology**; Japan v. 34, n. 3, p. 113-117, 2004.
- WEISER, Martin R. *et al.* Is Routine Intraoperative Frozen-Section Examination of Sentinel Lymph Nodes in Breast Cancer Worthwhile?. **Annals of Surgical Oncology**, v. 7, n. 9, pág. 651-655, 2000.

YOON, Kwang H. *et al.* Is the frozen section examination for sentinel lymph node necessary in early breast cancer patients?. **Annals of surgical treatment and research**; Korea, v. 97, n. 2, p. 49-57, 2019.