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ANALYSIS OF TIME INTERVAL BETWEEN BREAST CANCER DIAGNOSIS AND TREATMENT

Análise do tempo decorrido entre diagnóstico e tratamento do câncer de mama

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ABSTRACT

Introduction: Breast cancer has a good prognosis when treated early. However, the mortality rate in Brazil is still high. The time interval between radiological suspicion and diagnosis/treatment impacts the survival. **Methods:** This is a retrospective cross-sectional study that assessed patients treated at a reference center, with abnormal breast imaging findings and subsequent confirmation of breast cancer, from January 2011 to June 2015. We reviewed variables related to the dates of the abnormal test result, first mastology appointment, biopsy, surgery, and the start of chemotherapy – when indicated. Time intervals were compared using the Friedman and Kruskal-Wallis tests with the software SPSS® 23.0. **Results:** We analyzed 65 patients. The median time between the abnormal test result and first mastology appointment was 35 days; between first mastology appointment and biopsy, 31 days; between biopsy and surgery, 85 days; and between surgery and chemotherapy, 137 days. The last two intervals showed significant differences ($p<0.001$). **Discussion:** Breast cancer patients had a significant delay until surgery and the start of chemotherapy. Early integration of the multidisciplinary team involved in this process and internal audits are necessary to optimize time intervals.

KEYWORDS: Breast cancer; chemotherapy; diagnosis; epidemiology; public health.

RESUMO

Introdução: O câncer de mama apresenta bom prognóstico quando tratado precocemente, entretanto, a mortalidade no Brasil continua elevada. O tempo entre suspeita radiológica e diagnóstico e tratamento tem impacto na sobrevida. **Métodos:** Foi realizado um estudo transversal e retrospectivo que avaliou pacientes atendidas em centro de referência com imagem mamária alterada e posterior confirmação de câncer de mama de janeiro de 2011 a junho e 2015. Foram revisadas variáveis relacionadas às datas do exame alterado, da primeira consulta, da biópsia, da cirurgia e do início da quimioterapia, quando indicada. Os intervalos de tempo foram comparados pelos testes Friedman e Kruskal-Wallis, pelo programa SPSS® 23.0. **Resultados:** Foram analisadas 65 pacientes. A mediana de tempo entre exame alterado e primeira consulta foi 35 dias, entre consulta na mastologia e biópsia foi 31 dias, entre biópsia e cirurgia foi 85 dias e entre cirurgia e quimioterapia foi 137 dias. Foram observadas diferenças significativas nos dois últimos intervalos ($p<0,001$). **Discussão:** As pacientes com câncer de mama apresentaram atraso significativo até a cirurgia e até o início da quimioterapia. Há necessidade da integração precoce da equipe multidisciplinar implicada nesse processo e auditorias internas a fim de otimizar os intervalos de tempo.

PALAVRAS-CHAVE: Câncer de mama; quimioterapia; diagnóstico; epidemiologia; saúde pública.

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INTRODUCTION

Breast cancer (BC) is the most prevalent malignant neoplasm among women (excluding non-melanoma skin tumors) and the most common cause of cancer mortality in this population[1]. In Brazil, according to estimates from the National Cancer Institute (*Instituto Nacional do Câncer* –INCA), BC was responsible for 14,388 deaths in 2013, and 57,960 new cases were expected in 2016[1]. Mortality rates for this disease are still high in the country, probably due to it being diagnosed in advanced stages, especially in social classes with lower purchasing power.

Despite the high BC incidence, up to 95% of patients can be cured if diagnosed in early stages[2]. Therefore, early diagnosis is a fundamental strategy to treat this cancer. The most effective measure for early BC diagnosis is mammography since mammographic screening can reduce mortality rates by up to 40%[3]. Several clinical studies have shown that early BC diagnosis and treatment can decrease the specific mortality of this neoplasm[4-6]. Recent results demonstrate that delaying the treatment of this cancer reduces overall survival[7-11]. Nevertheless, available data on the period between finding the suspicious breast lesion and BC diagnosis and treatment are scarce, and these variables could impact the prognosis and differ according to regions of the country, depending on geographic and socioeconomic factors.

This study evaluated the time interval between radiological suspicion and BC diagnosis and treatment in a public hospital reference in oncology in Southern Brazil. Based on these results, our secondary objective was to understand the reason for the greater delay in the process and discuss strategies to optimize the flow of patients.

METHODS

This was an observational retrospective cross-sectional study, approved by the Scientific and Editorial Committee of Hospital Geral de Caxias do Sul and the Committee for Ethics of Universidade de Caxias do Sul. We assessed all consecutive patients treated at Hospital Geral de Caxias do Sul (a tertiary level III hospital, reference for the 5th Health Coordination of Rio Grande do Sul), who presented a mammographic image and/or breast ultrasound classified in categories 4 and 5 of the Breast Imaging Reporting and Data System (BI-RADS®)[12,13] between January 1, 2011 and June 30, 2015, followed by histological confirmation (via percutaneous biopsy, fine needle puncture, or excision of the lesion) of malignant breast neoplasm. After identifying the patients, the researchers reviewed the outpatient and hospital medical records. The patient characteristics analyzed related to age, ethnicity, prior history of smoking, menopausal status, modality of test with abnormal imaging, type of radiological abnormality, BI-RADS® category, histological subtype and grade, clinical stage (CS), surgical modality, and adjuvant treatment – when applicable.

We evaluated the following intervals:

- date of the abnormal imaging test until the date of the first mastology appointment;
- date of the first mastology appointment until the date of biopsy;
- date of biopsy until the date of surgery;
- date of surgery until the date of the start of chemotherapy (when applicable).

Patients were excluded if they received neoadjuvant treatment, had distant metastases at diagnosis, ductal carcinoma *in situ*, and incomplete medical records.

For the statistical analysis, we used the software SPSS® version 23.0 (SPSS® Inc.; Illinois, USA). The choice of measures of central tendency and dispersion of values that compose the samples, as well as statistical tests to compare them was based on types of distribution, according to the Shapiro-Wilk test. Values of each quantitative variable were organized and described by median, mean, and standard deviation. Qualitative data were represented by absolute and relative frequencies. We used the Friedman test to compare time intervals, and the Kruskal-Wallis test to compare three or more populations. All tests adopted a statistical significance value of 5% ($p \leq 0.05$).

Definitions

The definition used for abnormal imaging tests was based on BI-RADS®[12,13], a classification that standardized the description of reports, systematized the categorization and management of lesions, and provided an internal audit system for breast imaging quality. Lesions defined as suspicious were classified as BI-RADS 4 and 5, requiring, therefore, biopsy for anatomopathological evaluation. Category 4 is subdivided into 4A, 4B, and 4C. In group 4A, the risk of malignancy is 10%; in 4B, it is a little higher, but, usually, lower than 50%; and in 4C, this value ranges from 50 to 95%[10,12]. Category 5 should be reserved for classical tumor lesions, in which malignancy will only be ruled out after surgical evaluation of the region; in this category, the chance of malignant lesion exceeds 95%[12,13].

We used the 8th edition of the BC staging system recommended by the Union for International Cancer Control (UICC), known as the TNM Classification of Malignant Tumors. This system is based on the anatomic extent of the disease, taking into account the characteristics of the primary tumor (T), the nature of lymph nodes from the chains of lymphatic drainage of the organ in which the tumor is located (N) and the presence or absence of distant metastases (M)[14].

RESULTS

We evaluated 88 patients with abnormal imaging test (BI-RADS 4 and 5) and confirmation of breast neoplasm after biopsy from January 1, 2011 to June 30, 2015. Out of the total sample, we excluded three women who did not have a BI-RADS category

described in the imaging test, two who had carcinoma *in situ*, ten who underwent neoadjuvant chemotherapy, five who had metastases at diagnosis, two with no relevant information on their medical records, and one for not being within the predetermined period. Thus, this analysis included 65 patients.

The mean age was 58.9 years. Table 1 summarizes the pathological and clinical characteristics of the patients. Among them, 75.4% were of Hispanic origin, 81.5% were non-smokers, and 76.9% were in post-menopause. Thirty-three patients (50.8%) were referred to the mastology center due to a suspicious lesion found in mammographic screening, and 32 (49.2%) presented abnormal breast ultrasound. The most frequent lesion in imaging tests was the presence of an isolated nodule — 84.6% of cases. Patients with lesions classified as BI-RADS 4 at diagnosis represented 86% of the sample, and BI-RADS 5, 14%. Regarding the histological subtype, 73.8% had invasive carcinoma of no special type (ductal), and 16.9% presented invasive lobular carcinoma; 63.1% had histological grade 2 and 29.2%, grade 3. Forty-one patients had CS IA (50.8%) and IB (12.3%) at diagnosis, while 15.4% presented CS IIA; 3.8%, CS IIB; and 7.7%, CS IIIA.

With respect to treatment, conservative breast surgery (lumpectomy) represented 66.2% of cases, and 73.8% of patients initially underwent sentinel lymph node biopsy. Concerning adjuvant treatment, 75.4% of subjects underwent radiotherapy; 53.8%, chemotherapy; and 87.7%, hormone therapy (Table 2).

Table 3 presents the time intervals between the abnormal test result and diagnosis and treatment. The median time between the date of the abnormal test result and the first mastology appointment was 35 days; between the first mastology appointment and biopsy was 31 days; between biopsy and surgery was 85 days; between surgery and the start of chemotherapy — when indicated —, was 137 days. The last two intervals showed significant differences ($p<0.001$). The interval between surgery and the start of chemotherapy was higher than all the other ones analyzed. Also, the period between biopsy and surgery was superior to that of abnormal test result until the first mastology appointment, and of the first mastology appointment until biopsy, with no significant difference between the last two.

The medians of the intervals presented no significant differences when we analyzed the patients according to their clinical stage (Table 4).

DISCUSSION

Several factors influence the overall survival of BC patients. Mammographic screening plays a fundamental role, reducing the mortality from this type of cancer by 30–40%, as it considerably increases the chance of early diagnosis[3,5,6]. On the other hand, the delay in starting adjuvant chemotherapy is associated with a worse prognosis for patients with breast neoplasm[7-11]. In addition, other usually underestimated and not routinely assessed factors might be related to a worse prognosis, such as the time interval from clinical and radiological suspicion to breast cancer diagnosis and treatment[15-19].

Table 1. Population characteristics.

Variables (n=65)	N	%
Age	58.9±10.4	
Ethnicity		
White	49	75.4
Black	2	3.1
Other	14	21.5
Tobacco use		
No	53	81.5
<20 packs/year	9	13.8
>20 packs/year	3	4.6
Menopausal status		
Pre-menopause	15	23.1
Post-menopause	50	76.9
Abnormal test result		
Ultrasound	32	49.2
Mammography	33	50.8
Type of abnormality		
Nodule	55	84.6
Microcalcifications	3	4.6
Nodule + microcalcifications	4	6.2
Breast asymmetry	3	4.6
BI-RADS		
BI-RADS 4	36	55.4
BI-RADS 4A	1	1.5
BI-RADS 4B	4	6.2
BI-RADS 4C	10	15.4
BI-RADS 5	14	21.5
Histological type		
Lobular	11	16.9
Invasive carcinoma of no special type	48	73.8
Other	6	9.2
Histological grade		
1	5	7.7
2	41	63.1
3	19	29.2
Clinical stage		
IA	33	50.8
IB	8	12.3
IIA	10	15.4
IIIB	9	13.8
IIIA	5	7.7

When we evaluated the time interval between the date of the abnormal imaging test and the first mastology appointment, at our institution, we found a median of 35 days. Although there is no ideal period for this interval, we consider this result acceptable, as it demonstrates an efficient flow of patients with suspicious lesions from Basic Health Units (*Unidades Básicas de Saúde* – UBSs) to the mastology center. Also, this information suggests that family doctors and gynecologists from UBSs in Caxias do Sul are prepared for the detection and appropriate referral of lesions suspicious for BC.

When we analyzed the time intervals between the first mastology appointment and biopsy, and between biopsy and surgery, we found medians of 31 and 85 days, respectively. According to Law no. 12,732, of November 22, 2012, the cancer patient will receive, free of charge, all treatments necessary from the public health system (*Sistema Único de Saúde* – SUS) within up to 60 days counted from the date the report of diagnosis is signed for the patient to start the first treatment — in compliance with the therapeutic need the case requires. Olivotto et al.[18] demonstrated that a delay in diagnosis is associated with a greater axillary lymph node involvement and larger tumors. However, in our study, the medians of the intervals presented no significant differences when we analyzed the patients according to their clinical stage.

Among the patients submitted to adjuvant chemotherapy, the median between the date of surgery and the start of chemotherapy was 137 days. The literature has no data establishing an ideal value for this time interval. In an American study that analyzed patients using records of the National Comprehensive Cancer Network (NCCN), Vandergrift et al.[11] found a median of six weeks between surgery and the start of chemotherapy. The American Society of Clinical Oncology (ASCO) suggests that the interval between diagnosis and treatment should not exceed 120 days[20,21]. Gagliato et al.[7] revealed that an interval between surgery and start of chemotherapy exceeding 60 days is associated with worse survival, particularly for patients in stage III, and with triple-negative and HER2 positive breast tumors. In a

Table 2. Treatments undergone.

Variables (n=65)	N	%
Surgery		
Lumpectomy/Quadrantectomy	43	66.2
Nipple-sparing mastectomy	2	3.1
Skin-sparing mastectomy	1	1.5
Modified radical mastectomy	19	29.2
Sentinel lymph node biopsy	48	73.8
Axillary drainage	25	38.5
Adjuvant radiotherapy	49	75.4
Adjuvant chemotherapy	35	53.8
Adjuvant hormone therapy	57	87.7
Tamoxifen	32	56.1
Anastrozole	12	21.1
Tamoxifen>Aromatase inhibitor	8	14.0
Aromatase inhibitor>Tamoxifen	5	8.8
Ovarian suppression	7	10.8

Table 3. Time intervals.

Interval (in days)	Mean±SD (median)	Minimum	Maximum
Abnormal test result – mastology appointment	49.1±44.40 (35.0)[a]	7	248
Mastology appointment – biopsy	44.3±46.0 (31.0)[a]	0	240
Biopsy – surgery	85.1±40.0 (85.0)[b]	0	174
Surgery – start of chemotherapy	153.5±99.5 (137.0)[c]	24	397

SD: standard deviation; medians followed by identical letters do not differ among themselves.

Table 4. Time interval according to clinical stage.

Interval	Clinical stage					p-value*
	Mean±SD (median)					
	1A (n=33)	1B (n=8)	2A (n=10)	2B (n=9)	3A (n=5)	
Abnormal test result – mastology appointment	47.4±46.4 (34.0)	69.8±77.3 (48.0)	43.2±18.2 (41.0)	45.8±22.3 (41.0)	45.0±32.3 (26.0)	0.747
Mastology appointment – biopsy	57.2±57.5 (37.0)	36.0±28.8 (30.0)	31.8±20.7 (28.0)	30.9±30.1 (31.0)	21.8±12.4 (27.0)	0.403
Biopsy – surgery	81.8±41.6 (83.0)	74.8±47.1 (86.0)	91.6±36.2 (90.5)	98.2±38.0 (110.0)	87.0±35.4 (98.0)	0.734
Surgery – chemotherapy	146.1±82.0 (125.0)	107.8±61.3 (108.0)	186.0±130.7 (173.0)	209.7±107.7 (268.0)	109.4±140.6 (47.0)	0.141

SD: standard deviation; *Kruskal-Wallis test.

similar study, Yu et al.[20] demonstrated that patients with more aggressive molecular subtypes, such as triple-negative, luminal B, and HER2 positive tumors, had worse survival when this delay was longer than eight weeks. Trufelli et al.[22] showed that, for each month of delay in beginning the adjuvant treatment, the risk of death increases 1.3%, representing a risk factor independent from other known ones.

Considering that BC is a heterogeneous and complex disease, we believe that one way of reducing these time intervals is integrating the multidisciplinary team primarily in the process of diagnosis and treatment. The patient with this cancer must be early monitored by a specialized multidisciplinary team that includes physicians (mastologist, clinical oncologist, radiologist, radiation oncologist, pathologist), nurse, psychologist, social worker, and physiotherapist, in order to improve the intervals between diagnosis and treatment and facilitate the entire process. Studies indicate that a multidisciplinary team caring for the patient optimizes the work and reduces the mortality rate, in addition to improving outpatient and hospital management[23].

Furthermore, we believe that routine internal audits of time intervals between radiological suspicion and diagnosis and treatment are fundamental to the excellence in BC treatment in reference centers. As important as the availability of modern chemotherapy and radiotherapy regimens and state-of-the-art equipment is decreasing time intervals between diagnosis and treatment, as they are also an indicator of the quality of health services and directly affect the survival of patients.

The strengths of our study include the comprehensive nature of the database with clinical and pathological characteristics of the patients, surgery description, adjuvant treatments received, and a rigorous assessment of intervals between the abnormal test result and diagnosis and treatment. In addition, the population of our study was quite homogeneous, consisting of patients referred from UBSs, treated exclusively by the SUS, who had their biopsies in our service and received only adjuvant treatments, since we excluded from this study those who received neoadjuvant chemotherapy or hormone therapy. On the other hand, we understand the limitations of our study, which involve its retrospective nature, the reduced sample of patients assessed, and the lack of evaluation of possible psychosocial factors that could contribute to the delay in diagnosis, such as fear of a cancer diagnosis, denial of the disease, and understanding of the process.

BC patients treated in our service had a significant delay between biopsy and surgery, as well as between surgery and the start of chemotherapy. Early integration of the multidisciplinary team involved in this process and routine internal audits are necessary to optimize the time intervals between diagnosis and treatment, and eliminate the negative impact on patient survival.

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