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PROBABILITY OF A HIGH RECURRENCE SCORE FOR BREAST CANCER ON THE ONCOTYPE DX TEST IN MALES: A CASE SERIES

Keywords: Nomograms; Genomics; Medical Records; Breast Neoplasms, Male.
Palabras clave: Nomogramas; Genómica; Registros médicos; Neoplasias de la mama masculina.

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ABSTRACT

Introduction: Male breast cancer (MBC) is a rare disease that accounts for 1% of breast cancers. The Oncotype DX test (a genomic signature that assesses the expression of 21 genes to estimate the recurrence score [RS]) has been widely used in MBC to select patients for adjuvant chemotherapy.
Objective: To describe 5 cases of MBC in which a nomogram was used to predict the probability of having a high Oncotype DX score for breast cancer and the need to perform genomic signature.
Materials and methods: Case series study in which five patients with MBC treated between 2007 and 2020 at a cancer institution in Teresina (Brazil) were included. A nomogram was performed to evaluate five clinical and pathological variables (age, body size, tumor size, grade, recurrence score status, and histologic type of carcinoma).
Case series: The mean age of the patients at diagnosis was 69 years (mean tumor size: 2.6cm). All patients received hormone therapy with tamoxifen, three received chemotherapy, and one received radiation therapy after breast surgery (mastectomy). During a median follow-up period of 88 months, one case had a recurrence (bone metastasis). Based on the nomogram results, two patients had a high probability of a high RS (36% and 45%) and only one patient (case 3) underwent Oncotype DX testing (RS: 20).
Conclusions: In the present series of five cases, based on the nomogram results, only two patients (cases 3 and 4) had a high probability of a high Oncotype DX recurrence score; however, due to financial constraints, this test was only performed on one of these two patients. The patient who underwent the test (case 3) did not receive adjuvant chemotherapy and remained alive with bone metastases until the end of the follow-up period. Conversely, the patient who could not undergo the examination (case 4) received adjuvant chemotherapy and was alive without any signs of disease.

Keywords: Nomograms; Genomics; Medical Records; Breast Neoplasms, Male.

RESUMEN

Introducción. El cáncer de mama masculino (CMM) es una enfermedad rara que representa el 1% de los casos de cáncer de mama. La prueba Oncotype DX, un test de laboratorio genómico que evalúa la expresión de 21 genes para estimar la puntuación de recurrencia (PR), se ha usado ampliamente en el manejo del CMM para seleccionar pacientes para quimioterapia adyuvante.
Objetivo. Describir cinco casos de CMM en los que se utilizó un nomograma para predecir la probabilidad de una alta PR de cáncer de mama Oncotype DX y la necesidad de realizar firma genómica.
Materiales y métodos. Estudio de serie de casos en el que se incluyeron cinco pacientes con CMM atendidos entre 2007 y 2020 en una institución oncológica de Teresina (Brasil) y en los que se realizó un nomograma que evalúa cinco variables clínicas y patológicas (edad, estado de la PR y tamaño, grado y tipo histológico del carcinoma).

Serie de casos. La edad media de los pacientes al momento del diagnóstico fue 69 años y la media del tamaño tumoral, 2.6cm. Todos los pacientes recibieron terapia hormonal con tamoxifeno, tres recibieron quimioterapia y uno recibió radioterapia después de la mastectomía. En un seguimiento medio de 88 meses, solo un caso tuvo recurrencia (metástasis ósea). Según los resultados del nomograma, dos pacientes tenían alta probabilidad de una alta PR (36% y 45%) y solo en un paciente (caso 3) se realizó la prueba de PR de cáncer de mama Oncotype DX (PR: 20).
Conclusiones. En la presente serie de cinco casos, según los resultados del nomograma, solo dos pacientes (casos 3 y 4) tuvieron alta probabilidad de tener una alta PR de cáncer de mama Oncotype DX; sin embargo, debido a problemas financieros, esta prueba solo fue realizada en uno de estos dos pacientes.
Palabras clave: Nomogramas; Genómica; Registros médicos; Neoplasias de la mama masculina.

INTRODUCTION

Male breast cancer (MBC) is a rare disease, accounting for approximately 1% of all breast cancers and less than 0.5% of all male cancers (1,2). The age distribution among men with breast cancer is unimodal, with a peak incidence at age 71 years (2).

The major predisposing risk factors for MBC are family history, liver failure resulting from various causes (including alcoholism and endemic diseases), prolonged hormone treatments, testicular tumors, orchitis, testicular trauma, prostate tumors, obesity, karyotype alterations (Klinefelter syndrome), and gynecomastia. Although gynecomastia is not considered a risk factor for MBC, it is often associated with it. Pathogenic mutations in the *BRCA1* gene are associated with some cases, but the correlation with pathogenic mutations in the *BRCA2* gene is stronger. Most histologic subtypes found in women are also observed in men, except for the lobular type, which is very rare. Male breast tumors have a higher probability of manifesting estrogen receptors (ER) and progesterone receptors (PR) (2,3).

Similar to female breast cancer (FBC), the occurrence of MBC also increases with age. However, unlike women, there is a higher incidence of breast cancer in African American men than in White men. In the majority of cases, the disease starts insidiously, with thickening of the breast glandular tissue, usually in the retroareolar region, skin retraction, presence of a solid node, blood-stained papillary discharge, and ulcers at a later stage (3,4).

Data from over 2 000 patients show that 93.7% of MBC cases are invasive carcinomas of no special type (NST), 2.6% are papillary, 1.8% are mucinous, and only 1.5% are lobular. As with FBC, MBC is treated with surgery, radiotherapy, chemotherapy, and hormone therapy. Disease prognosis, correcting for age, and stage are similar between men and women (4).

The Oncotype DX recurrence score for breast cancer is a genomic signature that evaluates the expression of 21 genes measured by reverse transcriptase-polymerase chain reaction (RT-PCR) —16 cancer-related genes and 5

reference genes in breast cancer—. This test estimates the recurrence score (RS), quantifying the 10-year risk of systemic recurrence and the benefit of adjuvant chemotherapy in patients treated with tamoxifen. Genomic signatures (particularly Oncotype DX) have been used to select MBC patients for adjuvant chemotherapy, but the number of publications on the subject is still low (5).

The objective of this study was to describe 5 cases of MBC in which a nomogram was used to predict the probability of having a high Oncotype DX RS and to establish the need to perform a genomic signature.

MATERIALS AND METHODS

Case series: Five patients with MBC treated from 2007 to 2020 at a private oncology healthcare center in the city of Teresina, Piauí, Brazil. A nomogram developed at the University of Tennessee was used to predict the probability of having a high Oncotype DX RS. This nomogram evaluates five clinical and pathological variables (age, tumor size, grade, PR status, and breast carcinoma histologic type) based on the TAILORx clinical trial results (6).

CASE SERIES

Table 1 describes the age, histologic type, grade, tumor size, ER, PR, HER2 (human epidermal growth factor receptor 2), angiolymphatic and perineural invasion, axillary node involvement, and histopathologic stage of the cases included.

Table 1. Description of 5 patients in the case series (age, histologic type, grade, tumor size, ER, PR, HER2, angiolymphatic and perineural invasion, axillary node involvement, and histopathologic stage).

Case	Age (years)	Histologic type	Grade	Tumor size (cm)	ER (+/-)	PR (+/-)	HER2 (+/-)	ALI (+/-)	PNI (+/-)	Axillary node involvement (+)	Histopathology stage
1	71	NST	G1	1.0	+	+	-	-	-	0+/2 (sentinel node)	T1N0M0
2	57	NST	G2	5.2	+	+	-	-	-	0+/1 (sentinel node)	T4bN0M0
3	88	NST	G3	3.2	+	+	-	-	+	0+/10	T2N0M0
4	67	NST	G3	1.0	+	+	-	-	-	0+/2 (sentinel node)	T1N0M0
5	63	NST	G2	2.8	+	+	-	-	-	5+/15	T2N2M0

NST: invasive carcinoma of no special type; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; ALI: angiolymphatic invasion; PNI: perineural invasion.

Source: Own elaboration.

The mean follow-up time was 88 months (21 to 180 months). All cases underwent breast surgery (mastectomy) and received adjuvant treatment with hormone therapy (tamoxifen). Three patients received chemotherapy and only one underwent radiotherapy after surgery. Case 3 was the only patient who had tumor recurrence (bone metastasis). Information on treatment, follow-up, outcomes, and probability of a high RS in the five patients included is presented in Table 2.

Table 2. Adjuvant treatment, follow-up, outcome, and probability of high RS in the five patients of the series.

Case	Chemo-therapy	Radio-therapy	Hormone therapy	Follow-up (months)	Survival	Probability of high RS on nomogram
1	No	No	Yes	36	ADF	3%
2	Yes	No	Yes	21	ADF	18%
3	No	No	Yes	75	AWD (bone metastasis)	45%
4	Yes	No	Yes	130	ADF	36%
5	Yes	Yes	Yes	180	DOC (acute myocardial infarction)	12%

ADF: alive and disease-free; AWD: alive with disease; DOC: death from other causes.
Source: Own elaboration.

Two patients had luminal B tumors and three had luminal tumors that did not contain the Ki67 value, so they could not be classified. Only one patient (case 3) underwent a genomic signature test (Oncotype DX), obtaining an RS of 20; it should be noted that he refused to receive adjuvant chemotherapy. Furthermore, two patients had a relevant family history of cancer and underwent a multigene panel for genetic predisposition (cases 2 and 5), with no pathogenic variants being detected. According to the results of the nomogram, two patients (cases 3 and 4) had a high probability (45 and 36%) of a high Oncotype DX RS.

DISCUSSION

In this case series, the mean age of the patient at the time of diagnosis was 69 years (ranging from 57 to 88 years). A study conducted by Liu *et al.* (1) in 289 673 patients with breast cancer, in which 2 054 patients were males, showed that 62% of male patients were aged 50 to 74 years and 28% were older than 74 years, which is consistent with the findings of this study given that advanced age is a risk factor for MBC (1-3,7).

MBC is typically more aggressive than FBC, with larger tumors and a higher rate of positive sentinel lymph nodes. However, men are less likely to develop

well-differentiated tumors (G1) (8). In this case series, only one patient had a G1 tumor. The mean tumor size was 2.6cm (ranging from 1.0-5.2cm), a figure that is consistent with the literature, indicating that the majority of MBC tumors are smaller than 5cm (8,9).

The aggressive course of the disease is associated with its histologic type, and NST is more common in men (present in all cases in this series) (10,11). Regarding the molecular subtype, according to The International Male Breast Cancer Program (IMBCP) and Johansson *et al.* (7), the two main subtypes are male simple, which is not found in FBC, and male complex (more prevalent), which is comparable to the luminal subtype of FBC. Accordingly, all cases in the present study were classified as luminal subtype (12,13).

Treatment for MBC depends on several factors, with histologic grade, tumor size, axillary node status, and molecular profile being the most relevant. In cases for which chemotherapy is not clearly indicated, genomic signature may be helpful in selecting or excluding a patient for chemotherapy treatment. Yadav *et al.* (14) analyzed a cohort of 10 873 patients with MBC from 2010 to 2014, finding an increased use of Oncotype DX RS, with 55.1% and 9% of patients having an RS <18 and >31, respectively. Since an RS >31 indicates the need for adjuvant chemotherapy, this tool decreases the indication of unnecessary chemotherapy (14). In the present study, only one patient had an Oncotype DX RS of 20, so chemotherapy was not indicated. However, the main limitation for performing genomic signature in Brazil is its cost, as these tests are not covered by the Unified Health System (public healthcare) nor the private healthcare systems.

Massarweh *et al.* (15) published what may be the largest case series of breast cancer to date, including 3 806 men and 571 115 women. The RS distribution in that study showed that the majority of male (58.0%) and female (58.2%) patients had an RS <18. However, RS ≥31 (high) was more common among men (12.4%) than among women (7.4%), and it predominated among male patients of all ages, particularly in those under the age of 40. Interestingly, aside from male patients under 40 years of age, RS <11 (low) or RS=0 are even more common in men than in women (15).

A nomogram developed by the University of Tennessee calculates the likelihood of having a high or low Oncotype DX RS based on the clinical and histopathological characteristics mentioned above. It should be noted that the nomogram was created using data from 65 754 Oncotype DX tests and patients with a negative ER+/HER2-/lymph node subtype and 6-50mm tumors captured by the National Cancer Data Base (NCDB) between 2010 and 2014. The findings were verified in 2015 on a different cohort of 18 585 patients (6).

Estimating the likelihood of having a high RS is critical to establish the therapeutic strategy to be adopted, since patients with a high RS (between 26 and 100) benefit from adjuvant chemotherapy in addition to hormone therapy (16,17). In this study, cases 3 and 4 were considered to have a high probability (45% and

36%, respectively) of presenting a high RS on the Oncotype DX test, but only case 4 received adjuvant chemotherapy followed by hormone therapy. Case 3, who was not given adjuvant chemotherapy, was the only patient who experienced systemic recurrence (bone metastasis).

TheOncotype DX RS was originally intended for ER-positive and node-negative patients, however it has been used in some cases with positive axillary nodes (18). The patient in the current series with axillary node involvement (case 5) was also analyzed using the nomogram, finding only a 12% probability of presenting a high RS on the Oncotype DX test. Even though the use of Oncotype DX RS in this type of patient is still not fully defined, it has been performed in these situations. A retrospective series that evaluated 272 women with ER+/HER2- tumors and N1 axillary node status found an RS <18 in 64.4% of the patients. A low RS was associated with a lower indication of chemotherapy. Furthermore, the 3-year recurrence-free survival was equivalent in the groups that received or did not receive chemotherapy and had an RS <18 (19). Adjuvant chemotherapy has also been proven to improve invasive disease-free survival and distant relapse-free survival in premenopausal women with one to three positive axillary lymph nodes and an RS of 0 to 25 (20).

Hormone therapy with tamoxifen is a standard adjuvant treatment for MBC in patients with positive estrogen and progesterone receptors. It increases overall survival and disease-free survival (21-23).

In FBC, radiotherapy is recommended following breast-conserving surgery and subsequent mastectomy in patients with a high RS. Nevertheless, despite studies demonstrating its benefit in local control, recurrence, and survival (in T4 or N+ patients), few male patients with MBC receive this treatment (24). The patients in the current case series followed this trend, and only one patient received adjuvant radiotherapy due to five positive axillary lymph nodes.

MBC is rare, and various studies have associated it with a lower overall survival rate when compared to FBC, which can also be attributed to a late diagnosis (11,25). In this case series, three patients were alive and disease free, one died from acute myocardial infarction, and one developed bone metastasis.

Pathogenic mutations in high penetrance dominant genes, particularly *BRCA2*, should be investigated in MBC patients, since there is a 1% risk of developing breast cancer in men with a pathogenic mutation of the *BRCA1* gene and a 7-8% risk in men with a pathogenic commutation in the *BRCA2* gene. These mutations may occur in various generations of the same family, but they can also occur as *de novo* mutations (26). In the present study, two patients (cases 2 and 5) had a relevant family history of cancer and underwent a multi-gene test to investigate pathogenic variants related to MBC, but no variants were detected. When pathogenic variants are detected, genetic counseling is recommended. However, in Brazil, the performance of genetic panels to investigate genetic predisposition

to cancer is limited by financial reasons since these tests are not covered by the SUS (public health system).

The preliminary experience with Oncotype DX in MBC patients in this study has significant limitations due to the small number of patients included and the fact that genomic signature was performed in only one patient due to financial constraints. However, cost-effective studies have demonstrated that Oncotype DX testing in male patients results in a more individualized treatment plan, and multicenter studies should be conducted to gain a more comprehensive understanding of this genomic tool in this scenario due to the rarity of MBC.

CONCLUSIONS

In the present series of five cases, only two patients (cases 3 and 4) had a high probability of having a high Oncotype DX breast cancer recurrence score based on the nomogram results; however, due to financial constraints, only one of these two patients underwent this test. Of these two patients, the one who underwent the test (case 3) did not receive adjuvant chemotherapy and was still alive with disease-related bone metastases at the end of follow-up period.

ETHICAL CONSIDERATIONS

This study is part of a project approved by the Institutional Review Board of the Universidade Estadual do Piauí, Teresina, Piauí (Brazil), under reference number 4.311.835 (CAAE: 30154720.0.0000.5209). All principles contained in Resolution No. 466/12 issued by the National Health Council were followed (27). The informed consent form was signed by all patients or relatives (in case of death).

CONFLICTS OF INTEREST

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