Survival Analysis of Male Breast Carcinoma

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October, 2013

Abstract

Introduction: Male breast cancer (MBC) is a rare disease corresponding to approximately 1% of all breast cancer cases and less than 1% of all male neoplasms. Each year, its incidence has been increasing what has contributed to a crescent interest in regard to the knowledge and understanding of this disease.

Objective: The main aim of this study consists of investigating the prognostic value of demographic, clinicopathologic, biomolecular and type of treatment variables in relation to overall survival time and the time of remission, which could contribute to infer about the appropriate type of therapy and the tumor's response to a given treatment, as well as the overall survival and disease-free interval in patients with MBC.

Material: The series encompassed 166 male patients with MBC diagnosed and treated in Portuguese Institute of Oncology Francisco Gentil, Lisbon, from 1970 to 2013. Mean follow-up time after both diagnosis and treatment were 81.9 months (range: 1-396 months) and 71.6 months (range: 0-396 months), respectively.

The mean and median ages of patients were, respectively, 64.9 and 66.5 years (31-89 years). Most tumors were ductal carcinomas (88%), moderately differentiated (G2) (55.2%) and of any size with extension (pT_4) (42.2%). Axillary nodal involvement (pN_{1-3}) was presented in 53.4% of cases, and in only 9.6% was detected the presence of distant metastases (pM_1). At the time of diagnosis, 38% of patients were classified as belonging to disease stage III. Most patients do not have a positive family history of cancer (92.8%) and other associated malignancies (91.6%). Estrogen and progesterone receptors were positive in 94% and 83.5%, respectively, and C-erbB-2 oncoprotein expression was present in 18.8% of cases. DNA content of tumoral cells was predominantly aneuploid (79.2%). 86.7% patients underwent surgery, and 54.5%, 63.6% and 32.7% received adjuvant hormonal therapy, radiotherapy and chemotherapy, respectively. Most patients (87.3%) do not conduct any type of neoadjuvant therapy.

Results: During the study, 57 (33.7%) patients died due to MBC and 62 (37.3%) had disease recurrence. Median survival time of patients was 327 months and median time of remission was 132 months. The 5- and 10-year overall survival rates were 70.1% and 56.7%, and corresponding disease-free interval rates were 62.9% and 52.5%, respectively. Based on a univariate analysis (simple Cox regression), the explanatory variables that significantly influenced the overall survival time were age, tumor size, lymph node status, distant metastases status, disease staging, the expression of the oncoprotein C-erbB-2 combined with HER2/neu oncogene amplification by FISH test, and the treatments neoadjuvant therapy, surgery and adjuvant radiotherapy. Most covariates that significantly influenced the disease-free interval were the ones that were related to the overall survival time, with the addition of progesterone hormone receptor expression, tumor differentiation and the hormonal therapy, and chemotherapy adjuvant treatments. For multivariate analysis (multiple Cox regression), a worse prognosis related to overall survival time was associated with the existence of nodal involvement (Relative risk=5.7), presence of distant metastases (RR=9.7), tumors of any size with extension (RR=3.8) and patients aged between 70 and 89 years (RR=5.8). Regarding disease-free interval, the significant factors associated with higher risk of disease recurrence were age ($RR_{40\text{-}69\ years}$=8.8 and $RR_{70\text{-}89\ years}$=16.3), high grade (poorly differentiated) tumors (RR=2.6), presence of lymph node

involvement (RR=5.7) and presence of distant metastases (RR=23.2). A smaller risk of disease recurrence was related to a progesterone receptor positive expression (RR=0.21). Tumor size did not show to be a significant risk factor for disease recurrence. In disease mapping, the risk of death due to MBC was similar in each selected area, being not possible to identify a pattern of spatial distribution of this risk that showed a relevant latent effect due to the geographic region.

Conclusion: The results confirm the adverse prognostic value of older age and disease extension (tumor size, nodal involvement and presence of metastasis) in MBC. In addition, a tumor poorly differentiation and a lack of progesterone receptors seem to have influence in disease-free interval.

Keywords: Male Breast Cancer; Prognostic Factors; Bayesian Spatial Frailty; Survival Analysis;

1. Introduction

Male breast cancer (MBC) is an uncommon malignant neoplasm among men worldwide. Because of its rarity, there is little information about it and treatment recommendations are derived from established guidelines for female breast cancer (FBC). Because MBC incidence has been rising annually [1], there has been an increasing interest in knowledge and understanding of this disease. Even though if MBC and FBC seem to be similar, there are distinct features in the etiology, prognosis and survival that should be investigated.

Several hormonal, environmental and genetic risk factors have been studied in order to clarify the disease prognosis, and therefore the patient's survival and disease recurrence. As in women, the most important prognostic factors for MBC are tumor size and lymph node status [1, 2].

Some studies suggest that men experience a worse prognosis than women, probably due to an advanced disease stage at presentation together with the older age of male patients, leading to increased morbidity. Nevertheless, when men and women are matched for age, stage and grade, a similar prognosis is shown [3].

In order to choose the type of appropriate therapy and tumor response to a given treatment, overall survival and disease-free interval are essential for understanding which predictive and prognostic factors are associated with MBC. Thus, the main objective of this study consists of determining the distribution of overall survival and disease recurrence in order to investigate predictive and prognostic factors for patients with MBC admitted at the Portuguese Institute of Oncology, in Lisbon, from 1970 through 2013.

2. Literature Review

2.1. Epidemiology

MBC is a rare disease accounting for less than 1% of all malignancies in men and for only 1% of all incidents of breast cancer. This year, in United States of America, it is estimated that 2240 (1%) men will be diagnosed with breast cancer of which 410 (18.3%) will die [4]. Its incidence varies greatly in different geographical areas and ethnic groups [1, 5, 6]. In Africa, a substantially higher proportion of MBC cases has been reported. In North America and in the Nordic countries its incident rate has increased [7–9]. By contrast, the annual incidence of MBC in Japan is significantly lower [10, 11]. The prevalence of MBC increases with age and the mean age of diagnosis in males is 65 years [1, 9, 12], which is older than that in patients with FBC [6, 7, 12].

2.2. Etiology and risk factors

Despite the etiology of MBC is not completely known, several risk factors have been identified. Similar to FBC, MBC is likely to be caused by the concurrent effects of different risk factors, including clinical disorders related to hormonal imbalances, certain occupational and environmental exposures, and genetic risk factors.

Genetic contributors to risk in men are similar, but not identical, to those in women, namely a positive family history is related to a higher risk of developing breast cancer for both male and female [13, 14]. Inherited mutations in BRCA increase the risk of MBC [15–17], and the risk is higher with inherited BRCA2 than BRCA1 mutations [18]. Other genes have been investigated for a potential role in predisposition to MBC, such as mutations in PALB2, the androgen receptor (AR), PTEN tumor suppressor gene, CYP17 and CHEK2.

MBCs are highly sensitive to hormonal changes. Particularly, an imbalance between an excess of estrogen and a deficiency of testosterone increases the risk of disease. It occurs, for example, when there are testicular abnormalities or a hyperestrogenic state derived from liver diseases or obesity [19]. Klinefelter's syndrome [20], hypogonadism [21], exogenous estrogen or testosterone use, orchitis, finasteride and a history of prostate cancer treated with estrogens have been implicated [22, 23]. Alcoholic behavior seems to represent a risk factor for the development of MBC [24]. Exercise appears [13, 25] to reduce risk and tobacco [13, 25, 26] use may also be protective, however other studies are required to confirm the findings.

Epidemiological studies have evaluated occupational and environmental risk factors, including radiation [27, 28], heat [29] and electromagnetic fields exposure [30], as possible contributors to MBC, but some data analysis have been inconclusive.

2.3. Diagnosis and clinical and pathologic features

The most common symptom in MBC patients is a painless subareolar lump, which is centrally located [31–33]. Other ones include a nipple involvement with retraction, discharge and ulceration [2, 33, 34]. The rarity of MBC and the low index of suspicion are responsible for delay in diagnosis. Therefore, male patients presented more advanced stages compared to those in woman [2, 32, 33]. Additionally to clinical history, the diagnosis is made by mammography or ultrasonography in a primary phase [35], and core biopsy that can prevent unnecessary surgical procedures [36]. The predominant histologic type of disease is invasive ductal carcinoma, which forms more than 90% of MBCs [1, 32, 33]. Lobular hystotype is very rare because the male breast lacks terminal lobules [32,

37, 38]. As in women, the majority of MBCs is low grade (I/II), predominantly grade II [17, 32, 39]. MBC has high rates of hormone receptor expression. Approximately, 75-91% and 50-82% of cancers express the estrogen and progesterone receptors, respectively [1, 2, 17, 40]. In contrast, the HER2 proto-oncogene is less likely to be overexpressed in cancers of male breast [40, 41].

2.4. Treatment

Local therapy for breast cancer is generally similar in men and woman. Surgical options for men include breast-conserving therapy and mastectomy [33, 42, 43]. Today, most patients undergo modified radical mastectomy with axillary lymph node dissection or sentinel node biopsy [33, 43, 44]. The first one is clearly important, because men in whom lymph node dissection was omitted have a poorer outcome [2, 45]. However, some complications are associated with this procedure. Consequently, sentinel node biopsy has been adopted as a standard procedure for the assessment of nodal involvement [46–48]. Post-surgical radiotherapy appears to be effective in preventing local relapses in MBC patients [2, 45, 49].

Although the data are limited, available studies suggest that adjuvant chemotherapy and chemotherapy to treat metastatic MBC improves outcomes [45, 50, 51]. Most patients that undergo chemotherapy are young, with high grade tumors and nodal involvement [32, 42, 44]. Adjuvant chemotherapy should be considered in situations where there is an elevated risk for developing primary cancer [32], in cases of rapid disease progression or absence or doubt about endocrine-responsiveness and acting as palliative therapy [33]. Adjuvant hormone treatment is an important part in MBC patients with hormone-receptor positive tumors. In the metastatic setting, tamoxifen clearly has activity against MBC, being associated its use with a reduced risk of recurrences and deaths [31, 42, 52]. However, the tolerance of tamoxifen in men has not been sufficiently studied, being its main side effects: deep venous thrombosis, reduction of libido and impotence [32]. So, in men who have a contraindication to tamoxifen, an aromatase inhibitor is often used, though data analysis supporting this approach are extremely limited [42].

2.5. Prognosis and survival

MBC has generally been related to a worse prognosis than FBC [6, 12, 33, 53]. That has been attributed to the both advanced age at diagnosis and delay detection of cancer [12]. However, several studies report a similar prognosis in men and woman, if patients are matched for stage and age. Estimates for overall survival and disease-free 5-year times are around 50-80% [1, 2, 54] and 45-68% [34, 54, 55], respectively. When grouped by stage of disease, 5-year overall survival is 75-100% for stage I, 50-87% for stage II, 33-64% for stage III, falling to 0-25% for stage IV [1, 33, 54].

As in women, the most important prognostic factors for MBC are tumor size [1, 2] and lymph node status [1, 42]. Men with larger size tumors have higher risk of death and recurrence of disease [1, 45, 56]. Similarly, men with lymph node involvement are associated with poorer prognosis [1, 56, 57]. Also, age at diagnosis appears as a prognostic factor for MBC, with an increased risk of death related to older patients[1, 31, 33, 44]. In univariate analysis, hormone receptor-negative status and high tumor grade were associated with poorer survival, but these factors do not appear to have independent prognostic value on multivariate analysis [1, 33, 44].

3. Materials and Methods

3.1. Study type and data collection

This is a survival study of a retrospective cohort data in patients with MBC for which it has been done an initial descriptive analysis and, subsequently, they have employed nonparametric, semi-parametric and parametric statistical techniques. The study population consisted of all 166 men diagnosed and treated with breast cancer at Portuguese Institute of Oncology, in Lisbon, from 1970 through 2013. There were no criteria for exclusion of patients. All patients were seen individually in a medical consultation, and then properly addressed and treated, being the diagnosis confirmed by histopathology (surgical biopsy). The patient data were obtained by review of the clinical records and consultation of the Regional Cancer Registry. There was no limitation or special authorization request for the acquisition of information about the clinicopathological and biomolecular variables. Because these are parameters of routine evaluation in the staging and monitoring of the disease, or potentially important prognostic factors for this type of research, the variables information acquisition was performed in the anatomical pathology laboratory.

3.2. Population characteristics

In total there are 25 variables, of which 21 are explanatory variables, being directly related to demographic, clinicopathological and biomolecular factors and type of treatment received by the patient. The remaining variables are either response variables i.e., overall survival time and remission time, or their indicator variables of death or disease recurrence. For some explanatory variables there were missing data.

The overall survival time was defined as the time, in months, from disease diagnosis until the occurrence of death due to breast cancer only. Men who did not die due to breast cancer, having died from other causes or stopped going consultations, were considered as censored observations. The remission time represents the time, in months, from the end of treatment (patient is free of cancer symptoms) up to the occurrence of relapse. The censored observations here corresponded to patients for whom no disease recurrence was observed during the study period.

In this study, 56 (33.7%) patients died due to MBC and 62 (37.3%) had recurrence of disease. Mean follow-up times were 81.9 months after diagnosis and 71.6 months after disease treatment.

Demographic and clinicopathologic variables: The mean and median age at diagnosis was 64.9 and 66.5 years, respectively (range 31-89 years). For the majority of the men, family history was negative (92.8%), tumor localization was unilateral (97%) and had no other associated neoplasm (91.6%). The most frequent histologic subtype was ductal cancer (88%). According to the Elston-Ellis grading [58], grade I and II was predominant (30.1% and 55.2%, respectively). Based on TNM classification system recommended by American Joint Committee on Cancer [59], most patients presented at diagnosis pT_4 tumors (42.2%), positive axillary nodes, pN_{1-3} (53.4%) and absence of distant metastasis, pM_0 (90.4%). Thus, there were 27.1% cases of stage 0 or I, 27.1% of stage II, 38% of stage III and 7.8% of stage IV. A summary of these variables is shown in Table 1.

Table 1. Demographic and clinicopathological features

Variable	Categories	Patients	(%)
Age (n=166)	31-39	7	4.2

	40-69	91	54.8
	70-89	68	41
Family history (n=166)	No	154	92.8
	Yes	12	7.2
Bilaterality (n=166)	No	161	97
	Yes	5	3
Histologic type (n=166)	Ductal	146	88
	Others	20	12
Tumor grade (n=163)	I+II	139	85.3
	III	24	14.7
pT (n=166)	$pTis+pT_1$	50	30.1
	pT_{2-3}	46	27.7
	pT_4	70	42.2
pN (n=163)	pN_0	76	46.6
	pN_{1-3}	87	53.4
pM (n=166)	pM_0	150	90.4
	pM_1	16	28.6
Disease stage (n=166)	0+I	45	27.1
	II	45	27.1
	III	63	38
	IV	13	7.8
Other neoplasm (n=166)	No	152	91.6
	Yes	14	8.4

pT (tumor size); pN (lymph node status); pM (distant metastasis status)

Biomolecular variables: Only 77 patients had DNA ploidy information. Of these, 61 had aneuploid DNA content. The positive rates of estrogen receptor (ER) and progesterone receptor (PR) were 94% and 83.5%. Most patients were negative for oncoprotein C-erbB-2 (81.2%) and among 75 patients tested for HER2/neu oncogene amplification by FISH test, 89.3% were negative cases. When these two variables were combined (CERFISH), the prevalence of negative cases was confirmed. Only 24 patients had information about mutation in BRCA2 gene, being the mutation absent in 66.7% of them. Table 2 summarizes biomolecular variables.

Table 2. Biomolecular features

Variable	Categories	Patients	(%)
DNA ploidy (n=77)	Diploid	16	20.8
	Aneuploid	61	79.2
ER (n=166)	Negative	10	6
	Positive	156	94
PR (n=164)	Negative	27	16.5
	Positive	137	83.5
CERBB2 (n=165)	"0"	134	81.2
	"2+"	25	15.2
	"3+"	6	3.6
FISH (n=75)	Negative	67	89.3
	Positive	8	10.7
CERFISH (n=163)	Negative	153	94.9
	Positive	10	6.1
BRCA2 (n=24)	No	16	66.7
	Yes	8	33.3

ER (estrogen receptor expression); PR (progesterone receptor expression); CERBB2 (C-erbB-2oncoprotein expression); FISH (HER2/neu oncogene amplification); CERFISH (+: CERBB2 "3+" or CERBB2 "2+"& FISH+;-:CERBB2"0" or CERBB2"2+"&FISH-); BRCA2 (BRCA2 gene mutation);

Treatment variables: Neoadjuvant treatment was only given in 12.6% of patients and 86.7% of patients underwent surgery. Adjuvant hormone therapy was given in 54.5% of cases, 63.6% of patients received adjuvant radiotherapy and adjuvant chemotherapy was delivered in 32.7% of patientes. A summary of treatment strategies is shown in Table 3.

Table 3. Treatment strategies

Variable	Categories	Patients	(%)
Neoadjuvant therapy (n=166)	No	145	87.3
	Radiotherapy	10	6
	Chemotherapy	11	6.6
Surgery (n=166)	No	22	13.3
	Yes	144	86.7
Hormone therapy (n=165)	No	75	45.5
	Yes	90	54.5
Radiotherapy (n=165)	No	60	36.4
	Yes	105	63.6
Chemotherapy (n=165)	No	111	67.3
	Yes	54	32.7

3.3. Test of independence for pairs of covariates

Chi-square and Fisher's exact test of independence were used to evaluate the hypothesis of non-association between two categorical variables [60]. The latter is especially useful when the number of observations is small (N<20). Significance of the test was defined when corresponding p-value was less than 0.05. In general, identical conclusions were obtained after employing both tests.

Demographic and clinicopathologic variables: Older ages at diagnosis was significantly associated with larger tumor size (p=0.01) and, consequently, more advanced stages of disease (p=0.02). A positive family history was related to mutation in BRCA2 gene (p=0.01). Bilateral tumors were found in 4 of 5 patients with BRCA2 mutation (p<0.01) and 60% of these tumors occurred in patients with positive family history (p=0.01). Histologic type was significantly associated with lymph node status (p=0.01) and progesterone receptor expression (p=0.03). Axillary nodal involvement was presented only in 25% of non-ductal cancers, being more frequent in ductal cancers (57.3%). PR expression was positive in all of non-ductal carcinoma cases. Only 18.8% of ductal carcinomas were PR negative. About 80% of patients with grade III tumors had BRCA2 mutation (p=0.02). pT_4 tumors were associated with a positive lymph node status (p<0.01) and the presence of distant metastasis (p<0.01). 77.6% of patients with pT_4 tumors had a positive lymph node status, while only 18% of pTis or pT_1 tumors had axillary involvement. 15 of 16 cases diagnosed with distant metastasis were classified as pT_4. In all pTis or pT_1 tumors, distant metastases were absent. Lymph node status was significantly associated with distant metastasis (p<0.01). All cases of negative lymph node status had absence of distant metastasis. Also in positive cases distant metastasis were uncommon. A significant association was found between the occurrence of other neoplasms and a family history (p<0.01). 28.6% of patients diagnosed with other neoplasms had a positive family history of cancer. Only 5.3% of patients diagnosed with breast cancer had positive familiar history.

Biomolecular variables: A significant association was also found between both hormone receptors expression (p<0.01). All positive cases for PR were positive to ER. 63% of negative PR cases were positive for ER. PR expression was related to adjuvant chemotherapy delivered (p=0.02). Only 27.9% of positive cases received chemotherapy after surgery. Among negative cases the difference was not significant. Positive cases of C-erbB-2 oncoprotein expression confirmed by FISH test were associated with distant metastasis (p<0.01) and disease stage (p=0.03). Most patients, with or without, distant metastasis were negative to C-erbB-2. In all stages, C-erbB-2 expression was absent.

Treatment variables: Neoadjuvant therapy was given in more advanced stages (p<0.01) and in larger size tumors (p=0.01). About 90.9% and 70% of patients that received chemotherapy and radiotherapy, respectively, were in stage III. Radiotherapy and chemotherapy were given in 80% and 91.8% of pT_4 tumors, respectively. Surgery was significantly associated with tumor size (p<0.01), lymph node status (p<0.01), distant metastasis (p<0.01), and disease stage (p<0.01). More than 95% of patients in early stages (0, I or II) were subjected to surgical procedure. 81% of stage III patients and only 38.4% of patients in stage IV did surgery. Adjuvant hormone therapy was associated with neoadjuvant treatment (p=0.02), family history (p=0.04) and bilaterality of tumor

(p=0.04). Most patients, with or without hormone therapy, did not receive neoadjuvant treatment. All men with bilateral tumor and 83.3% of them with positive family history received hormone therapy. 68.3% of patients with ductal cancer received radiotherapy. Radiotherapy was related to more aggressive tumors, namely to larger size tumors ($p<0.01$) and a positive lymph node status ($p<0.01$). Thus, more than 50% of cases that received adjuvant radiotherapy corresponded to advanced stages of disease (III and IV). Only 33.3% of patients diagnosed in stages 0 or I received radiotherapy. Additionally to radiotherapy, in 40% patients was delivered adjuvant chemotherapy and 81.9% did not receive neoadjuvant therapy. Most of patients diagnosed with bilateral tumor (80%) and positive family history (66.7%) were submitted to adjuvant chemotherapy. Also, chemotherapy was delivered in less differentiated tumors (50% *vs* 29.8%). The majority of patients with positive and negative lymph node status did not receive chemotherapy. 95.5% of patients submitted to chemotherapy did not receive neoadjuvant treatment and, for those ones who received, the treatment was only radiotherapy. Concerning adjuvant treatment, additionally to chemotherapy, 83.3% of patients received hormone therapy and 77.8% radiotherapy.

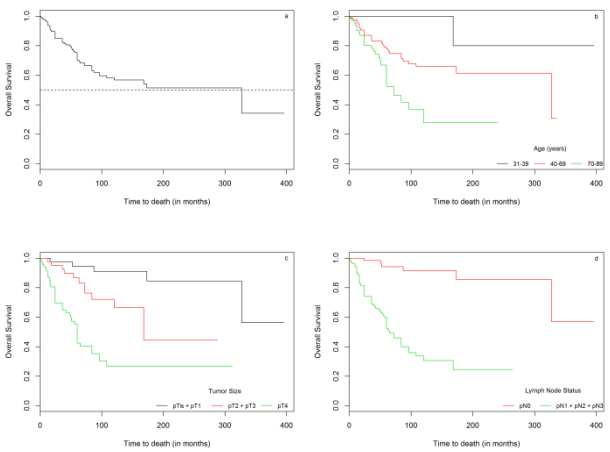
4. Results

4.1. Non-parametric methods

Survival curves were estimated based on the non-parametric Kaplan-Meier estimator [61] and the differences among the category curves were assessed by the log-rank test [62]. A p-value less than 0.05 was considered significant.
Overall survival and disease-free interval curves for the categories of each categorical explanatory variable that showed significant differences among related curves are displayed in Figure 1 and Figure 2, respectively.

Overall survival time

The estimated 5- and 10- year overall survival (OS) rates for all patients were 70.1% and 56.7%, respectively. Median survival time was 327 months. As shown in Table 4, log-rank test indicated that OS was significantly better for patients who had younger age, smaller tumor size, negative lymph node status, negative distant metastasis, less advanced disease at diagnosis, negative amplification of HER2/neu by FISH, C-erbB-2 negative expression, no mutations in BRCA2 gene and underwent surgery. Neoadjuvant therapy and adjuvant radiotherapy were associated with a lower survival of the patients.



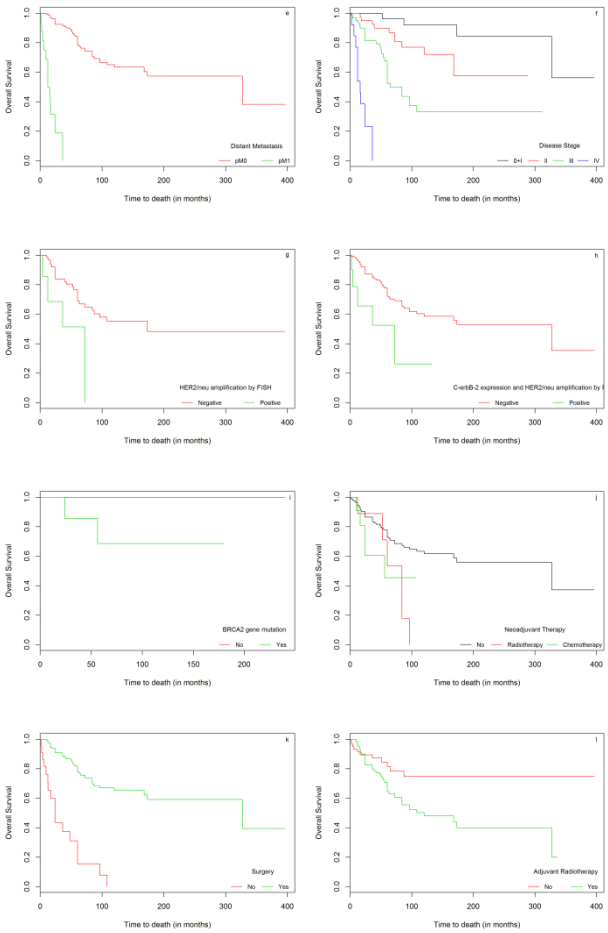


Figure 1: Kaplan-Meier curves of overall survival in respect to: a) entire group, b) age at diagnosis, c) tumor size, d) lymph node status, e) distant metastasis; f) disease stage, g) HER2/neu amplification by FISH, h) C-erbB-2 expression and HER2/neu amplification, i) mutation in BRCA2, j) neoaduvant therapy, k) surgery and l) adjuvant radiotherapy.

Table 4: Estimated $OS_{5/10years}$ rates, median survival time and p-value (log-rank test)

Variable	Categories	Median survival time (months)	$OS_{5/10years}$ (%)	p-value
Age	31-39	-	100/100	0.001
	40-69	327	77.7/65.8	
	70-89	72	52.4/27.7	
pT	$pTis+pT_1$	-	94.7/91.9	<0.001
	pT_{2-3}	168	86.7/66.6	
	pT_4	60	42.4/26.9	
pN	pN_0	-	94.3/91.6	<0.001
	pN_{1-3}	65	52.5/30.6	
pM	pM_0	327	78.4/63.4	<0.001
	pM_1	13.5	0/0	
Stage	0+I	-	96.4/92	<0.001
	II	-	89.9/72.2	
	III	65	52.5/33.2	
	IV	16	0/0	
FISH	Negative	173	69/55.2	0.01
	Positive	72	51.4/0	
CERFISH	Negative	327	72.1/58.6	0.008
	Positive	72	52.5/26.3	
BRCA2	No	-	100/100	0.042
	Yes	-	68.6/68.6	
Neoadjuvant therapy	No	327	72.9/61.7	0.023
	Radiotherapy	84	53.3/0	
	Chemotherapy	56	45.5/45.5	
Surgery	No	24	15.5/0	<0.001
	Yes	327	77.8/65.3	
Radiotherapy	No	-	81.5/74.8	0.013
	Yes	120	64.5/47.9	

The number of patients for each variable is the same used in the population characteristic's analysis.

Remission time

The estimated 5- and 10- year disease-free interval (DFI) rates for all patients were 62.9% and 52.5%, respectively. Median remission time was 132 months. As shown in Table 5, lower tumor grade, smaller tumor size, negative lymph node status, negative distant metastasis status, less advanced disease at diagnosis, positive PR expression and surgery had a positive influence on DFI. Again, neoadjuvant therapy and radiotherapy were associated with lower disease-free survival of the patients. Also, hormone therapy and adjuvant chemotherapy had a negative influence in DFI.

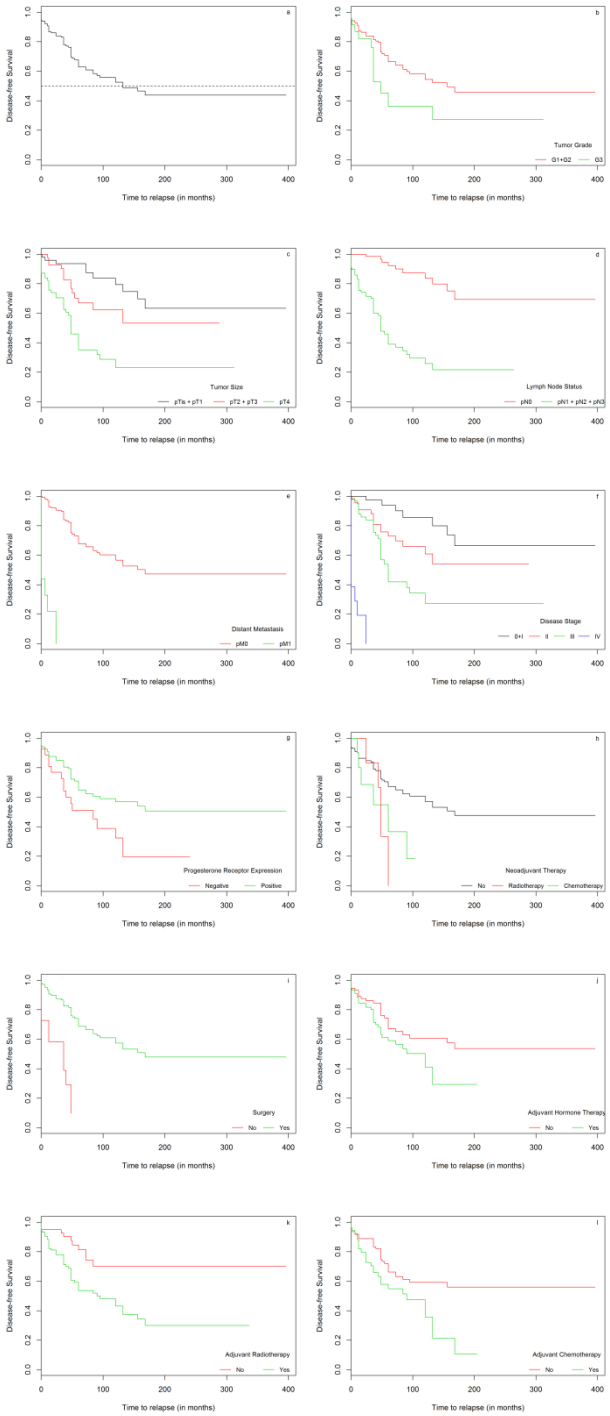


Figure 2: Kaplan-Meier curves of disease-free interval in respect to: a) entire group, b) tumor grade, c) tumor size, d) lymph node status, e) distant metastasis, f) disease stage, g) PR expression, h) neoaduvant therapy, i) surgery, j) adjuvant hormone therapy, k) adjuvant radiotherapy and l) adjuvant chemotherapy.

Table 5: Estimated $DFI_{5/10years}$ rates, median remission time and p-value (log-rank test)

Variable	Categories	Median remission time	$DFS_{5/10years}$ (%)	p-value
Tumor grade	I+II	156	66.4/54.4	0.04
	III	48	36.2/36.2	
pT	$pTis+pT_1$	-	93.7/79.4	<0.001
	pT_{2-3}	-	67/62.2	
	pT_4	48	35.2/23	
pN	pN_0	-	92.3/83.8	<0.001
	pN_{1-3}	48	38.9/25.9	
pM	pM_0	168	67.9/56.7	<0.001
	pM_1	0	0/0	
Stage	0+I	-	93.9/85.6	<0.001
	II	-	72.9/60.8	
	III	60	41.9/27.4	
	IV	0	0/0	
PR	Negative	84	51/32.4	0.012
	Positive	-	64.9/56.9	
Neoadjuvant therapy	No	168	67.3/57.2	0.033
	Radiotherapy	48	0/0	
	Chemotherapy	60	36.6/18.3	
Surgery	No	36	9.7/9.7	<0.001
	Yes	168	68.7/57.4	
Hormone therapy	No	-	67.1/60.7	0.039
	Yes	120	59/41.1	
Radiotherapy	No	-	81.4/70.2	0.001
	Yes	95	53.7/43.1	
Chemotherapy	No	-	66.2/59.2	0.006
	Yes	90	54.9/35.6	

The number of patients for each variable is the same used in the population characteristic's analysis.

4.2. Cox regression model

Initially, (semi-parametric) Cox regression model [63] was adjusted for each explanatory variable to evaluate their influence on both overall survival time and remission time of disease (univariate analysis). After the determination of significant individual covariates on survival and remission times, it was performed a Cox regression model fitting with all explanatory variables simultaneously (multivariate analysis). Covariates that have some missing values were excluded from this analysis, namely FISH, DNA ploidy and BRCA2 mutation variables. Also, bilaterality, family history and other neoplasm variables were excluded because they could cause a bias in the analysis (e.g., bilateral cancer and other neoplasms had a small number of cases, and family history acquisition is very subjective). Data now comprise 158 patients. Wald test was employed to test the nullity of the regression coefficients (β), considering a 10% significance level. Notice that the risk function related to Cox regression model for a patient with covariate vector $\boldsymbol{z}$ at time t is given by $\lambda(t;\boldsymbol{z}) = \lambda_0(t) exp(\boldsymbol{z}'\boldsymbol{\beta})$, where $\lambda_0(t)$ is the baseline risk function.

1. Univariate analyses: The explanatory variables found significant for overall survival and remission times by log-rank test were also significant by Wald test, although the database had been reduced.

2. Multivariate analyses: The variables describing the type of treatment were excluded by clinical indication. Besides their inclusion did not result in any major differences in the results. Disease stage variable was also excluded because its definition results from combination of tumor size, lymph node status and distant metastasis status variables. A backward stepwise procedure based on Akaike's Information Criterion [64] was used to select the Cox model with the major influential prognostic factors. Therefore, the variables included in the initial model were age, histologic type, grade and size of tumor,

nodal status, distant metastasis, expression of estrogen and progesterone hormone receptors and, finally C-erbB-2 oncoprotein expression.

Overall survival time: Table 6 shows the results of the selected Cox model to the data (AIC=387.57).

Table 6: Multivariate analysis of prognostic factors for overall survival time.

Variable	$exp^{\hat{\beta}}$	$C.I._{95\%}$ ($exp^{\hat{\beta}}$)	p-value
Age (years)			
40-69	3.84	[0.49;30.01]	0.200
70-89	5.80	[0.72;46.77]	**0.099**
pT			
pT_{2-3}	1.95	[0.58;6.57]	0.279
pT_4	3.80	[1.17;12.33]	**0.026**
pN			
pN_{1-3}	5.73	[2.11;15.55]	**0.001**
pM			
pM_1	9.71	[4.23;22.32]	**<0.001**

Axillary nodal involvement and existence of distant metastasis were statistically the most significant risk factors to death due to MBC. The relative risk (RR) of death was 5.73 for pN_{1-3} versus pN_0 and 9.71 for pM_1 versus pM_0 tumors. Also, patients with pT_4 tumors and with ages between 70 and 89 years were found to have higher risk of death in comparison with patients who had pTis or pT_1 tumors and ages ranged 31-39, respectively. The RR of death in patients aged 40-69 years and with pT_{2-3} tumors did not show influence on overall survival time.

Remission time: The initial fitted model had C-erbB-2 oncoprotein and ER hormone expression variables, in addition to the variables of the model represented below (AIC=441.73). However, from a clinical point of view, the obtained results were contradictory, because, normally, a worse prognosis is associated with negative estrogen receptors expression and intense labeling of C-erbB-2 oncoprotein. Thus, these two variables were excluded from the model. Table 7 displays the selected Cox model to the data (AIC=448.88).

Table 7: Multivariate analysis of prognostic factors for remission time.

Variable	$exp^{\hat{\beta}}$	$C.I._{95\%}$ ($exp^{\hat{\beta}}$)	p-value
Age (years)			
40-69	8.77	[1.09;70.40]	**0.041**
70-89	16.25	[1.86;141.71]	**0.012**
Tumor Grade			
III	2.57	[1.30;5.08]	**0.006**
pT			
pT_{2-3}	1.16	[0.48;2.80]	0.746
pT_4	1.92	[0.83;4.43]	0.125
pN			
pN_{1-3}	5.67	[2.64;12.22]	**<0.001**
pM			
pM_1	23.18	[8.08;66.50]	**<0.001**
PR expression			
Positive	0.41	[0.22;0.76]	**0.005**

Tumor size was not a significant risk factor for disease recurrence. As for overall survival time, axillary nodal involvement and the occurrence of distant metastasis remained the most statistically significant risk factors. Indeed, the RR of disease-free interval was almost six fold for pN_{1-3} versus pN_0 tumors, and approximately 24 times for pM_1 versus pM_0 tumors. Also, the patients older than 40 years at diagnosis had higher risk of disease recurrence. In addition, tumor grade and PR expression were significant prognostic factors to disease-free survival. The risk of disease recurrence was almost 60% lower for positive PR expression tumors versus negative PR expression ones. A patient with poorly differentiated tumors (grade III) had 2.6 times higher risk of the disease recurrence than a patient with well or moderately differentiated tumors.

Finally, in order to evaluate the quality of the fitted models, we employed a residual analysis and a test of proportionality of the risk functions in the Cox models fitted to overall survival and remission times.

4.3. Disease mapping

In order to evaluate the extra variation between geographic areas (disease mapping) under overall survival study in MBC risk, we performed a (parametric) spatial survival analysis (Weibull regression) under a Bayesian perspective [65].
The dataset consists of 121 patients (72.9%), identified by region, i.e., the county and district in which they resided. Due to the scarcity of patients coming from the North of the country and Islands and the fact that MBC is a rare disease, it was decided to group counties, because some of them had a small number of cases (<2 patients). The final size of dataset encompassed 116 patients involving 16 geographic areas (regions): the districts of Leiria, Santarem, Portalegre, Setúbal, Évora, Beja and Faro and coastline-north, central-north and interior-north Lisbon zones, and the municipalities of Lisbon, Sintra, Cascais/Oeiras, Odivelas, Amadora and Loures. Table 8 summarizes the distribution of MBC incidence by regions.

Table 8: MBC incident by regions

Geographical area	Case number
Leiria	3
Santarém	6
Portalegre	4
Amadora	5
Cascais/Oeiras	7
Lisbon	26
Loures	8
Odivelas	5
Sintra	11
Central-North Lisbon	4
Interior-North Lisbon	1
Coastline-North Lisbon	6
Setúbal	16
Évora	3
Beja	2
Faro	9
Total	116

Deviance Information Criterion (DIC) was used to select. Bayesian Weibull models [66], which were fitted based on the best covariates that explained the overall survival time in the Cox model: age, presence of distant metastases, lymph node status and tumor size. Table 9 contains the structure of two spatial Weibull models and their respective values of DIC. Model 2 was selected due to the slightly lower value of DIC. Notice that these Bayesian spatial survival models were implemented through the software WinBugs [67] after 20000 iterations of sampling and 10000 iterations of burn-in.

Table 9: DIC values based on fitted models

Models	DIC
1: $\log(u_{ij}) = \alpha + \beta_{idade1} Idade_{i1} + \beta_{idade2} Idade_{i2} + \beta_{pT1} pT_{i1} + \beta_{pT2} pT_{i2} + \beta_{pN} pN_i + \beta_{Met} Met_i + b_j$	354.18
2: $\log(u_{ij}) = \alpha + \beta_{idade1} Idade_{i1} + \beta_{idade2} Idade_{i2} + \beta_{pN} pN_i + \beta_{Met} Met_i + b_j$	354.01

Table 10 displays the estimates of the model parameters for the selected model (model 2), while Table 11 displays the *posterior* means of spatial relative risk of death due to MBC, defined as $exp(\boldsymbol{\beta})$. Both quantities were calculated from the spatial Weibull survival model under Bayesian approach to the 16 regions. The spatial relative risk estimates can be visualized in Figure 3. Geographic areas with the greatest impact on the spatial relative risk of MBC are represented by darker shades. Notice that regions having higher risk of death

are Setúbal district and Amadora. On the contrary, the districts of Portalegre and Leiria are the regions that have a smaller influence on the risk of death. However, the values obtained for each region are very close, not allowed an appropriate and effective evaluation of these spatial random effects. These results are justified both by the small size number of patients in each region and by the reduced number of regions.

Table 10: Estimates of the parameters for the Bayesian Weibull model

	Mean	Median	s.d.	$C.I._{95\%}$
α	-10.92	-10.77	1.81	[-14.90;-7.80]
$\beta_{40-69\ anos}$	1.633	1.449	1.321	[-0.412;4.781]
$\beta_{70-89\ anos}$	2.513	2.327	1.330	[0.453;5.652]
$\beta_{met:sim}$	3.175	3.160	0.615	[2.007;4.428]
$\beta_{pN:sim}$	2.152	2.111	0.603	[1.096;3.457]
σ	0.359	0.197	0.421	[0.029;1.545]
τ	1.34	1.33	0.204	[0.968;1.77]

s.d. (standard deviation); C.I. (credible interval)

Table 11: Estimates of the spatial relative risks due to MBC by geographical areas

	Mean	Median	s.d.	$C.I._{95\%}$
$exp(Leiria)$	0.927	0.975	0.230	[0.346; 1.330]
$exp(Santarém)$	0.989	0.993	0.207	[0.569;1.427]
$exp(Portalegre)$	0.924	0.968	0.245	[0.363;1.387]
$exp(Amadora)$	1.161	1.020	0.618	[0.701;2.577]
$exp(Cascais/Oeiras)$	1.044	1.004	0.292	[0.590;1.796]
$exp(Lisbon)$	1.113	1.024	0.306	[0.769;2.011]
$exp(Loures)$	0.984	0.995	0.196	[0.537;1.390]
$exp(Odivelas)$	1.233	1.021	1.519	[0.714;2.925]
$exp(Sintra)$	1.092	1.013	0.370	[0.703;2.017]
$exp(Central - North\ Lisbon)$	1.028	0.999	0.311	[0.591;1.675]
$exp(Interior - North\ Lisboa)$	1.006	0.994	0.392	[0.428;1.674]
$exp(Coastline - North\ Lisbon)$	1.064	1.006	0.340	[0.643;1.920]
$exp(Setúbal)$	1.244	1.045	0.571	[0.809;2.867]
$exp(Évora)$	1.022	0.996	0.298	[0.544;1.709]
$exp(Beja)$	0.992	0.989	0.308	[0.410;1.681]
$exp(Faro)$	0.984	0.974	0.402	[0.295;1.890]

s.d. (standard deviation); C.I. (credible interval)

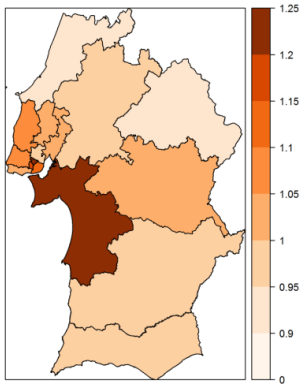


Figure 3: Spatial relative risks due to MBC in each study area

5. Discussion

Because MBC is an uncommon disease, a deeper knowledge and understanding of its etiology and prognostic factors are fundamental to determine the best and most effective type of therapy for a particular patient.

The main aim of this paper was to analyze the overall survival and disease-free interval of 166 males with breast cancer diagnosed and treated in the Portuguese Oncology Institute Francisco Gentil, in Lisbon, between 1970 and 2013. In addition, it was elaborated a spatial survival analysis of the distribution of risks of death in order to obtain exploratory elements for a more comprehensive analysis in future.

5.1. Population characteristics

In this study, it was found an elevated mean and median ages for patients at diagnosis (66.5 and 64.9 years, respectively) [1, 9, 12], confirming an increased incidence of MBC in older men (Table 1) [1, 9, 39]. In most patients, there was no family history of cancer, which corroborates other findings [2, 68, 69]. For patients with complete data, the majority had no mutations in the BRCA2 gene, in contrast to some studies linking increased incidence of MBC with mutations in this gene [18, 70]. Also, it was found a significant association between the presence of mutation in BRCA2 and the family history, although there is no previous evidence that there is a relationship between these factors [15, 71, 72]. In addition, as noted in another series [17], it was verified that patients with mutations in BRCA2 are associated with higher tumor grade (G3). Similar to other studies, the proportion of cases in the main variables analyzed showed the same distribution. The predominant histological type was the ductal carcinoma (88%), a finding similar to other studies [1, 32, 33, 68]. Due to the absence of lobular units in the male breast, there was little frequency of lobular carcinoma (1.2%) [32, 37, 38], which contrasts to that found in women, where more than 10% of cancer cases are of this type [1, 73]. As similar in woman, prevalent tumors are well or moderately differentiated (G1 or G2), with a predominance of G2 [17, 32, 39, 74]. Similarly to that found in other studies, it was observed a higher proportion of patients in stages II (27.1%) and III (38%) [2, 32, 33], diagnosed with pT4 (42.2%) [32], pM_0 (90.4%) [32, 68] and $pN_{1\text{-}3}$ (53.6%) tumors [2, 32, 34, 39, 40, 75]. Positive rates determined for both ER (94%) and PR (83.5%) were slightly higher than those found in other studies [1, 2, 17, 34, 40, 75], where these rates ranged between 75-91% and 50-82%, respectively. Although the literature describes an increased positivity rate of hormone receptors with increasing age [1, 40, 76], the present study found no significant association between both. With regard to the oncoprotein C-erbB-2 expression, it is believed to be less expressed in men than in women [40, 41]. Considering the HER2/neu amplification by FISH test, we found a rate of 6.1% positivity, lying slightly above the 5.3% value determined in another series [75].

Neoadjuvant therapy, adjuvant chemotherapy and radiotherapy were correlated with tumor size, and consequently to the disease stage. Patients diagnosed at more advanced stages and with larger tumors and/or extension are more likely to receive neoadjuvant therapy. Surgical procedure was performed in 86.7% of cases. Only 3.5% of those who underwent surgery belonged to stage IV and 54.5% of patients who did not belonged to stage III. 98% of patients in stage 0 underwent surgery for breast cancer treatment. This corroborates the fact that patients in more advanced stages usually are not subjected to surgical procedures (inoperable tumors). In relation to the treatment administered after surgery, it was observed that 63.6%, 54.5% and 36.7% received radiotherapy, hormone therapy and chemotherapy, respectively. An association between the delivery of chemotherapy and the tumor grade was found, showing that in patients with poorly differentiated cancers (G3), chemotherapy is the preferred treatment, which is in agreement with the expected [42]. Other studies indicate an increased use of chemotherapy in advanced disease stages and in cases with lymph node involvement [32, 44]. Approximately 78.3% of patients with pT_4 tumors and 79.3% of those with

nodal involvement (pN_{1-3}) underwent radiotherapy after surgery. The radiotherapy is associated with more aggressive tumors, i.e. with larger sizes and/or extension and lymph node involvement [42]. The hormonal treatment is usually given in cases with positive expression of hormone receptors and in patients diagnosed at an older age [42]. However in the present study, it was not found a significant association between these variables and the realization of hormone therapy. It was observed that the hormone treatment was given to all men with bilateral cancer and most of those who had positive family history of cancer (83.3%).

5.2. Survival analysis

The estimated 5-year overall survival and disease-free rates in the entire group were 70.1% and 62.9%. Comparing with other results [1, 2, 34, 54, 55], the obtained values are close. The estimated values for these rates at 10 years were 56.7% and 52.5%, respectively. The result for 10-year overall survival rate is higher than the survival rates found in other studies [1, 2, 42, 55]. OS was significantly longer for patients who had younger age, smaller tumor size, negative lymph node status, negative distant metastasis status, less advanced disease at diagnosis, negative amplification of HER2/neu by FISH, C-erbB-2 negative expression, no mutations in BRCA2 gene and underwent surgery. Neoadjuvant therapy and adjuvant radiotherapy were associated with a lower survival of patients. Considering the disease stage, the 5-year survival rates were 96.4%, 89.9%, 52.5% and 0% for stages 0 or I, II, III and IV, respectively. These values are within the range of those determined in earlier studies (75-100% for stage I, 50 to 87% for stage II, 33 to 64% for stage III and 0-25% for stage IV) [1, 33, 54]. Lower tumor grade, smaller tumor size, negative lymph node status, negative distant metastasis status, less advanced disease at diagnosis, positive PR expression and surgery had a positive influence on DFI. Again, neoadjuvant therapy and radiotherapy were associated with poorer disease-free survival of patients. In addition, hormone therapy and adjuvant chemotherapy had a negative influence in DFI.

Fitting a Cox model, taking into account only one of the variables (univariate analysis), it was observed that the risk factors that were statistically significant in the survival time of patients do not differ from those determined by the log-rank test. Most variables that significantly affect the disease-free interval were the same those affecting the overall survival time (with the exception of CERFISH), with the addition of PR expression, tumor grade, and the adjuvant treatments hormone therapy and chemotherapy. These results were consistent with those determined by the log-rank test. In contrast to some studies, the tumor grade and the PR expression were not significant for the survival time in univariate analyses [1, 33, 44, 57]. After selecting the Cox model taking into account the AIC and its respective fit, the risk of death due to MBC is higher for older men, aged between 70 and 89 years (RR=5.8), confirming previous results [1, 31, 33, 44]. Patients diagnosed with cancers classified as pT_4 (RR=3.8), pN_{1-3} (RR=5.7) and pM_1 (RR=9.7) are associated with a worse prognosis. The incidence of disease recurrence is associated with older ages ($RR_{40-69years}$=8.8 and $RR_{70-89years}$=16.3), poorly differentiated tumors (RR=2.6), positive lymph node status pN_{1-3} (RR=5.7) and the presence of distant metastasis (pM_1) (RR=23.21). A smaller disease recurrence risk was related to a positive PR expression (RR=0.41). In addition, in patients diagnosed with larger size/extension tumors, the recurrence risk of disease was higher (pT_{2-3} (RR=1.2) and pT_4 (RR=1.9), but did not show significant influence.

As expected, tumor size, lymph node status and presence of distant metastases have a significant influence on the risk of death and occurrence of disease relapse (with exception of tumor size for the latter) [1, 2, 34, 42, 54]. However, one of these studies considers the nodal status as the only significant prognostic factor in the overall survival and disease-free interval [54]. It was found that the disease recurrence risk values obtained for the variables ER and oncoprotein C-erbB-2 "3" expression did not clinically correspond to the previously expected, since generally higher risk of relapse is associated with negative expression of estrogen receptors, as well as the intense labeling of the C-erbB-2 oncoprotein. Careful data observation suggests that these results were possibly biased due to the small number of cases, either with lack of expression of estrogen receptors or with intense labeling of C-erbB-2 in relation to the others. Therefore, it was decided to remove these two variables from the Cox model, and fit the model again. For both Cox models (overall survival and remission time) the results of residual analysis and evaluation of the proportional risk functions supported the suitability of the fitted Cox models.

5.3. Spatial analysis

The vast majority of MBC cases corresponds to patients residing in central and southern regions of Portugal, with higher incidence in the municipalities of Lisbon and district of Setúbal (Table 8).

Considering 16 regions (counties or districts) and fitting the (parametric) spatial Weibull survival, some of the explanatory variables were considered influential on overall survival time, such as age, lymph node status and the presence of distant metastases at diagnosis. It was also estimated the spatial relative risk of death due to MBC. The observed spatial pattern showed that the highest risk of death was in the district of Setúbal and the municipality of Amadora, being lower in the districts of Leiria and Portalegre (Table 11, Figure 3). This study was done as exploratory purpose, since the obtained results did not allow us to evaluate the existence of a spatial random effect. The reason for this stems essentially from the fact that the subject number in each region and the number of regions used were reduced.

6. Conclusions

The results obtained in this work showed the clinical and epidemiological profile of patients diagnosed with MBC, as well as the overall survival and disease-free interval risk functions for them, according to demographic, clinicopathological and biomolecular features and type of therapy performed. It was also evaluated the prognostic value of some variables in overall survival and disease-free interval by fitting Cox regression model. From the obtained results, we concluded that: (1) the significant risk factors associated with the overall survival are the age at diagnosis, tumor size, lymph node status and the distant metastases status; (2) the significant risk factors associated with the disease-free interval are the age at diagnosis, tumor grade, nodal status, distant metastases status and PR expression. Tumor size did not show to be a significant risk factor for disease recurrence; (3) it was not possible to observe a relevant spatial pattern of the risk of death due to MBC.

Although most of the presented results are consistent with the previously studies, it was found that there are some discrepancies, namely in the Cox model for the remission time of disease. As mentioned above, the estimated risk of disease recurrence for the C-erbB-2 "3+" expression goes against the clinically expected because in these cases the risk should be higher than in "0" cases. Also, patients whose tumors expressed ER positivity rates had a higher recurrence risk, which not corresponds to the expected. These results can be related to limitations derived from the sample itself, namely: a) the lack of information at diagnosis on some of the variables

due to non-existence or intermittent use of some laboratorial techniques during such a long follow-up period; b) a little knowledge about the disease etiology (particularly for patients diagnosed in the 70's and 80's); c) the asymmetry of MBC distribution of covariates for each category; d) the methods of collecting information is subjective, such as family history.

Finally, it should be noted that this complex public health problem, which represents breast cancer worldwide, requires special attention by the scientific community, health care providers, health managers and the general public. Therefore, it is extremely important to carry on doing research to get knowledge of predictive and prognostic factors for determining the best and most effective type of therapy for patients and the tumor's response to a given treatment related to breast cancer.

Bibliography

1.Giordano SH, Cohen DS, Buzdar AU, et al. (2004) Breast carcinoma in men: a population-based study. Cancer 101:51–57. doi: 10.1002/cncr.20312

2.Cutuli B, Lacroze M, Dilhuydy JM, et al. (1995) Male breast cancer: results of the treatments and prognostic factors in 397 cases. European Journal of Cancer 31A:1960–1964.

3.Willsher PC, Leach H, Ellis I, et al. (1997) A comparision outcome of male breast cancer with female breast cancer. The American Journal of Surgery 173:1995–1998.

4.Siegel R, Naishadham D, Jemal A (2013) Cancer Statistics, 2013. 63:11–30. doi: 10.3322/caac.21166.

5.O'Malley CD, Prehn AW, Shema SJ, Glaser SL (2002) Racial/ethnic differences in survival rates in a population-based series of men with breast carcinoma. Cancer 94:2836–2843. doi: 10.1002/cncr.10521

6.Greif JM, Pezzi CM, Klimberg VS, et al. (2012) Gender differences in breast cancer: analysis of 13.000 breast cancers in men from the National Cancer Data Base. Annals of Surgical Oncology 19:3199–3204. doi: 10.1245/s10434-012-2479-z

7.Miao H, Verkooijen HM, Chia K, et al. (2011) Incidence and outcome of male breast cancer: an international population-based study. Journal of Clinical Oncology 29:4381–4386. doi: 10.1200/JCO.2011.36.8902

8.Contractor KB, Kaur K, Rodrigues GS, et al. (2008) Male breast cancer: is the scenario changing. World journal of surgical oncology 6:58. doi: 10.1186/1477-7819-6-58

9.Hodgson NCF, Button JH, Franceschi D, et al. (2004) Male breast cancer: is the incidence increasing? Annals of Surgical Oncology 11:751–755. doi: 10.1245/ASO.2004.01.001

10.Fentiman IS, Fourquet A, Hortobagyi GN (2006) Male breast cancer. Lancet 367:595–604. doi: 10.1016/S0140-6736(06)68226-3

11.Curado MP, Edwards B, Shin HR, et al. (2007) Cancer Incidence in Five Continents, Vol.IX, 160th ed., pp. 532–537.

12.Gnerlich JL, Deshpande AD, Jeffe DB, et al. (2011) Poorer survival outcomes for male breast cancer compared with female breast cancer may be attributable to in-stage migration. Annals of Surgical Oncology 18:1837–44. doi: 10.1245/s10434-010-1468-3

13.Brinton LA, Richesson DA, Gierach GL, et al. (2008) Prospective evaluation of risk factors for male breast cancer. Journal of the National Cancer Institute 100:1477–1481. doi: 10.1093/jnci/djn329

14.Ewertz M, Holmberg L, Tretli S, et al. (2001) Risk factors for male breast cancer. Acta Oncologica 40:467–471.

15.Evans DG, Bulman M, Young K, et al. (2001) High detection rate for BRCA2 mutations in male breast cancer families from North West England. Familial Cancer 1:131–133.

16.Ottini L, Masala G, Amico CD, et al. (2003) BRCA1 and BRCA2 Mutation Status and Tumor Characteristics in Male Breast Cancer : A Population-based Study in Italy. Cancer Research 63:342–347.

17.Ottini L, Rizzolo P, Zanna I, et al. (2009) BRCA1/BRCA2 mutation status and clinical-pathologic features of 108 male breast cancer cases from Tuscany: a population-based study in central Italy. Breast Cancer Research and Treatment 116:577–586. doi: 10.1007/s10549-008-0194-z

18.Tai YC, Domchek S, Parmigiani G, Chen S (2008) Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. Journal of the National Cancer Institute 99:1811–1814.

19.D'Avanzo B, La Vecchia C (1995) Risk factors for male breast cancer. British Journal of Cancer 71:1359–1362.

20.Evans DB, Crichlow RW (1987) Carcinoma of the male breast and Klinefelter's syndrome: is there an association? Cancer Journal for Clinicians 37:246–251.

21.Medras M, Filus A, Jozkow P, et al. (2006) Breast cancer and long-term hormonal treatment of male hypogonadism. Breast Cancer Research and Treatment 96:263–265. doi: 10.1007/s10549-005-9074-y

22.Park S, Kim J-H, Koo J, et al. (2008) Clinicopathological characteristics of male breast cancer. Yonsei Medical Journal 49:978–86. doi: 10.3349/ymj.2008.49.6.978

23.Thellenberg C, Malmer B, Tavelin B, Grönberg H (2003) Second primary cancers in men with prostate cancer: an increased risk of male breast cancer. The Journal of Urology 169:1345–1348. doi: 10.1097/01.ju.0000056706.88960.7c

24.Guénel P, Cyr D, Sabroe S, et al. (2004) Alcohol drinking may increase risk of breast cancer in men: a European population-based case-control study. Cancer Causes & Control 15:571–580. doi: 10.1023/B:CACO.0000036154.18162.43

25.Hsing AW, McLaughlin JK, Cocco P, et al. (1998) Risk factors for male breast cancer (United States). Cancer Causes & Control 9:269–275.

26.Casagrande JT, Hanisch R, Pike MC, et al. (1988) A case-control study of male breast cancer. Cancer Research 48:1326–1330.

27.Thomas DB, Rosenblatt K, Jimenez LM, et al. (1994) Ionizing radiation and breast cancer in men (United States). Cancer Causes & Control 5:9–14.

28.Ron E, Ikeda T, Preston DL, Tokuoka S (2005) Male breast cancer incidence among atomic bomb survivors. Journal of the National Cancer Institute 97:603–605. doi: 10.1093/jnci/dji097

29.Cocco P, Figgs L, Dosemeci M, et al. (1998) Case-control study of occupational exposures and male breast cancer. Occupational and Environmental Medicine 55:599–604.

30.Pollán M, Gustavsson P, Floderus B (2001) Breast cancer, occupation, and exposure to electromagnetic fields among Swedish men. American Journal of Industrial Medicine 39:276–285.

31.Ahmed A, Ukwenya Y, Abdullahi A, Muhammad I (2012) Management and outcomes of male breast cancer in Zaria, Nigeria. International Journal of Breast Cancer. doi: 10.1155/2012/845143

32.Bourhafour M, Belbaraka R, Souadka A, et al. (2011) Male breast cancer: a report of 127 cases at a Moroccan institution. BMC Research Notes 4:219–223. doi: 10.1186/1756-0500-4-219

33.Ribeiro GG, Swindell R, Harris M, et al. (1996) A review of the management of the male breast carcinoma based on an analysis of 420 treated cases. The Breast 5:141–146.

34.Goss PE, Reid C, Pintilie M, et al. (1999) Male breast carcinoma: a review of 229 patients who presented to the Princess Margaret Hospital during 40 years: 1955-1996. Cancer 85:629–639.

35.Jiang L, Xue X, Chen X (2002) Diagnostic and therapeutic analysis to 5 cases of male breast cancer. The Chinese-German Journal of Clinical Oncology 1:175–176. doi: 10.1007/BF02851719

36.Westenend PJ (2003) Core needle biopsy in male breast lesions. Journal of Clinical Pathology 56:863–865.

37.Brinton LA, Carreon JD, Gierach GL, et al. (2011) Etiologic factors for male breast cancer in the U.S. Veterans affairs medical care system database. Breast Cancer Research and Treatment 119:185–192. doi: 10.1007/s10549-009-0379-0.

38.Burga AM, Fadare O, Lininger RA, Tavassoli FA (2006) Invasive carcinomas of the male breast: a morphologic study of the distribution of histologic subtypes and metastatic patterns in 778 cases. Virchows Archiv 449:507–12. doi: 10.1007/s00428-006-0305-3

39.Anderson WF, Jatoi I, Tse J, Rosenberg PS (2010) Male breast cancer: a population-based comparison with female breast cancer. Journal of Clinical Oncology 28:232–239. doi: 10.1200/JCO.2009.23.8162

40.Muir D, Kanthan R, Kanthan SC (2003) Male versus female breast cancers: a population-based comparative immunohistochemical analysis. Archives of Pathology & Laboratory Medicine 127:36–41.

41.Bloom KJ, Govil H, Gattuso P, et al. (2001) Status of HER-2 in male and female breast carcinoma. American Journal of Surgery 182:389–392.

42.Cutuli B, Le-Nir CC-S, Serin D, et al. (2010) Male breast cancer. Evolution of treatment and prognostic factors. Analysis of 489 cases. Critical Reviews in Oncology/Hematology 73:246–254. doi: 10.1016/j.critrevonc.2009.04.002

43.Zhou F-F, Xia L-P, Guo G-F, et al. (2010) Changes in therapeutic strategies in Chinese male patients with breast cancer: 40 years of experience in a single institute. Breast 19:450–455. doi: 10.1016/j.breast.2010.04.007

44.Ravi A, Bang H, Karsif K, Nori D (2012) Breast cancer in men: prognostic factors, treatment patterns, and outcome. American Journal of Men's Health 6:51–58. doi: 10.1177/1557988311416495

45.Yildirim E, Berberoğlu U (1998) Male breast cancer: a 22-year experience. European Journal of Surgical Oncology 24:548–552.

46.Gentilini O, Chagas E, Zurrida S, et al. (2007) Sentinel lymph node biopsy in male patients with early breast cancer. The Oncologist 12:512–515. doi: 10.1634/theoncologist.12-5-512

47.Flynn LW, Park J, Patil SM, et al. (2008) Sentinel lymph node biopsy is successful and accurate in male breast carcinoma. Journal of the American College of Surgeons 206:616–621. doi: 10.1016/j.jamcollsurg.2007.11.005

48.Boughey JC, Bedrosian I, Meric-Bernstam F, et al. (2006) Comparative analysis of sentinel lymph node operation in male and female breast cancer patients. Journal of the American College of Surgeons 203:475–480. doi: 10.1016/j.jamcollsurg.2006.06.014

49.Atahan L, Yildiz F, Selek U, et al. (2006) Postoperative radiotherapy in the treatment of male breast carcinoma: a single institute experience. Journal of the National Medical Association 98:559–563.

50.Patel HZ, Buzdar AU, Hortobagyi GN (1989) Role of adjuvant chemotherapy in male breast cancer. Cancer 64:1583–1585.

51.Ribeiro GG, Swindell R (1992) Adjuvant tamoxifen for male breast cancer (MBC). British Journal of Cancer 65:252–254.

52.Fentiman IS (2013) Endocrine therapy for male breast cancer. Journal of Steroids & Hormonal Science 4:1–5. doi: 10.4172/2157-7536.1000112

53.Zhou F, Huang R, Jiang J, et al. (2011) A meta-analysis based on case-control studies shows the similar prognosis between male and female patients with breast cancer. The Chinese-German Journal of Clinical Oncology 10:311–316. doi: 10.1007/s10330-011-0765-z

54.Yoney A, Kucuk A, Unsal M (2009) Male breast cancer: a retrospective analysis. Cancer Radiothérapie 13:103–107. doi: 10.1016/j.canrad.2008.11.011

55.Baojiang L, Tingting L, Gang L, Li Z (2012) Male breast cancer: A retrospective study comparing survival with female breast cancer. Oncology Letters 4:642–646. doi: 10.3892/ol.2012.809

56.Zhou F, Xia LP, Wang X, et al. (2010) Analysis of prognostic factors in male breast cancer : a report of 72 cases from a single institution. Chinese Journal of Cancer 29:184–188.

57.Wu D, Li C, Fan Z, Zhang S (2005) Male breast cancer. A report of 34 cases. Chinese Journal of Cancer Research 17:298–300.

58. Elston CW, Ellis IO (1991) Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology 19:403–410.

59.Edge SB., Byrd DR., Compton CC., et al. (2010) AJCC Cancer staging manual, 7th ed. 649.

60.Paulino CD, Singer JM (2006) Análise de Dados Categorizados. Edgard Blucher, São Paulo, pp. 648.

61.Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. Journal of the American Statistical Association 53:457–481.

62.Mantel N (1966) Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemotherapy Report 50:163–170.

63.Cox DR (1972) Regression models and life tables. Journal of the Royal Statistical Society B 34:187–220.

64.Akaike H (1973) Information theory and an extension of the maximum likelihood principle. In: Petrov BN, Csaki F (eds) Proceedings of the Second International Symposium on Information Theory. Akademiai Kiado, Budapest, pp 267–281

65.Silva GL, Dean CB (2006) Uma introdução à análise de modelos espaço-temporais para taxas, proporções e processos de multi-estados. Associação Brasileira de Estatística, São Paulo, pp. 111.

66.Paulino CD, Amaral Turkman MA, Murteira B (2003) Estatística Bayesiana. Fundação Calouste Gulbenkian, Lisboa

67.Lunn DJ, Thomas A, Best N, Spiegelhalter D (2000) WinBUGS – A Bayesian modelling framework: concepts, structure, and extensibility. 10:325–337.

68.McLachlan SA, Erlichman C, Liu FF, et al. (1996) Male breast cancer: an 11 year review of 66 patients. Breast Cancer Research and Treatment 40:225–230.

69.Rayson D, Erlichman C, Suman VJ, et al. (1998) Molecular markers in male breast carcinoma. Cancer 83:1947–1955.

70.Ottini L, Silvestri V, Rizzolo P, et al. (2012) Clinical and pathologic characteristics of BRCA-positive and BRCA-negative male breast cancer patients: results from a collaborative multicenter study in Italy. Breast Cancer Research and Treatment 134:411–418. doi: 10.1007/s10549-012-2062-0

71.Ding YC, Steele L, Kuan C-J, et al. (2011) Mutations in BRCA2 and PALB2 in male breast cancer cases from the United States. Breast Cancer Research and Treatment 126:771–8. doi: 10.1007/s10549-010-1195-2

72.Friedman LS, Gayther SA, Kurosaki T, et al. (1997) Mutation analysis of BRCA1 and BRCA2 in population male breast cancer. American Journal of Human Genetics 60:313–319.

73.Anderson WF, Devesa SS (2005) In situ male breast carcinoma in the Surveillance, Epidemiology, and End Results database of the National Cancer Institute. Cancer 104:1733–1741. doi: 10.1002/cncr.21353

74.Ge Y, Sneige N, Eltorky MA, et al. (2009) Immunohistochemical characterization of subtypes of male breast carcinoma. Breast Cancer Research 11:R28. doi: 10.1186/bcr2258

75.Rudlowski C, Friedrichs N, Faridi A, et al. (2004) Her-2/neu gene amplification and protein expression in primary male breast cancer. Breast Cancer Research and Treatment 84:215–223. doi: 10.1023/B:BREA.0000019953.92921.7e

76.Anderson WF, Althuis MD, Brinton LA, Devesa SS (2004) Is male breast cancer similar or different than female breast cancer? Breast Cancer Research and Treatment 83:77–86. doi: 10.1023/B:BREA.0000010701.08825.2d