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Original Research

Pathological characterisation of male breast cancer: Results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program

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KEYWORDS
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Histological grade

Abstract ***Aim:*** Several prognostic histological features have been established in female breast cancer (BC), but it is unknown whether these can be extrapolated to male BC patients. The aim of this study was to evaluate the prognostic value of several histological features in a large series of male BC.
Methods: Central pathology review was performed for 1483 male BCs collected through part 1 of the European Organisation for Research and Treatment of Cancer (EORTC) International Male BC Program. Pathology review included histological subtype, grade, mitotic activity index (MAI), presence of a fibrotic focus and density of tumour-infiltrating lymphocytes (TILs). These features were correlated with clinical outcome. The relationship between these features and surrogate molecular subtypes using immunohistochemistry was also assessed.
Results: Median follow-up for overall survival (OS) was 7.1 years. Overall histological grade was not significantly associated with OS ($p = 0.129$). MAI, the presence of a fibrotic focus and a low TIL density however were correlated with unfavourable OS ($p = 0.023$, $p = 0.004$ and $p = 0.011$, respectively). BC subtype correlated with TIL density ($p = 0.015$), as we observed a higher density for human epidermal growth factor receptor type 2 (HER2) positive BC compared to luminal HER2-negative subtype. No association was observed between subtype and fibrotic focus.
Conclusions: Histologic grade was not significantly correlated with clinical outcome in this series, unlike what is seen in female patients. These results contribute to our understanding of male BC and indicate the importance of further research on the optimisation of risk stratification and treatment decisions for male BC patients.

1. Introduction

Male breast cancer (BC) is uncommon, accounting for less than 1% of all BCs [1]. Because of this low prevalence, characterising this disease has been tremendously challenging, and current management is largely following female BC treatment algorithms. However, although male and female BCs share several similarities, they also have many differences. For example, male BC occurs at a higher age, and men usually present with a more advanced clinical stage [2,3]. In addition, several studies reported that male and female BCs differ regarding molecular characteristics, including gene expression profiles, epigenetic alterations and the distribution of surrogate BC subtypes based on immunohistochemical surrogates [4–7]. In male BC, the frequency of luminal A subtype and to a lesser extent luminal B subtype is higher, whilst the frequency of non-luminal human epidermal growth factor receptor type 2 (HER2) positive and basal-like subtypes is lower than those reported for female BC [8–10].

The majority of male BCs are ductal carcinomas while lobular carcinomas seem to be rare in male BC patients, accounting for 1% of all male BCs [11]. However, current data are limited as they are mainly based on small series without central pathology review. Besides, data regarding several other histological features in male BC, including Mitotic Activity Index (MAI), lymphovascular invasion, presence of a fibrotic focus and density of tumour-infiltrating lymphocytes (TILs) are scarce [12–16].

In female BC, histological grade is a well-established prognostic feature [17–19]. In male BC, there is no consensus regarding the prognostic impact of histological grade [3,20], so the identification of additional histological features with a potential prognostic value is warranted.

Density of TILs and the presence of a fibrotic focus are not routinely assessed in daily practice, but have been widely studied in female BC and other solid tumours [21–24]. In female BC, a higher density of TILs has been reported to be associated with inhibition of tumour progression and to a better response to chemotherapy, especially in triple negative and HER2-positive BC [25–27]. Regarding male BC, data regarding the presence and significance of TILs is based on a series with 18 male BC patients only, so no definite conclusions could be drawn [28]. The presence of a fibrotic focus has been reported in 25% of male BC cases [29].

In summary, with only a few, mainly small single-center studies available regarding histological features in male BC, this is a field that needs further research in order to improve risk stratification and patient management. Our study population, which includes 1483 male BC patients, is the largest male BC population with central pathology review studied so far, which enables further characterisation of male BC.

2. Materials and methods

2.1. Patients

Clinicopathological data were obtained from the retrospective part of the EORTC 10085/TBCRC/BIG/NABCG International Male BC Program: a large international joint analysis of clinical and biological data of male BC patients, diagnosed between 1990 and 2010; European Organisation for Research and Treatment of Cancer (EORTC); Translational Breast Cancer Research Consortium (TBCRC); Breast International Group (BIG); North American Breast Cancer Groups (NABCG). Details of this study have been described previously [30]. Briefly, invasive BC in males above 18 years of age at the time of diagnosis was included if a formalin-fixed paraffin-embedded (FFPE) tissue sample of the excision specimen was accessible for central pathology review and if enough follow-up existed. In this study we adhered to the Declaration of Helsinki and the Code of Conduct of the Federation of Medical Scientific Societies in The Netherlands (http://www.fmwv.nl). When applicable in the site, informed consent from patients according to the International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use/ Good Clinical Practices guidelines (ICH/GCP) and applicable national laws was obtained.

2.2. Central pathology review

Out of the 1800 eligible male BC patients enrolled in the main study, only patients with available central lab assessments were analysed (N = 1483) for the present substudy. For each patient, one tumour tissue block was centrally collected. A tissue microarray (TMA) was constructed for central immunohistochemical (IHC) staining assessment of oestrogen receptor (ER), progesterone receptor (PgR), HER2 and Ki67. ER and PgR were scored according to the Allred scoring system[31]. HER2 status was scored according to the American Society of Clinical Oncology (ASCO)-College of American Pathologists (CAP) guidelines [32]. In one of the European central labs (The Netherlands), central review of histological features was performed by a dedicated breast pathologist (CvD or PvD), based on a haematoxylin and eosin (H&E) stained whole tissue slide (N = 1203 out of 1483; the remaining cases were included in the TMA, but whole slides were not available for review). This included histological subtyping (according to the World Health Organisation [WHO] classification), grading (according to the modified Bloom and Richardson score), presence of a fibrotic focus, density of TILs and lymphovascular invasion [17]. In some cases, additional immunohistochemical stainings were performed (e.g. E-cadherin) to improve subtyping. A fibrotic focus was defined according to the criteria described by van den Eynden *et al.* [33]. Fig. 1 provides an example of a male BC with a fibrotic focus. Density of TILs was scored in four categories (minimal, mild, moderate and severe) according to Lee *et al.* [14], as illustrated in Fig. 2. The presence of

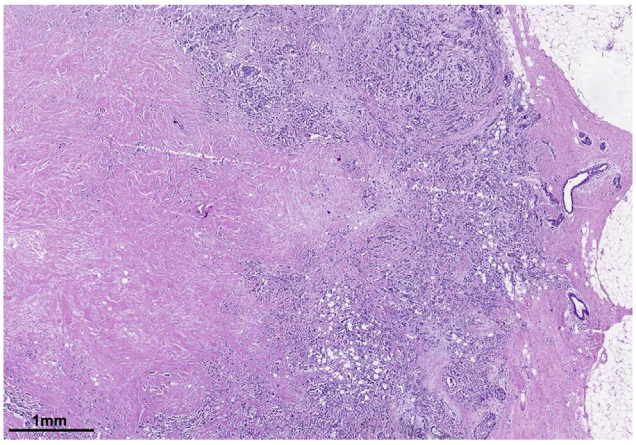

Fig. 1. Example of an invasive ductal carcinoma with a fibrotic focus (left) surrounded by a cellular zone of infiltrating tumour cells at the periphery.

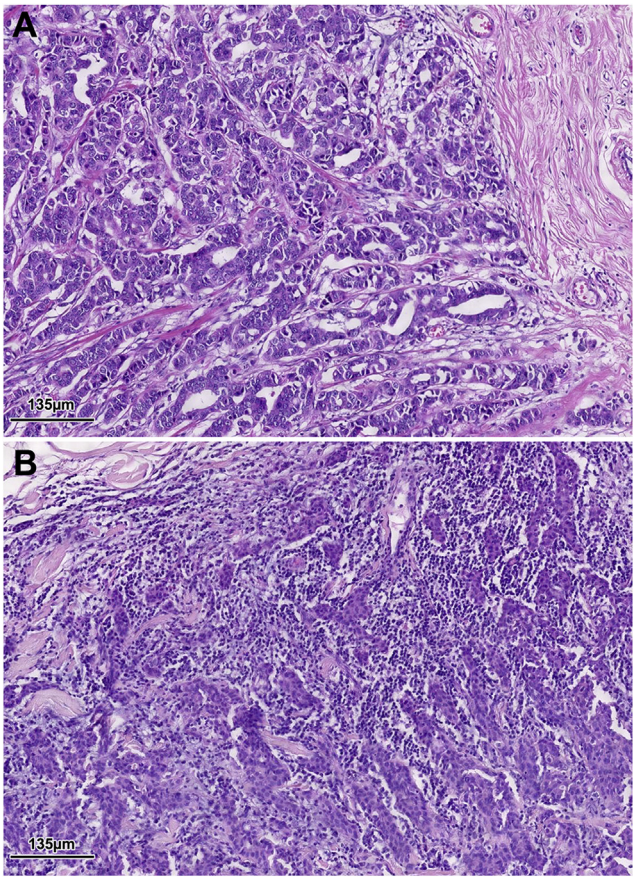

Fig. 2. Examples of male BC cases with a minimal (A) and severe (B) density of TILs.

lymphovascular invasion outside the invasive component was recorded as absent or present. IHC-based surrogate BC subtypes were defined according to the 2013 St. Gallen consensus guidelines (referred to as surrogate BC subtypes) [34].

2.3. Statistics

The analyses that correlate histological features with clinical outcome were restricted to patients with non-metastatic (M0) disease at diagnosis. These survival analyses are summarised by the Kaplan–Meier curves, hazard ratios (HRs) and their associated 95% Wald confidence intervals and the score test p-value in the univariate Cox Model. Relapse-free survival (RFS) was defined as the time until locoregional recurrence, distant progression or death due to any cause. Overall Survival (OS) was defined as the time until death due to any cause. Patients without an event for the above end-points were censored at the last date known to be alive. The end-points were calculated from the time of first diagnosis. Additional analyses include the assessment of association between histological features (fibrotic focus and TILs) and surrogate BC subtype, for all patients with known subtype, irrespective of the metastatic status. In the analysis with surrogate BC subtype, a Fisher exact test was used for fibrotic focus and a trend test (in the proportional odds model) for TILs.

3. Results

3.1. General patient- and tumour characteristics

Clinicopathological features of 1483 male BC patients are shown in Tables 1 and 2. Patients' age ranged from 25 to 98 years (median age: 68.4 years). The majority of M0 patients (95.9%) were treated with a mastectomy; the remaining cases (4.0%) were treated with breast-conserving surgery or received no surgery (0.1%). Median follow-up was 6 years for RFS and 7.1 years for OS. The most frequent histological subtype was invasive ductal carcinoma not otherwise specified (86.6%). Invasive lobular carcinomas (classic or a variant) were rare and only seen in 1.4% of cases. Carcinomas were graded as grade 1 (21.8%), grade 2 (50.1%) or grade 3 (28.1%). Based on immunohistochemistry, the majority of carcinomas were classified as luminal A (41.9%) or luminal B (57.1%). Non-luminal HER2-positive and basal subtypes were infrequent (0.1% and 1%, respectively).

3.2. Histological grade

Overall histological grade was not significantly correlated with RFS (p = 0.099, HR = 1.19, 95% CI 0.85–1.67 for grade 2 versus grade 1 and HR = 1.5, 95% CI 1.02–2.20 for grade 3 versus grade 1) or OS (p = 0.129, HR = 1.27, 95% CI 0.95–1.70 for grade 2 versus grade 1 and HR = 1.39, 95% CI 1.00–1.93 for grade 3 versus grade 1) [30]. However, analysis of MAI showed a significant association between MAI and outcome. The median RFS was 10.3 years for patients with 0–7 mitoses/2 mm^2, 7.4 years for patients with 8–12 mitoses/2 mm^2 and 6.5 years for patients with ≥13 mitoses/2 mm^2 (p = 0.024, HR = 1.41, 95% CI 1.03–1.94 for MAI 8–12 versus MAI 0–7, and HR = 1.45, 95% CI 1.06–1.96 for MAI≥13 versus MAI 0–7; Fig. 3a). OS showed a similar trend: median OS equals 11.8 years, 8.4 years and 8.4 years, respectively (p = 0.023 for trend, HR = 1.39, 95% CI 1.07–1.82 for MAI 8–12 versus MAI 0–7 and

Table 1
Baseline patient- and tumour characteristics of 1483 male BC patients. Reported percentages were calculated after exclusion of missing data.

Characteristics	No (%, excluding missing data)
Age at diagnosis	
Median	68.4 (yrs)
Metastasis-status	
M0	1054 (71.1)
M1	57 (3.8)
Mx	372 (25.1)
T-stadium (M0-patients)	
T1	511 (48.7)
T2	402 (38.3)
T3	21 (2.0)
T3	116 (11.0)
Missing	4
N-stadium (M0-patients)	
N0	592 (59.4)
N1	321 (32.2)
N2	53 (5.3)
N3	30 (3.0)
Missing	58
(Neo-) adjuvant treatment for M0 patients	
Adjuvant radiotherapy	
No	422 (51.5)
Yes	397 (48.5)
Missing	235
(Neo-) adjuvant chemotherapy	
No	576 (70.2)
Yes	245 (29.8)
Missing	233
Adjuvant endocrine therapy	
No	189 (23.2)
Yes	627 (76.8)
Missing	238
Adjuvant Trastuzumab treatment for Her2-positive cases	
No	5 (25.0)
Yes	15 (75.0)
Missing	12
Metastases-sites for M1 patients	
Bone	10 (22.2)
Lung	6 (13.3)
Soft tissue	1 (2.2)
Distant lymph nodes	3 (6.7)
Skin/subcutaneous tissue	2 (4.2)
Other	1 (2.2)
Combination of sites	22 (48.9)
Missing	12

Table 2
Baselinepathological features of 1483 male BC patients. Reported percentages were calculated after exclusion of missing data.

Pathological features	No (%, excluding missing data)
Histological subtype	
Ductal NOS	1019 (86.6)
Lobular classic	9 (0.8)
Lobular variant	7 (0.6)
Mixed	70 (5.9)
Micropapillary	32 (2.7)
Invasive papillary	4 (0.3)
Mucinous	15 (1.3)
Cribriform	7 (0.6)
Tubular	4 (0.3)
Metaplastic	2 (0.2)
Adenoid cystic	5 (0.4)
Other	6 (0.5)
- Secretory	*2 (0.2)*
- Apocrine	*3 (0.3)*
- Clear cell	*1 (0.1)*
Missing	303
Histological grade	
1	260 (21.8)
2	598 (50.1)
3	336 (28.1)
Missing	289
Surrogate BC subtype	
Luminal A	585 (41.9)
Luminal B, Her2-negative	687 (49.2)
Luminal B, Her2-positive	107 (7.9)
Non-luminal Her2-positive	2 (0.1)
Basal	13 (1.0)
Not defined	2 (0.1)
Missing	87
Fibrotic focus	
Present	385 (32.2)
Absent	811 (67.8)
Missing	287
Density of TILs	
Minimal	304 (25.4)
Mild	721 (60.3)
Moderate	149 (12.5)
Severe	22 (1.8)
Missing	287
Lymphovascular invasion	
Present	250 (20.9)
Absent	947 (79.1)
Missing	286

HR = 1.31, 95% CI 1.00–1.72 for MAI≥13 versus MAI 0–7; Fig. 3b).

3.3. Fibrotic focus

Thirty-two percent of cases showed a fibrotic focus, which was associated with reduced RFS and OS. The median RFS was 5.6 years for patients with a fibrotic focus compared to 10.2 for patients lacking a fibrotic focus ($p < 0.001$, HR 1.67, 95% CI 1.29–2.18; Fig. 4a). The median OS was 8.2 years for patients with a fibrotic focus compared to 11.5 years for patients lacking a fibrotic focus ($p = 0.004$, HR 1.39, 95% CI 1.11–1.74; Fig. 4b).

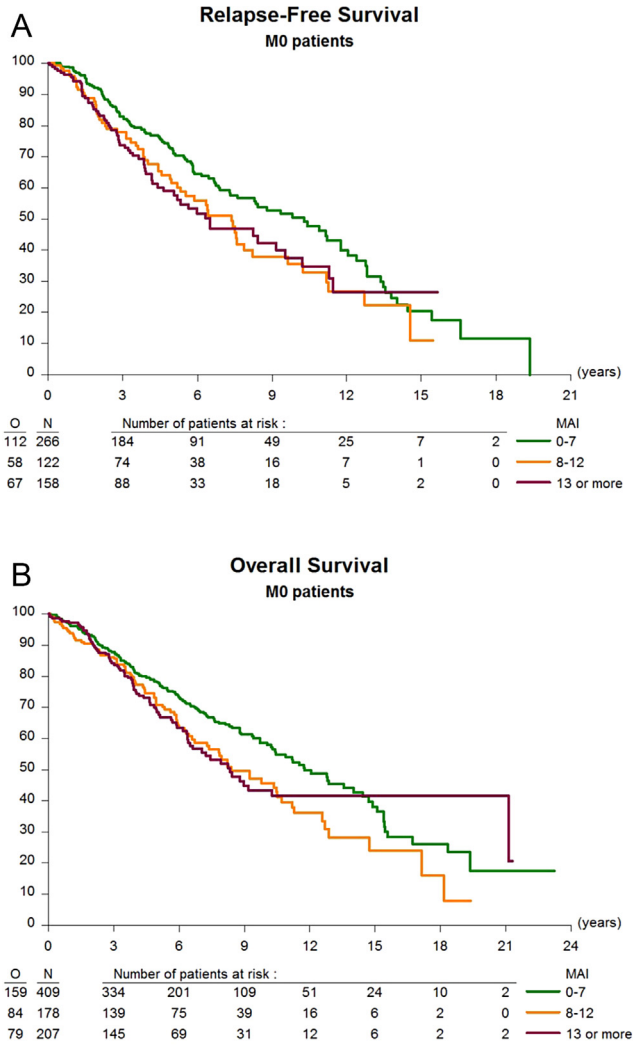

Fig. 3. a. Relapse free survival for mitotic activity index (MAI) categories 0–7, 8–12 and ≥ 13 mitoses/2 mm^2 in M0 patients ($p = 0.024$). b. Overall survival for mitotic activity index (MAI) categories 0–7, 8–12 and ≥ 13 mitoses/2 mm^2 in M0 patients ($p = 0.023$).

No significant association was observed between the presence of a fibrotic focus and surrogate BC subtype ($p = 0.059$).

3.4. Density of TILs

The majority of patients had either a minimal or mild density of TILs (25.4% and 60.3%, respectively). Remaining cases were scored as moderate (12.5%) or severe (1.8%). Density of TILs was associated with RFS ($p = 0.020$, HR = 0.69, 95% CI 0.52–0.90 for mild versus minimal, HR = 0.59, 95% CI 0.39–0.90 for moderate versus minimal and HR = 0.65, 95% CI 0.24–1.78 for severe versus minimal; Fig. 5a) and OS ($p = 0.011$, HR = 0.68, 95% CI 0.53–0.87 for mild versus minimal, HR = 0.71, 95% CI 0.49–1.03 for moderate versus minimal and HR = 0.46, 95% CI

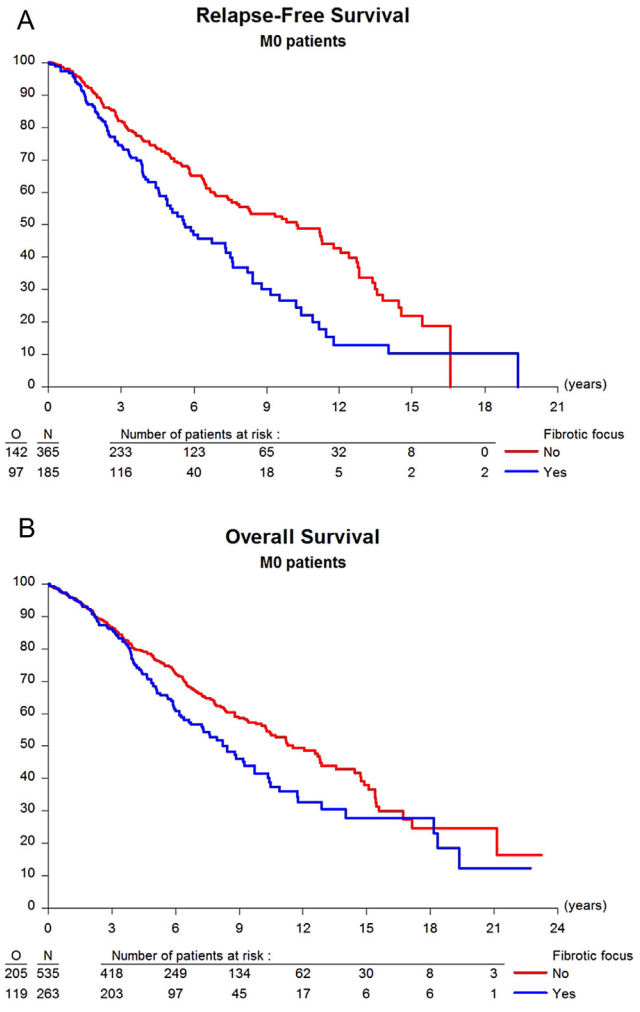

Fig. 4. a. Relapse free survival for M0 patients with and without a fibrotic focus ($p < 0.001$). b. Overall survival for M0 patients with and without a fibrotic focus ($p = 0.004$).

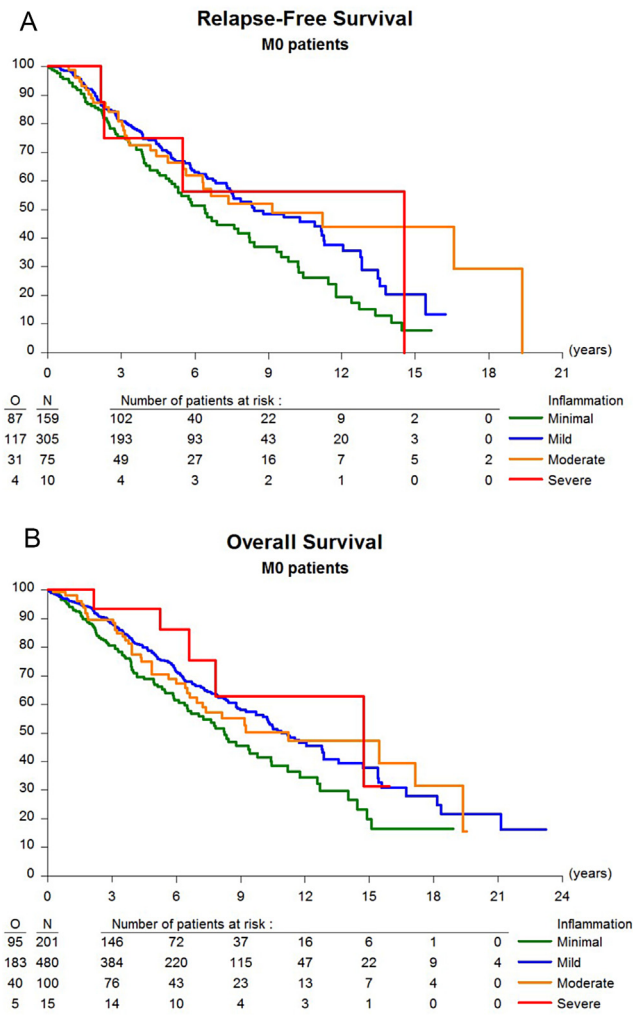

Fig. 5. a. Relapse free survival for each density-category of tumour-infiltrating lymphocytes for M0 patients ($p = 0.020$). b. Overall survival for each density-category of tumour-infiltrating lymphocytes for M0 patients ($p = 0.011$).

0.19–1.14 for severe versus minimal; Fig. 5b). Patients with a minimal density of TILs had the worst RFS and OS when compared to the other groups.

The density of TILs was also associated with surrogate BC subtype as shown in Table 3 ($p = 0.015$). Luminal B HER2-positive subtypes were more often associated with a moderate to severe density of TILs as compared to luminal HER2-negative subtypes. The groups of patients with non-luminal HER2-positive and basal subtypes were too small for conclusions.

3.5. Lymphovascular invasion

Lymphovascular invasion was detected in 20.9% of cases. The median RFS was 8.2 years for the group without lymphovascular invasion and 7.4 years for the group with lymphovascular invasion, with no difference in outcome between the two ($p = 0.755$, HR = 1.05, 95% CI 0.78–1.42) and no association with OS ($p = 0.684$, HR = 0.95, 95% CI 0.72–1.24).

4. Discussion

The aim of the present study was to describe and analyse several pathological features in male BC. Our descriptive study is unique as it includes the largest male BC population ever studied using central pathology review, and it includes histological features that are not assessed in routine daily practice, including fibrotic focus and density of TILs.

In female BC, the most common histological subtype is ductal carcinoma not otherwise specified (74.3%) and the second most common subtype is a lobular carcinoma (11.8%) [3]. In our study, we reported a relatively high proportion of ductal carcinomas (86.6%) and a low proportion of lobular carcinomas (1.4%), which is consistent with literature [3,10,35].

In female BC, histological grade has prognostic value, with a significantly worse RFS and OS corresponding with a higher grade [17]. In our male BC study

Table 3
Relationship between surrogate BC subtype and the different density categories of TILs. Patients with missing data are excluded from the table and association test.

Surrogate BC subtype								
	Luminal A (N = 476)	Luminal B HER2-negative (N = 591)	Luminal B HER2-positive (N = 62)	Non-luminal HER2-positive (N = 2)	Basal (N = 13)	Not defined (N = 2)	Total (N = 1146)	Test for trend
Density, No (%)								
Minimal	124 (26.1)	159 (26.9)	9 (14.5)	0 (0.0)	1 (7.7)	0 (0.0)	293 (25.6)	p = 0.015
Mild	301 (63.2)	340 (57.5)	38 (61.3)	2 (100)	11 (84.6)	0 (0.0)	692 (60.4)	
Moderate	44 (9.2)	80 (13.5)	13 (21.0)	0 (0.0)	1 (7.7)	2 (100)	140 (12.2)	
Severe	7 (1.5)	12 (2.0)	2 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	21 (1.8)	

population, histological grade did not significantly correspond with RFS or OS. Therefore, the grading system that was developed for females could perhaps not be extrapolated to males. Another potential explanation could be that we used OS and not BC-specific survival. The male BC population is relatively old as compared to the female BC population and a substantial proportion of patients die from other diseases. Also, the adjuvant treatment in this study was not defined by the protocol and not standardised. Therefore, grade could have played a role in the choice of adjuvant treatment, and the latter could have affected outcome. A multivariate prognostic factor analysis is foreseen in a pooled analysis after completion of the prospective part of the male BC program.

The majority of carcinomas in our population were classified as grade 2 (50.1%), followed by grade 3 (28.1%), which is similar to the grade-distribution in females [36,37]. In our series, a high mitotic count (≥8 mitoses/2 mm^2) was associated with unfavourable outcome, but further subdivisions did not have additional discriminative value.

In female BC, a fibrotic focus is described in 20–50% of the cases and the presence of a fibrotic focus correlates with a more aggressive tumour behaviour [13,21,24]. This is consistent with our series, in which we reported a fibrotic focus in about one-third of cases and a correlation with adverse outcome.

Density of TILs has been described to have both prognostic and predictive implications in female BC [25–27]. Although the composition of the TILs seems to be important, scoring of density of TILs on an H&E-stained slide also has prognostic significance without knowing the details of the subpopulations [27]. In line with these female BC studies, we found an improved outcome in patients with a higher density of TILs. In our study, we scored the density of TILs in four categories, according to the definition described by Lee *et al.* [14]. As this is not a generally used scoring method, this is a limitation of our study. However, at the start of this retrospective male BC program, no uniform scoring methods of TILs were published. Recently, Salgado *et al.* published recommendations for the evaluation of TILs in order to accomplish a more uniform and reproducible scoring system [26]. This scoring method, in case it becomes generally used in future studies, may contribute to an easier extrapolation of results. The current study demonstrated a significantly higher density of TILs in the luminal HER2-positive subtypes compared to the luminal HER2-negative subtypes, which is in line with the results from previous female BC studies [14,38].

As previously mentioned, our study is unique in its population size, especially considering the rarity of the disease. But our study also has limitations, some of them are mentioned above. Most important, the treatments that were received by the patients were not highly standardised, which could have confounded the association observed between some pathological markers and outcome. Therefore, analyses correlating baseline factors with outcome should be considered hypothesis generating only and cannot yield definite conclusions regarding their prognostic value. The currently ongoing prospective registry of the Male BC program, which will be a more recent and homogeneous series, allows us to verify these findings prospectively. In addition, there was a relatively high number of missing data regarding the disease-status, and therefore OS results should be considered more reliable than RFS results. Finally, we reviewed only one H&E-stained slide per patient.

In conclusion, our current results demonstrated that overall histological grade was not significantly correlated with outcome, unlike what is known in female BC, although MAI, the presence of a fibrotic focus and density of TILs strongly correlated with survival. This descriptive study contributes to our understanding of male BC and may generate new hypotheses for the optimisation of risk stratifications and treatment decisions.

Conflict of interest statement

None declared.

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