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ORIGINAL ARTICLE

Characterization of male breast cancer: results of the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Program

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Background: Male breast cancer (BC) is rare, managed by extrapolation from female BC. The International Male BC Program aims to better characterize and manage this disease. We report the results of part I, a retrospective joint analysis of cases diagnosed during a 20-year period.

Methods: Patients with follow-up and tumor samples, treated between 1990 and 2010, in 93 centers/9 countries. Samples were centrally analyzed in three laboratories (the United Kingdom, the Netherlands and the United States).

Results: Of 1822 patients enrolled, 1483 were analyzed; 63.5% were diagnosed between 2001 and 2010, 57 (5.1%) had metastatic disease (M1). Median age at diagnosis: 68.4 years. Of 1054 M0 cases, 56.2% were node-negative (N0) and 48.5% had T1 tumors; 4% had breast conserving surgery (BCS), 18% sentinel lymph-node biopsy; half received adjuvant radiotherapy; 29.8% (neo)adjuvant chemotherapy and 76.8% adjuvant endocrine therapy (ET), mostly tamoxifen (88.4%). Per central pathology, for M0 tumors: 84.8% ductal invasive carcinomas, 51.5% grade 2; 99.3% estrogen receptor (ER)-positive; 81.9% progesterone receptor (PR)-positive; 96.9% androgen receptor (AR)-positive [ER, PR or AR Allred score $\geq$3]; 61.1% Ki67 expression low (<14% positive cells); using immunohistochemistry (IHC) surrogates, 41.9% were Luminal-A-like, 48.6% Luminal-B-like/HER-2-negative, 8.7% HER-2-positive, 0.3% triple negative. Median follow-up: 8.2 years (0.0–23.8) for all, 7.2 years (0.0–23.2), for M0, 2.6 years (0.0–12.7) for M1 patients. A significant improvement over time was observed in age-corrected BC mortality. BC-specific-mortality was higher for men younger than 50 years. Better overall (OS) and recurrence-free survival (RFS) were observed for highly

ER+ ($P = 0.001$), highly PR+ ($P = 0.002$), highly AR+ disease ($P = 0.019$). There was no association between OS/RFS and HER-2 status, Ki67, IHC subtypes nor grade.

Conclusions: Male BC is usually ER, PR and AR-positive, Luminal B-like/HER2-negative. Of note, 56% patients had T1 tumors but only 4% had BCS. ER was highly positive in >90% of cases but only 77% received adjuvant ET. ER, PR and AR were associated with OS and RFS, whereas grade, Ki67 and IHC surrogates were not. Significant improvement in survival over time was observed.

Key words: male breast cancer, retrospective analysis, consortium, clinical and biological characteristics

Introduction

Male breast cancer (BC) is a rare disease that accounts for less than 1% of all cancers in men [1] and about 1% of all BC [2]. Although its incidence increased by about 26% over the past 25 years, male BC focused basic and clinical research is limited, and most available data come from observational retrospective studies [2–4]. Several genetic disorders (e.g. Kleinefelter's syndrome) can increase the risk of the disease by 50-fold [5]. A family history of breast and ovarian cancer is reported in approximately 15%–20% of men with BC, conferring a relative risk of 2.5 [6]. Moreover, 10% of men with BC have a *BRCA2* mutation, and fewer have a mutated *BRCA1* [7]. The American Society of Clinical Oncology (ASCO) therefore recommends that all men with BC should be offered genetic counseling and testing, regardless of family history [8]. Other genes reported to be mutated in male BC patients are *PTEN*, *p53* and *CHEK2* [9]. Additional risk factors include obesity, testicular abnormalities or pituitary adenomas that led to hormonal imbalance, gynaecomastia, cirrhosis, exogenous estrogens in men (treated for prostate cancer or transsexuals taking estrogens), race (black men have increased incidence) and radiation exposure [8].

The management of male BC is mainly extrapolated from knowledge about female BC [8]. Currently the most common surgical management is a modified radical mastectomy, whereas breast-conserving treatment (lumpectomy plus radiation therapy) is carried out in no more than one in seven patients [10]. For chemotherapy and radiation therapy, similar indications and regimens to female BC are used. Tamoxifen is the adjuvant endocrine treatment of choice and recommended for hormone-receptor positive tumors, for at least 5 years [8, 11]. The use of aromatase inhibitors in the adjuvant setting is discouraged. The Advanced Breast Cancer (ABC) International Consensus Guidelines state that in metastatic male BC patients who need treatment with an aromatase inhibitor, a concomitant LHRH agonist or orchiectomy is preferred [12, 13].

Many attempted male BC clinical trials to date have closed due to lack of recruitment. There is an unmet need for dedicated research for this disease, to improve understanding of the underlying biology and potential differences from female BC, and to optimize its clinical management. Due to the rarity of this cancer, dedicated research can only be successful if carried out in a worldwide collaborative network. With this purpose, the European Organization for Research and Treatment of Cancer (EORTC), in collaboration with the Translational Breast Cancer Research Consortium (TBCRC), the North American Breast Cancer Group (NABCG) and the Breast International Group (BIG) launched, in 2006, a global effort aiming to characterize the biology of male BC and to develop clinical trials, called the 'International Male BC Program'. This program consists of three parts: a retrospective collection of male BC treated in participating centers, over 20 years, for whom centralized clinical information and tumor samples were collected (part I); a prospective registry of newly diagnosed cases during a period of approximately 30 months, with clinical data and tumor samples (part II); and prospective clinical studies to optimize the management of these patients (part III). This article describes the primary results of part I.

Patients and methods

This retrospective cohort study enrolled male patients with histologically proven BC, diagnosed between 1990 and 2010, in all participating institutions. Patients with all disease stages (early, locally advanced and metastatic) were included, irrespective of the treatment received. Availability of a tissue sample (formalin fixed paraffin embedded; FFPE) of good quality was mandatory for enrollment. Biological material was handled and analyzed centrally according to published guidelines for adoption across BC clinical trials, conducted by BIG and NABCG in 2009 [14]. Because there were three central laboratories assessing the main biomarkers, one in the United States and two in Europe, common protocols were developed to ensure a uniform analysis and reporting of the results.

This is a retrospective, descriptive study, with no a priori sample size. The study was constructed to enroll a minimum of 500 patients and a maximum of 1800. The objectives of the present analysis are to describe patient and disease characteristics (including histological and pathological markers), treatment(s) administered and clinical outcomes. Patient outcomes [relapse-free survival (RFS), overall survival (OS)] are summarized and stratified by key patient and disease characteristics. Analyses were carried out separately for metastatic (M1) and nonmetastatic (M0) tumors, when considered relevant. The association between the studied biomarkers and RFS and OS was explored in M0 patients.

FFPE samples were initially analyzed at two central laboratories for estrogen receptor (ER), progesterone receptor (PR) androgen receptor (AR), HER2 and Ki67 ($N = 1483$). Afterwards, the remaining European samples were sent to a third central laboratory (Rotterdam) for the assessment of histology, grade, fibrotic focus, mitotic activity index and inflammation density ($N = 1203$). Of the latter, only grade and histology are included in this manuscript, and all others are reported in a separate paper [15].

ER, PR and AR are reported by Allred scores; positivity was defined as a score ≥ 3; with high positivity as a score of seven or eight [16]. HER2 status is characterized per ASCO-CAP guidelines and BC subtype surrogates are characterized according to an adaptation of the 2013 St Gallen consensus guidelines [17, 18]. Definition of immunohistochemistry (IHC) surrogates for BC subtypes as adapted from the St Gallen consensus guidelines and their operationalization within the study are detailed in Table 1. For BC subtype surrogate definition, level of Ki-67 expression was reported as the proportion of positive cells as follows: low expression <20% and high expression: ≥ 20% [18]. The low expression level was further dichotomized (< 14%, and ≥14% to <20%) for descriptive purposes only to have a more detailed overview accounting for the inter-laboratory measurement variability in Ki-67 measurement.

Table 1. BC subtype surrogate definition based on an adaptation of the 2013 St Gallen Consensus guidelines

Subtype	2013 St Gallen Consensus definition [15]	Operationalization within the study
Luminal A-like	ER positive AND	ER Allred score ≥3 AND
	PR positive[a] AND	PR Allred score≥5 AND
	HER2 negative AND	HER2 negative AND
	Ki-67 'low'	Ki-67 <20%
Luminal B-like (HER2 negative)	ER positive AND	ER Allred score≥3 AND
	HER2 negative AND	HER2 negative AND
	(Ki-67 'high'[b] OR	(Ki-67 ≥20% OR
	PR 'negative or low'[a])	PR Allred score <5)
Luminal B-like (HER2 positive)	ER positive AND	ER Allred score≥3 AND
	HER2 over-expressed or amplified	HER2 positive
	Any Ki-67	
	Any PR	
HER2 positive (nonluminal)	ER absent AND	ER Allred score<3 AND
	PR absent AND	PR Allred score <3 AND
	HER2 over-expressed or amplified	HER2 positive
Basal	ER absent AND	ER Allred score <3 AND
	PR absent AND	PR Allred score<3 AND
	HER2 negative	HER2 negative

[a]A low PR value may be used to distinguish between Luminal-A like and Luminal-B like (HER2-negative).
[b]A majority of the panel voted that a threshold of ≥20% was indicative of 'high' Ki-67 status.

Grading was carried out according to Bloom and Richardson Nottingham modification.

Laboratory methods

Tissue blocks were received at central laboratory, logged, reviewed for sufficient tissue and subjected to pathology quality assurance and tissue marking. Then six cores (0.6 mm^2) were extracted and placed on six replicate tissue microarrays (TMAs). Standard IHC techniques were used to stain triplicate TMAs for ER (SP1; Roche/Ventana, United Kingdom), PR (Clone 16; Leica/Novocastra, United Kingdom), AR (Clone ER179(2); Abcam, United Kingdom), Ki67 (MIB1; DAKO, United Kingdom) and HER-2 (Clone 45B; Roche/Ventana). Assays were carried out using the Ventana Benchmark XT (Ventana Medical Systems) automated stainer using a single batch of antibody and reagents. Each run included a quality-control TMA possessing samples with varying expression of each marker and runs were accepted only if histoscore interrun variation was <15%. Imaging of the stained slides was carried out using the Ariol SL-50 image analysis system (Leica Biosystems, Newcastle, United Kingdom) using previously validated algorithms [19]. Each TMA was scanned, mapped to positional map and individually assessed for tumor content (tumor areas were marked and checked and a second pathology quality assurance assessment was carried out). The actual number and percentage of cells in each category were recorded, with a minimum of 100 tumor cells per marker and per patient required for eligibility. Membrane staining and scoring for HER-2 utilized similarly validated algorithms using Definiens Tissue Studio v2.1 (Definiens, Munich, Germany). HER-2 protein was considered positive if IHC staining 3+ and negative for IHC 0 and 1+ [20]. In cases where IHC was equivocal (2+), fluorescence in situ hybridization (FISH) using the Vysis Pathvision HER-2 probe set (Abbott Laboratories) was used to determine HER-2 positivity according to the 2013 ASCO-CAP guidelines [17]. FISH was carried out according to the manufacturer's instructions. The TMAs were imaged and analyzed using the BioView Imaging System (BioView, Billerica, MA) with FDA and CE-marked imaging/scoring solutions for HER2/CEP17.

Statistical analysis

Statistical analysis of clinical data, long-term outcomes and local and central pathology data were carried out centrally at EORTC. The analysis population consists of patients eligible for the study and for whom a central pathology assessment for at least ER, PR, AR, HER-2 or Ki67 was available. Descriptive statistical analysis was carried out for patient, disease characteristics and treatment(s) administered. Time trends in treatment administration were investigated using the score test in a logistic model (generalized logistic for breast surgery, nodal management chemotherapy regimen and endocrine treatments) with the date of diagnosis expressed in decades as a covariate. The reported percentages in the Results section are based on the number of nonmissing values as the denominator. In the tables, the amount of missing data is reported, as well as the percentages including or excluding the missing data.

RFS is defined as the time until the first loco-regional recurrence, distant progression or death due to any cause; and only defined within the subset of M0 patients, for whom local recurrence, distant progression and survival status/dates are not missing.

BC-specific mortality (BCSM) is defined as the time until death, if death is preceded by a distant relapse, and only defined in the subset of patients for whom distant relapse information and survival status/dates are not missing; all other deaths are censored at the death date.

Time-to-Distant Relapse is defined only in the subset of M0 patients for whom distant relapse information and survival status/dates are not missing. Deaths in the absence of distant recurrence are considered as competing risk.

OS is defined as the time until date of death (due to any cause). OS was only defined within the subset of patients for whom survival status/dates were not missing.

The endpoints were calculated from the time of first diagnosis of BC. Patients without an event for the above endpoints were censored at the last date known alive. Kaplan–Meier curves were drawn for three main patient categories: lymph node negative early BC (M0N0), lymph node positive early BC (M0N+) and metastatic BC (M1).

For 473 patients from the Netherlands, a survival update was received before database lock, which was only informative regarding survival status without disease assessment information nor cause of death. Therefore, these data were only used for OS analyses.

OS and RFS were analyzed per Kaplan–Meier method, reported hazard ratios (HR) were based on univariate Cox Models and *P*-values on the score test (equivalent to the unadjusted logrank test in case of two groups).

For age-corrected BCSM by period of diagnosis (1990–1995, 1996–2000, 2001–2005, 2006–2010), patients were classified into four age groups (41–50, 51–60, 61–70, 71–80); each group received a constant weight across each time period, proportional to the total number of patients in that age group. Patients outside these groups were excluded. In the Kaplan–Meier analysis, mortality curves rather than survival curves are shown for this endpoint. The reported risk sets are those from the unweighted analysis by time period.

Role of the funding source

The funding source had no role in study design or conduct, data collection, data management, data analysis, data interpretation or writing of the report.

Results

Patient and disease characteristics

Of 1822 patients enrolled, 22 (1.2%) were ineligible based on clinical characteristics and 317 (17.6%) were ineligible since no specimen was available for central pathology assessment, leaving 1483 patients for the present analysis (Table 2). Median follow-up was 8.2 years (range: 0.0–23.8) for all patients and 7.2 years (range: 0.0–23.2), for M0 patients.

Median age at diagnosis was 68.4 years, with only 24 (1.6%) patients diagnosed younger than 40 years.

Among patients with known M status at diagnosis, the majority (1054 patients, 94.9%) were diagnosed with early BC and approximately half of these (592 patients, 56.2%) with N0 disease. The number of patients diagnosed with *de novo* metastatic disease was 57 (3.8%). For 372 patients (25.1%) information on M status at diagnosis is lacking. Table 3 describes patients and disease characteristics for every 5-year period from 1990 to 2010 and overall.

Treatment

Patterns of treatment are detailed in Table 4. The vast majority of M0 patients 794 (95.9%) underwent (modified) radical mastectomy, with only 4% (33 patients) treated with breast conserving surgery (BCS). Most (76.4%, 628) patients underwent axillary nodal dissection with or without previous sentinel lymph-node biopsy (SLNB), whereas 17.9% had SLNB only. The proportion of patients with surgical axillary management increased significantly throughout the years (trend over time $P < 0.001$).

Post-mastectomy adjuvant radiation therapy (RT) was delivered to 130 N0 patients (31.6%) and to 237 N+ patients (68.1%). Among patients treated with BCS, all N+ and 10 (45.5%) N0 patients received adjuvant RT (supplementary Table S1, available at *Annals of Oncology* online). Adjuvant chemotherapy was administered to 245 (29.8%) patients, 105 (42.3%) patients with an anthracycline-based regimen, 79 (32.3%) patients with an anthracycline and taxane–based regimen and 36 (14.6%) patients with CMF. Adjuvant endocrine therapy (ET) was prescribed to 627 (76.8%) patients, primarily with tamoxifen. About 3% (32 patients) received aromatase inhibitors and 2.5% (26 patients) a sequence of tamoxifen followed by an aromatase inhibitor, for a total duration of 5 years. A significant trend over time for a higher percentage of adjuvant ET use is observed ($P < 0.001$). Among 32 HER-2-positive patients, diagnosed from 2006 onwards, 75% (15 patients) received adjuvant trastuzumab.

Central pathology review

Central pathology data for M0 patients (1054 patients) are shown in Table 5. The majority (84.8%) were invasive ductal carcinomas, mainly (51.5%) histologic or Nottingham grade 2. Almost all were ER positive (99.3%), with 93.4% highly positive. PR positivity was present in 81.9% of cases, highly positive in 37.8%. AR positivity was found in 96.9%, highly positive in 87.6%. HER-2 positivity was seen in 91 patients (8.7%). Ki-67 expression was centrally assessed in 1033 samples: 778 (75.1%) had <20% positive cells including [633 (61.1%) with <14% positive cells and 145 (14.0%) with ≥14% and <20% positive cells] and 255 (24.9%) had ≥20% positive cells corresponding to high Ki-67 expression. Most patients had a luminal-like BC subtype (based on IHC surrogates), with 48.6% Lumina-B-like/HER-2-negative and 41.9% Luminal-A-like. HER-2-positive subtype was found in 9.1% of cases, mostly Luminal-B-like-HER-2-positive, and 0.3% were triple negative.

Central pathology review data for the 57 patients with M1 disease at diagnosis are summarized in supplementary Table S2, available at *Annals of Oncology* online.

Overall outcomes

Median OS was 10.4 years [95% confidence intervals (CI), 8.8–11.8] in early BC N0M0, 8.4 years (95% CI, 7.1–9.4) in early BC N + M0 and 2.6 years (95% CI, 2.0–3.7) in M1, respectively (Figure 1). Supplementary Table S3, available at *Annals of Oncology* online, describes disease status data for M0 and M1 patients. Of M0 patients, 36.3% died due to disease progression (40.9% missing that information). Among M0 patients, median RFS by nodal status was 8.6 years (95% CI, 7.4–11.2) for N0 and 6.4 years (95% CI, 5.8–7.5) for N-N3 disease (Figure 1). Supplementary Figure S1, available at *Annals of Oncology* online, shows RFS according to tumor size, supplementary Figure S2, available at *Annals of Oncology* online, shows BCSM by disease status and supplementary Figure S3, available at *Annals of Oncology* online, shows time-to-distant relapse for M0 patients by nodal status.

There were 112 second primary cancers diagnosed, with a cumulative incidence of 8.8% at 5 years and 15.3% at 10 years. The most common cancers were prostate (26.7%), colorectal (11.6%), lung (10.7%) and non-melanoma skin cancer (8.9%) (supplementary Table S4, available at *Annals of Oncology* online).

Outcomes in relation to period of diagnosis and age

Mortality and BCSM were calculated for every 5-year period from 1990 till 2010. Overall mortality decreased significantly over

Table 2. Adapted CONSORT diagram

1822 enrolled patients

Eligible patients (*N*=1800) (98.8%)

Ineligible patients (*N*=22) (1.2%)
Reason not eligible *N* (%)
Female and/or No inv. BC 12 (54.5)
Year of diagnosis < 1990 8 (36.4)
Year of diagnosis > 2010 2 (9.1)

Central assessment(s) of ER, PR, AR, HER2 and/or Ki67 available (*N*=1483)
82.4% of eligible patients
Analysis population

Central assessment(s) of ER, PR, AR, HER2 and/or Ki67 not available (*N*=317)
17.6% of eligible patients
European Union (EU) (N = 276)
16.5% of eligible EU patients
No Sample received (*N*= 58)

Sample received, but not eligible (*N*=218)

United States (*N*=41)
31.5% of eligible US patients
No sample received (*N*= 29)

Sample received, but not eligible (*N*=12)

Central laboratory United States (*N*=89)

Central laboratory EU 1 (*N*=1394)

Additional biomarker assessment grade, histology,. . . central laboratory EU 2
In analysis population (*N*=1203)

Not in analysis population (*N*=151)

Reasons sample not eligible (*N*=230)	*N* (%)
Insufficient material	80 (35.2)
Missing cores	38 (16.7)
Too thin	37 (16.3)
No invasive tumor	32 (14.1)
Biopsy	15 (6.6)
No block identifier	12 (5.3)
Nodal sample	6 (2.6)
Other/missing	10 (4.3)

the study period, from 44.8% (95% CI, 38.5–51.7) in 1990–1995 to 26.9% (95% CI, 22.6–31.9) in 2006–2010 (Figure 2A). There is a less pronounced improvement in BCSM over time, especially after the nineties, as measured by age-corrected BCSM (Figure 3). The 5-year age-corrected BCSM rates were 15.1% (95% CI, 14.4–15.8) for cases diagnosed between 1990 and 1995, 8.3% (95% CI, 7.8–8.8) for cases between 1996 and 2000, 7.8% (95% CI, 7.3–8.3) for cases between 2001 and 2005 and 7.6% (95% CI, 6.9–8.4) for cases between 2006 and 2010.

A difference of 25% in 5-year mortality estimates was seen for patients diagnosed ≥75 years old (52.0%, 95% CI, 47.0–57.1) compared with those diagnosed ≤40 years old (26.9%, 95% CI, 13.1–50.5) (Figure 2B). BCSM by age is presented in Figure 3.

Outcomes in relation to biological markers (ER, PR, AR, HER2, Ki67) for M0 patients

Due to the very low number of ER-negative tumors, the association of ER with outcome could not be assessed. We therefore looked at the prognostic value of the level of positivity. Median RFS of 6.4 years (95% CI, 3.6–11.8) and median OS of 7.8 years (95% CI, 4.4–15.0) were observed for patients with *low ER expression* (Allred scores 3–6), whereas for those with *high ER expression* (Allred scores 7–8), median RFS and OS were 7.5 years (95% CI, 6.8–8.4) and 9.4 years (95% CI, 8.6–10.4), respectively (Figure 4A).

Patients with *negative PR expression* (Allred scores 0–2) had median RFS and OS of 6.9 years (95% CI, 5.2–9.5) and 8.4 years (95% CI, 6.6–10.5), respectively; patients with *low PR expression* (Allred scores 3–6) had median RFS and OS of 6.5 years (95% CI, 5.6–7.8) and 8.4 years (95% CI, 7.3–9.7), respectively; and patients with *high PR expression* (Allred scores 7–8) had median RFS and OS of 8.6 years (95% CI, 7.3–11.2) and 11.2 years (95% CI, 9.3–14.7), respectively (Figure 4C).

There were also very few patients with *negative AR expression (Allred scores 0–2), which makes the comparison between negative and positive AR difficult and very wide confidence intervals, not allowing for a final conclusion; we therefore also looked at the prognostic value of the level of positivity.* Patients with *low AR expression(Allred scores 3–6)* had median RFS and OS of 5.9 years (95% CI, 4.7–7.8) and 7.0 years (95% CI, 5.8–9.4), respectively; and those with *high AR expression* (Allred scores 7–8) had median RFS and OS of 7.4 years (95% CI, 6.7–8.3) and 9.3 years (95% CI, 8.4–10.5), respectively (Figure 4B).

Supplementary Figure S4, available at *Annals of Oncology* online, depicts OS according to Ki67 expression (no significant differences) and supplementary Figure S5, available at *Annals of Oncology* online, according to HER-2 status (no significant differences).

Table 3. Patient and tumor characteristics by period of diagnosis

	Period of diagnosis				Total (*N* = 1483)	Total	Test for trend over time
	1990–1995 (*N* = 225) *N* (%)	1996–2000 (*N* = 317) *N* (%)	2001–2005 (*N* = 457) *N* (%)	2006–2010 (*N* = 484) *N* (%)	*N* (%)	(% excl. Missing)	
Age at diagnosis							No significant trend
≤40	5 (2.2)	4 (1.3)	8 (1.8)	7 (1.4)	24 (1.6)		(*P* = 0.589)
41–50	18 (8.0)	31 (9.8)	28 (6.1)	40 (8.3)	117 (7.9)		
51–65	63 (28.0)	97 (30.6)	144 (31.5)	148 (30.6)	452 (30.5)		
66–75	77 (34.2)	93 (29.3)	134 (29.3)	147 (30.4)	451 (30.4)		
>75	62 (27.6)	92 (29.0)	143 (31.3)	142 (29.3)	439 (29.6)		
Median	69.0	67.9	69.1	67.9	68.4		
M status at diagnosis							No significant trend
M0	135 (60.0)	185 (58.4)	344 (75.3)	390 (80.6)	1054 (71.1)	(94.9)	(*P* = 0.105)
M1	7 (3.1)	16 (5.0)	19 (4.2)	15 (3.1)	57 (3.8)	(5.1)	
Mx	83 (36.9)	116 (36.6)	94 (20.6)	79 (16.3)	372 (25.1)		
For M0 patients (at diagnosis):	(*N*=135)	(*N*=185)	(*N*= 344)	(*N*=390)	(*N*=1054)		No significant trend
pN status							(*P* = 0.962)
pN0	75 (55.6)	99 (53.5)	184 (53.5)	234 (60.0)	592 (56.2)		
pN1	40 (29.6)	49 (26.5)	112 (32.6)	120 (30.8)	321 (30.5)		
pN2	7 (5.2)	9 (4.9)	20 (5.8)	17 (4.4)	53 (5.0)		
pN3	2 (1.5)	7 (3.8)	8 (2.3)	13 (3.3)	30 (2.8)		
Nx	11 (8.1)	21 (11.4)	20 (5.8)	6 (1.5)	58 (5.5)		
For M1 patients (at diagnosis):	(*N*=7)	(*N*=16)	(*N*=19)	(*N*=15)	(*N*=57)		
Site *of M*							
Bone	1 (14.3)	1 (6.3)	4 (21.1)	4 (26.7)	10 (17.5)		
Lung	0 (0.0)	0 (0.0)	3 (15.8)	3 (20.0)	6 (10.5)		
Soft tissue	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	1 (1.8)		
Distant lymph node	0 (0.0)	2 (12.5)	1 (5.3)	0 (0.0)	3 (5.3)		
Skin/subcutaneous	0 (0.0)	1 (6.3)	0 (0.0)	1 (6.7)	2 (3.5)		
Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (1.8)		
Combination	3 (42.9)	6 (37.5)	7 (36.8)	6 (40.0)	22 (38.6)		
Missing	3 (42.9)	6 (37.5)	3 (15.8)	0 (0.0)	12 (21.1)		

Overall, there is a percentage of missing data for most variables, similar to that observed in clinical trials. However, for the Netherlands, there is a larger group of patients for whom a higher percentage of missing baseline, disease status and treatment data exist. Because this is a retrospective study, this issue could not be prevented or resolved, and because for many of these patients central pathology assessment is available, they were included in the analysis population. To investigate a possible selection bias when reporting such percentages, the nonmissing variables have been compared across countries for a few important covariates. We concluded that there is no evidence for a selection bias when interpreting the percentages restricted to the nonmissing data or when excluding patients with missing locoregional or distant progression status from the RFS analysis. However, because a potential bias cannot be totally excluded, OS results should be considered more reliable than RFS results. pN status according to AJCC 7. The test for a trend over time for age, M status and N status corresponds to the score test in a logistic regression (cumulative logit for age and N stage) with the date of diagnosis expressed in decades as a covariate. OS, overall survival; RFS, relapse-free survival.

Outcomes in relation to histological grade for M0 patients

Median OS for patients with grade 1 tumors was 12.8 years (95% CI, 10.3–15.4), for those with grade 2 tumors was 10.3 years (95% CI, 8.4–11.3) and for those with grade 3 tumors was 9.0 years (95% CI, 6.5–12.9) (Figure 4E). The HR for death for grade 3 versus grade 1–2 was 1.17 ($P = 0.218$).

Outcomes in relation to IHC surrogate of molecular subtype for M0 patients

For Luminal A-like BC, median RFS was 8.3 years (95% CI, 7.1–9.6) and median OS was 9.5 years (95% CI, 8.4–11.2). For Luminal B-like/HER-2-negative BC, median RFS was 6.7 years (95% CI, 5.8–7.9) and median OS was 8.8 years (95% CI, 7.9–10.5). For Luminal B-like/HER-2-positive BC, median RFS was 10.0 years (95% CI, 5.9–11.2) and median OS was 10.0 years (95% CI, 7.23 to Not estimable) (Figure 4D). Information regarding triple-negative subtype is not reported due to limited number of patients.

Discussion

Our study is the largest published series of male BC patients with centrally reviewed clinical data and tumor samples. These results

Table 4. Patterns of treatment by period of diagnosis

Early breast cancer (M0) treatment (local and/or systematic)

	Year of diagnosis				Total ($N = 1054$)		
	1990-1995 ($N = 135$) *N* (%)	1996-2000 ($N = 185$) *N* (%)	2001-2005 ($N = 344$) *N* (%)	2006-2010 ($N = 390$) *N* (%)	*N* (%)	Total (% excl. Missing)	Test for trend over time
Breast surgery							No significant trend
No surgery	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)	(0.1)	(P=0.979)
Breast-conserving surgery	3 (2.2)	10 (5.4)	9 (2.6)	11 (2.8)	33 (3.1)	(4.0)	
(Modified) radical mastectomy	95 (70.4)	148 (80.0)	261 (75.9)	290 (74.4)	794 (75.3)	(95.9)	
Missing	37 (27.4)	27 (14.6)	73 (21.2)	89 (22.8)	226 (21.4)		
Management of regional nodes							Significant trend
Nothing	9 (6.7)	14 (7.6)	14 (4.1)	10 (2.6)	47 (4.5)	(5.7)	(P<0.001)
ALND +/− SNB	89 (65.9)	137 (74.1)	211 (61.3)	191 (49.0)	628 (59.6)	(76.4)	
SNB	1 (0.7)	4 (2.2)	46 (13.4)	96 (24.6)	147 (13.9)	(17.9)	
Missing	36 (26.7)	30 (16.2)	73 (21.2)	93 (23.8)	232 (22.0)		
Adjuvant radiotherapy							No significant trend
No	49 (36.3)	73 (39.5)	147 (42.7)	153 (39.2)	422 (40.0)	(51.5)	(P=0.3874)
Yes	48 (35.6)	81 (43.8)	123 (35.8)	145 (37.2)	397 (37.7)	(48.5)	
Missing	38 (28.1)	31 (16.8)	74 (21.5)	92 (23.6)	235 (22.3)		
(Neo)adjuvant chemotherapy							Significant trend
No	82 (60.7)	128 (69.2)	179 (52.0)	187 (47.9)	576 (54.6)	(70.2)	(P<0.001)
Yes	14 (10.4)	28 (15.1)	91 (26.5)	112 (28.7)	245 (23.2)	(29.8)	
Missing	39 (28.9)	29 (15.7)	74 (21.5)	91 (23.3)	233 (22.1)		
If yes, (neo)adjuvant chemotherapy regimen:							Significant trend (P<0.001)
CMF	9 (6.7)	6 (3.2)	18 (5.2)	3 (0.8)	36 (3.4)	(4.4)	
Anthracycline based	4 (3.0)	18 (9.7)	49 (14.2)	34 (8.7)	105 (10.0)	(12.8)	
Anthracyclines and taxanes	0 (0.0)	1 (0.5)	18 (5.2)	60 (15.4)	79 (7.5)	(9.6)	
Other	0 (0.0)	2 (1.1)	4 (1.2)	13 (3.3)	19 (1.8)	(2.3)	
Missing	1 (7.1)	1 (3.6)	2 (2.2)	2 (1.8)	6 (2.5)	(0.7)	
Adjuvant endocrine therapy							Significant trend
No	53 (39.3)	69 (37.3)	41 (11.9)	26 (6.7)	189 (17.9)	(23.2)	(P<0.001)
Yes	44 (32.6)	84 (45.4)	227 (66.0)	272 (69.7)	627 (59.5)	(76.8)	
Missing	38 (28.1)	32 (17.3)	76 (22.1)	92 (23.6)	238 (22.6)		
If yes, specify planned treatment							Significant trend (P=0.0011)
Tamoxifen	41 (30.4)	77 (41.6)	196 (57.0)	240 (61.5)	554 (52.6)	(67.9)	
Aromatase inhibitor (AI)	0 (0.0)	1 (0.5)	11 (3.2)	20 (5.1)	32 (3.0)	(3.9)	
Tamoxifen followed by AI	0 (0.0)	4 (2.2)	14 (4.1)	8 (2.1)	26 (2.5)	(3.2)	
Tamoxifen + LHRH	0 (0.0)	0 (0.0)	6 (1.7)	1 (0.3)	7 (0.7)	(0.9)	
AI+ LHRH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	(0.0)	
Other	3 (2.2)	2 (1.1)	0 (0.0)	3 (0.8)	8 (0.8)	(1.0)	

The test for a trend over time corresponds to the score test in a logistic model (generalized logit for breast surgery, nodal management, chemotherapy regimen and endocrine therapies) with the date of diagnosis expressed in decades as a covariate.

show that the majority of male BC cases are ductal invasive carcinomas, with very low incidence of invasive lobular carcinoma. This can be partially explained by the infrequent formation of terminal lobules in male breast tissues, a phenomenon associated with estrogen exposure in females, although there are some case reports of invasive lobular carcinomas in male patients [21–23].

The majority of these tumors are grade 2, as previously reported [2, 24–26] but importantly we found no association between histological grade and outcome (univariate models) as previously seen in a small Swedish study [27] but not seen in the second largest international series [24]. If confirmed, this finding has clinical implications for treatment decision making regarding adjuvant chemotherapy, in particular for N0 disease.

Regarding the expression of the common receptors, we found that male BC is almost always ER+, PR + and AR+. A trend towards higher OS was observed in patients with highly ER+ disease, highly

Table 5. Results from central pathology review for early breast cancer (M0) patients

	M0 (*N* = 1054) *N* (%)	Total (% excluding Missing)	Test trend over time
ER central laboratory (Allred score pooled)			No significant trend
0–2	7 (0.7)	(0.7)	(*P*= 0.8762)
3–4	20 (1.9)	(1.9)	
5–6	41 (3.9)	(4.0)	
7–8	967 (91.7)	(93.4)	
Missing	19 (1.8)		
PR central laboratory (Allred score)			Significant trend (*P*= 0.028)
0–2	184 (17.5)	(18.1)	Average increase in
3–4	221 (21.0)	(21.7)	Allred score of 0.45 per
5–6	228 (21.6)	(22.4)	10-year period
7–8	385 (36.5)	(37.8)	
Missing	36 (3.4)		
AR central laboratory (Allred score)			No significant trend
0–2	32 (3.0)	(3.1)	(*P*= 0.2135)
3–4	28 (2.7)	(2.7)	
5–6	67 (6.4)	(6.5)	
7–8	900 (85.4)	(87.6)	
Missing	27 (2.6)		
KI67 central laboratory (cut at 14% and 20%)			Significant trend (*P*< 0.001)
0%–<14%	633 (60.1)	(61.3)	Average increase in % of
14%–<20%	145 (13.8)	(14.0)	positive cells of 4.9 per
20%–100%	255 (24.2)	(24.7)	10-year period
Missing	21 (2.0)		
KI67 central laboratory (cut at 20%)			
0%–<20%	778 (73.8)	(75.3)	
20%–100%	255 (24.2)	(24.7)	
Missing	21 (2.0)		
HER2 central laboratory			No significant trend
Negative	935 (88.7)	(89.6)	(P = 0.407)
Positive	91 (8.6)	(8.7)	
Equivocal	18 (1.7)	(1.7)	
Missing	10 (0.9)		
Clinico-pathological subtypes (2013 St Gallen consensus)			
Luminal A	417 (39.6)	(41.9)	
Luminal B HER2−	483 (45.8)	(48.6)	
Luminal B HER2+	89 (8.4)	(8.9)	
HER2 positive (nonluminal)	2 (0.2)	(0.2)	
Basal	3 (0.3)	(0.3)	
Not defined (ER−, PR+)	0 (0.0)	(0.0)	
Missing	60 (5.7)		
Histological type			
Invasive ductal	678 (64.3)	(84.8)	
Mixed type	51 (4.8)	(6.4)	
Mucinous	10 (0.9)	(1.3)	
Invasive lobular classic	5 (0.5)	(0.6)	
Cribriform pure	5 (0.5)	(0.6)	
Invasive lobular variant	3 (0.3)	(0.4)	
Tubular pure	3 (0.3)	(0.4)	
Adenoid-cystic	3 (0.3)	(0.4)	
Invasive papillary	2 (0.2)	(0.3)	
No cancer on slide	1 (0.1)	(0.1)	
Other	39 (3.7)	(4.9)	
Missing	254 (24.1)		
Histological grade			
I	171 (16.2)	(21.5)	

Continued

Table 5. *Continued*

	M0 (*N* = 1054) *N* (%)	Total (% excluding Missing)	Test trend over time
II	409 (38.8)	(51.5)	
III	214 (20.3)	(27.0)	
Missing	260 (24.7)		

The test for a trend over time for ER, PR, AR and Ki-67 corresponds to the F-test in a linear model for the Allred scores and the percentage of positive cells for Ki-67 as a response and with the date of diagnosis expressed in decades as a covariate. The test for a trend over time for HER2 corresponds to the score test in a logistic model with the date of diagnosis expressed in decades as a covariate.

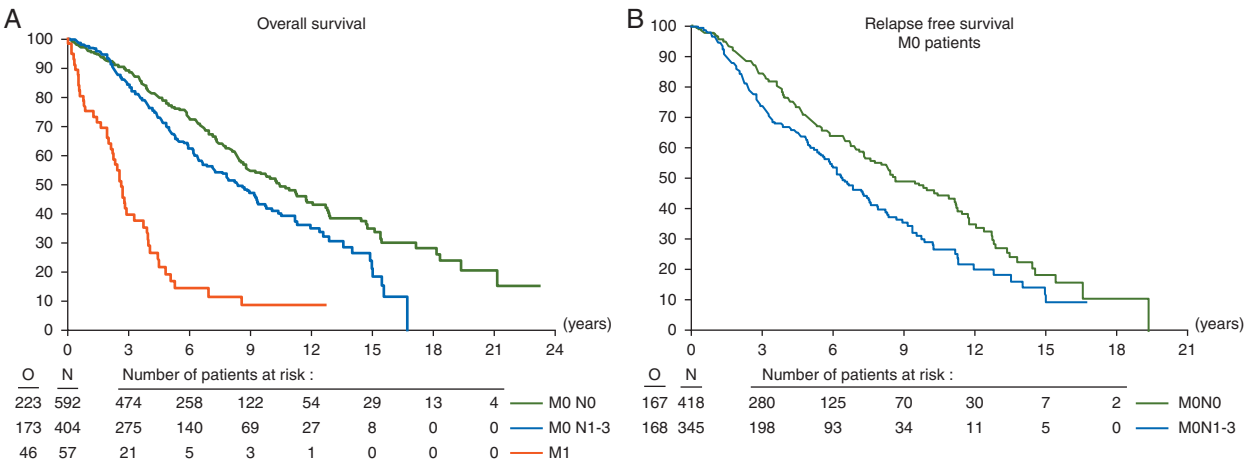

Figure 1. (A) Overall survival Kaplan–Meier curves for all patients, by stage of diagnosis. Events considered for this endpoint were death by any cause. (B) Relapse-free survival Kaplan–Meier curves for early breast cancer (M0) patients by nodal status. Events considered for this endpoint were locoregional recurrence, distant progression and death by any cause.

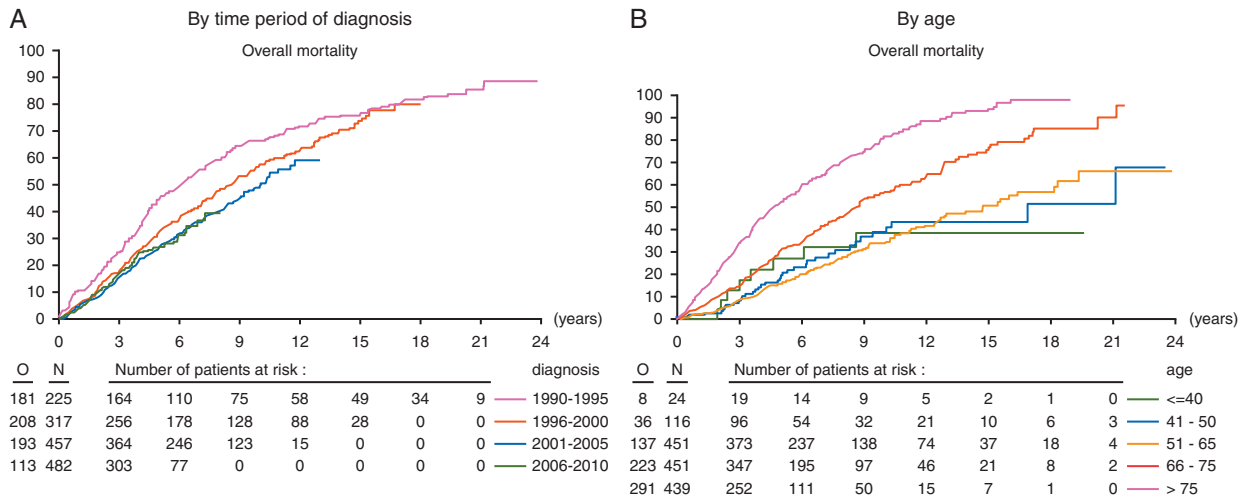

Figure 2. Overall mortality Kaplan–Meier curves for all patients by time period of diagnosis and by age at diagnosis. Events considered for this endpoint were death by ay cause, the same as for overall survival (the reverse of the mortality numbers).

PR+ disease and highly AR+ (Allred scores 7–8) as compared with low expression of the receptor (Allred scores 3–6). However, due to low numbers of cases with absence of these receptors and lack of treatment standardization in this retrospective series, the prognostic value of all biomarkers requires confirmation, which is planned in the ongoing prospective part of the International Male BC Program. HER-2 expression was uncommon, and no association between outcome and HER-2 status was seen.

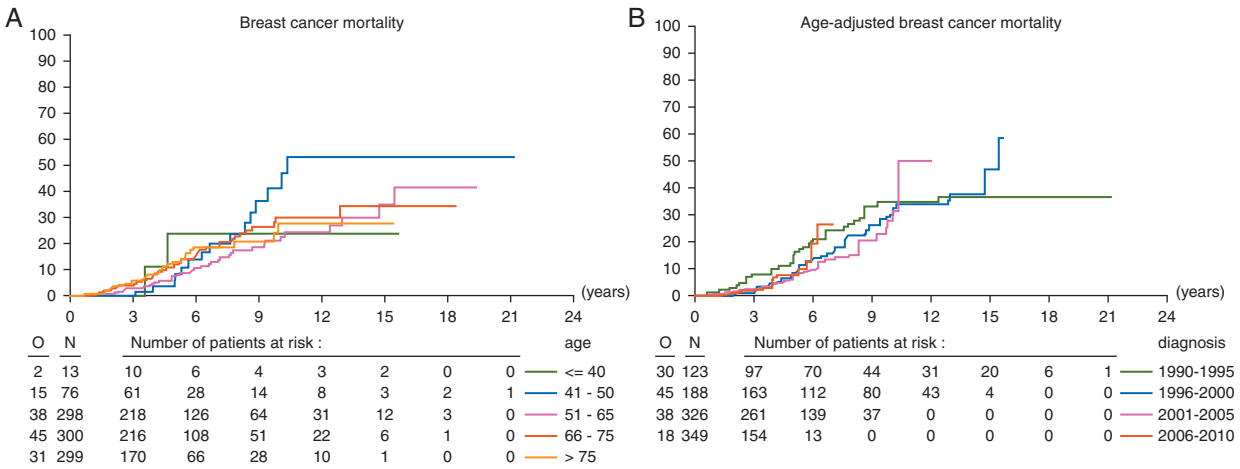

Figure 3. (A) Breast cancer–specific mortality Kaplan–Meier curves for all patients by age at diagnosis. Due to missing data, for breast cancer mortality, only deaths following a distant relapse were considered events. All other deaths, not preceded by a distant relapse, were censored on the death date. (B) Kaplan–Meier curves for age-adjusted breast cancer mortality by period of diagnosis. Patients were classified into four age groups (41–50, 51–60, 61–70 and 71–80 years). Patients outside these groups are excluded. The breast cancer–specific mortality was calculated separately for each age group, in each period of diagnosis. The plotted curve corresponds to a weighted analysis, where each of the four age groups receives an equal weight within each period.

High (≥20%) Ki67 expression was seen in only 24.9% of cases. Utilizing IHC surrogates, the majority of patients had a Luminal B-like/HER-2-negative (48.6%) or a Luminal A-like (41.9%) disease. Despite the current debate about the high degree of inter-laboratory variation in Ki-67, the cut-off of 20% was considered to define IHC surrogates for BC subtypes based on an adaptation of the 2013 St Gallen consensus guidelines. There was no association between OS and Ki67 or IHC surrogates for BC subtypes.

Previous reported data on molecular subtyping and genomic profiling of male BC tumors are scarce. Most cases have been classified as Luminal-A-like or Luminal-B-HER-2-negative-like [28], with significant differences between male and female BC samples [24, 26, 29, 30]. However, in some of these studies distinction between Luminal A and B was not clear, namely without any proliferation measure associated [24]. Our work of deep characterization of male BC samples is ongoing, namely using RNA sequencing and the Nanostring platform, and these results are expected to detect important biological differences between BC in males and females, with potential clinical implications.

The low number of HER-2+ and triple-negative BC in our series, also observed in previous reports [24, 26, 31–33], lead us to recommend a second pathology review whenever these subtypes are reported in male BC patients, before treatment decisions are made.

Regarding the disease management throughout the 20-year period of the current study, some troublesome findings deserve discussion. Although 48.5% of patients had T1 tumors, only 4% percentage had BCS. This is consistent with smaller retrospective reports and can be explained partially by the male breast anatomy and mainly by old practice patterns. Evaluation of less aggressive approaches, such as BCS with or without oncoplastic techniques, as well as nipple-sparing and skin-sparing mastectomies, is clearly needed. However, the fact that the majority if not all BCs occurring in males develop centrally, beneath the nipple, may impact surgical decisions.

SLNB has been proved feasible in men, and we observed a significant trend over the years towards a less aggressive axillary nodal management, showing that this procedure is gradually being implemented in this patient population ($P < 0.001$).

In our series, adjuvant RT was not delivered to 45% patients treated with BCS (regardless of nodal status), nor to a significant proportion (30.7%) of patients with node positive tumors treated with mastectomy. Since current recommendations suggest the use of similar algorithms for RT decision-making in male as in female BC patients, and male patients usually have a higher stage at diagnosis, these low rates of adjuvant RT are a major concern.

We observe a significant trend over time toward increased chemotherapy (anthracycline) use ($P < 0.001$). Since male BC is mainly of Luminal subtype, future studies should evaluate the role of proliferation biomarkers and genomic tools, to assist in patient selection for adjuvant chemotherapy.

Even though ER was highly positive in >90% of cases, adjuvant ET was given only to 76.8% patients. The reasons for this underuse of an effective and low toxicity therapy are unknown. Fortunately, we observed significantly more administration of adjuvant tamoxifen in recent years ($P < 0.001$). Furthermore, some patients received adjuvant aromatase inhibitors, a treatment that cannot be recommended in male patients, without an LHRH agonist. In males, 80% of circulating estrogens result from peripheral aromatization of androgens and 20% are directly secreted by the testicles [34, 35]. Aromatase inhibitors reduce estradiol by 50% and increase testosterone levels by 5% [36], and hypothalamic–pituitary negative feedback loop interferes with marked estrogen suppression by aromatase inhibitors in men, in the absence of (chemical) castration. Consequently, aromatase inhibitors should be avoided unless used in association with medical or surgical orchiectomy, which obviously has much higher toxicity than tamoxifen alone. In a small MD Anderson cohort, tamoxifen was associated with decreased recurrence and improved OS (HR = 0.45, $P = 0.01$) [11]. In a retrospective analysis of SEER data and another from the German Cancer Registry, survival among early male BC patients was improved with the use

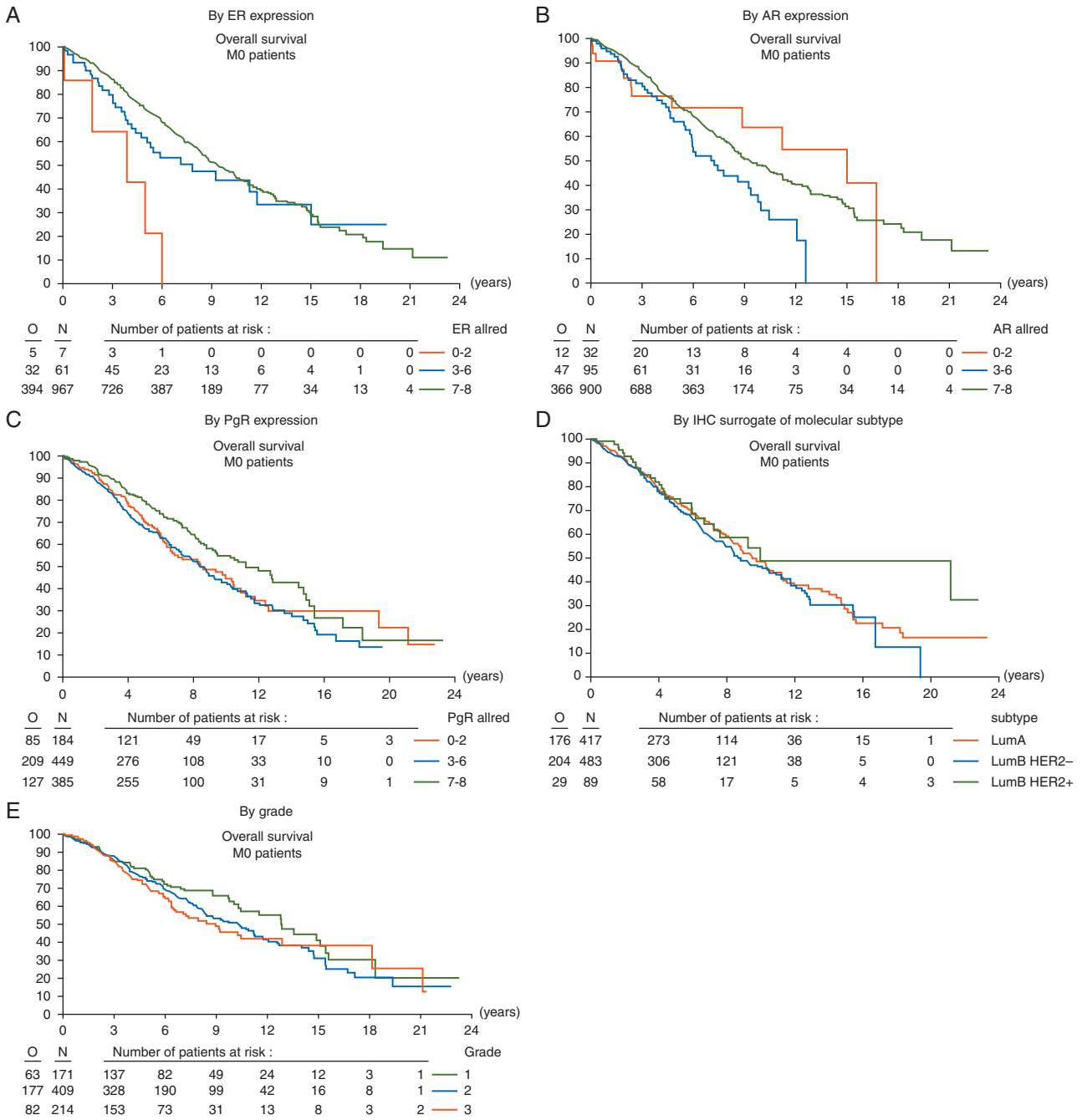

Figure 4. Overall survival Kaplan–Meier curves for early breast cancer (M0) patients (A) according to estrogen receptor (ER) expression (measured by Allred score); (B) according to androgen receptor (AR) expression (measured by Allred score); (C) according to progesterone receptor (PR) expression (measured by Allred score); (D) according to immunohistochemistry (IHC) surrogate of molecular subtype and (E) according to histological grade.

of adjuvant tamoxifen but not with adjuvant aromatase inhibitors [37, 38].

We acknowledge several limitations of the present study. Due to its retrospective nature and the fact that not all data were systematically collected in all patients, the cohort studied may not be entirely representative of the whole male BC population. For certain variables, such as disease status at baseline and cause of death, no information is available for a substantial number of patients; therefore, the relative frequencies of the categories of such variables and some of the outcome analysis (namely RFS) may be biased due to selective missing data. We carried out sensitivity analysis excluding patients with missing assessments (data not shown) and could not find evidence for a selection bias. Nevertheless, we consider that OS results may be more reliable than RFS or BCSM results. The treatments received were not controlled by a protocol and, given the rarity of the disease and absence of randomized data, they were also not highly standardized. Due to this heterogeneity, the findings regarding associations between biomarkers and outcomes should be taken with caution and need to be confirmed.

Some of these limitations are being addressed in Part II of the International Male BC Program, which consists of a prospective registry of male BC patients, newly presenting at participating sites, with prospective sample collection and quality of life assessments.

Notwithstanding its limitations, the present study represents an impressive worldwide effort to collect long-term clinical and outcome data and centrally assessed biological information, for a rare disease and is a model that could be followed for other rare cancers. Our consortium will also soon provide prospective data on the biology of male BC and clinical trial data evaluating news therapies. The worrisome findings of lower quality of care patterns seen call for the development of consensus guidelines and the need for inclusion of male patients in BC clinical trials to obtain the necessary information to guide treatment decisions in this population.

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Disclosure

The authors have declared no conflicts of interest.

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