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ORIGINAL ARTICLE

Treatment outcomes for male breast cancer: a single-centre retrospective case–control study

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ABSTRACT

Background

Male breast cancer (BC) is a rare disease, and the availability of information on treatment outcomes is limited compared with that for female BC. The objective of the present study was to compare disease-free (DFS) and overall survival (OS) for men compared with women having early-stage BC.

Methods

This retrospective case–control study compared men and women treated for stage 0–IIIB BC at a single institution between 1981 and 2009. Matching was based on age at diagnosis, year of diagnosis, and stage. Treatment, recurrence, and survival data were collected. Kaplan–Meier analysis was used to calculate OS and DFS.

Results

For the 144 eligible patients (72 men, 72 women), median age at diagnosis was 66.5 years. Treatments included mastectomy (72 men, 38 women), radiation (29 men, 44 women), chemotherapy (23 men, 20 women), and endocrine therapy (57 men, 57 women). Mean DFS was 127 months for women compared with 93 months for men ($p = 0.62$). Mean OS was 117 months for women compared with 124 months for men ($p = 0.35$). In multivariate analysis, the only parameter that affected both DFS and OS was stage at diagnosis.

Conclusions

This case–control study is one of the largest to report treatment outcomes in early-stage male BC patients treated in a non-trial setting. Male patients received systemic therapy that was comparable to that received by their female counterparts, and they had similar OS and DFS. These results add to current evidence from population studies that male sex is not a poor prognostic factor in early-stage breast cancer.

KEY WORDS

Male breast cancer, treatment, outcomes comparison

1. INTRODUCTION

Male breast cancer (BC) is a rare disease[1], representing 1% of all BCs and 0.25% of all male cancers[2]. Risk factors for male BC include family history, increased estrogen exposure, androgen deficiency (for example, in Klinefelter syndrome, liver cirrhosis, and obesity), radiation exposure, certain occupational exposures[3], and inherited *BRCA*[4] gene mutations. It is estimated that men with *BRCA2* mutations carry a 6.8% lifetime risk—102 times the risk in the general population—of developing BC[5].

Most male BC patients (90%) present late in their 7th decade of life and typically with more advanced disease[6]. The biology of BC in men is thought to be similar to that seen in postmenopausal women[7], but some differences have been noted. Men are more likely than women to have endocrine receptor–positive BC (80%–90%)[1,8,9], but the incidence of human epidermal growth factor receptor 2 (HER2) protein overexpression in men as reported in the literature is variable (1%–30%). A recent large U.S. retrospective study[10] found that, with consistent HER2 testing, 14.9% of male BC patients overexpressed HER2—a rate comparable to that seen in female BC patients. To date, little work has been done on molecular subtyping in male BC. Kornegoor *et al.*[11] found that, compared with women, a higher proportion of men had the luminal type B and basal-like subtypes of BC.

Historically, treatment strategies for male BC have been based on observational studies and case reports. No randomized controlled trials in male BC patients have evaluated optimal treatment strategies for this population. Current systemic treatment recommendations have been extrapolated largely from approaches used

in the female BC population[12–14]. The use of tamoxifen has been recommended in endocrine-sensitive male BC, with less evidence of efficacy for aromatase inhibitors (AIs)[15]. The role of targeted therapies (for example, trastuzumab) in male BC has largely been unexplored.

Male sex has traditionally been considered a poor prognostic indicator in BC. That understanding is thought to be attributable, in part, to advanced stage at time of diagnosis. The literature on treatment outcomes for male BC has yielded varied results. A U.S. National Cancer Institute population-based study[16] found that, despite advances in BC survival, men continued to do worse than women over the period 1973–2005. A population study from Sweden[17] showed that, compared with their female counterparts, men with BC had worse overall survival (41% vs. 55%). Similarly, in a 2012 study from the United States, OS was worse in men than in women (74% vs. 83%); however, that observation was attributed to higher stage at time of diagnosis[18]. These population-based studies have a number of limitations: They included higher-stage male BC patients who did not always receive treatment equal to that received by their female counterparts. The latter point is further supported by an Australian study demonstrating that men did not receive treatment equal to that received by women with BC[19].

Although the literature suggests that outcomes in male BC patients are worse than those in female patients, emerging data suggest that, with equivalent treatment, outcomes might be similar. Using the U.S. Surveillance, Epidemiology, and End Results database, Giordano *et al.*[1] found that men had worse OS, but similar age-adjusted relative survival. Further examples in the literature have demonstrated that, with equal treatment, men and women have similar prognoses. A population cohort study from Sweden with 242 male patients and more than 30,011 female patients found no survival differences between the sexes[20]. A case–control population study from France that included 58 male patients and 116 female patients found no difference in DFS between the men and women[21]. A 30-year study of populations in Australia and South Asia found a 5-year OS of 85% for both sexes[22]. Similarly, a matched-pair analysis from Germany comparing male and female BC patients ($n = 108$ in each group) was unable to find any difference in OS or DFS[23].

Given the discrepancy in the literature, we conducted a case–control study to examine treatment outcomes (DFS and OS) of male and similar female BC patients treated at our institution over a 30-year period. Our secondary objective was to identify factors affecting treatment outcomes.

2. METHODS

Men presenting with stages 0–IIIB BC at The Ottawa Hospital Cancer Centre between 1981 and 2009 were included in the study. Age at diagnosis, stage, type of surgery, and cancer treatment (including chemotherapy, radiation therapy, and endocrine therapy) were collected from patient records. Matched controls (1:1) used for this analysis were obtained from a previous dataset of male and female patients with estrogen receptor (ER)–positive early-stage BC[24].

Matching was based on age at diagnosis (±2 years), year of diagnosis (±1 year), and disease stage[25]. Kaplan–Meier analysis was used to calculate OS and DFS, and the log-rank test was used to detect differences between the curves. Univariate and multivariate analyses using a Cox proportional hazards model examined the effects of sex, stage at diagnosis, and treatment on OS and DFS. Statistical analyses for this research were performed using the SAS software application (version 9.2: SAS Institute, Cary, NC, U.S.A.).

The study was approved by the Ottawa Hospital Research Ethics Board and complies with ethical standards of research in Canada[26].

3. RESULTS

We identified 98 male BC patients attending the Ottawa Hospital Cancer Centre who were diagnosed between 1981 and 2009. Patients were excluded if an appropriate match could not be found ($n = 10$), if they had stage IV disease at time of diagnosis ($n = 7$), if they had a histologic subtype other than invasive ductal carcinoma ($n = 5$), or if they were known to be ER-negative ($n = 4$). The remaining 72 male BC patients were included in the analysis and were compared with 72 matched female BC patients.

Table I presents the baseline characteristics of the study population. The demographics in both groups were similar. Median age at diagnosis was 66.5 years (range: 30–85 years) in both groups. Median follow-up was 45 months for men (range: 2–204 months) and 55 months for women (range: 4–241 months).

All 72 men underwent mastectomy [compared with 38 women (53%)], and all but 6 men had a lymph node dissection. Independent of the type of surgery (breast-conserving or mastectomy), all women underwent sampling of the axilla (axillary node dissection or sentinel lymph node biopsy, or both).

Adjuvant chemotherapy was given to 20 women (28%) and 23 men (32%). Chemotherapy regimens varied, but most were anthracycline–taxane based {FAC [5-fluorouracil (5FU)–doxorubicin–cyclophosphamide], FEC (5FU–epirubicin–cyclophosphamide), FEC-D (FEC followed by docetaxel), and AC/T (doxorubicin–cyclophosphamide followed by paclitaxel)}, with few patients receiving single-agent regimens. Adjuvant radiation therapy was given to 44 women (61%) and 29 men (40%). In both groups, 42.5–55 Gy were given to the chest wall.

All female patients had ER-positive disease. Breast cancer was ER-positive in 59 of the 72 men (82%); the remaining men had tumours of unknown ER status. An equal number of men and women (79%)

TABLE I Baseline characteristics of the study patients

Variable	*Men*		*Women*	
	(n)	*Value*	*(n)*	*Value*
Mean age at Dx (years)	72	65.4±11.47	72	65.56±11.66
Mean tumour size (cm)	70	2.2±0.90	71	2.11±1.38
Stage at diagnosis (%)				
0	2	2.78	2	2.78
I	23	31.94	23	31.94
IIA	31	43.06	31	43.06
IIB	11	15.28	11	15.28
IIIB	5	6.94	5	6.94
ER status (%)				
Positive	59	81.94	72	100.00
Unknown	13	18.06		
PR status (%)				
Borderline	2	2.78	2	2.78
Negative	4	5.56	4	5.56
Positive	52	72.22	65	90.28
Unknown	14	19.44	1	1.39
HER2 status (%)				
Borderline	1	1.39	1	1.39
Negative	25	34.72	21	29.17
Positive	4	5.56	2	2.78
Unknown	42	58.33	48	66.67
Radiation to breast (%)				
No	42	59.15	28	38.89
Yes	29	40.85	44	61.11
Chemotherapy (%)				
Declined	6	8.33	5	6.94
None	24	33.33	25	34.72
Not recommended	22	30.56	19	26.39
Yes	20	27.78	23	31.94
Endocrine treatment (%)				
AI	11	15.28	12	16.67
AI/tamoxifen	11	15.28	20	27.78
Tamoxifen	35	48.61	25	34.72
None	15	20.83	15	20.83

Dx = diagnosis; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2; AI = aromatase inhibitor.

received endocrine treatment. Of the 13 men with BC of unknown ER status, 7 received adjuvant hormonal treatment with tamoxifen.

No significant difference was found between the sexes in the primary outcomes of OS and DFS. Figures 1 and 2 show the Kaplan–Meier curves respectively comparing DFS and OS for the study groups. Mean DFS was 127 months for women (25th percentile: 100 months; median: 174 months; 75th percentile: could not be calculated) compared with 93 months for men (25th percentile: 80 months; median: 102 months; 75th percentile: could not be calculated; $p = 0.62$). Mean OS was 117 months for women (25th percentile: 94 months; median: 136 months; 75th percentile: could not be calculated) and 124 months for men (25th percentile: 80 months; median: 115 months; 75th percentile: 190 months; $p = 0.35$). Some values could not be calculated because of censoring. Significant differences were noted: DFS was improved in patients presenting with earlier-stage disease ($p < 0.01$) and in those treated with endocrine therapy ($p = 0.03$). There was no significant difference in OS between treatment groups. Earlier stage of disease was associated with better OS, although the difference did not reach statistical significance ($p = 0.07$).

Table II outlines the results of the univariate and multivariate analyses of the effect of sex, stage, and treatment modalities on OS and DFS. In the univariate and multivariate analyses, neither DFS [univariate hazard ratio (HR): 1.18; $p = 0.62$; multivariate HR: 1.318; $p = 0.44$] nor OS (univariate HR: 1.295; $p = 0.46$; multivariate HR: 1.599; $p = 0.16$) was significantly different between the sexes. In univariate analysis, patients receiving endocrine therapy had a significantly worse DFS (HR: 2.694; $p = 0.04$), but in multivariate analysis, the difference was no longer statistically significant (HR: 1.823; $p = 0.254$). In multivariate analysis, early-stage disease was associated with improved DFS (HR: 0.249; $p = 0.007$) and OS (HR: 0.423; $p = 0.05$). A significant survival benefit with the use of chemotherapy was also observed (HR: 0.395; $p = 0.03$).

In a subgroup analysis, male patients with BC of unknown ER status ($n = 13$) were compared with the female patients (Figures 3 and 4, Table III). Notably, the male patients were not denied endocrine therapy despite their unknown ER status. Multivariate analysis of the subgroup showed no significant difference between the sexes in DFS (HR: 1.33; $p = 0.46$) or OS (HR: 1.46; $p = 0.36$). In the subgroup, use of chemotherapy was found to have significant benefit for OS (HR: 0.34; $p = 0.03$), and a lower stage of disease showed a trend toward significance as a factor for DFS (HR: 0.33; $p = 0.06$).

4. DISCUSSION AND CONCLUSIONS

This case–control study is one of the largest to report on treatment outcomes in early-stage male BC treated in a clinical setting. The study demonstrates that, when male BC patients receive local and systemic therapy (surgery, radiation, chemotherapy, endocrine) comparable to that received by their female counterparts, no statistically significant difference in DFS or OS is detectable after adjustments for age, year of diagnosis, and disease stage. In Kaplan–Meier, univariate, and multivariate analyses, we were unable to demonstrate a statistical difference between the sexes.

Our secondary study objective was to elucidate other determinants of DFS and OS in male BC. Compared with patients diagnosed with later-stage disease,

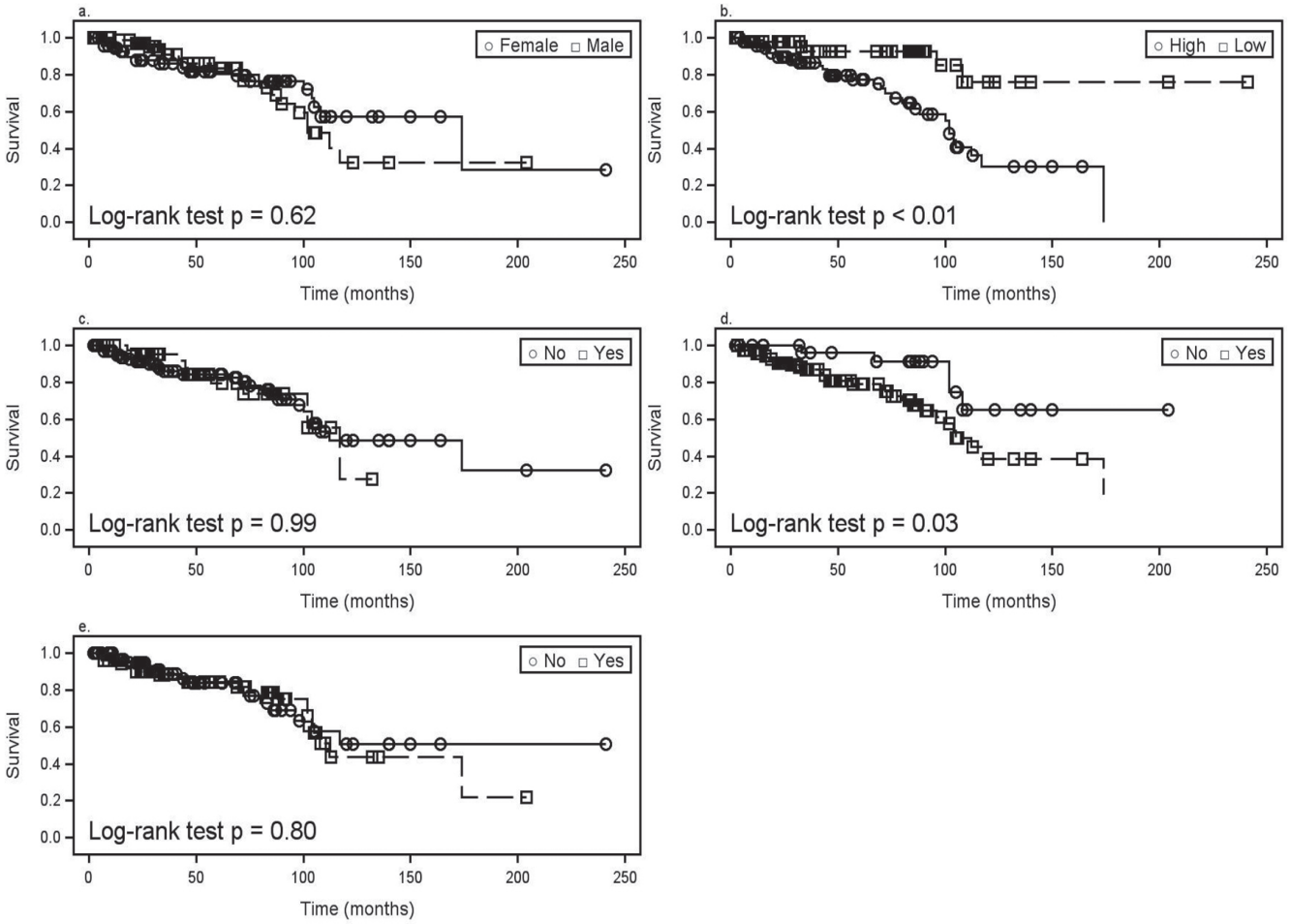

FIGURE 1 *Kaplan–Meier probability curves for disease-free survival in (a) men compared with women,* p *= 0.62; (b) high compared with low stage at diagnosis,* p *< 0.01; (c) chemotherapy compared with no chemotherapy,* p *= 0.99; (d) endocrine therapy compared with no endocrine therapy,* p *= 0.03; (e) radiation therapy compared with no radiation therapy,* p *= 0.80 (log-rank* p *values). Individual data points on the curves represent patients lost to follow-up.*

those diagnosed with early-stage disease were found to have a significant increase in DFS and OS. Multivariate analysis demonstrated an OS benefit with use of chemotherapy. Although there was a trend in the univariate analysis toward worse outcomes with the use of endocrine therapy, that association was not statistically significant in the multivariate analysis.

Our results show that men with BC received treatment comparable to that received by appropriately matched women with BC; however, that observation might not be true at all institutions. An Australian review published in 2009 found that men were less likely to receive surgery and significantly less likely to receive adjuvant radiation therapy (p = 0.001), chemotherapy (p = 0.014 in one group), or tamoxifen (p = 0.001)[21]. Although the authors did not examine treatment outcomes, their work raises important questions about current approaches to treatment of male BC patients.

In our study, a number of men were treated with AIS either alone (n = 11) or in series with tamoxifen (n = 11). The evidence to support the role of AIS in male BC is sparse, being based mainly on retrospective case reports and case series. Recently, Eggemann *et al.*[15] compared AIS with tamoxifen in male BC and found that AIS carried a mortality risk that was increased by a factor of 1.5 (p = 0.007). Similar concerns have been noted in the female population. Amir *et al.*[27] reported significantly increased morbidity from cardiovascular events (odds ratio: 1.26) and bone fractures (odds ratio: 1.47), and a nonsignificantly increased risk of mortality associated with the use of AIS in postmenopausal BC patients.

Our study has a number of limitations, including its retrospective nature, a small sample size, and the fact that it was conducted at a single institution. The small sample size affects the power and significance of the findings. The small number of events

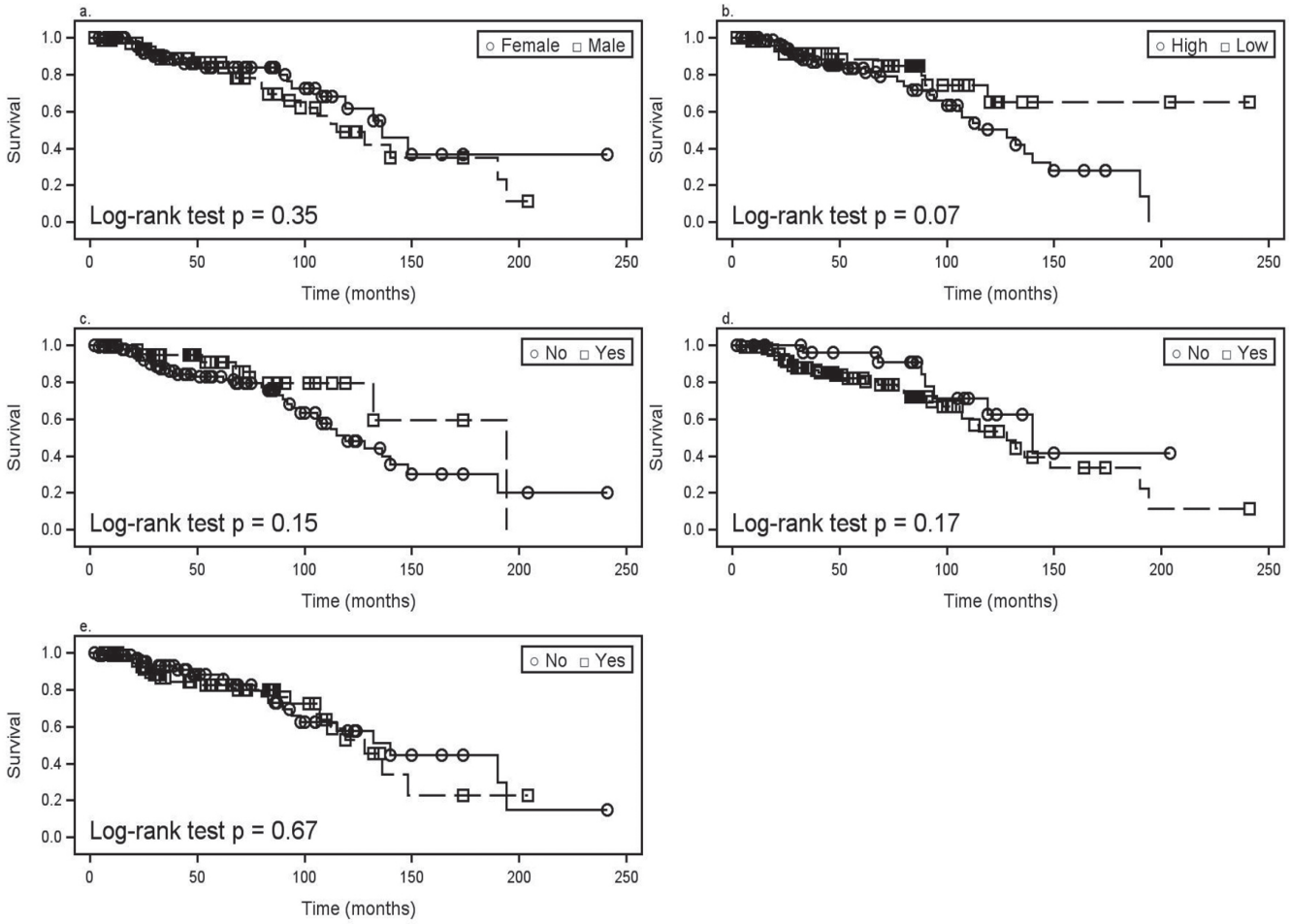

FIGURE 2 Kaplan–Meier probability curves for overall survival in (a) men compared with women, p *= 0.35; (b) high compared with low stage at diagnosis,* p *= 0.07; (c) chemotherapy compared with no chemotherapy,* p *= 0.15; (d) endocrine therapy compared with no endocrine therapy,* p *= 0.17; (e) radiation therapy compared with no radiation therapy,* p *= 0.67 (log-rank* p *values). Individual data points on the curves represent patients lost to follow-up.*

TABLE II Survival analysis by Cox proportional hazards modelling

Survival type and parameter	*Univariate*				*Multivariate*			
	HR	*95% CL*		p *Value*	*HR*	*95% CL*		p *Value*
Disease-free survival								
Sex (men vs. women)	1.181	0.612	2.28	0.62	1.295	0.647	2.593	0.46
Stage (0 or I vs. II or III)	0.229	0.089	0.593	0.002	0.249	0.091	0.684	0.007
Chemotherapy (yes vs. no)	1.005	0.481	2.100	0.99	0.611	0.280	1.334	0.22
Endocrine therapy (any vs. none)	2.694	1.040	6.980	0.04	1.823	0.666	4.988	0.24
Radiation therapy (yes vs. no)	1.093	0.558	2.143	0.80	0.972	0.478	1.975	0.94
Overall survival								
Sex (men vs. women)	1.345	0.716	2.527	0.36	1.581	0.815	3.066	0.18
Stage (0 or I vs. II or III)	0.447	0.204	0.977	0.04	0.423	0.178	1.003	0.05
Chemotherapy (yes vs. no)	0.551	0.243	1.247	0.15	0.395	0.171	0.913	0.03
Endocrine therapy (any vs. none)	1.751	0.772	3.973	0.18	1.525	0.628	3.703	0.35
Radiation therapy (yes vs. no)	1.144	0.610	2.146	0.67	1.306	0.676	2.525	0.43

HR = hazard ratio; CL = confidence limits.

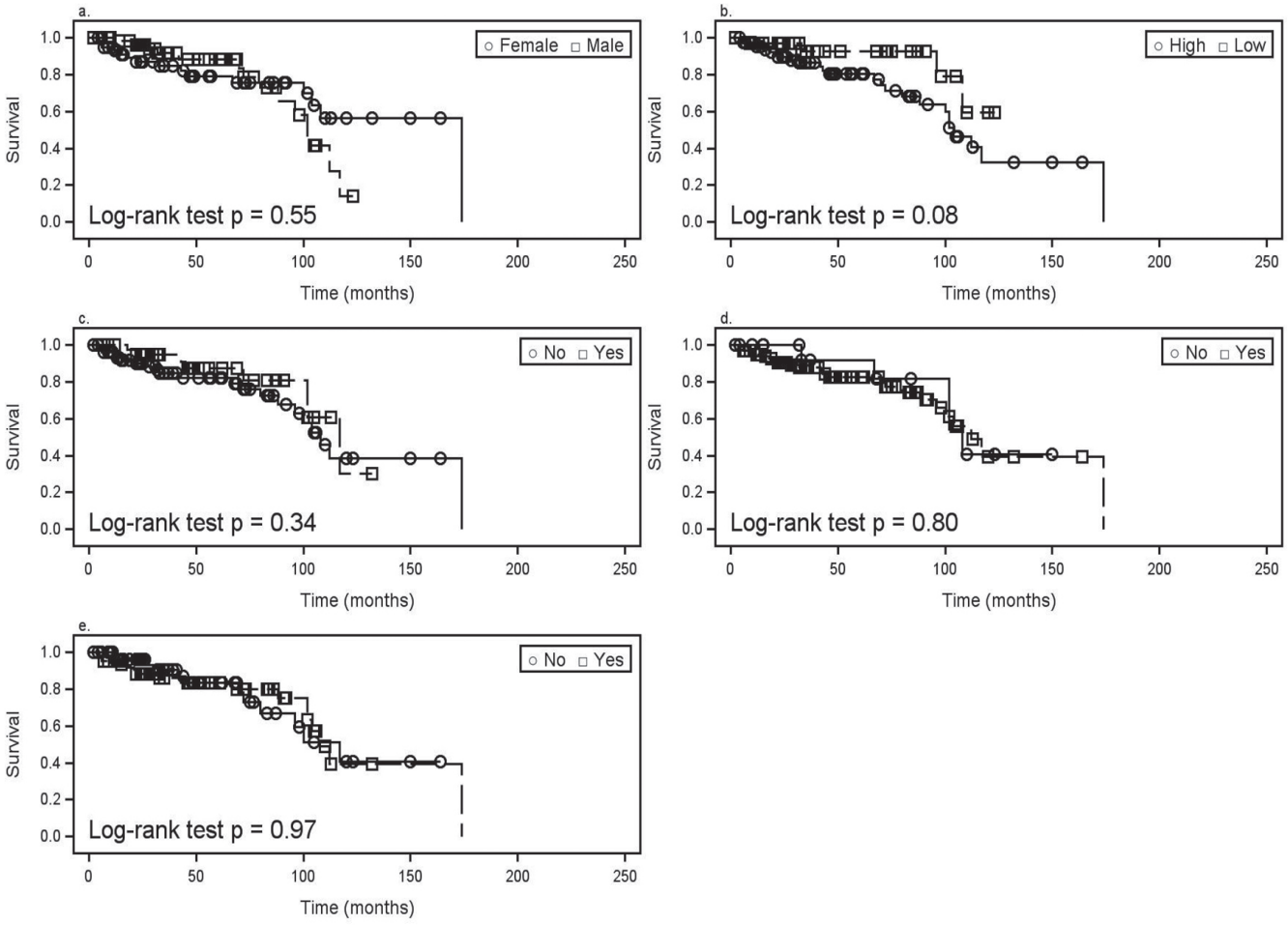

FIGURE 3 Kaplan–Meier probability curves for disease-free survival in the subgroup of men with unknown estrogen receptor status: (a) men compared with women; (b) high compared with low stage at diagnosis; (c) chemotherapy compared with no chemotherapy; (d) endocrine therapy compared with no endocrine therapy; (e) radiation therapy compared with no radiation therapy (log-rank p *values). Individual data points on the curves represent patients lost to follow-up.*

(deaths and recurrence) in the early-stage population further diminishes the strength of the analysis. The study focused on early-stage BC patients, and many patients were lost to follow-up. The median duration of follow-up was short in both groups (3.7 years in men, 4.6 years in women) because many patients were discharged back to their primary care physicians. Another limiting factor is the selection bias that might have occurred during selection of the control group for comparison. One often-cited limitation in similar retrospective analyses of male BC is the need to compare patient outcomes over a long period of time as therapeutic advances take place. We overcame that limitation in our study by searching for matching female control subjects who were diagnosed within 1 year of the male BC case. With respect to the matching, no specific statistical methods were used to adjust the data. Our model had intrinsic adjustment, in the sense that the matches were made based on the variables of interest: stage, age, and time of diagnosis. Looking at the model, we felt that further adjustment would skew the results rather than improve reliability (which would be the sole purpose of adjusting for matching). That decision is, in itself, an assumption and constitutes another possible limitation of this work.

Our results add to the current evidence from population-based studies[1,20–23] suggesting that sex is not prognostic for poor treatment outcomes in male BC. More recent studies suggest that male sex is a poor prognostic factor only in BC patients who are not provided with the best BC treatment. Efforts should be made to educate clinicians to ensure that men presenting with BC are referred early and provided all therapeutic options available to women.

Looking to the future, some promising work is being done: the European Organisation for Research and Treatment of Cancer and the Southwest Oncology

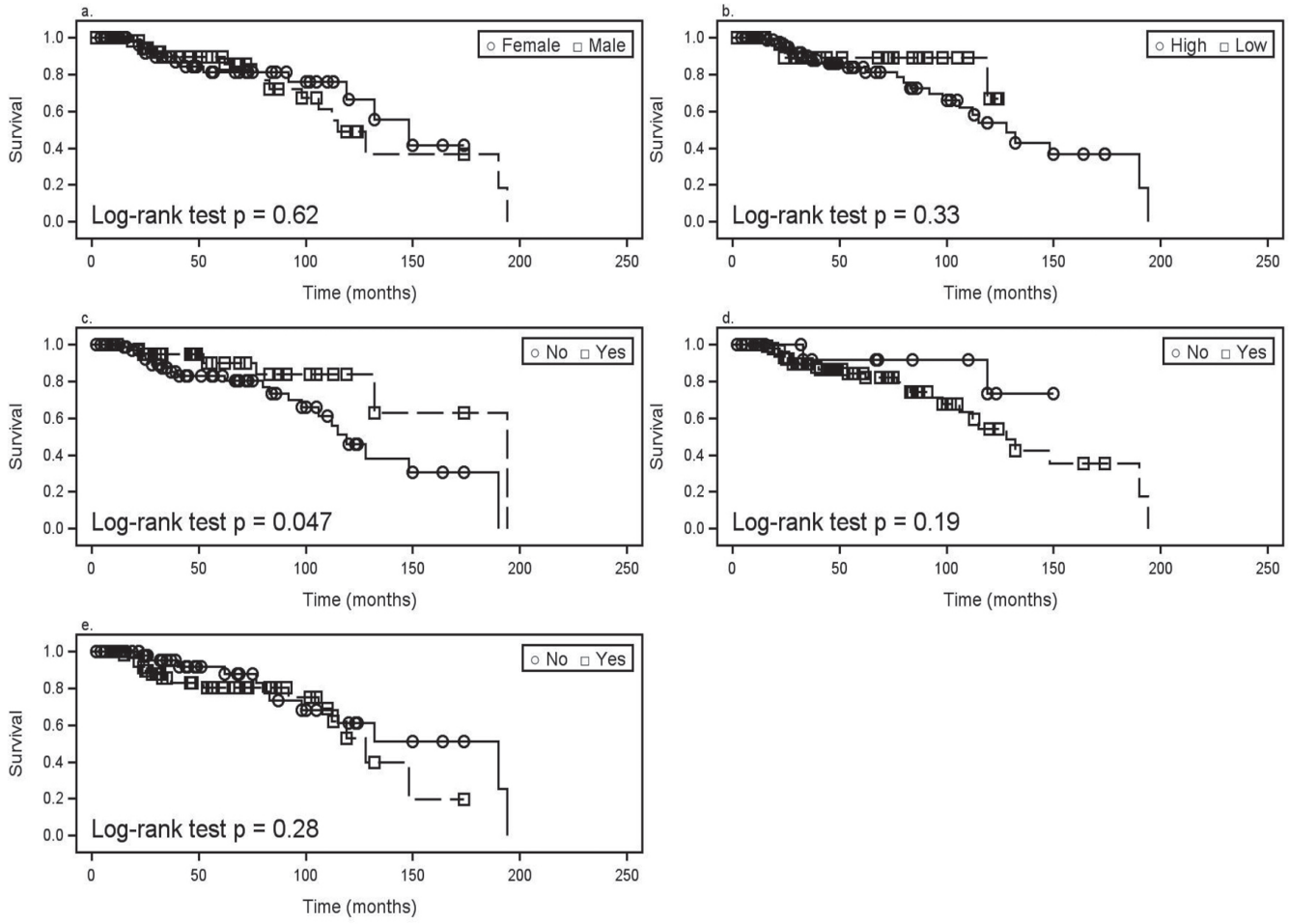

FIGURE 4 Kaplan–Meier probability curves for overall survival in the subgroup of men with unknown estrogen receptor status: (a) men compared with women; (b) high compared with low stage at diagnosis; (c) chemotherapy compared with no chemotherapy; (d) endocrine therapy compared with no endocrine therapy; (e) radiation therapy compared with no radiation therapy (log-rank p *values). Individual data points on the curves represent patients lost to follow-up.*

TABLE III Survival analysis by Cox proportional hazards modelling, comparing the subgroup of men with unknown estrogen receptor status (n = 13) with the women

Survival type and parameter	*Univariate*				*Multivariate*			
	HR	*95% CL*		p *Value*	*HR*	*95% CL*		p *Value*
Disease-free survival								
Sex (men vs. women)	1.26	0.59	2.67	0.55	1.33	0.62	2.88	0.46
Stage (0 or I vs. II or III)	0.40	0.14	1.145	0.09	0.33	0.11	1.03	0.06
Chemotherapy (yes vs. no)	0.67	0.30	1.53	0.34	0.56	0.24	1.29	0.17
Endocrine therapy (any vs. none)	1.14	0.43	3.03	0.80	0.90	0.33	2.49	0.84
Radiation therapy (yes vs. no)	1.02	0.48	2.17	0.97	0.97	0.44	2.13	0.95
Overall survival								
Sex (men vs. women)	1.22	0.56	2.64	0.62	1.46	0.65	3.29	0.36
Stage (0 or I vs. II or III)	0.59	0.20	1.73	0.33	0.69	0.22	2.19	0.53
Chemotherapy (yes vs. no)	0.39	0.15	1.02	0.06	0.34	0.13	0.91	0.03
Endocrine therapy (any vs. none)	2.57	0.60	10.96	0.20	2.45	0.55	11.05	0.24
Radiation therapy (yes vs. no)	1.55	0.70	3.45	0.28	1.78	0.76	4.16	0.18

HR = hazard ratio; CL = confidence limits.

Group are currently conducting a large study (1800 male patients) in Europe and North America using tissue-block analysis to examine the relationship between biomarkers and clinical outcomes in male BC (search for NCT01101425 at http://clinicaltrials.gov/). Their work will help to define differences in male BC biology and response to therapy that have not previously been reported. The development of a national male BC registry would further facilitate the evaluation of modern treatment strategies and patient outcomes in the male population with BC. Such a registry would facilitate the conduct of prospective trials to evaluate differences in tumour biology, treatment strategies, and clinical outcomes in men. The rarity of male BC and inconsistencies in the approach to treatment of male BC speak to the need for development of consensus guidelines on appropriate management and treatment. Such guidelines will become increasingly important in the coming years as personalized medicine and targeted therapies become the standard of care.

5. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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