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Original Article

Treatment Outcomes in Male Breast Cancer: A Retrospective Analysis of 161 Patients

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Abstract

Aims: Male breast cancer is a rare disease with limited evidence-based guidelines for treatment. This study aimed to identify demographic, pathological and clinical factors associated with its prognosis.

Materials and methods: A retrospective review of 161 male breast cancer patients diagnosed at a single institution from 1987 to June 2017 was conducted. Patient demographics, disease characteristics, treatment and outcome were extracted and included in competing-risk analysis and the univariate Cox proportional hazard model for univariate analysis. Factors with $P < 0.10$ were included in multivariable analysis.

Results: The mean age at diagnosis was 67 years (standard deviation = 11.2) and the median follow-up duration was 5.3 years (range 0–25 years). There were 48 deaths, including 23 cancer-specific deaths. The actuarial median survival was 19.9 years. In multivariable analysis, factors associated with overall survival were size of tumours (hazard ratio 2.0; 95% confidence interval 1.4–2.7, $P < 0.0001$) and diagnosis of metastatic disease (hazard ratio 8.7; 95% confidence interval 1.9–40.6; $P = 0.006$). Of 138 patients without metastases at diagnoses, 11 had local-regional recurrence and 26 had distant metastases. In the multivariable model for local-regional recurrence, a more recent year of diagnosis was associated with reduced risk (hazard ratio 0.9, 95% confidence interval 0.8–1.0, $P = 0.008$), whereas more positive lymph nodes was associated with higher risk (hazard ratio 2.2, 95% confidence interval 1.2–4.0, $P = 0.01$). A higher risk of metastases was associated with more positive lymph nodes (hazard ratio 1.9; 95% confidence interval 1.1–3.3; $P = 0.03$) and tumour size (hazard ratio 1.8; 95% confidence interval 1.1–2.9; $P = 0.01$). A higher risk of any recurrence or metastases was associated with the number of positive nodes (hazard ratio 1.9; 95% confidence interval 1.2–3.0; $P = 0.005$) and tumour size (hazard ratio 1.6; 95% confidence interval 1.1–2.2; $P = 0.01$).

Conclusion: In general, tumour size and more positive lymph nodes were associated with worse prognosis. Larger powered studies are needed to identify prognostic factors with smaller effect sizes.

Key words: Breast cancer; male; treatment outcomes

Introduction

Male breast cancer is rare and accounts for 0.6% of all breast cancer diagnoses [1]. This has resulted in a lack of evidence-based treatment guidelines due to difficulties in conducting large-scale randomised controlled trials. The current understanding of its biology and treatment guidelines has been based on epidemiological and retrospective studies, and extrapolation from studies on female breast cancer.

Factors associated with the risk of male breast cancer include family history, increased oestrogen exposure or hypoandrogenism, radiation/occupational exposure and heritable elements such as *BRCA1* and *BRCA2* gene mutations [2]. The characteristics of male breast cancer have been found to resemble postmenopausal female breast cancer in several studies [3,4]. However, there is increasing evidence that male breast cancer differs in aetiology, clinical-pathological presentation and outcomes when compared with female breast cancer. For example, lobular carcinomas are the second most common subtype in female breast cancer (11.8%), but present rarely in males (1%) [5,6].

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In addition, male breast cancer is almost always oestrogen hormone receptor positive and when compared with female breast cancer there is an under-representation of *BRCA1* mutations and an over-representation of *BRCA2* mutations [3]. Moreover, an analysis of the immune-histopathological characteristics of male breast cancer by Abreu *et al.* [7] suggested that male breast cancer may be divided into multiple prognostic subgroups that highlight differences in tumourigenesis.

Management of male breast cancer includes surgical excision, radiotherapy and systemic therapy in the form of chemotherapy, hormonal therapy for oestrogen receptor (ER) positive or progesterone receptor (PR) positive patients, or trastuzumab for patients with human epidermal growth factor receptor (HER2/neu) overexpression [8]. Although the overall survival of male breast cancer has improved in the last decade, there remains a lack of evidence-based data for its management [9]. The objectives of this present study were to evaluate the demographic, clinical, pathological characteristics and treatments associated with outcomes in male breast cancer.

Materials and Methods

A retrospective review of patients who were diagnosed from 1987 to June 2017 at the Odette Cancer Centre was conducted. Ethics approval from Sunnybrook Health Sciences Centre was obtained before the start of the study. Patient demographic, treatment, pathology, biomarkers, years of cancer diagnosis (1987 to <2000, 2000 to <2010, 2010 to 2017) and follow-up data were extracted. Biomarker data on ER, PR and HER2/neu status were used to divide cancer into subtypes of luminal A-like (ER/PR+, HER2/neu−), luminal B-like (ER/PR+, HER2/neu+) or triple negative (ER/PR−, HER2/neu−) based on definitions by Ge *et al.* [10].

Clinical-pathological features were individually correlated to overall survival, risk of local-regional recurrence and risk of metastases. Overall survival in years was defined as the time from diagnosis to the date of death or to the last follow-up. Risk of recurrence or metastases was calculated for patients without metastases at diagnosis (M0) and was defined as the time from breast cancer diagnosis to breast cancer recurrence/metastases.

Patients, disease and treatment characteristics were summarised as mean, standard deviation and range for continuous variables, and proportions for categorical variables. The univariate Cox proportional hazard model was used to identify significant covariates related to overall survival. Kaplan–Meier overall survival curves, hazard ratios, 95% confidence intervals and *P*-values were generated. The generalised R^2 statistic (between 0 and 1) was calculated based on the likelihood ratio statistic for testing the global null hypothesis; the larger the R^2, the stronger the association with the outcome [10]. A competing risk analysis was conducted for local-regional recurrence, distant metastases or any recurrence/distant metastases in non-metastatic patients. The cumulative incidence function was estimated and plotted as well. To search for significant predictive factors of local-regional recurrence, distant metastases or any recurrence/distant metastases, univariate Cox proportional subdistribution hazard models were carried out using Fine and Gray's method, considering death as the competing risk [11]. Subdistribution hazard ratios with 95% confidence intervals and *P*-value were estimated for each factor. In the multivariable analysis, all variables with $P < 0.10$ from the univariate analysis were selected for inclusion in the backward stepwise selection procedure. The final model would only keep the significant predictive factors with $P < 0.05$. All analyses were conducted using Statistical Analysis Software (SAS version 9.4 for Windows, Cary, NC) and R package (version 3.2.0).

Results

Baseline Patient, Pathological and Treatment Characteristics

Patient characteristics are summarised in Table 1. The median age of 161 patients at diagnosis was 67 years (range 34–92). The median duration of follow-up since diagnosis was 5.3 years (range 0–25 years). Only two patients (1.2%) had bilateral breast cancer. Twenty-five (15.5%) patients had gynaecomastia.

Seventy-three (45.3%) patients had a family history of cancer. Of the 34 patients with known *BRCA* status, three had *BRCA1* mutation (8.8%) and eight had *BRCA2* mutation (23.5%). This included one patient who had a *BRCA1* mutation of uncertain significance. There were 54 patients with previous, secondary or subsequent malignancies (33.5%), the most common of which was prostate cancer ($n = 23$) followed by basal cell carcinoma ($n = 7$).

Disease characteristics and pathology are summarised in Table 2. Most patients presented with stage 2 disease ($n = 63$, 39.1%) and no nodal involvement ($n = 61$, 37.9%), while 11 patients had metastatic disease (6.8%). The most common histological type was invasive ductal carcinoma, no specific type ($n = 146$, 90.7%) although there were 15 (9.3%) patients with other histological types. Overall, most patients were luminal A-like ($n = 86$, 53.4%), followed by luminal B-like ($n = 15$, 9.3%), with one triple-negative patient. The most common Nottingham histologic score was 2 ($n = 75$, 63.0%).

Treatments are summarised in Table 3. Most patients underwent surgery ($n = 143$, 88.8%), the most common of which was mastectomy ($n = 133$, 93.0%). Other treatment modalities included radiotherapy to the breast or chest wall ($n = 95$), chemotherapy ($n = 69$), systemic hormonal therapy (for 122 of 142 patients with ER/PR overexpression) or trastuzumab (for nine of 16 patients with HER2/neu overexpression).

Outcome

Of 161 patients there were 48 deaths (median time to death: 5.4 years; interquartile range [IQR] 2.1–9.0), of which 23 (47.9%) were breast cancer specific. Figure 1A shows the

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