

Aim of the study: The purpose of this retrospective study is to evaluate the clinicopathological features and treatment results of male breast cancer presented to our tertiary referral center.

Material and methods: Between January 1998 and December 2005, a total of 39 men with breast cancer treated at Alexandria Main University Hospital and their medical records were reviewed.

Results: The median age of patients was 59 years. Only 3 (7.7%) patients had positive family history. All patients presented by breast swellings that were associated with axillary mass in about one third of them. Around 80% had hormone receptor positive (estrogen and/or progesterone receptors). Two third of patients had advanced T-stage (T3 and T4). Left sided breast cancer occurred in 51.3%. Infiltrating ductal carcinoma was the most common type of histology encountered and grade 2 was the predominant grade of tumor. Modified radical mastectomy was the most common (87.2%) type of surgery done followed by chemotherapy for 32 patients and loco-regional radiotherapy for 20 patients. Tamoxifen was administered in 31 patients. Distant relapse occurred in 7 patients (17.9%) and local recurrence occurred in 2 patients (5.1%). The 5-year disease-free survival (DFS) was 82% and the 5-year overall survival (OS) rate was 84%. Only negative axillary lymph node and positive hormone receptor status were significantly associated with favorable DFS and OS. T-stage, grade of tumor and type of chemotherapy given had no statistically significant impact on either DFS or OS.

Conclusions: Male breast cancer is still under-investigated and further researches are warranted.

Key words: breast cancer, male.

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Male breast cancer: a clinicopathological study of an Egyptian population (Alexandria experience)

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Introduction

The incidence of male breast cancer (MBC) is low, constituting less than 1% of all breast cancer cases [1, 2]. In central and eastern Africa breast cancer rates are higher and reach 6% of cancers in men, which could be explained by hyperestrogenism due to endemic hepatic infectious disease [3]. A large epidemiological study has shown a growing incidence of male breast cancer of 1% in one year [1]. The male-to-female ratio of incidence in breast cancer is about 1% in western countries, but it was markedly higher in North Africa – 2.7% and even higher in Sub-Saharan countries – 4.9%. Moreover, in Africa the age at diagnosis of breast cancer was seven years later in men than in women [4].

The most important risk factors are family history and mutations of *BRCA*. More than twice the proportion of males with breast cancer have a family history, compared with 7% in the overall male population [5].

Other important risk factors are: Klinefelter syndrome, oestrogen or testosterone use, orchitis/epididymitis, obesity, lack of exercise, and exposure to radiation [6].

Invasive ductal carcinoma constitute approximately 90% of breast cancers in men, whereas only 1.5% of cases are lobular cancers, compared to about 15% of cases in women, which could be explained by the lack of lobules and acini in male breast tissue [5, 7].

The most common type of male breast cancer is hormone receptor positive – 82%, 15% are human epidermal growth factor receptor 2 (HER2)-positive (young patients more likely), and 4% are triple negative. An interesting phenomenon is that non-Hispanic black males are more frequently triple negative – 9% compared to Hispanic – 6% and non-Hispanic white – 3%. A study has shown that non-Hispanic black males had the worst outcomes [8].

Optimal treatments are still vague, and further work is clearly needed to better understand this disease [1–3, 9, 10].

The surgical, systemic, and radiation treatment of males with breast cancer are similar to the rules in the approach for women and depends on the extent of disease at presentation and other risk factors.

Due to the relative rarity of MBC, prospective randomised trials are lacking, and management of MBC is based on either retrospective series or extrapolation from that of females [1, 11]. Therefore, we try in this retrospective study to evaluate the clinicopathological features and treatment results of MBC presented to our tertiary referral centre.

Material and methods

In this retrospective study, the medical files of 39 men with pathologically proven breast cancer, who presented to the Clinical Oncology department,

Alexandria Main University Hospital during the period from January 1998 to December 2005, were reviewed. Patients with clinical evidence of distant metastases at the time of presentation have been excluded. Data regarding history and clinical presentation, investigations, and treatment received were collected and correlated to local recurrence, distant metastasis, and survival.

The overall survival (OS) was calculated from the date of diagnosis to the date of death or last follow-up. Disease-free survival (DFS) was defined as time from date

of diagnosis to date of local recurrence or distant failure, depending on what occurred earlier. Patients without disease recurrence were censored at last follow-up.

Survival was estimated using the Kaplan–Meier product-limit method using SPSS (v. 22) software (SPSS Inc., Chicago, IL, USA). Patient and tumour characteristics, namely age, T-stage, grade of tumour, axillary lymph node (LN) status, and hormone receptor status, were studied to determine the effect of each variable on survival rates. The two-sided log-rank test was used to test the association between patient variables and survival. $P \leq 0.05$ was considered as significant.

Table 1. Patients and disease characteristics of male breast cancer

Characteristics	No. (%)
Age (median)	59 years (range: 33–80)
Family history	
Positive	3 (7.7)
Negative	36 (92.3)
Side	
Right	19 (48.7)
Left	20 (51.3)
Presentation	
Breast mass	39 (100)
Axillary swelling	11 (28.2)
Nipple discharge	6 (15.4)
T-Stage	
T1	1 (2.6)
T2	10 (25.6)
T3	8 (20.5)
T4	20 (51.3)
N-Stage	
Positive	16 (41)
Negative	18 (46.2)
Unknown	5 (12.8)
Histology	
IDC	36 (92.3)
Others	3 (7.7)
Grade	
1	1 (2.6)
2	30 (76.9)
3	2 (5.1)
Unknown	6 (15.4)
Hormone receptor status	
ER+ and/or PR+	31 (79.5)
ER– and PR–	7 (17.9)
Unknown	1 (2.6)
Surgery	
Lumpectomy	5 (12.8)
MRM	34 (87.2)

IDC – infiltrating ductal carcinoma; MRM – modified radical mastectomy; ER – oestrogen receptor; PR – progesterone receptor

Results

Patients' characteristics

Thirty-nine patients were included in this analysis. The median age of patients was 59 years (range: 33–80 years). Only three patients (7.7%) had positive family history. All patients presented by breast mass and about one third of them had axillary mass. Only six patients experienced nipple discharge. Around 80% had positive hormone receptor (oestrogen and/or progesterone receptors). Two thirds of patients had advanced T-stage (T3 and T4). Left-sided breast cancer occurred in 51.3%. Infiltrating ductal carcinoma (IDC) was the most common type of histology encountered, and grade 2 was the predominant grade of tumour. Table 1 shows the characteristics of the patients. Figures 1–6 shows paraffin and immunostained sections of two patients.

Treatment

The majority of patients (87.2%) underwent modified radical mastectomy (MRM). Adjuvant chemotherapy CMF (cyclophosphamide, methotrexate, 5-fluorouracil) and CAF (cyclophosphamide, doxorubicin, 5-fluorouracil) regimens were given for 11 and 21 patients, respectively. Loco-regional radiotherapy was offered to 20 patients. Tamoxifen was administered in 31 patients as an adjuvant after chemotherapy and/or radiotherapy.

Disease-free survival

Seven patients (17.9%) suffered a distant relapse and two patients suffered a local recurrence (5.1%). The commonly involved sites were bone (four patients), lung (three patients), and liver (two patients; one patient developed multiple metastatic sites). The five-year DFS for the entire group was 82% (Fig. 7A). DFS at five years for axillary node-negative patients was 100% and for axillary node-positive patients was 44% ($p = 0.001$). Patients with positive hormone receptors had significantly better five-year DFS (88%) compared to those with negative hormone receptors (25%; $p = 0.000$). T-stage ($p = 0.541$), grade ($p = 0.835$), and type of adjuvant chemotherapy received ($p = 0.447$) had no impact on the five-year DFS (Fig. 8).

Overall survival

The five-year overall survival rate of patients was 84% (Fig. 7B). In univariate analysis, patients with negative ax-

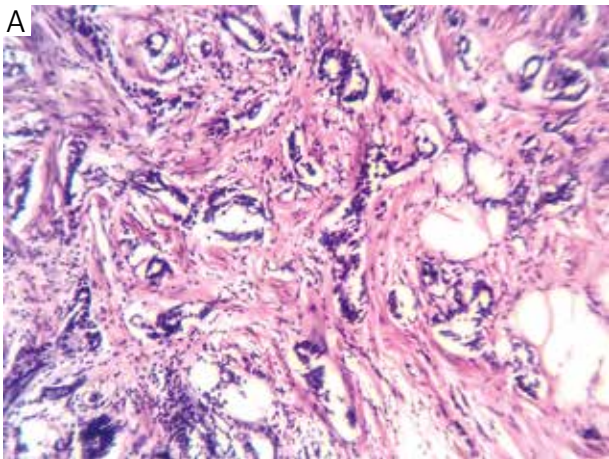


Fig. 1. A case of infiltrating ductal carcinoma of no special type (NST) Grade II showing streaks & ductules of pleomorphic and hyperchromatic ductal carcinoma cells among collagenic stroma (H&E, original magnification 200×)

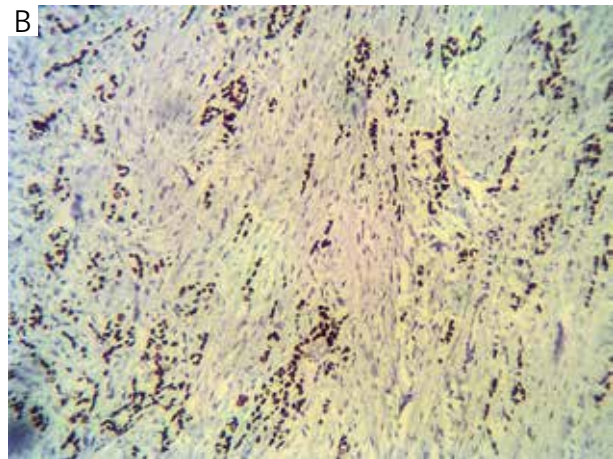


Fig. 2. Immunostained section for ER receptor showing a strong nuclear uptake in almost all of the malignant cell nuclei (original magnification 200×)

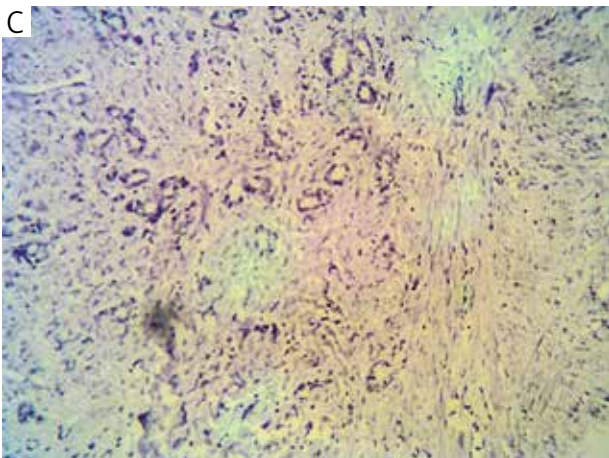


Fig. 3. Immunostained section for PR receptor showing weak nuclear staining in 20% of the malignant cell nuclei (original magnification 200×)

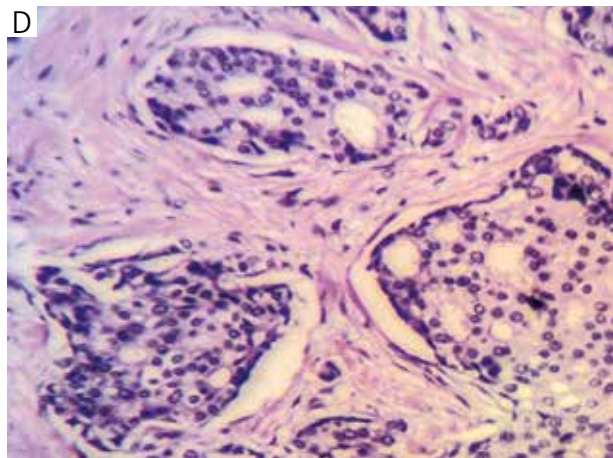


Fig. 4. Paraffin section for another case of infiltrating ductal carcinoma of no special type (NST) Grade II showing groups and nests of pleomorphic and hyperchromatic ductal carcinoma cells (original magnification 200×)

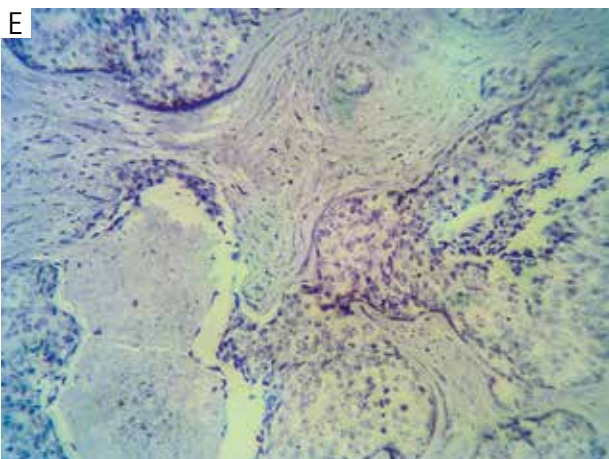


Fig. 5. immunostained section from ER receptor showing negative nuclear uptake in all malignant cells (original magnification 200×)

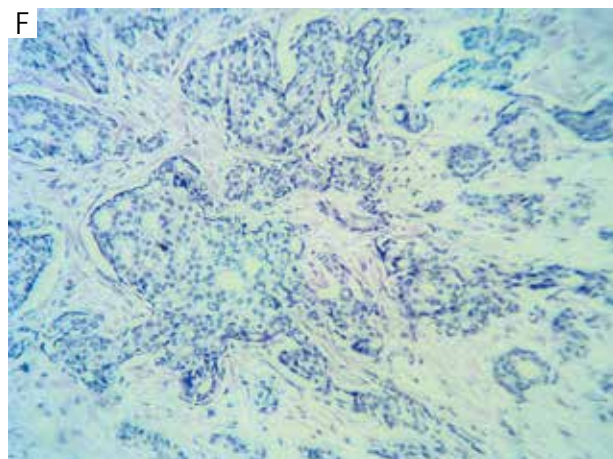


Fig. 6. Immunostaining for PR receptor showing negative nuclear uptake in all malignant cells (original magnification 200×)

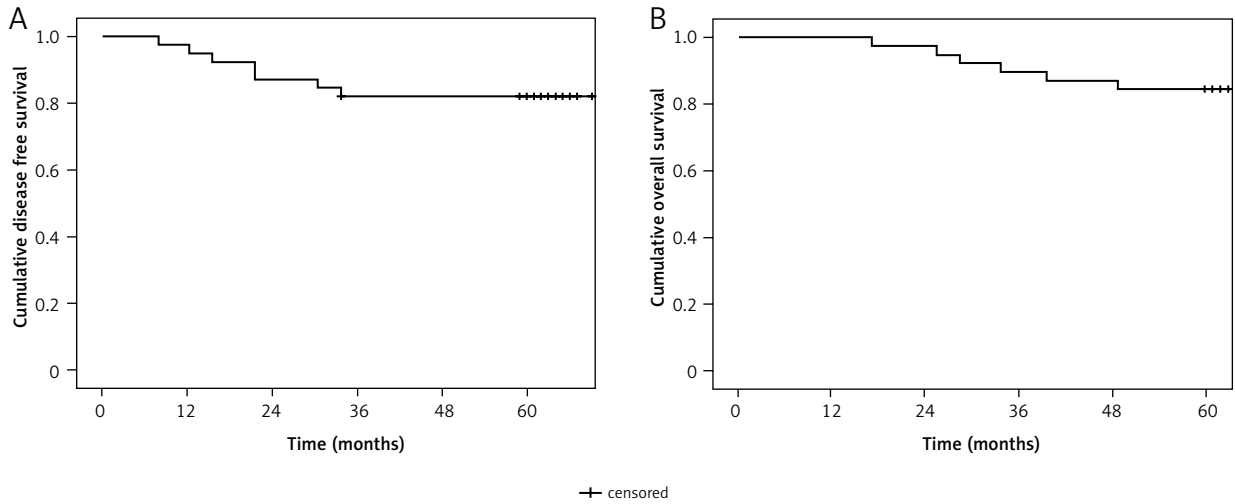


Fig. 1. A) Disease-free survival and B) overall survival rates for men with breast cancer

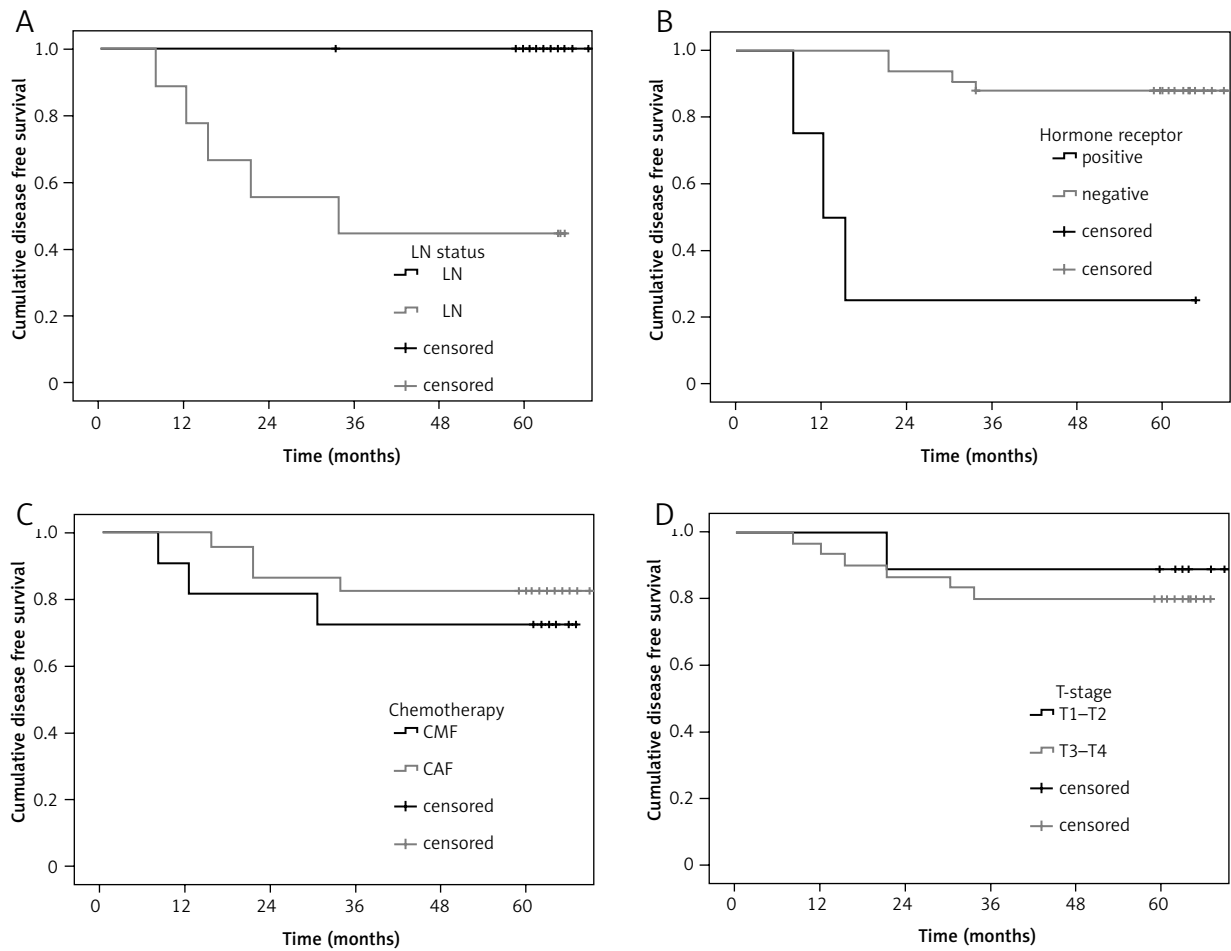


Fig. 2. Disease-free survival rates for men with breast cancer according to LN status (A), hormone receptor status (B), chemotherapy regimen (C), and T-stage (D)

illary node had significantly better OS compared to those with positive axillary node ($p = 0.001$). The subset of patients with positive hormone receptors had significantly better five-year OS compared with those with negative hormone receptors ($p = 0.000$). There was no statistically significant difference in OS based on T-stage, grade of tumour, or type of chemotherapy given.

Discussion

The earliest recorded case of MBC is described in the Edwin Smith papyrus from Egypt (3000–2500 BC); in modern times, the British physician John of Arderne is reported to be the first to discover this disease in a male patient in the 14th century [12, 13]. Male breast cancer, despite being increased in the last decades, is still a rare disease and under-evaluated [1]. Thus, collection of comprehensive data on the presentation and management of MBC may help to optimise the outcome of patients.

The median age of our patients was 59 years, which is consistent with that reported by Crichlow [11]. Unlike female breast cancer, the age at diagnosis in men had no impact on DFS or OS in our series, and this is agreement with that reported by Borgen *et al.* [14].

Consistent with literature [1, 15, 16], we have demonstrated that men tend to have more advanced disease with larger tumour size and more frequent lymph node involvement (about 50% of our patients). This could be explained by the lack of a screening program (unlike for women), smaller breast tissue, unawareness of patients, and lack of expectation among treating physicians; furthermore, the stigma of cancer in general, and breast cancer (a disease of woman) in particular, make men seek medical advice later.

Men are significantly more likely to have hormone receptor-positive disease than women. Similar to that reported by Giordano *et al.* [1], 80% of men had hormone receptor-positive tumours in our series, compared with 67–76% in women [9, 17, 18].

Oestrogen receptor is expressed in 75–97%, progesterone receptor in 59–96%, and HER2 in 1.7–29% in MBC in different series [19].

Surgery is the keystone in the treatment of MBC followed by adjuvant therapy [20–22]. Post-operative chemotherapy was given in about 80% of patients depending on the extent of tumour (T- & N-stage), hormone receptor status, age, performance status of the patients, and associated co-morbidities. Adjuvant radiotherapy was applied in about half of our patients due to any of the following: involvement of the skin and/or pectoral muscle and areola, inadequate margins, and metastatic spread to the axillary lymph nodes. Tamoxifen was the only adjuvant hormonal therapy experienced in our patients with hormone receptor-positive disease.

The five-year survival rate of patients was 84%, which is consistent with that reported by previous studies [2, 14]. Survival is comparable with reports from developed countries and higher than other series from Africa [23, 24]. Borgen *et al.* [14] found that the five-year OS was 85%. Relapse-free survival at five years for axillary node-negative

patients was 87% and for node-positive patients was 30%. Five-year survival was 100% for the node-negative subset and 60% for the node-positive subset. Like in female breast cancer, we found that the most powerful predictors of outcome in men were axillary lymph nodes status and hormone receptors status. However, T-stage did not impact the survival because only one patient had T1, and we analysed T1 & T2 together [20, 25].

The current study documents improved survival rates compared to those that have been historically reported for male breast cancer patients, and these may be a reflection of the proper adjuvant treatment received in most of our patients [21, 22, 26–29]. The survival figures reported are similar to currently accepted figures reported for female breast cancer [2, 14].

To our knowledge, this is the first trial from our heavily populated city with more than four million persons to address this issue. We know that our study has some limitations, being a retrospective trial with selection bias, small sample size, and a lack of information on risk factors such as testicular disease, benign breast conditions, and the Klinefelter syndrome. Moreover, pathological data regarding BRCA1, BRCA2, Her2/neu, and Ki-67 are not available [30]. Multivariate analysis was not performed to determine the independent effect of each variable in the presence of other variables.

In conclusion, MBC is very similar to female breast cancer but has certain unique features, which should be further explored in future research. In the absence of solid evidence, adjuvant treatment should be strongly considered and should be based on the greater base of knowledge available for carcinoma of the female breast.

The authors declare no conflict of interest.

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