

Clinical Paper

Long Term Follow Up of Male Breast Cancer.

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ABSTRACT

Introduction: Male breast cancer accounts for less than 1% of breast cancers with published overall and disease free survival being lower than in females.

Aims: To determine treatment and long term outcomes for male breast cancer patients in our unit.

Methods: A database has been maintained for all breast cancer patients diagnosed in our unit since 1993. Patients were identified using the database and information was collated on patient demographics, tumour pathology, treatment and outcomes using the database and retrospective chart review. Patients were followed to cause of death.

Results: From 1994-2009 twenty-four cancers were diagnosed in twenty-two patients. Mean age at diagnosis was 69. Male breast cancer patients were treated using similar principles to female breast cancer. Twenty patients underwent mastectomy, two patients underwent wide local excision. No patients developed local recurrence. One patient died from their breast cancer with systemic metastases. 10-year overall survival was 22%, 10 year disease-specific survival was 80%. Other causes of death included medical co-morbidity and secondary cancers.

Discussion: Disease free survival in our unit is comparable to other published studies. High age at diagnosis and co-morbidity are the most important factors in determining overall outcome. Treatment pathways for male breast cancer should follow guidelines for female disease in order to optimise outcomes. Future research at national or international level is necessary to ensure the most effective treatments are implemented for male breast cancer patients.

Keywords: male breast cancer, treatment, outcomes.

INTRODUCTION

Male breast cancer is an uncommon disease, accounting for less than 1% of malignancies in men, and less than 1% of all breast cancers. Approximately 300 men in the UK are diagnosed with the disease each year¹. Incidence appears to be increasing, which may be a reflection of increasing longevity in the population or the rising rates of obesity in developed countries².

The bimodal age distribution seen in female breast cancer is absent in males, where peak incidence occurs around the age of 70³. The aetiology is not fully understood, although, as in females, hormonal, environmental and genetic factors have been implicated. Hormonal imbalance occurring endogenously secondary to testicular abnormalities increases risk. Additionally, exogenous oestrogens such as in men treated for prostate cancer increases risk, and individuals with Klinefelter's syndrome (47XXY) have a 20-50 times higher risk of developing the condition⁴. Obesity, a common cause of hyperoestrogenism, has been implicated. Gynaecomastia, physiological male breast tissue, does not increase risk⁵. Genetic factors appear to play more of a role in males than in females with approximately 10% of men with breast cancer carrying *BRCA2* mutations, while mutations in *BRCA1* are

exceedingly rare⁶. Recently, the *CHEK2* 1100delC variant has been found to give a 10-fold risk of male breast cancer independent of *BRCA1* or *BRCA2*⁷.

Male breast cancer presents at a later age and often more advanced stage with larger tumour size and more frequent nodal involvement than in females. As a consequence, overall survival rates are lower for men and have not improved over the last number of years as female outcomes have³.

Treatment guidelines are largely based on existing knowledge from treatment of females as no randomised controlled trials exist to support a specific therapeutic approach. Retrospective studies have not suggested different treatment algorithms should be employed. As with females, treatment involves surgery, with simple mastectomy followed by either sentinel node biopsy or formal axillary clearance being the procedure of choice. As the condition is predominantly hormone-receptor-positive, hormonal therapy is an essential component of treatment⁸. Tamoxifen treatment is considered

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the optimum for oestrogen receptor positive disease as several retrospective trials have reported improved disease-free and overall survival rates in those given adjuvant Tamoxifen⁹. Contrastingly, aromatase inhibitors have been linked to a 1.5-fold increase in risk of mortality compared to tamoxifen. Overall survival has been shown to be significantly better in patients given tamoxifen as compared with aromatase inhibitors¹⁰.

The South Eastern Health and Social Care Trust serves a population of approximately 440,000 people in Belfast and North County Down. It provides services for both secondary and tertiary referral and plays an important role in breast screening. Each year approximately 300 new cases of breast cancer are diagnosed, with 1-2 of these being in men. The aim of this study was to determine patient demographics, treatment approaches and outcomes for patients in our unit from 1994-2009.

PATIENTS AND METHODS

A database has been maintained for all breast cancer patients diagnosed in our unit since 1993. Patients diagnosed with the condition from 1994 to 2009 were identified and data was collected from the database and retrospective chart review with review of histopathological reports. Patients were followed to cause of death by reference to the database and this was confirmed using Northern Ireland Electronic Care Record (NIECR). All patients with the condition were included for analysis. No patients were excluded. Information collated included patient demographics, tumour pathology, treatment and outcomes. Due to the fact that not all tumours were examined for hormone receptor status in the mid-nineties, no information was available on human epidermal growth factor (HER-2) status for 16 tumours. Furthermore 7 tumours were not examined for oestrogen receptor (ER) status and 15 tumours not examined for progesterone receptor (PR) status. Unfortunately, no histological grading was stated on the histopathology reports for 2 tumours. All other data was complete. Unit policy has been to treat male breast cancer on the basis of tumour biology, staging and comorbidity as would be best practice with females. Data were collected on Microsoft Excel (Microsoft Corp, Redmond, WA, USA) and then analysed using SPSS (Version 12, SPSS Inc, Chicago, IL, USA). Age, tumour size and Nottingham Prognostic Index (NPI) were expressed as mean and standard deviation.

RESULTS

From 1994-2009, 24 breast cancers were diagnosed in 22 patients. One patient had synchronous and one patient metachronous breast cancer. Mean age at diagnosis was 69 years (SD 8.84). The patient with metachronous breast cancer had Klinefelter's syndrome.

Twenty patients underwent simple mastectomy with nipple removal, with 2 patients having bilateral mastectomy, one concurrently and the other a second mastectomy 4 years after his initial surgery. The remaining 2 patients underwent wide local excision with nipple preservation, with one of these

individuals requiring mastectomy due to proximity of tumour to surgical margins. 2 patients had sentinel node biopsy and 22 had an axillary node clearance. One patient, with synchronous cancer underwent bilateral axillary node clearance. One patient, with metachronous breast cancer underwent axillary clearance at his first operation and sentinel node biopsy at his second. Mean tumour size was 19mm (SD=-13.9) and Mean Nottingham Prognostic Index (NPI) was 3.38 (SD+/- 1.36). Tumour characteristics are summarised in Table 1. Adjuvant therapy is summarised in Table 2.

TABLE 1
Characteristics of Tumours (Total n =24)

Histological Type	
Infiltrating ductal	20
Papillary	1
Mixed ductal and lobular	1
Ductal Carcinoma in situ	2
Tumour Grade	
1	4
2	14
3	4
No data available	2
Hormone Receptor Status	
ER status examined	17
ER +ve	17
ER -ve	0
ER status not examined	7
PR status examined	9
PR +ve	9
PR - ve	0
PR status not examined	15
HER2 status examined	8
HER2 +ve	0
HER2 -ve	8
HER2 status not examined	16
Nodal disease	
Nodes +ve	6
Nodes -ve	18
Stage (TNM)	
1	11
2a	6
2b	3
3a	1
3b	1
3c	1
4	0



* One patient, who had bilateral metachronous disease, developed deep vein thrombosis on Tamoxifen and treatment was stopped.

TABLE 2
Adjuvant therapy

Hormonal treatment	21 (95%)
Chemotherapy	1 (5%)
Radiotherapy	11 (50%)

No patient had distant metastases at presentation. Only 6 patients had node positive disease. No patients developed local recurrence. As only one patient has had metastases after treatment, no prognostic factors have been correlated. One patient developed systemic relapse 9 years after his initial diagnosis, with lung metastases. He underwent a successful lobectomy, but developed intracerebral metastases and despite chemotherapy died 48 months after his diagnosis of metastatic cancer. No patients have died as a result of their treatment. Fourteen patients have died in total, with causes of death including cardiac failure, stroke, myocardial infarction, lymphoma and primary lung cancer. Four patients have been followed up for less than 10 years (Table 3).

TABLE 3

Median follow up (months)	115
5 year overall survival	67%
5 year disease specific survival	90%
10 year overall survival	22%
10 year disease specific survival	80%

DISCUSSION

This retrospective case series is limited by its small size as is often the case with male breast cancer studies worldwide. Our results show similar demographics to other studies, with a high mean age at diagnosis and a comparable frequency of histopathological type of disease. The rate of nodal involvement is lower than other studies published^{3,5,11}.

Surgery has been the mainstay of our treatment protocols, with the most commonly performed operation being mastectomy and axillary node clearance. In recent years' sentinel node biopsy has been more common, and as patients were selected carefully based on tumour size, no patients have required further axillary surgery. We have performed wide local excision with nipple preservation in 2 patients, one of which required mastectomy due to close proximity of surgical margins.

All patients were started on Tamoxifen and completed a duration of treatment of 5 years with the exception of one patient who required cessation of therapy due to deep vein thrombosis. Although not all patients were tested for hormone receptor status in the mid-nineties, our results suggest that all the patients in our unit tested for hormone receptor status had

oestrogen receptor positive breast cancer. Oestrogen receptor status was however unknown in 7 cases. HER2 status was negative when tested however results were unavailable for 16 tumours. No patients received Trastuzumab.

Retrospective studies investigating the benefit of radiotherapy have suggested better local control with radiotherapy and improved overall survival for stage 1 disease but no association with improved cause-specific survival¹². The role for adjuvant chemotherapy is not well established¹³.

Eleven patients had radiotherapy and no patient, either in the radiotherapy or no radiotherapy groups developed local or regional recurrence. One patient who did have radiotherapy developed distant metastases. It is impossible to ascertain if this means our selection process for radiotherapy is effective and accurate or if there is no difference resulting from radiotherapy.

Only one patient developed systemic disease and had chemotherapy and so we are unable comment on its benefit. Other studies have reported an uptake of chemotherapy in the region of 33%¹³. Despite only one patient in this study receiving chemotherapy, outcomes have been excellent with regard to disease free survival. This may suggest chemotherapy is not particularly useful unless systemic disease exists.

Historically, overall survival and disease free survival for male breast cancer have been lower than that of female breast cancer³. Contributory causes include a lack of awareness in the population, later stage at diagnosis and reduced uptake of adjuvant treatment. In more recent years overall and disease specific survival have been shown to comparable with females when matched for age and stage¹⁴. Our study shows ten-year disease free survival (80%) in our unit is comparable to other published studies^{5,14}. Only one patient has died from their breast cancer. Ten-year overall survival is consistent with other reported studies at 22%, showing that the high age at diagnosis is the most important factors in determining outcome. In particular, comorbidity and development of second cancers appears to be more important than in females.

CONCLUSIONS

In this small retrospective case series, treatment of male breast cancer has been based on principles similar to those for females, namely pathology, tumour biology, and patient co-morbidity. It is likely that age at diagnosis and medical co-morbidity were the most important prognostic factors in determining ten-year overall survival. Mastectomy and Tamoxifen would appear to be the most effective treatments. We suggest that males should be treated proactively and no differently from females.

Outcomes for male breast cancer would appear to be consistent with that described in the literature^{5,14}. However, given the fact that numbers are limited, the question of whether the prognosis for breast cancer is worse in males than in the female population remains unanswered.



It is difficult, if not impossible to carry out adequately powered randomised controlled trials as they would necessarily involve multiple centres and a long study period. Due to speed of progress in the treatment of female breast cancer, where large randomised controlled trials are feasible, it may be most appropriate to concentrate on providing males with comparable treatment to females, specifically best treatment practices for post-menopausal breast cancer. Future research must be at national or international level to ensure the most effective treatments are implemented for these patients. An ongoing international retrospective male breast cancer programme with prospective study by The European Organisation for Research and Treatment of Cancer (EORTC) may provide additional understanding of optimal treatment approaches and long term outcomes for male breast cancer patients.

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