

GENERAL CHARACTERISTICS OF MALE BREAST CANCER PATIENTS IN BURSA REGION

Nilüfer Avcı¹, Mehmet Ali Balcı², İrfan Esen², Gülen Tandođan², Mustafa Merter², Erdem Çubukçu¹, Fatih Ölmez¹, Belkıs Nihan Coşkun², Mustafa Hartavi², Şahsine Tolunay³

¹Uludađ Üniversitesi Tıp Fakóltesi, Medikal Onkoloji Anabilim Dalı, Bursa, Türkiye

²Uludađ Üniversitesi Tıp Fakóltesi, İç Hastalıkları Anabilim Dalı, Bursa, Türkiye

³Uludađ Üniversitesi Tıp Fakóltesi, Patoloji Anabilim Dalı, Bursa, Türkiye

BURSA BÖLGESİNDE ERKEK MEME KANSERLİ HASTALARIN GENEL ÖZELLİKLERİ

ÖZET

Giriş: Erkek meme kanseri tüm meme kanseri olgularının %1'den azını oluşturmaktadır. Bu çalışmada merkezimizde takip ve tedavi edilen erkek meme kanserli olguların klinik ve patolojik özelliklerini inceledik.

Materyal ve Metod: Erkek meme kanserli hastaların klinik ve patolojik verileri, dosyaların retrospektif olarak taranması ile elde edildi.

Sonuçlar: Çalışmaya alınan toplam 16 hastanın ortalama yaşı 60 (41-75) olarak bulundu. En sık gözlenen meme kanseri tipi (%81.3) infiltratif duktal kanserdi. Tanı sırasında erkek meme kanserleri çoğunlukla lokal ileri evre (%50, evre 3) idi. Hormon reseptör durumuna bakıldığında olguların çoğunun (%81.3) ER ve/veya PR pozitif olduğu gözlemlendi. HER2 ekspresyonu hastaların 9'da incelenmişti, ve 4 olguda (%25) pozitif idi. Genel sağ kalım 3 (1-12) yıl, hastaliksız sağ kalım 2 (1-8) yıl olarak saptandı.

Tartışma: Kadınlarda meme kanserine dair bilgiler artmasına rağmen, erkek meme kanserlerinin tedavisine dair bilgiler sınırlıdır. Bu nedenle erkek meme kanserlerinde tedavi ile ilişkili randomize çalışmalara ihtiyaç vardır.

Anahtar sözcükler: meme kanseri, erkek

ABSTRACT

Introduction: Male breast cancer constitutes less than 1% of all cases of breast cancer. In this study, we analyzed clinical and pathological features of male breast cancer cases, which had been followed up and treated at our institution.

Material and Method: The data regarding the main clinicopathological features of the male breast cancer patients were retrieved from the patients' records retrospectively.

Results: A total of 16 patients were included in the analysis with a median age of 60 (41-75). The most common cell type was infiltrating ductal carcinoma, comprising 81.3% of all cases. Most patients were staged as locally advanced (50% – stage 3) at the time of diagnosis. Estrogen and/or progesterone receptor positivity were found in 13 patients (81.3%). HER2 status could be examined in 9 patients, and 4 patients (25%) found to be positive for HER2 overexpression. Overall survival was 3(1-12) years and disease-free survival was 2 (1-8) years.

Discussion: Despite the increasing knowledge about breast cancer in women, little is known in case of male breast cancer management. Therefore, there is a strong need to perform randomized studies for the treatment of male breast cancer.

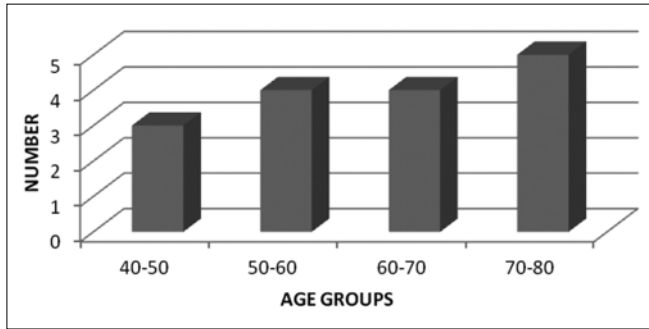
Key words: breast cancer, male

Introduction

While the incidence of female breast cancer has decreased for the last years, the increased incidence of male breast cancer is spectacular (1). In USA, 1910 cases of newly diagnosed male breast cancer were seen only in 2009 and, of these cases, 440 were fatal (2). Male breast cancer accounts for 0.5% of all cases of breast cancer and for less than 0.2% of all male cancers. The incidence of male breast cancer may vary between the regions; its incidence is higher in North America and Europe and lower in Asia (3). Mean age of onset is 65-67 years and it onsets at more advanced age compared to women (3,4). Although epidemiological literature for female breast cancers is wide spread, there are limited data for male breast cancers. In case-controlled meta-analyses, it was reported that male breast cancer was more commonly seen in the people who have never get married; in Jewish men; in those with a known benign

breast disease; in those who received radiotherapy to their chest; in those with testicular abnormalities (undescended testicle, orchitis); in those with chronic hepatic disease; and in the users of finasteride. Genetic factors are important. Although rarely seen, Klinefelter syndrome is a high-risk factor for the development of breast cancer. In the men with a familial history of breast cancer, the incidence of male breast cancer is increased. In the previous studies, it was demonstrated that this risk was more increased in the carriers of BRCA2 mutation compared to the carriers of BRCA1 (1,3). Clinical characteristics and the treatment of male breast cancer have some similarities and differences compared to female breast cancer.

It is thought provoking that, despite the advances in the diagnosis and the treatment of breast cancer, the decrease in death rate was lower in men compared to women (1). Today, the awareness



Graphic 1. Distribution of the patients by age groups.

for breast cancer is increased with the help of the studies done with women. However, in the community, the awareness for male breast cancer is still low.

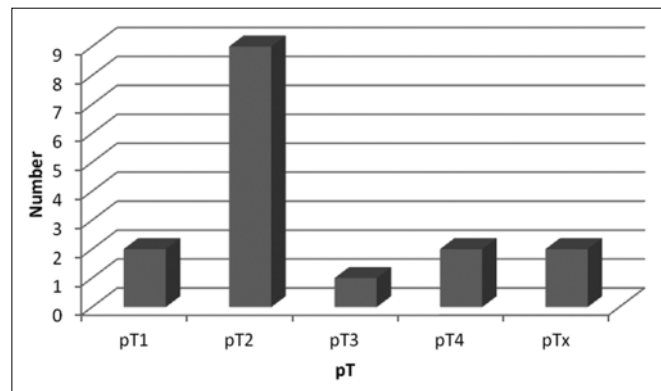
In this study, we examined the clinical and pathological characteristics of the patients with male breast cancer, who have been followed-up and treated in our center. In addition, we aimed to remind the necessity to increase the awareness for the early diagnosis of male breast cancer as much as female breast cancer.

Material and Method: We retrospectively screened the files of the patients diagnosed with male breast cancer, who have been periodically followed-up in Uludag University, Faculty of Medicine, Medical Oncology clinic between 1997 and 2010. Age and demographic characteristics of a total of 16 patients were evaluated. Histological type of the tumor, tumor size, lymph node metastasis, hormone receptor status, previously administered therapeutic modalities and survivals were examined.

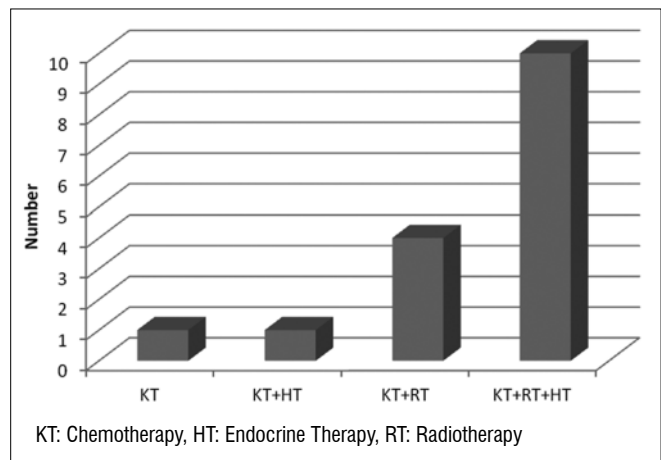
Results: Median age of a total of 16 patients was 60 (41-75) (Graphic 1). Of our cases, 10 were smokers. When histological subtype was assessed, the most commonly observed subtypes in men were invasive ductal breast cancer (13 patients, 81.3%), invasive papillary cancer (2 patients, 12.5%) and invasive lobular cancer (1 patient, 6.3%) (Table 1). Tumor diameter was 2.1-5 cm in 81.3% of the subjects (Graphic 2). While the majority of the subjects (n=10) had grade 2 breast cancer, the remaining had grade 3 breast cancer (n=6). When the staging performed at the time of diagnosis was reviewed, it was seen that, of the subjects, 37.5% had Stage 3A, 31.3% had Stage 2B, 12.5% had Stage 3B and 6.3% had Stage 4A disease. However, only 6.3% of the subjects had the diagnosis at Stage 1. Additionally, due to missing data in the files, the staging at the time of diagnosis could not be done in 6.3% of the subjects. Of the subjects, 13 underwent modified radical mastectomy and 3 underwent total mastectomy. Surgical margin was negative in 75%, positive in 18.8% and unknown in 6.3% of the subjects. All subjects were given adjuvant chemotherapy. In the adjuvant chemotherapy 11 subjects received FEC (5-fluorouracil+epirubicin+cyclophosphamide), 3 subjects received FEC+docetaxel and 2 subjects received CMF (cyclophosphamide+methotrexate+fluorouracil). Adjuvant radiotherapy was given to 14 subjects. It was not

Table 1. Distribution of histopathological types.

Histopathology	N	%
Invasive ductal cancer	13	81,3
Invasive papillary cancer	2	12,5
Invasive lobular cancer	1	6,3

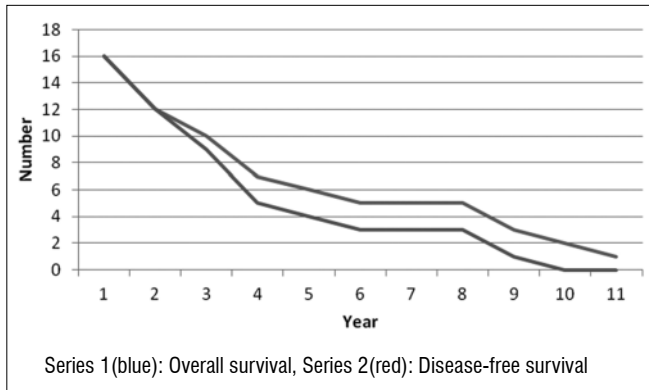


Graphic 2. Pathologic tumor size.



Graphic 3. Additional therapies.

known whether other 2 subjects received radiotherapy (Graphic 3). The examination of hormone receptor status revealed that, of the subjects, 81.3% were ER-positive, 12.5% were ER-negative and 6.3% had an unknown ER status. Human epidermal growth factor receptor-2 (HER2) was positive in 25% and negative in 31.3% of the subjects. Unfortunately, HER2 was not studied in 6 subjects between 1996 and 2002 and HER2 was not specified in the pathology report of one subject. In other words, HER2 status was unknown in 43.8% of the subjects. While endocrine therapy was given to 11 subjects, 5 subjects had no information about the treatment given in the registries (Graphic 3). There was no data for the use of Herceptin. Death occurred only in 1 subject due to intracranial metastasis and due to pneumosepsis in 1 subject.



Graphic 4. Disease-free and overall survival by years

Overall survival was 3 (1-12) years and disease-free survival was 2 (1-8) years (Graphic 4).

Discussion

The breast cancer had a lower incidence in men compared to women and the incidence rate reported in the studies varied by region, ranging from 1% in Europe to up to 5-15% in Western Africa (3-4-5-6-7). Age of onset of breast cancer is greater in men compared to women and mean age of onset was reported to be 67 years in the literature (5). Median age of initial diagnosis we found in the patients with male breast cancer that we have followed-up in the region of Bursa was consistent with the literature.

Male breast cancer manifests itself as a usually painless subareolar mass, which may be accompanied by retraction, ulceration, bleeding and discharge of the nipple. Bilateral involvement is very rare, with an incidence of 2% reported in the literature (8). In our cases, we did not observe bilateral involvement. For the mammography used in the differential diagnosis between breast cancer and gynecomastia, the sensitivity was 92% and specificity was 90%. Ultrasound is important in the evaluation of nodal involvement (9).

The distribution of histological subtypes of breast cancer is different between men and women and male breast anatomy is important in the occurrence of these differences. Invasive ductal cancers were the most commonly observed subtypes (90%) and papillary cancers followed them. In the anatomy of male breast, lobular histology is very rare due to the absence of terminal lobules (1). In our subjects, consistent with the literature, the distribution rates of histological subtypes were as follows: invasive ductal cancer, 81.3%; invasive papillary cancer, 12.5%; and invasive lobular cancers, 6.3%.

In the cases of breast cancer, the rates of estrogen (ER) and progesterone (PR) receptor positivity were higher in men compared to women. In the literature, there are various insights about HER2. While HER2 positivity was 15% in two previous studies (10-11-12), the literature contains some studies that reported higher

positivity rates for men compared to women (30-56%) (1). While HER2 positivity was 25% in our followed-up subjects; it was unknown in 43.8% of the subjects. Therefore, in our study, it was challenging to compare HER2 positivity obtained in men with HER2 positivity observed in women.

In male breast cancers, important prognostic factors include tumor's diameter and lymph node involvement. Mean tumor diameter is 2.4 cm. Death rate is greater by 40% in the patients with a tumor diameter of 2-5 cm compared to those with a tumor diameter of <2 cm. Similarly, death rate is greater by 50% in the men with lymph node involvement compared to those without lymph node involvement (13).

Breast cancer is detected at more advanced stages in men compared to women. While more than 40% of the patients have stage 3 or 4 disease at the time of diagnosis in Western countries, this percentage reaches to 54%-100% in Africa (7). In our subjects, the majority of the patients had stage 3 disease at the time of diagnosis, whereas only 6.3% had stage 1 disease. The low level of breast cancer awareness among men may explain this very low rate of early diagnosis in the region of Bursa.

Local therapies administered for the treatment of early stage male breast cancer are similar to those administered in women. Most commonly used surgical method is modified radical mastectomy. Generally, lumpectomy cannot be done due to small amount of breast tissue and to central localization of the tumor. Axillary lymph nodes are often evaluated during the surgical intervention. For T3/T4 tumors at the time of diagnosis and inflammatory breast cancers, pre-surgical chemotherapy should be considered. Similar to female breast cancers, adjuvant radiotherapy is recommended for the patients with a high risk for relapse (4 or more axillary lymph node involvements, T3, T4). Many studies showed that adjuvant radiotherapy improved the local recurrence, but did not have an effect on the survival (13-14). In men, data for adjuvant chemotherapy are not as abundant as in women. In male breast cancers, adjuvant chemotherapy is recommended if there is no response to endocrine therapy, if the tumor diameter is >1 cm and if there is axillary lymph node involvement (regardless of the tumor size). In the literature, anthracycline-containing combinations were recommended for the patients without axillary lymph node involvement and taxane-containing combinations for the patients with axillary lymph node involvement (8).

During the chemotherapy, we gave FEC to 11 patients, FEC+docetaxel to 3 patients and CMF to 2 patients. For hormone receptor-positive early stage breast cancers, it is recommended to administer adjuvant tamoxifen for 5 years following the surgery. Tamoxifen is less tolerated in men and its side effects include decreased libido, weight gain, hot flush and depression (16). Among the cases of male breast cancer followed-up in our hospital, 10 received tamoxifen and none of them discontinued the therapy due to side effects.

For the treatment of metastatic hormone receptor-positive male breast cancer, endocrine therapy (tamoxifen) is the commonly preferred therapeutic modality. More than 80% of these patients have a response to tamoxifen. Systemic chemotherapy should be considered in the patients who are refractory to endocrine therapy, in those with fast visceral metastases and in those with hormone-negative metastatic breast cancer. Although there are limited data about the use of aromatase inhibitors in the adjuvant therapy, they are efficient in the treatment of metastatic male breast cancer (1). In 15 patients with metastatic male breast cancer treated with aromatase inhibitors (exemestan, letrozol or anastrozol), clinical benefit was reported in 53% (16). Addition of gonadotropin releasing hormone (GnRH) analogues to the therapy may increase the efficacy of the aromatase inhibitors. The role of fulvestrant is not clear. In the treatment of HER2-positive male breast cancer, trastuzumab should be added to the therapy (1).

While the prognosis of breast cancer was reported to be poorer in men compared to women, a thorough examination performed in the following years by age, grade and stage at the time of diagnosis revealed that the prognosis was similar compared to women (6). However, the survival is shorter in male breast cancers (8). In Bursa region, overall survival was 3 years and disease-free survival was 2 years in the cases of male breast cancer that were followed-up.

Conclusion

It is important that death rate was higher in male breast cancers compared to female breast cancers. Although Bursa is a Western city, the rate of diagnosis of breast cancer at an advanced stage was remarkable. However, it would be useful to evaluate these data along with larger series that also include other regions of our country and to initiate several campaigns in order to increase the awareness for male breast cancer.

References

1. Onami S, Ozaki M, Mortimer E. J, Kumar S. Male breast cancer: An update in diagnosis, treatment and molecular profiling. *Maturitas* 2010; 65:308-314. (PMID: 20138719)
2. Madeira M, Mattar A, Jose Barata R, Dornelles Mora C. A case report or male breast cancer in a very young patient: What is changing? *World Journal of Surgical Oncology* 2011; 9:16. (PMID: 21291532)
3. Weiss R. J, Moysich B. K, and Swede H. Epidemiology of male breast cancer. *Cancer Epidemiology, Biomarkers&Prevention* 2005; 14:20-26. (PMID: 15668471)
4. Jemal A, Murray T, Ward E. Cancer statistics, 2005. *CA* 2005; 55:10-30. (PMID: 15661684)
5. Ewertz M, Holmberg L, Karjalainen S. Incidence of male breast cancer in Scandinavia, 1943–1982. *IJC* 1989; 43:27-31 (PMID: 29108299)
6. Anderson WF, Althuis MD, Brinton LA, Devesa SS. Is male breast cancer similar or different than female breast cancer? *Breast Cancer Res Treat* 2004; 83:77-86. (PMID: 14997057)
7. Rachid S, Yacouba H, Hassane N. Male breast cancer:22 case reports at the National Hospital of Niamey- Niger (West Africa). *Pn African Medical Journal* 2009; 3:15. (PMID: 21532724)
8. Santos VM, Cintra Osterne EM, Castro RA. Bilateral male breast cancer: too many concerns? *Asian Pac J Cancer Prev* 2007; 8:640-641. (PMID:18260745).
9. Evans GF, Anthony T, Turnage RH. The diagnostic accuracy of mammography in the evaluation of male breast disease. *Am J Sug* 2001; 181:96-100. (PMID: 11425067)
10. Rudlowski C, Friedrichs N, Faridi A. Her-2/neu gene amplification and protein expression in primary male breast cancer. *Breast Cancer Res treat* 2004; 84:215-223. (PMID: 15026619)
11. Muir D, Kanthan R, Kanthan SC. Male versus female breast cancers. A population- based comparative immunohistochemical analysis. *Arch Pathol Lab Med* 2003; 127:36-41. (PMID: 12521364)
12. Giordano SH. A Review of the diagnosis and management of male breast cancer. *The Oncologist* 2005; 10:471-479. (PMID: 16079314)
13. Giordano SH, Cohen DS, Buzdar AU. Breast carcinoma in men: a population-based study. *Cancer* 2004; 101:51-57. (PMID: 15221988)
14. İren S, Yirmibeşođlu E, Bora H, Akmansu M, Pak Y. Erkek meme kanserinde postoperatif adjuvan radyoterapi: Retrospektif deđerlendirme. *Meme Sađlıđı Dergisi* 2010;6:1
15. Anelli TF, Anelli A, Tran KN. Tamoxifen administration is associated with a high rate of treatment-limiting symptoms in male breast cancer patients. *Cancer* 1994; 74:74-77. (PMID: 8004585)
16. Doyen J, İtalyano A, Largillier R. Aromatase inhibition in male breast cancer patients: biological and clinical implications. *Ann Oncol* 2010; 21:1243-1245. (PMID: 19861576)

Correspondence

Nilüfer Avcı
Tel : +90(224) 2951325
E-mail : nilavci@uludag.edu.tr