

Original Research Article

HER-2 Positive Breast Cancer in Men – A Pilot Study

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Abstract : The aim of the study was to describe the biological characteristics of male patients with confirmed rare diagnosis of male breast cancer (MBC) in Slovakia. We retrospectively analyzed data from oncology centres from pathological findings in 67 men diagnosed with breast cancer in the period 2008 to 2013 in Slovakia. Each patient was assessed at the time of breast cancer diagnosis for age, estrogen receptor positivity and HER-2 positivity status. The results of the study showed that the average age of men at the time of diagnosis with HER-2⁺ status was 62 ± 2.5 years and with HER-2⁻ status was 68 ± 3.1 years. Her-2 was overexpressed in 16 of the 67 patients (24 %) (Significant paired T-test, $p = 0.0187$) and estrogen receptors (ER) were positive in 54 of all 67 patients (81 %). Fourteen of the 16 HER-2⁺ patients were ER⁺/HER-2⁺ (88 %), while 40 of the 51 HER-2⁻ patients were ER⁻. The findings of this pilot study show that men with breast cancer were older than women at the time of diagnosis. Most patients with breast cancer had ER⁺ and HER-2⁻ tumours. The evaluated biological characteristics of MBC in Slovakia are comparable with existing literature data. These results may help us to understand better the behaviour of MBC and improve therapeutic strategies for the management of male oncology patients in Slovakia.

Keywords: male breast cancer, HER-2, estrogen receptor, HER-2/ER-CER.

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INTRODUCTION

Male breast cancer (MBC) is a rare disease and it accounts for less than 0.6 % of all diagnosed breast cancer and less than 1 % of all cancers in men. Worldwide however the number of newly-diagnosed MBC cases increased from 8.5 thousand in 1990 to 23.1 thousand in 2017, with the age-standardized incidence rate significantly increased from 0.46/100000 to 0.61/100000 [1].

The aetiology of breast cancer in men does not have such a broad background compared to that in women, but a link between genetic diseases and estrogen and testosterone imbalances is suspected [2]. The low incidence of this type of cancer in men is not conducive to clinical trials with a large number of patients, but literature sources in recent years point to therapeutic approaches and treatment interventions in men with breast cancer, and examine histological,

pathological and pathophysiological differences between women and men [3, 4].

In fact there are also several differences between the genders regarding the epidemiology, tumour biology, clinical behaviour, histological type, therapy, prognosis and survival in breast cancer. The average age at diagnosis in men with breast cancer is 67 years compared to 62 years in women [5].

Initial diagnosis of MBC often occurs at a later stage than in female BC, and male BC often exhibits more advanced disease features, such as larger tumour size, higher lymph node involvement and distant metastases at the time of diagnosis [6]. Estimates of in situ carcinoma in men are approximately 10 %; the remaining 90 % can be attributed to infiltrating ductal carcinoma. Infiltrating lobular carcinoma, medullary lesions and tubular or neuroendocrine tumours are very rare in men, as is triple negative breast cancer (TNBC) [7].

MBC usually expresses the estrogen receptor (ER), progesterone receptor (PR) and androgen receptor (AR) and is hormonally responsive, which plays an important role in prognosis and therapy. Regarding genetics, MBC is more likely to occur in the setting of a BRCA2 mutation rather than BRCA1 mutation [8].

The aim of this study was to analyse and report the biological characteristics of MBC as a rare disease in Slovakia. These data are needed to optimize the diagnosis and treatment of breast cancer in men.

MATERIAL AND METHODS

We performed a retrospective analysis of data from nine oncology centres from pathological findings in 67 men who were diagnosed with C50 - breast cancer during the period 2008-2013 in Slovakia. We identified individual cases using the HERweb database. We recorded the following data for each patient: age at the time of diagnosis of breast cancer, cytosolic estrogen receptor (CER) positivity and human epidermal growth factor receptor 2 (HER-2) positivity status. The data obtained were processed anonymously.

Immunohistochemistry

Breast cancer was diagnosed by incision or excisional biopsy of breast lumps. Whole specimens had been examined by the local pathologists at each centre. Estrogen receptor was determined by means of immunohistochemistry (IHC). HER-2 status was determined either with IHC or fluorescent in situ hybridisation (FISH). Tumours with 3+ IHC score and FISH positivity were considered as HER2⁺. Tumours with 2+ IHC scores were assayed with FISH. Tumours with 1+ and/or 0 IHC and FISH negativity were considered as HER2⁻.

STATISTICAL ANALYSIS

Data were analysed using GraphPad 9.0. Continuous variables were expressed as mean ± standard deviation (SD). For comparison of means, independent unpaired sample T-test, ANOVA Tukey's multiple comparisons test and Mann-Whitney test were used, as well as Chi-square test, with $p < 0.05$ considered as significant.

RESULTS

In this study we present the results of data processing for 67 men with diagnosis of C50 - breast cancer (MBC), which were obtained in the period 2008 - 2013 in Slovakia. The mean age at diagnosis with HER2⁺ status was 62 ± 2.5 years and with HER2⁻ status it was 68 ± 3.1 years.

Analysis of HER2⁺/HER2⁻

We monitored HER-2 positivity or negativity in patients. In our cohort we had 16 patients (24 %) with HER2⁺ status and 51 patients (76 %) with HER2⁻ status. The number of patients with MBC and the incidence of HER2 in each year are shown in Graph 1. The number HER2⁻ males is significantly higher in each year compared to the incidence of HER2⁺ males (Figure 1).

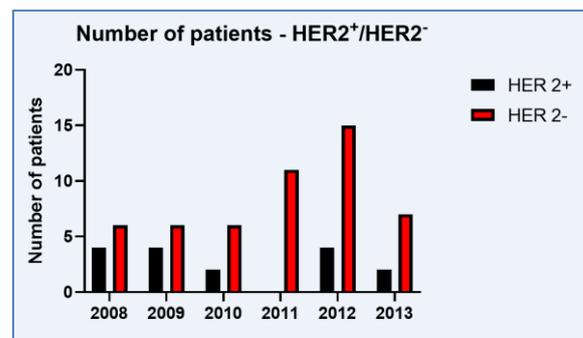


Fig-1: Incidence of HER2⁺ and HER2⁻ breast cancer tumors in men in the period 2008-2013

In 2008 ten men were diagnosed with C50, four of whom had HER2⁺ breast cancer while six were HER2⁻. In 2009 the number of patients diagnosed with C50 was identical to 2008 and the positivity rate was identical as well. In 2010 we found a 20 % decrease in the incidence of C50 and a 50 % decrease in HER2⁺. In 2011 the number of patients with this diagnosis increased by 10 % compared to 2008, but in contrast to the previous years we had a 100 % decrease in HER2⁺ breast cancer patients in our group, but a 50 % increase in HER2⁻ tumour patients. In 2012 the number of patients increased by 60 % compared to 2008, but the HER2⁺ tumour rate did not change. The group of men with HER2⁻ breast cancer increased 1.5 -fold compared to 2008. In 2013 the number of patients decreased by 10 % compared to the first year of observation, the number of HER2⁺ breast cancers was 50 % lower, but the number of HER2⁻ tumours increased by 10 %. The incidence of HER2⁻ tumours compared to HER2⁺ was significantly higher in the years 2008-2013 ($p = 0.0022$, unpaired T-test, Mann-Whitney).

Analysis CER⁺/CER⁻

In addition to HER-2 positivity we also monitored cytosolic estrogen receptor (CER) levels in our cohort. Of the 67 patients diagnosed with C50 breast cancer in the period 2008-2013, 54 men (81 %) had proven presence of CER. In the group of 16 HER2⁺ men we also found the presence of CER⁺ in 14 (87.50 %) of the patients (RR 1.685; 95 % CI 0.5394-6.351). In the monitored group of 51 HER2⁻ MBC we did not detect the presence of CER in 40 (78.43 %) of the patients (RR 0.8754; 95% CI 0.6865-1.309) (Figure 2) (Figure 3).

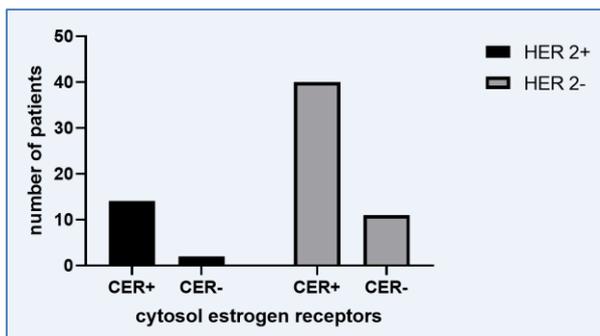


Fig-2: Incidence of HER2⁺/HER2⁻ and CER⁺/CER⁻ breast cancer tumors in men in the period 2008-2013

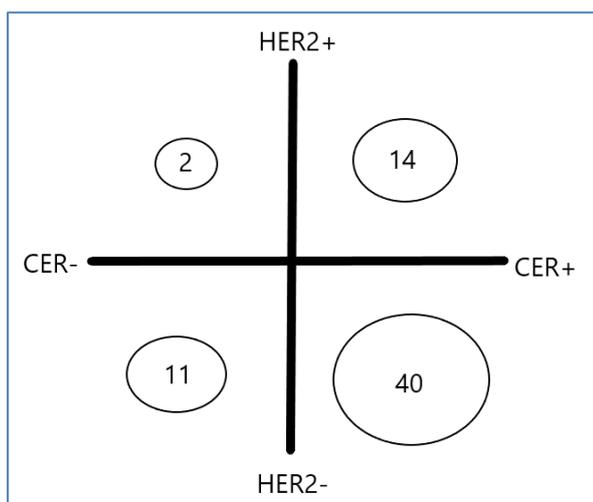


Fig-3: Incidence of HER2⁺/CER⁺, HER2⁺/CER⁻, HER2⁻/CER⁺ and HER2⁻/CER⁻ breast cancer tumours in men in the period 2008-2013.

Therapy

We did not have complete data on the treatment of patients in our cohort, but we recorded treatment with tamoxifen in those for whom we were able to identify the subsequent therapeutic procedure.

DISCUSSION

MBC is a rare disease and initial diagnosis often occurs at a later stage than in female breast cancer. In our experience the mean age at diagnosis for men with breast cancers was 62 ± 2.5 years with HER2⁺ status and 68 ± 3.1 years with HER2⁻ status.

The results obtained are comparable to data from previous studies indicating that the mean age at diagnosis in men with breast cancer is 67 years, which is 5 to 10 years more than the average age at the time of diagnosis in women [9, 10]. Similar data are reported by Ottini *et al.* [11], Ruddy and Winer [12] and Masci *et al.* [13]. Unlike these results, however, in a small group of patients Amirifard and Sadeghi [14] reported the mean age of patients with MBC as less than 50 years (24-85 years).

Men have rudimentary breast tissue [15]. It does not usually differentiate or form lobules, so in men the tumour type is usually ductal carcinoma. In the case of invasive carcinomas, the structure of histological subtypes is similar in both women and men; however, the relative distribution varies [9]. Data from more than 2,000 male patients in the Surveillance, Epidemiology, and End Results (SEER) cancer registry indicate that 93.7 % of MBC are ductal or unclassified carcinomas, 2.6 % are papillary, 1.8 % are mucinous, and only 1.5 % are lobular. Ductal carcinoma in situ makes up approximately 10 % of breast cancers in men [16].

According to the available information from oncology centres, we cannot confirm the claims in the studies, as our database did not contain the same data. In our study of MBC, we found HER2⁺ tumour in 16 patients (24 %) and HER2⁻ status in 51 patients (76 %). Similarly, to our results, Arslan *et al.* [17] reported 23 % patients with MBC had HER2⁺ tumour in a cohort of 148. Masci *et al.* [13] examined HER2 expression in 85 MBC cases and found 16 % positivity, and Amirifard and Sadeghi [14] examined HER2 expression in 17 MBC cases and found 12 % positivity in a small cohort of patients.

Updated studies using standardized HER2 assessment methods have shown lower rates of HER-2 expression in male breast cancer (up to 15 %) compared to breast cancer in women (18-20 %) [18-20]. The presence of HER2 is associated with poor prognosis in women, but not necessarily in men [21-13].

In our group of patients, in addition to HER-2⁺ we also examined the concentration of cytosolic estrogen receptors (CER). It is reported that approximately 90 % of breast cancers in men express the estrogen receptor and 81 % of MBC express progesterone receptors [9]. In the current study, 54 of our MBC patients (81 %) had CER⁺ tumours.

The data obtained are comparable to the data of Bender *et al.* [22], who found 79 % ER- positive in a cohort of 98 men with MBC in a retrospective study in 1999-2013 at the Cancer Hospital III of the National Cancer Institute of Brazil, Rio de Janeiro, Brazil. Similar data were reported by Masci *et al.* [13] and Amirifard and Sadeghi [14]. The National Cancer Institute SEER database between 1973 and 2005 reveals that 92 % of the 5 494 MBC, but only 78 % of the 838 805 female breast cancer cases were ER-positive [23].

We compared the presence of cytosolic estrogen receptors between groups of patients positive and negative for HER2 receptors. In 16 men who had HER2 receptor positive breast cancer, we also discovered the presence of cytosolic estrogen receptors in 14 (88 %) of them.

Similar data were reported by Arslan *et al.* [17], who retrospectively evaluated the medical records of 118 MBC patients at seven cancer centres between the years 1986 and 2009. HER2⁺ breast cancer was reported in 18 patients and 16 of them (89 %) were ER⁺/HER2⁺.

Most men with breast cancer have no identifiable risk factors. However, several risk factors for breast cancer in men have been identified: genetic and epigenetic alterations, high estrogen and low androgen levels, liver disease, chest wall irradiation, obesity, alcohol abuse, smoking, some occupational and environmental exposures, race and ethnicity [3].

In our retrospective study, we had limited data in this regard, and further analysis would be needed. Adjuvant therapy of breast cancer in men is similar in individual stages as in women [24]. Given the high prevalence of ER positivity, tamoxifen remains the gold standard of adjuvant hormonal therapy [14, 25, 2]. Several studies report gender differences in compliance with tamoxifen therapy, in the sense that males are less likely to accept side-effects than females [2, 3]. There are insufficient data on the efficacy of the use of aromatase inhibitors (AIs) in the treatment of breast cancer in men. The gender differences in efficacy of adjuvant aromatase inhibitors may relate to testicular estrogen synthesis, which is unaffected by AIs [26].

We did not obtain complete data on the treatment of patients in our cohort, but in those for whom we were able to identify a subsequent therapeutic procedure, we recorded treatment with tamoxifen.

Specific and overall survival in MBC (1,986 patients in the SEER database) appears to show significantly higher specific survival in the general population due to the higher average age of this population and deaths from other comorbidities. The SEER database indicates that survival is equivalent in men and women with early-stage breast cancers. In male veterans with stage III and IV cancer, the results of a study by Nahleh *et al.* [27] suggest that overall survival was similar in both groups and overall at a low level (stage III: 2.56 years for male breast cancer vs 5.51 years for female breast cancer; stage IV: 1.47 years for breast cancer in men vs 2.22 years for breast cancer in women), which is consistent with the SEER results.

Our data suggest that men with breast cancer are older than women at the time of diagnosis. Most cancer patients had CER⁺ and HER2⁻ tumours. Subtype-specific survival was difficult to assess due to unavailable information on the treatment and survival of patients with breast cancer. In order to develop new possibilities for therapeutic intervention in our conditions, it will be necessary to create databases with the most accurate information not only about the type of cancer, but also about the treatment and survival of

patients with cancer. Further studies focusing on biological characteristics of the disease are necessary for better understanding of breast cancer in men and for optimizing care in all male patients.

Our study has limitations due to its retrospective nature, missing data, lack of data on individual risk factors, and a relatively small sample size.

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Author's contributions

All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Instruction and informed consent of the patient in accordance with § 6 of Act No. 576/2004

Patient consent for publication

Instruction and informed consent of the patient in accordance with § 6 of Act No. 576/2004

Competing interests

The authors declare that they have no competing interests.

Abbreviations

MBC - Male breast cancer

BC - breast cancer

TNBC - triple negative breast cancer

PR - progesterone receptor

AR - androgen receptor

ER - estrogen receptor

IHC - immunohistochemistry

FISH - fluorescent in situ hybridisation

CER - cytosolic estrogen receptors

HER2⁺ - human epidermal growth factor receptor 2 positive

HER2⁻ - human epidermal growth factor receptor 2 negative

CER2⁺ - cytosolic estrogen receptors positive

CER2⁻ - cytosolic estrogen receptors negative

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