DOI: 10.31618/ESU.2413-9335.2023.1.91

Евразийский Союз Ученых.
Серия: медицинские, биологические и химические науки

Ежемесячный научный журнал

№ 10 (91)/2023 Том 1

ГЛАВНЫЙ РЕДАКТОР

РЕДАКЦИОННАЯ КОЛЛЕГИЯ

Журнал зарегистрирован Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций.

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МЕДИЦИНСКИЕ НАУКИ

RELEVANCE OF DIAGNOSTICS AND TREATMENT OF BREAST CANCER IN MEN

DOI: 10.31618/ESU.2413-9335.2021.1.91.1491

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ABSTRACT

Breast cancer in men is a rare disease, accounting for approximately 0.1% of all malignant breast tumors in men and from 0.6% to 1% of all malignant breast tumors. The incidence of breast cancer in men increases with age for unknown reasons: the average age of men at the time of diagnosis is 67 years, compared with women, whose similar indicator is 57 years. Despite advances in the diagnostics and treatment of breast cancer in women, understanding and strategy for the treatment of breast cancer in men are limited and generally extrapolated from existing knowledge about breast cancer in women. In particular, the molecular subtypes of breast cancer in men have not been studied, although these subtypes have been associated with both biological and clinical features of breast cancer in women. It has been proven that molecular subtypes have an important prognostic value in breast cancer in women. Molecular assessment of tumors plays a significant role in the 22 prescriptions of adjuvant chemotherapy, and therefore the role of genetic testing increases.

Key words: breast cancer, gynecomastia, oncoepidemiology, hormone therapy.

Introduction

Breast cancer (BC) in men is a rare disease, accounting for less than 1% of all breast tumors [1-4]. The rarity of this disease in men causes a considerable number of medical errors in its diagnostics and treatment. The incidence of breast cancer in men varies synchronously with the "female" breast cancer in different countries, which indirectly indicates the common causes of the disease in men and women [5-7]. Interest in BC in men increases due to an increase in the spread of this disease [8]. Most of the data on breast cancer in men have been collected from retrospective studies over the past several decades, and treatment recommendations are extrapolated from the results of studies in women with breast cancer.

Many epidemiological features of “male” breast cancer are similar to those of women. The incidence of breast cancer increases with age, but in men it occurs 5-10 years later than in women [9-10]. Primary breast cancer sometimes occurs in men who have received estrogens for prostate cancer. BC also occurs in men with pituitary prolactinoma and excessive production of estrogens in the body; hypogonadism may also be a predisposing factor. A number of studies have revealed a high incidence of orchitis in men with breast cancer [11]. Difficulties in diagnosing breast cancer in men are associated with the need to make a differential diagnosis between breast cancer and gynecomastia [12]. At the same time, cancer is often mistaken for gynecomastia, "pathogenetic" hormone therapy with androgens is mistakenly prescribed, which further stimulates the growth and metastasis of a malignant tumor. It is believed that 30–40% of breast cancer cases in men are developed on the background of gynecomastia.

Chemotherapy for breast cancer in men is not used as widely as in women, mainly because these tumors usually respond well to hormonal influences. Given the prevalence of hormone-positive forms, adjuvant and therapeutic endocrine therapy should play an important role. The molecular subtypes of breast cancer in women were initially identified by gene expression analysis using DNA microarrays. In 2000, Perou et al. divided breast cancer into 5 subtypes based on cluster analysis of gene expression: luminal A, luminal B, HER2-overexpressed, low-claudine and basal-like. However, in routine clinical practice, subtyping by gene expression profiling is currently difficult to implement. Therefore, immunohistochemical assessment of estrogen receptors (ER), progesterone receptors (PR), HER2 / neu, Ki-67 was used as substitutes for DNA microarrays in determining the subtypes of breast cancer. Using this technique, the following biological subtypes of breast cancer were identified: Luminal A, Luminal B (HER2-negative), Luminal B (HER2-positive), HER2 - over-expressing and triple-negative. It should be noted that the determination of the level of the proliferation marker Ki-67 is a difficultly reproducible technique that is not performed in all medical institutions. Moreover, the separation values of the Ki67 level are different in different centers. Therefore, a reliable assessment of the Ki-67 index is not available, the degree of histological malignancy can be used as an alternative to assessing proliferation (G).

It has been proven that molecular subtypes have an important prognostic value in breast cancer in women. In a number of studies these biological subtypes correlated well with clinical outcomes determined by the overall survival rate and the appearance of distant metastases, at the same time, the worst outcome was observed in HER2 - overexpressing and basal-like subtypes of breast cancer. Based on such studies, it is assumed that chemotherapy is appropriate with a high degree of malignancy, high proliferative activity of the tumor (Ki67>20%), absence of ER and PR, high expression of HER2. The need for chemotherapy in the treatment of "luminal-A" and "luminal-B" (HER2-negative) breast cancer remains unclear.

Despite advances in the diagnostics and treatment of breast cancer in women, understanding and strategy for the treatment of breast cancer in men are limited and generally extrapolated from existing knowledge about breast cancer in women. In particular, there are only a small number of studies on the molecular subtypes of breast cancer in men. Molecular evaluation of tumors plays an essential role in the prescribing adjuvant chemotherapy, and therefore the role of genetic testing increases. Thus, it remains relevant to further in-depth study diagnostics features, as well as the clinical course, prognosis and sensitivity to certain types of systemic treatment of various biological subtypes of breast cancer in men. This will allow to individualize the local and systemic treatment of this disease.

Aim of the study is to improve the results treatment results of breast cancer in men.

Material and methods

The research analyzed the database of the first Cancer Registrar in Uzbekistan, which includes information on more than 5000 breast cancer patients of both sexes who received treatment at RSSPMCO & R, as well as in all branches of our Center. 114 men with breast cancer (BC) had been registered in the database by 2017. When analyzing the indicators of general and relapse-free survival of patients, we used data obtained from outpatient cards recording the status of observed patients, using direct telephone contacts with patients or their relatives, as well as from the database of the registry offices in Tashkent city. During observation in the department of outpatient diagnostics and therapy patients were periodically examined in order to exclude a relapse of the disease. During telephone contact, patients were interviewed about the treatment received, control examinations and checkups, dates of relapses occurrence and distant metastases and their localization, as well as about the treatment received about these events. The analysis of total and relapse-free 5-year survival included all patients whose diagnosis of breast cancer was confirmed by histological examination of surgical material (111 patients). The analysis of the efficiency of diagnostic tests also included patients whose diagnosis of breast cancer was determined based on the results of cytological examination of a punctate or histological examination of a trepan biopsy of the breast, but it was not confirmed by the data of histological examination of the surgical material (3 patients).

Ultrasound examination of the mammary glands was performed for men with suspected breast cancer. X-ray mammography was performed for men with suspected malignant breast tumor according to physical examination. Mammography was performed in two projections: craniocaudal and mediolateral. When a focus of unclear genesis was detected, the patients underwent puncture fine-needle biopsy or trephine biopsy, including ultrasound navigation, followed by pathomorphological examination of the material. The obtained material was sent to the pathomorphological laboratory for histological and immunohistochemical (IHC) studies and determination of the histological type of cancer, the degree of malignancy (G), the level of expression of estrogen and progesterone receptors, the expression of HER-2 / neu and, in some cases, to determine the level of the proliferation marker Ki67. The suitability of tests for the diagnosis of breast cancer in men was determined by their ability to distinguish patients from “healthy” and was assessed by the indicators of sensitivity and positive predictive value. Due to the small number of actually healthy people (3 cases), it was not possible to assess the specificity and negative predictive value of these methods.

The sensitivity of a test is its ability to detect disease. Sensitivity is expressed by the ratio of the number of individuals who showed a truly positive test to the number of those who are actually carriers of the desired disease (sensitivity = a / (a+c)). Specificity characterizes the ability of the test to identify persons without disease, and is determined by the ratio of the number of those who demonstrated a truly negative test to the number of actually healthy people in relation to the pathology that is the subject of screening (specificity = d / (b+d)). Ideally, the sensitivity and specificity should be close to 100%, but in reality, no test used to diagnose a particular disease fully meets these requirements. Therefore, among those who showed a positive test during the diagnostic examination and sent for an in-depth diagnostic study, persons will be identified who do not actually have the alleged disease, which indicates a false positive result of this diagnostic method.

On the other hand, in the process of in-depth diagnostics, it is possible to identify persons who really suffer from this disease, despite the fact that their diagnostic test was negative; in this case, we talk about a false negative test result. Sensitivity and specificity are essentially opposite concepts. Ultimately, the relationship between the levels of sensitivity and specificity of a diagnostic test means reaching a certain threshold for the accuracy of the examination. The ability to achieve a balance between sensitivity and specificity largely determines the efficiency of the diagnostic program. It should be remembered that specificity is relevant to most screening individuals, i.e. to healthy people, and sensitivity, on the contrary, concerns the minority suffering from the disease [Semiglazov V.F. et al., 1996]. An important parameter for evaluating diagnostic tests is a positive predictive value, which is calculated after the completion of a diagnostic examination of individuals. A positive predictive value is the percentage of verified tumor cases among individuals with positive tests (true positive + false positive). Along with this, there is the concept of a negative predictive value, which is determined by the ratio of the number of healthy individuals to the total number with a negative test (true negative + false negative). Thus, the indicator "predictive value" characterizes the likelihood that positive or negative results are proven correctly [Semiglazov V.F. et al., 1992; Yunkerov V.I. et al., 2019]. The high level of negative predictive value of the test helps to reduce the number of “unnecessary” and invasive diagnostic procedures undertaken as part of an in-depth examination. Immunohistochemical study was performed on the material of trephine biopsy or using the surgical material. When the results of the

immunohistochemical study on the trepan biopsy materials and the surgical preparation diverged, under the condition of primary surgical treatment, the results of the immunohistochemical study of the surgical material were taken into account. In cases of different immunohistochemical data before and after neoadjuvant treatment, the division of patients into different biological subtypes of breast cancer was carried out based on the results of the expression of steroid hormone receptors and HER2 / neu, determined from the data of trephine biopsy before the beginning of neoadjuvant systemic treatment. The expression of steroid hormone receptors was assessed semi-quantitatively using the Allred scoring system. Only the nuclear reaction was evaluated. The result was presented as the sum of two values: the intensity of staining of tumor cells (0 - absent, 1 46 - weak, 2 - moderate, 3 - pronounced) and the number of positive tumor cells (0 = no staining; 1 - less staining). Expression of HER2 / neu was considered positive with an immunohistochemical value of 3+. When assessing the expression of HER2 / neu equal to 2+ on the basis of immunohistochemistry, a study is necessary to detect the presence or absence of amplification. This method is fluorescent hybridization in situ (FISH). The assessment of the presence of amplification of the HER2 / neu gene was carried out by counting the signals that mark the centromeric region of chromosome 17 and the signals that mark the HER / neu gene.

Results

The stage of breast cancer was diagnosed in 108 cases. In three patients, regional lymph nodes were not removed, therefore, the staging of the process in these cases was not performed. Ductal carcinoma in situ was diagnosed in three cases (TisN0M0). The proportion of patients with stage II and III was 41% (n = 43) and 44.8% (n = 47), respectively, while the proportion of patients with stage I was 8.5% (n = 9) and stage IV - 5, 7% (n = 6).

Data on the status of steroid hormone receptors and HER2 / neu were available in 87 cases. The distribution of patients by biological (IHC) subtypes of breast cancer was as follows: Luminal A - 47 (54%); Luminal B (HER2 - negative) - 28 (32.1%); Luminal-B (HER2 - positive) - 4 (4.6%); Three times negative - 8 (9.2%) (Tab. 1).

Table 1

Clinical and pathomorphological features of various biological subtypes of breast cancer

Clinical stage of the disease	Luminal A n=46	Luminal B (HER2negative) n=28	Luminal B (HER2positive) n=4	Three times negative n=8
I	4(8.7%)	3(10.7%)	0	0
II	25(54.3%)	8(28.6%)	0	4(50%0
III	16(34.8%)	15(53.6%)	4(100%)	2(25%)
IV	1(2.1%)	2(7.1%)	0	2(25%)
pN0	22(47.8%)	4((14.3%)	0	3(37.5%)
pN+	24(51.1%)	24(85.7%)	4(100%)	5(62.5%)

The sensitivity index of mammography was 96.4%, ultrasound - 93.8%, puncture biopsy - 69.5%, trephine biopsy - 94.8%. The positive predictive value when using X-ray mammography was 97.6%, ultrasound - 97.8%, puncture biopsy - 98.3% and trephine biopsy - 98.2%. Mammographywas performed in two projections: craniocaudal and mediolateral.

When studying the biological subtype of the disease, the maximum proportion falls on the luminal A subtype, amounting to 54% (47 cases). The proportion of luminal-B HER2 negative breast cancer was 32.1% (28 cases), the proportion of triple-negative tumors was 9.2% (8 cases). The minimum specific weight was observed at luminal B HER2 - positive breast cancer amounting to 4.6%. No cases of HER2-overexpressing breast cancer were identified. One case of ductal carcinoma in situ was classified in the luminal A subtype group.

The largest proportion of patients with stage I was noted with luminal-B HER2 negative breast cancer and made up 10.7%. The specific weight of the disease stage I with luminal A subtype is 8.7%. There were no cases of disease stage I with luminal-B HER2 positive and triple-negative subtypes.

The second stage of the disease occurs with approximately the same frequency in luminal A and triple-negative subtypes, accounting for 54.3% and 50%, respectively. The proportion of patients with luminal-B HER2 negative breast cancer stage II was 28.6%. The maximum proportion of stage III patients is observed with luminal-B HER2 positive breast cancer and was 100%.

The proportion of patients with stage III with luminal A, luminal-B HER2 negative and triple-negative subtypes was 34.8%, 53.6% and 25%, respectively. The maximum proportion of patients with stage IV was observed with triple-negative breast cancer (25%). Stage IV breast cancer with luminal A and luminal-B HER2 negative subtypes was rare: 2.1% and 7.1%, respectively.

Discussion

The mean age of patients at the time of diagnosis was 62 ± 1.1 years, which was 5 years more in comparison with women, the same indicator for whom is 57 years. Our study showed that with earlier terms of going to the doctor from the moment the first signs of the disease appeared, breast cancer in men was detected at an earlier stage. X-ray mammography, breast ultrasound and trephine biopsy are highly sensitive methods for diagnosing breast cancer in men. The sensitivity index of puncture biopsy was 69.5%, which, in comparison with that for trephine biopsy, gives

reason to consider this method as insufficiently sensitive in the diagnostics of this disease.

The most common histological type of tumors in men was invasive ductal carcinoma (83.8%). Tumors of a high degree of malignancy were much less common and accounted for only 20% of all tumors. Currently, there are only a small number of studies on the molecular subtypes of breast cancer in men. In this study, the maximum specific weight fell on the luminal A subtype, accounting for 54% of all subtypes. No cases of HER2-97 overexpressing breast cancer have been reported. Three of 6 patients with metastatic breast cancer had bone metastases, two had metastases to the lungs and there was a combination of metastatic lesions of bone tissue and lungs in one case.

The maximum rate of local-regional recurrence was observed in luminal-B HER2-positive breast cancer and was equal to 25%. The highest value of the relative risk (RR) of distant metastasis was noted for luminal B (HER2 - positive) breast cancer and was equal to 2.63. In the luminal-A subtype, more often in comparison with other subtypes, there were cases of distant metastasis to the bone, less often - visceral metastases, and not a single case of metastasis to the brain was recorded.

Due to the small number of patients of stages I and IV, an analysis of the overall survival for stages II (conditionally early) and III (conditionally locally advanced) was carried out. The 5-year survival rate at stage II reached 87.7%, the 5-year survival rate of patients with stage I was 58.3%. There was not a single stage IV patient who survived 5 years. Due to the small number of patients with stage I and IV (9 and 6 cases, respectively), to assess the relationship between stage and prognosis, an additional analysis of overall survival in groups of patients with stages II (conditionally early) and III was carried out. At stage II, the 5-year overall survival rate of patients reached 87.7%, at stage III it was 62%. In patients without lymph node involvement and in patients with metastatic lymph node involvement, the 5-year overall survival rates were 83% and 59%, respectively ($p < 0.05$). As expected, patients with metastatic lesion of regional lymph nodes had lower rates of both overall and relapse-free survival.

Additionally, the overall 5-year survival rate of patients was analyzed depending on the level of the proliferation marker Ki67. The overall 5-year survival rates in patients with Ki67 <20% and Ki67 ≥ 20% were 100% and 58%, respectively ($p = 0.042$). The 5-year relapse-free survival rate was 65% in the group of patients with a Ki67 value <20% versus 53% in the group with a Ki67 value ≥ 20% ($p = 0.15$). We noted a tendency towards a worsening of the 5-year relapse-free survival rate with a Ki67 value of ≥ 20%. We analyzed the overall and disease-free survival of patients depending on the biological subtype of the tumor. Due to the small number of cases of luminal B HER2 - positive and triple-negative breast cancer, these subtypes, together with luminal B HER - negative subtype were combined into one group and named "non-luminal A" subtype (or all others). The 5-year overall survival rates in patients with luminal A compared with all other subtypes were equal to77% and 52%, respectively ($p = 0.043$). The 5-year disease-free survival rates in patients with luminal A and other subtypes were 67% and 50%, respectively ($p > 0.05$). There was a clear trend towards higher rates of recurrence-free survival in patients with luminal A subtype compared with other subtypes of breast cancer. When comparing the 5-year overall survival rates of patients with luminal-A breast cancer who received adjuvant endocrine therapy and patients who first received adjuvant chemotherapy, then endocrine therapy, regardless of the stage, no statistically significant differences were obtained (88% versus 69%, respectively, $p = 0.071$). However, we observed a tendency towards an improvement in the 5-year overall survival rate in the group of patients who received endocrine therapy alone.

Conclusion

Men are characterized by a belated visit to the doctor. The timing of tumor detection before going to the doctor in 69% of patients exceeded 6 months. Moreover, 53% of these patients had stage III breast cancer.

The most common risk factors for developing breast cancer in men are: grade II-III obesity (46%), prostate disease (28%), testicular pathology (11%), hereditary family history (8%).

Among the studied methods for diagnosing breast cancer in men, mammography and ultrasound were the most accurate: sensitivity indices were 96.4% and 93.8, respectively. The sensitivity index when performing trephine biopsy and histological examination was significantly higher than when performing puncture biopsy and cytological examination (94.8% versus 69.5%, $p = 0.5$).

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