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Diagnosis and Treatment of Breast Cancer in Men

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Abstract

Male breast cancer (BC) is an uncommon condition, representing less than 1% of all breast tumors [Aksel S.M., 2006; Merabishvili V.M., 2011]. The infrequency of this condition in men results in a significant number of medical errors in its diagnosis and treatment. The prevalence of breast cancer in men correlates with that of female breast cancer across many nations, suggesting shared etiological factors for the disease in both genders [Semiglazov V.F. et al., 2010, 2014]. Interest in male breast cancer is rising due to a growing prevalence of the condition [Giordano SH et al., 2004].

Keywords: breast cancer, gynecomastia, oncoepidemiology, hormone therapy.

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Introduction

The majority of data regarding male breast cancer has been gathered from retrospective studies conducted over recent decades, with treatment recommendations derived from findings in female breast cancer studies. Numerous epidemiological characteristics of "male" breast cancer resemble those of females. The prevalence of breast cancer escalates with age; nevertheless, in men, it manifests 5-10 years later than in

women [Semiglazov V.F., 2006]. Primary breast cancer may occasionally develop in males who have been administered estrogens for prostate cancer treatment. Breast cancer can also occur in men with pituitary prolactinoma and elevated estrogen production; hypogonadism may serve as a predisposing factor. Numerous studies have demonstrated a significant prevalence of orchitis in men diagnosed with breast cancer [Semiglazov V.F., Migmanova N.S., 2010]. The challenges in identifying breast cancer in males stem from the necessity of differentiating it from gynecomastia [Thomas DB et al., 1992]. Cancer is sometimes misidentified as gynecomastia, leading to the erroneous prescription of "pathogenetic" hormone therapy with androgens, which exacerbates the growth and metastasis of a malignant tumor. It is estimated that 30-40% of male breast cancer cases arise in the context of gynecomastia. Chemotherapy for breast cancer in men is less prevalent than in women, primarily because these tumors typically exhibit favorable responses to hormone therapies. Due to the widespread occurrence of hormone-positive variants, adjuvant and curative endocrine therapy should assume a significant role. The molecular subgroups of breast cancer in women were first discerned via gene expression analysis employing DNA microarrays. Perou et al. classified breast cancer into five subtypes—luminal A, luminal B, HER2-overexpressing, low-claudine, and basal-like—based on a cluster analysis of gene expression conducted in 2000. Nonetheless, in standard clinical practice, the identification of subtypes using gene expression profiling is presently challenging to execute. Consequently, immunohistochemistry assessment of estrogen receptors (ER), progesterone receptors (PR), HER2/neu, and Ki-67 was employed as DNA alternatives for microarrays in identifying breast cancer subtypes. This approach detected the following biological subtypes of breast cancer: Luminal A, Luminal B (HER2-negative), Luminal B (HER2-positive), HER2-overexpressing, and triple-negative. It is important to acknowledge that assessing the Ki-67 proliferation marker is a challenging procedure that is not universally implemented across all medical facilities. Furthermore, the Ki67 level separation values vary between different centers. Consequently, in the absence of a dependable evaluation of the Ki-67 index, the histological grade of malignancy (G) may serve as a substitute for measuring proliferation. Molecular subgroups have demonstrated significant predictive relevance in female breast cancer. Several studies indicated a strong correlation between these biological subtypes and clinical outcomes, specifically overall survival and the incidence of distant metastases, with the most adverse outcomes associated with HER2-overexpressing and basal-like subtypes of breast cancer [Sorlie et al., 2001, 2003; Sotiriou et al., 2003]. This research suggests that chemotherapy is suitable for tumors with a high degree of malignancy, elevated proliferative activity (Ki67>20%), absence of estrogen and progesterone receptors, and significant HER2 expression. The necessity of chemotherapy for treating "luminal-A" and "luminal-B" (HER2-negative) breast cancer is still ambiguous. Notwithstanding progress in the diagnosis and therapy of breast cancer in women, comprehension and strategies for treating breast cancer in males remain constrained and are predominantly derived from established insights regarding breast cancer in women. Specifically, there exists a limited number of studies regarding the molecular subtypes of male breast cancer. The molecular evaluation of tumours is crucial for the determination of adjuvant chemotherapy, hence enhancing the significance of genetic testing. Consequently, it is pertinent to conduct a comprehensive examination of the diagnostic characteristics, clinical progression, prognosis, and responsiveness to specific systemic therapies of diverse biological subtypes of male breast cancer, which will enhance the personalisation of both local and systemic treatment for this condition. The primary objective of this study is to enhance the outcomes of breast cancer treatment in males.

Methodology

The work analyzes the database of the first Cancer Registry in Uzbekistan, which includes information on more than 5,000 breast cancer patients of both sexes who were treated at the RCNPMCIR as well as in all branches of our center For 2017. 114 men with breast cancer (breast cancer) were registered in the database. When analyzing the indicators of general and relapse-free survival of patients, data obtained from outpatient records recording the status of observed patients, through direct telephone contacts with patients or their relatives, as well as from the database of the Registry Office of Tashkent were used. During observation in the outpatient diagnostics and therapy department, patients were periodically

examined in order to exclude a recurrence of the disease. During telephone contact, patients were interviewed about the treatment received, follow-up examinations and examinations, dates of recurrence and distant metastases and their localization, as well as about the treatment received regarding 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 effectiveness of diagnostic tests also included patients whose diagnosis of breast cancer was established based on the results of cytological examination of a punctate or histological examination of a trepan biopsy of the breast, but was not confirmed by 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, patients underwent puncture fine needle biopsy or trepan biopsy, including under ultrasound navigation, followed by a 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 expression level of estrogen and progesterone receptors, the expression of HER-2/pei and, in some cases, to determine the level of the Ki67 proliferation marker. The suitability of tests for the diagnosis of breast cancer in men was determined by their ability to distinguish patients from "healthy" ones and was assessed by indicators of sensitivity and positive predictive value. Due to the small number of actually healthy (3 cases), it is not possible to assess the specificity and negative predictive value of these methods. The sensitivity of a test is its ability to detect a disease. Sensitivity is expressed by the ratio of the number of people who have shown a truly positive test to the number who are actually carriers of the desired disease [sensitivity = a / (a+c). Specificity characterizes the ability of the test to identify people who do not have a disease, and is determined by the ratio of the number of those who demonstrated a truly negative test to the number of actually healthy ones in relation to the pathology that is the subject of screening [specificity = d / (b+d). Ideally, sensitivity and specificity should approach 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 were sent for an in-depth diagnostic study, persons who do not actually have the alleged disease will be identified, which indicates a falsely positive result of this diagnostic method. On the other hand, in the process of in-depth diagnosis, it is possible to identify people who really suffer from this disease, despite the fact that their diagnostic test was negative; in this case, we are talking about a falsely negative test result. Sensitivity and specificity are essentially opposite concepts. Ultimately, the ratio 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 effectiveness of the diagnostic program. It should be remembered that specificity is relevant to the majority of people involved in screening, i.e. to healthy people, and sensitivity, on the contrary, concerns a 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, determined by the ratio of the number of healthy individuals to the total number having a negative test (true negative + false negative) . Thus, the indicator "predictive value" characterizes the probability that positive or negative results are proved 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 manipulations undertaken as part of an in-depth examination. Immunohistochemical examination was performed on trepan biopsy material, or on surgical material. When the results of the immunohistochemical study on trepan biopsy materials and the surgical preparation differed, 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, patients were divided into different biological subtypes of breast cancer based on the results of expression of steroid hormone receptors and HER2/neu, determined by trepan biopsy data before the start of neoadjuvant systemic treatment. The expression of steroid hormone receptors was evaluated by a semi-quantitative method using the Allred scoring system. Only the nuclear reaction was evaluated. The result is 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 – with less staining. The expression of HER2/neu was considered positive with an immunohistochemical value of 3+. When evaluating the expression of HER2/neu equal to 2+ based on an immunohistochemical study, a study is necessary to identify the presence or absence of amplification. This method is fluorescent in situ hybridization (FISH). The assessment of the presence of amplification of the HER2/neu gene is carried out by counting the signals that mark the centromeric region of chromosome 17 and the signals marking the HER/neu gene.

Result and Discussion

Mammography was conducted in two views: craniocaudal and mediolateral. Upon detection of a focus of indeterminate origin, patients received fine needle aspiration or trepanation biopsy, involving ultrasound guidance, followed by a pathomorphological analysis of the specimen. The acquired specimen was dispatched to the pathomorphological laboratory for histological and immunohistochemical (IHC) analyses, as well as for the identification of the histological cancer type, the grade of malignancy (G), the expression levels of oestrogen and progesterone receptors, the expression of HER-2/pei, and, in certain instances, the evaluation of the Ki67 proliferation marker level. The appropriateness of diagnostic tests for breast cancer in men was evaluated based on their capacity to differentiate patients from healthy individuals, assessed by metrics of sensitivity, specificity, and positive predictive value. The expression of steroid hormone receptors was assessed using a semi-quantitative approach based on the Allred score system. 96 Immunohistochemical analysis was conducted on trepan biopsy specimens or surgical specimens. This study included 111 individuals, all of whom had breast cancer verified through histological evaluation of surgical specimens. The mean age of patients at diagnosis was 62 ± 1.1 years, which is 5 years greater than that of women, whose mean age is 57 years. The study demonstrated that earlier medical intervention resulted in the detection of male breast cancer at an earlier stage following the emergence of initial symptoms. X-ray mammography, breast ultrasonography, and trepan biopsy are highly sensitive techniques for identifying breast cancer in males. The sensitivity index for mammography was 96.4%, for ultrasound examination of the mammary glands it was 93.8%, and for trepan biopsy, it was 94.8%. The sensitivity index of puncture biopsy was 69.5%, which, when compared to that of trepan biopsy, suggests that this approach is inadequately sensitive for diagnosing this condition. The predominant histological variant of tumors in men was invasive ductal carcinoma (83.8%). Highly malignant tumors were significantly less prevalent, comprising about 20% of all tumors. Currently, there exists a limited number of studies regarding the molecular subtypes of breast cancer in males. The molecular evaluation of tumors in males is essential for the determination of adjuvant chemotherapy, hence elevating the significance of genetic research. The luminal A subtype constituted the largest proportion, representing 54% of all subtypes in this investigation. No instances of HER2-97 overexpressing breast cancer have been documented. Among the six patients with metastatic breast cancer, three exhibited bone metastases, two presented with lung metastases, and one instance was a combination of both bone and lung tumors. The highest incidence of local-regional relapses was recorded in luminal-in HER2-positive breast cancer, amounting to 25%. The highest relative risk (RR) of distant metastasis was observed in luminal B (HER2-positive) breast cancer, with a value of 2.63. In the luminal-A subtype, instances of distant bone metastasis were more prevalent than in other subtypes, visceral metastases were less frequent, and no occurrences of brain metastasis were documented. Owing to the limited patient population in stages I and IV, an analysis of the overall survival rate for stages II (conditionally early) and III (conditionally locally progressed) was conducted. The total survival rate at stage II was 87.7%, while at stage III it was 62%.

Conclusion

Men are distinguished by a delayed consultation with a physician. In 69% of patients, the duration of tumour discovery prior to consulting a physician surpassed 6 months. Simultaneously, 53% of these individuals were diagnosed with stage III breast cancer. The predominant risk factors for the onset of breast cancer in men include: obesity of grades II-III (46%), prostate disorders (28%), testicular pathologies (11%), and hereditary familial history (8%). Among the evaluated modalities for diagnosing breast cancer in males, mammography and ultrasonography exhibited the highest accuracy. The study reported sensitivity indicators of 96.4% and 93.8%, respectively. The sensitivity index during trepan biopsy and histological evaluation was markedly superior to that of puncture biopsy and cytological examination (94.8% vs. 69.5%, p=0.5).

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