RESEARCH ARTICLE

The significance of hormone receptors in male breast cancer

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Background: Male mammary glands are usually considered a rudimentary organ. However, they may be exposed to similar pathological influences as female breasts. These pathological influences may cause the development of malignant breast tumors. Breast cancer in males is a rare disease; nevertheless, it is a serious problem. According to numerous national cancer registries from around the world, this disease takes 1% on average in the structure of morbidity of malignant neoplasms of this organ in both sexes.

Methods: In our study (168 patients) estrogen receptors were positive in the tumors of 75% of patients. The positive rate of progesterone receptors was observed in 44% of patients. The detection rate of steroid hormone receptors in malignant tumors of the male breast ranges from 65 to 100%, depending on the criteria for identifying their positivity level. The hormone therapy in the early and late stages of cancer include antiestrogens, steroid and non-steroid aromatase inhibitors, both as monotherapy and in combination with LHRH-agonists, fulvestrant and other hormonal agents.

Results: There was no dependence found between the receptor status of the tumors and the age of patients with breast cancer. Breast cancer in men has a more aggressive course than the same disease in women. This means lower survival rate of male patients, greater number of locally advanced and metastatic cases, with delayed primary treatment, and resistance to treatment compared to female breast cancer patients. The incidence of receptor positive tumors in men does not increase with age, as observed in women with breast cancer. Despite numerous reports on the effectiveness of hormone therapy in men with breast cancer, many aspects of this type of therapy remain largely unexplained.

Conclusion: Hormone therapy appears the most effective in patients with the so-called feminization syndrome, which includes signs of hyperestrogenemia, as well as in patients with multiple unfavorable prognostic signs (stage III of cancer, low differentiation of tumor cells, status of regional lymph nodes N2-3 and medium, severe and morbid obesity). Orchiectomy does not increase the survival rate; therefore, its application is impractical.

Key Words: *Male breast cancer; Hormone receptors; Sex hormones; Endocrine treatment; Mammary glands*

Abbreviations: ER-Estrogen Receptors; ER-α-Estrogen Receptors Alpha; ER-β-Estrogen Receptors Beta; FAI-Free Androgen Index; LHRH-Luteinizing Hormone-Releasing Hormone; PR-Progesterone Receptors; PSA-Prostate-Specific Antigen; PSAP-prostate-Specific Acid Phosphatase; SEER-Surveillance, Epidemiology, and End Results; SHBG-Sex Hormone Binding Globulin

INTRODUCTION

Male mammary glands are usually considered a rudimentary organ. However, they may be exposed to similar pathological influences as female breasts. These pathological influences may cause the development of malignant breast tumors. Breast cancer in males is a rare disease, nevertheless, it is a serious problem. According to numerous national cancer registries from around the world, this disease takes 1% on average in the structure of morbidity of malignant neoplasms of this organ in both sexes. Thus, breast cancer takes 0.2% on average in the structure of the incidence of malignant neoplasms in men. The analysis of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data indicates an increase in the incidence of male breast cancer by 26% over the 30-year period since 1983. The mortality rate has remained relatively stable since 1975 [1].

Today, many aspects of male breast cancer remain unexplored. The reason is that the information about the disease in question is based mainly on the retrospective analysis of small groups. Clearly, a prospective study of this problematic issue is associated with certain difficulties. These are, first of all, a considerable period of time necessary to accrue the sufficient number of patients with this rare nosological form, as well as changes in approaches to diagnosis and treatment observed in the long process of the examination of patients. Meanwhile, the treatment of males who developed breast cancer used to be and still is based on the knowledge acquired in the course of the treatment of women with this disease.

Sex hormones in males within the normal range and in cancer: The normal range

Testicles are responsible for the synthesis of male sex hormones (androgens) and the formation of the sperm. Of these testosterone is the most important androgen, both in terms of its activity and the quantity produced by the male body. Androstenedione and dehydroepiandrosterone are other androgens. These androgens are weaker in their activity and are secreted by the adrenal glands. Male adrenal androgen secretion does not play a significant role. In contrast, in females it is essential in the formation of secondary sexual characteristics [2,3].

Testosterone is synthesized in Leydig cells of the testicles (under the influence of luteinizing hormone). It plays an important role in spermatogenesis and the development of secondary sexual characteristics. Testosterone is a powerful anabolic hormone whose concentration in blood plasma is low before puberty. With the beginning of puberty the amount of this hormone increases rapidly and reaches the normal adult male level. There may be some decline in testosterone levels as males age. The body of a healthy male produces up to 7 mg (7000 μg) of testosterone per day, of which approximately 0.25% is transformed into estradiol. For comparison, an adult female produces up to 0.5 mg (500 μg) of testosterone per day, half the amount of which is transformed into estradiol. One of the ways of testosterone metabolism is the aromatase enzyme in peripheral tissues. As a result of this process, extragonadal production of estrogens increases the production of estrogens in healthy males, in females of menopausal age and in certain pathological conditions.

Estrogens in the male body are represented mostly by estradiol which is present in the blood plasma of healthy males in small concentrations. About 15% of it is produced by the testicles, while the rest is the result of testosterone metabolism in the other systems of the body. The extragonadal formation of estrogen in males occurs in adipose tissue, muscle, liver and

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kidneys. This way of estrogen formation is also typical for postmenopausal and castrated females. Healthy males, on average, produce up to 0.05 mg (50 μg) estradiol per day.

Progesterone in men is produced by seminal vesicles and adrenal glands in very small amounts. It is an intermediate for the synthesis of all steroid hormones. Progesterone is, by its nature, progestin or gestagen. The normal level of progesterone in men is 0,5-5.2 nmol/l.

Progesterone is an intermediate precursor for other hormones: testosterone, cortisol and neurosteroids. Progesterone inhibits the conversion process of testosterone, which, in turn, reduces the risk of benign hyperplasia and prostate cancer. In addition, progestrerone is a hormone that counteracts estrogen. Therefore, progesterone may moderate the effects of other female sex hormones in males with elevated estrogen levels due to feminization syndrome [4,5].

Progesterone inhibits monoamine oxidase which is an enzyme responsible for the breakdown of serotonin. It also improves the function of serotonin receptor in the brain, and it's too high or low levels may cause serious problems in the chemical processes in the brain.

Sex Hormone Binding Globulin (SHBG) binds testosterone and estradiol in plasma, but has a greater affinity to testosterone. SHBG concentration in male plasma is approximately 2 times higher than in females. The normal concentration of free testosterone in males is 1-2% of the total testosterone level. Changing the concentration of transport proteins, this ratio may change, therefore it is advisable to examine the level of SHBG in addition to measuring total testosterone. Free Androgen Index (FAI) is calculated as the ratio of the molar concentration of total testosterone to the SHBG molar concentration, expressed in percentage, correlates with the content of bioligically available free testosterone and is used as an informative marker of androgen status. If the SHBG concentraion decreases, the ratio of free testosterone to free estradiol increases, although there is absolute increase in the concentrations of both hormones. If the SHBG concentration increases, the ratio of free testosterone to free estradiol decreases. Thus, in both sexes' high SHBG concentration results in enhancement of estrogen effects, while low SHBG concentration enhances androgen effects [6-9]. Table 1 shows the factors that increase and decrease SHBG concentration in blood plasma.

TABLE 1

Factors that increase and decrease SHBG concentration in blood plasma

Increase	Decrease
Estrogens	Androgens
Hyperthyroidism	Hypothyroidism
Liver cirrhosis	Glucocorticoids
	Malnutrition and malabsorption
	Conditions associated with loss of protein
	Obesity, especially in females

Breast cancer

Among all pathological processes in male mammary glands the development of breast cancer is of greatest importance. This problem has been studied insufficiently due to the rarity of the disease. Table 2 shows the reasons that can lead to breast cancer in men.

TABLE 2

Risk factors for the development of breast cancer in males

Age
Population of Western Europe vs. population of the Far East and Japan
High socio-economic status
Breast cancer in the family
Jewish origin
Effects of ionizing radiation
Elevated levels of female sex hormones
Threats related to professional activities:
employment in the production of soaps and perfumes
performing work in hot shops, steel mills and blast fumaces
activities related to electromagnetic fields
harmful effects of petroleum on workers of petrol stations and car service stations
Reduced testicular function due to:
post mumps orchitis
incorrect plastic of hernial ring in the inguinal hernia
cryptorchidism
Klinefelter syndrome
Hyperprolactinemia due to:
head trauma
prolactinoma
use of medicines that increase the levels of prolactin in the blood
Peutz-Jeghers syndrome
Gynecomastia
Excess weight from an early age

As shown in Table 2, if we discard some genetic aspects and external influences (for example, ionizing radiation), the risk of developing breast cancer in men can increase due to the so-called feminization, which may be a result of both genetic influence and the unfavorable effects of the environment [10]. It concerns, first of all, men with testicular dysfunction, often caused by orchitis, for example. Increased risk of developing breast cancer in men is also associated with reduced testicular function due to incorrect plastic of hernia gate. Bilateral cryptorchidism also increases the threat of this disease [11,12]. The established causative link between breast cancer in men and Klinefelter's syndrome (chromosomal disease in men caused by sex chromosome polysomy, characterized by primary hypogonadism, oligo- and azoospermia and eunochoidism) [13,14]. Such pathological conditions, as a rule, result in reduction or decline in testosterone levels that causes imbalance in estrogens-androgens ratio in the male body [15]. Similar imbalance of male and female sex hormones occurs in chronic liver diseases, for example, cirrhosis. In this case, the level of estrogens increases due to insufficient estrogen disintegration [16]. Men who take estrogen for medical reasons also run the risk of developing breast cancer [17].

Additional risk of breast cancer occurs for men in certain occupations, in particular, those exposed to constant overheating. Permanent long overheating can result in testicular dysfunction and reduced testosterone levels [18].

The relation of breast cancer to gynecomastia is controversial, but probable as gynecomastia is one of the manifestations of the above mentioned feminization [19-21].

MATERIALS AND METHODS

Hormone receptors in males within the normal range and in cancer

The first predictive molecular markers for breast cancer in women were Estrogen Receptors (ER) and Progesterone Receptors (PR). They are proteins that specifically bind these steroid hormones and then induce the transcription of genes involved in the processes of differentiation, proliferation, adaptation and protein biosynthesis. The important prognostic significance is associated primarily with high sensitivity of ER- and PR-positive tumors to hormonal therapy by anti-estrogens.

It was believed until recently that steroid hormone receptors were localized in cytosol. In early proposed a two-stage model of interaction of steroid hormones with a target cell, which was based on the binding of the hormones with cytoplasm receptor proteins. As a result, the affinity of hormone-receptor complex to nuclear chromatin sharply increases and it is translocated from

the cytoplasm to the nucleus. Then the mechanism of transcription begins and the hormone-receptor complex dissociates [22-25].

In the formulated a new model of steroid hormone reception, according to which the receptor distribution between the nucleus and cytoplasm is uneven, with strong predominance of concentration in the nucleus, and the stability of receptor binding with nuclear structures increases significantly in the presence of hormone-ligands by the formation of hormone receptor complexes that do not dissociate upon the beginning of the mechanism of transcription.

In 1975, an American research team headed by L. Terenog reported 31 women treated for I and II stages of breast cancer. The periods between recurrence and deaths in these patients were longer if there were estrogen receptors found in the tumor, and shorter in their absence.

Other authors also pointed out the relation between estrogen receptors and the prognosis. Thus, G. Fletcher published in 1978 the results of long observation of 48 women with IV stage of breast cancer. Eight years upon the beginning of the treatment, the survival was higher in women with estrogen receptor positive tumors [26-30]. The interval between the primary treatment and recurrence was twice as long in patients with estrogen receptor positive tumors.

Summarizing the findings of a number of authors in his monograph, cites 877 studies of receptor status of breast tumors in women and concludes that all published results agree in defining the relationship between the state of estrogen receptors and the survival of patients. The author states that patients with estrogen receptor positive tumors have statistically significant higher chances of survival than those with estrogen receptor negative tumors.

In suggested that breast tumors contain progesterone receptors whose synthesis is directly stimulated by estrogens. According to the authors, the simultaneous presence of estrogen and progesterone receptors in the tumor increases its sensitivity to endocrine therapy, which is a valuable basis for the differential selection of patients for this type of therapy.

Found androgen receptors in breast tumors. Individual breast tumors proved glucocorticoid dependent. Glucocorticoid receptors are found in breast tumors in women in approximately 50% of cases. Since the discovery of the receptors there have increasingly appeared new findings in literature on their structure, properties, interaction with other characteristics of tumor growth. Hormone receptors in breast tumors in men were identified almost simultaneously with those in women.

Many researchers were primarily interested in the relationship between estrogen and progesterone receptors in breast tumors in men and the prognosis of the disease. As subsequent findings show, there are significant differences between the levels of steroid hormone receptors in the breast tumors of men and women.

In malignant tumors of male mammary glands the levels of hormone receptors is higher on average than in female malignant breast tumors 35. This primarily concerns increased levels of estrogen and progesterone receptors. Clinically significant levels of hormone receptors are found in over 85% of male breast tumors. Notably, the incidence of receptor positive tumors in men does not increase with age, in contrast to women with breast cancer. The detection rate of receptor-positive tumors in men of any age group is roughly comparable with that of women at postmenopausal age [31-35].

Conducting a meta-analysis of 993 cases of breast cancer in men, 12303 cases of breast cancer in African American women and 141045 cases of breast cancer in Caucasian women, came to the following conclusions. The highest proportion of receptor positive tumors was cancer of male breasts. Moreover, the author emphasizes that in white men the levels of receptor positivity does not depend on the age of patients and histological variant of the tumor. Besides, cumulative survival in breast cancer in men depends on the patients' race, with black and Asian patients having the worst odds to survive the 5- and 10-year limit, unlike Caucasian men.

Further study of the receptor status of male mammary glands makes it clear that hormone receptor positive tumors are characterized by significant biological heterogeneity. The function of ER and PR may be different from that in women. Estrogen receptors have α- and β- fractions. Thus, ER alpha (ER-α) and ER beta (ER-β) are singled out. ER are located in different tissues of the human organism. ER-α mostly show expression in the endometrium, stromal cells of the ovaries and the hypothalamus. In men, ER-α are identified in the epithelial cells of the efferent duct. ER-β are expresses in the ovarian granulosa cells, the tissues of the kidney, brain, bones, myocardium, lungs, prostate gland and endothelial cells.

The role of ER-α and ER-β in breast tumor in men has not been studied sufficiently. The principal difference between the receptor status of male and female breast tumors is as follows: the beta-faction of estrogen receptors is in much higher quantity in men. This accounts for higher proportion of receptor-positive breast tumors in men, as ER-β in female breast tumors are relatively rare [36,37].

Today it is believed that the presence of ER-β in female breast tumors is a favorable prognostic factor. However, the heterogeneity of ER in men can cause ambiguous and controversial response to antiestrogen hormone therapy [38].

Some authors raise the issue of clinical significance of receptors of other steroid hormones of tumors of male patients with breast cancer. Thus, in their study of tumors of men with breast cancer make a conclusion about the significant impact of androgen receptor expression in the tumors. In addition, overexpression of the androgen receptor is associated with poor prognosis. The level of androgen receptor affects both the disease-free survival and the overall survival.

A possible correlation between the levels of androgen receptors in malignant tumors of the male breast and Prostate-Specific Antigen levels (PSA) and Prostate-Specific Acid Phosphatase (PSAP) [39,40]. This assumption was based on the fact that the PSA and PSAP levels in normal and cancer-affected prostate are regulated by androgen, as well as the level of androgen receptors at breast cancer in men. Therefore, according to the researchers, male patients with breast cancer who have shown overexpression of the androgen receptor in the tumor should have increased levels of PSA and PSAP. Also, an immunohistochenical research of 26 male breast cancer cases has been carried out to study androgen receptor levels and compare the results with PSA and PSAP levels in these patients. Overexpression of androgen receptors was observed in 81% of cases, increased PSA levels in 23% of patients, while increased PSAP levels were not found. Overexpression of androgen receptor levels combined with increased PSA levels were observed in four patients. Thus, in case of increased PSA levels found in screening of men, except for prostate cancer, breast cancer should be suspected.

According to studies, androgen receptors in breast tumors are found in a large number of cases (95%). This fact seems to necessitate further in-depth studies of the role of androgen-receptor status of malignant male breast tumors in the pathogenesis of the disease [41-44].

Endocrine treatment of male mammary glands: clinical aspects

The data presented in this chapter are based upon the analysis of scientific literature and our own research of 174 cases of breast cancer in men.

Male breast cancer tumors are immunophenotypically different from those occurring in women. First of all, this concerns different pathogenesis in the development and progression of the disease. Such differences may play a key role in the therapeutic effect on the tumors, requiring different strategies of treatment of male and female breast cancer [45,46].

Many authors point out different clinical significance of steroid hormone receptors in male and female breast cancers tumors. The comparative analysis of the results of immunohistochemistry test of estrogen and progesterone receptors in male and female breast cancer tumors shows that the levels of estrogen- and progesterone-receptors are statistically higher in males. However, this fact proves not so much different biological properties of the tumor cells of breast cancer in men and women, as the need to apply different therapeutic approaches in the treatment of this disease in male and female patients [47-49].

With such consistently high levels of steroid hormone receptors found in men with breast cancer, it seems logical to assume that the application of antiestrogens and aromatase inhibitors, as well as orchiectomy (similar to ovariectomy in women) will have the most effective therapeutic effect on the pathological process. These approaches express a general tendency to extrapolate the knowledge acquired in the course of treatment of breast cancer in women on breast cancer pathology in men.

Chronologically, orchiectomy was the earliest hormone therapy of breast cancer in men. It was applied until about early 1970s on many patients along with surgery and radiation therapy. However, further studies showed that it did not result in higher survival rates of patients with breast cancer.

Since the beginning of tamoxifen era, this drug was tested for the treatment of male breast cancer. According to borgen antiestrogens treatment of men with breast cancer completely justified itself. The effect of tamoxifen on survival of male patients with breast cancer. All patients had operable stages II or III of the disease and in terms of adjuvant treatment after radical surgery were prescribed only tamoxifen (20 mg daily for 1-2 years). 61% of patients survived 5 years compared with 44% in the control group. N Robert points out that since 1977, since the date of its approval in the USA, tamoxifen has been consistently used in the practice of treatment of male breast cancer patients. This was primarily due to high rates of positivity of steroid hormone receptors of male breast tumors.

Including tamoxifen in the scheme of treatment of male breast cancer, as most breast tumors have positive estrogen and progesterone receptors. According to M.Volm, tamoxifen is the agent of choice in the complex therapy of male breast cancer taking into consideration that most cancers are estrogen-receptor-positive.

Emphasize that hormonal treatment is an essential part of adjuvant therapy of breast cancer in men as male breast cancer tumors have a high degree of positivity of steroid hormone receptors. Because of the low efficiency of orchiectomy, tamoxifen is used the standard modern hormone treatment of this disease [50].

On the other hand, the effectiveness of hormone therapy in breast cancer patients due to biological differences between breast cancer in men and women. According to Z Nahleh, these differences, especially concern the role of estrogens and male sex hormones in the pathogenesis of the disease. The author also claims that it is questionable that the positivity of steroid hormone receptors in malignant tumors of the male breast has the same prognostic value as in those occurring in women. Although current use of tamoxifen in breast cancer of men is accepted, the problem of hormone therapy for this disease, according to needs further study.

The view that extrapolation of the principles of hormone treatment of breast cancer in women on male breast cancer is inappropriate. Attention is drawn to significant biological differences between male and female malignant breast tumors. According to the authors, although male patients with breast cancer recorded positive response to antiestrogens in some cases, the optimal regimen of hormone therapy for this disease is still unknown.

The study included 168 patients with breast cancer who were examined and treated at the Transcarpathian Regional Oncology Center, the Institute of Oncology of the Academy of Medical Sciences of Ukraine and the Russian Oncology Research Center named academician NN Blokhin of the Russian Academy of Medical Sciences from 1946 to 2000, retrospectively. In all patients the diagnosis was confirmed histologically [51-55]. The mean age of patients was 56.1 ± 11.2 years. The youngest patient was 19 years old, the oldest-82 years old.

In our study estrogen receptors were positive in the tumors of 75% of patients. The positive rate of progesterone receptors was observed in 44% of patients.

Statistical analysis

Statistical processing of the material was performed using the application program STATISTICA, version 7.0 '2004 Edition of StatSoft, Inc. Survival analysis methods were used to study cumulative life expectancy. In particular, the LogRank (Mantel-Haenszel) test was used for the two-factor analysis, and the Gehan's Wilcoxon test with Kaplan-Meier graphing was used for the multifactor analysis. In addition, multifactor analysis was performed by Cox regression, which combines methods of nonparametric analysis (survival tables) and parametric (regression analysis). In other cases, variance, regression and correlation analyzes were used (if data censorship need not be taken into account), in particular, methods, Student's method and plotting of linear regression with validation for differences in correlation factors.

RESULTS

There was no dependence found between the receptor status of the tumors and the age of patients with breast cancer. The analysis of survival of patients with different receptor status of the tumor has shown that there is no relationship between the levels of estrogen and progesterone receptors and life expectancy of patients with male breast cancer.

Thus, the level of steroid hormone receptors in male breast cancer is not a valid prognostic sign of survival and the metastasis free period in these patients. On the basis of a multifactor analysis by Cox regression method, it has been found that the most significant impact on the survival of men who have breast cancer has the status of regional lymph nodes category N (Table 3).

TABLE 3

Influence of various factors on the cumulative survival rate of patients with male breast cancer

Factor	p	Score
Category N	0.00005	1
Body mass index	0.049361	2
Histological variant	0.077028	3
Age	0.132629	4
Category T	0.506261	5
Level of steroid hormone receptors	0.644916	6
Presence of gynecomastia	0.987885	7

According to our data, in the group of patients with the positive receptor status of the tumor the use of antiestrogens did not have a statistically significant effect on the survival and the duration of metastasis free period without recurrence as compared to the patients who did not receive this type of hormone therapy.

The multifactor analysis of the effect of methods of treatment on the survival of patients with male breast cancer by the method of Cox regression has revealed that hormone therapy by antiestrogens does not have a statistically significant effect on the cumulative survival of patients with male breast cancer (Table 4).

TABLE 4

Influence of methods of treatment on cumulative survival of patients with male breast cancer

Method of treatment	P	Score
Radiotherapy	0.000023	1
Radical surgery	0.050727	2
Orchiectomy	0.183032	3
Chemotherapy	0.254391	4
Hormone therapy by antiestrogens	0.87137	5

The results given refer to the total number of patients. To identify the impact of different methods of treatment on the survival rate of patients with unfavorable prognostic signs, a group of patients with the following characteristics was formed: the third stage of the disease; N2-3; 2-nd and 3-rd degree of malignant tumors (G2-G3); medium, severe and morbid obesity. The summary of multifactor analysis by Cox regression is shown in Table 5. As we can see, for this group of patients hormone therapy by antiestrogens has become statistically significant (p=0.038). Orchiectomy, chemotherapy and surgery had little or no effect in these cases.

TABLE 5

Influence of treatment methods on the cumulative survival of patients with male breast cancer considering unfavorable prognostic signs

Treatment	P	Score
Radiotherapy	0.03598	1
Hormone therapy by antiestrogens	0.038337	2
Orchiectomy	0.18602	3
Chemotherapy	0.280162	4
Radical surgery	0.536076	5

DISCUSSION

Besides antiestrogens, some authors reported about the attempts to apply aromatase inhibitors for male breast cancer. According to M Volm, the latest generation of aromatase inhibitors replaced the use of tamoxifen in the

treatment of women and is now a reasonable alternative in hormone therapy of male breast cancer. In turn, B Zabolotny reported about the successful treatment of breast cancer in men with the use of letrozole. Giordano S reported about the treatment of 5 male patients with breast cancer with the use of anastrozole. It is a well-known fact that aromatase inhibitors are the final enzyme of estradiol synthesis. However, the role of aromatase in men has not been studied as well as in women. As Doyen J point out, men produce 80% of circulating estrogens by aromatization of testicular and adrenal androgens, while the remaining 20% are produced directly in the testes. Studies on healthy men have shown that treatment with non-steroid aromatase inhibitors results in a significant decrease in estradiol levels in the plasma. However, today there are no data on the impact of aromatase inhibitors on the level of estradiol in the plasma of male breast cancer patients.

Alongside with the reports on positive impact of aromatase inhibitors on the course of breast cancer in men, there are a number of reports about the lack of any effect of their application, and even about much higher level of side effects from the administration of these agents. They did not notice any positive effect from using aminoglutetimid in 5 patients and did not register any clinical response to the use of anastrozol. Therefore, one should take into account the opinion of that despite a wide range of aromatase inhibitors, the data on their effectiveness in the treatment of men with breast cancer are limited.

In literature, there are also individual reports about the use of other hormone treatment and its impact on the course of breast cancer. Thus, there are reports about the use of LHRH-agonists also called luteinizing hormone-releasing hormone agonists), Cyproterone Acetate and Fulvestrant. However, all the reports are based on a small number of cases.

Breast cancer in men has a more aggressive course than the same disease in women. This means lower survival rate of male patients, greater number of locally advanced and metastatic cases, with delayed primary treatment, and resistance to treatment compared to female breast cancer patients. This is primarily due to biological differences between male and female breast cancers. These differences concern different anatomical structure of the male and female breasts, different hormonal backgrounds of men and women, different receptor statuses of the tumors, the influence of biological factors on the development of the tumor and other factors.

The detection rate of steroid hormone receptors in malignant tumors of the male breast ranges from 65 to 100 per cent, depending on the criteria for identifying their positivity level [56]. The incidence of receptor positive tumors in men does not increase with age, as observed in women with breast cancer. The detection rate of receptor positive tumors in men of any age group approximates that of postmenopausal women. However, the clinical significance of the levels of steroid hormone receptors in male breast tumors has not been finally established to date. Most scholarly papers on this subject emphasize the existence of correlation between the presence of clinically significant levels of steroid hormone receptors and response to hormonal therapy. However, final conclusions have not been made. There is no consensus so far regarding the prognostic significance of the levels of steroid hormone receptors in male breast cancer. Some researchers have reported more favorable course of later-stage breast cancer in men compared to the course of the disease in women. However, whether this is the result of higher detection rate of the positive levels of steroid hormone receptors, is still unknown. There is a contradiction among experts in determining the prognostic significance of the levels of steroid hormone receptors in male patients with breast cancer. Thus, some researchers insist on the correlation between the levels of estrogen and progesterone receptors in tumors and overall survival of patients with male breast cancer [57,58]. On the other hand, some experts claim that there is no significant influence of the levels of steroid hormone receptors on the survival rate of the patients with this disease.

To date, more findings support the idea that there is no correlation between the levels of estrogen and progesterone receptors and life expectancy of the patients with male breast cancer. The analysis of the impact of the receptor status of the tumor on the duration of the metastasis free period also proves against the prognostic value of this parameter of the tumor. Thus, the levels of steroid hormone receptors in breast tumors in men is not a credible significant sign of the survival and duration of metastasis free period in male breast cancer patients. Androgen receptors in breast tumors are found in a great number of cases (95%). This fact proves the need for further in-depth study of the role of the androgen-receptor status of malignant tumors in men in the pathogenesis of the disease [59,60].

Hormone therapy of breast cancer in men is based entirely on the most proven principles of the effectiveness of treatment of breast cancer in women. Current practice lacks controlled clinical trials of the effectiveness of a particular regimen of hormone therapy of the malignant tumors under discussion that would confirm the necessity of their application in male patients. The hormone therapy in the early and late stages of cancer include antiestrogens, steroid and non-steroid aromatase inhibitors, both as monotherapy and in combination with LHRH-agonists, fulvestrant and other hormonal agents. Despite numerous reports on the effectiveness of hormone therapy in men with breast cancer, many aspects of this type of therapy remain largely unexplained [61].

CONCLUSION

Hormone therapy appears the most effective in patients with the so-called feminization syndrome, which includes signs of hyperestrogenemia, as well as in patients with multiple unfavorable prognostic signs (stage III of cancer, low differentiation of tumor cells, status of regional lymph nodes N2-3 and medium, severe and morbid obesity). Orchiectomy does not increase the survival rate; therefore, its application is impractical.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This retrospective study meets ethical standards of the Uzhhorod National University EC\IRB as is recognized by its approval number 25643.

CONSENT FOR PUBLICATION

Not applicable as this is a retrospective chart review.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The author declares that they have no competing interests.

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AUTHOR'S CONTRIBUTION

Yevhen Hotko concepted and designed the manuscript, collected, analyzed and interpreted the data, wrote the manuscript.

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