

## MALE BREAST CANCER: CLINICAL PRESENTATION, DIAGNOSIS, TREATMENT

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Despite male breast cancer is rare in occurrence, it is a serious problem. In 2012, 130 men in Ukraine got breast cancer that constituted 0.74% from all patients with mentioned pathology detected in the course of year. Every year in Ukraine approximately 100 men die from breast cancer. Still many aspects of male breast cancer remain unstudied. It occurs since information about mentioned disease is mainly based on retrospective analysis of small groups. Treatment of men, who got breast cancer, is based on knowledge, which has been obtained in treatment of women with this pathology. This article is based on the results of analysis of 168 cases of breast cancer in men, who have been examined and treated in the period from 1956 to 2012. In paper the peculiarities of clinical manifestations of male breast cancer have been determined, the optimal volume of diagnostic procedures in men with suspicion of breast cancer has been established, the mammographic signs have been detected and the possible histological variants of disease have been determined, clinical course peculiarities of male breast cancer have been defined, the most essential factors of prognosis of the disease have been fixed. Furthermore, in article optimal volume of surgical treatment of male breast cancer has been substantiated, the role and place of radiotherapy in treatment of this pathology has been determined. It has been proved that adjuvant polychemotherapy should be applied to the patients with male breast cancer independently from stage of process. Also optimal schemes of this kind of treatment have been determined. The efficacy of hormonal therapy with antiestrogen in patients with positive receptors of steroid hormones and at presence of unfavorable prognostic factors of disease has been demonstrated. The inefficiency of orchiectomy as one of the widespread kinds of hormonal therapy of male breast cancer has been defined.

**Key Words:** male breast cancer, diagnostics, treatment, prognosis.

This article is based on the results of analysis of 168 cases of breast cancer in men, who have been examined and treated in Zakarpattia Regional Oncological Dispensary, Institute of Oncology of AMS of Ukraine and N.N. Blokhin Russian Cancer Research Center of Russian Academy of Medical Sciences in the period from 1946 to 2012. In all patients the diagnosis has been histologically verified. Average age of patients has constituted  $56.1 \pm 11.2$ . The youngest patient was 19 years old, the oldest — 82.

### CLINICAL PRESENTATION OF MALE BREAST CANCER

The most widespread symptom is presence of tumors in mammary gland [2, 4]. Due to relatively small sizes and small mass and volume of parenchyma of mammary gland in men, the tumor node may be detected almost in the early stages of development of malignant neoplasm.

At the same time, particular complications in diagnostics may arise only in patients, whose tumor develops on the background of gynecomastia [3]. Presence of gynecomastia in anamnesis is quite variable and depends on the way it has been diagnosed: histologically or clinically. Approximately in 5% of patients the synchronous or metachronous bilateral breast cancer is observed [5].

Mean age of breast cancer patients constitutes 60–65 years old. The risk of breast cancer in men increases essentially on the seventh decade of life years [2, 7]. However, this disease may occur in wide enough age range — from young to old age (there is a case in researches described, when breast cancer occurred in 9-year boy) [10]. The examples of development of this disease in patients of elderly age, in particular, older than 90, exist. The index of mean age of men, in average, is 5 years higher, than the same index in female breast cancer patients.

Mostly tumor is located in central parts of breast, exactly in subareolar area. That is why in the half of patients on the moment of the first appeal for medical help the symptom of retraction of the nipple is being detected [5, 16]. Nipple discharge is found relatively rarely and has color from serous to sanguinolent or rust [27].

The middle size of tumor in first time diagnosed patients constitutes 3–3.5 cm. However, size of tumor in its first detection may equal 0.5–12 cm and more [2, 5, 27]. Tumor is usually located under the nipple or off-center near the areola, than it involves the whole tissue of gland, shrinking it and grows into the skin and nipple. Tumor does not reach significant sizes: usually, it does not exceed 2 cm; rarely its diameter achieves 5 cm. Fixing of skin above the tumor is observed in approximately one third of patients (symptoms of “umbilication”, “platform”, “lemon skin”, etc.). In the same number of patients on the moment of detection of breast cancer was observed ulcering of skin above the tumor [6].

Pain in mammary gland is quite unstable symptom of breast cancer in men, but in the majority of cases this very symptom makes majority of patients appeal for the medical help. Pain in mammary gland

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**Abbreviations used:** AC – doxorubicin + cyclophosphamide; CAF – cyclophosphamide + doxorubicin + 5-fluorouracil; CMF – cyclophosphamide + methotrexate + 5-fluorouracil; CT – chemotherapy; NDEA – nonsteroid drugs with estrogen activity; RME – radical mastectomy; RT – radiotherapy.

in the presence of malignant neoplasm is met relatively rarely — in every sixth-seventh patient [19].

Approximately in every second case in the first visit of patients the enlarged axillary lymph nodes are detected [20]. However, reliability of clinical evaluation of status of axillary area is not high: false-positive results of examination of these areas concerning the subject of metastatic involvement of lymph nodes oscillates within the limits 8–50%, the same as diapason of false-negative results — 18–40% [3, 4, 16, 27]. At the same time, metastatic involvement of axillary lymph nodes is histologically determined in more than 50% of men, who first time appealed for medical help concerning breast cancer.

### **DIAGNOSTICS OF MALE BREAST CANCER**

Study of male breast in the presence of neoplasms includes radiological mammographic study and paracentetic biopsy of tumor with cytological and/or histological study of biopsy material, which was obtained by thin needle paracentetic biopsy of tumor [12, 14]. In single cases in diagnostics of breast diseases in men is recommended to apply ultrasonography.

The main mammographic features of male breast cancer include mass of increased intensity with blurred edges, which is well visualized and in the majority of cases includes microcalcinations [11]. At that the pathologic focus in major cases is located subareolar.

Ultrasonography of mammary glands in men is used rather rarely, than radiologic investigation. However, very often it is not less informative, than mammography. Ultrasound study of lymph nodal neoplasms in parenchyma of mammary gland is especially informative in those cases, when it is needed to differentiate solid and cavernous (cystic) tumors. In the majority of cases, tumors have solid structure (in 80% of patients). In 20% of patients ultrasonography determines cystic neoplasms, which may be caused by the development of papillary intraductal non-invasive carcinomas. Thus, radiologic and ultrasound method of study of mammary glands in men have undoubted advantages, but using them together increases the quality of diagnostics [15].

Histological study of tumor tissue of male mammary glands is the most precise diagnostic method. By its histological structure, human breast cancer does not differ from female breast cancer [1]. At that it is concerned both tumors, which have developed on the background of gynecomastia, and without it. In men occurred almost all known histological forms of breast cancer. In the majority of cases in men are to be found intraductal carcinomas [8, 17]. Along with it, in men are detected also rare and peculiar histological variants of breast cancer (papillary carcinoma, grid cancer, mucosal cancer, cancer with apocrine metaplasia, etc.). Quite probable is also detection of lobular cancer, which almost always develops on the background of gynecomastia [1, 17]. Non-invasive carcinomas are to be found in not much as in 5% of men, who appeal for medical help concerning breast cancer. In-

vasive carcinomas in men more often, than in women, have high degrees of malignancy [1].

### **CLINICAL SIGNIFICANCE OF HORMONE RECEPTORS IN TUMOR IN PATIENTS WITH MALE BREAST CANCER**

Hormone receptors in tumors of breast in men have been determined almost simultaneously with the same in women. Of the first-priority is the question of connection between estrogen and progesterone receptors in tumors of male mammary glands and prognosis of the disease [21]. As our developments have showed, between levels of receptors of steroid hormones in tumors of mammary glands of men and women essential differences take place. In malignant tumors of male mammary gland the level of hormone receptors, in average, is higher, than in malignant female breast tumors [22, 25]. First of all, this increasing of levels concerns the receptors of estrogen and progesterone. Clinically significant levels of hormone receptors are contained in more than 85% of tumors of male breast [21, 22, 24, 25]. At that the presence of receptor-positive tumors in men does not grow with the age, as it is observed in women, who are breast cancer patients. Frequency of detection of receptor-positive tumors in men of any age group is approximately comparable with the same one in women in post-menopausal period.

There are biological differences between male and female breast cancer. One of the main of them is more aggressive clinical course of mentioned disease in men. It is caused by higher number of estrogen-receptor-positive tumors in men. However, it does not influence the cumulative survival of patients compared with female breast cancer patients. That is high levels of estrogen and progesterone receptors in tumors of male mammary glands are not associated with better or worse survival of patients. Mentioned fact is the evidence not so much of different biological properties of tumor cells of male and female breast cancer, as of need to use different therapeutic approaches in treatment of this pathology in both sexes.

### **TREATMENT OF MALE BREAST CANCER**

#### **Surgical treatment of male breast cancer**

In the early stages of disease surgical intervention is considered to be most effective [11, 13, 15, 28]. Approaches to surgical treatment of male breast cancer have been changed over the last 50 years. In previous years prevalence has been given to the radical mastectomy according to the Halsted — Meyer, today the priority is given to the organ-saving surgeries. In proposed study mostly has been performed radical mastectomy according to Patey (45.45% of cases). Not so often in patients has been performed radical mastectomy according to the Halsted-Meyer and surgery with saving of both pectoral muscles (21.68 and 20.28% respectively). Other kinds of surgical treatment (sectional resection, mastectomy, palliative resection of tumor) have been performed quite rarely.

Studying the influence of kind of surgical treatment on the cumulative survival of patients, duration of recurrence-free and metastases-free periods, we have obtained quite interesting data. In particular, it is said about statistically significant differences between overall survival of patients, who underwent radical mastectomy by Halsted — Meyer and those, who underwent radical mastectomy by Patey or surgery with saving of both pectoral muscles. At that coefficient of five-year survival rate in first group of patients was worse, than in last two groups. At the same time, all groups of patients with different kinds of surgical interventions were homogenous and comparable by parametric data of patients and tumors.

The same may be stated concerning ten-year survival. Patients, who underwent radical mastectomy by Halsted — Meyer, had significantly lower chances to overcome this time cell compared with patients, who underwent radical mastectomy by Patey or surgery with saving of both pectoral muscles.

Comparing rates of five-year and ten-year survival among patients, who underwent radical mastectomy by Patey and radical mastectomy with preservation of both pectoral muscles, statistically significant difference was impossible to reach. Concerning recurrence-free and metastases-free survival of patients, who underwent different kinds of surgical treatment, statistically significant differences between them have not been observed. Table 1 is given below represents frequency of local recurrences and generalizations of process according to the type of performed surgical treatment.

**Table 1.** Frequency of local recurrences and generalizations of process in male breast cancer patients according to the type of surgical intervention

Surgery	Recurrences of tumor (%)	Generalization of process (%)
RME by Halsted – Meyer	7.69	62.96
RME by Patey	5.08	42.86
RME with preservation of both pectoral muscles	4.00	27.59
Mastectomy	0	66.67
Sectional resection	40.00	20.00
Total	6.72	42.19

First conclusion made from contained data concerns surgical intervention. Surgical resection in volume of sectional resection in male breast cancer patients is not enough. However, no difference in recurrence-free survival between groups of patients, who underwent sectional resection of mammary gland compared with other groups, has been statistically determined. It occurs in consequence of small number of patients, who underwent sectional resection. However, 40% of recurrences in this group are the evidence of insufficient radicalism of mentioned type of surgical treatment.

Better survival of patients, who underwent radical mastectomy by Patey and radical mastectomies with preservation of both pectoral muscles in contrast to the patients, who underwent radical mastectomies by Halsted — Meyer, is the evidence of: last type of surgical treatment should be performed only in case

of strict recommendations, to be exact, when invasion of pectoral muscles by tumor takes place.

Moreover, approximately similar frequency of recurrences of tumor in groups with different types of radical mastectomies (by Halsted — Meyer, by Patey and with preservation of both pectoral muscles) gives ground to state that prevalence shall be given to radical mastectomy with preservation of both pectoral muscles. Performance of surgical intervention in male breast cancer patients does not the increase the number of local recurrences of tumor and does not influence the growth of risk of remote metastases of tumor compared with other types of radical mastectomies. In addition, mentioned type of intervention is much more physiological and less traumatic compared with radical mastectomies by Patey and especially by Halsted — Meyer. Thus, on the basis of obtained information may be recommended radical mastectomy with preservation of both pectoral muscles as surgery of choice in male breast cancer in case of signs of invasion of tumor in greater pectoral muscle.

**Radiotherapy of male breast cancer**

After performance of RME with preservation of both pectoral muscles, chest wall undergoes irradiation on the side of involvement and areas of lymph collectors on the side of involvement: axillary zone and supraclavicular areas. Postsurgical RT is prescribed in 12–14 days after radical surgical intervention (or after full recovery of patient after surgical intervention) and is carried out by method of standard dose fractionation. Total focal dose on zones of regional metastasis constitutes 45 Gr, on area of postsurgical scar — 55–60 Gr [21].

Among taken for examination patients the radiotherapy has been performed in half of male patients. Total presentation of efficacy of used method is more than convictive. Patients with I–III stages of breast cancer, whose treatment plan of breast cancer included radiotherapy, had significantly better cumulative survival ( $p = 0.00003$ ). Chances to live over five and ten years had 82 and 68% of patients respectively, who received radiotherapy, against 48 and 29% of patients, whose treatment plan did not include radiotherapy.

Further statistical researches of selected material have showed that radiotherapy is effective not in all patients with early stages of breast cancer. Comparing cumulative survival of patients and different stages of disease, we have determined that use of radiotherapy in statistical plan does not essentially influence the five-year and ten-year survival rate in the first stage of male breast cancer. This method is effective in patients with II and III stages of disease. It gives opportunity of 40% increase of the five-year and 31% increase of ten-year survival of patients with II stage of male breast cancer ( $p = 0.01$ ). In patients with III stage of disease the use of radiotherapy in treatment program allows to improve five-year survival by 26% and ten-year survival — by 32% ( $p = 0.03$ ). Thus, this fact of survival improvement among such patients, who underwent radiotherapy, is reliable. In patients

with I stage of disease this regularity has not been observed. Taking into account that the majority of men with I stage of disease underwent radical mastectomy in different variants, we may assume that in mentioned patients there is no sense to supplement radical surgical treatment with radiation method.

Concerning patients with II and III stages of disease, the obvious is tendency to significant improvement of five-year and ten-year survival in groups of patients, whose treatment program included radiotherapy. Thus, radiation method is considered to be important part of comprehensive treatment of men with II and III stages of breast cancer. This method gives opportunity to improve significantly survival of mentioned category of patients.

Analysis of influence of irradiation on the frequency of recurrence of tumor has showed almost three times more recurrences in group of men, who did not undergo radiotherapy (10 against 3.5%).

Analyzing influence of radiotherapy on the metastases-free survival of patients, we also should note its positive influence on the selected rate. Clear tendency to reduction of frequency of generalization of process in group of patients, who received radiotherapy, in contrast to those patients, whose comprehensive treatment program did not include this method, is observed ( $p = 0.004$ ). Thus, on the basis of represented data we may state that there is common positive impact of radiotherapy of male breast cancer on metastases-free survival of patients. Nevertheless, we should refrain from further commentaries, since there is a need in further studies of this problem with greater number of patients.

#### **Hormonal therapy of male breast cancer**

Hormonal therapy of mentioned disease, the same as chemotherapy (CT), is fully based on the most approved effective principles of treatment of female breast cancer [2, 4, 5]. In modern practice there are no controlled clinical trials of efficacy of one or another regimen of hormonal therapy of analyzed malignant neoplasm, which would confirm necessity of its use in men. In our study, hormonal therapy has been used in 56 patients, and it is 44% from their total number. At the same time, several types of hormonal therapy have been used:

- glucocorticosteroids (cortisone, prednisone, prednisolone);
- anti-estrogens (tamoxifen, toremifene, etc.);
- nonsteroid drugs with estrogen activity (NDEA; synestrol);
- other hormonal therapy.

Consideration of cumulative survival of patients dependently on kind of carried out hormonal treatment did not give statistically reliable differences. If not taking into consideration small third and fourth groups (with use of NDEA and other hormonal therapy), than in comparison of both length of life and frequency of recurrence and remote metastasis between patients, whose plan of hormonal therapy included glucocorticoids and antiestrogens, there is no significant difference.

In 75% of patients with male breast cancer, estrogen-receptor-positive tumors have been detected. At that their receptor status did not depend on age of patients. In group of patients with positive receptor status of tumor the intake of anti-estrogens had no statistically significant impact on survival, duration of metastases-free and recurrence-free periods compared with patients, who did not receive this kind of hormonal therapy. The same the essential deviation in survival, frequency and remote metastasis in group of men with negative receptor status of tumor concerning estrogen receptors between patients, who were recommended and not recommended to use anti-estrogens respectively, has not been observed. Thus, intake of anti-estrogens did not influence the life length rate, recurrence-free and metastases-free periods neither in patients with positive nor in patients with negative estrogens and progesterone receptors on the surface of tumor cells in the I–III stages of male breast cancer.

However, it should be noted that in the study of degree of influence of treatment methods on survival male breast cancer patients, taking into consideration the unfavorable prognostic signs (III stage of disease, N2–3, II and III stages of malignancy of tumor, moderate, grave and pathological obesity), it has been determined that in mentioned group of patients the anti-estrogen hormonal therapy gained the significance ( $p = 0.038$ ). That is why, in our opinion, this type of hormonal therapy in case of estrogen and/or progesterone-receptor-positive tumors should be included into the comprehensive treatment of male breast cancer patients.

In our study first time has been studied the influence of orchiectomy as single type of hormonal therapy on the indexes of cumulative survival, duration of recurrence-free and metastases-free periods in breast cancer patients in early stages of disease. Comparison of survival rates of patients from two age categories (younger and older than 56), who underwent orchiectomy, has showed: this type of treatment does not influence the length of life in both cases. Comparison of groups of patients, who underwent orchiectomy and who did not undergo this kind of treatment, has determined the following. Orchiectomy in male breast cancer patients does not cause the improvement of survival, as well as does not help to decrease the frequency of recurrence and remote metastasis of tumor.

#### **CT of male breast cancer**

In our study CT has been performed in 63% of patients. Mostly the following regimens have been used:

- CMF (cyclophosphan + methotrexate + 5-fluorouracil).
- With antibiotics of anthracycline line.
- With tiophosphamide (both in plan of CT and in combination with cyclophosphamide) — systemic administration of drugs.
- With tiophosphamide (both in plan of CT and in combination with cyclophosphamide) — intra-arterial administration of drugs.
- With drugs of taxane group (paclitaxel, docetaxel).

On the basis of analysis of cumulative survival of patients with I–III stages of male breast cancer and dependently on type of used CT quite controversial results have been obtained. The highest found out to be survival in group, which received tiophosphamide-contained regimens of CT (88% — five-year survival and 81% — ten-year survival). Patients with CMF regimen had significantly lower rates of the similar survival (49 and 35% respectively). Concerning patients with CT regimens, which contain anticyclines and taxanes, five-year survival in such groups, has constituted 40%. Moreover, difference in survival of patients of all four groups turned out to be statistically significant ( $p = 0.02$ ). It happened, in our opinion, cause of heterogeneity of comparable groups of patients, who received different regimens of CT. As long as we have analyzed material, which was gathered in the last 60 years, it was impossible to form group, which would be comparable for statistical processing. That is why number of patients with I and II stages of disease, who administered tiophosphamide, is much higher, than with III stage. And vice versa — patients, who underwent CT with use of antibiotics of anthracycline group or taxanes, mainly were in III stage of disease. Recurrence-free survival of such patients (with use of tiophosphamide) also significantly differs in better direction. In our opinion, it happened in consequence of aforesaid reason. If we take into account analysis of metastases-free survival, we will not detect reliable prevalence of any type of CT.

In group of patients with male breast cancer of I–III stages of process, who received regimens of CT with tiophosphamide, the last one was administered both systemically and intraarterial. In the result, two comparable by all parameters groups of patients with taking into account way of administration of CT drug, have been formed. Analysis of cumulative survival of patients with male breast cancer according to the systemic or intraarterial administration of CT drugs, has given the following. Statistically significant difference between groups of patients with different way of administration of CT drugs has not been obtained ( $p = 0.18$ ). Moreover, it seems that there are better survival rates in group of patients, who got systematic administration of CT drugs. For recurrence-free and metastases-free survival of patients differences have also not been obtained in mentioned groups of patients. Thus, according to our data, between systemic and regional intraarterial administration of CT drugs there is no statistically significant differences concerning length of life, recurrence-free and metastases-free periods in patients with male breast cancer.

Thus, taking into account aggressive character of growth of malignant tumors of mammary gland in men, CT is recommended to be started almost in the early stages of disease.

Making the decision concerning the expediency of carrying out adjuvant CT, first of all, we should take into account status of axillary lymph nodes on the side

of involvement, size of primary tumor, stage of differentiation of cells and its receptor status, as well as general condition of patients. In plan of adjuvant treatment the prevalence is given to the combinations of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) or cyclophosphamide, doxorubicin and 5-fluorouracil (CAF).

In patients with locally-diffused and metastatic male breast cancer CT is used obligatory, if there is no contraindications to it [9, 23]. Systemic CT in patients with neglected forms of breast cancer is carried out, as usual, with palliative aim. Its efficacy does not exceed 30–40% [9, 21, 23]. Sometimes in patients with not much neglected disease this index reaches 50%. Proposed schemes of treatment may be based both on the one component (monochemotherapy) and on the combination of CT drugs, for example, CMF, or scheme on the basis of anticyclines. Mostly is used polychemotherapy. It is more effective in early not treated patients. Also schemes of polychemotherapy on the basis of taxanes are used or taxanes are carried out in regimen of monochemotherapy.

#### **FACTORS OF PROGNOSIS OF MALE BREAST CANCER**

Studying the prognostic peculiarities of male breast cancer, we have concluded that this disease develops more aggressively, than in women with the same pathology. Higher aggressiveness lies in lower survival of male patients, greater number of neglected cases at first appeal for medical help, resistance to the treatment compared with female breast cancer [18]. First of all, it is conditioned, as it is emphasized, by biological differences between male and female breast cancer. Mentioned differences lie in different anatomic structure of male and female mammary glands [8]. These differences are characterized by different hormonal backgrounds in men and women, different receptor status of tumors, different influences of biological factors on the development of tumors and by many other aspects.

In clinical conditions at absence of generalized process the most important indexes of prognosis of disease is size of tumor (T category) and presence or absence of histologically confirmed metastases in regional lymph nodes (pN category) [8, 18, 26]. In other words, one of the most essential prognostic factors of male breast cancer is stage of process.

Study of influence of tumor on the length of life, recurrence-free and metastases-free periods, has determined that this parameter of tumor influences only overall survival of male breast cancer patients. The bigger is the size of primary tumor, the lower number of patients is able to overcome five-year and ten-year life mark. Five years survived 80% of patients with size of tumor up to 2 cm in biggest dimension, 62% of patients — with tumors 2–5 cm, and 22% — with tumors, which sizes exceeded 5 cm in biggest dimension. Ten-year survival in mentioned groups has constituted 70, 28 and 10%, respectively ( $p = 0.000001$ ).

This tendency has been determined also in case of T category in patients with male breast cancer (taking into account invasion of tumor in neighbor organs and structures). With growth of mentioned category, the survival of patients decreases. Taking into account fact of dissemination of tumor on the neighbor structures, statistically significant is difference of metastases-free survival of patients with T1–3 categories against T4.

Studying frequency of development of remote metastases in patients with male breast cancer, we have determined the following tendency. In absence of dissemination of tumor on the neighbor structures five-year survival without signs of generalization achieve 71% of patients, ten-year — 60%, while these indexes in patients with T4 have constituted 43 and 29%, respectively ( $p = 0.036$ ).

Thus, size of tumor is important prognostic factor, which influences the life of patients with mentioned pathology. Besides, prognosis of the disease essentially worsens in case of invasion of tumor in neighbor structures (skin and muscles), since risk of generalization of process increases.

The next prognostic sign in patients with male breast cancer is status of regional lymph nodes. At that important is not only the fact of its involvement by metastases, but also quantitative characteristics of mentioned rate. In our study patients without involvement of lymph nodes have overcome five-year and ten-year boundary in 82 and 73% of cases, respectively. In patients with N1 these indexes equaled 61 and 39%, and at N2 — 39% and 8% ( $p = 0.002$ ). Thus, we have determined that status of regional lymph nodes in male breast cancer patients is important prognostic sign of the disease and it influences the survival of patients. Analyzing the influence of status of regional lymph nodes on the metastases-free survival of patients, we have determined that this parameter is connected also with frequency of generalization of process in patients with male breast cancer. In 85% of patients without metastatic involvement of regional lymph nodes the progression of the disease in five years after beginning of treatment was absent and in 75% — after ten years. In contrast, in patients with status of regional lymph nodes N1 taken into consideration indexes constituted 49% and 41% respectively, and at N2 — 26% for five-year metastases-free survival, and boundary in ten years from this group of patients no one has overcome ( $p = 0.005$ ).

Concerning the quantitative characteristics of involved by metastases regional lymph nodes, its statistically significant influence ( $p = 0.035$ ) on the survival of patients with male breast cancer has been determined. Influence of this index on the metastases-free survival of patients did not achieve level of statistical significance, despite it verges towards it ( $p = 0.057$ ).

On the basis of above mentioned data has been made a conclusion that such parameter of tumor process in male breast cancer patients, as state of regional lymph nodes, is one of the most important prognostic factors. At the same time, significant is not only the fact of involvement by metastases of regional

lymph collectors, but also number of altered by metastases lymph nodes.

In study, patients with I stage of breast cancer had highest chances to survive: 95% of patients overcame five-year and ten-year mark. Concerning patients with II stage of disease, 65% of them survived more than five years and 43% — more than ten years. In patients with III stage of disease indexes of five-year and ten-year cumulative survival have achieved 52 and 29% respectively ( $p = 0.00001$ ). Certainly, we should expect the fact of dependence of survival of patients with male breast cancer on stage of process. Thus, in our opinion, the comparison of indexes of cumulative survival of male breast cancer patients with correspondent index in women with the same pathology dependently on stage of process, is interesting. In Table 2 are represented the comparative data of five-year survival rate in men and women with breast cancer according to the stage of process. Data concerning survival of men are obtained in result of analysis of assembled by us data, and the source of data, which reflect five-year survival of women with breast cancer, are taken from yearly bulletin of American Cancer Society (“Staging and Survival Rates of Breast Cancer”, 2012).

**Table 2.** Comparative indexes of five-year survival in men and women, who are breast cancer patients, dependently on stage of disease

Stage of disease	Five-year survival rate in men* (%)	Five-year survival rate in women** (%)
I	95.5	100.0
II	64.6	86.5
III	52.2	60.5
IV	16.3	20.0

\*data of our study; \*\*data of American Cancer Society.

Certainly, recognizing that statistical correctness of represented comparison is not very high, nevertheless quite expedient is conclusion that male breast cancer compared with this disease in women is more aggressive. This fact, in our opinion, is one more evidence of different biological nature of male and female breast cancer.

The same conclusion about significant impact of male breast cancer stage on the risk of generalization of process may be done, basing on the analysis of metastases-free survival in our group of patients. In the first stage of disease five-year metastases-free survival has constituted 97%, and ten-year — 83%. In the second stage of disease rates of five-year and ten-year metastases-free survival have constituted 61 and 58%. In patients with III stage of male breast cancer these values were on the level of 43 and 22% ( $p = 0.0002$ ). In other words, with growth of staging of disease the frequency of generalizations of male breast cancer essentially and statistically increases.

Taking into account mentioned above, it should be noted that stage of male breast cancer is important prognostic sign concerning the length of life and metastases-free period. Moreover, stage of breast cancer in patients does not influence on the frequency of recurrence of tumor.

Other studied parameters of tumors in breast cancer patients, which influence the life length, metastases-

free and recurrence-free periods were histological variant of tumors and its receptor status. Concerning the histological variant of tumors, the stage of its malignancy has been taken into consideration. Comparison of cumulative survival of patients with different histological variants of tumors has determined: there is statistically significant difference between survival of patients with first grade of malignancy in contrast to the patients with second and third stages of malignancy of tumor cells. During the comparison of patients with II and III stages of malignancy of tumor, no significant difference between levels of survival has been obtained. Among patients with I stage of malignancy of tumor the five-year and ten-year span survived respectively 90 and 73% of patients, while these parameters for patients with II grade of tumor malignancy have constituted 54% and 39%, and at third grade of malignancy — 36 and 21%.

Analyzing risk of development of generalization of process in male breast cancer patients with different stages of tumor malignancy, we have succeeded to clarify that mentioned sign also influences the length of metastases-free period. In absence of difference between periods of course of disease without remote metastases in case of I and II stages of tumor malignancy, this statistically significant difference of duration of metastases-free period in patients with III stage of malignancy ( $p = 0.04$ ) has been obtained. If five-year metastases-free survival in patients with I and II stages of malignancy of tumor was within the limits from 69 to 64%, and ten-year — from 62 to 58%, than only 40 and 23% of patients with III stage of tumor malignancy survived respectively 5 and 10 years without signs of generalization of process.

Thus, stage of malignancy of tumor is important prognostic sign of male breast cancer. Histological variant of tumor essentially influences the survival of patients and duration of metastases-free period. The higher is the stage of malignancy of male breast cancer, the lower is length of life of patients and is higher the risk of development of remote metastases of tumor.

On the basis of analysis of selected for research material has been determined that there is no dependence between levels of estrogen and progesterone receptors and length of life of patients with male breast cancer. Analysis of the impact of receptor status of a tumor on the duration of metastases-free period also proved the lack of prognostic value of this parameter of tumor. Thus, the level of receptors of steroid hormones in male breast tumors is not significant probable sign concerning survival and duration of metastases-free period in the examined patients.

In order to determine the stage of influence of one or another factor or parameter of tumor on the clinical course of disease not separately, but interacting with other factors or parameters, the multiple-classification analysis by method of Cox Regression has been conducted. By such procedure the prognostic value of each from mentioned factors in their common, comprehensive impact on the clinical course has been determined.

It has been determined that status of regional lymph nodes (N category;  $p = 0.00005$ ) has most significant impact on the survival of patients with male breast cancer. Other factors are the following: body mass index ( $p = 0.049$ ), histological variant of tumor ( $p = 0.077$ ), age ( $p = 0.133$ ). Level of interaction of other characteristics with life length, such as size of tumor and T-category, levels of estrogen receptors, presence of gynecomastia is insignificant.

## CONCLUSIONS

1. In the majority of breast cancer patients, tumor is located in para-areolar and subareolar areas. Its most often symptoms are “platform”, “umbilication”, “lemon skin”, ulcer above the tumor, pathological discharge from nipple, enlarged regional axillary lymph nodes.

2. Gynecomastia shall be evaluated as background disease, but not preneoplastic, which may cause incidence of oncological pathology of mammary gland in men.

3. In case of suspicion of male breast cancer the optimal volume of diagnostic procedures is palpation examination of studied organ and inguinal areas, mammographic examination of both mammary glands and morphological verification of pathologic neoplasms of mammary gland by cytological and/or histological study of punctate.

4. Mammographic signs of male breast cancer are the following: presence of nodes of increased density with blurred edges, symptom of radiance of node outlines, micro-calcifications.

5. Treatment of male breast cancer shall be comprehensive.

6. Recommended volume of surgical intervention in patients with male breast cancer is radical mastectomy with preservation of both pectoral muscles, which does not augment the number of local recurrences of tumor, does not increase frequency of generalizations of process, and does not decrease rates of overall survival of patients.

7. Radiotherapy is important supplement to the radical surgical treatment of patients with operable form of male breast cancer and it allows to achieve significant increase of duration of life and metastases-free period. Radiotherapy shall be applied in postsurgical period in patients with II–III stages of disease. In case of first stage of male breast cancer radiotherapy is not recommended.

8. Adjuvant polychemotherapy shall be used in all male breast cancer patients independently from stage of process. The prevalence is given to the common CMF schemes or regimens, which contain antracyclines (AC, CAF, FEC).

9. Hormonal therapy is recommended for patients with estrogen-receptor-positive and/or progesterone-receptor-positive tumors. The drugs of choice are anti-estrogens (tamoxifen, toremifene, etc.).

10. In patients with locally diffused and metastasing male breast cancer the surgical treatment, radiothe-

rapy, chemotherapy and hormonal therapy have only palliative character.

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