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ABSTRACT

Breast cancer is the most common cause of death among women from malignant tumors. Metastatic breast cancer is not currently a curable disease.

According to most authors, especially in developing countries, from 50 to 70% of patients already have advanced forms of the disease upon admission (locally common forms, in the form of lesions of regional lymph nodes and distant metastases to various organs). The nature and frequency of distant breast cancer metastases is very diverse. In 40-80% of cases, breast cancer metastasizes to bone. However, it can metastasize other organs and systems, for example, to the liver, lungs, ovaries, brain, and others.

Diagnosis and treatment of distant breast cancer metastases is an urgent problem in oncammammology, since mortality in these forms remains very high, and the long-term and immediate results of treatment are still very unsatisfactory.

The conducted therapy, being palliative, is aimed at improving "quality" and prolonging life. The most effective for conducting palliative therapy for this group of patients is various chemotherapy regimens. But traditionally used chemotherapy regimens do not always turn out to be effective; on the contrary, cytostatics weaken the body's resistance and deplete the body's immunobiological reserve, sometimes they worsen not only the quality of life, but also shorten the duration.

Key words: breast cancer, metastatic breast cancer, non-adjuvant chemotherapy, adjuvant chemotherapy, sentinel lymph node, overall survival.

INTRODUCTION

At the present stage, a steady increase in the incidence of malignant neoplasms is noted. This changes not only the structure, but also the dynamics of the incidence of cancer.

Oncological diseases are one of the main causes of death on the planet. Cancer mortality ranks second in the world - after cardiovascular disease.

Every year more than one million women are diagnosed with breast cancer worldwide. Over half of whom will die from the disease. Breast cancer is the most common cancer and the leading cause of cancer mortality rate for women and the leading cause of cancer mortality rate for women.

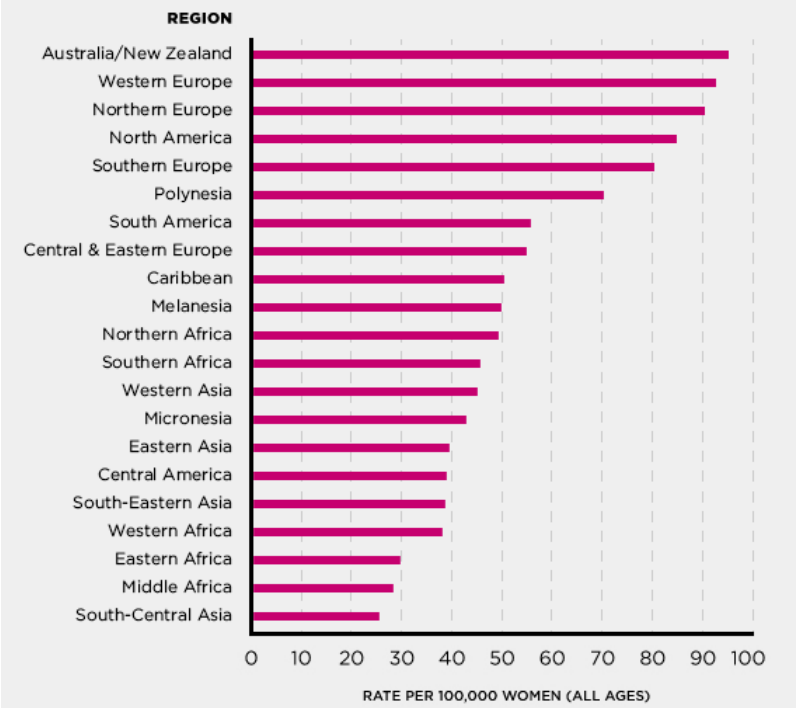
In case you have preparatory your scan for statistics on breast cancer, you've arrived at the perfect place. Here you will find all the pertinent information apropos breast cancer.

Breast cancer incidence (new cases) rates worldwide

Breast cancer is the most extensively recognized cancer in women around the biosphere. It is evaluated that more than 1.7 million new occurrences of breast cancer happened among women worldwide in 2017 (latest information accessible).

Rates of breast cancer fluctuate among various congregations of individuals. Rates change amongst women and men and among individuals of various ethnicities and ages. They oscillate the world over.

Breast cancer frequency rates around the world fluctuate. In general, advanced countries (such as the U.S., England and Australia) have higher rates than developing countries (such as Cambodia, Nepal and Rwanda).



BREAST CANCER INCIDENCE WORLDWIDE

According to statistics from the World Health Organization, in 2017 cancer diseases claimed 9.6 million lives in the world - this is every sixth death. The population of Uzbekistan, as well as other lower-middle-income countries, is a high-risk group for cancer.

Data on all oncological diseases in the Republic of Uzbekistan show that from 2010 to 2017, the detection of the disease is growing. If in 2010 19115 patients with oncology were diagnosed for the first time, then by 2017 it had grown to 22730, the difference between these years had grown by 3615 in absolute numbers. We can see rapid growth from 2015 to 2017.

Of these, with breast cancer in 2010, the number of newly diagnosed patients was 2273, by 2017, 3192, the difference between them was 919 people.

The increase in cases detected naturally affected the incidence rate. It also grew from 7.9 to 10.0 per 100,000 of the population.

According to the Cancer Register of the Republican Cancer Research Center in Uzbekistan, breast cancer (20.4%) has the largest proportion in the structure of female mortality from malignant neoplasms. Next, in decreasing order, are neoplasms of the cervix (13.1%), stomach (8.5%), ovaries (5.4%), esophagus (5.1%), lungs (4.1%), lymphoma (4 , 1%), lips, oral cavity, pharynx (3.3%), central nervous system (3.1%), rectum (2.8%), bones and soft tissues (2.7%), skin (2, 5%), colon (2.4%), leukemia (2.4%), kidney (1.9%), bladder (0.85%), larynx (0.78%).

In Uzbekistan, the incidence of breast cancer also continues to grow, despite the fact that the data were obtained only according to official statistics, without in-depth epidemiological studies.

It should be noted that in relation to stomach cancer in most countries of the world, there is a steady tendency towards a decrease in the incidence rate, while other cancer localizations have a rapid upward trend. As for breast cancer [2, 3, 36, 38, 47], cancer of the endometrium, ovaries [20, 24], it is these diseases that occupy a leading place in the structure of the oncological incidence of the female population of developed countries.

Breast cancer (BC) is one of the most common forms of malignant neoplasms. This, on the one hand, explains the great interest in studying various aspects of the diagnosis and treatment of this pathology, on the other hand, the possibility of obtaining, in a relatively short time, high-quality scientific material, which can be the basis of medical diagnostic standards. A steady increase in the incidence of tumors of the reproductive system of women, including breast cancer, cannot but cause well-founded anxiety, since despite the undoubted success in treatment, mortality continues to increase [15, 17-18, 25,26, 74].

Thus, the incidence of malignant neoplasms of the organs of the reproductive system in our country and abroad is determined by four localization of tumors: breast cancer, cervical cancer, uterine cancer and ovarian cancer.

The general trend in the incidence of cancer of the reproductive system in women is an increase in the number of hormone-dependent tumors. The basis of this trend is a significant increase in the population of endocrine-metabolic disorders inherent in the diseases of civilization [30].

The pathology of the endocrine-metabolic system is the basis of many oncological diseases, including breast cancer. The hormonal effect is based on a mechanism that directly affects the proliferation and differentiation in the target tissue, as well as a potentiating effect that increases the likelihood of genetic rearrangements [65].

One of the main ways to realize hormonal effects is through metabolism. On this basis, it is more correct to talk about endocrine-metabolic, and not purely hormonal disorders as carcinogenesis modifiers.

Their role can be manifested both at the stage of the onset of neoplasm and in the process of tumor progression at various clinical stages of the disease [75, 76].

Of course, the background that can have an undeniable effect on the biological and morphological properties of a developing tumor is the ontogenetic development of the endocrine system, along with ethnic, genetic, dietary, climatogeographic, and other factors that determine the functioning of the endocrine glands [29, 37, 57].

Of particular importance in the processes of hormonal carcinogenesis are age-related changes in the functioning of the endocrine system. In general, malignant neoplasms are a disease of older age groups and this is due to both the effect of aging itself and the accumulation of external carcinogenic effects over time [19, 47, 53, 59].

The endocrinological aspects of modern oncology are very diverse and at the same time in the modern clinic there is the concept of “hormone dependence” of individual malignant tumors. It does not mean that hormonal factors in the pathogenesis and clinic of other tumors do not play any role, however, the selection of a group of such tumors is not accidental, and, of course, breast and endometrial cancer are among these tumors [29, 40, 54].

Breast cancer in the United States occurs in one out of every eight women. 185 thousand primary patients are diagnosed annually, and on average 43,500 die. Breast cancer is the second leading cause of death after lung cancer among women. The risk of developing bone metastases is extremely high, and autopsy data confirm the following - from 50 to 85% of women with breast cancer have bone metastases. About 6-21% of metastatic bone disease manifests itself as a single or solitary lesion [85].

A scintigraphic study of solitary pathology is determined in 11% of cases according to the report of T. and T. T. (1998) and his colleagues among breast cancer patients [69]. Differences in the localization of bone metastases are due to the peculiarities of the histological structure of the tumor. With scintigraphy in 56% of cases, metastasis was localized in the spine and only 6% in the ribs. Spinal lesions are the most common for metastatic disease. It was interesting according to their data that rib damage was detected only by scintigraphic examination. During the continuous screening of breast cancer patients, 86 out of 306 abnormalities were revealed, and only 7% of them were malignant. The authors recommend confirming these studies with an X-ray examination. They believe that scintigraphy is very sensitive in detecting costal pathology, but with less specificity

and should be carried out in conjunction with radiography. Somewhat earlier Boxer D.I. and others (1989) described that in 88% of cases, solitary metastasis was also localized in the spine [84].

According to Peintinger F. (The Burnham Institute), breast cancer spreads to bone in 70% of cases in the form of distant metastases [62]. Patients with bone metastases often suffer from bone fractures, severe pain, hypercalcemia and paralysis. However, the mechanism of bone metastasis is still not clear. One possible reason is the penetration of a tumor into the bone marrow through the influence of cytokines and growth factors, which are responsible for the proliferation of breast cancer cells.

The mechanism of specific adhesion that occurs between bone endothelial cells (covering the walls of blood vessels) and breast cancer cells that enter the bloodstream more accurately explains this process. The authors proposed the hypothesis that this mechanism is realized through the interaction of specific receptors, and that modern and latest molecular studies are needed to confirm this mechanism. In their initial experiments, they used a massive set of various complexes in which protein particles were fixed on the surface of virus-sensitive substances called phages.

Then they incubate these phage or peptide complexes with cultures of bone marrow endothelial cells. In particular, they identified complexes such as glycosyl-phosphatidylinositol, a protein called CD59. The authors hope to prove this in an experiment in mice in order to further use certain markers to detect micrometastases or circulating complexes in the bloodstream. Those. work, undoubtedly, has a scientific and preventive direction.

There are recent publications that vascular endothelial growth factor, factor-C, promotes lymphangiogenesis, which subsequently leads to further activation of lymphatic metastases (Nakamura Y., 2003). This was shown in 113 patients with invasive ductal breast cancer using the immunohistochemical method for determining the marker of lymphatic endothelial cells (subplanin). There was a significant correlation between the high density of the lymphatic vessels, subplanin-positive invasion and metastases in the lymph nodes, which naturally adversely affects the prognosis of patients [55].

About half of all pathological fractures occur in breast cancer. The main methods of treatment in this case, and this is the achievement of recent years, are bisphosphonates (Aredia, Fosamax, Didronel and others). These drugs block the progression of tumor cells in the bones, leading to a decrease in bone lesions and fractures. Bisphosphonates can also stop the spread of breast cancer to other organs, such as the lungs, but the cause of this protective mechanism is unknown. In bones, osteocolasts are stimulated by cancer cells and resorb calcium, leading to pain and fractures. These drugs block osteoclastic cells and prevent bone fragility. Some authors recommend that all patients with breast cancer take bisphosphonates to prevent bone fractures [54].

Pain is a common symptom of bone damage in breast cancer. A pathological fracture can cause severe pain. In some cases, patients ignore these symptoms,

referring to other pathological conditions. Of the common symptoms, there may be hypercalcemia. Breast cancer metastases to the spine, ribs, pelvis and proximal limbs. These lesions are often osteoblastic, but can be purely lytic, with poor marginalization, lack of matrix, and cortical destruction.

Other manifestations may also include compression fractures of the spine and cysts due to osteoarthritis caused by a tumor. You also need to remember about bone sarcomas (osteosarcoma and chondrosarcoma). On average, survival after a diagnosis of bone metastasis improved to 24-36 months. Bisphosphonates increase these periods slightly longer [17].

Treatment of pathological fractures for orthopedic surgeons does not have the goal of curability. Their main role is • in orthopedic stabilization of the weakened bone and even before the fracture occurred. Delay in treatment is combined with an increased risk of complications and a decrease in a favorable prognosis. Upon receipt of a prolonged remission, reconstructive surgery may be considered.

According to the latest data, tumors not only with distant metastases, but also with metastases to regional lymph nodes began to be attributed to metastatic breast cancer. Such breast cancer in domestic or Russian literature is referred to as locally advanced cancer. Nevertheless, on the recommendation of the memorandum of the 27th international symposium on breast cancer in San Antonio, USA since 2004, it was proposed to distinguish two forms of the tumor - isolated or local and common or metastatic breast cancer [52, 69].

Plankett T.A. with co-authors for 1975-1991 gt. analyzed 859 cases with metastases of breast cancer in the bones [67]. All observations were retrospectively divided into 4 groups: an isolated skeleton lesion; metastases in bones and soft tissues; damage to the bones and organs of the chest cavity; metastases in the liver and bones. Pathological fractures were more often detected in patients with isolated bone lesions. The developmental periods of pathological fractures did not differ significantly in different groups, but their frequency in the presence of liver damage was the highest, with an average life expectancy of 5.5 months. ($p < 0.001$).

Pain syndrome was most often observed in patients of the 1st group. They often showed symptoms of spinal cord compression. They were significantly more likely to undergo radiation therapy. The authors emphasize that patients with advanced breast cancer and with isolated skeletal lesions should be observed most thoroughly and in a timely manner to prevent complications. The authors recommend that all patients prescribe bisphosphonates.

Roche N. and colleagues (2003) observed metastases of breast cancer in the liver in 71 patients out of 1179 for 1985-1997. [73]. Of these, in 20 observations, the liver was the only and first focus of localization of metastases. Survival of patients with metastases in the liver was significantly lower than with metastases in other organs, regardless of age, stage of the disease, histological type of tumor. Of 72 patients, 46 patients received treatment; a positive effect after treatment was observed in 30.4%. Chemotherapy alone was effective in 18% of the 53 treated.

The positive effect of only endocrine or immunotherapy was not observed.

The therapeutic effect in patients receiving chemo-hormone therapy was significantly higher than after chemotherapy alone.

Perri L. et al. (1999) described an interesting case of metastasis in a 79-year-old patient with complaints of epigastric pain and weight loss for several months after sectoral resection of the right breast with axillary lymph node dissection for invasive ductal cancer [64].

The tumor edge of the resection was negative. According to the adjuvant treatment protocol, radiation therapy was additionally carried out. A comprehensive examination revealed stiffness of the walls of the stomach, however, the mucous membrane was intact throughout. With multiple endoscopic biopsies, no signs of cancer were detected. With a diagnosis of gastric cancer of the type linitis plastica, the patient was taken for laparotomy, where they found a total lesion of the stomach and distal esophagus.

An implantation site of the tumor was found in the omentum. The last is excised. In connection with the severity of the condition and the high risk of complications, the patient did not have a gastrectomy. A jujunostoma for nutrition was imposed. A biopsy of the wall of the stomach and histological examination of the implant confirmed metastases of breast cancer. Metastases gave an intense reaction to progesterone receptors. An outpatient course of treatment with tamoxifen was carried out, which did not give an effect.

In a hospital, 2 courses of chemotherapy were performed, but after 14 months. after the operation, the patient died. Isolated metastatic lesions of the gastrointestinal tract with breast cancer are rare. As a rule, a surface biopsy is not very informative. A deep biopsy of the organ wall is recommended. Previously described 31 similar observations. A case of metastatic lesion of the stomach 30 years after a radical mastectomy is described. - Known cases of high sensitivity of the tumor to hormone therapy.

The authors, however, believe that early diagnosis and radical treatment of unusual breast metastasis can be quite effective.

Saczherro R. et al. (2001) described metastasis of metaplasical breast cancer, where unusual morphological features and clinical and morphological parallels were given [84].

Metaplastic tumor is a special manifestation of a low-grade invasive ductal or lobular carcinoma. The term "metaplasic" was first proposed in 1973 to refer to a sarcomatoid variant of invasive cancer. The synonyms proposed in different years are known: - carcinosarcoma, spindle cell cancer, pseudosarcoma, matrix-producing cancer, etc.

The tumor in typical cases consists of malignant cells in combination with a whole spectrum of other elements: spindle-shaped, flat, chondroid. The authors presented the observation of this form of neoplasm in a patient of 67 years. The tumor was manifested by multiple lung metastases. Histologically, cancer metastases were manifested mainly by spindle-shaped malignant elements with a wide range of transitional forms.

An aspiration biopsy of foci in the lungs with a thin needle revealed spindle-shaped cells, signs of proliferation of mesenzyme with a minimal epithelial component. There was an assumption of primary tumor multiplicity. However, an immunocytochemical study confirmed the epithelial histogenesis of the tumor. It was also possible to establish the source of metaplastic cancer - this is breast tissue. The authors discuss the fact of the difficulty of cytological diagnosis of such tumors. As a rule, metaplastic cancer does not metastasize to the lymph nodes, but is manifested by distant metastases. Timely recognition of the tumor will help to avoid the wrong treatment tactics. The authors also recommend that cytologists pay special attention to the clinical situation and have an idea of the morphological features of metaplasized cancer.

Fleming F.J. et al. (2004) show the role of axillary lymph node biopsy. A prospective analysis was performed of 180 patients who underwent a biopsy of axillary lymph nodes from July 1999 to November 2002, where 54 (30%) patients had one or more positive axillary lymph nodes [88]. All of them were subject to total lymphatic dissection. Of this subgroup, 26 out of 54 patients had additional metastases in the form of extranodal lesions. (OR = 17.39, 95% confidence interval 1.69 - 178.96).

The authors made an important conclusion that invasive breast cancer and positive lymph nodes, as well as extranodal lesions or macrometastases, are independent prognostic factors in assessing the prevalence of breast cancer.

Hasebe T. S. et al. Showed that the histological characteristics of the tumor play an important role in the progression of ductal breast cancer [54]

We studied the state of blood vessels (the presence of embolization of blood vessels, cell atypia, the number of mitotic and apoptotic figures, the degree or degree of fibrosis of tumor cells) in 247 patients with ductal breast cancer in accordance with histological parameters. The proportional Cox method was used with multivariate analysis, which showed that the presence of two or more mitotic figures in the vessels of the tumor statistically significantly reduces the survival time ($p = 0.002$) and reduces the time of appearance of distant metastasis ($p = 0.005$).

The presence of apoptosis (more than 2 in the vessels of the tumor) and embolization significantly increase mortality.

I

The purpose of the RegPso study! B. and his co-authors consisted in studying the role of phenotypic characteristics of the tumor on the process of metastasis. Metastatic signs of lobular and ductal breast cancer, histological subtypes, and expression of E-Kaderin were compared [66].

In this case, metastatic lobular cancer was classified retrospectively into classical alveolar, solid, tubular-lobular, annular cell or pleomorphic subtypes. Histologically, in 81% of cases there was a classical form, pleomorphic type was noted in 15% of cases. In 88% of cases, E cadenin was not detected. In general, the frequency of multiple metastatic breast cancer was higher with the lobular form (25%) than with ductal breast cancer (15.8%) ($p = 0.016$). This was statistically

significant for bone metastases (p = 0.02) and other organs as well (peritoneum, ovaries, digestive tract, skin) (p <0.001).

In lobular cancer, there was no significant relationship between the localization of metastases, the histological subtype, and the level of E-cadenin at primary admission. In conclusion, the authors note that multiple metastasis is more common in lobular than in ductal breast cancer. This can be explained by the presence of small-cell tumors, which are characteristic of lobular breast cancer and which can cause pronounced metastasis to different organs .. A high frequency of pleomorphic tumors was noted in the group of patients with metastatic lobular breast cancer, but the signs of metastatic sites did not belong to the histological subtype of primary tumors.

Some authors (T. Lepeg et al., 2005) have shown the role of calponin in the gene profile of metastatic cells, in particular, inhibition of metastatic cells under the influence of calponin [42]. It is known that metastasis depends on the ability of tumor cells to migrate, the degree of vascularization and the formation of a new place where metastasis is formed. The authors found in an experiment that calponin effectively inhibits the cellular ability to form metastatic colonies, especially with melanoma and adenocarcinoma of the mammary gland through the formation of short chains and modules of CLIK-23 matrices.

Periostin is an identified gene that is predominantly expressed in the periosteum and is important in the formation and maintenance of bone structure. Sasaki H. et al. Studied periostin levels using the latest DNA technology for detectable and chemo-luminescent methods in 58 patients with breast cancer and 44 patients with small cell lung cancer with bone metastases [74]. They have shown that serum periostin levels can be a tumor marker for detecting metastatic breast cancer.

The level of periostin was significantly higher in patients with breast cancer with bone metastases (92.0 ± 28.6 ng / ml) compared with those patients who did not have metastases (55.0 ± 16.6 ng / ml, p = 0 , 04). But with bone metastases from lung cancer, such changes were not detected, although there was a definite correlation. So with an increase in T or N, the level of periostin increased significantly (T4, 126.5 ± 29.7 ng / ml versus T2, 64.9 ± 16.1 ng / ml, p = 0.03) and T4 compared to T1, 36, 3 ± 7.5 ng / ml, p = 0.01; N3, 108.7 ± 17.3 ng / ml in comparison with N2, 49.7 ± 10.9 ng / ml, p = 0.01). Thus, it was shown that periostin plays a significant role in the process of metastasis by accelerating the adhesion of molecules and tumor cells.

Wernicke M. et al. (2003) showed that gualuronin can play a leading role in the invasion and metastasis of breast cancer [85]. Gualuronin is an extracellular polysaccharide that is involved in tumor invasion and may cause stromal myxoid changes. The authors studied the relationship between these changes and the status of axillary lymph nodes, the degree of tumor differentiation and mortality. Patients had negative or positive lymph nodes and were followed up over a 10-year period.

By the method of logistic regression, a strict relationship was shown between positive lymph nodes and stromal myxoid changes, tumor size, desmoplasia,

lymphoid infiltration, the degree of tumor differentiation, tumor embolism and multifocal. Stromal myxoid changes were often combined with the young age of patients and lymphoid embolization (P <0.001). When studying mortality and its relationship with stromal myxoid changes, a very weak correlation was found (P <0.01). An obvious connection between them was in the case of low-differentiated myxoid changes and tumor sizes of more than 2 cm (P <0.008).

The purpose of the studies of Yakatig U. and his colleagues was to study the expression of angiogenic and lymphangiogenic factor in the process of metastasis. Angiogenic factor or vascular endothelial growth factor is an important link in the damage to lymphatic vessels and the promotion of lymphatic metastasis [53]. We studied 105 patients with invasive breast cancer with evaluation of the expression of vascular endothelial growth factor, the state of lymph nodes and other clinical and pathological parameters using the immunohistochemical method.

Moreover, it was found that in 86 cases (81.9%) there was an increased expression of this factor. It statistically significantly correlated with metastases in the lymph nodes (P = 0.0238). A study of survival by the Kaplan-Meier method showed that the expression of endothelial vascular growth factor has a prognostic value and is statistically significant in relation to both disease-free (P = 0.0023) and overall survival (P = 0.0222). Multivariate analysis with the Cox regression model showed that this factor is also an independent prognostic factor affecting disease-free survival.

In conclusion, it was noted that the expression of endothelial growth factor is combined with an increase in the frequency of metastasis to the lymph nodes and is a new additional factor in the prognosis of breast cancer, and can also be valuable in assessing the effectiveness of treatment as a biological marker.

O. T. and his colleagues (2003) found that prostoglandin is involved in the process of metastasis [155]. So prostaglandin E2 (PE2) is produced mainly in bones by osteoblasts and stimulates bone resorption. In this study, they experimentally in mice by introducing breast tumor cells into the femur and tibia examined the role of PE2 in bone osteolysis in breast metastasis. It turned out that through the complex mechanisms of interaction of tumor cells, the expression of cyclooxygenase-2 (a key molecule in the differentiation of osteoclasts) PE2 can induce to produce and enhance bone resorption, i.e. has direct significance in the metastasis of breast cancer.

Aspects of diagnosis, treatment and prognosis for metastatic breast cancer.

Diagnosis of breast metastases presents certain difficulties. Many research methods have been proposed, ranging from general clinical examination and palpation to nuclear magnetic resonance and computed tomography [8, 59, 64, 69, 71, 72, 78, 83, 84, 87]. Radio thermometry is actively used in the algorithm for the complex study of mammary glands [8, 55].

Russian scientists (Nechushkin MI and others, 2003) have proposed modern research methods, such as video-assisted thoracoscopic parasternal lymphadenectomy in the diagnosis of the prevalence of breast cancer [41]. Recently, molecular and histochemical methods of research using tumor and tissue

markers have been proposed, which make it possible to clarify the prevalence of the tumor process, conduct an adequate assessment of the treatment, and trace long-term results [11, 14, 35, 85].

Nevertheless, X-ray methods for examining breast cancer and other tumor lesions of the breast remain fundamental and significant types of diagnosis [44, 51, 84].

An important link in the process of metastasis is the state of regional lymphatic collectors. Identification of pathological changes in regional lymph nodes is fundamental in the prognosis and choice of treatment for breast cancer [22].

Talakhadze N.T. et al. provide an overview of the methods of radiation examination of parasternal lymph nodes [77]. The method of scintimammography with 99tTc - technetril is considered in detail. In the observations of the authors, the sensitivity of the method was 96.5% and the specificity was 95.4%.

Over the past 5 years, various methods have been developed for identifying sentinel lymph nodes, which are the first in the path of lymph outflow from a primary tumor in the mammary gland [46]. Thus, injections of dye or radioisotopes into the periareolar zone of the tumor or directly into the tumor itself before its removal, or in the tumor bed after its removal, are proposed. Using these injections, it became possible to determine axillary and / or parasternal "sentinel" nodes in 95% of patients with primary breast cancer. Sometimes it is one node, sometimes two or more sentinel lymph nodes.

If these nodes are removed and do not contain tumor elements, then with a probability of 95-97% it can be argued that the axillary lymph nodes do not contain tumor metastases and thereby refuse axillary lymphadenectomy. Speaking about the role of the sentinel node, it was noted that some tumors have “sentinel” nodes, both in the axillary zone and in the retrosternal. Some have a "guard" node only in the sternum. The possible role of removing the sternal nodes in the event that they are the only way out of the lymph from the tumor is currently under discussion. However, most experts believe that these nodes should not be removed or biopsy.

It goes without saying that surgeons must have some experience in applying this technique under the guidance of specialists who have mastered this method before they can use it in everyday practice. It was recommended that at least 30-40 biopsy procedures of the “sentinel” node be performed, followed by a complete axillary dissection, before it could be concluded that the surgeon had even minimal competence in this matter. This minimum number of observations should have 5% or less false-negative results and an acceptable level of identified “watchdog” nodes.

Another ALMANAC study (axillary lymphatic marking versus axillary dissection) [47] assessed the ability of mammologist surgeons to master new biopsy techniques for a sentinel lymph node. According to a study by Mansel C.D. biopsy of the “sentinel” lymph node followed by axillary dissection in case of detection of its metastatic lesion or removal of axillary lymph nodes was performed in patients with operable breast cancer without clinical signs of

metastases to the axillary lymph nodes. All surgeons participating in the study underwent an audit stage, when during the treatment of the first 40 patients they were all identified and

a sentinel node biopsy followed by axillary dissection, regardless of the biopsy results. Sentinel nodes were identified using an injection of a radiopharmaceutical around the tumor, as well as intraoperative administration of a blue dye and a manual gamma sensor. According to the study protocol, each surgeon should achieve 90% localization and 5% false-negative results in the audit phase. 400 patients in the audit phase 10 surgeons performed a biopsy of the sentinel lymph node. The detection rate of the sentinel lymph node was 96.6%, the false-negative rate (when there were no metastases in the lymph node and muscle lymph nodes were detected) was 5%.

Thus, 10 surgeons met the requirements and were able to participate in the randomization phase. Despite the various results shown by surgeons during the first phase, most surgeons required 40 procedures to meet audit criteria.

Further, Mansel R. E., (2004) reported potential risk factors for errors in the localization of the axillary “sentinel” lymph node. High body mass index (above 30), a tumor in the inner quadrants of the breast, invasive lobular cancer are regarded as statistically significant risk factors for errors in determining the location of the sentinel lymph node. Tumor size and lymph node status are not factors that influence localization.

Another interesting report (Louis-Sylvestre S., 2001) was an update of a prospective randomized study comparing lumpectomy with radiation therapy to the axillary region and lumpectomy with axillary lymphodissection [45]. For the period 1982-87. 657 patients after a continuous operation for breast cancer T <3 cm, N0 or Nia, were randomized into two groups, one of which received radiation on axillary zone, and the other - lymphodissection. All patients received postoperative breast irradiation. The average age of these women was 51.2 years. Metastatic lesion of one lymph node was noted in 57% of patients, from 2 to 3 lymph nodes in 34% and 3 or more lymph nodes in 9% of patients who underwent axillary lymph node dissection. Updating the study data showed that patients with axillary dissection reliably less frequently observed relapse in the axillary zone, however, there were no differences in the incidence of distant metastases, relapse-free and overall survival, even with an extension of the observation period.

It has been suggested that with a positive sentinel lymph node, the use of both axillary dissection and irradiation of the axillary zone can equally be recommended.

A large number of researchers are looking for factors that can predict with high probability the absence of metastatic damage to axillary lymph nodes. Sharp S. et al. [77] reported that tumors with a high degree of differentiation (grade I) with sizes <1 cm have a very low probability of damage to the lymph nodes and they should not undergo axillary lymphadenectomy.

Seavolt and colleagues analyzed the results of treatment of 111 patients older than 70 years and the size of the primary tumor less than 1 cm.

They concluded that it was possible to refuse to perform axillary lymphadenectomy in this group of patients.

Elangovan A.E. et al. [81] showed that lymphovascular invasion of the primary tumor is combined with the detection of a metastatic lesion of the sentinel lymph node and concluded that patients with lymphovascular invasion and tumor sizes greater than 2 cm are shown to perform axillary lymphadenectomy without prior biopsy of the sentinel node.

Peitinger F. et al. [60] reported on a comparison of the quality of life and mobility of the upper limb after axillary dissection and after a sentinel lymph node biopsy. It was noted that patients after a sentinel biopsy had less severe pain and more active movements of the shoulder and the entire upper limb than patients after lymphadenectomy. The quality of life, based on the European Organization for the Study of Cancer Research and Treatment (EPRTC) questionnaire, the McGill questionnaire, and the visual analogue pain scale, was better in patients after the biopsy.

Thus, the dissection of the sentinel lymph node is not currently the standard in the treatment of breast cancer patients, but further study of this technique is promising in order to exclude the execution of axillary lymphadenectomy in the absence of its metastatic lesion.

The main prevention of relapses and distant metastases is the right treatment choice. In this case, combinations of various methods of radical therapy can be successfully used (surgical, radiation, chemotherapeutic and radiation).

The goal of preoperative chemotherapy (XT) in a known operable patient is to reduce the size of the tumor to perform organ-preserving treatment and to affect the primary focus and micrometastases to improve the prognosis of the disease [1, 2]. In the literature (Wolff A.C., Davidson N.E, 2000) several randomized trials have been reported on the role of preoperative XT [87]. Most of them have shown that preoperative XT does not improve results of treatment of patients with operable breast cancer in comparison with adovant XT. As an illustration, in this paper, we used the results of the most representative study (Fisher B., 1998) of NSABP B-18 [115]. In this study, 1,500 women with operable breast cancer received 4 courses of XT l ^ with a combination of AS (doxorubicin 60 mg / m and cyclophosphamide 600 mg / m every 3 weeks) before or after the operation.

As a result of the study, the following answers were received. The effectiveness of preoperative XT is not inferior to (but does not exceed) the results of adovant XT. Relapse-free and overall survival rates were the same for both groups. Further, during preoperative XT, the full effect was recorded in 36% of patients, partial in 43%, stabilization in 18%, and progress in only 3%. A morphological study in 13% of patients confirmed complete resorption of the tumor tissue.

The effect of chemotherapy was correlated with the duration of the relapse-free period, but did not have a significant effect on life expectancy. Only patients with morphologically confirmed complete regression showed significantly better results of both 5-year relapse-free and overall survival. And finally, preoperative

chemotherapy made it possible to reduce the stage of the disease, both by reducing the size of the primary tumor (the frequency of the objective effect of the primary tumor on chemotherapy was 80%) and axillary lymph nodes (complete clinical regression was observed in 73% patients with previously palpable nodes, 32% of them morphologically confirmed). The detection rate of metastases in axillary lymph nodes was 41% in the preoperative chemotherapy group and 57%> in the adovant chemotherapy group. All this made it possible to slightly increase the frequency of organ-sparing surgeries, which amounted to 67% and 60% in the preoperative and adovant chemotherapy groups, respectively.

Does this mean that the use of preoperative chemotherapy has no prospects? Not at all. Preoperative chemotherapy can be used primarily in patients for whom organ-sparing surgery at the first stage is not possible. In this case, a successful preoperative chemotherapy may allow a similar operation to be performed. The B-18 study convincingly showed that the achievement of morphologically confirmed complete tumor regression was significantly improves long-term treatment results. T.O. complete morphological regression is an indicator of high sensitivity to ongoing chemotherapy of not only the primary focus, but also distant micrometastases. It is the 'successful elimination of distant micrometastases that leads to an improvement in disease-free and overall survival. It becomes apparent that the goal of preoperative CT is to morphologically confirm the complete destruction of the primary tumor. All other clinical effects are not critical.

At present, it has been shown that an increase in the effectiveness of preoperative chemotherapy is possible due to an increase in the number of courses of preoperative chemotherapy, the use of modern effective antitumor drugs, such as taxanes, in the combinations of preoperative chemotherapy, a more careful selection of patients with factors predicting the high effectiveness of preoperative chemotherapy and an early assessment of the effectiveness of preoperative chemotherapy [37, 72, 73].

So, at the 24th annual conference on the treatment of breast cancer in San Antonio (USA), preliminary results of two randomized trials on the use of preoperative chemotherapy were reported, which allow us to assess the prospects of the first two of the above approaches . French researchers (Fumoleau R. et al, 1999) evaluated the feasibility of 6 courses of chemotherapy with a combination of doxorubicin (60 mg / m) and paclitaxel (200 mg / m 3 hours) compared with 4 courses [20].

An increase in the number of treatment courses at the preoperative stage led to an increase in the number of morphologically confirmed complete tumor regressions from 17% to 28%.

The NSABP-27 study is more complex and involves 4 courses of preoperative chemotherapy for AS in all patients [NSABP Investigators]. In the second group, after the operation, adjuvant treatment with 4 courses of docetaxel will be performed. In the third group, docetaxel treatment will be performed at the preoperative stage [54].

The immediate results of 4 courses of AS and a combination of 4 courses of AS and 4 courses of docetaxel were reported. The addition of docetaxel and an increase in the duration of preoperative chemotherapy led to an increase in the number of pathologically complete tumor regressions from 14% for AS and 26% for AC docetaxel.

Preliminary results of two reported studies emphasize the promise of intensification of preoperative chemotherapy by increasing the number of treatment courses and the inclusion of new effective cytostatics. An increase in the number of morphologically complete effects should lead to a significant improvement in long-term results in patients with morphologically complete tumor resorption.

Gradishar W. J. et al. (2004) evaluated the efficacy and toxicity of a combination of capecitabine and paclitaxel in patients with disseminated breast cancer in an open multicenter study [27]. The study (phase II) included 47 patients with metastatic breast cancer. All patients underwent treatment according to the scheme: capecitabine 1650 mg / m2 from 1 to 14 days + paclitaxel 175 mg / m2 on 1 day with an interval of 3 weeks. The treatment continued until progression, severe toxicity or the patient's decision to discontinue treatment. The general condition of patients on the Karnowski scale was at least 90%. Forty-four patients (94%) received chemotherapy for advanced breast cancer for the first time. The frequency of the objective effect was 51%: in 15% of the patients, a complete regression of the disease was noted, and in 36%, a partial regression. Disease stabilization for no less than 180 days was observed in 19% of patients, clinical improvement was achieved in 70% of patients. The average duration of the antitumor effect was 12.6 months, the average time to progression is 10.6 months, and the average total life expectancy is 29.9 months. Among the side effects, alopecia, palmar-plantar syndrome, nausea and weakness of all degrees were most often encountered. Neutropenia of 3-4 degrees was observed in 15% of patients, alopecia of 3-4 degrees - in 13% of patients, palmar-plantar syndrome - in 11%. They concluded that the combination of capecitabine and paclitaxel showed high efficacy and a satisfactory toxicity profile in the treatment of patients with disseminated breast cancer.

Winer E.R. and colleagues (2004) compared the efficacy of paclitaxel in standard and high doses in the treatment of patients with advanced breast cancer [186]. The study included 474 patients who had not previously been given chemotherapy or had received first-line chemotherapy for breast cancer. All patients were prescribed 3-hour infusions of paclitaxel once every 28 days at different doses of 175 mg / m2, 210 mg / m2 and 250 mg / m2. All patients completed a questionnaire on quality of life at the beginning of treatment and after 3 courses of chemotherapy.

An increase in the dose of paclitaxel did not affect the frequency of the objective effect (23%, 26%, and 21%, respectively), time to progress, and life expectancy. In groups with an increased dose of the drug, hematological toxicity and neurotoxicity were more often noted. The quality of life in the three groups

was the same. An increase in the dose of paclitaxel does not improve the results of treatment of patients with disseminated breast cancer. A dose of paclitaxel 175 mg / m2 should be considered as a standard chemotherapy regimen.

Until 2003, patients with breast cancer with metastases to the supraclavicular lymph nodes were classified as patients with disseminated disease (M1). In the 2003 TNM classification, such patients are assigned to the group with stage IIIC. A study was undertaken to compare the long-term survival of patients with isolated breast metastases to the supraclavicular lymph nodes and patients with stages IIIB and M1 (other distant metastases).

A retrospective study of Olivotto J. (2003) included 336 patients with stage IIIB, 233 patients with stage M1, and 51 patients with metastases to the supraclavicular lymph nodes (nodal-Ml) [156]. Over 20 years, overall survival was 13.2% for a group of patients with metastases to the supraclavicular lymph nodes, 9.4% for a group with stage IIIB and 1.3% for stage M1. Twenty-year "breast-specific" survival was 24.1% for patients with metastases to the supraclavicular lymph nodes (nodal-Ml), 30.2% for

stage IIIB and 3.9% for patients with long-term intervals. It was concluded that patients with isolated metastases to the supraclavicular lymph nodes have a significantly better prognosis than patients with distant metastases (M1), their overall survival is comparable to the survival of patients with stage IIIB. Thus, changes in the classification of TNM that relate these patients to the group with stage IIIC seem reasonable.

Burstein H. and colleagues (2000) determined the efficacy and tolerability of weekly docetaxel infusions in women with metastatic breast cancer [101]. The treatment was performed on 29 patients who received weekly docetaxel at a dose of 40 mg / m / week. in the form of a one-hour infusion. Each cycle consisted of 6 weeks of therapy followed by a two-week break. Treatment was carried out until disease progressed, development of unacceptable toxicity, or patient failure. Adjuvant chemotherapy was previously performed in 52% of patients; 21% of those included in the study received chemotherapy for the metastatic process. Almost a third of patients (31%) had previously used anthracyclines. 66% of patients had liver metastases. Toxicity was evaluated in all patients, efficacy - in 27. The average number of infusions was 18 with a total total dose of docetaxel 720 mg / m2. No full effects were observed, in 12 (41%) patients there was a partial tumor regression, achieved in all of them during the first two courses. Similar efficacy was observed in previously treated patients with anthracyclines. In 17% of patients, stabilization of the disease lasting more than 6 months was observed. In general, the regimen was well tolerated. Grade 4 toxicity not noted. ' Only 28% of patients developed grade 3 toxicity, mainly neutropenia and weakness. Acute toxicity, including myelosuppression, was unexpressed. The severity of weakness, fluid retention and conjunctivitis increased with an increase in the number of administrations, but rarely exceeding 2 degree. Dose reduction was conducted in 8 of 29 patients, mainly due to the development of weakness. Thus, the weekly use of docetaxel was effective in patients with metastatic breast

cancer. The toxicity of this regimen differs from that with the "normal" (every 3 weeks) use of docetaxel.

The goal of M. M. and his colleagues (2004) was to study the response to chemotherapy as a predisposing factor in the treatment of metastatic breast cancer [70]. A total of 1,430 patients were examined from 1977 to 1992 who received chemotherapy based on anthracycline antibiotics. FROM Using statistical methods of multivariate analysis and a regression model, it was shown that an objective response to chemotherapy was observed in 60% of patients. About 15 biological parameters were used. It was noted that the main prognostic factors are: adjuvant chemotherapy, the presence of lung metastases, the initial status of patients and pleural effusion. The authors hope that with the widespread introduction of taxanes into XT regimens, more encouraging results can be obtained.

According to some data on the study of phase 3 chemotherapy, Avastin or Bevacizumab with Paclitaxel is the first chemotherapy line for breast cancer. It was shown that relapse-free survival from such chemotherapy is two times more effective than using Paclitaxel alone. Overall survival also increases.

Some researchers (Hartmann L.C., et al., 1999) consider the possibility of prophylactic mastectomy of the opposite breast in order to prevent metastasis in it [89].

Thus, there is a relatively high incidence of metastatic forms of breast cancer. According to most authors, especially in developing countries, from 50 to 70% of patients already have advanced forms of the disease upon admission (locally common forms, in the form of lesions of regional lymph nodes and distant metastases to various organs). The nature and frequency of distant breast cancer metastases is very diverse. In 40-80% of cases, breast cancer

metastasizes to bones. However, it can metastasize other organs and systems, for example, to the liver, lungs, ovaries, brain, and others. Diagnosis and treatment of distant breast cancer metastases is an urgent problem in oncammammology, since mortality in these forms remains very high, and the long-term and immediate results of treatment are still very unsatisfactory. Breast cancer is the most common cause of death among women from malignant tumors. The lack of effective screening methods for the early detection of this pathology, many women are treated in advanced stages of the disease. Metastatic cancer the mammary gland is not currently a curable disease. The conducted therapy, being palliative, is aimed at improving “quality” and prolonging life. The most effective for conducting palliative therapy for this group of patients is various chemotherapy regimens. But traditionally used chemotherapy regimens do not always turn out to be effective; on the contrary, cytostatics weaken the body’s resistance and deplete the body’s immunobiological reserve, sometimes they worsen not only the quality of life, but also shorten the duration. Currently, there is no single standard and tactics for treating patients with breast cancer, and the development of tactics and treatment standards for this category of patients is one of the relevant directions in the treatment of breast cancer.

Thus, in the treatment of metastatic breast cancer, it is necessary to provide adequate local treatment of the primary lesion, control of metastatic regional and distant metastases, which prevents the further spread of the tumor process and leads to an increase in survival and an improvement in the quality of life of patients. When choosing a treatment method, it is necessary to take into account the localization of metastasis, histological the structure of the primary tumor, the age and general condition of the patient, her menstrual status, the presence of concomitant diseases, previous treatment for primary breast cancer.

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