



A Modern Approach to Diagnosis and Treatment of Breast Cancer Releases

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Relevance : Despite recent advances in the treatment of breast cancer, the incidence of relapses remains quite high. At the same time, there is no unified therapeutic tactics for recurrent tumors, and the literature data on this issue are ambiguous. The effectiveness of one or another therapeutic method has not been sufficiently clarified, and the determination of the tactics of therapeutic measures and their results in relapses are of certain theoretical and practical interest.

Purpose of the study. Improving the results of diagnosis and treatment of patients with recurrent breast cancer

Material and methods. We analyzed the results of diagnosis and treatment of 60 patients aged 24 to 84 years who received treatment for local recurrence of breast cancer for the period 2015 - 2020. The average age of the patients was 53.6 ± 0.2 years. The average time for the onset of relapse was 17.3 ± 4.3 months. ($p < 0.01$).

Results. Combined methods of treatment of breast cancer metastases, have an undoubted advantage in terms of overall ($68.3 \pm 8.9\%$) 5-year survival of patients, compared with local or systemic methods ($41.7 \pm 9.1\%$ overall survival) ($p < 0.05$).

Conclusion. A comparative analysis of the combined, local and systemic approaches to the treatment of patients with recurrent breast cancer shows that their use is sometimes determined by the localization, prevalence, number of recurrent nodes, as well as the general condition of patients, their age, menstrual status, and the presence of concomitant diseases. At the same time, complex, combined and local approaches to the treatment of recurrent breast cancer provide a higher frequency of local cure, which prevents further spread of the tumor process.

Key words : breast cancer, local recurrence, radical mastectomy, monotherapy, overall survival

Among all malignant tumors in women, breast cancer occupies a special place in terms of its high incidence and clinical features. The number of newly diagnosed cases of breast cancer is increasing every year. With this development in the 21st century, there is a high probability of registering more than one million breast cancer cases per year.

Specialists are making great efforts to find the best way to influence the disease. Perhaps, none of the localizations of cancer can be considered as difficult for choosing a rational and adequate treatment, as is breast cancer. This is due to the extraordinary variety of options for the clinical manifestation and course of the disease and, therefore, the need to take into account when planning treatment, many factors, any of which may be decisive in the prognosis of the disease and, accordingly, the fate of the patient.

Purpose of the study. The purpose of this study was to study the effectiveness of research methods and select the optimal methods of treatment for patients with recurrent breast cancer, aimed at improving the quality of life and increasing the overall survival rate.

Material and methods. The material for the study was the data of 60 patients who received treatment for recurrent breast cancer in the TCB RSSMCOR in the period from 2015 to 2020.

The significance of the following prognosis factors was assessed: reproductive status and age of patients, histological structure of the primary tumor at the time of surgical treatment, its prevalence and methods of treatment.

The age of the patients varied from 24 to 84 years. The average age of patients with relapses was 53.6 years. The largest number of cases - 57.7% - fell on the age of 40 to 60 years. It is at this age that the main number of patients with breast cancer falls, respectively, and the number of relapses is also detected more often among this contingent of patients. In young women and in women in early menopause, more aggressive forms of breast cancer occurring with rapid dissemination of the process are more often detected.

The rate of its growth, the degree of invasiveness and the tendency to metastasis depend on the molecular subtype of the tumor, and the prognosis of the disease is also largely determined. The proportion of patients with relapses was 35.2% with three-fold negative forms of the tumor, 25.3% with luminal B and 1.1% with luminal A. The timing of relapse was 16.4 ± 2.7 months, 25.3 ± 3 , 2 and 32.5 ± 3 , b, respectively, molecular subtypes $p < 0.05$). As can be seen, with a triple negative form of breast cancer, relapses develop more often and in a shorter time, compared with subtypes with receptor expression.

The prevalence of the primary breast tumor is important in predicting the recurrence process. With a tumor process designated as T_4 , the greatest number of relapses was noted - 37.4%, with T_3 this indicator was 32.3%, with T_2 - 24.2%, with T_j only 5.6%. We identified one case of local recurrence in T_{is} , which accounted for 0.5% of the total number of patients with recurrent breast cancer.

An important prognostic sign is the presence of metastatic lymph nodes. The proportion of patients with lymph node metastases was 41 (68.7%), without them 19 (31.3%).

Most often, relapses were detected during the first and second years of follow-up - 41.2% and 25.8% of the total number of relapses. In the third and fourth years of follow-up, the number of relapses was 14.3% and 9.9%. In a period of five years or more, relapses were found in 8.8% of patients.

The rate of development in local relapses was statistically higher, but not significant, than in regional ones. With local (in the area of the postoperative scar, the anterior surface of the chest wall - on the side of the primary tumor) relapses, the recurrence period was 28.3 ± 3.8 months. With regional (in the axillary, supraclavicular, cervical, parasternal lymph nodes on the affected side) relapses, the

average recurrence time was 32.9 ± 3.3 months. And in case of relapses in the mammary gland after organ-preserving treatment, the mean period of recurrence was 25.6 ± 4.2 months.

Although a relapse is usually observed within 5 years from the establishment of the diagnosis, it can appear at any time and early, and in some cases preclinical diagnosis, relapse allows timely and adequate therapy, and this is a real way to improve the results of treatment and the quality of life of patients with recurrent breast cancer. This can only be ensured; using complex diagnostic methods.

The clinical manifestations of recurrence in breast cancer depend on the clinical and anatomical form of the secondary tumor (localization, number of recurrent nodes, their size, invasion of the chest wall, skin, surrounding structures, infection), the presence of distant metastases and the general condition of patients.

Ultrasound examination made it possible to visualize and get an idea of the localization, size of the tumor and the structure of the surrounding tissues, as well as to differentiate postoperative and post-radiation changes in soft tissues. The tumor was detected as a hypoechoic formation with an indistinct, often radiant contour. With a size of up to 1.0 cm, it had an almost homogeneous structure; in larger formations, anechoic cavities and hyperechoic inclusions appeared (in the form of small dots and twisted lines or polygonal structures). The ultrasound picture with lesions of regional lymph nodes was characterized by the following features: a lumpy outer contour, a heterogeneous structure due to areas of heterogeneous density, compaction in the form of cords and scars, as well as the presence of liquid areas of various shapes and sizes.

CT was used to determine the prevalence of breast cancer recurrence on the soft tissues of the anterior chest wall, destruction of bone structures, invasion into the anterior mediastinum, and clarification of the spread in regional lymph nodes.

The final stage in any diagnostic search for recurrent breast cancer is morphological examination. Which establishes the morphological diagnosis of recurrence, the degree and nature of the spread of the process in the surrounding tissues and characterizes the receptor status of the recurrent tumor. Diagnosis of recurrent breast cancer should be based on a comprehensive and complete assessment of all clinical, laboratory, instrumental and morphological data. Only an integrated approach to the diagnosis of this pathology with obligatory morphological examination will make it possible to develop adequate treatment tactics and improve the immediate and long-term results of treatment.

Results. Local relapses, depending on localization, are subdivided into: local, i.e. localized on the chest wall after radical mastectomy; regional - in the regional lymph nodes on the side of the lesion and relapses in the mammary gland after organ-preserving operations. The most favorable results in the treatment of recurrent breast cancer were obtained with the localization of the latter in the mammary gland: 1 year survived $90.3 \pm 5.3\%$, 3 years - $75.0 \pm 8.2\%$, more than 5 years - $66.0 \pm 8.5\%$ (in relation to local recurrence $p < 0.01$). With regional relapses, almost the same survival rate was noted - 1 year survived $90.0 \pm 5.5\%$, 3 years - $71.0 \pm 8.2\%$, more than 5 years - $62.2 \pm 8.9\%$ (in relation to local recurrence $p < 0.05$). The overall survival rate for local relapses is the lowest - $68.6 \pm 4.2\%$ survived 1 year, $39.9 \pm 4.5\%$ survived 3 years, and $37.5 \pm 4.4\%$ over 5 years. In the study of relapse-free survival, which was defined as the time from the start of treatment for recurrent breast cancer until signs of disease progression appear (detection of distant metastases, re-emergence of loco-regional recurrence). The following data were obtained: with the localization of relapses in the mammary gland, the following were: 1 year without relapses lived $83.3 \pm 6.7\%$, 3 years - $62.4 \pm 8.7\%$, more than 5 years - $49.0 \pm 9.0\%$ (in relation to local recurrence $p < 0.01$). With regional relapses, relapse-free survival turned out to be slightly worse - 1 year without relapses lived $66.7 \pm 8.6\%$, 3 years - $37.1 \pm 8.8\%$, more than 5 years - $37.1 \pm 8.8\%$ (in relation to local relapses $p < 0.05$). Disease-free survival in local relapses was the lowest - $39.3 \pm 4.4\%$ lived without relapses for 1 year,

15.9 + 3.3% for 3 years, and only 13.8 + 3.1% for more than 5 years. It should be noted that the frequency of local cure in regional relapses was achieved two times less often than in local relapses and relapses in the mammary gland: $36.7 \pm 8.8\%$ versus $71.1 \pm 4.1\%$ and $74.2 \pm 7.9\%$, respectively ($p < 0.001$). The lower survival rate for local renewal in comparison with regional and relapses in the mammary gland is explained by the more rapid spread of tumor cells along the lymph outflow pathways, with the localization of recurrent nodes on the anterior surface of the chest, and, accordingly, rapidly progressing dissemination of the malignant process. When the recurrence is localized in the mammary gland or in regional lymph nodes, the recurrent focus remains localized for some time within the organ or lymph node, and with timely treatment, effective local control is provided.

According to the methods of treatment for recurrent breast cancer, the patients were divided into 2 groups: the first study group consisted of 33 (55.3%) patients who received combined treatment (radiation therapy, chemotherapy-hormonal or targeted therapy for recurrent breast cancer. the group consisted of 27 (44.7%) patients who received only local treatment (radiation therapy or chemotherapy) for recurrent breast cancer.

Irradiation techniques were from wide-field to local, with equivalent total focal doses in the range of 24 - 36 Gy and irradiation modes up to 1 fraction of 4 Gy. After mastectomy, the method of radical radiation therapy was used with a single dose of 2 - 2.5 Gy and a total focal dose of 44 - 50 Gy. In parallel with radiation therapy, less often after it, the patients underwent chemotherapy. Most often, patients were prescribed the TR regimen (in 50.0% of cases), less often AS - 26.7%, GP was prescribed in 23.3% of patients. More often, 4 courses of chemotherapy were carried out - in 67.7% of cases, 6 courses in 32.7%. Side effects during chemotherapy were observed in 31 (93.3%) patients, the main ones were nausea, vomiting, neutropenia, leukopenia, diarrhea, stomatitis and alopecia. Hormone therapy was performed in patients with the expression of estrogen and progesterone receptors according to immunohistochemical studies. Ovarian function was switched off in patients with preserved menstrual function using luteinizing hormone releasing hormone (LHRH) agonists zoladex - in 3.3% of cases, radiation castration - 3.3% and oophorectomy - 6.8%. With the same frequency (3.3%), hormone therapy with a progestin - medroxyprogesterone acetate was carried out. Tamoxifen was used most often in 81% of cases during hormone therapy. Patients who had a relapse of the disease 12 months or more after discontinuation of tamoxifen therapy for a primary tumor retained a chance of response with repeated treatment with this drug. Patients who relapse during tamoxifen treatment or less than 12 months after cessation have antiestrogen-resistant tumors and have been treated with alternative approaches (aromatase inhibitors, androgens, progestins). The main side effects observed with the use of hormone drugs were such as hot flashes, edema, hypertrichosis, acne, hoarseness, increased blood pressure, thrombotic complications, uterine bleeding, weight gain, headache, gastrointestinal disorders.

Targeted therapy was carried out in parallel with chemotherapy to patients. Trastuzumab was used most often in 22.8% of cases, less often pertuzumab in 8.8%.

Monochemotherapy (doxorubicin or taxotere) was used in 7.5% of patients with recurrent breast cancer. One and two courses were received by 3.0% and 7.5% of patients, and due to poor tolerance and the absence of signs of disease progression, they refused further courses. Three (13.5%) and four (20.9%) courses were also limited with severe side effects and exacerbation of concomitant diseases. Side effects during chemotherapy were observed in 85.1% of patients. Gastrointestinal disorders (nausea, vomiting, diarrhea) were noted in 13 (47.8%), neutropenia - 1 (4.5%), leukopenia - 2 (7.5%), stomatitis - 2 (7.5%)) and alopecia - 5 (17.9%).

In local relapses, the dose from 40 Gy to 50 Gy was applied to the half of the chest with the same name and the area of regional metastasis. Intact areas of regional lymph outflow exposed to radiation

at the stage of primary tumor treatment were not re-irradiated. With isolated regional relapses, the entire supraclavicular-axillary zone of the same name was irradiated up to 40-50 Gy. Relapse-free survival with local treatment was: $61.5 \pm 8.8\%$ lived without relapses for 1 year, $28.1 \pm 8.2\%$ for 3 years %, more than 5 years only - $25.6 \pm 7.9\%$. In general, $73.3 \pm 8.1\%$ survived 1 year, $51.0 \pm 9.1\%$ - 3 years, $43.7 \pm 9.1\%$ - more than 5 years.

Based on the study of the immediate and long-term results of treatment of recurrent breast cancer, it was found that a combined approach involving the use of systemic methods of treatment has an undoubted advantage in terms of overall (64.0% and 52.8% , respectively) and relapse-free survival of patients ($42 \pm 8\%$ and 28.4% , respectively), compared with only a local or only a systemic approach (43.7% and 31.8% - general and 25.6% and 21.2% - relapse-free, respectively).

Therefore, when choosing a treatment strategy for recurrent breast cancer, it is necessary to focus on a combined approach, which can improve the patient's quality of life, as well as increase her life expectancy.

Conclusions: The combined method of treating recurrent breast cancer has an undoubted advantage in terms of overall ($64.0 \pm 8.9\%$ and $52.8 \pm 6.7\%$, respectively) and disease-free 5-year survival of patients ($42.8 \pm 9.0\%$ and $28.4 \pm 5.5\%$, respectively), compared with local or systemic methods ($43.7 \pm 9.1\%$ and $31.8 \pm 6.5\%$ - total and $25.6 \pm 7.9\%$ and $21.2 \pm 5.5\%$ - relapse-free, respectively) ($p < 0.05$).

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