EFFICIENCY OF NEOADJUVANT POLYCHEMOTHERAPY IN PATIENTS SUFFERING FROM MAMMARY GLAND CANCER. THERAPEUTIC PATHOMORPHISM

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Introduction.

The expediency of applying neoadjuvant polychemotherapy (the Neoadjuvant Polychemotherapy), especially for comprehensive treatment of patients suffering from locally advanced (the Locally Advanced) forms mammary gland cancer (the Mammary Gland Cancer) has become out of question, so far [1-4]. Despite the successful early diagnostics of Mammary Gland Cancer, in almost 25 % patients, as of the moment of setting the diagnosis the locally advanced forms of the diseases are recorded (the Locally Advanced Mammary Gland Cancer), namely: mammary gland tumors over 5 cm, tumor if smaller size, occupying most of the gland (where the latter is small) or tumors of any size, advancing to the skin, the chest wall or as accompanied by metastases into auxiliary, internal mammary, and supraclavicular lymph glands on the affected side [1,3,4]. This category of patients requires long-term treatment consisting of preoperative (neoadjuvant) therapy, surgery and postoperative (adjuvant) therapy of cancer. [2,4-7]. 5-year survival rate for Locally Advanced Mammary Gland Cancer ranges from 27 to 60% and depends largely on the extent of the primary tumor process spread and adequacy of ongoing cancer therapy [1,2,5,9]. According to the National Institute of Cancer Neoadjuvant Polychemotherapy application does not significantly affect the long-term outcomes of patients with Locally Advanced Mammary Gland Cancer. It was noted that when applying such therapy the difference in 5-year survival rate is 3 to 6%, which coincides with the data of global multicenter randomized studies. It is very important to create conditions after application of Neoadjuvant Polychemotherapy to carry out radical, reconstructive and restorative operations in this category of patients. The interest in the problem of pre-operative cancer therapy is permanently growing, since s neoadjuvant treatment in Mammary Gland Cancer allows reducing the scope of surgery in some patients and creates favorable conditions for carrying out organ preserving or recovery operations [1-4,5,6,8,9]. Since 1990 the National Institute of Cancer has been analyzing the results of neoadjuvant antineoplastic effect on mammary gland tumor with thorough studying the therapeutic pathomorphosis [8,10]. Over the last decade, on the basis of morphological studies of angio (vascular) genesis of different tissue types of Mammary Gland Cancer it was proved that tumor vascularization plays a key role in the disease progression and is a significant factor in disease forecasting [8,10,11]. Goal of the Paper - to study the therapeutic pathomorphosis and microscopic features of the tumor tissue in Mammary Gland Cancer after neoadjuvant cancer therapy and evaluate efficiency thereof. Subject and Methods of the Study. The clinical, radiological and morphological analysis was undertaken covering the direct results of comprehensive treatment applied to 223

patients with locally advanced forms of mammary gland cancer - stage IIB - IIIB. The modern standard treatment for patients with the tumor process spread is use of neoadjuvant anticancer therapy, such as polychemotherapy (Polychemotherapy). Optimization of cytotoxic therapy is one of the promising directions to improve outcomes of Mammary Gland Cancer.

The developments carried out in this area, make it possible to potentiate the Polychemotherapy efficiency due to: first, creation of new chemotherapeutic agents, second, improving the methods of drugs transport to the tumor, third, using the modifiers of Chemotherapic Treatment (Chemotherapic Treatment) and, fourth, prescribing individualized chemotherapy regimens.

The study covered 72 patients with Locally Advanced Mammary Gland Cancer, who received Neoadjuvant Polychemotherapy under a standard procedure FAC, 69 patients who received preoperative selective intraarterial chemotherapy (Intraarterial Polychemotherapy) and 82 patients with initially unresectable Locally Advanced Mammary Gland Cancer (T4N0-2M0, T1-4N3M0) with the use of Chemotherapic Treatment during the preoperative period (of which 42 patients received Chemotherapic Treatment under the standards, 40 - after courses of Neoadjuvant Polychemotherapy under a standard procedure FAC underwent radiotherapy (Radiotherapy) along with phthorafurum cytostatic as a modifier (see Table 1).

Table 1.

Distribution of BC patients depending on the stage of cancer and methods of neoadjuvant therapy

stage of process	TNM criteria	Number of patients, absolute number (%)		
		CT (n=72)	CRT (n=82)	IACT (n =69)
II B	$T_2 N_1$	4 (5,5)	2 (2,4)	2 (2,9)
III A	$T_3 N_1$	30 (41,7)	10 (12,2)	12 (17,4)
III A	$T_2 N_2$	16 (22,2)	17 (20,7)	12 (17,4)
III A	$T_3 N_2$	12 (16,7)	20 (24,4)	21 (30,4)
III B	$T_4 N_{1-2}$	10 (13,9)	33 (40,3)	22 (31,9)

The morphological analysis was held using the surgical specimens (removed tumors of the mammary gland). The retrospective study covered the archive control group - 40 patients with Mammary Gland Cancer, who received no antineoplastic treatment before surgery. The Neoadjuvant systemic polychemotherapy (Systemic Polychemotherapy) was held under the FAC procedure – up to 4 courses with 3 weeks intervals between the courses. The following chemotherapy drugs were used: doxorubicine 50 mg / m 2, 5-fluorouracil 500 mg / m2 and endoxane - 500 mg/m2. The Intraarterial Polychemotherapy session was held using angiography with anatomic vascular access to mammary gland cancer (catheterization of vessels was

conducted at the Department Radiological Surgery of the National Institute of Cancer (Chief Physician prof. O.G. Yugrinov.) The first phase consisted of radiological surgery and angiographic study of tumors and metastases. Then state of the vessels was assessed, along with their diameter, type of tumor vascularization. Then the catheter was placed in a vessel, taking part in the blood supply to the tumor, the catheter was kept there for Intraarterial Polychemotherapy. Then catheter - administration of chemotherapy drugs was conducted, using drugs meter DLV-1. During one session the following drugs were introduced: doxorubicine - 40 mg/m2 cisplatin - 60 mg/m2). Cytostatic infusion was carried out at a speed of (2-2.5) mL per minute (3-4) hours a day (2-3) days. After Intraarterial Polychemotherapy, the catheters were removed in the radiological surgery room. Three weeks by means of clinical examination, mammography and ultrasound diagnostics the closest results of Intraarterial Polychemotherapy evaluated, subject to which a plan for further treatment was developed. After surgery, the therapeutic pathomorphosis was studied. Microscopic examination of Mammary Gland Cancer tissue samples, stained with hematoxylin-eosine and picrofuchsine, an analysis of medical pathomorphosis was held along with morphometry of the relevant (drainage) vessels of Mammary Gland Cancer stroma in histological sections, which were made in the peripheral, intermediate and central zones of the tumor. Neoadjuvant cancer therapy under the initially unrespectable forms of Mammary Gland Cancer was carried out as follows: the group I (the main) included 40 patients who underwent comprehensive treatment using traditional Chemotherapic Treatment with radiomodifiers (fluopyrimides), while 4 patients were subject to courses of Neoadjuvant Polychemotherapy under procedure FAC (cyclophosphamide 500 mg/m2, 5-fluorouracil 500 mg/m2, doxorubicine 50 mg/m2, and then - a course of remote radiotherapy (Remote Radiotherapy) for radical program (mammary glands (RVD Gr 2, SVD 40-45 Gr) inguinal lymph glands (RVD Gr 2, SVD 40 Gr) parasternal and supraclavicular areas (RVD Gr 2, SVD 40-45 Gr, the course of Remote Radiotherapy was carried out under a radical with cytostatic drug " Phthorafurum" (800 mg in the morning and 400 mg in the evening) for the purpose of radiomodification. Group II (the control one) consisted of 42 patients who were subjected traditional Chemotherapic Treatment, without modifiers (4 courses of Neoadjuvant Polychemotherapy under procedure FAC and a course of Remote Radiotherapy for radical program. Results and Discussion thereof.

The immediate results shown by the methods of Neoadjuvant anticancer therapy were studied using clinical, radiographic, morphometric methods. The clinical and radiographic evaluation criteria for positive outcomes of Neoadjuvant Polychemotherapy included reducing the size of the tumor or its disappearance, reduction or disappearance of regional metastases, restructuring of the tumor with the appearance of hyperechoic areas and areas of necrosis, decrease, up to complete disappearance of tumor vascularization signs, emergence of calcificates in loci of Mammary Gland Cancer, coinciding with the vector of the sclerotized vessels, reducing the size of lymph glands with increase of their acoustic density, absence of skin edema, loss of Mammary Gland fixation to the chest wall. The first outcomes were assessed 3 weeks after treatment according to the classification RECIST, which

included indicators of tumor response, such as full and partial regression, process stabilization and process progression (see Table 2).:

Table 2.

Response rate

Number of patients	CR (Complete Response)	PR (Partial Response)	SD (Stable Disease)	PD (Progressive Disease)
IACT (n=69)	6 (8,7 %)	32 (46,4 %)	29 (42,0 %)	2 (2,9 %)
CT (n=72)	2 (2,8 %)	22 (30,6 %)	42 (58,3 %)	6 (8,3 %)
CRT (n=82)	10 (12,2 %)	39 (47,6 %)	33 (40,2 %)	0

The clinical and radiological studies revealed that complete tumor regression after Neoadjuvant Polychemotherapy was reduction of the tumor size, establishing normal areal anatomy, with ultrasound diagnostic the signal became homogeneous, edema and infiltration of the skin disappeared, during the treatment the blood supply system of the tumor dramatically reduced up to disappearing. Along with partial regression of the tumor process the tumor reduction by more than 30% was recorded, as compared with the initial data, with ultrasound diagnostic the signal became more homogeneous, but heterogeneous structure of the tumor remained in place, along with distinct blood supply system.

Complete regression of the tumor and absence of the blood supply system was found in 6 (8.7%) patients with nodal forms of Mammary Gland Cancer after Intraarterial Polychemotherapy (in 4 - after 2 courses of Intraarterial Polychemotherapy), in 2 (2.8%) after 4 courses of Systemic Polychemotherapy and 10 (12.2%) after modified Chemotherapic Treatment. When combining the Chemotherapic Treatment the effect of cytostatic therapy, according to the monitoring research data, was more distinct in patients of the groups subjected to Chemotherapic Treatment with radiomodifiers (fluopyrimides). In 29 patients (70.7%) the partial or complete regression of mammary gland tumors observed. The Patients of the control group, which underwent the traditional Chemotherapic Treatment, demonstrated full and partial regression only in 18 (43.9%) cases. The difference is statistically significant and shows a better control of the tumor with inclusion of modifiers into the comprehensive treatment procedure. Thus, the use of Neoadjuvant Polychemotherapy for treatment of Locally Advanced Mammary Gland Cancer allowed achieving an objective response to treatment (objective clinical and radiological effects) in most patients.

Complete disappearance of regional metastases in the auxiliary lymph glands area was found in more than 80% of cases.

Vascular and trophic support of tumor parenchyma viability from non-tumor stroma

allows considering vascularization state of Mammary Gland Cancer, as an objective factor influencing the disease progress.

The control group clearly displays numerous microvasculature stroma of Mammary Gland Cancer (see Fig. 1), while the venous and lymphatic microvessels contain multiple cancer cells and their complexes - so-called tumor emboli (see Fig. 2). Following Intraarterial Polychemotherapy the perivascular necrosis emerge in Mammary Gland Cancer, at the areas of parenchyma and stroma, located near the vessels, which were used for delivery of chemotherapy drugs. An especially important morphological sign of Intraarterial Polychemotherapy efficiency is death of cancer emboli in the lumens of venous and lymphatic vessels, as anatomical tracts for potential metastasis (see Fig. 3). Emergence of the parenchyma and stroma necrosis indicates penetration of chemotherapy drugs molecules through arterial vascular wall, while death of cancer cells in the drainage vessels of Mammary Gland Cancer indicates the transition of chemotherapy drugs molecules from arterial channel into venous one, and into the venous-lymphatic anastomoses (see Fig. 4). Use of the Intraarterial Polychemotherapy allows achieving a significant scope of Mammary Gland Cancer parenchyma and stroma devitalization at the preoperative phase of treatment, in the form of subtotal or even total necrosis. Eventually, after 2-3 weeks of chemotherapy drugs infusion into the transport vessels, its walls restructuring is developing along with narrowing of the lumens obturation. It would be logical to assume that repeated infusions of chemotherapy drugs (several courses Intraarterial Polychemotherapy) initially cause chemical damage to the endothelium and muscle tissues joining elements of vascular membranes, which then leads to vascular thrombosis at different stages of development (see Fig. 6). Subject the foregoing, multi damaging effect of Intraarterial Polychemotherapy becomes apparent, which, due to precise delivery of chemotherapy drug via the arterial vessels, supplying blood to the tumor, lead to necrosis of parenchyma and stroma, death of intravascular tumor emboli with subsequent blockage or restriction of blood and lymph circulation due to development of thrombosis and sclerosis of vascular stroma. When applying 1 to 2 courses of the Systemic Polychemotherapy only, no such widespread changes in tumor happens, as regards therapeutic pathomorphosis. Only piecemeal necroses of tumor parenchyma develop, preserving the structures of cancer complexes" adjacent areas, and the tumor emboli remain practically unaffected by Systemic Polychemotherapy (see Fig. 5). For objectification of studying the therapeutic pathomorphosis, developing as a result of antineoplastic Neoadjuvant Polychemotherapy, the results of tumor parenchyma quantitative content analysis is summarizes subject to the results of morphometry (see Table 3).

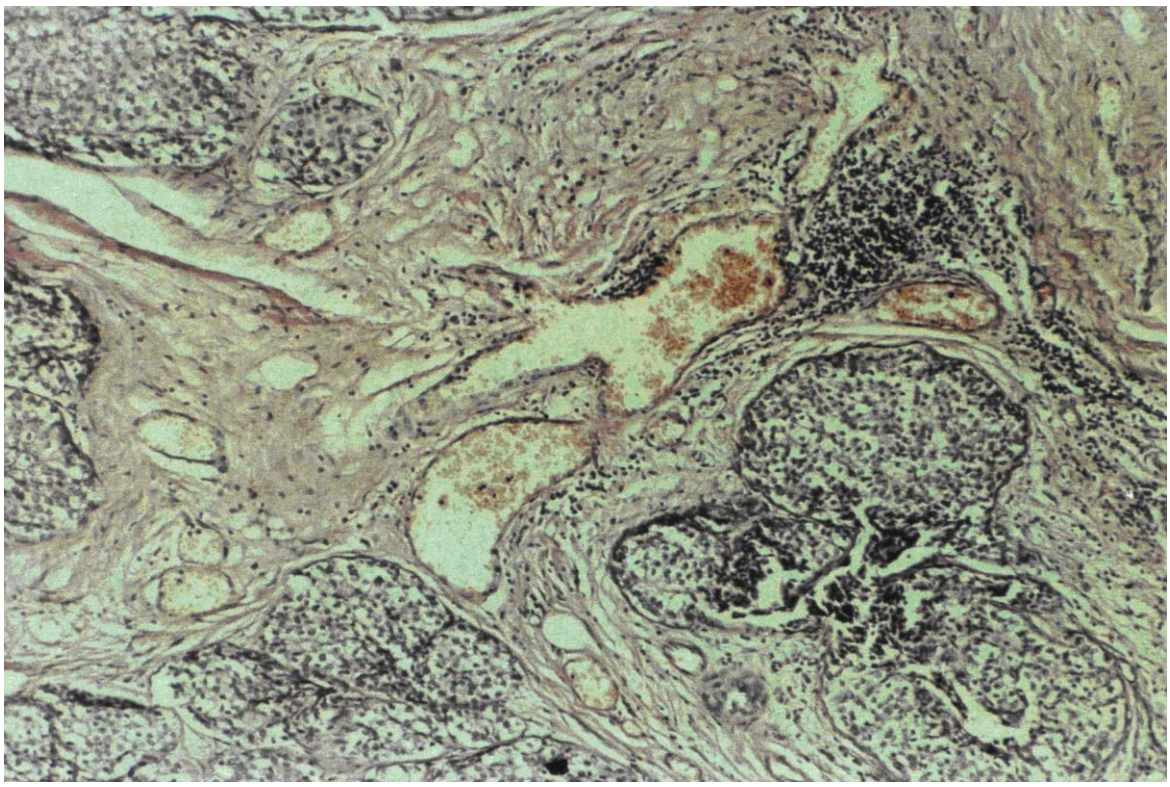

Fig. 1. High density of BC stromal vascularization. Control (surgical material without antineoplastic influence). Hematoxylin-eozin. Z.x200.

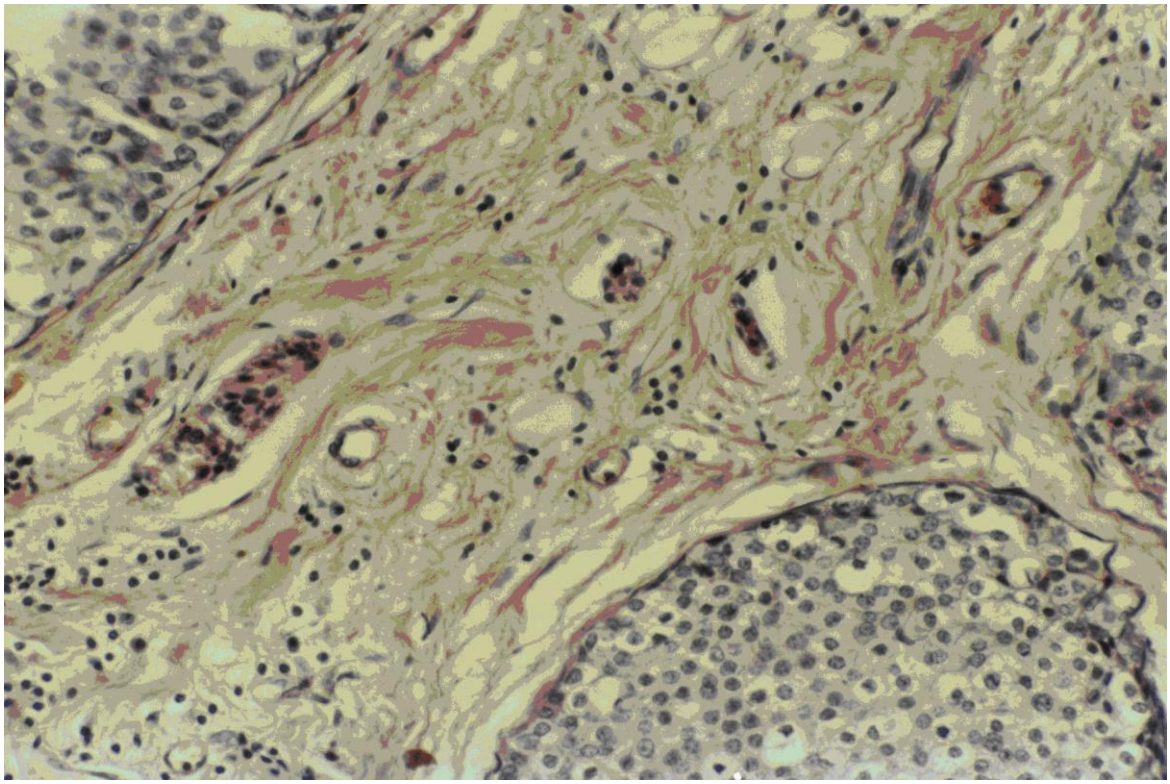

Fig. 2. Multiple tumor embols in the venous and lymphatic lumen of BC vascular stroma. Control (surgical material without antineoplastic influence). Hematoxylin-eozin. Z.x200.

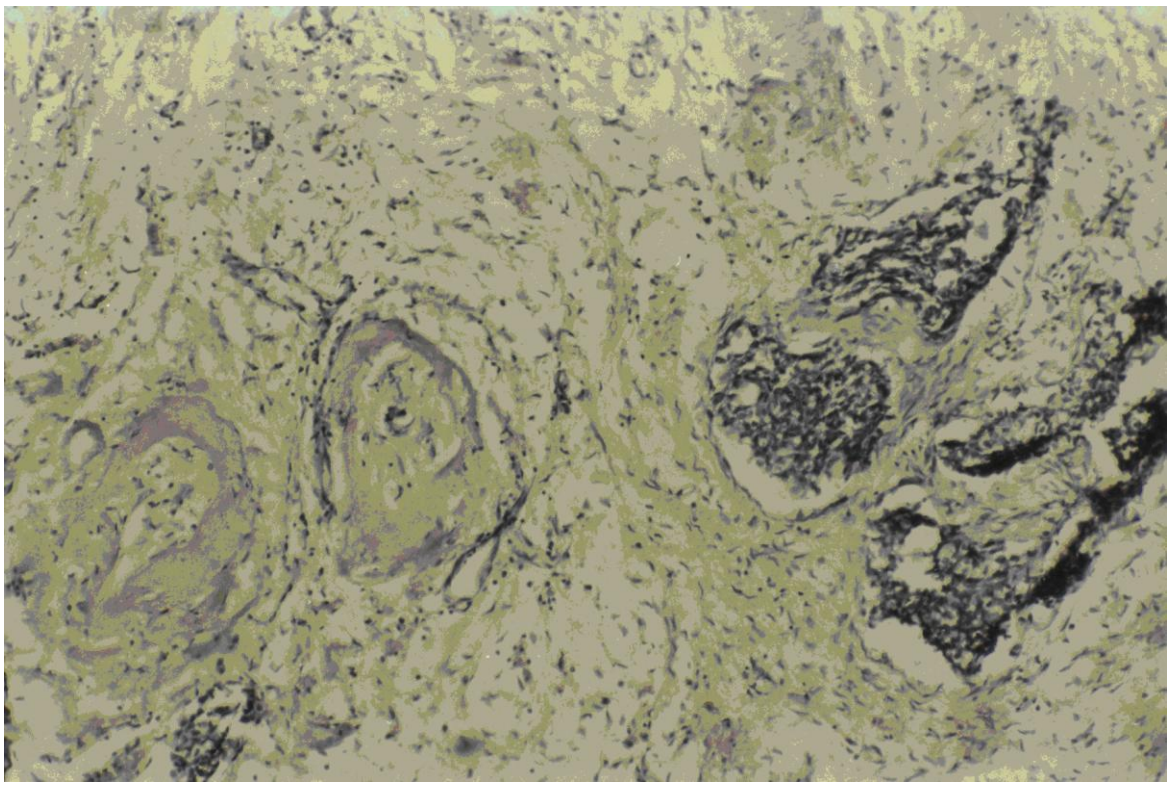

Fig.3. Complexes of dead cancer cells bordering with structurally preserved cancer complexes. BC state after 3 courses of NACT. Z.x200.

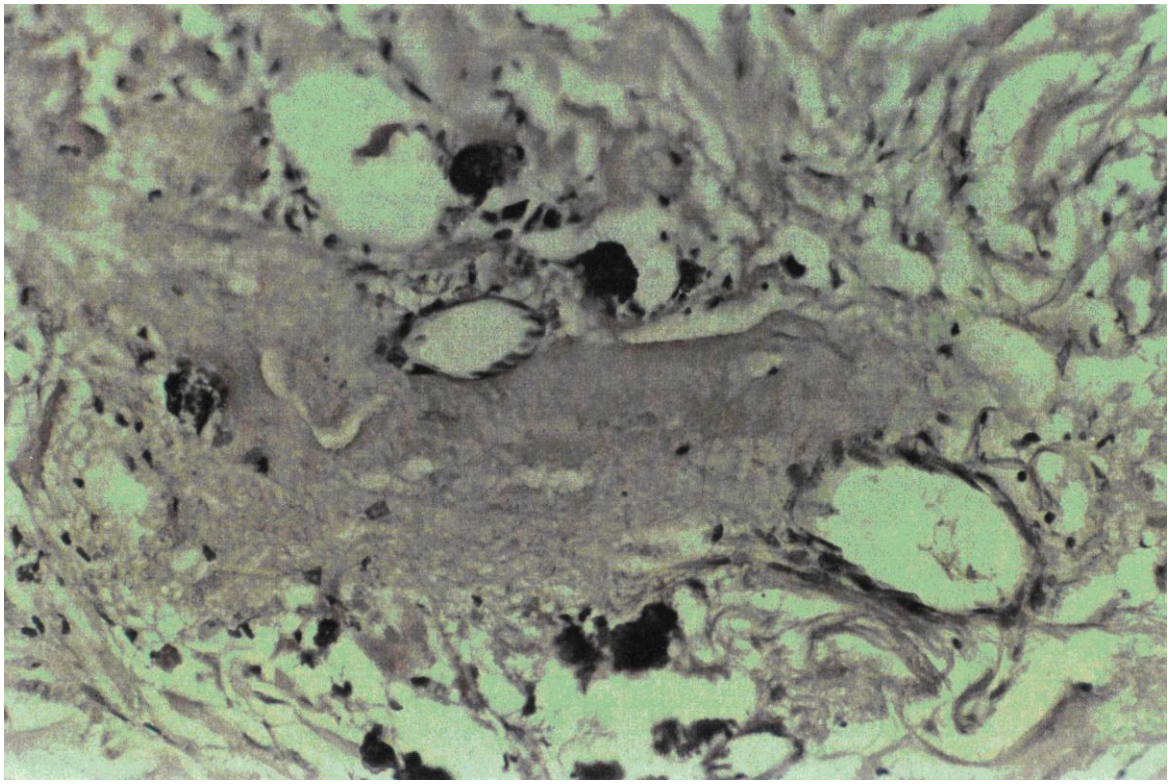

Fig. 4. Dead cancer cells and their accumulation (tumor embols) as an amorphous hematoksylin cells in the lumen of venous and lymphatic vessels. Perivascular partial necrosis of BC parenchyma and stroma. State after 4 courses NACT. Hematoxylin-eozin. Z.x200.

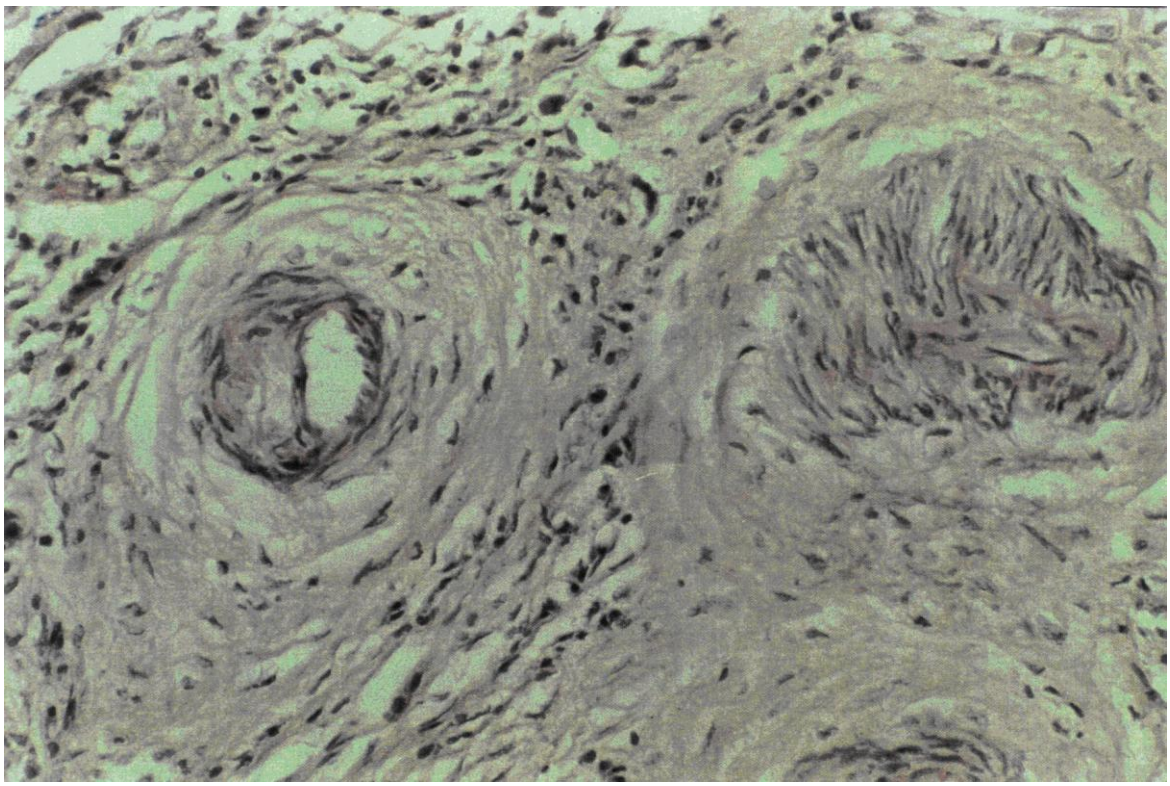

Fig. 5. Tumor embolus in the lumen of BC lymphatic vessels. State after 2 courses NACT. Hematoxylin-eozin. Z.x120.

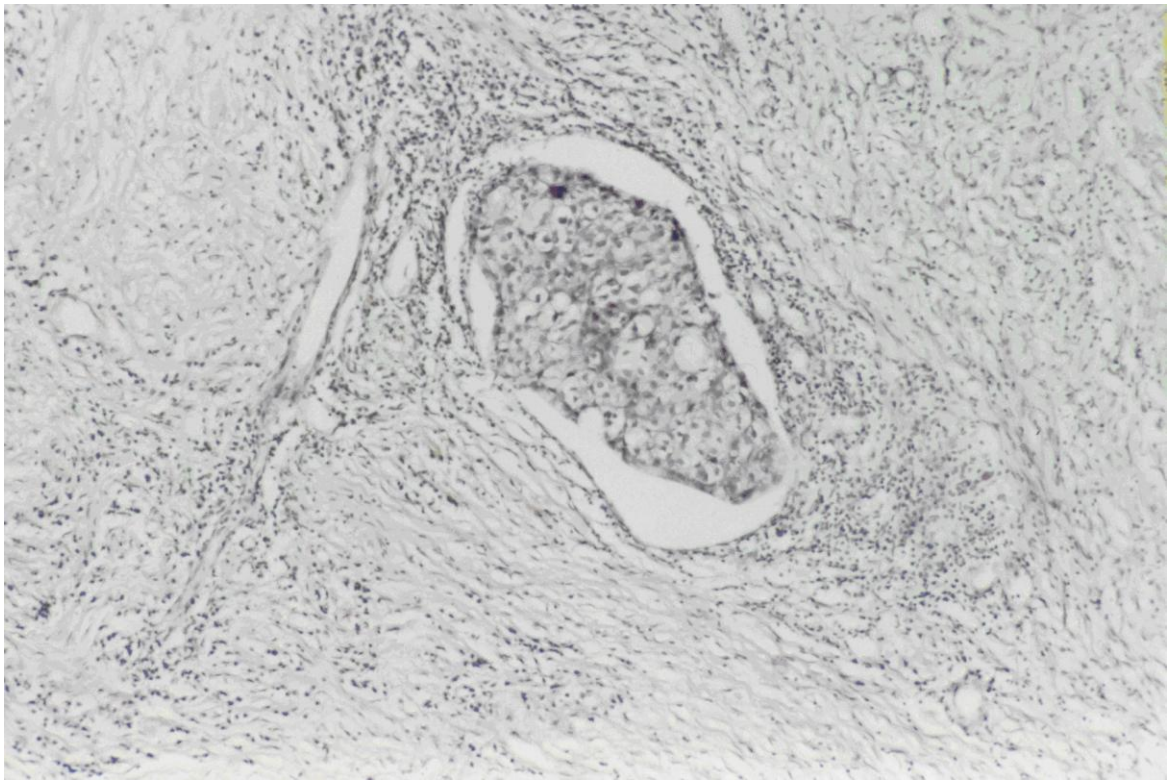

Fig. 6. Chemical thrombosis of two transport vessels at different stages of development ("fresh" and "old" blood thrombus in a state of organization). State after 4 courses NACT. Hematoxylin-eozin. Z.x200.

Table 3.

Morphometric evaluation of antitumor effect preoperative anticancer treatment methods

Regimes of neoadjuvant anticancer treatment	Number of patients	Partial content of structural saved residual tumor parenchyma (M±m, %)	P
Control (only operation)	40	78,6 ± 7,7	$P_{1-2} < 0,05$ $P_{1-3} > 0,05$ $P_{1-4} < 0,05$
IACT	69	26,2 ± 6,44	$P_{1-5} < 0,05$ $P_{1-5} < 0,05$
CT (1 course)	72	70,8 ± 8,9	$P_{1-6} < 0,05$ $P_{1-7} < 0,05$
CT (2 courses)	10	50,4 ± 6,8	$P_{2-3} < 0,05$ $P_{2-4} < 0,05$
CT (3 courses)	9	36,0 ± 4,1	$P_{2-5} < 0,05$ $P_{3-4} < 0,05$
CRT (according to the standards)	42	31,44 ± 2,9	$P_{4-5} < 0,05$ $P_{2-7} < 0,05$
Modified CRT	40	13,02 ± 2,3	$P_{4-7} < 0,05$

Note: Tumor cells count was performed in structurally saved foci that were not exposed to chemotherapy or showed chemoresistance. These cells had no structural signs of damage, abnormal mitosis or apoptosis.

The Comparative analysis of the obtained values shows the probable prevalence of the modified combined methods of Chemotherapic Treatment and Intraarterial Polychemotherapy, as compared with 1-3 time courses of the Systemic Polychemotherapy (P <.05). After 1 course of the Systemic Polychemotherapy the volume ratio of viable tumorous parenchyma (Volume Ratio of Viable Tumorous Parenchyma) was not significantly different from the controls (70.8 ± 8.9% and 78.6 ± 7.7%, respectively) during the 2 courses of the Systemic Polychemotherapy the values of Volume Ratio of Viable Tumorous Parenchyma decreased to 50.4 ± 6.8%, when using 3 courses Systemic Polychemotherapy - to 36.0 ± 4.1%. When studying the therapeutic pathomorphosis after Chemotherapic Treatment it was found that the group using the modifiers showed the Volume Ratio of Volume Ratio of Viable Tumorous Parenchyma – 13.02 ± 2.3%, in the group Chemotherapic Treatment under traditional methods – 31.44 ± 2.9%, respectively (P < 0,05).

It was proved that neoadjuvant modified chemioradiotherapy promotes degradation vascular and trophic, and metabolic support of the tumor parenchyma, allowing to convert initially unresectable tumors into resectable ones due to reduction thereof, helping to create conditions for reduction of surgical intervention scope, downgrading

the stage of the disease, destroying subclinical micrometastases, and predetermining the feasibility if continued Polychemotherapy in the adjuvant mode. The morphometric evaluation of the therapeutic pathomorphosis efficiency in Locally Advanced Mammary Gland Cancer after Neoadjuvant Polychemotherapy gives an opportunity to impartially determine of its application antineoplastic efficiency using the operational material, helping to plan and adjust subsequent stages of treatment. Detailing the results of the morphometry we may resume that single and 2 time courses of the Systemic Polychemotherapy are insignificant, as compared with controls.

In order to obtain an objective clinical and morphological effect (tumor reduction for more than 50%) one should undergo at least 3 courses of intravenous Systemic Polychemotherapy, or modified Chemotherapic Treatment, or Intraarterial Polychemotherapy. With regards to the study of tumors vascularization state in Mammary Gland Cancer the morphometry of carcinomas vascular stroma was held in the group of the Systemic Polychemotherapy and in the control group. Following Intraarterial Polychemotherapy such studies are not possible because many of microvessels in the tumor are changed as a result of cytotoxic drugs effect: the abnormal blood rheology change - aggregation of blood cells, sludge-phenomenon (cell agglutination, thrombosis with stenosis or the vascular lumens obturation with the cell, fibrine or mixed microtrombs, plasma impregnation of vascular walls with the development of fibrinoid necrosis and perivascular plasmorrhagia, sclerosis with obliteration of the vessels lumen, up to the loss of the latters' image on tissue samples. All these factors prevent accurate registration of real quantitative content of microvessels after Intraarterial Polychemotherapy in areas of dead tumor parenchyma and stroma. Study of angiogenesis state and its role in the forecasting assessment of the disease progress sufficiently demonstrate morphometric parameters of tumors vascularization in those patients, where the preoperative anticancer therapy methods were not used (see Table. 4). As for determining of tumor vascularity state under Mammary Gland Cancer in patients who received Intraarterial Polychemotherapy, it can be determined by visual analysis of angiographic and ultrasound imaging through the neoadjuvant treatment and after completion thereof, immediately before the surgeries. According to the obtained data one may come to an unambiguous conclusion as for independence of the Mammary Gland tumors hypervascularization factor, which may have an independent and critical role in the forecasting evaluation of the disease, and along with immunohistochemical parameters of tumors' molecular features may have a crucial meaning when planning adjuvant treatment. The results of medical pathomorphosis study demonstrate efficiency and promising nature of Neoadjuvant Polychemotherapy in treating patients with Locally Advanced Mammary Gland Cancer. However, only morphological analysis of cancer as a local display of the disease, does not provide a comprehensive view of the cancer patients' treatment efficiency at the level of the entire organism.

Table 4

Prognostic clinical and morphological evaluation on the criterion "stroma vascularization state"

Tumor vascularization state at the first sight microscope		Prognosis	The risk of metastasis	metastases after surgery	
Number of vessels	Density of distribution			Number of cases, abs.(%)	survival rate
Over 50	Hypervascularization	Worst	High	20 (50)	1 year
Till 20 to 50	Moderate vascularization	Bad	Moderate	9 (22,5)	3 years
Less 20	Hypovascularization	Satisfactory	Low	11(27,5)	5 years

Therefore, results of tumors therapeutic pathomorphosis should be correlated with remote results of treatment. The completed studies indicate pathogenic role of therapeutic pathomorphosis and the state of tumors vascularization through the disease progress in the Mammary Gland Cancer.

When studying the surgical specimens of patients with Mammary Gland Cancer, which in the preoperative phase of treatment were influenced by different methods Neoadjuvant Polychemotherapy, it became apparent that these methods allow dedicated anticancer therapy to destroy cancer cells found in drainage - venous and lymphatic microvessels, along with their anastomoses, with subsequent development of chemically induced necrosis in tumor parenchyma, development of thrombosis and vascular sclerosis. Due to the chemically determined occlusion and obliteration of their tumor vessels the lymphomicrocricular channel reduction took place, limiting development of neoangiogenesis. Devitalization of tumor parenchyma to the achievement of hypovascularization before surgery due to Neoadjuvant Polychemotherapy may improve the conditions of ablation during surgery and reduce the risk of metastasis. Undertaking Neoadjuvant Polychemotherapy allows launching comprehensive treatment to induce the antitumor effect on tumor focus and subclinical metastases, prevent the generalization process, provide information about the tumors sensitivity to cytotoxic drugs and thus avoid ineffective adjuvant therapy. In case of locally advanced initially rescetable forms of Mammary Gland Cancer (stages IIB - IIIB) the comprehensive treatment should begin with neoadjuvant systemic anticancer therapy. Studying of the therapeutic pathomorphosis after applying the Systemic Polychemotherapy proves reasonability of the preoperative use of at least 3 to 4 courses of systemic treatment. In case of initially rescetable mammary gland tumors or swelling infiltrative forms of Mammary Gland Cancer it is appropriate to apply modified or combined Chemotherapic Treatment Intraarterial or

Polychemotherapy (subject to availability of angiographic equipment and clinical experience of catheterizing arterial vessels that take are directly involved in the blood supply of the mammary gland), which are also applied locally. This approach creates the preconditions for improving the life quality of operated patients and improves the results of their survival rate.

List of References

1. Oncology / Under editorship of I.B. Schepotin / Kyiv: Knyga Plyus. – 2006. – 496 pages.
2. E.K. Vozny, N.Yu. Dobrovolskaya. 15 Year Experience in Comprehensive Treatment of Patients Suffering from Locally Advanced Mammary Gland Cancer, Applying Neoadjuvant Polychemotherapy. Materials of the X Russian Oncologic Congress. Moscow, November 21 – 23, 2006 – pages 64 – 66.
3. Ye.Yu. Garbukov, Ye.M. Slonimskaya, I.A. Krasulina. Neoadjuvant Chemotherapy Treatment of Patients Suffering from Mammary Gland Cancer // Siberian Oncologic Journal, 2005 – No. 2. – Page 14.
4. R.V. Donskikh, V.F. Semiglazov, V.V. Semiglazov et al. Neoadjuvant Treatment of Patients Suffering from Mammary Gland Cancer // Mammalogy No. 1 - 2007. – Pages 34 - 38.
5. V.F. Semiglazov. Neoadjuvant and Adjuvant Treatment of Patients Suffering from Mammary Gland Cancer // Moscow - 2008 – 288 pages.
6. A.S. Tatrchenko, V.V. Velikaya, Applying Various Patterns of Neoadjuvant Polychemotherapy in Comprehensive Treatment of Patients Suffering from Locally Advanced Mammary Gland Cancer // Siberian Oncologic Journal. - 2009 – Annex No. 1 – Pages 193 – 194.
7. L.A. Syvak, S.A. Layalkin, M.M. Maydanevych, A.V. Askolskiy, M.Yu. Klymanov. The Contemporary Aspects of Neoadjuvant Polychemotherapy in Patients Suffering from Mammary Gland Cancer // Oncology 2011. – volume 13, No. 2. – pages 100-102.
8. I.I. Smolanka, S.Yu. Sklyar. Efficiency Improving Methods for Comprehensive Treatment of Patients Suffering from Mammary Gland Cancer - Kyiv – 2007. – 192.
9. G.V. Bondar, I.Ye. Sedakov, O.I. Balshova, A.V. Khomenko. Evaluating Post-Mortem Pathologic Changes and Survival Ability under Selective Intraarterial Polychemotherapy Treatment of Locally Advanced Mammary Gland Cancer // Morphology. – 2011. – T. V, – No. 1. – pages 13-23.
10. K.A. Galaknin, Ye.G. Kuryk, N.N. Melnyk. Chemotherapeutic Pathomorphism of Malignant Tumors // Ukrainian Chemotherapeutic Journal 2000**. –** No. 4**. –** pages 8-13.