

## COMPARATIVE CHARACTERISTICS OF THE METHODS OF CHEMODRUGS ADMINISTRATION IN THE TREATMENT OF PATIENTS WITH LOCALLY-ADVANCED BREAST CANCER

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### Abstract

The development of new methods of treating patients with breast cancer (BC) causes no doubts at anyone at present moment. The statistical data testify to steady growth of BC sickness rate during recent 20 years without tendency to stabilization. The special attention is paid to the development of new methods of treating BC patients (regional forms of disease) with unfavorable factors for forecast of tumor growth. The presented methods of treatment of patients with locally-advanced breast cancer consist in giving complex treatment using two simultaneous ways of administration of chemodrugs – selective intra-arterial and endolymphatic in combination with a systemic one. The results obtained demonstrated greater efficacy of treatment with combinations of selective intra-arterial chemotherapy with a systemic one compared with endolymphatic chemotherapy in combination with the systemic one for the treatment of this disease.

**Materials and methods.** The present study was based on the data of 285 patients with locally-advanced forms of breast cancer HER/2-neu positive and basal-like biological subtypes, with the stages T4N0-2M0, the treatment was given in Donetsk regional antitumor center and Odessa University Clinic in 2000–2014.

During the research for an adequate analysis of the results of treatment by the technique under consideration there were formed two groups of patients. The first investigated group included 221 patients, in 168 patients were diagnosed HER/2-neu positive tumors in immunohistochemical conclusion and 53 patients had basal-like biological subtype of the tumor. The program of the comprehensive treatment of patients in this group included the internal thoracic artery catheterization through the upper epigastric artery, two or three cycles of SIAPCT in combination with intravenous one with an interval of 21 days, evaluation of the effect of radiation therapy (RT) on the breast and zone of the regional lymph outflow in the static mode SFD – 2–2.5 Gy, CFD – 40 Gy, the interval, estimation of the effect. Mastectomy in the patients of the investigated group was performed only when there was a complete or partial tumor response (136 surgeries in a radical scope). Courses of intraarterial PCT were given in continuous long-term infusion (4 hours) by the scheme CMF, CAF or CAMF. Taking into account the possibility of local complications against the background of administration of some chemotherapeutic agents (most often – doxorubicin), half of the drug dose was administered intravenously.

The total course doses of chemodrugs were calculated according to BSA criteria.

The control group included 64 patients, 45 were identified to have HER/2-neu positive and 19 basal-like subtypes of breast cancer.

The program of comprehensive treatment of the patients of this group includes endolymphatic chemotherapy according to the method developed by Donetsk regional antitumor center. As the main method of administration of chemodrugs in the lymphatic system there was used infusion introduction with the help of the system for intravenous drip, infusion rate was 0.3–0.5 ml/min that allowed us to exclude the possibility of extravasation of the chemodrug solution. The course dose of the drug was administered endolymphatically within 5–7 days. At the interval of 21 days two or three courses of ELPHT were given combined with the intravenous administration of anthracyclines (at the end of each cycle the catheter was removed, the catheterization was performed repeatedly). Then the effectiveness of the treatment by the criteria of RECIST was evaluated. Radiation therapy (RT) to the breast and area of the regional lymph outflow was given in a static mode SFD – 2–2.5 Gy, CFD – 40 Gy followed by evaluation of the effect. Mastectomy in the patients of the control group was performed only at the complete or partial tumor response (36 operations in a radical scope). Courses of endolymphatic PCT were given by the continuous long-term infusion (up to 8 hours) scheme of CMF, CAF or CAMF. Taking into account the possibility of local complications against the background of introduction of some chemotherapeutic agents, intercalator doxorubicin was administered intravenously, and antimetabolites and alkylating agents (methotrexate, 5-fluorouracil and cyclophosphamide) in all schemes were introduced endolymphatically.

**Results.** The average life expectancy of patients of the investigated group was  $3.43 \pm 0.18$  years, while in the control group it was  $2.82 \pm 0.3$  that significantly exceeded the statistical data of domestic and foreign authors. Indices of total 3-year survival rate of patients of the investigated group were  $59.9 \pm 4.5$  % and 5-year –  $43.1 \pm 5.5$  months.

In the control group indices of cumulative 3- and 5-year survival rates were significantly lower –  $37.8 \pm 6.6$  % and  $25.2 \pm 7.0$  % months respectively.

#### **Conclusions.**

1. The results of complex treatment of locally-advanced breast cancer with unfavorable prognostic factors of tumor growth by the developed technique by using a combination of selective intra-arterial injection and intravenous chemotherapy in a pool of the internal thoracic artery in combination with radiation and hormonal therapy exceed the results of standard treatment programs for the patients with locally-advanced breast cancer with performing mastectomy and systemic chemotherapy.

2. The method developed by the authors can be recommended for widespread use in these patients.

**Keywords:** Locally-advanced breast cancer, complex treatment, intra-arterial chemotherapy, endolymphatic chemotherapy.

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## **1. Introduction**

The problem of breast cancer (BC) becomes more urgent every year that is characterized by an increase of the annual morbidity from this disease and rejuvenation of this pathology. BC is a leader in the structure of morbidity so it is a very urgent task to develop new methods of treatment of this disease. Statistical data show a steady increase in the incidence of breast cancer in the past 20 years with no tendency to stabilization [1, 2]. The morbidity is 70.1 cases per 100,000 of female population in 2013, and the mortality rate is (32.0 %). The technique of selective intra-arterial polychemotherapy (SIAPCT) and the technique of endolymphatic polychemotherapy (ELPCT) developed in Donetsk regional anti-tumor center demonstrated its sufficiently high efficacy for both primary and metastatic tumor foci that allowed to achieve complete or partial response of the tumor in a large percentage of the follow-up [3, 4].

Particular attention is paid to the development of new methods of treatment of the patients with breast cancer (locally-advanced forms of the disease) with unfavorable prognostic factors of tumor growth [5–10].

## **2. The purpose of the work**

To improve the immediate and long-term results of treatment of the patients with locally-advanced forms of breast cancer by optimizing the routes of administration of chemotherapeutic drugs, to make a comparative characteristic of the methods of delivery of chemodrugs to the tumor focus.

### 3. Materials and methods

The present study was based on the data of 285 patients with locally-advanced forms of breast cancer HER/2-neu positive and basal-like biological subtypes, with the stages T4N0-2M0 whose treatment was given in Donetsk regional antitumor center and Odessa University Clinic in 2000–2014.

During the research for an adequate analysis of the results of treatment by the technique under consideration there were formed two groups of patients. The first investigated group included 221 patients, in 168 patients were diagnosed HER/2-neu positive tumors in immunohistochemical conclusion and 53 patients had basal-like biological subtype of the tumor. The program of the comprehensive treatment of patients in this group included the internal thoracic artery catheterization through the upper epigastric artery (a patent № 29318 of Ukraine of 01.07.2000, a patent № 2169014 of the Russian Federation of 20.06.2001), two or three cycles of SIAPCT in combination with intravenous one with an interval of 21 days, evaluation of the effect of radiation therapy (RT) on the breast and zone of the regional lymph outflow in the static mode SFD – 2–2.5 Gy, CFD – 40 Gy, the interval, estimation of the effect. Mastectomy in the patients of the investigated group was performed only when there was a complete or partial tumor response (136 surgeries in a radical scope). Courses of intraarterial PCT were given in continuous long-term infusion (4 hours) by the scheme CMF, CAF or CAMF. Taking into account the possibility of local complications against the background of administration of some chemotherapeutic agents (most often – doxorubicin), half of the drug dose was administered intravenously. Infusion of chemodrugs in the mode of selective intra-arterial administration with CMF was given using a dispenser of drugs as follows:

- cyclophosphamide: the first, fourth, seventh day – 150 mg/hour (600 mg);
- methotrexate: the second, fifth – i/a by 10 mg /hour (40 mg), the eighth day i/v – 40 mg;
- fluorouracil: the third day – 200 mg/hour (800 mg), the sixth, the ninth day – 150 mg/hour (600 mg).

The protocol of the CAF scheme in the mode of selective intra-arterial chemotherapy:

- cyclophosphamide: the first, fourth, seventh day – 150 mg/hour (600 mg);
- doxorubicin: The second, fifth i/a – 5 mg/hr, the eighth day i/v – 40 mg;
- fluorouracil: the third day – 200 mg/hour (800 mg), the sixth, the ninth day – 150 mg/hour (600 mg).

The protocol of the CAMF scheme in the mode of selective intra-arterial chemotherapy:

- cyclophosphamide: the first, fourth, seventh day – 150 mg/hour (600 mg);
- methotrexate: the second, fifth, eighth day i/a – 10 mg/hr;
- doxorubicin: the ninth day i/v – 80 mg;
- fluorouracil: the third day – 200 mg/hour (800 mg), the sixth, the ninth day – 150 mg/hour (600 mg).

The total course doses of chemodrugs were calculated according to BSA criteria.

The number of cycles of chemotherapy was determined based on the evaluation of treatment effectiveness by the RESIST scale (Response Evaluation Criteria in Solid Tumors), general condition of the patients, presence and severity of local and systemic complications. On an average the patients received 2–3 cycles of CMF to achieve the effect in the neoadjuvant mode. If there was no effect anthracyclines (1–2 cycles) were included in the chemotherapy regimen [3–5]. In the course of evaluating the effectiveness of the method used in therapy of solid tumors the RECIST scale was used. In all cases tumors were evaluated as measurable. There was determined the maximum size of all foci of affection, the size before treatment was considered as the baseline compared with that after treatment [11–15].

In evaluation of the therapeutic effect dynamics of objective state of the patients was taken into consideration as well as the results of clinical and laboratory examinations, dynamic trephine biopsy (evaluation of tumor pathomorphism after PCT) [16–20].

### 4. Evaluation of long-term results of treatment

The clinical course of the disease and long-term results of treatment were evaluated by the following parameters:

- life expectancy without recurrences and new metastases;
- frequency of lymphatic and hematogenous metastasis;
- corrected five-year survival rate.

These indices are calculated in all investigated contingent of patients and separately for the control and investigated groups, depending on the variants of palliative treatment.

Calculation of long-term results was made from the beginning of treatment.

The control group included 64 patients, 45 were identified to have HER/2-neu positive and 19 basal-like subtypes of breast cancer.

The program of comprehensive treatment of the patients in this group included endolymphatic chemotherapy according to the method developed by Donetsk regional antitumor center (a patent of Ukraine № 33909 of 25.07.2008, Bull. № 14 «A method of chemotherapy in patients with malignant tumors») that consisted of catheterization of the deep lymphatic vessel of the thigh. As the main method of administration of chemodrugs in the lymphatic system there was used infusion introduction with the help of the system for intravenous drip, infusion rate was 0.3–0.5 ml/min which allowed us to exclude the possibility of extravasation of the chemodrug solution. The course dose of the drug was administered endolymphatically within 5–7 days. At the interval of 21 days two or three courses of ELPHT was given combined with the intravenous administration of anthracyclines (at the end of each cycle catheter was removed, the catheterization was performed repeatedly). Then the effectiveness of the treatment by the criteria of RECIST was evaluated. Radiation therapy (RT) to the breast and area of the regional lymph outflow was given in a static mode SFD – 2–2.5 Gy, CFD – 40 Gy followed by evaluation of the effect. Mastectomy in the patients of the control group was performed only at the complete or partial tumor response (36 operations in a radical scope). Courses of endolymphatic PCT were given by the continuous long-term infusion (up to 8 hours) scheme of CMF, CAF or CAMF. Taking into account the possibility of local complications against the background of introduction of some chemotherapeutic agents, intercalator doxorubicin was administered intravenously, and antimetabolites and alkylating agents (methotrexate, 5-fluorouracil and cyclophosphamide) in all schemes were introduced endolymphatically.

Infusion of chemodrugs in the mode ELPHT by the CMF scheme was as follows:

- cyclophosphamide: from the second to the fourth day – 400 mg/m<sup>2</sup>;
- methotrexate: the first and fifth day – 30 mg/m<sup>2</sup>;
- 5-fluorouracil: from the second to the fourth day – 500 mg/m<sup>2</sup>.

Infusion of chemotherapy according to the CAF protocol in the ELPHT mode was as follows:

- cyclophosphamide: from the second to the fourth day – 400 mg/m<sup>2</sup>;
- fluorouracil: from the second to the fourth day – 500 mg / m<sup>2</sup>;
- doxorubicin: on the first day i/v – 50 mg/m<sup>2</sup>.

CAMF protocol in the mode ELPHT was given as follows:

- cyclophosphamide: from the second to the fourth day – 400 mg/m<sup>2</sup>;
- methotrexate: the first and the fifth day – 30 mg/m<sup>2</sup>;
- 5-fluorouracil: from the second to the fourth day – 500 mg/m<sup>2</sup>;
- doxorubicin: on the first day i/v – 30 mg/m<sup>2</sup>.

The total course doses of chemodrugs for each chemotherapy scheme were consistent with a standard one, calculated according to the criteria of BSA.

The number of cycles of chemotherapy was determined on the basis of evaluation of the effectiveness of treatment, general condition of the patients, the presence and severity of toxic complications. On an average the patients received 2–3 cycles to achieve the effect in the neoadjuvant mode. If there was no effect, anthracyclines were included in the ELPHT scheme (cycle 1–2) [3–5].

On examination of the patients under study and of the control group metastases were not detected during primary visit.

Histological examination of the operating materials in the investigated group of the patients demonstrated predominated tumors of the following morphological structure:

- infiltrating carcinoma, 3stage of malignancy – 32 (23.53±2.8 %);
- infiltrating carcinoma, 2 stage of malignancy – 23 (16.91±3.5 %);
- ductal invasive cancer – 18 (13.24±2.3 %) cases.

The patients in pre-menopause with hormone-dependent tumors were performed bilateral tubovariectomy simultaneously with catheterization or were given agonists of releasing hormone.

Postmenopausal patients on the basis of immunohistochemical data were administered conservative hormonal therapy.

In the control group of patients with histological examination of surgical material tumors were often presented by the following morphological variants:

- infiltrating carcinoma, 3 stage of malignancy – 11 ( $30.56 \pm 3.6\%$ );
- infiltrating carcinoma, 2 stage of malignancy – 4 ( $11.11 \pm 2.8\%$ );
- ductal invasive cancer – 1 ( $2.78 \pm 1.4\%$ ) cases.

There were no revealed statistically significant differences in the frequency of different morphological variants between the patients of the control and investigated groups ( $p=0.87$ ).

Also there was no statistically significant difference in the distribution of staging in category N patients in the controls and group under the investigation ( $p=0.06$ ).

The analysis of the age, the prevalence of tumor, presence of comorbidity of the patients showed that they were homogeneous in the control and investigated groups.

All patients were informed in detail with the objectives of the study, the programs of therapeutic and diagnostic procedures and gave their written informed consent for this type of treatment.

In accordance with the protocol of this study the scheme of complex treatment of all patients included radiation therapy which was given at the radiological department of Donetsk regional antitumor center. Irradiation of the primary lesion and regional areas was performed by gamma – therapeutic devices “Rokus” and “Agat” in the classical modes of dose fractionation.

Hormone therapy was given in accordance with modern views and approaches to this problem. Pharmacological or surgical ablation was performed in the patients with preservation of the menstrual function and presence of steroid hormone receptors in the tumor after which the anti-estrogen drugs were administered for 2–3 years, followed by administration of aromatase inhibitors or antiestrogens extension up to 5 years. Anti-estrogens or aromatase inhibitors were prescribed to all patients in postmenopause who have not been studied the hormonal status of the tumor or the hormonal status of the tumor was positive. At absence of the tumor hormone receptor hormone therapy was not given.

## 5. Results

Evaluation of the effect of the treatment was carried out in the period after neoadjuvant chemotherapy.

Traditionally to assess the objective effect of chemotherapy there were used the well-known criteria of the WHO Expert Committee. The evaluation of the tumor size and metastases was used as a derivative of the two largest perpendicular sizes. It should be noted that the instrumental tests were made in the same hospital (DRATC) in compliance with the principles of continuity (one apparatus and the same specialists). For linear measurements of breast tumors there was used a medical caliper of McGhan company with divisions of 0.1 mm.

After neoadjuvant chemotherapy courses the percentage of complications (leukopenia) in the investigated group was  $3.62 \pm 1.0\%$ , in the control group –  $3.13 \pm 0.8\%$ .

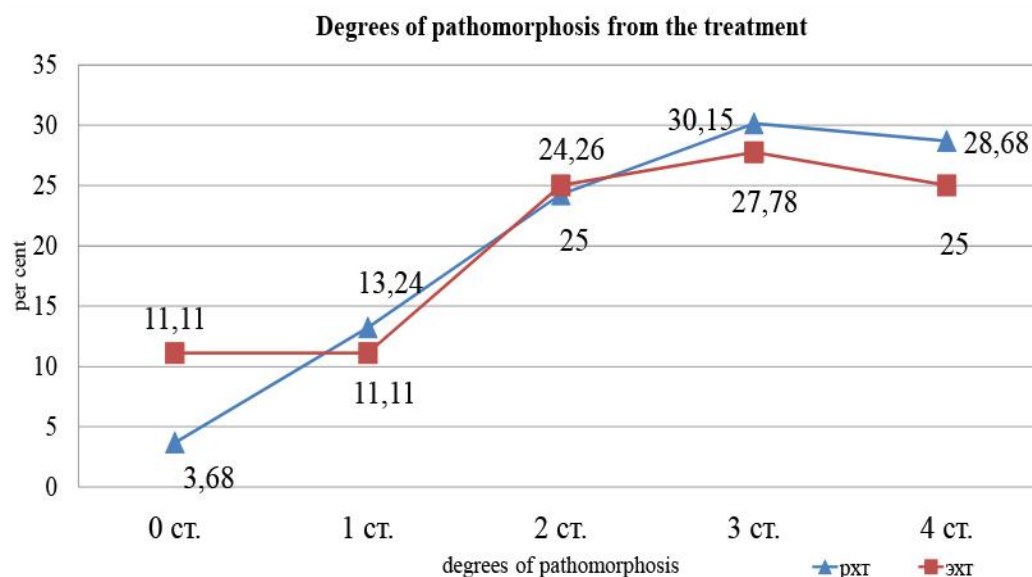
In the investigated group by the nature of surgical treatment there were performed 130 (95.59 %) operations by Madden and 6 (4.41 %) operations in the modification of Halstead; of them: 18 ( $13.24 \pm 3.5\%$ ) patients were diagnosed pathomorphosis of 1 stage, 33 ( $24.26 \pm 4.9\%$ ) – pathomorphosis of 2 degrees. In 41 ( $30.15 \pm 6.3\%$ ) cases pathomorphosis was of 3 stage and in 39 ( $28.68 \pm 5.4\%$ ) pathomorphosis was of 4 stage.

In the control group, 33 (91.67 %) operations were performed in the modification of Madden 3 (8.33 %) – modified by Halstead. The first degree pathomorphism was detected in 4 ( $11.11 \pm 2.2\%$ ) patients. Pathomorphosis of the 2nd degree was in 9 ( $25.0 \pm 5.1\%$ ) patients. In 10 ( $27.78 \pm 5.2\%$ ) cases there was pathomorphosis of the 3<sup>rd</sup> degree and in 4 ( $11.11 \pm 2.2\%$ ) – 0 pathomorphosis (**Fig. 1**).

Postoperative complications in the test group were:  $1.5 \pm 5.15\%$ , whereas in the controls it was  $8.33 \pm 2.3\%$ . Lymphorrhea in the patients of the investigated group was observed in  $3.68 \pm 1.1\%$ , in the controls – in  $2.78 \pm 0.9\%$ . Secondary healing –  $1.47 \pm 0.4\%$  was observed in the investigated group,  $2.78 \pm 0.9\%$  – in the controls. Also there was identified a case of the regional necrosis  $2.78 \pm 0.9\%$  in the control group.



Differences in distributions of the effectiveness evaluation of treatment for the patients in the control and investigated groups by the RECIST scale are statistically significant ( $p=0.02$ ) (Table 1).



**Fig. 1.** Dynamics pathomorphosis degree depending on the treatment:  $\Delta$  – Patients who received both intra-arterial and systemic combination chemotherapy;  $\square$  – Patients receiving ELPHT and systemic chemotherapy

**Table 1**

The effectiveness of treatment of the patients

Effect by the scale RECIST	Investigated group %±m %		Control group %±m %	
Total	11	8.09±2.3	2	5.56±3.8
Partial	107	78.68±3.5	17	47.22±8.3
Stabilization	17	12.50±2.8	15	41.67±8.2
Advance	1	0.74±0.73	2	5.56±3.8

The effectiveness of the treatment was evaluated by mammography in investigating two sizes of the primary tumor in the frontal and lateral projections (Table 1).

During the follow-up patients of the study group were revealed the following variants for the continuation of the disease after treatment: advance of the disease – in 35 (15.84±3.1 %) patients, 10 (4.52±1.8 %) patients had metastatic bone disease. Pulmonary metastases were found in 7 (3.17±1.1 %) patients in 14.21 months. The metastatic liver disease was diagnosed at the control examination in 4 (1.81±0.5 %) patients after 13.41 months. Metastatic pleurisy was in 4 (1.81±0.4 %) patients in 12.64 month, brain damage – in 2 (0.90±1.2 %) patients on an average in 7.82 months. Intradermal metastases were detected in 2 patients, the average interval was 7.27 months. Recurrence into the postoperative scar was found in 1 (0.45±1.4 %) patients, on an average within 19.5 months. The supraclavicular lymph node metastatic lesion was found in 1 (0.9±0.2 %) case, in 3.22 months. Metastases in the contralateral axillary lymph nodes were detected in 3 (1.36±1.1 %) patients in 14.96 months after completion of treatment. Metastasis in the pectoralis major muscle was in 1 (0.9±0.2 %) case in 11.74 months after chemoradiotherapy and surgery.

The results of the dynamic observation in the patients of the control group were as follows: 14 (21.54±3.6 %) patients showed a continuation of the disease. 1 (1.54±1.2 %) patient was diagnosed metastatic pleuritis, the average time interval was 11.40 months. Bone metastases were revealed

in 7 ( $10.77 \pm 3.3$  %) patients in 13.82 months, metastases to the lungs – in 4 ( $6.15 \pm 2.3$  %) patients, on an average in 10.64 months, intradermal metastases – in 1 ( $1.54 \pm 1.2$  %) patient on an average in 14.2 months. Recurrence into the surgical scar was detected in 2 ( $3.45 \pm 1.3$  %) patients, on an average in 11.87 months, metastasis in the mediastinal lymph nodes – 1 ( $1.54 \pm 1.1$  %) patient in 33.14 months after completion of treatment.

All patients diagnosed with continuation of the disease have received palliative symptomatic treatment.

Consideration of cases of the disease in the area of continuing postoperative scar revealed the following results: in the control group the average period of metastasis was 14.2 months; while in the investigated group the average period was 19.5 months.

Median survival for patients of the investigated group was 14.7 months, while for the patients in the control group it was 10.7 months.

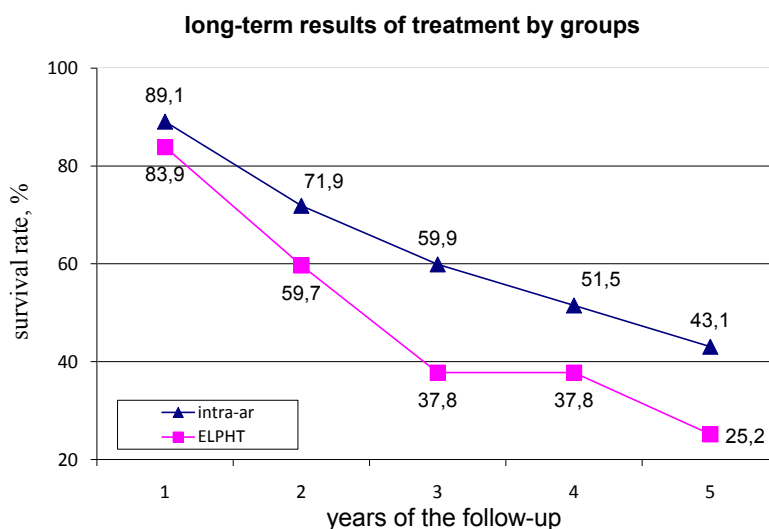
## 6. Discussion of the results

At comparing the survival curves both groups of patients showed a statistically significant difference ( $p < 0.001$  when using log-rank test with Yates correction). It was found that the patients achieved a complete or partial effect of treatment by the RECIST scale live longer after selective intra-arterial chemotherapy. Full or partial response by the RECIST scale was often reported in patients in the investigated group having better survival rates.

All patients diagnosed with a continuation of the disease received palliative chemo- and hormone treatment.

The average life expectancy of patients of the investigated group was  $3.43 \pm 0.18$  years, while in the control group it was  $2.82 \pm 0.3$  that significantly exceeded the statistical data of domestic and foreign authors. Indices of total 3-year survival rate of patients of the investigated group were  $59.9 \pm 4.5$  % and 5-year –  $43.1 \pm 5.5$  months.

In the control group indices of cumulative 3- and 5-year survival rates were significantly lower –  $37.8 \pm 6.6$  % and  $25.2 \pm 7.0$  % months respectively (Fig. 2).



**Fig. 2.** Dynamics of the five-year cumulative survival rate according to the treatment:  
Δ – patients who received both intra-arterial and intravenous polychemotherapy; □ – patients treated with systemic ELPHT + systemic chemotherapy

## 7. Conclusions

1. The results of complex treatment of locally-advanced breast cancer with unfavorable prognostic factors of tumor growth by the developed technique by using a combination of selective intra-arterial injection and intravenous chemotherapy in a pool of the internal thoracic artery in combination with radiation and hormonal therapy exceed the results of standard treatment pro-

grams for the patients with locally-advanced breast cancer with performing mastectomy and systemic chemotherapy.

2. The method developed by the authors can be recommended for widespread use in these patients.

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## MATRIX METALLOPROTEINASE-9 AND INFLAMMATION IN DIFFERENT TYPES OF MULTIPLE SCLEROSIS

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