

Treatment of patients with high risk soft tissue sarcoma.

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Summury.

Research purpose - to compare the results of the combined treatment of patients with STS of high risk with application of different methods of neoadjuvant treatment. To research it was attracted 41 patient with STS, which parted on two groups depending on got neoadjuvant chemotherapy – three- or quarternary. Quarternary neoadjuvant system chemotherapy was satisfactorily carried patients, and for did not excel such the displays of toxicness at three-component. A tendency is shown to the increase in a basic group as compared to control indexes 2-years survival: general - 85,7 % but 80,0 % accordingly, and non-recurrence - 80,95 % but 70,00 % accordingly ($p > 0,05$). Found out statistically a reliable ($r < 0,05$) increase in the basic group of non-metastatic 2-years survival to 76,19 % against 50,00 % in a control group.

Key words: soft tissue sarcoma, combined treatment, chemotherapy, radiation treatment, surgical treatment.

Entry.

Treatment of patients with the sarcoma of soft tissue (STS) is one of unsolved problems of clinical oncology. For adults they make (1,0 - 2,5 %) all malignancy. In 2010 year in Ukraine approximately 1750 cases of disease are incorporated on STS, and a level of morbidity was 3,54 on 100000 the standardized population of Ukraine [1]. Among the persons of sex of men this index is some more high, than for women and evened 4,03 ‰ and 3,26 ‰ accordingly.

It should be noted that STS is characterized aggressive motion and unfavorable prognosis which does treatment of this contingent of patients an intricate problem [2]. The leading method of treatment of patients with this pathology is surgical which can be divided into two groups of interferences: limb sparing and amputations of extremities. The method of choice is a wide resection within the limits of healthy tissue. Amputations are executed approximately in 10 % patients, and before similar operations were used almost in every the second case [2].

Thus, character of malignancy of soft tissue, especially high degree of risk, which are accompanied a frequent relapse, needs multimodal approach with bringing in of many specialists-oncologists: oncosurgeons, radiologists, chemotherapeutics [32, 33, 34, 35].

The prospective randomized research was executed on treatment of patients with STS of high risk with the use of different charts of neoadjuvant treatment.

Research purpose - to compare the results of the combined treatment of patients with STS of high risk with application of different methods of neoadjuvant treatment.

Object and research methods.

It was attracted 41 patients on STS of high degree of risk to research. High risk feet present for patients in time: deep location of tumor (under fasciae), exposure of high- and undifferentiated forms of sarcomas, size of tumor more than 5 see in one of measurings, and also in the case of relapse of disease. Before research patients were attracted without heavy concomitant pathology in the stage of decompensate.

Before the beginning of research patients were randomized on two groups: basic and control. A basic group (21 persons) treated oneself as follows: neoadjuvant system quarter-component chemotherapy (vinkristine, dakarbazine, doxorubicin, ciklofosfan - CyVADIC), radiation therapy, surgical treatment, system adjuvant chemotherapy, adjuvant radiation therapy. A control group (20 persons) got such treatment: neoadjuvant system three-component chemotherapy (vinkristine, doxorubicin, ciklofosfan - VAC), surgical treatment, system adjuvant chemotherapy, adjuvant radiation therapy.

The estimation of results of treatment was foreseen by the study of answer of tumor on neoadjuvant therapy after the change of his sizes from data of x-ray computer tomography (CT) and magnetic-resonance tomography (MRT) and medical pathomorphoses - by volume fate of viable tumor parenchyma.

All patients before the beginning of treatment was conducted CT or MRT, which the sizes of tumor were measured during. Analogical procedure took place before the surgical stage of treatment for the study of consequences of neoadjuvant therapy. By us were the used criteria of RECIST 1.1 (2000) answer for therapy for patients with STS.

During the lead through of neoadjuvant treatment adverse effects were estimated after a scale NCIC.

For the estimation of medical pathomorphosis histological preparats made from tissues of central, intermediate and peripheral areas of tumor for operating material. Colorings of histological preparates conducted haematoksiline-eozin. The estimation of therapeutic pathomorphoses was conducted by the method of hystostereometry, with the use Avtandilov ocular test net of. At counts determined of volume fate of viable tumor parenchyma in percents. For the quantitative criteria of account of death of tumor parenchyma, induced neoadjuvant therapy, a chart – scale of estimation of medical pathomorphoses was used on operating material after G.A. Lavnikova. If volume fate of viable tumor parenchyma hesitates from 100 to 50 %, it I degree of medical pathomorphoses, interval from 50 to 20 % answers the II degree of medical pathomorphoses, from 20 to 1 % - to the III degree, complete loss of tumor parenchyma - to the IV degree.

The statistical processing of the got data is conducted with the use of the programs of Excel (MS Office 2003, XP) and StatIstIca 6,0 (StatsoftInc., USA). The indexes of survivability settled accounts after the method of Kaplan-Mayer.

Results and their discussions.

In the basic group (21 man) of men it was 11 (57,2 %), women – 9 (42,8 %). There were 10 men (50 %) and 10 women (50 %) persons entered in a control group (20 people). Distributing of patients on sex in the probed groups is resulted in a table 2.

In a basic group patients got on from 19 to 68 years old, swingeing majority in age after 40 (62%) middle age is $(43,5 \pm 4,8)$ years. In a control group age of patients hesitated from 18 to 72 years old, also mainly in age more than 40 years (70 %), middle age made $(49,1 \pm 5,1)$ years. Difference in middle age, becoming ill in 5,6 years statistically unreliable ($p > 0,05$). Detailer information about the age-dependent structure of basic and control

groups is resulted in a table 3. Thus after age-old descriptions basic and control groups of patients with the STS of high degree of risk were similar.

By all patient of basic and control groups before the beginning of treatment morphological research was conducted which it was discovered at, that in all there are high- and undifferentiated (G3-G4) forms of STS, which were located under fasciae and more than 5 sm had a size in one of measurings. Coming from aforesaid all patients had the III stage of disease, or G3-4T2bN0M0.

Description of basic and control groups after the morphological structure of tumor is presented in a table 4. Considerable enough was an amount of malignant mesenchymomas - 7 (33,3 %) in a basic group, and malignant fibrotic histiocytoma (MFH) – 7 (35,0 %) in control. Other morphological forms were observed rarer. Important is information about localization of disease for patients on STS of high degree of risk, which is given in a table 5. Most often the point of development of tumor was a thigh – 13 cases (61,8 %) in a basic group and 11 cases (55,0 %) in control.

We can do conclusion, that after basic descriptions basic and control groups of patients on STS were homogeneous enough and similar.

Lead through of neoadjuvant treatment in basic and control groups not accompanied the expressed adverse-effects. Most often there was alopecia of I degree in both groups: in a basic group in $(52,4 \pm 11,1)$ % patients, in control – in $(65,0 \pm 10,9)$ %. A difference is between them in 12,6 % it was statistically unreliable ($p > 0,05$). Also often enough there was nausea under time and after introduction of chemotherapy: in a basic group in $(52,4 \pm 11,1)$ % patients, in control – in $(65,0 \pm 10,9)$ % . The difference fixed between them is in frequency in 12,6 % also was statistically unreliable ($p > 0,05$). One of complications, that met, a change of composition of peripheral blood was. So leucopenia of I degree was marked in $(38,1 \pm 10,9)$ % patients in a basic group, and in $(25,0 \pm 9,9)$ % patients in control. A present difference is 13,1 % and it was unreliable statistically ($p > 0,05$). It is not marked reliable

difference in frequency of development of neutropenia in both groups. In a basic group the neutropenia of I degree was diagnosed in $(33,3 \pm 10,5)$ % patients, and in control – in $(20,0 \pm 9,2)$ % it is a difference in 13 % was not meaningful ($p > 0,05$). The decline of amount of thrombocytes (thrombocytopenia of I degree) was observed in a basic group in $(19,0 \pm 8,8)$ % patients and in $(15,0 \pm 8,2)$ % - in control, that a difference was statistically not reliable. Treatment of complications was conducted after well-known principles and resulted in their reverse development for all patients during 4 – 6 days. Other complications carried single character and did not influence on motion of treatment. Thus a substantial difference in the displays of toxics during neoadjuvant treatment in basic and control groups was not observed.

By all patient of basic and control groups the conducted estimation of effect on the conducted neoadjuvant treatment after the criteria of RECIST 1.1 (2000). The got results are demonstrated in a table 6. The analysis of the resulted data shows that in a basic group part of complete and partial regressions made $(33,6 \pm 7,5)$ %, and in control - $(15,0 \pm 5,2)$ %. A difference is 18,6 % between groups was statistically reliable ($p < 0,05$). Tumor progression, that showed up in the increase of its sizes, was observed in both groups identically often - $(9,6 \pm 4,6)$ % in a basic group and $(10,0 \pm 4,1)$ % – in control, that a difference between them was unimportant ($p > 0,05$). Our information is consonant the results of Pezzi C.M. [57], what reveals to about a different degree regressions of tumors on 40 % patients, and P.Pisters, from M.D. Anderson Cancer Center, which looked after partial and complete regression in 28 % patients [58].

To all patients who were brought over to research, the surgical stage of treatment was executed. In a basic group 20 by a patient a wide resection was executed, in 1 (4,8 %) is amputation of extremity in connection with local advanced tumor. In a control group amputation of extremity it was executed also in 1 patient (5 %) in connection with lesion of bone structures and wide

resection is executed in other patients. Morphometric researches of evaluated tumors in basic and control groups are presented in a table 7. In a basic group III and the IV degree of pathomorphoses were observed in 7 patients ($33,3 \pm 7,5$) %, that more than in a control group – 3 patients ($15,0 \pm 5,2$) %. That pathomorphoses is more expressed - III and the IV degree - on 18,3 % more frequent observed in a basic group ($p < 0,05$).

If to compare the mean value of volume fate of viable tumor parenchyma in a basic group, it was evened ($26,2 \pm 9,6$) %, and in control – ($37,1 \pm 10,8$) %. It is thus possible to talk about a tendency to the increase of cytotoxic influence of neoadjuvant treatment and increase of level of tumor devitalization in a basic group on 10,9 % as compared to control, but this difference was unreliable ($p > 0,05$). It should be noted that 100 % medical pathomorphoses was achieved in one case in a basic group which coincides with reports about single supervisions from literature information [61].

The study of results is conducted in basic and control groups. In a basic group the local relapses of disease arose up in 2 patients in a term from 4 to 8 months, in a control group - in 3 patients in a term from 5 to 14 months. Lung metastases were observed in a basic group in 5 patients and there were from 6 to 18 months after treatment, and in control – in 9 patients in the same terms. In a basic group died 4 patients, in control – 5 patients. In a table 8 resulted information about 2-years survival of patients in basic and control groups.

Common 2-years survival of patients on STS of high risk in a basic group was evened ($85,71 \pm 6,63$) %, that was higher on 5,71 % as compared to control ($80,00 \pm 7,94$) %, but a difference was not statistically reliable ($p > 0,05$). Detailer information on this question is presented on picture 1.

Non-recurrence 2-years survival of patients on STS of high risk in a basic group was ($80,95 \pm 7,29$) %, that on 10,95 % higher than in control ($70,00 \pm 9,25$) %, but the difference was statistically unreliable ($p > 0,05$). Detailer information on this question is presented on picture 2.

Non-metastatic 2-years survival of patients on STS of high risk in a basic group – $(76,19 \pm 7,56) \%$ – was on 26,95 % higher than in control $(50,00 \pm 9,80) \%$, that was statistically reliable ($p < 0,05$). The detailed information after to the occasion is presented on picture 3. Thus analysis of results in patients with STS of high risk in basic and control groups showed a tendency to the increase of general and non-recurrence 2-years survival in a basic group ($p > 0,05$), and reliable increase of non-metastatic 2-years survival in a basic group ($p < 0,05$).

Conclusions:

1. Quarternary neoadjuvant system chemotherapy was satisfactorily carried patients, and for did not excel such the displays of toxiness at three-component chemotherapy.
2. A tendency is shown to the increase in a basic group as compared to control indexes 2-years survival: general - 85,71 % and 80,0 % accordingly, and non-recurrence - 80,95 % and 70,0 % accordingly ($p > 0,05$).
3. Found out statistically a reliable ($p < 0,05$) increase in the basic group of non-metastatic 2-years survival to 76,19 % against 50,0% in a control group.

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Table 2 – Sex distributing of patients with STS of high risk
in basic and control groups

Patients sex	Basic group		Control group	
	n	%	n	%
Male	12	57,2	10	50,0
Female	9	42,8	10	50,0
Total	21	100,0	20	100,0

Table 3 – Age-dependent structure of basic and control groups

Patients age, years	Basic group		Control group	
	n	%	n	%
19-29	4	19,0	2	10,0
30-39	4	19,0	4	20,0
40-49	5	23,8	2	10,0
50-59	5	23,8	6	30,0
60 and more	3	14,4	6	30,0
Total	21	100,0	20	100,0

Table 4 – Distributing of patients with STS of high risk on histological forms in basic and control groups

Histological forms	Patients groups				Total	
	Basic group		Control group			
	n	%	n	%	n	%
Malignant mesenchimoma	7	33,3	2	10,0	9	21,9
Rhabdomiosarcoma	1	4,8	2	10,0	3	7,3
Liposarcoma	4	19,0	1	5,0	5	12,3
Angiosarcoma	3	14,3	3	15,0	6	14,6
Neurosarcoma	1	4,8	1	5,0	2	4,9
MFH	2	9,5	7	35,0	9	21,9
Leiomyosarcoma	1	4,8	2	10,0	3	7,3
Synovial sarcoma	2	9,5	2	10,0	4	9,8
Total	21	100,0	20	100,0	41	100,0

Table 5 – Distributing of patients with STS of high risk on
localization in basic and control groups

Tumors localization	Patients groups				Total	
	Basic group		Control group			
	n	%	n	%	n	%
Forearm	1	4,8	3	15,0	4	9,8
Shoulder	1	4,8	1	5,0	2	4,9
Thigh	13	61,8	11	55,0	24	58,3
Shin	2	9,5	3	15,0	5	12,3
Trunk	3	14,3	1	5,0	4	9,8
Foot	1	4,8	1	5,0	2	4,9
Total	21	100,0	20	100,0	41	100,0

Table 6 – Estimation of effect of neoadjuvant treatment for patients with STS of high risk on RECIST regression in basic and control groups

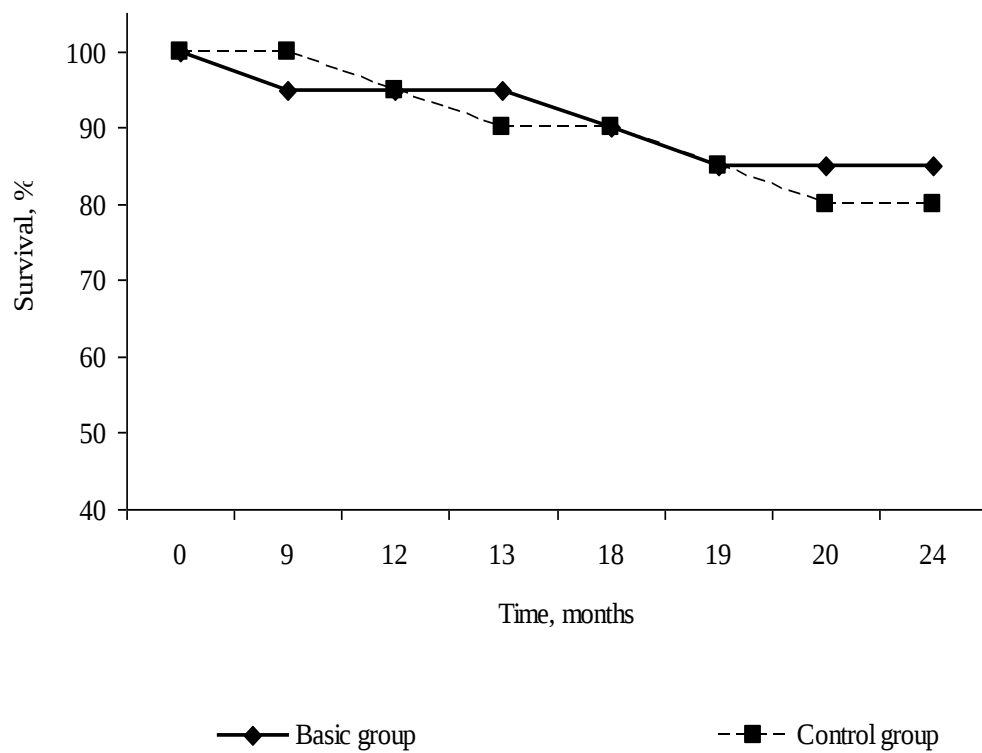
RECIST criteria	Basic group		Control group	
	n	%	n	%
Complete regression	1	4,8	0	0,0
Partial regression	6	28,8	3	15,0
Stabilization	12	56,8	15	75,0
Progression of disease	2	9,6	2	10,0
Total	21	100,0	14	100,0

Table 7 – Comparative estimation of pathomorphoses in patients with STS of high risk in basic and control groups

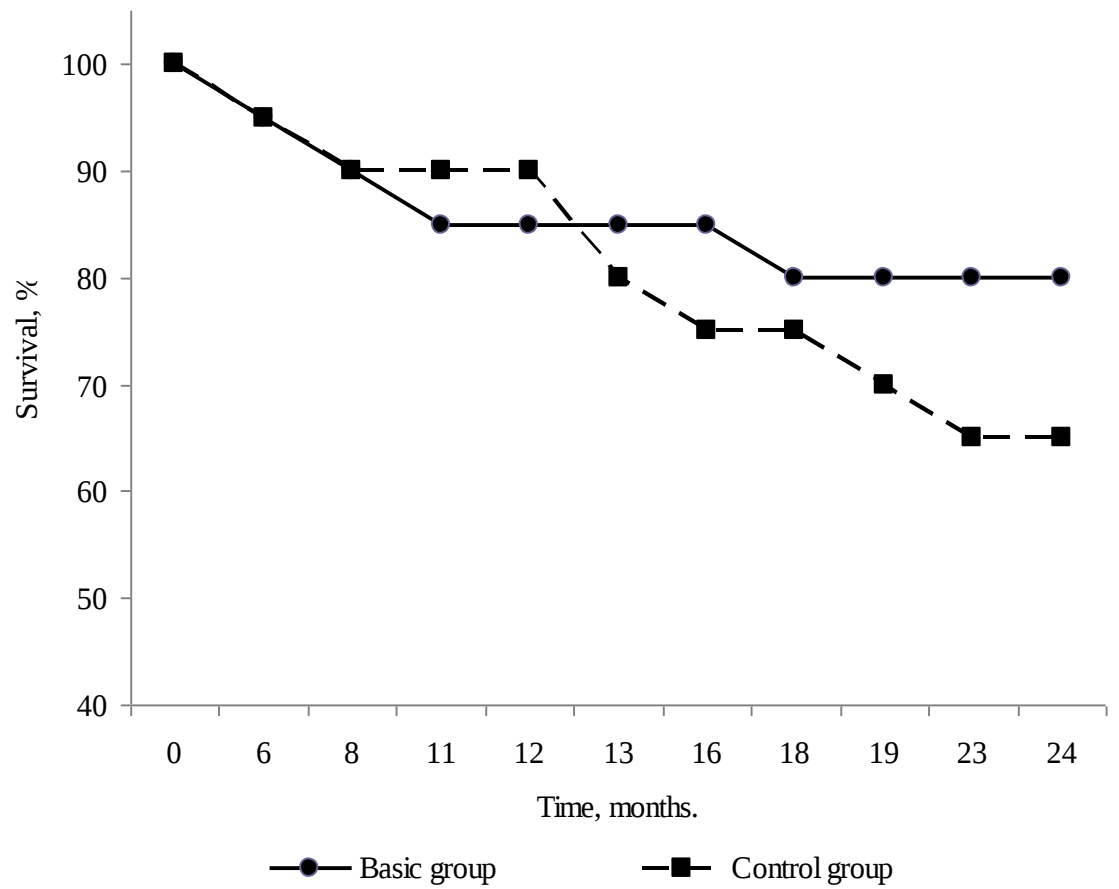
Degree of pathomorphoses	Basic group		Control group	
	n	%	n	%
I	1	4,8	3	15,0
II	13	61,9	14	70,0
III	6	28,5	3	15,0
IV	1	4,8	0	0,0
Total	21	100,0	14	100,0

Table 8 – Indexes of 2-years survival of patients with STS of high risk
in basic and control groups

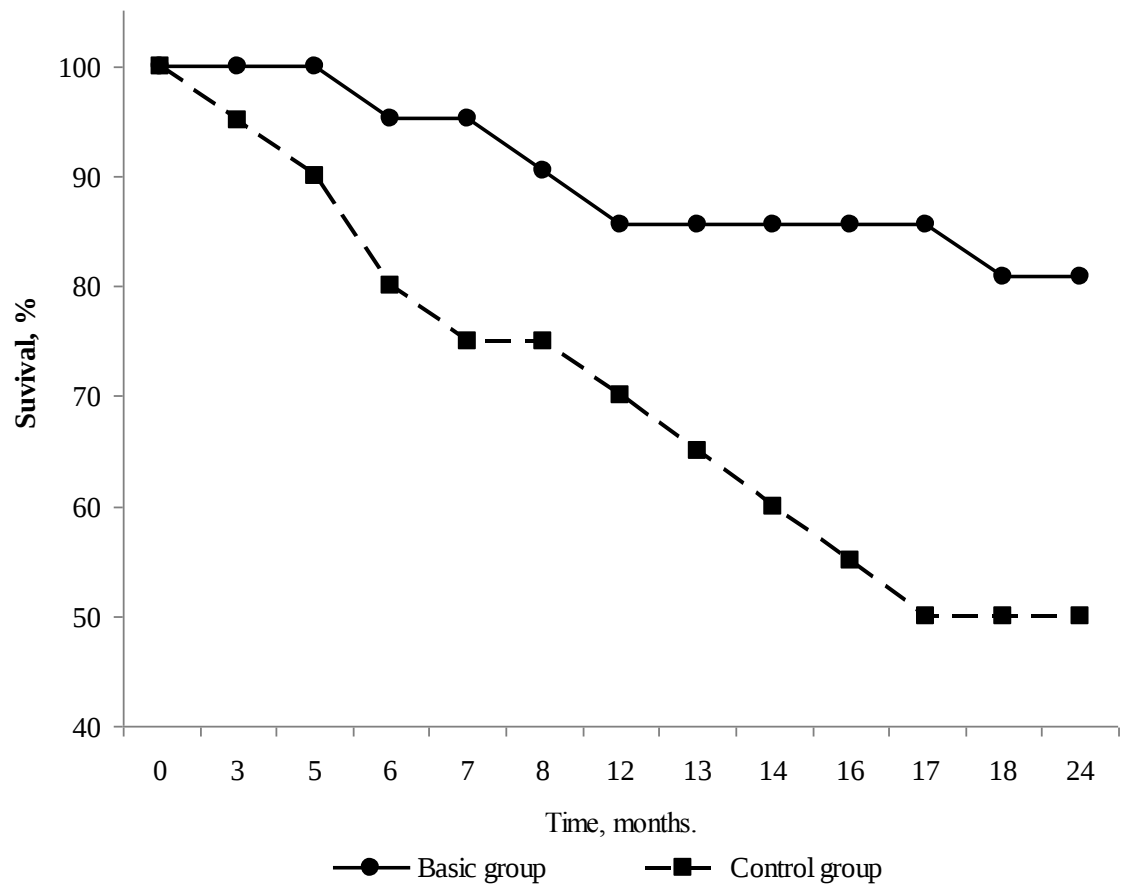
Types of survival	2-years survival of patients (M $\pm$ m)	
	Basic group	Control group
Common	85,71 $\pm$ 6,63	80,00 $\pm$ 7,94
Non-recurrence	80,95 $\pm$ 7,29	70,00 $\pm$ 9,25
Non-metastatic	76,19 $\pm$ 7,56	50,00 $\pm$ 9,80



Picture 1 – Common 2-years survival of patients with STS of high risk in basic and control groups.



Picture 2 – Non-recurrence 2-years survival of patients with STS of high risk in basic and control groups.



Picture 3 – Non-metastatic 2-years survival of patients with STS of high risk in basic and control groups.