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## RESULTS OF THE TREATMENT OF THE PATIENTS WITH MALIGNANT FIBRO HISTIOCYTOMA OF LOW LIMBS SOFT TISSUES

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### Abstract

The basis of the research was the analysis of the results of treatment of 130 patients with malignant fibrous histiocytoma of limbs soft tissues. The patients were treated at the National Cancer Institute from 1985 to 2016. The analysis made showed that the overall survival rate of the patients under examination depends on the location of the primary tumor. Indicators of recurrence-free survival differ significantly depending on the localization of the tumor. In relapsing patients overall survival is different and depends on the method of treatment. In the course of the first six years, the indicators of overall survival are better in the patients underwent only surgical treatment. The overall survival rate for all patients with MFH depends on the treatment method.

**Key words: malignant fibrous histiocytoma of soft tissues, general survival, recurrent-free survival, surgical, combined, and complex treatment.**

### INTRODUCTION

Malignant fibro histiocytoma (MFH) is one of the most common forms of soft tissues sarcoma and ranges from 15 to 30% among all soft tissue neoplasia. It considered to be the most common form of sarcoma in patients over 40 y. o. [1-6].

MFH localizes in the limbs soft tissues in 70-75% of cases, with half of the cases in the lower extremities. In 2/3 of the patients the tumor locates deep in the muscles [7-12].

MFH belongs to the group of soft tissue sarcomas, which, according to the peculiarities of growth, clinical course and prognosis, are among the most aggressive human tumors [13-14].

Mortality rate in the first year after diagnosis makes up 32.0 - 34.5% [15-17]. Despite the constant improvement of the treatment methods, including the modern ones of radiation and chemotherapy, the results remain unsatisfactory. Unfortunately, 40-60% of the patients at the time of diagnosis have already the III-IV stage of the disease, of which at least 80% have malignant tumors of high degree [18].

The most striking feature of soft tissues (ST) MFH and soft tissues sarcomata (STS) in general is their ability to persistent recurrence. Many scholars consider the development of the relapses after tumor removal as a rule rather than an exception. The frequency of local recurrence after the removal of the primary tumor, despite significant advances in the treatment of MFH, can be compared with the data half a century ago which now also varies in a wide range of 25 to 60% of cases, and depending on the nature of treatment of the primary tumor and its biological characteristics can reach 90% [19, 3, 20].

Following on the results of a prospective study of 951 patients with primary STS of the limbs with the aim to determine the independent prognostic factors of local recurrence, metastasis and survival, using standard factors which included and the analysis of histological type of the tumor, the authors came to the conclusion that the biological behavior of STS is different among the histological subtypes and requires further investigation [21].

A number of researchers point out that controversy regarding the prognostic value of the histological type of STS is largely due to the lack of large randomized trials, which, in turn, is complicated by the relative rarity of the tumor [19].

**THE OBJECTIVE:** to study the general and non-recurrent survival of patients with MFH of limbs soft tissues, depending on the tumor's location and the overall survival rate of patients depending on the type of treatment.

#### **OBJECT AND METHODS.**

The research was based on the analysis of the treatment of 130 patients with MFH of limbs soft tissues who were treated at the National Cancer Institute (Kiev) from January, 1995 to December, 2016. The study included 64 (49.2%) males and 66 (50.8%) women. The average age of patients was 55.7 years and ranged from 17 to 75 y.o.

The statistical processing of the results obtained was carried out using the statistical program of medical statistics STATISTICA 6.0. The following statistical methods were used: standard descriptive, parametric and nonparametric. Students' t-criterion was used to assess the reliability of the differences in the expression of the markers examined and other clinical

and pathological parameters. Correlation analysis was performed by calculating Pearson's correlation coefficient. The survival of patients was analyzed by Kaplan-Meier's method, the reliability between the curves - according to the log-rank test. Reliable considered discrepancies at  $p < 0.05$ .

## RESULTS AND THEIR DISCUSSION

A comparative analysis of the overall survival of patients with MFH of limbs soft tissues, taking into account the location of the primary tumor, showed that this indicator varies depending on the localization of the primary process. A year after the treatment, the digital values of overall survival were different, depending on the location of the tumor and were from  $95.6 \pm 4.3\%$  to  $66.7 \pm 15.7\%$ . In the presence of MFH in the thigh's soft tissues this index was  $87.6 \pm 4.1\%$ , the shin's -  $95.6 \pm 4.3\%$ , the shoulder's -  $82.6 \pm 7.9\%$ , the forearm -  $95.4 \pm 6.2\%$ , and the buttocks -  $66.7 \pm 15.7\%$ . Two years later, overall survival was highest at the tumor's localization in the tissues of the forearm ( $86.8 \pm 10.05\%$ ) and the lowest in its the presence in the soft tissues of the buttocks ( $44.4 \pm 16.6\%$ ). One year more, the data indicators decreased significantly and were within the range of  $57.8 \pm 6.2\%$  for MFH of thigh's soft tissues,  $54.6 \pm 10.6\%$  for MFH of low leg,  $58.1 \pm 10.7\%$  for MFH of shoulder's soft tissues,  $78.1 \pm 12.2\%$  for forearm and  $38.9\% \pm 16.2\%$  for the buttocks. The best indicators of overall survival were observed in 84 months in the group of patients with localization of the tumor process in the forearm's soft tissues and worst - with the localization of the pathological process in the buttocks (Fig.1).

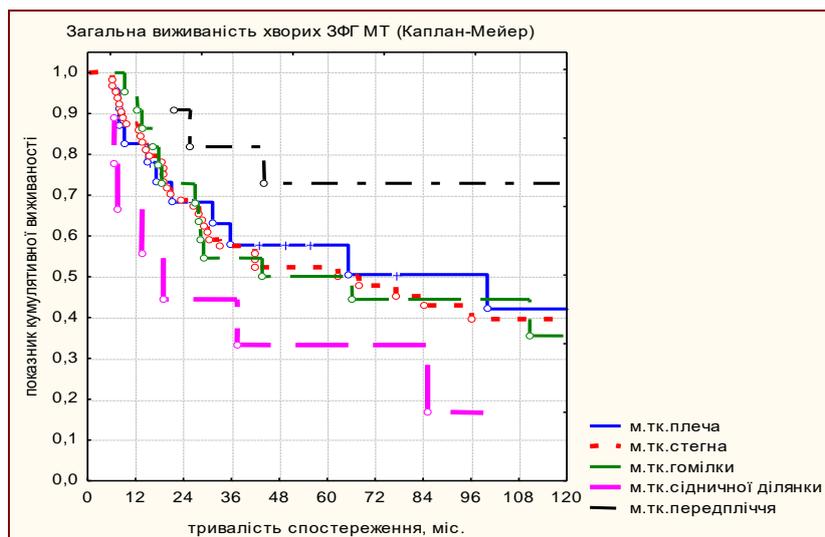


Fig. 1. Graphic representation of the overall survival indices in patients with MFH of soft tissues taking into account the localization of the tumor process (statistical analysis by the Kaplan-Meier 's method)

Indicators of non-recurrent survival at MFH of soft tissues differ significantly depending on the location of the primary tumor. Already in a year after the received treatment they ranged  $72.7 \pm 13.4\%$  for the patients with localization of the process in the forearm's soft tissues and  $22.2 \pm 13.8\%$  for the patients with the buttocks' tumor location. In the case of the thigh's soft tissues defeat the indices of non-recurrent survival were in the range of  $51.6 \pm 6.2\%$ ; if the low legs were damaged the recurrence - free survival constituted  $60.8\% \pm 10.1\%$ , at the location of pathological process in shoulder it was  $55.5 \pm 10.4\%$ . In the course of the year, they constantly decreased and in 24 months, that is, in two years, in thigh's lesion patients the recurrence – free survival was  $31.3 \pm 5.7\%$ , and with the lesion of low leg's soft tissues it was  $34.7 \pm 9.9$ ;  $46 \pm 10.5\%$  at shoulder's damage;  $45.4 \pm 15.0\%$  at forearm's lesion and  $16.6 \pm 12.4\%$  at buttocks' damage. At this time, higher rates of recurrence-free survival were found in shoulder's damaged patients, and not the forearm, as it was in the pre-term observation period. Three years later, these figures are reduced by 87.5 - 59%. \*Thus, with MFH localization in the thigh's ST, recurrence-free survival rate reduces by 68.7% and constitutes  $24.8 \pm 5.4\%$ ; with its localization in ST of the shin it decreases by 79.2% and equals  $20.8 \pm 8.6\%$ , when localized in the shoulder's MT, it is reduced by 63.5% and is within the range of  $36.5 \pm 10.3\%$ , at forearm's location it is reduced by 59.1% and constitutes  $40.9 \pm 14.8\%$ , and with the buttocks' MT damage the recurrence – free survival rate reduces as much as 87.5% and is at the level  $12.5 \pm 10.6\%$ . The best indicators of recurrence-free survival are in the group of patients with localization of the tumor process in the forearm, the worst - in the group of patients with localization of tumors in buttocks' MT. As with the analysis of overall survival rates, the best digital values were in the group of patients with MFH of forearm's ST, the worst - in the group of patients with MFH of buttocks. This tendency is noted in the dynamics of the entire period of observation of recurrence-free survival of the patients under observation.

In five years, a 80.4% impairment of recurrence-free survival in the patients with MFH of thigh's ST was fixed; at the case of low-leg damage it constituted 87%; shoulder - 84.4%; forearm – 67.3% and buttocks - 93%, i.e. indicators of recurrence-free survival throughout the observation period are rapidly decreasing (Fig. 2).

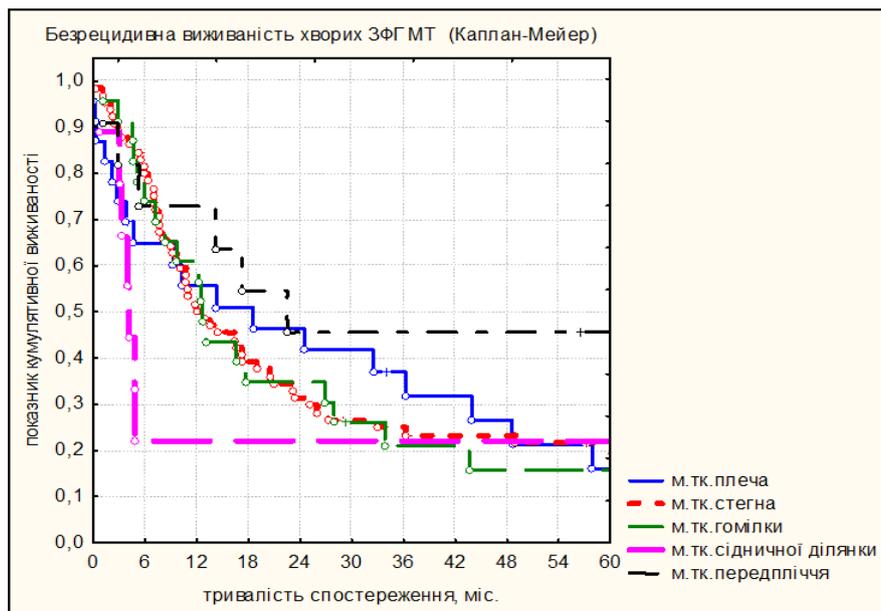


Fig. 2. - Graphic representation of recurrence-free survival in patients with MFH of soft tissues, taking into account the localization of the tumor process (statistical analysis by Kaplan-Meier's method)

In studying the survival of the patients with MFH of soft tissues who were treated for the development of local relapses, compared with recurrence-free patients, it was found that the indicators of cumulative survival in the patients with relapses were significantly lower. According to the data obtained, the development of local relapses affects the indicator of cumulative survival of the patients. Thus, among relapses-free patients, the cumulative survival rate in a year after the treatment was 0.88, while for the patients with recurrences of the disease, it was within the limits of 0.68. During the observation, the survival rate of patients in these subgroups reduced, but there was a significant difference between them (Fig. 3).

In order to evaluate the efficacy of the treatment in patients with recurrent forms of MFH, patients were divided into groups who received only surgical treatment - as an independent method, combined and integrated treatment, with the study of overall survival in each of the groups.

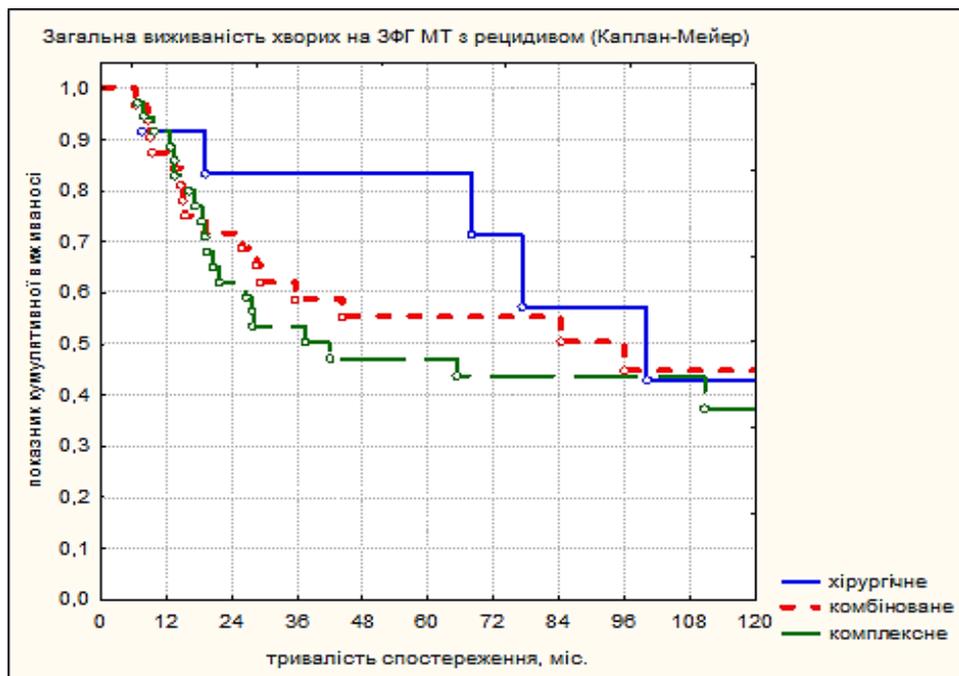
The analysis of overall survival rates was made with the use of Kaplan- Meier's method. It showed that in a year the overall survival rate among the patients after surgical and complex treatment methods were at the same level -  $91.6 \pm 7.9\%$  and  $91.5 \pm 4.6\%$ . After combined treatment the indicators of survival were the lowest and constituted  $87.5 \pm 5.7\%$ .



*Fig. 3.* Graphic representation of survival in MFH soft tissues patients without relapses and in the local relapses patients (statistical analysis by Kaplan-Meier's method)

Two years later, the overall survival rate decreased in all the groups, but with varying intensity. In the patients with surgical treatment only, it decreased by 8.3% from one to two years and amounted  $83.5 \pm 10.7\%$ ; the patients who got a combined treatment it decreased by 15.6% and amounted to  $72.0 \pm 7.9\%$ . The most significant fall of this indicator was noted in the group of complex treatment patients - 29.1%, and constituted  $62.4 \pm 8.2\%$ . Three years later, the overall survival was the best in the group of patients after surgical treatment and constituted  $78.9 \pm 11.8\%$ ; after combined treatment it was at the level of  $59.2 \pm 8.7\%$  and the lowest rate was observed after complex treatment; it amounted to  $53.5 \pm 8.5\%$ . Overall survival after four years of observation decreased by almost 50% in combined and integrated treatment patients, where it amounted to  $55.8 \pm 8.8\%$  and  $47.2 \pm 8.6\%$ , correspondingly. In the group of patients with surgery only, this indicator decreased by 21.1% and was within  $74. \pm 12.8\%$ . The five-year overall survival rate was also highest in patients treated only with surgery and corresponded to  $69.3 \pm 13.7\%$ . In patients who underwent combined treatment it was  $53.9 \pm 8.9\%$  and the lowest rates were in the group of patients who received combined treatment -  $45.5 \pm 8.6\%$ . Further analysis of the general survival data showed that after surgery the survival index maintained the highest for one year more. Later on, overall survival rates turned to be better in combined treatment patients and the worse in patients with surgery only. Then we found features in general survival rate among patients with local recurrences, who underwent different treatment methods. In the first six years after treatment, the indicators of

overall survival are better in the group of patients who underwent only surgery. Later, the best results were fixed in combined treatment group. The parameters of the combined treatment group correspond to the best digital values of overall survival than those of the group where the complex treatment was conducted throughout the whole period of observation, with the exception of the results of one-year survival where the overall survival rate in the groups of patients after surgical and integrated treatment was practically within the same limits -  $91.6 \pm 7.9 \%$  and  $91.5 \pm 4.6\%$ , respectively (Figure 4).



*Fig.4* - Graphical representation of the overall survival rate of patients with SFG MT who had recurrence of the disease depending on the type of treatment (Kaplan-Meier statistical analysis).

The data obtained gave occasion to the analysis of overall survival in patients with recurrences depending on the type of treatment for MFH of limbs soft tissues. In this case as previously all the patients were distributed in three groups according to the treatment method applied. So, the first group consisted of the patients who underwent only surgery, the patients of the second group got combined treatment, and the third group patients had multiple treatment. There were differences between the groups mentioned in the indexes of one-year overall survival. The highest overall survival was fixed in multiple treatment group – it constituted  $90.9 \pm 3.8\%$ ; it was followed by the indicators of combined treatment, which

constituted  $87.6 \pm 4.7\%$ , and the indicators in the group of patients who received only surgical treatment were at the rate  $80.7 \pm 7.7\%$ . Two years after the treatment, the trend in general survival changes somewhat. The best indicators of overall survival we observed in the group of patients who received combined treatment –  $75.1 \pm 6.2\%$ ; it was followed by a group of patients with surgical treatment –  $72.8 \pm 7.7\%$ , and significantly lower indicators were in the group of patients after with complex treatment -  $63.4 \pm 6.5\%$ . The best indicators of three - year overall survival are in the patients underwent surgical treatment –  $64.5 \pm 9.5\%$ ; the indicators in the combined treatment patients were somewhat lower - they constituted  $60.2 \pm 7.0\%$ , and the indicators in the group of patients with complex treatment were the worst -  $54.0 \pm 6.7\%$ . Over two following years, the overall survival rates were the best in the surgical treatment group, while later on these indexes were inferior to those after combined treatment (Fig. 5).

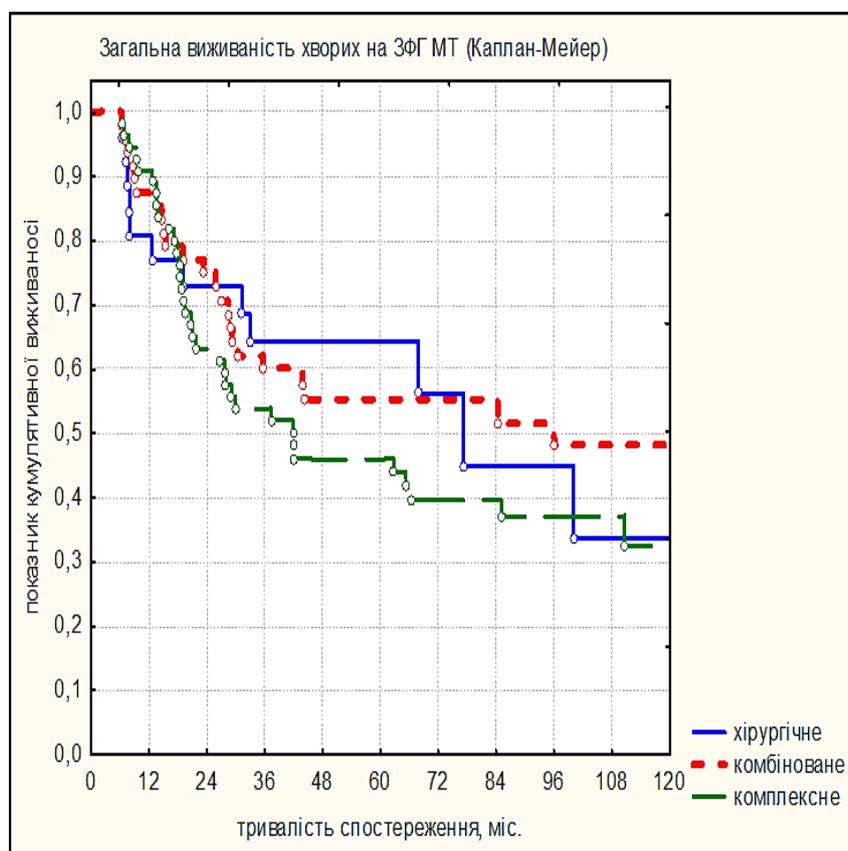


Fig. 5. - Graphic representation of the overall survival of patients with SFG MT depending on the type of treatment (statistical analysis by the Kaplan-Meier method).

#### CONCLUSIONS:

1. Overall survival of patients with malignant fibro histiocytoma (MFH) of low limbs soft tissues depends on the primary tumor location. Indicators of recurrence - free survival significantly differ depending on the tumor localization. The development of local relapses affects the cumulative survival rate of the patients, which is significantly lower in relapses patients than in relapses-free patients.

2. In patients with relapsing forms of ST MFH overall survival is different and depends on the method of treatment. One - year overall survival, after surgical and complex treatment, is at the same level and constitutes  $91.6 \pm 7.9\%$  and  $91.5 \pm 4.6\%$ , respectively; after combined treatment it is slightly lower -  $87.5 \pm 5.7\%$ . For number of the first six years, overall survival rates are better in the surgical treatment patients, and in the subsequent period it is better after combined treatment.

3. Overall survival of MFH patients depends on the method of its treatment. The best one year survival is in the patients who received complex treatment -  $90.9 \pm 3.8\%$ , the indicators after combined treatment are  $87.6 \pm 4.7\%$ , and in the third place are indicators of the patients with surgical treatment -  $80.7 \pm 7.7\%$ . Two years later the best indicators have the combined treatment patients, then a group of patients underwent surgical treatment and significantly lower are the indicators in the group with complex treatment. Later, the surgical treatment indicators are the best, while in time they are inferior to those after combined treatment.

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