

TREATMENT OF PATIENTS WITH METASTATIC OSTEOSARCOMA IN THE LUNGS

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Summary. The analysis of the world approaches in the treatment of patients with osteosarcoma who developed lung metastases after combined treatment of a local tumor was performed. The results of our studies of the effect of second-line systemic chemotherapy and radical surgery in patients with osteosarcoma metastases in the lungs were presented. The results showed that the majority of treated patients showed more than a three-year survival, which indicates the need of radical treatment in this group of patients.

Keywords: osteosarcoma, metastasis of osteosarcoma, a second -line chemotherapy.

According to international standards , patients with osteosarcoma should receive systemic multiagent chemotherapy followed by surgery and adjuvant chemotherapy [1-4]. The multi-mode approach to the treatment of osteosarcoma requires that patients to be treated in a multidisciplinary team that includes professionals such as chemotherapist ,orthopaedic oncologist , thoracic surgeon , pathologist , radiologist , a specialist in rehabilitation. A multi-disciplinary approach provides a treatment that allows to achieve optimal survival and quality of life for patients.

It is believed that the majority of patients with osteosarcoma at the time of initial application or at the end of treatment the primary source, have micrometastases that we not able to find with methods of diagnosis . Thus, micrometastases require systemic therapy . In 40-30 % of patients who received treatment for osteosarcoma bone relapse tumor as distant metastases. For the most patients (90 %) distant metastasis are detected in lungs [5], since this is a target

organ osteosarcoma cells because of their biological ossobenko [6]. Patients with metastatic osteosarcoma demonstrate dramatic as mortality in this group as a result of various research varies between 90 % and 60 % [7-9].

The rapid development of molecular biology makes it possible to understand a lot about the process of metastatic sarcomas . While studying the mechanism of introducing tumor target organs in a number of studies have proved that the recurrent tumor that develops in the form of metastases in distant from the primary chamber body has a slightly different phenotype, which explains its resistance to first line chemotherapeutic treatments [20-21 , 7-8] . Metastases are composed of cell clones which are different from the primary tumors ploidy enzyme profile karyotype and chemosensitivity[22-24 , 9-11] . Therapeutic schema intended for the primary tumor , therefore, unlikely to be successful in treating metastatic disease. Changing the biological behavior of metastatic cells is the result of specific molecular changes. Metastasis is the final and most important step in carcinogenesis of malignant tumors [25]. Metastatic sarcoma cells to perform the following steps for the formation of distant tumor node : 1 - invasion through extracellular matrix and host entry into the circulation , and 2 - to survive in the bloodstream , 3 - stability of the host immune system , 4 - fixing and extravasation in the target organ ; 5 - adhesion 6 - survive in the microenvironment of the target 7 - formation of vasculature for growth in the target organ [26]. Each step is equally important and should be fully completed by tumor cells to achieve the formation of metastases. During this path sarcoma cells , changing its genome exhibit greater stability than the primary focus [27-29] .

Until the end of the 80s there was an opinion that it is not necessary to draw any kind of treatment for patients with re-emerged metastasis of osteosarcoma. To date, aware of the fact that the re-emergence of recurrent sarcoma in the lungs after treatment is not a contraindication for further treatment . Modern studies have shown that the conduct of combined treatments for recurrent tumors as discovered again demonstrates the effectiveness with a median survival of 33.9 months

(without signs of the disease from 3 to 179 months) [17]. This indicates that the patient needs the radical treatment, whenever possible.

Effective treatment for recurrent osteosarcoma requires local and systemic therapy. Local therapy consists of surgical treatment, which is aimed to radically remove the tumor or radiation therapy, which is a palliative method. Systemic therapy aimed at the elimination of tumor cells throughout the body, and includes chemotherapy. Combination therapy system combined with local treatments allows to maximize the patient's chances for recovery.

Historically speaking, the usefulness of the radical treatment of patients with metastatic osteosarcoma in lungs has been proven by researchers in the 70s, when after the removal of all lesions in the lung disease-free survival at 3 years in 30% of patients was achieved. Even in patients with repetitive relapses, the successful local treatment may achieve long-term remission, that has been proven by researchers from Italy [6]. A large number of publications and numerous studies prove the effectiveness of radical treatment in this group of patients. For patients with pulmonary metastases of osteosarcoma combination of radical metastasectomy and chemotherapy is the way to improve the long-term results or even potentially cure.

Debated is the question of holding only surgical treatment, or a combination of chemotherapy and surgery to remove lesions in the lungs. For example, researchers from Norway is shown in 60 patients with metastatic osteosarcoma in an easy 5-year overall survival rate of 50% of patients with a combination of chemotherapy and metastasectomy, and in 24% - using surgery alone [34]. Also for combination therapy for metastatic relapse osteosarcoma lung were scientists Institute Rizzoli (Italy), in the observation of 162 patients with metastases, the 5-year overall survival of the patients showed 53% with a combination treatment, and 12% - surgery alone [12]. Research carried out by the Italian scientists noted the overall five-year survival rate of 40% of patients with the use of neoadjuvant chemotherapy, surgery and adjuvant chemotherapy. Also, a group of U.S.

researchers said (2005) that the detection of metastases in the lungs of patients with osteosarcoma to perform surgical treatment of lung , followed by adjuvant chemotherapy. The result of this study showed the overall five-year survival rate of 35 % [9].

While analyzing the literature on the surgical removal of lung metastases of osteosarcoma there is no doubt about the need to implement this method. Many authors have provided data about the surgery as an independent method of treatment of osteosarcoma remote metastasis [7, 29, 35 , 36]. Yet comparing the data of current research (Table) it can be argued that only the combination of chemotherapy and radical surgical procedures can achieve high life expectancy in patients with relapsed metastatic osteosarcoma to the lungs. The use of chemotherapy in the treatment of metastases in patients with poor pathomorphosis (less than 90% by Huvos) in primary care, of course, doubtful and disputable. It is proved that poor pathomorphosis is a poor prognostic factor in the treatment of primary tumors and in the treatment of patients with relapsed metastatic bone sarcoma lung [39]. There is no consensus on the effectiveness of the use of second-line chemotherapy, as well as the standard of care for patients with osteosarcoma relapse [8]. This was the first aim of our study - to show the efficacy of second-line therapy in combination with surgical methods of removing osteosarcoma lung metastases.

Table. The results of treatment of patients with metastatic osteosarcoma to the lungs according to the Cooperative Osteosarcoma Study (COSS)

	No of patients	All (N = 576)				P
		2-year survival		5-year survival		
		Overall	Event-free	Overall	Event-free	
All patients	576	0.38	0.02	0.23	0.02	
Chemotherapysecond line						
Yes	381	0.41	0.03	0.25	0.02	.089
No	173	0.33	0.04	0.22	0.03	
Typesofdrugs						
Platinumagents	304	0.42	0.03	0.26	0.03	
Topo II inhibitors	228	0.44	0.03	0.28	0.03	
Alkylators	173	0.40	0.04	0.22	0.03	
Anthracyclines	69	0.34	0.06	0.20	0.05	
High-dosemethotrexate	53	0.42	0.07	0.20	0.06	
Carboplatin + etoposide	205	0.42	0.04	0.27	0.03	
Radiotherapy						
Yes	58	0.14	0.05	0.05	0.03	.0002
No	501	0.41	0.02	0.26	0.02	

It is proved that the shorter is the period between the end of treatment and detection of recurrence of the tumor, the worse is the prognosis long-term results [17]. Analysis of data from 1,700 patients with osteosarcoma in the study Cooperative Osteosarcoma Study (COSS) showed that the longest period after treatment to recurrence of the tumor was 14.3 years [25].

While studying the problem of metastatic osteosarcoma, our attention was focused on the study of risk factors for metastasis schemes for second-line systemic chemotherapy, the use of methods of local influence, the study of disease-free and overall survival.

In a retrospective analysis of the materials of the National Cancer Institute noted : five-year overall survival in patients with metastatic lung disease who were treated from 1994 to 2002 was 4 %. Such low rates are probably due to lack of treatment algorithm in this group of patients , the lack of criteria for the selection of patients according to risk factors and indications for a radical special treatment.

As shown in a retrospective analysis of the majority of cases (84%), the detection of metastases in the lungs, the patient received symptomatic treatment.

MATERIALS AND METHODS

In the period from 1998 to 2013, 240 patients with localized osteosarcoma of the extremities from various locations were receiving combination therapy according to the accepted standard treatment of sarcomas of bone at the National Cancer Institute. The protocol includes: neoadjuvant chemotherapy –cisplatin 120 mg/m², doxorubicin 60 mg/m², methotrexate 12 mg/m²; radical surgical removal of the tumor with reconstruction of the joint; adjuvant chemotherapy according to therapeutic pathomorphosis of tumor: a good response, we used the same drugs , but in mono, in low - intensified chemotherapy ifosfamide 9 mg/m², etoposide 150 mg/m² [2, 4, 5, 10, 13, 30].

In the diagnosis in this group of patients, binding methods were: CT scan of the chest cavity and the primary lesion, the histological verification.

After completion of chemotherapy, all patients are subject to monitoring, which includes the obligation to perform CT of the chest and abdomen, x-ray of primary affected area every 3 months for the first year, every 6 months - the second year, in a subsequent once every year.

In the course of follow-up in 89 patients revealed metastases in the lungs. Median follow-up from the end of the treatment of metastasis was 22 months (6-38 months). In 86 (96.6 %) showed bilateral pulmonary involvement, 3 patients (3.4%) - one-sided . Metastases to the lung tissue is ascertained on the basis of X-ray data. Evaluation of the CT scan of the chest in the dynamics (Fig. 1), followed by a comparison of the morphological analysis (Fig. 2) in the material of the remote nodes.

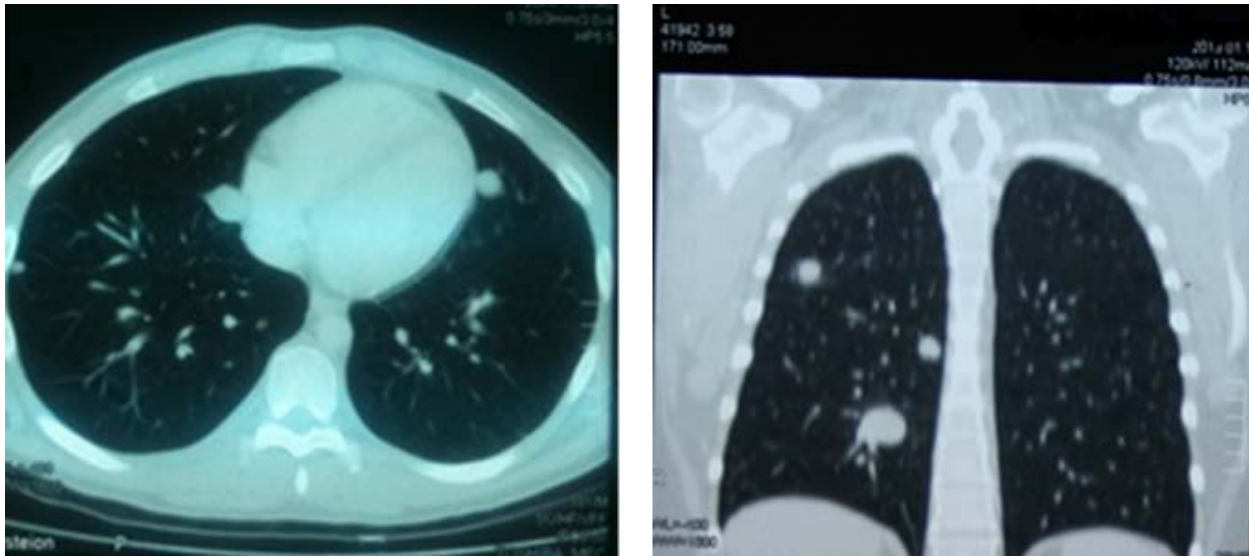


Fig. 1. CT-imaging of metastatic osteosarcoma in lung

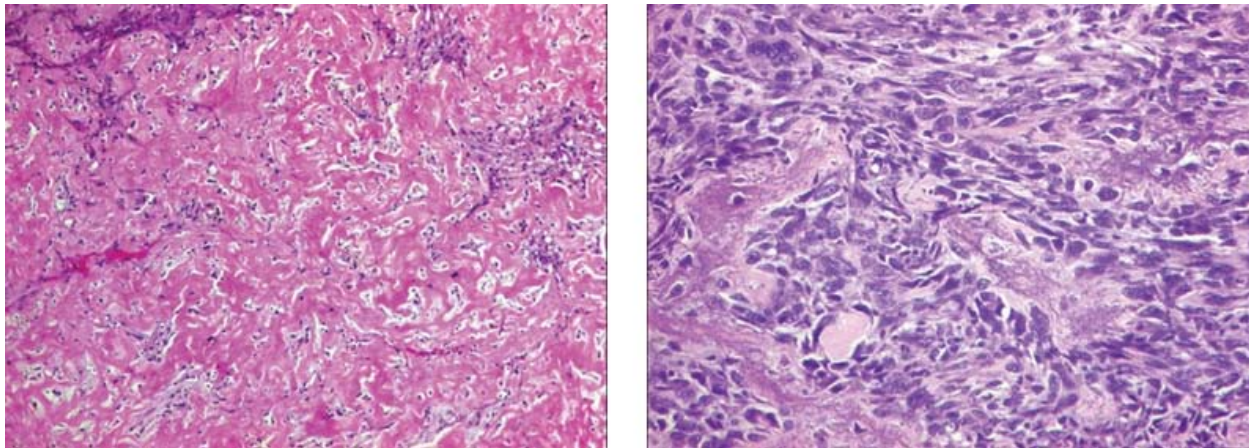


Fig. 2. Photomicrographs of metastatic osteosarcoma

All patients started treatment with neoadjuvant chemotherapy: carboplatin 600 mg/m^2 (300 mg/m^2 - 2 days), etoposide 300 mg/m^2 (150 mg/m^2 - 2 days) - 1st and 3rd blocks, ifosfamide 9 g/m^2 (3 g/m^2 per day with mesna 4 g/m^2 - 4 days), etoposide, 300 mg/m^2 (150 mg/m^2 for 2 days) - 2nd block 21 day intervals [27]. After 3 courses conducted CT control with the assessment of response to chemotherapy and the decision together with the specialist thoracic surgical oncology, about the possibility of surgical treatment in the amount of resection of lung tumor.

RESULTS AND DISCUSSION

Of the 240 patients treated at the National Cancer Institute with the osteosarcoma of extremity with stage IIB, 89 were diagnosed with metastases in the lungs. All patients underwent 3 blocks of second-line chemotherapy. The stabilization process after chemotherapy, which was shown to stop the growth in the already identified sites and the absence of new, was achieved in 61 patients (68.5 %). In 28 (31.5 %) on the results of CT scan was noted the appearance of new metastases (Fig. 3).

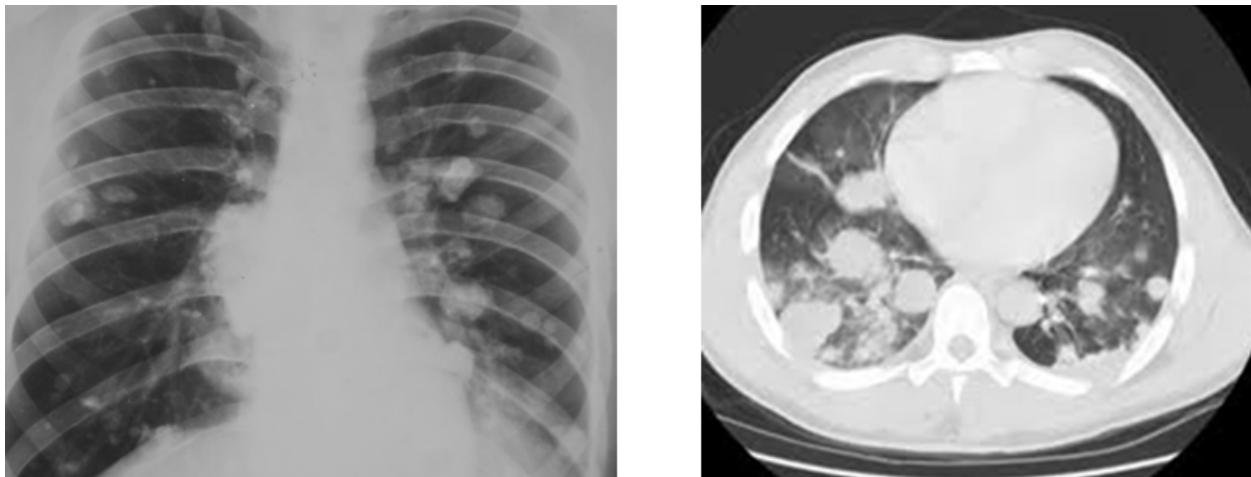


Fig. 3. Progrission metastatic process in patient K., 25 y.

The first group comprised 29 patients who, after three chemotherapy cycles underwent radical removal of the lung tumor nodules (Fig. 4). In 3 patients had previously revealed unilateral lung node, and 26 - metastatic nodes were identified in two ways. In case of bilateral lesions, 3 patients underwent one-stage bilateral lung resection. The remaining 23 patients, surgical resection was performed with an interval of 10-14 days.

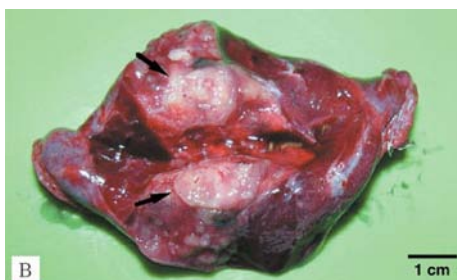


Fig. 4. Macropreparations remote node osteosarcoma with lung

The second group included 60 patients who were considered inoperable for one of two reasons: because of the progression of the disease or the inability to remove all metastases. This group of patients received palliative radiation therapy to the lungs to ODS 30 Gy .

Overall three-year survival rate of patients in both groups was 12.3 % in the group with surgery - 35.6 %, non- surgical treatment - 1.6 % ($p < 0.05$) (Fig. 5) . In patients who died of disease progression , the median survival from the time of detection of recurrence was 10 months. Of these, 85 % of patients died in the first year and 12% - in the second, and 3% - third.

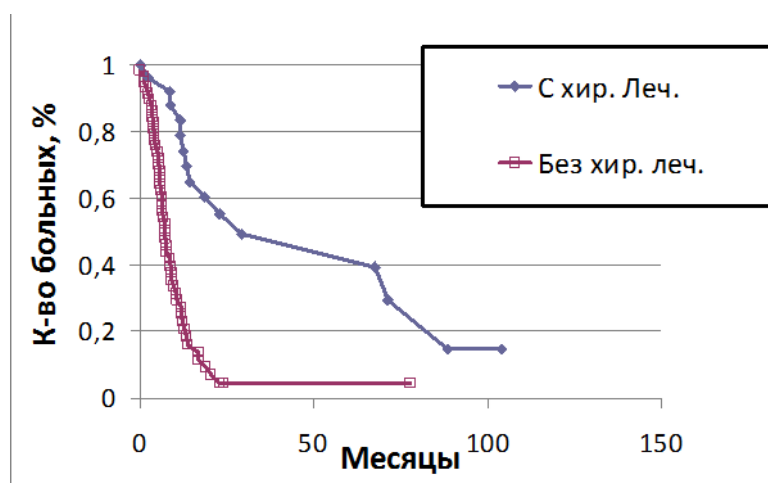


Fig. 5. Survival of patients with metastatic osteosarcoma by treatment

A direct correlation between the survival of patients on the number of metastatic nodes and the length of remission before metastasis. In the study, only 27% of patients survived for three years with more than two nodes metastatic lung , whereas a 3-year survival rate of patients diagnosed with not more than two tumor nodes was 46 % . Patients whose relapse was recorded in the period up to 1 year after the end of treatment showed the worst three-year survival rate , which was 16% in patients with metastases over a period of 2 years of a three-year survival rate was 41%.

CONCLUSIONS

The appearance of recurrence of osteosarcoma in the form of distant metastases in the lungs after combined treatment is an indication for radical special treatment. The usefulness of the treatment in this group of patients proved life expectancy and a high percentage of positive responses to the treatment. Most of the treated patients experience a three-year milestone. The data presented in many international studies give reason to say that patients with recurrent metastatic osteosarcoma in the lungs have a high potential to a complete cure. The study established risk factors for metastasis. It is proved that there is a high probability of metastasis in patients with poor pathomorphosis of primary bone tumor, and they are at risk . These data are necessary for the development of new methods and the means used in the adjuvant treatment of patients with sarcomas of the skeleton. There is a direct dependence of survival on the number of diagnosed tumor nodules and the duration of the interval between the end of primary treatment and before the relapse. The appearance of more than two metastatic sites in the lung during the first year of observation is extremely unfavorable factor for long-term results .

Analyzing the data of worldwide research and taking into account our own experience , we can conclude that the problem requires more study, because there is no consensus on the effectiveness of second-line chemotherapy, priority of treatment (surgery or chemotherapy). Also, the success of the treatment of this pathology is still an individualization of treatment, the criteria for which to date have not been developed . All these unresolved issues come up against us for more research to development of new approaches in the treatment of patients with osteosarcoma .

Undoubtedly , the success of treatment and long-term outcomes of patients with relapsed osteosarcoma in form of the lungs metastasis depend on how radical removal of lesions in the lungs, but the main treatment for this group of patients is still a combination of second-line chemotherapy of surgical techniques with local control . Our study demonstrates the highest three-year survival rate (35.6 %) in

patients with relapsed metastatic osteosarcoma with the successful use of this combination of methods specific treatment.

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