



## Isolated Limb Perfusion – A Single Center Experience

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### Abstract

**Introduction:** Isolated limb perfusion is a method of locoregional treatment of tumors in the upper and lower extremities with high doses of chemotherapeutic agents that are delivered to the tumor in conditions of hyperthermia with the intention to keep the maximum drug concentration in the tumor and minimize systemic effects.

**Aim:** The aim of our study was to analyze the initial results and responses of patients to isolated limb perfusion as a surgical intervention and to show the justification of performing this procedure in carefully selected patients.

**Material and Methods:** This retrospective study was conducted at the Clinic for Surgical Oncology of the Institute for Oncology and Radiology of Serbia. The study included 42 patients who underwent isolated limb perfusion procedure with the cytostatic melphalan in the period from 2015 to 2021.

**Results:** The number of females included in the study was 27 (64.3%) and the number of males 15 (35.7%). The average age of patients was 57 (16-77) years. Isolated perfusion of the lower extremity was performed in 35 (83.3%) patients, while the upper extremity was treated in 7 (16.7%) patients. The total number of patients who had a good response to the procedure was 27 (69.2%), while 12 (30.8%) did not respond to isolated perfusion. 70.6% of patients with advanced and/or recurrent melanoma and 61.1% of patients with advanced soft tissue sarcoma had a positive treatment outcome. Patients with aggressive fibromatosis responded well in 100% of cases.

**Conclusion:** Isolated limb perfusion is an effective therapeutic option for well-selected patients with locoregional advanced disease. This procedure can successfully treat both locally advanced and recurrent melanomas and soft tissue sarcomas, as well as patients with aggressive fibromatosis.

**Keywords:** Isolated limb perfusion; Melanoma; Soft tissue sarcomas; Aggressive fibromatosis

### Introduction

Isolated extremity perfusion is a method of locoregional treatment of tumors on the upper and lower extremities with high doses of chemotherapy agents (cytostatics) that are delivered to the tumor under conditions of hyperthermia with the intention of keeping the maximum concentration of the drug in the tumor and minimizing the systemic effect of the drug [1]. This method involves the vascular isolation of a specific anatomical part of the limb followed by intra-arterial perfusion with heated cytostatics, whereby by combining the synergistic effect of hyperthermia and high doses of chemotherapy agents, a higher concentration of cytotoxic drugs is achieved, and thus a better effect of therapy compared to systemic application, as well as a reduction in systemic absorption medicine [2]. Isolated extremity perfusion is a method that has found its application in locoregional therapy of well-selected patients with tumors of soft tissues and skin who do not have disease outside the extremity [3].

The indications for this procedure are: potentially resectable locally advanced sarcomas, where the method is applied as a neoadjuvant therapy in order to shrink the tumor and enable better surgical options; recurrent sarcomas; potentially resectable multiple in transit melanoma metastases or multiple melanoma recurrences localized only on the extremity; palliative therapy of unresectable soft tissue and skin tumors in order to avoid limb amputation [3,4].

General limitations for performing isolated limb perfusion are: Extension of the disease beyond the limb on which perfusion is performed; infiltration of major blood vessels to be cannulated; previous radiotherapy of the region; poor general condition of the patient and anesthesiological ineligibility for the procedure [3].

The aim of our study was to analyze the initial results and patient responses to isolated limb perfusion and demonstrate the justification of performing this procedure in carefully selected

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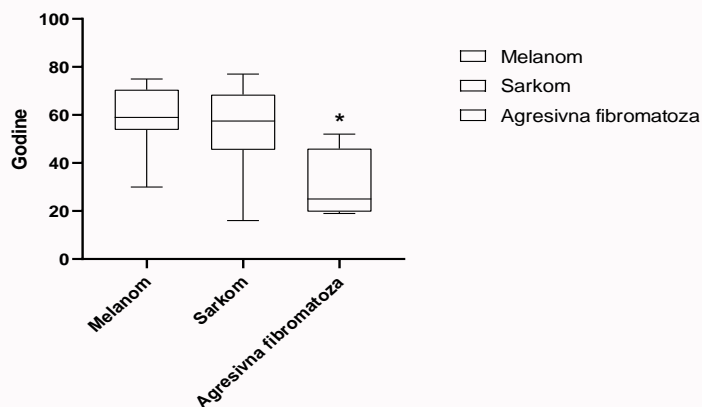
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**Figure 1:** Age of patients in relation to tumor type.  
\* p<0.05 compared to both groups

patients.

## Materials and Methods

This is a retrospective cohort study that was conducted at the Clinic for Oncological Surgery of the Institute of Oncology and Radiology of Serbia. The study included patients who underwent the procedure of isolated extremity perfusion with the cytostatic Melphalan in the period from 2015 to 2021. A total of 42 patients were included in the study. The data were collected from the electronic database of the Institute of Oncology and Radiology of Serbia. The following were taken from the data: 1) basic demographic data on gender and age; 2) definitive histopathological findings; 3) tumor localization (upper, lower extremity); 4) response to surgical treatment. The response to the applied treatment was evaluated clinically and radiologically (MR/CT) at the first postoperative control, which was in the period of 6 to 20 weeks after the intervention, through the terms "partial regression", "complete remission" and "stable disease".

### Statistical analysis

Data were analyzed using parametric and non-parametric statistical methods. Descriptive parameters of observed characteristics are given as arithmetic mean, standard deviation, median and Interquartile Range (IQR), nominal values of observed characteristics are shown as absolute frequencies (%). Mann-Whitney U test and Kruskal-Wallis test were used for continuous non-parametric data. Categorical data were analyzed using the Chi-square test and the Fisher exact test. Those tests where the probability of the null hypothesis was less than 0.05 were considered statistically significant. The statistical software package IBM SPSS 26 was used in data processing.

## Results

The demographic characteristics of the patients are given in Table 1. The average age of the patients who underwent the isolated perfusion procedure was 57 (16-77) years. The number of female patients was 27 (64.3%), and the number of male patients was 15 (35.7%).

The ages of the patients in the different groups are given in Table 2. There is a statistically significant difference in age between patients treated for aggressive fibromatosis and patients treated for melanoma and sarcoma (p<0.05) (Figure 1). There is no statistically significant difference in age between patients in terms of gender, response to therapy and tumor type (melanoma/sarcoma).

**Table 1:** Demographic characteristics of patients.

Age	
x ± sd; median (min-max, IQR)	54.67 ± 16.86; 57 (16-77, 25)
Gender	
Male (n(%))	15 (35.7)
Female (n(%))	27 (64.3)

**Table 2:** Age of patients in different groups.

	Age	P
	x ± sd, median (min-max, IQR)	
Gender		
Male	49.60 ± 18.24; 57 (16-72, 33)	0.222
Female	57.48 ± 15.69; 57 (19-77, 22)	
Type of tumor		0.026
Melanoma	58.94 ± 13.76; 59 (30-75, 17)	
Sarcoma	55.70 ± 16.27; 57.5 (16-77, 23)	
Aggressive fibromatosis	30.25 ± 14.98; 25 (19-52, 33)	
Response to treatment		0.578
Yes	59.50 ± 9.96; 57 (43-77, 16)	
No	53.26 ± 18.53; 57 (16-75, 29)	

**Table 3:** Tumor characteristics in relation to HP findings and localization.

	N (%)
Melanoma	18 (42.9%)
Sarcoma	20 (47.6%)
Aggressive fibromatosis	4 (9.5%)
Upper extremity	35 (83.3%)
Lower extremity	7 (16.7%)

Tumor characteristics are given in Table 3. Out of the total number of patients, 20 (47.6%) were operated on for sarcoma, of which the most were those with liposarcoma (9.5%), malignant peripheral nerve sheath tumor (7.1%) and angiosarcoma (7.1%) (Figure 2). 18 (42.9%) patients were operated on for melanoma, and 4 (9.5%) patients were treated for aggressive fibromatosis. Isolated perfusion of the lower limb was performed in 35 (83.3%) patients, while isolated perfusion of the upper limb was performed in 7 (16.7%) patients.

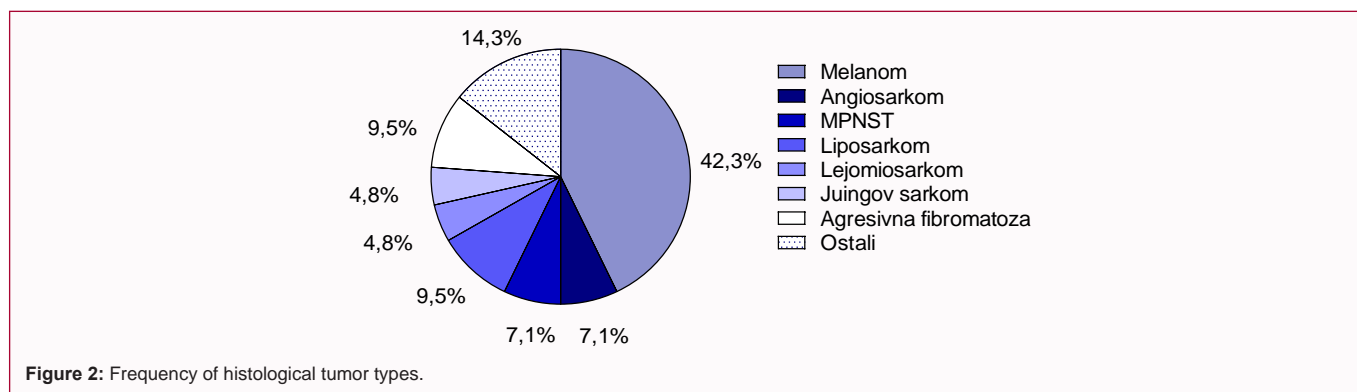


Figure 2: Frequency of histological tumor types.

Table 4: Response to treatment in relation to tumor type and location.

		Response to treatment		In total
		Yes	No	
TUMOR	Melanoma	12 (70.6%)	5 (29.4%)	17
	Sarcoma	11 (61.1%)	7 (38.9%)	18
	Aggressive fibromatosis	4 (100%)	0 (0%)	4
EXTREMITY	Lower Extremity	24 (75%)	8 (25%)	32
	Upper Extremity	3 (42.9%)	4 (57.1%)	7

Assessment of response to isolated perfusion in relation to tumor type is given in Table 4. 27 (69.2%) patients had a good response to the procedure, and 12 (30.8%) patients did not respond to surgical treatment. In the group of patients with melanoma, 12 (70.6%) patients responded, and 5 (29.4%) patients did not. In patients with sarcoma, 11 (61.1%) patients had a positive treatment outcome, and 7 (38.9%) did not respond to the procedure. All patients treated for aggressive fibromatosis responded well to surgical treatment (100%).

There is a significant difference in the response to surgical treatment in relation to tumor localization, which can be seen in Table 4. A total of 24 (75%) patients who were treated for lower extremity disease responded successfully to treatment, while 8 (25%) patients who also had a tumor on the lower extremity did not respond to surgical intervention. As for patients with tumors on the upper extremities, 3 of them (42.9%) achieved remission, while 4 of them (57.1%) did not respond to therapy.

A total of 18 out of 25 (72%) women responded well to treatment, compared to men there is no statistically significant difference, 9 out of 14 (64.29%) of them had a good response to isolated limb perfusion.

## Discussion

Comparing the age structure of the patients, the values in our group of patients with sarcoma (57 years) are not significantly different compared to the studies done by Neuwirth et al. [5] (56 years) and Grunhagen et al. [2] (54 years). Regarding patients with recurrent and/or advanced melanoma, the values in our group (59 years) are lower compared to the study done by Schellerer et al. [6] (63 years). In the group of patients with aggressive fibromatosis, the age difference between our study (25 years) and the study by van Broekhoven et al. [7] (28 years) is not significant. Comparing the structure of patients according to gender, there is a significant difference in the gender distribution in our study (female 64.3%; male 35.7%) and the study by Neuwirth et al. [5] (female 48%; male 52%).

According to a study by Neuwirth et al. [5] the frequency of

soft tissue sarcoma in relation to HP finding (malignant fibrous histiocytoma 21%; liposarcoma 16%; synoviosarcoma 11%; leiomyosarcoma 7%) was different in relation to the frequency of soft tissue sarcoma in our study (liposarcoma 20%; myxofibrosarcoma 15%; angiosarcoma 15%; leiomyosarcoma 10%).

The success of the procedure in patients with advanced sarcomas in our study (61.11%) is slightly lower compared to the study by Neuwirth et al. [5] (72%) and Cherix et al. [8] (67%). In relation to the study of Mullinax et al. [9] (58%) and Hayes et al. [10] (53%) there is a slightly higher success rate of the procedure in our study of patients with sarcoma (61.11%).

The positive response in patients with melanoma in our study (70.59%) is slightly lower compared to the studies by Schellerer et al. [6] (90%), Dossett et al. [11] (80%) and Tulokas et al. [12] (77%). A possible explanation for the different response of melanoma to therapy can be found in the studies of Moreno-Ramirez et al. [13] and Rossi et al. [14] that show better results and response to therapy in the treatment of melanoma with the joint application of the cytostatics Melphalan and Tumor Necrosis Factor (TNF) compared to the mono-application of Melphalan. Our group of melanoma patients who were successfully treated (70.59%) is slightly higher than the number of patients who were successfully treated for melanoma in the study by Martin-Tellez et al. [15] (64.1%).

The success of isolated limb perfusion in patients with aggressive fibromatosis in our study (4/4, 100%) is higher compared to the success of the study by Lev-Chelouche et al. [16] (5/6, 85%).

## Conclusion

Isolated limb perfusion is an effective therapeutic option for patients with locoregionally advanced disease. Locally advanced and recurrent melanomas and soft tissue sarcomas, as well as patients with aggressive fibromatosis, can be successfully treated with this procedure. This type of treatment should be offered to well-selected patients, taking into account their disease stage, comorbidities and

overall prognosis.

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