



## Resection or radiofrequency ablation of colorectal liver metastasis

### Resekcija ili radiofrekventna ablacija metastaze kolorektalnog karcinoma u jetri

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#### Abstract

**Background/Aim.** Liver resection is the treatment of choice for solitary colorectal liver metastases in suitable candidates. Recently, radiofrequency ablation (RFA) has become a very popular procedure in the treatment of liver metastases. The aim of this study was to compare outcomes in patients with solitary colorectal liver metastasis who had been subjected to resection or ablation. **Methods.** In this retrospective study we analyzed and compared patients with solitary colorectal liver metastases treated by resection or ablation in the University Hospital Centre “Dr Dragiša Mišović” in Belgrade from January 2002 until December 2009. **Results.** In this study 94 (67.1%) patients underwent resection whereas 46 (32.9%) patients underwent RFA. Most of the resected patients (59.6%) required major hepatectomy. The median follow-up time was 28.4 months. Tumor abla-

tion was a significant predictor of the overall survival ( $p = 0.002$ ; OR 3.75; 95% CI 1.696–8.284). Our study demonstrated longer disease free-survival in the group of resected patients compared to the RFA group (37.6 *vs* 22.3 months,  $p = 0.073$ ). The median overall survival was 56.3 months for patients who underwent resection *vs* 25.1 months for those in the RFA group ( $p = 0.005$ ). **Conclusion.** This study shows that the patients with solitary hepatic colorectal cancer metastases should be considered for hepatic resection whenever it is feasible, because this procedure provides superior long-term survival as compared to radiofrequency ablation.

#### Key words:

colorectal neoplasms; digestive system surgical procedures; liver neoplasms; neoplasm metastasis; catheter ablation, treatment outcome.

#### Apstrakt

**Uvod/Cilj.** Hirurška resekcija jetre predstavlja metod izbora u lečenju pojedinačnih metastaza kolorektalnog karcinoma u jetri kod odgovarajućih bolesnika. Radiofrekventna ablacija postaje sve popularnija metoda za lečenje metastaza u jetri. Cilj ove studije bio je da uporedi ishode bolesti kod bolesnika sa pojedinačnom metastazom kolorektalnog karcinoma u jetri koji su lečeni hirurškom resekcijom u odnosu na bolesnike koji su lečeni radiofrekventnom ablacijom (RFA). **Metode.** U ovoj retrospektivnoj studiji analizirani su bolesnici sa pojedinačnom metastazom kolorektalnog karcinoma u jetri koji su lečeni u KBC „Dr Dragiša Mišović“ u Beogradu u periodu od januara 2002. do decembra 2009. godine. Poređeni su ishodi bolesti nakon hirurške resekcije jetre i nakon RFA metastaza u jetri. **Rezultati.** Studijom je bilo obuhvaćeno 94 (67,1%) bolesnika podvrgnutih resekciji jetre, dok je 46 (32,9%) bolesnika lečeno radiofrekventnom ablacijom. Kod većine

bolesnika (59,6%) podvrgnutih hirurškoj resekciji učinjena je *major* hepatektomija. Prosečna dužina praćenja bolesnika bila je 28,4 meseca. Utvrđeno je da RFA tumora predstavlja značajni prediktor dužine ukupnog preživljavanja ( $p = 0,002$ , OR 3,75, 95% CI 1,696–8,284), te da je duže preživljavanje bez tegoba bilo u grupi bolesnika sa resekcijom u poređenju sa RFA grupom (37,6 *vs* 22,3 meseca,  $p = 0,073$ ). Prosečno ukupno preživljavanje iznosilo je 56,3 meseca u grupi bolesnika sa hirurškom resekcijom naspram 25,1 mesec u RFA grupi ( $p = 0,005$ ). **Zaključak.** Kod odgovarajućih bolesnika sa pojedinačnom metastazom kolorektalnog karcinoma u jetri trebalo bi razmotriti hiruršku resekciju kad god je to izvodljivo, jer pruža duži period preživljavanja nego lečenje radiofrekventnom ablacijom.

#### Ključne reči:

kolorektalne neoplazme; hirurgija digestivnog sistema, procedure; jetra, neoplazme; neoplazme, metastaze; ablacija preko katetera; lečenje, ishod.

## Introduction

Colorectal cancer (CRC) remains one of the leading causes of mortality caused by malignancy. Approximately 25% of all colorectal cancer patients at the time of initial diagnosis already have liver metastases, and additionally 50% will develop distant metastases in the next 5 years<sup>1</sup>. Treatment of colorectal cancer patients with metastases on the liver is a therapeutic challenge and requires multidisciplinary treatment. Nevertheless, surgery is the treatment of choice for these patients. Survival data shows that with modern, multidisciplinary treatment, 25–60% of patients with liver resection to treat CRC metastases survive more than 5 years<sup>2–7</sup>. The goal of operation is to remove all metastatic tumor tissue with acceptable resection margins. Some studies show that narrow margins do not have influence on survival, and that complete removal of metastases with minimal margins can be acceptable when it is not possible technically to obtain wider margins<sup>8–10</sup>. Due to the importance of liver disease reduction in cases with metastases that cannot be resected, new methods of local treatment of metastases are developed, among which is radiofrequency ablation (RFA). RFA uses thermal energy produced by radiofrequency generator to destroy tumor and a small part of surrounding healthy tissue<sup>1, 3, 4, 11</sup>. The five-year survival rate after RFA in different studies ranges from 14% up to 27%<sup>1, 3, 5, 11–13</sup>.

## Methods

The study is a retrospective analysis of patients with solitary CRC liver metastases treated with RFA or surgical resection, in the University Hospital Centre “Dr Dragiša Mišović” in Belgrade, from January 2002 until December 2009. Metastases are considered resectable when it is possible to remove the tumor with negative resection margins, leaving functionally sufficient liver tissue. The patients with extrahepatic metastases are excluded from this study. RFA was performed with open approach after laparotomy to all patients in this group, and the criteria for RFA were unresectability of metastases and comorbidity (accompanying diseases and conditions), which significantly increased the risk of liver re-

section. Data about chemotherapy were not known for all the patients, and for most were not reliable, so these were not considered in this study. The patients treated with RFA were compared with the patients treated by liver resection by using *t*-test,  $\chi^2$ -test and Fisher's exact test where appropriate. Statistical analysis was performed by using JMP 4.0 and SPSS version 16 software. Continuous variables were compared using Student's *t*-test, and categorical variables were compared by using  $\chi^2$ -test. The survival was plotted by Kaplan-Meier method, and compared using the *log-rank* test. A value  $p < 0.05$  was considered significant. The overall survival was calculated from the moment of diagnosis until death. Cox regression method was used in order to establish independent predictors of disease outcome. Multivariate analysis was performed with the Cox's proportional hazards model.

## Results

A total of 140 patients with solitary CRC liver metastases were indentified from the database of operated patients in the University Hospital Centre “Dr Dragiša Mišović” in Belgrade within the period from January 2002 until December 2009. The median follow-up time was 28.4 months. The median age of the patients was 62.9 years, among which were 74 (52.9%) male and 66 (47.1%) female patients.

Primary tumor localization was mostly on the left colon and rectum, and most often localization was the sigmoid colon with 32.9%, then cecum and ascending colon with 31.4%, the rectum with 21.4%. In 10% of the patients, primary localization was unknown. Most of the patients had locally advanced primary tumor, 72.9% with T3 stage, and 60% of the patients had regional lymph nodes metastasis during the initial operation of the colon. Synchronous metastases in the liver were seen in 66 (47.1%) of the patients (Table 1).

Liver metastases were resected in 94 (67.1%) of the patients, while in 46 (32.9%) of the patients RFA was performed. The majority of resected patients (59.6%) underwent major hepatectomy. The most often anatomic resection was right hepatectomy (29.8%) then left hepatectomy (12.8%) and extended right hepatectomy (12.8%). Extra-anatomic “wedge” resections were represented with 12.8% (Table 2).

Table 1

Primary and metastatic tumors characteristics		
Tumor characteristics	n	%
Depth of primary tumor invasion		
T1	2	1.4
T2	10	7.1
T3	102	72.9
T4	12	8.6
unknown	14	10.0
Primary tumor localization		
cecum and ascending colon	44	31.4
transverse colon	4	2.9
descending colon	2	1.4
sigmoid colon	46	32.9
rectum	30	21.4
unknown	14	10.0
Lymph node involvement (N1)	84	60.0
Synchronous primary tumor and metastasis	66	47.1

Most of the patients (89.4%) had R0 resection, with the median resection margin of 1.8 cm.

Table 4

Type of liver resection		
Type of resection	n	%
Right hepatectomy	28	29.8
Left hepatectomy	12	12.8
Extended right hepatectomy	12	12.8
Extended left hepatectomy	4	4.3
Central liver resection	2	2.1
Left lateral segmentectomy	10	10.6
Right posterior segmentectomy	6	6.4
Resection of one segment	8	8.5
Wedge resection	12	12.8

Comparing the patients with RFA and those with resection showed no significant difference regarding sex ( $p = 0.632$ ), age ( $p = 0.992$ ) and lymph node involvement ( $p = 0.368$ ) in these two groups. The patients in the resection group had significantly larger metastases in the liver (5.5 cm in relation to 3.85 cm in the RFA group,  $p = 0.004$ ) (Table 3).

The median disease free survival was 37.6 months for the group of resected patients, and for the RFA group it was 22.3 months ( $p = 0.073$ ). The median overall survival was 56.3 months for the resected patients, while for the RFA group it was 25.1 months ( $p = 0.005$ ). There were no significant predictors of recurrence using univariate analysis. Age, T-stage, N-stage, resection margins, size of metastasis and RFA individually did not affect the recurrence rate (Table 4).

Local recurrence predictors

Factor	Univariate $p$ -value
RFA vs resection	0.07
Metastasis size	0.092
Lymph node involvement (N1)	0.20
Age	0.557
Gender	0.544
Tumor invasion (T-stage)	0.663
Primary tumor localization	0.910
Resection margin	0.569

RFA – radiofrequent ablation.

The significant difference regarding a shorter overall survival period in the RFA group was established using multivariate analysis ( $p = 0.002$ ; OR 3.75; 95% CI 1.696–8.284). Age, T-stage, N-stage, resectional margin and size of metastasis did not individually affect the overall survival period (Table 5).

From the RFA group 16 (34.8%) patients developed local intrahepatic recurrence. In 6 (13.0%) of the patients, recurrence was on the ablation site or its margin. In the group of resected patients, 12 (12.8%) patients developed local intrahepatic recurrence ( $p = 0.026$ ). One of them had recurrence on the resection area. There were no significant differences in the occurrence of extrahepatic metastases between the RFA and the resection group (21.7% and 18.9%, respectively;  $p = 0.2$ ).

There were no significant differences in the postoperative complications rate ( $p = 0.35$ ) between the two groups. In the group of resected patients, 23 (48.9%) had complications

Table 3

Demographics and tumor characteristics of the patients

Characteristics	RFA	Liver resection	$p$ -value
Gender (male), (%)	52.2	51.1	0.632
Age (years)	62.2	60.8	0.992
Size of liver metastases (cm)	3.8	5.5	0.004
Lymph node involvement (N1), (%)	52.17	63.83	0.368
Depth of primary tumor invasion (T-stage)			0.11
T1	0	2	
T2	2	8	
T3	34	68	
T4	4	8	
unknown	6	8	
Synchronous metastasis (%)	43.48	48.94	0.627

RFA – radiofrequent ablation.

Table 5

Overall survival predictors

Factor	Univariate $p$ value	Hazard ratio	95% CI
RFA vs resection	0.006	2.5	1.3–4.8
Age	0.407		
Gender	0.558		
T stage	0.995		
Primary tumor localization	0.946		
Resection margin	0.330		
Size of metastasis	0.975		
Lymph node involvement (N1)	0.842		

RFA – radiofrequent ablation; CI – Confidence interval.

of any kind, while in the RFA group, 18 (39.1%) of the patients had complications. Nevertheless, complications in the RFA group were minor, mostly prolonged fever, while in the group of resected patients major complications were registered. There was one (1.1%) postoperative death in the group of resected patients. A patient with metastasis size  $6 \times 7$  cm, located between the right and the middle hepatic vein, underwent extended right hepatectomy. Because of liver bleeding, the patient was reoperated after 18 h, and adequate hemostasis was accomplished. On the fourth postoperative day the patient died from massive myocardial infarction. In the RFA group, there was no postoperative mortality.

## Discussion

Surgical resection of CRC liver metastases is not possible for many patients despite indisputable improvement of surgical technique<sup>14, 15</sup>. The main limiting factors are anatomic localization of metastases, functionally insufficient remnant liver, extensive comorbidity or the presence of extrahepatic metastases<sup>16</sup>. Resection could not be performed in cases of metastases invading the portal vein, hepatic artery or the cava vein, or the portal vein thrombosis<sup>17</sup>. Several studies show that patients with unoperated liver metastases have a low 5-year survival rate<sup>12, 15</sup>. Patients with CRC liver metastases treated only with chemotherapy have poor prognosis with the approximate median survival of 21 months, despite its enormous improvement<sup>2</sup>. The most usual cause of death is the progression of liver illness, leading to liver insufficiency.

Some patients are not ideal candidates for the liver solitary metastases resection, even though that is the method of choice. Furthermore, the incidence and severity of complications after RFA are more acceptable to surgeons than those after resection of the liver. These factors have, among others, increased popularity of RFA in treatment of liver metastases. Despite its attractiveness, RFA can give worse results than resection to patients that could be operated<sup>3</sup>.

We tried to establish if there is a significant difference in the outcome for patients with solitary CRC liver metastases, treated by resection or RFA. Our data show that resection of the liver is superior to RFA. Therefore, we believe that resection of CRC liver metastases remains the method of choice for solitary lesions on the liver. Due to patients who are not suitable candidates for hepatectomy, new "less invasive" methods for treatment of liver metastases are promoted. One of the most popular methods is thermal ablation of metastases using radiofrequency power. During previous few years, RFA was suggested as alternative for surgical resection for patients with CRC metastases on the liver. In 2003, Oshowo et al.<sup>4</sup> published that the 3-year survival was 55% for patients with solitary metastases in the liver that were resected, while in the group where solitary metastases were treated by RFA, survival was 53%. In that study, RFA was used only for patients considered unsuitable for surgical resection. This selection was made in our study as well, because surgical opinion in our hospital is that CRC liver metastasis resection has to be done whenever it is possible, and

RFA is reserved for patients with non-resectable metastases, or have other severe accompanying diseases that significantly increase the risk concerning extensiveness of liver surgery.

Our study showed a longer disease free survival in the group of resected patients comparing to the RFA group (37.6 vs 22.3 months, respectively;  $p = 0.073$ ). Many factors are related with higher risk of recurrence after treatment of CRC metastases in the liver. Most commonly described factor is the size of metastases. In our study, the size of metastases was significantly larger in the group of resected patients than in the RFA group. A recent study has shown that the incidence of local recurrence increases by 33% after RFA of metastases larger than 3 cm<sup>2</sup>. Aloia et al.<sup>5</sup> have analyzed patients with solitary colorectal metastases in the liver and compared patterns of local recurrence after hepatectomy and RFA. They have established that RFA was associated with the high (37%) incidence of local recurrence, unrelated to the size of metastases, and with shorter disease-free survival and survival period. Our study showed a significantly higher incidence of local recurrence in the group of patients with RFA (34.8%), compared to the resection group (12.8%). A recurrence rate after RFA in our study was similar to those published in recent studies<sup>5, 11</sup>. Unfortunately, repeated treatment of local recurrence with RFA is often impossible or unsuccessful<sup>12, 18</sup>. That is the reason why we believe that resection of the liver should be offered to all patients with resectable CRC liver metastases.

We found no significant differences between the two groups of patients in characteristics of primary tumor, including depth of tumor invasion (T-stage), involvement of lymph nodes (N-stage) or synchronicity of metastases. Despite similarities between the two groups in traditional predictors of survival, liver resection showed significantly better results. The only statistically significant predictor of the overall survival was the type of treatment (resection or RFA). The differences in the disease-free survival and the overall survival between the resected and RFA patients cannot be explained by differences in demographic characteristics, characteristics of primary tumor, characteristics of metastases or other perioperative factors. That proves oncological superiority of resection comparing to RFA.

Abdalla et al.<sup>3</sup> have published a retrospective analysis of patients with CRC liver metastases submitted to resection, RFA or a combination of these two methods. They have shown a 4-year survival of 65% in the group of resected patients, while in the RFA group it was 22%. Interesting fact is that this percent in the group of patients submitted to both resection and RFA was only 36%. These data show that RFA individually, or in combination with resection, does not provide the length of survival comparable with that after resection of the liver in treatment of CRC liver metastases. RFA was used in treatment of solitary metastases localized on the places impossible to leave a negative resection margin. In their study, there is a statistically significant difference in survival between patients submitted to resection and those submitted to RFA ( $p = 0.025$ )<sup>3</sup>. These data support our results that the median

survival of the patients in the resection group is significantly longer than in group treated with RFA.

There are certain limitations of our study. Firstly, this is a retrospective study with some unknown data. Secondly, resection was done to our patients wherever it was possible, leaving RFA for unresectable metastases or for those with seriously damaged health by comorbidities. It is possible that those factors contributed to the difference in the duration of survival. Finally, not all the patients in this study were treated by chemotherapy, and those who were did not receive identical protocols, and we did not have data about chemotherapy of a certain number of patients. Therefore, the con-

clusions of this study should be interpreted with some caution.

### Conclusion

Patients with solitary CRC liver metastases should be considered for surgical liver resection whenever it is feasible, because it provides a long-term survival compared to treatment with radiofrequency ablation. This study promotes aggressive resection of solitary liver metastases, because RFA is associated with a shorter disease free-survival and a shorter overall survival.

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Received on June 28, 2012.

Revised on September 8, 2012.

Accepted on December 5, 2013.