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Factors Influencing Recurrence Rate and Survival of Patients with Colorectal Metastases after Liver Resection

Stefan Petrovski[1,2]*, Aleksandar Serafimov[1,2], Ljubica Adzi-Andov[1,3], Elena Joveva[1,2], Marija Karakoleva[1,2], Ilija Milev[1,2]

[1]Faculty of Medical Sciences, Goce Delcev University, Shtip, Macedonia; [2]Clinical Hospital Shtip, Shtip, Macedonia; [3]Specialized Hospital for Gynecology and Obstetrics Dr. Organdziski, Shtip, Macedonia

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***Correspondence:** Stefan Petrovski, MD, PhD, Associate Professor of Surgery, Faculty of Medical Sciences, Goce Delcev University, Clinical Hospital Shtip, Shtip, Macedonia. E-mail: stefan.petrovski@ugd.edu.mk
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Abstract

BACKGROUND: Early recurrence implies low percentage of long survival, whereas the opportunity for re-resection in selected patients represents optimal treatment with long survival. The total 5-year survival rate after hepatectomy is up to 50%, with a number of factors that are independent clinical predictors of long survival.

AIM: This study aims to analyze the patient's data from the clinic of general and hepatobiliary surgery in Aleksandrovska Hospital in Sofia, Republic of Bulgaria, in the treatment of patients with colorectal metastases of the liver and to determine the survival factors in those patients.

MATERIALS AND METHODS: A retrospective study was conducted between of January 1st, 2006 and December 31st, 2015. A total of 239 patients were included: 179 patients were treated with radical operation, 5 with palliative intervention, while 55 operative explorations were performed.

RESULTS: The type and the extent of resection do not affect the occurrence of local recurrence. The size, number, and metastase localization do not affect the occurrence of intrahepatic recurrence but showed characteristics of significant predictors in cumulative and mean survival.

CONCLUSION: Metastases type, number and localization and metastases in lymphatic nodes and other organs were determined as predictors of long survival of patients with colorectal metastases after resection.

Introduction

Early recurrence of colorectal metastases in the first 6 months after liver resection is 22.8%, while total recurrent rate is 72%. There are a number of factors that have influence on early recurrence as R1 resection, extra-hepatic metastatic disease (EHD) before hepatectomy, and positive lymph nodes after primary tumor resection [1]. Synchronous metastases and multiple lesions represent independent clinical predictors of early recurrence [2]. Overall survival (OS) and disease-free survival (DFS) in multiple studies were >40% and >30%, respectively [3], [4]. The size of potentially resectable colorectal liver metastases (CRLM) has been studied as a prognostic factor, but the findings are inconclusive [5]. CRLM >3 represents an independent prognostic factor with low survival percentage [6]. Bilobar distribution of colorectal metastases remains disputed and in some studies is determined as a bad prognostic factor, while in others has no effect on survival [7].

Materials and Methods

A retrospective study was conducted between January 1st, 2006 and December 31st, 2015. A total of 239 patients were included: 179 patients were treated with radical operation, 5 with palliative intervention, while 55 operative explorations were performed. The follow-up period of the patients operated on for CRLM in the Clinic was 5 years after resection of the liver. The study included all patients with liver metastases from colorectal carcinoma (CRC) regardless of their age and gender; the study included all patients with liver metastases from CRC: Synchronous metastases, metachronous metastases, and metastases appearing with local recurrence of cancer; Exclusion criteria were patients who did not meet inclusion criteria and patients who refused to participle in the study. The endpoints were to determine the factors for long survival in patients with CRLM after liver resection. Statistical analysis of the collected material to determine the factors for survival was done using the SPSS-19 statistical program.

Table 1: Distribution of resection type in patients with local recurrence (Chi-square test)

Variable	Recurrence		p
	Yes	No	
Type of operation			
Atypical resection	5	24	
Resection of 2 segments	1	17	
Resection of 3 segments	2	6	
Resection of>3 segments	0	3	
Left lobectomy	2	11	
Left hemihepatectomy	0	3	
Right hemihepatectomy	0	11	
Metastasectomy	4	7	
Resection+other procedure	3	11	
Scope of operation according to the number of resected liver segments			
Large	7 (12.07)	51 (87.93)	0.11[a]
Small	14 (23.33)	46 (76.67)	

[a]Chi-square test

Results

In 118 patients with CRC, included in the study there is no medical documentation for previous liver resection. In 21 patients (17.8%) a recurrence was diagnosed and re-resection was performed.

Local recurrence is often seen after atypical resection or metastasectomy, but it does have statistical value. Therefore, it can be concluded that the type and scope of resection do have statistical significance on the risk of occurrence of local recurrence (p=0.11) (Table 1). Other factors, such as type, size, number, localization, and preoperative values of CEA do not have a significant influence on the rate of recurrence after liver resection (p = 0.99) (Table 2).

Table 2: Influence of different factors in the occurrence of local recurrence of colorectal carcinoma after liver resection

Variable	Recurrence (%)		p
	Yes	No	
Number of liver metastases			
1	9 (17.65)	42 (82.35)	0.99[a]
2–4	8 (18.18)	36 (81.82)	
>4	4 (17.39)	19 (82.61)	
Biggest metastases (cm)			
<5	12 (21.82)	43 (78.18)	0.4[a]
≥5	8 (15.38)	44 (84.62)	
Metastases localization			
Unilateral	12 (14.63)	70 (85.37)	0.17[a]
Bilateral	9 (25)	27 (75)	
Other organ metastases			
No	17 (17)	83 (83)	0.73[a]
Yes	4 (23.53)	13 (76.47)	
CEA			
Mean±SD	156.6±288.9	64.19±141.8	0.84[d]
Median (IQR)	24.54 (4.03–184.97)	25.82 (6.4–90.9)	

[a]Chi-square test, [d]Mann–Whitney test, **$P<0.05$. CEA: Carcinoembryonic antigen, SD: Standard deviation, IQR: Interquartile range.

The analyses of CRC patients' – resectable and non-resectable, showed mean OS of 31.4 months and medial survival of 22 months. Cumulative survival in the 1st year is 79.6%; 25.9% in the 3rd year and 19.2% in the 5th year (Table 3), while 5-year cumulative survival (Kaplan–Mayer) is shown in Figure 1.

Table 3: Cumulative survival in colorectal carcinoma patients

Survival	Cumulative survival % (SE)		
	1 year	3 year	5 year
Overall survival	80 (0.029)	25.9 (0.03)	19.2 (0.025)

SE: Standard error.

We have analyzed a number of factors that have an influence on the survival of patients with CRC. The identification of the significant predictors in determining the risk of lethal outcome is extremely important for the optimal selection of patients for surgical treatment and the selection of an appropriate surgical strategy.

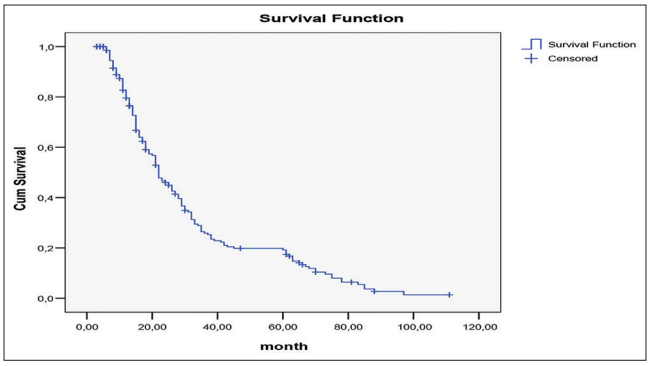

Figure 1: Cumulative survival of patients with colorectal metastases of the liver after resection

A comparison of the group with synchronous metastases showed that 76 (80%) were diseased, while in the group of metachronous metastases a number of 93 patients (82.3%) were diseased.

The mean survival in patients' group with synchronous metastases was 26.097 months, while patients with metachronous metastases had a mean survival of 35.699 months. The medial survival in both groups was 18 and 26 months, respectively. There is statistically significant difference in the survival of patients with synchronous and metachronous metastases. p = 0.008 and p = 0.002, respectively. CRC patients with metachronous metastases have significantly longer survival (Table 4 and Figure 2).

Table 4: Cumulative survival analysis of patients with synchronous and metachronous metastases

Type of metastase	Egzitus, n (%)	Cumulative survival % (SE)		
		1 year	3 year	5 year
Synchronous	76 (80)	73.7 (0.07)	17.1 (0.04)	12.8 (0.04)
Metachronous	93 (82.3)	84.3 (0.035)	32.6 (0.047)	24.1 (0.034)

SE: Standard error.

Cox regression analysis showed that hazard ratio – Exp (B) for liver metastases has a confidence interval (CI) 1.4995 (1.098–2.022) and p = 0.01, so the risk of lethal outcome in patients with synchronous metastases is about 1.5 times higher than those with

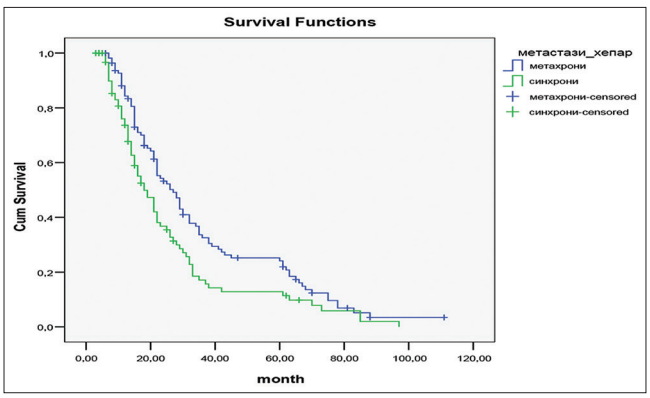

Figure 2: Survival curve depending of type of liver metastases, log rank (Mantel-Cox) p = 0.008, Breslow p = 0.002***

metachronous metastases. These results clearly show that the type of liver metastases in CRC patients is a significant prognostic factor of survival.

Another prognostic factor that we analyzed was the presence of lymph node metastases and EHD. Mean survival in groups with and without regional lymph node metastases and extrahepatic metastases was 23.7 months and 35.6 months, respectively, and has shown to have a statistical significance (p < 0.00001) (Figure 3).

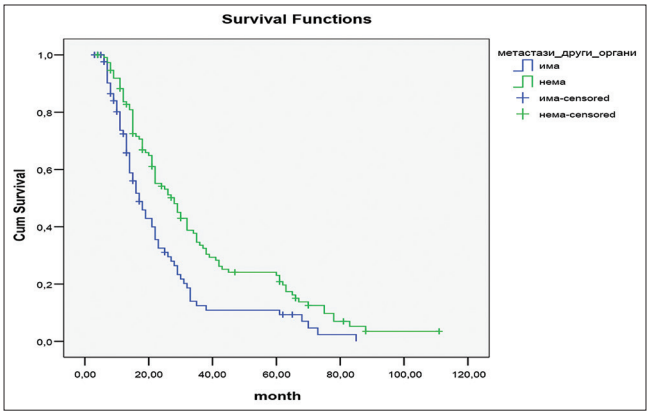

Figure 3: Survival curve depending of presence of other organ metastases, log rank (Mantel-Cox) p = 0.001, Breslow p < 0.0001

The presence of metastases in other organs was confirmed as a significant predictor of survival (p < 0.001). The value of HR 1.715 95% (1.25–2.354) has shown that the presence of metastases in the locoregional lymph nodes and extra-hepatic metastases increases the risk of lethal outcome to 70.6%.

In terms of the number of liver metastases, the least lethal outcomes were registered in the group of patients who had one lesion–66.23%. In the group of patients with 2–4 metastases, 86.96% had lethal outcome, while in the group who had more than 4 lesions 93.55% had lethal outcome. The shortest mean survival had the group with more than 4 lesions (23.6 months), while the longest mean survival was registered in the group of patients with solitary liver lesion (40.6%) (Table 5). The difference in the survival of the three groups is statistically significant (p = 0.001), which determines the number of metastases as a significant predictor for survival. The results are confirmed using the log-rank and Breslow tests, and also regression analysis (Figure 4).

Table 5: Cox regression analysis of the influence of the number of metastases on survival

Number of metastases	p	exp (B)	95% CI for exp (B)
Referent category–solitary lesion			
2–4 metastases	0.043*	1.475	1.013–2.149
>4 metstases	<0.0001	2.02	1.382–2.951

CI: Confidence interval. *p<0.05

The values for Hazard ratio, as shown in Table 5, suggest that patients who had 2–4 lesions are at 1.5 higher risk of lethal outcome, while in the group of patients with more than 4 lesions the risk is 2× times higher, than patients with a solitary liver lesion.

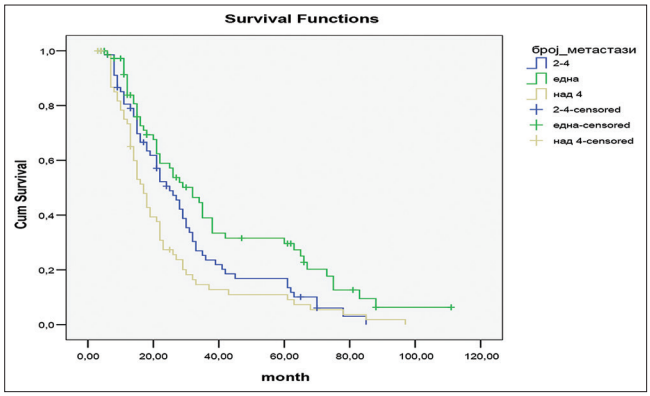

Figure 4: Survival curve in relations to number of liver metastases, log rank (Mantel-Cox) p = 0.001, Breslow p = 0.001

With follow-up on the long-term results of the treatment, a lethal outcome was observed in 72.73% of the CRC patients with unilateral localization, while in the group with bilateral distribution, 92.045% of the patients had a lethal outcome. The mean survival in the group of patients with lesions in two liver lobes is shorter than those with one-lobe localization (22.599 vs. 38.608, respectively). The difference in survival was statistically significant (p < 0.0001) (Figure 5).

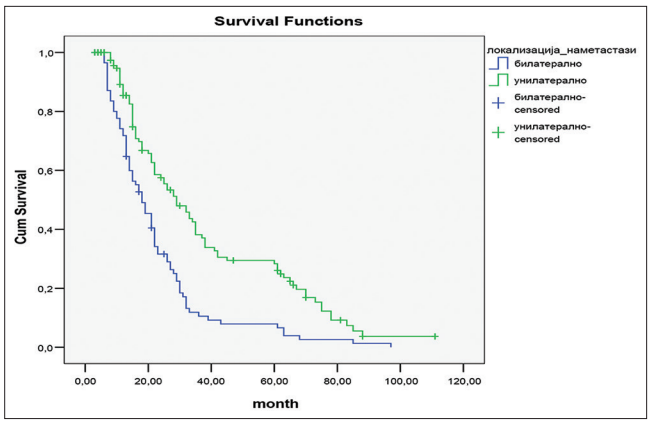

Figure 5: Survival curve in relation to metastases localization, log rank (Mantel-Cox) p < 0.0001, Breslow p < 0.0001

Regression analysis determined the location of metastases as a significant prognostic factor of survival (p < 0.0001). The value of the hazard ratio was 1.999 CI 95% (1.468–2.722) shows that the risk of lethal outcome

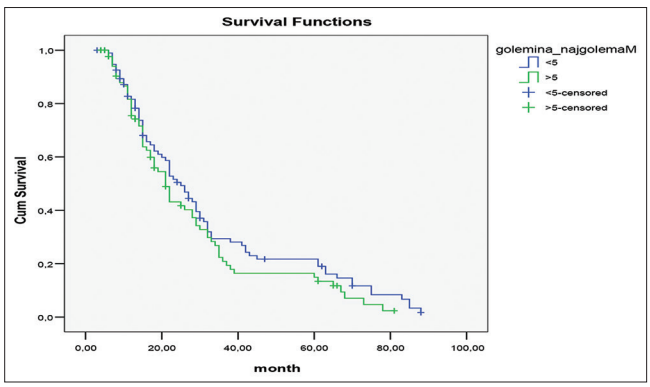

Figure 6: Survival curve in relation to the size of the biggest liver metastasis, log rank (Mantel-Cox) p = 0.212, Breslow p = 0.34

is 2× times higher in the group of patients with bilobar distribution. Liver metastases size analysis showed that mean survival is longer (32.708 months) in the group of patients with the biggest metastasis below 5 cm, in relation to the group of patients who had the biggest lesion of more than 5 cm. That difference in survival was shown as statistically significant (Figure 6).

Discussion

The recurrent rate after liver resections of colorectal metastases is above 67%, while re-resection represents an optimal treatment in patients with resectable recurrence, with 5-year survival up to 70.2% versus 24.0%, respectively [8]. The ability for oncological R0 (negative marginal status) resection represents the golden standard in building surgical strategy for hepatectomy and lower rate of recurrence, while the ability for R1 resection should be considered in patients with not enough residual parenchyma or in the need of multiple resections [9]. Resection type and extension were not singled out as factors with significant influence on the presence of local recurrence, but it was more often observed in the group of patients with atypical resection and metastasectomy (p = 0.11). As a factor of influence in early recurrence were shown number of metastases and the presence of EHD, while carcinoembryonic antigen (CEA) showed characteristics of independent clinical predictors for early recurrence [10], [11]. Atypical resection is the most common technique used in surgical practice (43%) and there is no difference in long-term survival in patients with R0 or R1 resection, while the type of resection does not seem to be factor of influence in survival [12]. In our study, the number of metastases, size, uni or bilobar localization, and presence of EHD and CEA were not determined as independent predictors of local recurrence. 5-year median and OS were 28.9 versus 28.8 months, respectively, for patients with local recurrence. The time of presence from primary resection and localization of metastases are known to be prognostic factors for survival [13]. In our study, OS is 31.2 months, while 5-year survival is 19.2%. In the group of patients with synchronous metastases, the 5-year survival was 12.8%, while the group of metachronous metastases had 24.1% survival; the type of metastases was shown as an independent predictor for survival (p = 0.008 and p = 0.002, respectively). The difference in differentiation between synchronous and metachronous metastases is disputable; in analysis of a larger number of patients it is determined that 1-year survival of 41.8% versus 49.9%, respectively, while 5-year survival was 6.2% versus 13.2% [14]. There is no clear clinical distinction between the type of metastases and survival of patients after resection or other treatment [15]. In the era of modern chemotherapy, 5-year survival of patients after resection is increased [16]. The OS after liver resection of colorectal metastases and DFS varies in different studies, >40% and >30%, respectively [3], [4]. In other studies, as factors of long-term survival were determined by the size of the biggest metastasis >4 cm, preoperative blood transfusions, postoperative major complication, positive marginal status, and KRAS mutation [3]. Ercolani *et al*. [17] report that the total volume of the metastases of the liver has a greater impact on survival than the number or location of the metastases. In our study, the size of the biggest metastasis (>5 cm) did not show any characteristics as factor of prediction (p = 0.223). The total diameter and the number of metastases (MDN) ≥30 represent a negative prognostic factor for survival [18]. In the group of patients with solitary metastasis, the longest survival was shown – 40.5 months, while the shortest was in the group of patients who had more than 4 metastases – 23.6 months, which determines the number of metastases as an independent predictor for survival (p = 0.0001). Tomlinson *et al*. [19] report for 5-year and 10-year survival of 29% and 25%, respectively, in patients with bilateral resection. Bilateral localization of CRC liver metastases was shown to be a significant survival predictor (p = 0.0001). Adam *et al*. [20] analyzed 46 patients from a total of 763, who had liver resection for colorectal metastases, with perihepatic regional metastases, including portal, ciliac, and retroperitoneal lymph nodes. They report of 5-year survival of 18% with lymph node metastases, compared with 53% without lymph node metastases. The presence of locoregional lymph node metastases after liver resection was shown as a predictive factor (p = 0.0001), also the presence of EHD was a significant survival factor (p = 0.001). There are number of factors, prognostic models, and clinical scores, their application has a significant role in patients selection, who would have benefit and long-term survival after liver resection.

Conclusion

Metastases type, number and localization, and metastases in lymphatic nodes and other organs were determined as predictors of long survival of patients with colorectal metastases after resection.

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