

Original article

PROGNOSTIC FACTORS AFFECTING SURVIVAL OF PATIENTS AFTER LIVER RESECTION DUE TO COLORECTAL LIVER METASTASES

ПРОГНОСТИЧКИ ФАКТОРИ КОИ ШТО ВЛИЈААТ НА ПРЕЖИВУВАЊЕТО НА ПАЦИЕНТИ ПОСЛЕ РЕСЕКЦИЈА НА ЦРНИОТ ДРОБ ПОРАДИ КОЛОРЕКТАЛНИ МЕТАСТАЗИ

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Abstract

Introduction. Colorectal liver metastases have a poor prognosis and only 2% have an average 5-year survival if left untreated. In recent decades there has been a development in the diagnosis, treatment and palliative treatment of patients with colorectal liver metastases, and despite radical resection the average five-year survival is between 25% and 44%.

Aim. To explore the experience of the Clinic in the treatment of colorectal liver metastases, comparing it with data from the literature and based on the comparison to determine the prognostic factors that affect survival after radical surgical treatment of patients.

Methods. A retrospective study was conducted at the Clinic of General and Hepato-pancreatic Surgery at the University Hospital "Aleksandrovska"-Sofia. The study comprised the period between 01.01.2006 to 31.12.2015. It included a total of 239 cases, of whom: 179 patients underwent radical interventions, 5 palliative and 55 patients underwent explorative interventions due to liver metastases. Clinical and pathological materials were analyzed using SPSS-19 to determine the prognostic significance of a number of factors in relation to the survival: gender, age, type and localization of metastases, postoperative stage of the primary tumor, type and volume of liver resection, extrahepatic metastases, preoperative values of CEA, postoperative values (AST, ALT).

Results. Factors that correlated with lower survival type: metastases (synchronous or metachronous), localization of metastases (uni-or bilobar), presence of the regional lymph node metastases and metastases to other distant organs and the impossibility of radical resection of liver were statistically significant with multivariate analysis. Elevated preoperative value of CEA, the value of

hemoglobin and stage IV disease also affected the survival of patients.

Conclusion. In patients with colorectal liver metastases only resection has potentially curative character. The surgical strategy for resection in context of increasing the percentage of patients with resectable potential is the only possible factor for long-term survival.

Keywords: colorectal metastases, radical resections, prognostic factors, survival, stage of the disease

Апстракт

Вовед. Колоректалните метастази на црниот дроб имаат лоша прогноза и само 2% имаат средно 5-годишно преживување ако не се лекуваат. Во последните неколку декади се забележа развој во дијагностицирањето, лекувањето и палијацијата на пациенти со колоректални метастази на црниот дроб, но и покрај радикалната ресекција средното петгодишно преживување е помеѓу 25% и 44%.

Цел. Да се проучи искуството на Клиниката во лекувањето на колоректални метастази на црниот дроб, споредувајќи ги со податоците од светската литература, и врз основа на тоа да се определат прогностичките фактори кои што влијаат на преживувањето после радикално хирушко лекување на пациентите.

Методи. Во клиниката по општа и црнодробно-панкреатична хирургија во УМБАЛ "Александаровска"-Софија е направено ретроспективно проучување помеѓу 01.01. 2006 до 31.12.2015, вклучувајќи 239 случаи претставени во Табела 1, подложени соодветно на 179 радикални интервенции, 5 палијативни и 55 експлоративни по повод колоректални метастази на црниот дроб. Клиничкопатолошкиот материјал се анализираше со помош на SPSS-19, за да се определи прогностичката значајност во однос

на преживувањето на редица фактори: пол, возраст, тип и локализација на метастазите, постоперативен стадиум на примарниот тумор, тип и обем на ресекцијата на црниот дроб, екстрахепатални метастази, предоперативни вредности на СЕА, постоперативни вредности на (AST, ALT).

Резултати. Фактори кои што корелираат со пониско преживување се типот на метастазите (синхрони или метахрони), локализацијата (уни- или билобарни), присуството на метастази во регионалните лимфни жлезди и во други далечни органи како и неможноста за радикална ресекција на црниот дроб се статистички значајни со мултиваријантната анализа. Покачени предоперативни вредности на СЕА, вредноста на Hgb и IV стадиум на болеста исто така имаат влијание на преживувањето на пациентите. **Заклучок.** Кај пациентите со колоректални метастази на црниот дроб само ресекцијата има потенцијално лечебен карактер. Хирушката стратегија за ресекција во контекст на зголемувањето на процентот на пациенти кои имаат ресектабилен потенцијал е единствен можен фактор за долгогодишно преживување.

Клучни зборови: колоректални метастази, радикални ресекции, прогностички фактори, преживување, стадиум на болеста

Introduction

Colorectal cancer CRC is the third most common cancer worldwide after lung cancer and breast cancer [1,2]. A large percentage of 50-70% of patients develops colorectal liver metastases (CRLM) because of hematogenous dissemination of primary cancer [3-7]. Synchronous metastases are diagnosed in 15-25% [8-10] during the primary diagnosis of CRC and in 20-25% [11-15] in

the first five years metachronous metastases develop. They represent the most common cause of death caused, so that 77% of untreated patients die in the first year, and only 14-23% survive more than three years [16-19]. Surgical resection represents the only curative treatment approach to patients with CRLM; in larger series patients treated with resection have a mean 5-year survival from 25% to 44% [15,20,21], but only 15-25% [22] of metastasis of liver are initially resectable. Poor prognosis of the disease is the cause of looking for opportunities to improve postoperative results which corresponds with defining determinants of survival.

Aim. To explore the experience of the Clinic in the treatment of colorectal liver metastases, comparing them with data from the literature, and based on the comparison to determine the prognostic factors that affect survival after radical surgical treatment of patients.

Methods and materials

A retrospective study was conducted at the Clinic of General and Hepato-pancreatic surgery at the University Hospital "Aleksandrovska"-Sofia. The study comprised the period between 01.01.2006 to 31.12.2015. It included a total of 239 patients (Table 1), of whom: 179 patients underwent radical interventions, 5 palliative and 55 patients underwent explorative interventions due to liver metastases. In addition, 119(49.8%) patients were diagnosed with synchronous metastases, 120(50.2%) patients with metachronous metastases, including 7(2.9%) with metachronous metastases with recurrence on the colon. With regard to sex structure of the patients there were 93(38.91%) women and 146(61.08%) men. Majority of patients were aged 61 to 70 years-88(36.82%), while a small percent belonged to the youngest age group under 40 years-9 (3.77%).

Table 1. Types of radical and palliative surgical interventions used for resections of patients with colorectal liver metastases, included in our study

Type of operation			
Radical N=179 (74.9%)		Palliative / biopsy N = 60 (25.1%)	
atypical resection	57	biopsy	55
resection of 2 segments	24	biopsy+biliary drainage	2
resection of 3 segments	18	thermoablation	1
resection of >3 segments	10	alcoholization	2
left lobectomy	15		
left hemihepatectomy	4		
right hemihepatectomy	12		
Metastasectomy	20		
resection+another procedure	19		
atypical resection+metastasectomy	9		
left lobectomy +atypical resection	5		
atypical resection+thermoablation	4		
atypical resection+alcoholization	1		

The follow-up period of the patients operated on for colorectal liver metastases in the Clinic, was 5 years after resection of the liver according to the method of Kaplan-Mayer. Statistical analysis of the collected material to determine the factors for survival was done using SPSS-19, and it included sex, age, type and localization of metastases, postoperative stage of primary tumor, type and amount of resection of the liver, extrahepatic metastases, preoperative CEA values and postoperative values (AST, ALT).

Results

The cumulative overall survival is shown in Table 2, and it was 79.6% in the first year, 25.9% in the third year, and 19.2% in the fifth year.

Table 2. Cumulative survival of patients after radical resection of colorectal liver metastases

	Cumulative survival % (Std.Error)		
	1-year	3-year	5-year
Total survival	80 (0.029)	25.9 (0.03)	19.2 (0.025)

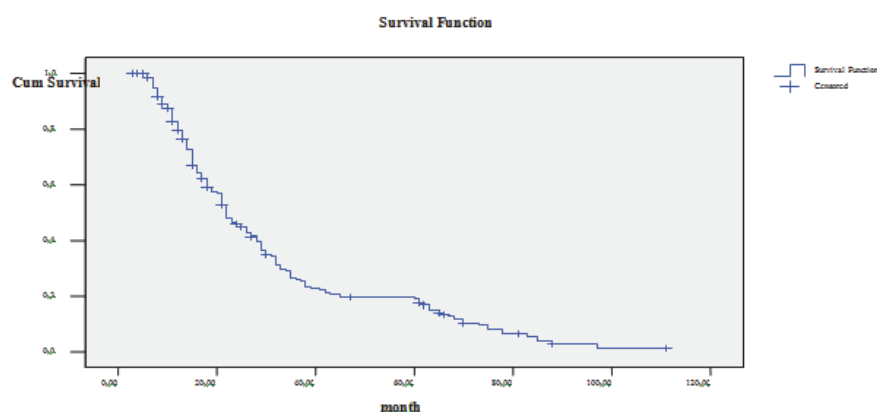


Fig. 1. Curve of survival in patients with colorectal cancer and liver metastases

Survival analysis by gender indicated that within the group of female patients 68 died (81.93%), while in the male patients group death occurred in 101(80.8%). The median survival for women with CRLM was 31.9 months

and for men shorter-30.8 months. The median survival was 25 months in female patients with CRLM and 22 months in male patients. However, the results did not show statistical significance ($p = 0.69$, $p = 0.7$).

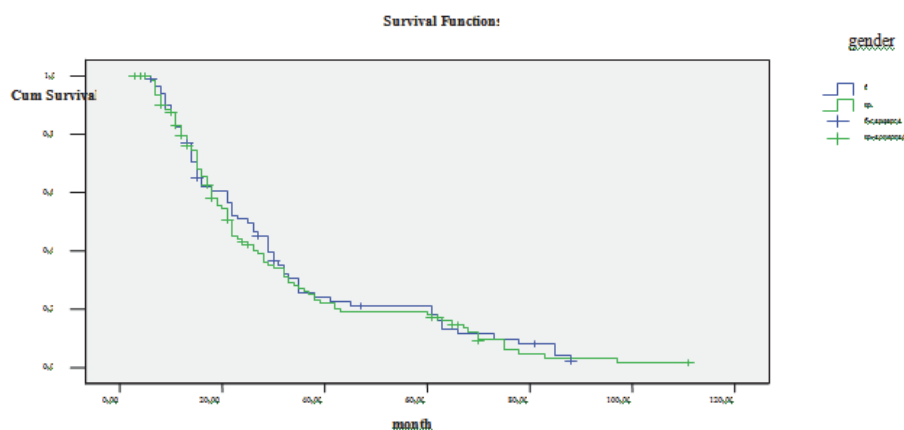


Fig. 2. Curve of survival according to sex of patients, Log Rank (Mantel-Cox) $p = 0.69$ Breslow $p = 0.7$

The analysis by age showed that the median survival was 34.3 months in patients under 40 years, 29.8 months in the age group 41-50 years, 29.2 months in patients

aged 51 to 60 years, 34.1 months in patients aged 61 - 70 years and 29.2 months in patients over 70 years. However, these differences were not statistically significant (Figure 3).

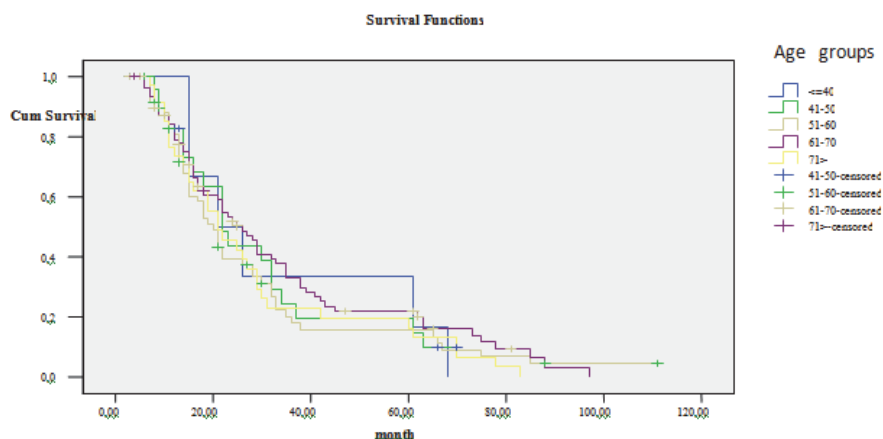


Fig. 3. Survival curves according to age, LogRank (Mantel-Cox) $p = 0.78$ Breslow $p = 0.74$

The analysis showed that the hazard ratio-Exp (B) for liver metastases was 1.49 95% CI (1.098-2.022), $p=0.01$. These factors suggest that the type of liver metastases in patients with colorectal cancer is a significant prognostic factor for survival. Statistical analysis showed

that there was a significant difference in survival time depending on the type of liver metastases ($p=0.008$, $p=0.002$). Patients with colorectal cancer and metachronous metastases had a significantly longer survival time.

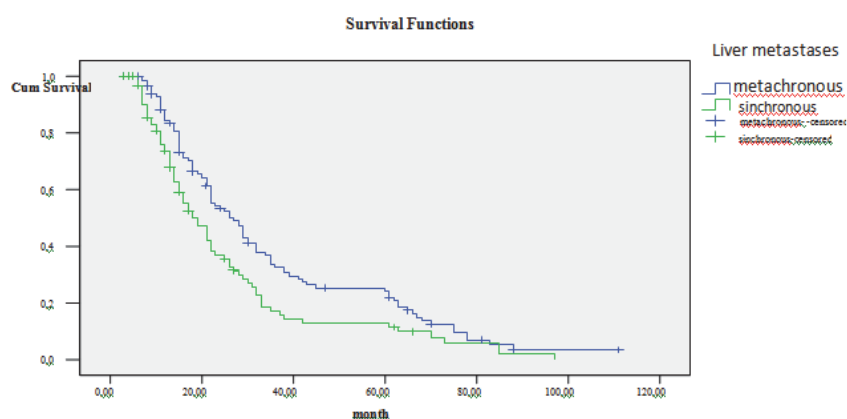


Fig. 4. Curve of survival depending on type of liver metastases

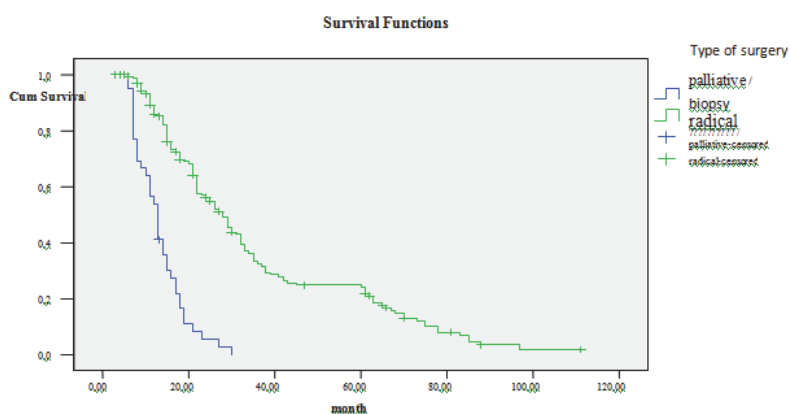


Fig. 5. Curves of survival depending on type of surgical resection

Radical intervention was also proved to be a significant factor for survival with Lesser Cox-regression analysis ($p < 0.0001$).

The value of HP of 0.203 95% CI (0.135 - 0.306) su-

ggests that the risk of fatal outcome in patients treated with radical intervention was 79.7% lower than in patients treated palliative or with biopsy.

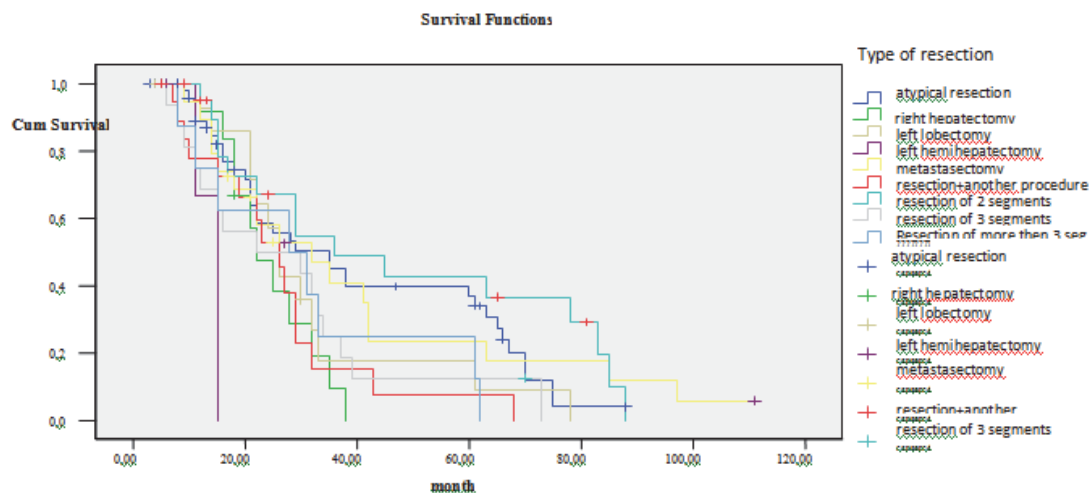


Fig. 6. Curves of survival depending on type of resection

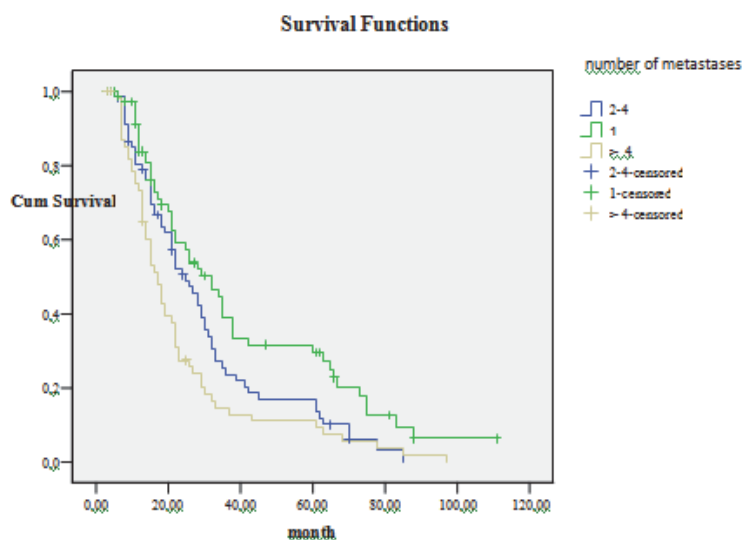


Fig. 7. Survival depending on metastases number

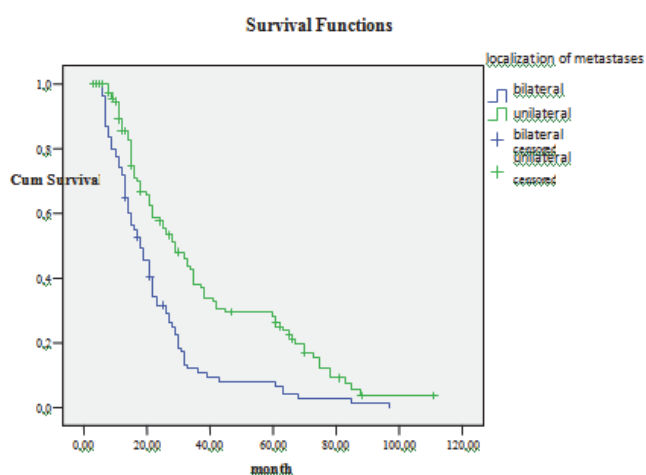


Fig. 8. Survival depending on localization of colorectal metastases

The statistical analysis of survival time showed that median survival was lowest in the group with left hemihepatectomy (about 14 months), and the highest

in the group with resection of two segments (48 months). Statistical tests confirmed the difference in the length of survival among the types of liver resections as significant ($p=0.004$, $p=0.043$), and type of resection in relation to the other factors in terms of survival as non-significant. Extent of resection was also not proved as a significant factor in terms of survival. The number of metastases was proved to be a significant predictor of survival in patients with colorectal cancer metastases of the liver. Patients with 2 to 4 metastases had a 1.5 times higher risk of fatal outcome compared to patients with one metastasis. Patients with more than 4 metastases had a twofold higher risk compared to patients with one metastasis. Statistical tests Log Rank and Breslow confirmed the difference in the length of survival time as significant ($p < 0.0001$). Patients with bilateral localization of liver metastases survived significantly shorter compared to patients with unilateral localization of metastases.

Table 3. Cox-regression analysis on the relationship between laboratory parameters and survival of patients with colorectal metastases

	p	Exp (B)	95% CI for Exp (B)
AST	0.069	1.004	1.00-1.008
ALT	0.894	1.00	0.996-1.004
GGT	0.129	1.001	1.000-1.001
direct bilirubin	0.266	1.027	0.98-1.007
total bilirubin	0.737	0.995	0.969-1.023
PRT	0.357	1.016	0.982-1.054
INR	0.16	1.372	0.882-2.134
HGB	0.007**	0.989	0.981-0.995
CA 199	0.117	1.00	1.000-1.001
CEA	0.008**	1.001	1.000-1.002
AFP	0.621	1.038	0.896-1.201
operative time	0.631	0.999	0.997-1.002
blood loss	0.084	1.001	1.000-1.001

Values of Hgb ($p=0.007$) and values of the tumor marker CEA ($p=0.008$) were confirmed as significant predictors. The risk of a fatal outcome was reduced by 11% by increasing the HGB by 1. Increasing tumor marker CEA 1 increased the risk of a fatal outcome by 0.1%.

Discussion

The surgical resection represents the only curative treatment approach in patients with CRLM; in larger series the treated patients with resection have mean 5-year survival rate of 25% to 44% [15,20,21], but only 15-25% [22] of liver metastases are initially resectable. Numerous publications indicate that gender and age do not significantly affect the survival of patients after resection of CRLM [23-25]. Many authors who compared synchronous with metachronous metastases, found superior results in favor of metachronous metastases [26-29], and others showed similar survival rates for both types of CRLM [30,31]. Tumor size of potentially resectable CRLM has been studied as a prognostic factor with contradictory results [32]. Ercolani *et al.* [33] demonstrated that the total tumor volume of liver metastases had a stronger impact on the survival compared to the number and location of metastases. In the multifactorial prognostic model described by Rees *et al.* [34] the number of CRLM >3 represents an independent prognostic factor for low rate of survival. Better survival of patients with four or more metastases was observed by Pawlik *et al.* [35], 5-year OS median survival of 50.9%, and Kornprat *et al.* [36], 5-year survival of 33% OS. The prognostic significance of bilobar distribution of colorectal metastases became controversial. Some studies indicate the bilobar distribution as a poor prognostic factor, while others are reporting that it does not affect survival [37,38]. Tomlinson *et al.* [39] report five and ten percent survival OS of 29% and 25% with bilateral resection. Type of resection of the liver does not affect the survival of patients with CRLM. Non-anatomical resection is inferior compared

to the anatomical resection regarding the marginal status, recurrent rate and survival [40]. Our study showed that the type of metastases, localization and inability to radical resection has a statistical significance in terms of survival. The type and extent of liver resection does not affect the survival, but the presence of metastases in the regional lymph glands, extrahepatic distant metastases, the elevated amount of CEA and stage IV disease have also significant effects on survival of patients after liver resection. Fong *et al.* [41] created a clinical risk score (CRS) using a regressive analysis of multiple clinical factors of patients resected due to colorectal liver metastases. They found five clinical criteria that have prognostic significance for survival: lymph node - initially positive, CEA >200 ng/ml, >1 lesion liver, lesion >5 cm, DFI less than 1 year from the initial resection. They noticed that patients with CRS of 0, 1, 2 have a fondness for survival and surgical resection is a rational therapy. Patients with CRS 3, 4 and 5 have low survival and therefore surgical resection should be planned in the context of chemotherapy.

Conclusion

There are several ways for treatment of patients with colorectal liver metastases: radiofrequent ablation, transarterial chemoembolization, chemo- and radiotherapy as well as in selected cases liver transplantation, but only liver resection has curative sense. The surgical strategy for resection in context of increasing the percent of patients with resectable potential is the only possible factor for long-term survival.

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