Long-term Results of Surgery for Colorectal Liver Metastases in Terms of Primary Tumour Location and Clinical Risk Factors

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Abstract. *Background/Aim:* The aim of the study was to evaluate the influence of primary tumour location and clinical risk factors for long-term results of surgery for colorectal liver metastases (CLMs). *Patients and Methods:* Overall survival (OS) and recurrence-free survival (RFS) were evaluated in 636 patients. Patients were divided by tumour location (right-/left-sided colorectal cancer: RCRC/LCRC; rectal cancer), and age, gender, number and size of CLMs, type of liver surgery and interval from primary operation were evaluated. *Results:* One-, 3- and 5-year OS and RFS were independent of primary tumour location ($p < 0.59$). CLM diameter was negatively associated with OS for the whole cohort ($p < 0.002$), and RCRC ($p < 0.03$) and LCRC ($p < 0.04$) groups, as well as for RFS of those with LCRC ($p < 0.04$). CLM number was negatively associated with RFS for the whole cohort ($p < 0.0001$), RCRC ($p < 0.02$), LCRC ($p < 0.0001$) and RC ($p < 0.02$). Radiofrequency ablation and combined procedures led to worse OS for the whole cohort ($p < 0.03$), and to worse RFS for the whole cohort ($p < 0.0003$) and for those with LCRC ($p < 0.03$). A shorter interval between primary colorectal cancer surgery and CLMs procedure was risky for poor OS and RFS of patients with CLMs from RCRC ($p < 0.05$), LCRC ($p < 0.05$) and RC ($p < 0.02$). *Conclusion:* Primary tumour location together with clinical risk factors are important for long-term results of surgery CLMs.

Globally, colorectal cancer (CRC) is the third most common carcinoma (1, 2). Colorectal liver metastases (CLMs) appear in more than 50% of patients at various time intervals from the diagnosis of CRC and are the main cause of death. However, thanks to the constantly increasing quality of multimodal procedures in the treatment of CLMs, where liver resections are the only radical treatment, there has been a steady improvement in the long-term results, with 5-year overall survival (OS) currently reaching 45-60%. However, 70% of patients experience a recurrence of CLMs at different time intervals, most often in the first 2 years after a liver operation (3-6).

In addition to many known risk factors influencing long-term survival of patients after surgical treatment of CLMs, recent studies report the location of the primary tumour being a significant prognostic factor for these patients (7, 8). Tumour biology is different for right- (RCRC) and left-sided CRC (LCRC), with different response to chemotherapy and target therapy. According to many contemporary meta-analyses, primary tumour sidedness has a decisive impact on OS and recurrence-free survival (RFS) for patients following liver resection for CLMs (9, 10). For resection of CLMs in the case of RCRC, OS is worse compared with those with LCRC but RFS is better. Various studies evaluated the long-term results of liver resection regarding tumour sidedness from various viewpoints, primarily the biological activity of primary CRC (11-13). Although most report significantly worse results for long-term OS in the case of surgical treatment of CLM from RCRC (14-16), the results for RFS are inconsistent. Neither is the definition of tumour sidedness consistent in many studies, and in some publications rectal cancer (RC) is included in LCRC, whereas others do not mention it at all due to the different oncological approaches.

The aim of our study was to evaluate the influence of primary tumour location in combination with the factors of age and gender of patient, size and number of CLMs, type of liver operation and the interval from resection of primary

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Table I. Demographic data, clinical characteristics, and type of operation(s) for study patients.

Characteristic		Total (n=636)	RCRC (n=128)	LCRC (n=334)	RC (n=174)	p-Value
Age, years	Mean±SD	63.8±9.3	64.4±9.1	63.9±9.8	62.7±8.3	0.09
Gender, n (%)	Male	418 (65.7)	78 (18.7)	207 (49.5)	133 (31.8)	0.002
	Female	218 (37.3)	127 (57.3)	50 (22.9)	41 (18.8)	
CLMs, mean±SD	Number	2.5±1.9	1.5±2.3	2.6±2.2	1.6±2.7	0.45
	Diameter	4.0±2.4	4.0±2.2	4.0±2.3	4.0±2.7	0.84
Interval between operations, years	Mean±SD	1.4±1.7	1.4±2.1	1.5±1.8	1.7±2.9	0.64
Resection	Large	173	38	93	42	0.49
	Small	276	64	133	79	
Therapy	RFA	124	19	70	35	
	Combined	63	13	32	18	

CLMs: Colorectal liver metastases; LCRC: left-sided colorectal cancer; RC: rectum cancer; RFA: radiofrequency ablation; RCRC: right-sided colorectal cancer. Bold values indicate statistical significance.

tumour to liver operation on the OS and RFS of patients with CLMs in order to add to the current literary findings from another point of view.

Patients and Methods

We analyzed data from 650 patients who had undergone operations for CLMs at a large tertiary hepatobiliary unit in 2002-2018. We excluded 14 due to the incompleteness of the required monitoring factors. For patients for whom we performed repeated liver operations due to CLM recurrence, in regard to the long-term results, we always considered the time-point of the first liver surgery. A multidisciplinary team decided on the indication for surgical treatment. The primary choice of operation was radical R0 resection with healthy liver tissue border >1 mm. Over the years of the study, small liver tissue-sparing resections came to predominate over large liver resections. Radiofrequency ablation (RFA) was performed in patients for whom a liver resection was contraindicated for various reasons (overall health patient status, location of CLMs, volume and function of liver parenchyma) providing there were no more than five metastases and their diameter was <5 cm. For some patients, a combination of resection with RFA was used with the aim of saving liver tissue.

Neoadjuvant oncological treatment was indicated for borderline resectable or primarily non-resectable CLMs. The response to preoperative oncological treatment was evaluated after 4-6 cycles using computed tomography. When there was a treatment response, patients were indicated for liver resection. Adjuvant oncological treatment was indicated for individual patients by an oncologist. All patients underwent regular follow-up examinations after liver resection or RFA.

We obtained written informed consent from all patients who participated in this study (approval no.: 363/2018).

Table I shows the characteristics of the whole cohort and of the subgroups. The primary location of tumour was right-sided in 128 (20.1%), left-sided in 334 (52.5%) and rectal in 174 (27.4%). We considered all primary tumours located from proximal to the splenic flexure to be RCRC, those located distal to the splenic flexure and the upper rectum to be LCRC, and tumours located in the middle and lower rectum to be RC.

Figure 1. Overall survival of the entire patient cohort and according to disease. LCRC: Left-sided colorectal cancer; RC: rectal cancer; RCRC: right-sided colorectal cancer.

In the whole patient cohort, there were 418 (65.7%) men and 218 (37.3%) women ($p<0.002$). The number of men in the RCRC, LCRC and RC groups was 78, 207 and 133, respectively. The average age of patients with CLMs was 63.8 ± 9.3 , with a median of 63.7 years. The average age did not differ significantly between groups ($p<0.09$). The median number of CLMs in the cohort was 3.4, and for RCRC, LCRC and RC tumours it was 2.3; 3.1 and 2.5, respectively; the average number of CLMs did not differ significantly ($p<0.45$). The average size of CLMs for the whole patient cohort was 4.0 ± 2.4 cm, and size did not differ significantly between groups ($p<0.84$). The average interval between surgery for the primary tumour and CLMs was 1.4 ± 1.7 years and did not differ significantly between groups ($p<0.64$). For 173 patients, we performed large liver resection (≥ 3 liver segments), for 276 small liver resection (< 3 segments) and for 124 RFA. Combined procedures were performed in 63 patients.

The statistical analysis was performed using SAS software (SAS Institute Inc., Cary, NC, USA). Basic statistical data, such as the average, standard deviation, variance, median, interquartile range,

Figure 2. Overall survival according to the diameter of colorectal cancer liver metastases for the whole patient cohort (A), for patients with right-sided (RCRC) (B) and left-sided (LCRC) (C) colorectal cancer, and those with rectal cancer (RC) (D).

minimum and maximum, were calculated for the measured parameters for the whole group and in the individual subgroups. The difference in continuous variables between the examined groups was tested using Kruskal-Wallis test. OS and RFS were calculated from the date of the first liver operation using Kaplan-Meier survival curves. The influence of the individual factors was tested using the log-rank test, Gehan-Wilcoxon test and Cox regression model. The statistically strongest cut-off of the individual factors met the condition of highest attained score of the Cox regression model. Statistical significance was designated at the threshold alpha of 5%.

Results

One-, 3- and 5-year OS for the whole patient cohort following surgery for CLMs was 91.3%, 61.7% and 53.3%, respectively; for patients with RCRC, it was 88.2%, 67.5% and 63.3%, respectively; for those with LCRC 92.2%, 69.7% and 52.6%, respectively, and for those with RC 91.1%, 64.1% and 49.4%, respectively ($p<0.59$, Figure 1).

Regarding the impact of the number of CLMs on OS, we did not find a statistically significant difference ($p<0.35$). The statistically strongest, yet statistically insignificant, cut-off for number of CLMs was four for the whole patient cohort [hazard ratio (HR)=1.2, 95% confidence interval (CI)=0.8-1.9, $p<0.3$] and for RCRC (HR=1.5, 95% CI=0.5-5.1, $p<0.5$), whilst it was two for both LCRC (HR=0.7, 95% CI=0.5-1.2, $p<0.2$) and RC (HR=1.6, 95% CI=0.9-2.9, $p<0.08$). Considering the size of CLMs, the statistically strongest diameter of CLMs was 5 cm for the whole patient cohort (HR=1.6, 95% CI=1.2-2.2, $p<0.002$), for RCRC (HR=2.2, 95% CI=0.5-1.2, $p<0.03$) and for LCRC (HR=1.6, 95% CI=1.0-4.9, $p<0.04$), whilst it was cut-off 4.5 cm for RC, without statistical significance (HR=1.5, 95% CI=0.8-2.7, $p<0.2$) (Figure 2).

The type of operation was significant for the length of survival for the whole patient cohort ($p<0.03$), where small liver resections led to the best and RFA to the worst results (Figure 3). The type of operation was not decisive for OS of patients with RCRC ($p<0.7$), LCRC ($p<0.1$) and RC ($p<0.4$).

Figure 3. Overall survival according to the type of surgery for the whole patient cohort (A), for patients with right-sided (RCRC) (B) and left-sided (LCRC) (C) colorectal cancer, and those with rectal cancer (RC) (D). RFA: Radiofrequency ablation.

The interval between primary operation and liver procedure was not decisive for the whole patient group ($p<0.2$), nor for those with RCRC and RC ($p<0.08$ and 0.54 respectively). For patients with LCRC, an interval from primary surgery to liver procedure shorter than 6 months was significantly predictive of poorer OS (HR=1.6, 95% CI=1.2-2.7, $p<0.05$) (Figure 4).

One-, 3- and 5-year RFS for the whole patient cohort was 58.8%, 16.9% and 11.8%, respectively; for patients with RCRC 55.9%, 30.8% and 25.2%, respectively; for those with LCRC 63.2, 22.7 and 15.5% and for RC 51.0, 21.2, 14.3% respectively ($p<0.2$; Figure 5). The statistically strongest cut-off RFS was five CLMs for the whole patient cohort (HR=2.1, 95% CI=1.5-2.7, $p<0.0001$), for RCRC (HR=2.3, 95% CI=1.1-4.9, $p<0.02$), and RC (HR=2.1, 95% CI=1.3-3.5, $p<0.002$), whilst for LCRC the cut-off was four (HR=1.9, 95% CI=1.4-2.6, $p<0.0001$) (Figure 6). Regarding the size of CLMs, the statistically strongest diameter of was 2.5 cm for the whole patient cohort (HR=1.3, 95% CI=0.9-1.6, $p<0.06$) and for those with LCRC (HR=1.5, 95%

CI=1.0-2.2, $p<0.04$), whilst the cut-off was 3.5 cm for RCRC (HR=1.5, 95% CI=0.9-2.3, $p<0.09$) and RC (HR=0.9, 95% CI=0.6-1.3, $p<0.6$) (Figure 7).

RFS in relation to the type of operation differed significantly considering the whole patient cohort ($p<0.0003$) and those with LCRC ($p<0.03$), with worse results of RFA and combined operations. The type of surgery was not decisive for RFS for patients with RCRC ($p<0.63$) and RC ($p<0.07$) (Figure 8). The interval between primary operation and liver surgery was not decisive for the whole patient cohort ($p<0.17$) and those with RC ($p<0.40$), but for patients with RCRC and with LCRC, an interval of less than 18 months (HR=2.5, 95% CI=0.2-1.0, $p<0.05$), and 6 months (HR=1.5, 95% CI=1.1-2.0, $p<0.02$), respectively, led to poorer RFS (Figure 9).

Discussion

The embryonic development of the colon differs in regard to location. Whereas the right colon develops from the

Figure 4. Overall survival according to the time to surgery of colorectal cancer liver metastases for the whole patient cohort (A), for patients with right-sided (RCRC) (B) and left-sided (LCRC) (C) colorectal cancer, and those with rectal cancer (RC) (D).

midgut, the left colon and rectum develop from the hindgut. These parts of the colon then differ in mucosal immunology and in gut microbiota. A higher density of eosinophilic leukocytes and intraepithelial T-cells has been shown in the proximal colon (17, 18). Tumours from both parts of the colon are further distinguished by certain clinicopathological properties that can influence the long-term survival of patients, both after resection of primary tumour and after operations for CLMs (19, 20). RCRC are more common in the older population with frequent comorbidities, in women, in patients with other malignancies, and those with insulin resistance. LCRCs are diagnosed in particular in people with a low-fibre diet, heavy smokers and in those who consume alcohol. Whereas clinical symptoms of LCRC (change in bowel habits and bleeding) are diagnosed more frequently, and therefore synchronous CLMs are discovered earlier, symptoms of RCRC arise late, with consequently later discovery of synchronous CLMs. Microsatellite instability, high CpG island methylation (leading to a worse reaction to

Figure 5. Recurrence-free survival of the entire patient cohort and according to disease. LCRC: Left-sided colorectal cancer; RC: rectal cancer; RCRC: right-sided colorectal cancer.

Figure 6. Recurrence-free survival according to the number of colorectal cancer liver metastases for the whole patient cohort (A), for patients with right-sided (RCRC) (B) and left-sided (LCRC) (C) colorectal cancer, and those with rectal cancer (RC) (D).

chemotherapy), and proto-oncogene p21^{ras} - RAS (*KRAS* codons 12, 13, 61, 146 and *NRAS* codons 12, 13, 61), proto-oncogene B-Raf (*BRAF*) and phosphatidylinositol-3-kinase (*PI3KCA*) mutation are more frequent in RCRC compared with LCRC. These mutations are also associated with more frequent multifocal CLMs. Compared with LCRC, RCRC is more poorly differentiated mucosal type and more frequently metastasizes into the drainage lymphatic nodes and the peritoneum. All of these features are given as the main cause of the greater biological aggression of RCRC and worse OS both for primary resections of colon and for resection of CLMs originating from RCRC (21-24).

Most of the recent studies describe worse long-term OS for patients with CLMs from RCRC (25-28). As regards RFS, the results of studies vary. Some describe worse RFS for LCRC (29), whereas others find no significant difference between RCRC and LCRC (30, 31). However, from all the studies it is evident that CLMs from RCRC have a more aggressive biological potential than those from

LCRC. This is also associated with the question of peri-operative oncological, in particular neoadjuvant, treatment for these patients. Certain studies in this sense state that a so-called up-front hepatectomy, *i.e.* hepatectomy without neoadjuvant chemotherapy, in the case of RCRC is associated with significantly worse OS and RFS, whereas the long-term results for hepatectomies performed after neoadjuvant oncological treatment do not differ according to the location of the primary tumour (32, 33). In contrast, other studies showed a fundamentally worse response to neoadjuvant chemotherapy and targeted therapy of patients with CLMs from RCRC (34, 35). With regard to the long-term results according to tumour location, those with CLMs from RCRC were found to have worse results regardless of the type of operation for CLMs (36).

In contrast with previous studies, in our group of 636 patients, we did not confirm clearly worse long-term OS or RFS for patients following liver procedures for CLMs from RCRC. This may be due to several factors. Firstly, the

Figure 7. Recurrence-free survival according to the diameter of colorectal cancer liver metastases for the whole patient cohort (A), for patients with right-sided (RCRC) (B) and left-sided (LCRC) (C) colorectal cancer, and those with rectal cancer (RC) (D).

different and non-unified definition of location of RCRC tumours in literature, whose location in the splenic flexure some classify as RCRC, and others as LCRC. The second problem is the non-uniform indication for neoadjuvant oncological treatment in current literature, and in many publications. This treatment is not given in connection with the surgical treatment of CLMs in general. In our group of patients, we did not include neoadjuvant oncological treatment as one of the evaluation criteria due to the fact that we indicate this treatment only for patients with borderline resectability or primary non-resectability of CLMs, regardless of the primary location of tumour. In the case of resectable CLMs, we perform primary resection with subsequent adjuvant oncological treatment. In our study, we also performed an as yet unpublished classification of rectal tumours from the aspect of their metastatic tendency, to the LCRC group in the case of the upper rectum, and to the RC group in the case of the middle and lower rectum. In many other works covering the results of surgical treatment of

CLMs according to primary location of tumour, the location of the tumour in the rectum is not given, or rectal tumours are simply classified as LCRC.

This study was limited by its retrospective nature. It was also a study performed over an interval of 19 years, during which more precise diagnostic and radiological methods as well as surgical techniques developed, primarily mini-invasive methods and methods sparing the liver parenchyma. In addition, there have been changes in the development of effective perioperative oncological treatment over this period. Unfortunately, it was not possible to evaluate this factor in our group of patients mainly due to our current indication for oncological treatment for patients with borderline resectability or primary non-resectability of CLMs. Due to a lack of data about gene mutations, especially for patients from the first years of monitoring, we were unable to adequately evaluate these factors for our group. However, these are currently sufficiently well-known as risk factors for the long-term results of surgical CLM treatment.

Figure 8. Recurrence-free survival according to the type of surgery for the whole patient cohort (A), for patients with right-sided (RCRC) (B) and left-sided (LCRC) (C) colorectal cancer, and those with rectal cancer (RC) (D). RFA: Radiofrequency ablation.

In conclusion, we assume that the primary tumour location is undoubtedly an important but not fundamental factor influencing the long-term results of surgery for CLMs. Along with the side location of the primary tumour, considering OS and RFS, other clinical risk factors can also be evaluated. It is evident from our results that every patient with CLMs must be evaluated individually by a multidisciplinary team, and the optimal multimodal treatment, the basis of which is liver resection, must be tailored to the patient.

Conflicts of Interest

No conflicts of interest exist.

Authors' Contributions

V. Treska: Conception, design, supervision, literature review, writing; Skala: data collection; K. Prochazkova: data collection and processing, analysis; Svejdoва: data collection; T. Petrakova: data

collection; J. Sebek: data collection; I. Riha: data collection; J. Rosendorf: data collection; R. Polak: data collection; T. Skalicky: critical review; V. Liska: design, critical review.

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Figure 9. Recurrence-free survival according to the time to surgery of colorectal cancer liver metastases for the whole patient cohort (A), for patients with right-sided (RCRC) (B) and left-sided (LCRC) (C) colorectal cancer, and those with rectal cancer (RC) (D).

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