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The Issue of Survival After Colorectal Liver Metastasis Surgery: Parenchyma Sparing *vs*. Radicality

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Abstract. *Background/Aim: Nowadays, obtaining optimal surgical margin of the resected metastasis and the parenchyma- sparing surgical technique are a great challenge for hepatic surgeons. The aim of this follow-up study was to investigate the prognostic value of the surgical margin and the parenchyma- sparing liver resection technique. Patients and Methods: We performed a retrospective analysis of the data of 319 patients [123 (36.6%) female and 196 (61.4%) male] who had colorectal cancer and underwent surgery to treat colorectal liver metastases in our Department between 2005 and 2014. Results: The most commonly used resection type was the non-anatomic resection (43%). Multivariate analysis indicated that there was no significant difference in survival (p=0.473) between the microscopically-negative (R0) and microscopically-positive (R1) resections, as well as between the resection types (p=0.257). Conclusion: Parenchymal-sparing non-anatomic resection and spray diathermy on the resection surface of the liver should be applied not only for hemostasis, but also to destroy the area containing possible tumor cells after an R1 resection and not to have worse survival outcomes.*

According to the latest WHO data, the worldwide incidence of colorectal cancer (CRC) is over 1.4 million. With approximately 447,000 newly-diagnosed cases per year, CRC is the most common gastrointestinal malignancy in Europe (1, 2). According to the Global Burden of Cancer Study (GLOBOCAN), CRC was found to be the third most frequently occurring cancer type and the third most common cause of cancer related deaths in Europe (3).

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The 5-year survival rate of CRC for stages I-III is estimated to be around 71%, however, it is only 13% in stage IV (4).

More than 50% of patients suffering from CRC develop liver metastases (CRLM). In 25% of the patients, synchronous hepatic metastases are present at the time of CRC diagnosis. On the other hand, about 40-50% of the patients develop metachronous liver metastases after resection of the primary CRC (5-7). According to epidemiological data a new or recrudescent hepatic metastasis is likely to develop in 50-75% of the patients even after an acceptable liver resection. However, only one-fifth of these metastases are resectable (8, 9).

In patients with untreated colorectal liver metastases the estimated median survival reaches only 5-8 months (10, 11).

Currently, the most effective therapies for patients with CRLM are: multi-modal chemotherapy, multiple ablation modalities and hepatic resection (6, 12, 13). Regarding surgical success, the current opinion is that patients with macroscopically-positive surgical margin (R2) have worse survival than patients with microscopically positive surgical margin (R1) and microscopically-negative surgical margin (R0) (14-25). However, the results of the studies investigating the effect of R1 and R0 on survival are controversial.

Recently, the surgical margin and liver parenchyma-sparing technique has become an issue among hepatic surgeons. In the case of CRLM the consensus – since the 1980s – was that the optimal surgical margin is more than 1 cm (14-17). In contrast, some studies could not reveal any negative effect on survival if the tumor free surgical margins were between 0 to 9 mm (18-23). In addition, some authors claim that CLRM patients with R1 resection do not have worse survival outcomes than patients with R0 resection (24-27).

The results of the most significant studies investigating this issue are presented in Table I.

Due to improvement in surgical and oncological therapies 5-year survival rate for CLRM patients is increasing, thus the need for repeated surgery becomes higher and higher.

Table I. *Resection margin and survival.*

Author	Year	Country	Number of patients	Neoadjuvant chemotherapy	Adjuvant chemotherapy	Resection margin	*p*-Value
Ekberg *et al.*	1986	Sweden	72	No	Yes*	Significant difference if resection margin is more than 10 mm	0.03
Elias *et al.*	1998	France	269	No	Yes*	Significant difference if resection margin is more than 9 mm	0.001
Kokodu *et al.*	2002	Japan	63	NA	NA	No significant difference if resection margin is more than 2 mm	0.9
Pawlik *et al.*	2005	Multicenter (USA, Italy, Switzerland)	557	No	Yes*	No significant difference if resection margin is more than 1 mm	0.63
Haas *et al.*	2008	France	436	Yes*	Yes*	No significant difference between R0 *vs.* R1 resection	0.27

*Not all patients.

On the other hand, in numerous cases, due to the chemotherapy-induced liver parenchyma injury and the effects of the currently used surgical techniques, patients do not have enough liver volume to provide sufficient liver function. Thus, a repeated resection is frequently contraindicated (8, 9, 28).

Nowadays, because of these factors some authors suggest to perform parenchyma-sparing surgery to keep as much liver tissue as possible. However, the use of the parenchyma sparing technique sometimes sacrifices R0 resection for keeping more liver volume.

The aim of this follow-up study was to investigate the prognostic value of the surgical margin and parenchyma-sparing on survival in patients who underwent resection of hepatic CRLM.

Patients and Methods

The present retrospective analytical study was based on the data of patients with colorectal liver metastases who underwent hepatic surgery between January 2005 and December 2014. All surgeries were performed at the Surgery Clinic of the University of Pécs, Pécs, Hungary.

Data collection was performed by using the hospital's medical database. No patients' rights were violated while acquiring data. The collected data were stored anonymously and were only used for scientific purposes.

Patients with non-CRC metastases, and patients with any other malignancies were excluded. The final database contained the following parameters: age, gender, T and N stadium of the primary tumor, type of resection, time of diagnosis of liver metastases, resection of liver metastases, diameter of the largest resected liver metastasis and the time of death.

Preoperative management. Patients were examined with liver-specific three-phase computed tomography (CT), and/or magnetic resonance imaging (MR), and/or 18(FDG)-positron emission tomography (PET-CT), and/or contrast-enhanced ultrasound, routine blood test and colonoscopy.

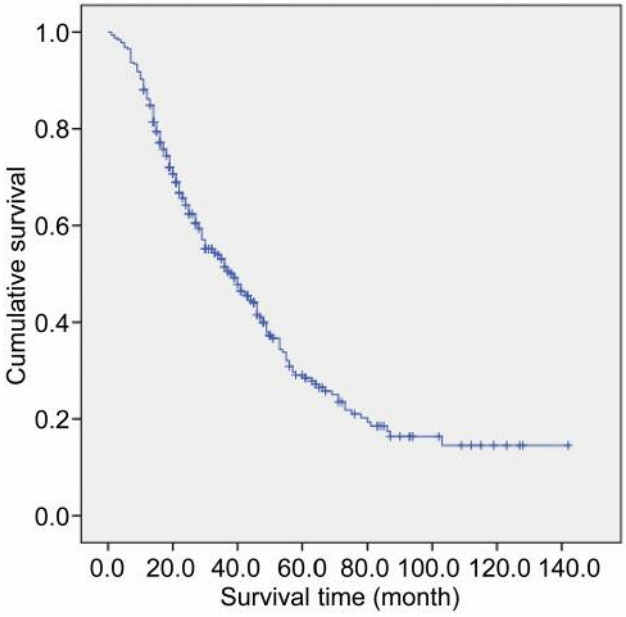

Figure 1. *Overall survival from the first liver surgery.*

All patients have been curatively treated for the primary colon neoplasm and did not have any surgical treatment for extrahepatic metastases. In the case of unresectable hepatic metastases, conversion chemotherapy was administered to allow surgical treatment.

Hepatic resection. After laparotomy abdominal exploration was performed. The number, size, localization, relation with intra-hepatic vascular structures of metastases, and the onset of additional lesions were confirmed by palpation and/or intra-operative ultrasound.

The resection types were: classic lobectomy or parenchyma sparing segmentectomy or non-anatomical metastasectomy. To perform liver parenchymal transection, Kelly clamp-crush technique, ultrasonic dissection (Harmonic Wave, Ethicon Endo-Surgery, (Johnson & Johnson, New Brunswick, NJ, USA), Cavitron Ultrasonic Surgical Aspirator (CUSA), (Covidien, Dublin, Ireland) and electrosurgical pencil (Covidien, Dublin, Ireland) were used. The major portal veins and bile ducts were ligated with non-absorbable sutures. In the few cases of major bleeding, intermitted Pringle maneuver was used to reduce hemorrhage.

The cutting surface was coagulated with electrosurgical pencil in "spray mode" to prevent postoperative bleeding in all cases.

Pathological review. All resected specimens underwent histopathological examination. During this, the number, the size, the histological type of metastases, and the resection margin were documented.

Data collection. Medical records and Population Registry Office date were used to perform data collection. Gender, median age, localization of the primary tumor, T and N stadium of the primary tumor, type of the liver resection, R status of the resection surface, and the size of the largest metastases were collected. The survival time referred to the interval between the resection of the primary tumor and the date of death and on the date of hepatic resection and the date of death. Patient data safety was not violated during data collection.

Statistical analysis. Statistical analysis was performed by IBM SPSS Statistics for Windows Version 22 (IBM Corporation, Armonk, NY, USA). Kaplan–Meier method, log rank test, ANOVA regression test and Cox multiple regression model were used for comparing survival to possible prognostic factors. All *p*-values lower than 0.05 were considered as statistically significant.

Results

Patients. Between January 2005 and December 2014, 528 patients underwent hepatic surgery for secondary liver cancer at our Regional Surgery Center. A total of 209 patients were excluded, because of the following: primary cancer was not CRC, synchronous extra-hepatic metastases were presented, onset of other type of previous malignancies.

Finally, we analyzed the data of 319 patients [123 (36.6%) female and 196 (61.4%) male] who had colorectal cancer and underwent a surgery to treat colorectal liver metastases. Patients with both synchronous and metachronous liver metastases were included. Fifty-three (16.7%) of these patients underwent a second liver surgery and eight (2.5%) patients had a third liver surgery. The median follow-up was 47 months. The mean overall survival from the first liver surgery was 51.5 months, with a median of 39 months. The 1-, 3-, and 5-year overall survival rates from the date of hepatic surgery were 85.9%, 51.2%, and 29%, respectively. The overall survival curve is shown in Figure 1.

The mean age of the patients at the time of the operation of the primary tumor was 60±0.67 years (range=27-84 years) and 62±0.57 years (range=28-85 years) at the time of the liver resection. Mean time between the primary tumor resection and the liver operation was 18.63±0.97 months (range=1-104 months). The origin of the primary tumor was the right side of the colon in 72 cases (22.6%). The left side of the colon was found to be the origin in 114 cases (35.7%). In the remaining 133 cases (41.7%) the rectum was identified as the origin of the primary tumor. Overall, 167 patients (52.4%) were over 60 years at the time of diagnosis of the primary tumor. The clinical characteristics of the involved patients are shown in Table II.

A total of 106 patients (33.2%) had synchronous and 213 patients (66.8%) had metachronous liver metastases.

Pre- and post-operative chemotherapy. Overall, 228 patients (71.5%) received neoadjuvant chemotherapy (FOLFOX, FOLFIRI XELOX, XELIRI) before the first liver surgery. 96 (30.1%) of these patients received biological therapy (Avastin, Vectibix, Erbitux) and 152 (64.7%) patients received adjuvant chemotherapy after the first liver surgery, including the 51 (16%) patients who received biological therapy.

Clinical characteristics of the involved patients and results of the performed univariate analysis of registered clinical factors are shown in Table II.

No significant differences were found in survival between the gender (p=0.667), age (p=0.241), location of the primary tumor (p=0.566), time of diagnosis of liver metastases (p=0.298) and type of resection (p=0.257). Patients with unresectable CRC liver metastases had significantly worse (p<0.001) survival. Patients with a large tumor number and size of resected liver metastases had significantly shorter (p=0.016) survival.

The most commonly used resection type was the non-anatomic resection (43%) and during this surgery sometimes 5-6 metastases were removed. One segment resection was performed in 19.7% of the cases and two or more segment resections in 27.1%. In the remaining 10.2% of the cases hepatolobectomy was performed (Figure 2).

Multivariate analysis of clinicopathological factors. The collected factors were tested with multivariate analysis to identify independent factors of survival. Detailed results are shown in Table III.

According to the multivariate analysis there were no significant differences (p=0.473) between the R0 and R1 resection surface on survival. On the other hand, R0 and R2 (p=0.031) and R1 and R2 (p=0.042) resections showed significant differences in survival. Patients with macroscopically positive resection surface had significantly shorter survival. According to the univariate analysis, patient with unresectable colorectal liver metastases had significantly shorter (p=0.001) survival.

Age, gender, localization of primary tumor, time of diagnosis of liver metastases and diameter of the largest metastases had no significant effect on survival.

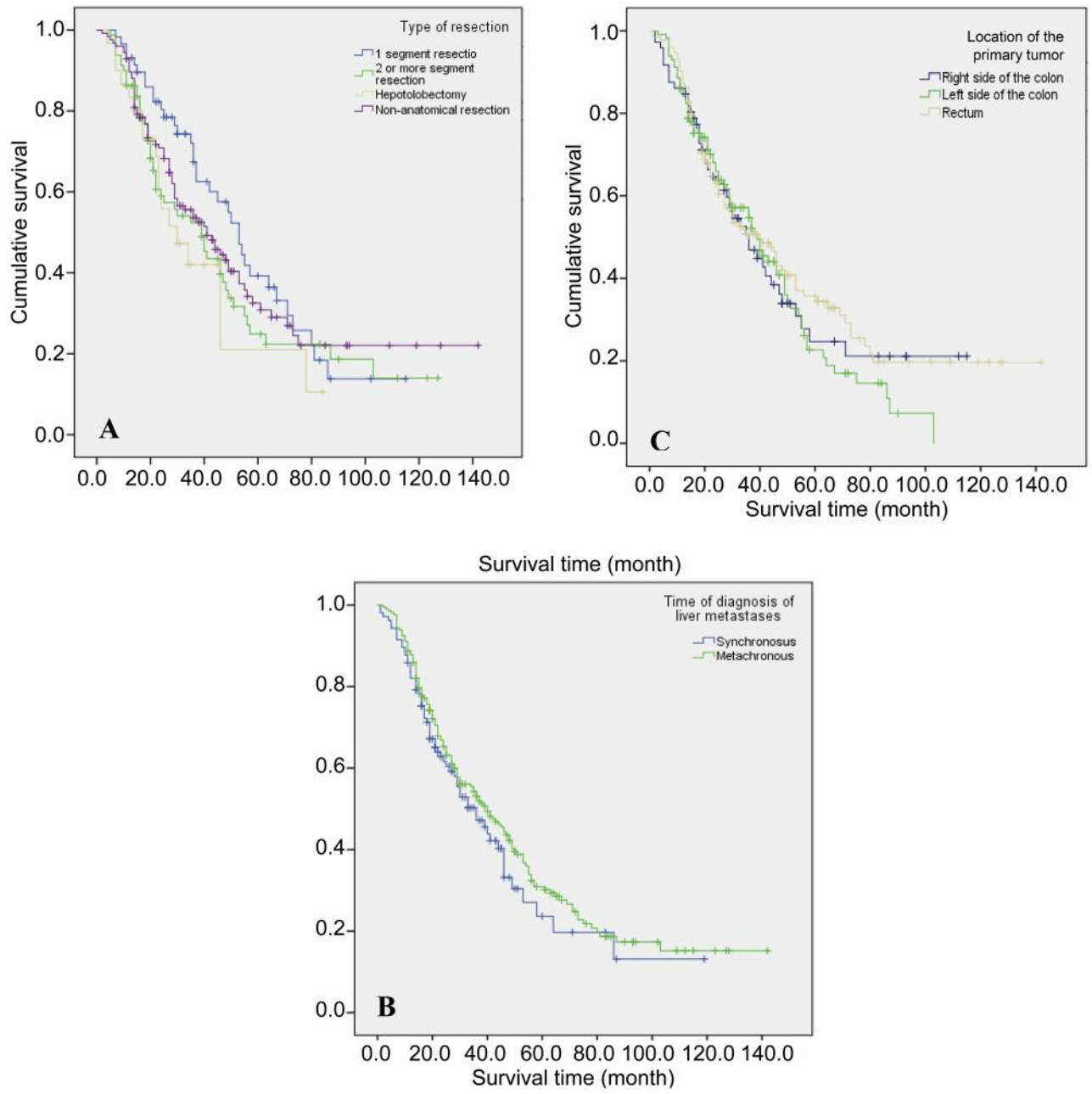

Figure 2. *Kaplan–Meier curves of survival (A: type of resection; B: time of diagnosis of liver metastases; C: location of the primary tumor).*

The resection radicality. In the case of 207 (70.2%) patients, the first liver resection margin was microscopically negative (R0), 54 (18.3%) patients' resection was microscopically positive (R1) while the remaining 34 (11.5%) patients' surgery showed macroscopically positive (R2) results.

The median and mean survival of patients with different resection types are shown in Table IV.

There was no significant difference (p=0.490) in survival between the R0 and R1 groups calculated on the interval between hepatic resection to the date of death. Comparing R0 to R1, the 1-year survival was 90.5% *vs*. 87.9%, the 2-years survival was 58.4% *vs*. 56.4% and the 5-years survival was 35.8% *vs*. 23.2%. However, comparing the survival of R1 to R2 (p=0.037) and R0 to R2 groups (p=0.002)

Table II. *Clinical characteristics of the involved patients and effects of the investigated clinical factors on survival.*

	No. of patients	Median survival (month)	Mean survival (month)	*p*-Value
Gender				
Male	196	37 (27.2-46.8)[a]	48.9 (42.6-55.3)[a]	
Female	123	40 (28.6-51.4)[a]	50.7 (41.4-60.1)[a]	0.667
Age				
<60	145	42 (31.1-52.9)[a]	55.0 (46.0-64.0)[a]	
>60	174	36 (28.8, 43.2)[a]	45.1 (38.9-51.29)[a]	0.241
Location of the primary tumor				
Right side of the colon	72	36 (24.9-47.0)[a]	47.6 (37,1-58,1)[a]	
Left side of the colon	114	39 (29.0-49.0)[a]	42.6 (36,6-48,7)[a]	0.566
Rectum	133	40 (28.3-51.7)[a]	55.9 (46.3-65.5)[a]	
Diameter of the largest resected liver metastases				
<5 cm	218	40 (34.1-45.9)[a]	52.2 (45.7-58.7)[a]	
>5 cm	77	30 (6.8-53.2)[a]	40.7 (48.7-58.7)[a]	0.147
Resection of liver metastases				
Yes	295	41 (35.1-46.9)[a]	54.4 (48.1-60.6)[a]	
No	24	12 (8.2-15.8)[a]	13.0 (1.8-16.4)[a]	<0.001
Time of diagnosis of liver metastases				
Synchronous	106	36 (26.0-46.0)[a]	44.5 (35.1-54.0)[a]	
Metachronous	213	40 (32.3-47.7)[a]	53.0 (46.1-60.0)[a]	0.298
Type of resection				
1 segment resection	58	53 (42.8-63.2)[a]	56.0 (46.4-65.6)[a]	
2 or more segment resection	80	39 (27.2-50.8)[a]	48.7 (38.5-59.0)[a]	
Hepatolobectomy	30	30 (15.9-44.1)[a]	37.8 (26.4-49.3)[a]	
Non-anatomical resection	127	41 (30.0-52.0)[a]	57.4 (47.2-67.6)[a]	0.257

[a]95% Confidence interval.

Table III. *Multivariate analysis of prognostic factors.*

	β	Wald x^2	Exp (B)	95%CI for Exp(B)		*p*-Value
Gender	0.146	0.433	1.157	0.759	1.789	0.511
Age	–0.003	0.061	0.097	0.097	1.018	0.805
Time of diagnosis of liver metastases	0.195	0.121	1.215	0.405	3.643	0.728
Liver resection	1.255	9.906	3.506	1.605	7.659	0.002
Location of primary tumor	0.176	1.446	1.192	0.895	1.587	0.229
Resection surface R0 *vs*. R1	0.141	0.514	1.152	0.783	1.694	0.473
Resection surface R0 *vs*. R2	0.264	4.641	1.302	1.024	1.656	0.031
Resection surface R1 *vs*. R2	0.533	4.135	1.704	1.019	2.850	0.042
Diameter of the largest metastases	0.002	0.395	1.002	0.996	1.007	0.530

significant differences were found (R1 *vs*. R2, $p=0.037$; R0 *vs*. R2, $p=0.002$). Seemingly, patients with R2 resection surface had significantly reduced 5-year survival compared to R0 or R1 patients.

Discussion

According to previous outcome studies, liver resection is the best treatment option for patients suffering from CRC with hepatic metastases (6, 10, 11). Approximately 50-75% of these patients develop new or recurrent CRLM after curative liver resection. Only one-fifth of these metastases can be treated surgically (8, 9). Several studies were performed to investigate the optimal surgical margin of hepatic resection. In 1986 Ekberg *et al*. suggested that the optical surgical margin should be more than 1 cm to achieve significantly higher survival (15). Twelve years later Elias *et al*. found that the sub-centimeter resection distance is significantly sufficient (22). In the early 2000s both Kokudo *et al*. and Pawlik *et al*. found that even 2-5 mm and 1-4 mm is enough to improve survival (19, 20). In 2008 Haas *et al*. were one of the first to publish a follow-up study including nearly 500

Table IV. *The median and mean survival of patients with different resection types.*

	R0	R1	R1	R2	R0	R2
Median survival (month)	46 (39.3-52.7)[a]	43 (32.1-53.9)[a]	43 (32.1-53.9)[a]	28 (20.7-35.3)[a]	46 (39.3-52.7)[a]	28 (20.7-35.3)[a]
Mean survival (month)	58.5 (50.1-66.2)[a]	51.5 (40-63)[a]	51.5 (40-63)[a]	34.1 (24.9-43.3)[a]	58.5 (50.1-66.2)[a]	34.1 (24.9-43.3)[a]
Survival						
1 year	90.5%	87.9%	87.9%	82.5%	90.5%	82.5%
2 years	58.4%	56.4%	56.4%	29.8%	58.4%	29.8%
5 years	35.8%	23.2%	23.2%	9.9%	35.8%	9.9%
p-Value	0.490		0.037		0.002	

[a]95% Confidence interval.

CRLM resected patients who did not show significant 5-year disease-free survival differences between R1 and R0 resected CRLM patients (25).

In line with Haas *et al*., this study showed that patients who underwent R1 liver resection did not have significantly worse 5-year survival compared to patients who had R0 resection. This can be explained by the following factors:

1. Multimodal neoadjuvant chemotherapy and adjuvant chemotherapy after hepatic metastasectomy: It has been shown that preoperative chemotherapy does not only convert the initially unresectable disease to resectable (downstaging-downsizing), but is also used to improve the complete resection rate, and increase disease-free survival for resectable CRC (29, 30, 31).

The multimodal neoadjuvant therapy of CRLM is based on the following cytotoxic agents: fluoropyrimidine [intravenous 5-fluorouracil (5-FU) and leucovorin (LV)], oxaliplatin (FOLFOX) and irinotecan (FOLFIRI). The therapy can be expanded with the use of biological targeted agents (bevacizumab, cetuximab, panitumumab) to increase its efficiency (32-34).

There is clear evidence that the adjuvant therapy after hepatic-metastasectomy is capable of reducing cancer reoccurrence and increasing survival (28).

2. "Kelly-clamp crashing technique": with clamp transection of the liver parenchyma (with a mosquito clamp) the surgeon is capable of crushing 2-4 mm parenchyma in the resection line (35-37).

3. Ultrasonic dissectors and other modern parenchyma dissectors (such as harmonic scalpels, or CUSA) which are nowadays used, "dissolves" hepatic tissue on the resection surface as well (35, 38). In a non-randomized study by Kim *et al*. the use of Harmonic Scalpels was associated with decreased operative time and decreased blood loss and transfusion requirement. However, there was also a significant increase in the incidence of postoperative bile leaks (39). CUSA can be used in cirrhotic as well as non-cirrhotic livers, and is associated with a low blood loss and low risk of bile leak (40).

4. We routinely coagulated the resection surface in "spray mode" with maximum energy to prevent bleeding. Gananadha *et al*. published an ex vivo investigation, in which the authors presented that the spray diathermia can cause 3-4 mm deep tissue destruction in the liver (41).

In addition to the factors listed above the expected survival is increasing. 5-year survival rates for hepatic colorectal metastases patients have almost doubled since the 1990s and the need for repeated surgeries is growing too (28).

Both animal and human investigations showed that the liver is capable of remarkable self-regeneration. However, the loss of physiological function seems to be almost directly proportional to the loss of parenchyma (42-44). Furthermore, it is well known that chemotherapy is associated with high incidence of parenchymal injury (45).

Taking this into account it is obvious that the resectable volume is finite and it would be important to remove the minimum amount of useful liver tissue as possible.

Moris *et al*. published a systematic review including 2505 CRLM resected patients, which did not show significant 5-year overall survival differences between parenchymal sparing and anatomic liver resection in CRLM patients. In agreement with these findings, in our investigation/follow-up study the type of resection (non-anatomic liver resections, segment resection, or lobectomy) had no significant effect on the 5-year survival.

Vascular R1 resection could be a barrier to make parenchymal sparing liver resection, but based on an observation cohort, vascular R1 resection achieved equivalent outcomes to R0 resection in the selected cases (46, 47).

In short, the present study showed that in the era of modern chemotherapeutics and developed surgical devices the 5-year survival is similar for a patient with R0 and R1 resection, and there seems to be no significant difference between anatomic and non-anatomic liver resection.

Conclusion

We suggest that in CRC patients receiving multimodal chemotherapy, the preferred surgical technique should be a parenchymal-sparing non-anatomic resection using modern surgical devices to keep as much liver parenchyma as possible. Furthermore, the resection surface should be coagulated to prevent bleeding and to reduce the number of remaining tumor cells. Of course, the goal is to achieve microscopically-negative surgical margin, but in some cases vascular microscopically-positive surgical margin and vascular R1 resection can be an acceptable result as there seems to be no significant difference in survival.

Conflicts of Interest

The Authors declare that there is no conflict of interest regarding the publication of this article.

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