Treatment strategies and outcome of surgery for synchronous colorectal liver metastases

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Summary

OBJECTIVES: To report survival following different operative strategies and perioperative chemotherapy in patients with synchronous colorectal liver metastases in a tertiary academic referral centre.

METHODS: We performed a retrospective analysis, based on a prospective database, of patients who presented with synchronous colorectal liver metastases. Follow-up data were obtained from medical records, letters or telephone contacts. The main endpoint was overall survival. An additional event of interest was postoperative mortality according to treatment strategy. Predefined variables were analysed to identify associated risk factors.

RESULTS: Overall, 109 patients undergoing liver resection for synchronous colorectal liver metastases between 2000 and 2010 were identified. The majority of patients had resection of the primary tumour first (n = 82), the classic approach; notably fewer were treated according to a combined (n = 20) or a reverse "liver first" strategy (n = 7). Most patients (92%) received preoperative, interval and/or postoperative chemotherapy. Median overall survival of the entire population was 33.6 months (interquartile range [IQR] 11–92.7 months). Patients undergoing classic surgery had a median overall survival of 40.3 months (IQR 14.9–96.6 months). The 3-year survival rates of the three patient groups were 53% in the classic, 47% in the combined and 58% in the reverse group. The lowest rate of 180-day mortality (9%) was after the classic surgical approach. On a multivariate Cox proportional hazards regression analysis, patient age >60 years (hazard ratio [HR] 2.1, 95% confidence interval [CI] 1.1–3.9; p = 0.018), R2-status (HR 2.08, 95% CI 1.03–4.2; p = 0.040), and >4 liver metastases (HR 2.4, 95% CI 1.2–4.6; p = 0.011) were associated significantly with worse overall survival.

CONCLUSIONS: In patients undergoing surgical resection for synchronous colorectal liver metastases, promising survival rates could be achieved, irrespective of the chosen surgical strategy. The presence of five or more liver metastases, patient age over 60 years and R2-status were found to be adverse risk factors.

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Introduction

Colorectal cancer is the third most common malignancy in men and women [1]. The liver is the most common site of haematogenous metastases. The last two decades have seen dramatic improvements in liver surgery techniques, and the limits of resectability have changed in recent years. Surgery remains the only potentially curative treatment for resectable liver metastases. According to the literature, 20 to 50% of patients with resected liver metastases will survive 5 years or longer [2–5], and complete resection of liver metastases has become a standard of care. In younger patients with healthy liver tissue, as much as 75% of the liver can be safely resected [6]. Perioperative mortality rates of less than 5% have been reported in high-volume expert centres [7].

However, despite liver resection with curative intent, recurrences are frequent and approximately half of them occur in the liver only [5]. Complementing liver surgery by chemotherapy has become a widely accepted approach, aiming to treat micrometastases and to improve outcome. A randomised study by the European Organisation for Research and Treatment of Cancer [8] demonstrated that perioperative administration of 5-fluorouracil (5FU)- and oxaliplatin-based chemotherapy improved progression-free survival and showed a trend towards improved overall survival over surgery alone for patients with resectable liver metastases [9]. The evidence for a benefit is less clear for adjuvant chemotherapy after liver resection. Pooled analyses suggest a benefit for 5FU-based regimens with or without oxaliplatin [10, 11]. Other studies demonstrated that some initially unresectable disease can be rendered resectable by preoperative chemotherapy [12]. However, the optimal chemotherapy regimen has not been defined yet.

Approximately 20% of newly diagnosed patients with colorectal cancer have synchronous liver metastases. The synchronous presentation of liver metastases is associated with a worse outcome [13]. The traditional ("classic") strategy for these patients has been resection of the primary tumour followed by liver resection, in combination with

chemotherapy. Another option is a combined approach with simultaneous resection of both the primary tumour and the liver metastases. The third option is the so called "reverse" strategy, with resection of the liver metastases first and then resection of the colorectal primary in a second step [14]. The latter strategy seems to be specifically attractive for patients with extensive colorectal liver metastases, and most patients receive chemotherapy beforehand in order to reduce the size of the liver metastases.

Our multidisciplinary team has routinely incorporated chemotherapy into the treatment plan for patients with synchronous liver metastases. Furthermore, while tailoring treatment to the specific needs of the patients, in recent years we have been considering all three surgical strategies. Treatment options were discussed at an interdisciplinary tumour board, and for individual recommendations both the presence or absence of symptoms and the extent of the disease were considered. Formal guidelines on which treatment strategy to choose did not exist.

The aim of this analysis was to review the treatment modalities implemented in a multidisciplinary setting in a tertiary academic referral centre, to report mortality after extended periods of 90 and 180 days after surgery, including the causes of death, and to report the disease-free and overall survival of the patients.

Methods

Data collection

We performed a retrospective analysis based on a prospectively collected database. Eligible patients for this analysis had newly diagnosed colorectal cancer with synchronous colorectal liver metastases, and were treated between May 2000 and October 2010 at the University Hospital Zurich. Patients who had undergone resection of their primary tumour at another institution were also eligible if the subsequent liver surgery was performed at our hospital. However, patients with incidental intraoperative discovery of synchronous liver metastases were excluded, as the presence of liver metastases was not known when the interdisciplinary therapeutic strategy was defined. Data not yet recorded in the prospective database were extracted from the electronic patient charts. We assessed the treatment strategy chosen, the type of chemotherapy regimen, including the use of the monoclonal antibodies cetuximab or bevacizumab (when applicable), the timing of the chemotherapy and the type of resection, as well as postoperative fatal complications and mortality rates at 90 and 180 days after surgery. The main endpoint was overall survival, calculated from the time of final resection to death or to last follow-up. Patient follow-up was obtained from medical records, letters or telephone contacts. This analysis was approved by the local ethical committee (KEK-ZH-Nr. 2015-0055).

Treatment strategies

Our non-codified policy was, and still is, to resect colorectal liver metastases either upfront shortly after resection of the primary tumour, or after 2 to 3 months of preoperative chemotherapy – often including monoclonal antibodies – in patients with a high tumour burden considered initially nonresectable. Radiological assessments including fluorodeoxyglucose-positron emission tomography / computed

tomography (FDG-PET/CT) and liver magnetic resonance imaging are performed at baseline and then every 2 to 3 months during active treatment, and approximately every 6 months during follow-up.

All patients were discussed (sometimes repeatedly) at our weekly multidisciplinary tumour board of expert liver surgeons, medical oncologists, radiation oncologists, gastroenterologists, radiologists and pathologists aiming for a consensual therapeutic recommendation. The main decision factors were the extent and location of the primary tumour, the preservation of sphincter function in the case of rectal primaries, the extent of the hepatic tumour load and, when patients had undergone neoadjuvant chemotherapy, the response and the amount of residual disease.

The surgical treatment strategies in patients with synchronous disease were defined as "classic" (resection of the primary followed by liver resection at a second operation), "combined" (combining colorectal and planned liver resection in a single operation) and "reverse" (first liver resection followed by resection of the colorectal primary at a second operation). In cases of complete radiological tumour regression after chemotherapy, the original volume of the liver parenchyma involved was resected. Depending on the tumour burden in the liver, either a one-step or a two-step liver resection was performed. A two-step approach consisted of a first surgery aiming at resection of only parts of the liver metastases and in most cases an additional ligation of the alternate side portal vein in order to induce hypertrophy to the remnant liver. The second liver surgery was then performed a few weeks later after adequate parenchymal hypertrophy had occurred. The modern approach of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS procedure) was not yet available at the cut-off date. Patients undergoing ALPPS are not included in this analysis. Radiofrequency ablation was used in a minority of patients in combination with liver resection, when complete surgical resection was not possible.

After liver surgery, the margins were determined through serial sectioning by a pathologist. A positive margin was defined as the finding of microscopic (R1) or gross (R2) disease at the inked liver resection margin. Patients who were assigned to a two-step procedure for their liver disease but did not proceed to the second step were also considered R2-resected.

Statistical analysis

We expressed the distribution of variables using means and standard deviation [15] for normally distributed data, and medians and interquartile ranges (IQRs) for non-normally distributed data.

We compared the primary endpoint (overall survival) between the three groups (classic vs combined vs reverse procedure) using univariate and multivariate Cox proportional hazards regression models that take into account time to event and censoring at either occurrence of event (death), loss to follow-up or end of follow-up, with results presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Confounding factors included in the multivariate model were chosen *a priori* based on clinical interest and scientific knowledge. Based on this, the multivariate model was adjusted for possible confounders such as age, R-status (R1/R2), nodal-status (positive/negative),

preoperative chemotherapy (yes/no), postoperative chemotherapy (yes/no) and number of lesions in the liver (≤4/>4). Kaplan-Meier survival curves were used to present disease-free and overall survival. The survival curves were also stratified according to R-status and administration of chemotherapy. A p-value ≤0.05 was considered statistically significant. All statistical analyses were performed using STATA software (version 13, Stata Corp., College Station, Texas).

Results

Patient and treatment characteristics
During the study period, May 2000 to October 2010, 109 patients undergoing liver resection for synchronous colorectal metastases were identified. Patient and treatment characteristic are summarised in table 1. The median age of the patients was 58 years. Over half of the patients (59, 54%) had >4 liver lesions and 19 patients (17%) presented with extrahepatic disease, mostly in the lungs and/or peritoneum.

In 82 patients the primary tumour was resected first, 20 had a combined resection of both primary and liver metastases, and 7 patients underwent liver resection followed by resection of the primary tumour (reverse strategy). The majority of patients having a classic or combined strategy had a colon tumour (77% and 75%, respectively); most patients in the reverse group presented with a rectal primary (71%). A greater proportion of the patients with bilobar hepatic

disease (71%) underwent the reverse strategy as compared with the other groups (classic 62%, synchronous 55%).

Of the 109 patients, 99 (92%) received chemotherapy, either before surgery, between two surgical steps, and/or after surgery. Sixty-eight patients (83%) in the classic strategy group received preoperative chemotherapy, compared with only 6 (30%) in the combined and 5 (71%) in the reverse group. Monoclonal antibodies (bevacizumab or cetuximab) were administered preoperatively to 38 patients (46%) in the classic strategy group, 4 patients (20%) in the combined and 4 patients (57%) in the reverse group. Three patients from the classic strategy group received an antiangiogenic tyrosine kinase inhibitor within a clinical study protocol (table 1).

Intraoperative characteristics and histological results of all three strategies are summarised in table 2. Macroscopically complete resection was achieved in 68 (83%), 18 (90%) and 7 (100%) patients, respectively, in the classic, combined and reverse strategy groups. A one-step liver surgery was performed in 55 patients (67%) in the classic strategy as compared with 14 patients (70%) and 6 patients (86%) in the combined and reverse groups.

Mortality after surgery
The overall 90-day mortality rate was 7%, 3 out of 82 (4%), 3 out of 20 (15%) and 1 out of 7 (14%), in the classic, combined and the reverse strategy groups, respectively. Overall mortality rates after 180 days was 9%, 25% and

Table 1: Patient demographics.

	All patients n = 109	Classic strategy n = 82	Combined strategy n = 20	Reverse strategy n = 7
Median age, years (interquartile range)	58.4 (51.8–66.6)	58.3 (51.8–66.0)	58.6 (52.3–72.7)	54.5 (47.9–66.7)
Sex, female/male, n (%)	37/72 (34/66%)	28/54 (34/66%)	7/13 (35/65%)	2/5 (29/71%)
Primary tumour, n (%)				
Colon	80 (73%)	63 (77%)	15 (75%)	2 (29%)
Rectum	29 (27%)	19 (23%)	5 (25%)	5 (71%)
Extrahepatic disease, n (%)	19 (17%)	15 (18%)	2 (10%)	2 (29%)
Lung	12 (11%)	8 (10%)	2 (10%)	2 (29%)
Peritoneum	4 (4%)	4 (5%)	0	0
Other	3 (3%)	3 (4%)	0	0
Number of initial hepatic lesions, n (%)				
≤ 4 lesions	50 (46%)	37 (45%)	11 (55%)	2 (29%)
> 4 lesions	59 (54%)	45 (55%)	9 (45%)	5 (71%)
Bilobar CRLM, n (%)	67 (62%)	51 (62%)	11 (55%)	5 (71%)
Preoperative chemotherapy, n (%)	79 (73%)	68 (83%)	6 (30%)	5 (71%)
Folfiri-based	20 (18%)	19 (23%)	1 (5%)	0
Folfox-based	45 (41%)	39 (48%)	3 (15%)	3 (43%)
5FU or capecitabine	3 (3%)	2 (2%)	0	1 (14%)
Floxuridine	2 (2%)	2 (2%)	0	0
Folfoxiri	2 (2%)	2 (2%)	0	0
Sequential Folfox- and Folfiri-based	7 (6%)	4 (5%)	2 (10%)	1 (14%)
Folfiri-based	20 (18%)	19 (23%)	1 (5%)	0
Preoperative monoclonal antibodies, n (%)				
None	30 (28%)	26 (32%)	2 (10%)	1 (14%)
Cetuximab	5 (5%)	3 (4%)	0	2 (29%)
Bevacizumab	38 (35%)	33 (40%)	3 (15%)	2 (29%)
Cetuximab and bevacizumab	3 (3%)	2 (2%)	1 (5%)	0
VEGF-TKI[*]	3 (3%)	3 (4%)	0	0
Missing data	30 (28%)	15 (18%)	14 (70%)	2 (29%)

5FU = 5-fluorouracil; CRLM = colorectal liver metastases; VEGF-TKI = vascular endothelial growth factor-tyrosine kinase inhibitor * Antiangiogenetic tyrosine kinase inhibitor or placebo within study protocol

29% (table 3). Notably, four of these patients developed fatal tumour progression within 180 days. The main causes for cumulative mortality up to 180 days after surgery were pulmonary failure (four patients), sepsis (two patients), small for size liver (two patients), and peritonitis and suicide (one patient each).

Survival

The median observation time from the time of liver resection was 24.3 months (IQR 11.5–46.2 months). The median overall survival of the entire population, including the patients who did not complete the planned resection strategy, was 33.6 months (IQR 11–92.7 months). In the classic resection group, the median overall survival was 40.3 months (IQR 14.9–96.6 months), in the combined resection group 12.5 months (IQR 4.5–61.4 months), and was not reached for the reverse strategy group (fig. 1). The 3-year survival rates of the three patient groups were 53%, 47% and 58%, respectively. The Cox proportional model for the combined vs the classic strategy showed a hazard ratio of 2.6 (95% CI 1.2–5.7; p = 0.021) in favour of the classic strategy. Reverse vs combined strategy revealed a hazard ratio of 0.2 (95% CI 0.04–0.98; p = 0.047) in favour of the reverse approach. The corresponding hazard ratio for the reverse vs the classic strategy was 0.6 (95% CI 0.2–2.1; p = 0.433). The median disease-free survival was 7.2 months (IQR 3–19.7 months) for all patients. The median disease free survival was 7.7 months (IQR 3.3–19.6 months) in the classic resection group, 7.4 months (IQR 2.3–20.7 months) in the combined resection group, and 3.3 months (IQR 2.5–6 months) for the reverse strategy group (fig. 2). No statistically significant difference was seen between the three groups: combined vs classic: HR 1.5, 95% CI 0.7-2.9; p = 0.297; reverse vs classic HR 2.0, 95% CI 0.9–4.5; p = 0.110; and combined vs reverse HR 0.8, 95% CI 0.2–3.1; p = 0.768.

Influence of perioperative chemotherapy

The use of any form of perioperative chemotherapy – preoperative, interval and/or postoperative – did not show any statistically significant influence when compared with the few patients (n = 10, 8%) not receiving any perioperative chemotherapy. The median overall survival was 31.5 months (IQR 2.1 months – not reached) without and 40.2 months (IQR 11.8–92.7 months) with chemotherapy (HR 1.2, 95% CI 0.4–3.9; p = 0.785) (fig. 3).

Predictive factors

In a multivariate Cox proportional hazards regression analysis, patient age >60 years (HR 2.1, 95% CI 1.1–3.9;

Figure 1: Overall survival according to treatment strategy. The classic approach refers to resection of the primary tumour first followed by liver surgery. The combined approach refers to simultaneous resection of the primary tumour and liver metastases. The reverse approach refers to resection of liver metastases before resection of the primary tumour. In the classic resection group, median overall survival was 40.3 months (IQR 14.9–96.6 months), in the combined resection group 12.5 months (IQR 4.5–61.4 months), and was not reached for the reverse strategy group. Classic vs combined strategy: HR 2.6 (95% CI 1.2–5.7; p = 0.021); classic vs reverse strategy: HR 0.6 (95% CI 0.2–2.1; p = 0.433); combined vs reverse strategy: HR 0.2 (95% CI 0.04–0.98; p = 0.047).
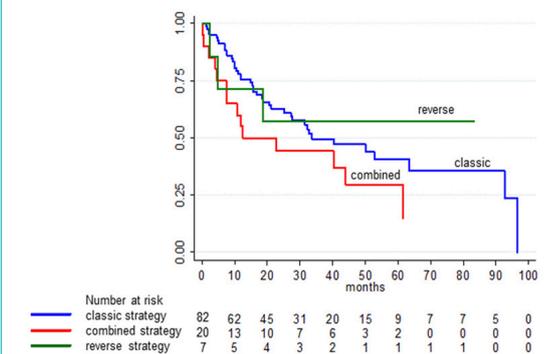
Table 3: Mortality rates after surgery.

	90-day mortality	180-day mortality
Classic	4% (3 out of 83)	9% (7 out of 82)
Combined	15% (3 out of 20)	25% (5 out of 20)
Reverse	14% (1 out of 7)	29% (2 out of 7)

Table 2: Intraoperative parameters and histological results.

	All patients n = 109	Classic strategy n = 82	Combined strategy n = 20	Reverse strategy n = 7
Nodal status positive, n (%)	77 (71%)	56 (68%)	15 (75%)	6 (86%)
R-status of liver resection, n (%)				
R0	61 (56%)	46 (56%)	11 (55%)	4 (57%)
R1	32 (29%)	22 (27%)	7 (35%)	3 (43%)
R2	16 (15%)	14 (17%)	2 (10%)	0%
Liver resection, n (%)				
One step	75 (69%)	55 (67%)	14 (70%)	6 (86%)
Two step	24 (22%)	17 (21%)	6 (30%)	1 (14%)
Relapse resection	1 (1%)	1 (1%)	0	0
Failed two step	9 (8%)	9 (11%)	0	0
Portal vein ligation, n (%)	22 (20%)	19 (23%)	3 (15%)	0
Type of liver resection, n (%)				
Hemihepatectomy incl. extended	63 (58%)	49 (60%)	10 (50%)	4 (57%)
Typical wedge	45 (41%)	32 (39%)	10 (50%)	3 (43%)
Atypical wedge	1 (1%)	1 (1%)	0	0
Additional surgery, n (%)				
Extrahepatic metastasectomy	3 (4%)	3 (5%)	0	0
Ablation	9 (8%)	7 (9%)	1 (5%)	1 (14%)

p = 0.018), R2-status (HR 2.08, 95% CI 1.03–4.2; p = 0.040), and presence of more than four liver metastases (HR 2.4, 95% CI 1.2–4.6; p = 0.011) were associated with a significantly worse overall survival.

Median overall survival in patients with R0 resection was 52.7 months (IQR 8.9 months – not reached), whereas survival for those patients with R1 resection was 20.5 months (IQR 6.3 months – not reached; R1 vs R0 HR 9.4, 95% CI 1.1–79.2; p = 0.040) and for patients with R2 resection status was 10.7 months (IQR 5.9 months – not reached; R2 vs R0 HR 8.6, 95% CI 0.9–79.2; p = 0.057). The corresponding hazard ratio for R1 vs R2 was 0.95 (95% CI 0.4-2.4; p = 0.92) (fig. 4).

Discussion

This study reports the outcome of patients with synchronous liver metastases of colorectal cancer treated by a multidisciplinary team at a Swiss tertiary referral centre. Most patients underwent classic surgery, with resection of the primary first. The best survival rates were observed in patients whose disease burden allowed for a complete resection (R0-resection).

Determining the best strategy for patients with synchronous liver metastases is challenging because a number of factors need to be taken into account. The reverse approach has expanded our treatment options for patients with synchronous liver metastases from colorectal primaries in recent years. During the observed decade, only a minority (20 out of 109 patients) were treated according to a combined strategy, and an even smaller number (7 out of 109 patients) according to a reverse treatment approach. Patients treated according to the reverse strategy had predominantly rectal primaries, advanced (more than four lesions) and/or bilobar liver disease.

The median overall survival was 34 months for all patients, including the patients who did not complete their planned two-step resection. The longest survival was seen in patients in the classic strategy group, with a median of 40 months. The relative risk of death was more than doubled in the combined compared with the classic strategy group (HR 2.6, 1.2–5.7; p = 0.021). This discrepancy is surprising, since fewer patients in the combined group had advanced/bilobar disease and extrahepatic spread, compared with the patients assigned to the classic approach. This difference in outcome may be in part due to the higher 90-day mortality rate in the combined patient group (15% vs 4%), though patient numbers were too small to perform meaningful statistical comparisons. However, if the estimated 3-year overall survival is taken into account, the results were rather similar in all three groups, at about 50%, highlighting the potential to achieve long-term survival with different surgical techniques.

Our survival results are in line with other reports, considering that the majority of the patients had extensive disease with five or more liver metastases, and more than 60% of the patients had bilobar disease [16–18]. In addition, almost 20% of our patients had extrahepatic tumour spread. The presence of synchronous liver metastases and extrahepatic spread are established adverse prognostic factors *per se*. However, this cohort of more than 100 patients represents real-world experience and the large proportion of patients with adverse risk factors may have contributed substantially to the outcome. As in other reports, our series suggests that aggressive treatment, incorporating chemotherapy and extended surgery, may improve out-

Figure 2: Disease-free survival according to treatment strategy. The median disease-free survival was 7.7 months (IQR 3.3–19.6 months) in the classic surgery group, 7.4 months in the combined resection group (IQR 2.3–20.7 months), and for the reverse strategy group 3.3 months (IQR 2.5–6 months). Combined vs classic strategy: HR 1.5 (95% CI 0.7–2.9; p = 0.297); reverse vs classic strategy: HR 2.0 (95% CI 0.9–4.5; p = 0.110); combined vs reverse strategy: HR 0.8 (95% CI 0.2–3.1; p = 0.768).
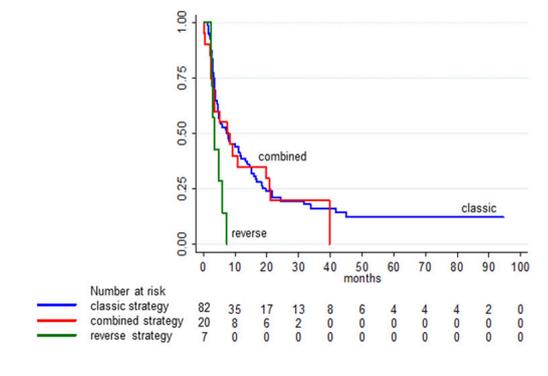

Figure 3: Impact of perioperative chemotherapy on overall survival. Median overall survival was 31.5 months (IQR 2.1 months – not reached) without chemotherapy vs 40.2 months (IQR 11.8–92.7 months) with any chemotherapy.
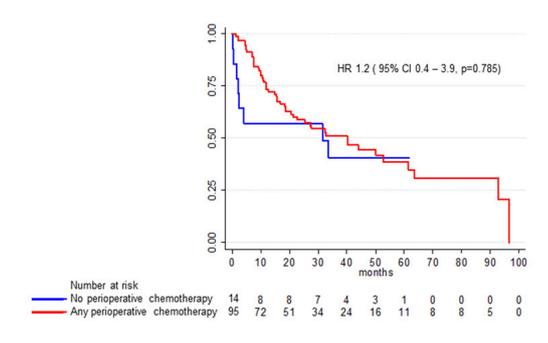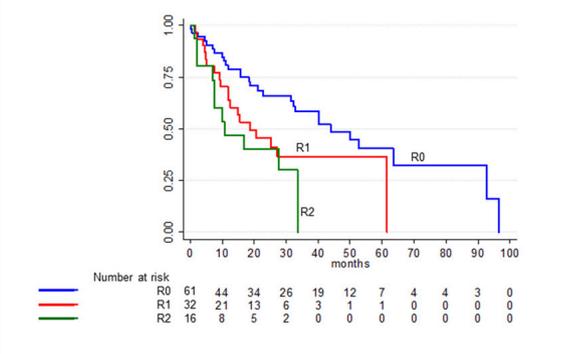

Figure 4: Overall survival according to resection status. Median overall survival in patients with R0 resection was 52.7 months (IQR 8.9 months – not reached), whereas survival for those patients with R1 resection was 20.5 months (IQR 6.3 months – not reached), and for patients with R2 resection status 10.7 months (IQR 5.9 months – not reached). R0 is associated with improved survival; R1 vs R0: HR 9.4 (95% CI 1.1–79.2; p = 0.040); R2 vs R0: HR 8.6 (95% CI 0.9–79.2; p = 0.057); R1 vs R2: HR 0.95 (95% CI 0.4–2.4; p = 0.92).

come in selected patients even with extensive tumour burden [19, 20].

Earlier studies have suggested different prognostic factors in order to improve patient selection for aggressive surgery [21–23]. Size and number of liver metastases, among others, were described as negative prognostic factors, although no consensus about the appropriate cut-offs was reached. Fong et al. developed a score [24], which includes number and size of liver metastases, preoperative carcinoembryonic antigen levels and lymph node positivity as independent risk factors. In our study, negative margins (R0) were associated with superior survival (53 months vs 20.5 months for R1 and 11 months for R2). Furthermore, we found that age >60 and more than 4 tumour lesions in the liver were significantly associated with a worse overall survival. Main reasons for early mortality were tumour progression, pulmonary failure and sepsis. Liver-related fatal perioperative complications occurred rarely (small for size liver, two patients).

For our patients following a classic strategy, chemotherapy was routinely administered between resection of the primary and liver resection. In patients undergoing combined resection, perioperative chemotherapy was commonly administered. In patients for whom the reverse strategy was chosen, chemotherapy was administered before liver resection in the majority of cases. A delay of chemotherapy in this particular population, allowing tumour progression, would probably preclude curative surgery. However, we found that chemotherapy administration, with or without monoclonal antibodies, showed a trend but did not significantly improve survival independently of the chosen strategy, compared with the patients who did not receive chemotherapy before or after liver surgery. This result is not surprising, as most patients had received some form of systemic treatment, and patient numbers in this analysis were too small to draw meaningful conclusions. However, a prospective randomised controlled trial and a few pooled analyses of available data suggest that perioperative or adjuvant chemotherapy may contribute to improved outcome [10, 11, 25].

This was a retrospective analysis at a single institution, and selection bias and other unknown confounders may be inherent. To control for confounding effects, we adjusted the results for possible, assesse, and known confounders by using multivariable regression analysis. Since we are a tertiary referral centre, some of the primary treatment decisions had been made at other institutions. Small patient numbers limit the statistical power to draw specific conclusions. Additionally, the comparison between strategies is formally difficult in a retrospective analysis because the choice strategy depends mainly on the extent of the disease; thus, differences in outcome may simply reflect the differences of the tumour burden between the groups. This assumption is supported by the rather short disease-free survival in patients undergoing reverse surgery as compared with the other two approaches, although numbers were too small to demonstrate statistically significant differences. Patient heterogeneity may be also an explanation for the higher mortality rates seen in the reverse and combined surgery groups compared with the classic surgery group. As every centre may apply different selection criteria for surgical treatment, the reported patient outcome may thus differ between institutions. Lastly, we cannot provide comprehensive data on second-line treatment, since this information was not systematically recorded. However, we assume that best available therapy was provided according to the treating physician.

In only a minority of patients with liver metastases of colorectal cancer can the metastases be completely resected. Innovative surgical and interventional techniques, such as portal vein embolisation or ligation, staged hepatectomy and radio frequency ablation, have been developed in recent years [6, 26, 27]. Recently, the ALPPS procedure has been introduced and shown promising results, especially in patients with extensive bilobar disease [28, 29]. Additionally, several reports have shown the potential of preoperative chemotherapy to successfully downsize the disease and thereby improve resectability [30, 31]. Our group has employed broadly both perioperative chemotherapy and an aggressive surgical strategy. Our data show that long-term survival can be achieved, specifically for patients with completely resection, with a median overall survival of 53 months. Unfortunately, most patients experience intra- or extrahepatic disease recurrence [32] regardless of the treatment strategy. This emphasises the need to develop more effective anticancer drugs and to carefully select patients for a particular surgical strategy.

Conclusion

In selected patients undergoing surgical resection for synchronous colorectal liver metastases, promising survival rates could be achieved, irrespective of the chosen surgical strategy. The treatment strategy depended on various factors, mainly the extent of liver disease, and was chosen for each individual patient by a multidisciplinary team. The presence of five or more liver metastases, patient age over 60 years, and R2-status were found to be adverse risk factors, whereas complete (microscopic) tumour resection is crucial for improved survival.

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