Int J Colorectal Dis (2013) 28:1009–1017
DOI 10.1007/s00384-013-1648-2

ORIGINAL ARTICLE

Metastatic recurrence after complete resection of colorectal liver metastases: impact of surgery and chemotherapy on survival

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Accepted: 21 January 2013 / Published online: 1 February 2013

Abstract
Purpose Surgery is the standard of care for resectable colorectal liver metastases (CRC-LM). Unfortunately, 60 % of patients develop secondary metastatic recurrence (SMR) after R0-resection of CRC-LM. We investigated the impact of surgical re-intervention and chemotherapy (Ctx) on survival in a consecutive series of patients with SMR.
Methods From 01/2001 to 11/2011, 104 out of 178 consecutive patients with R0-resection of CRC-LM developed SMR and were evaluated. The impact of surgical and Ctx re-interventions on recurrence free (RFS) and cancer-specific survival (CSS) was analyzed. Median follow-up was 28.0 (95 %CI: 19.4–37.4) months.
Results SMR occurred in 81 patients at a single site (49× liver, 18× lung, 14× other) and in 23 patients at multiple sites. Forty-two patients were scheduled for primary surgery. Fifty-three patients were classified as non-resectable and treated with median 5.0 [IQR, 3.0–10.0] cycles of Ctx, combined with an EGFR/VEGF-antibody in 27 patients. Nine patients received best supportive care only. R0/R1 resection could be achieved in 35 patients primarily and even in 8 patients secondarily after Ctx. Surgical morbidity and mortality were 16 and 0 %, respectively. The 5-year RFS rates for patients with R0 versus R1-resection were 22 and 24 % (p=0.948). The 5-year CSS rate for R0/R1-resected patients was 38 % versus 10 % for those patients treated by Ctx alone (p<0.001).
Conclusion In SMR, surgical re-intervention is feasible and safe in a remarkable number of patients and offers significantly longer CSS compared to patients without resection.

Keywords Colorectal cancer · Liver resection · Second metastatic recurrence · Conversion chemotherapy · Secondary resectability

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Data have in part been presented at the 2012 ASCO Gastrointestinal Cancers Symposium, January 19–21 2012 in San Francisco, USA

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Introduction

Distant metastases are the predominant mode of failure of adjuvant or neoadjuvant multimodal treatment in CRC. More than 50 % of CRC patients experience distant metastases during the course of malignancy and the liver represents the predominant site of first metastatic relapse (CRC-LM). Regarding international guidelines, there is interdisciplinary consensus that complete (R0) resection is the only curative option in the treatment of patients with CRC-LM [1]. Five-year overall survival (OS) rates up to 58 % have been reported by specialized centers [2], but primary liver resection is an option only in 20 % of patients [3]. However, innovative

treatment approaches like preoperative intensive intravenous chemotherapy (Ctx) combined with targeted therapy (CELIM trial [4]) and two-stage liver resection with portal vein ligation [5, 6] have achieved secondary resectability in 28–75 % of patients, initially deemed non-resectable. Recently, the updated survival analysis of the CELIM trial has shown a higher median OS of 46.7 months for R0-resected patients compared to 27.3 months for non-resectable patients (p=0.002). These data demonstrate that a Ctx-induced conversion to secondary resectability is not only a technical issue but also associated with a survival benefit [7].

Unfortunately, approximately 60 % of patients develop early second metastatic recurrence (SMR) within 3 years after the first liver resection [8]. The main sites of these SMR are the liver or the lung but in 30 % of patients multiple sites can be affected [9]. Previous studies have demonstrated that in selected patients re-resection of isolated hepatic [10–14] or pulmonal [15, 16] SMR might result not only in encouraging survival rates similar to those after resection of the first metastatic recurrence but also in higher quality of life compared to continued palliative Ctx [17]. In their single-center experience, Adam et al. have even demonstrated a 5-year OS of 34 % after the third hepatectomy for recurrent liver metastases [18]. Therefore, efforts need to be focused on optimizing multidisciplinary treatment regimens to increase the number of patients suitable for resection of SMR. However, there is very rare evidence on the impact of surgery and Ctx in a consecutive cohort of patients suffering from SMR after previous R0-resection of first CRC-LM.

Therefore, in the present single-center study, we analyzed the feasibility as well as impact of surgical re-intervention and Ctx on survival in a series of consecutive patients with SMR.

Material and methods

Study population

From 01/2001 to 08/2011, 178 patients with liver-only colorectal metastasis (CRM) underwent histopathologically confirmed complete resection (R0-status was defined as tumor free resection margin ≥0.1 cm) of all CRC-LM at the Department of General and Visceral Surgery, University Medical Center Göttingen. Until the last date of observation (November 30th 2011), 104 of these patients developed SMR within a median recurrence free interval of 7.5 (95 %CI, 1.0–34.4) months. These patients represent the actual study cohort. All patient data had been prospectively collected in a database and study related procedures were approved by the local ethics committee and in accordance with the Helsinki Declaration of 1975, as revised in 2008.

Table 1 summarizes the clinicopathological data of all 104 patients including treatment procedures of both, the primary tumor and the first CRC-LM. Before resection of CRC-LM the standardized staging covered clinical examination, serum level of carcinoembryonic antigen (CEA), chest-X-ray or thoracic computed tomography (CT), contrast-enhanced abdominal CT or magnetic resonance imaging (MRI) and starting from 2006 on a fluorodeoxyglucose (^{18}F)-positron emissions tomography (FDG-PET). Standard treatment recommendation after first liver resection was a “wait and see”-strategy according to national S3-guidelines [19]. Despite this fact, 35 patients were treated by anti-CEA-radioimmunotherapy with ^{131}I-labetuzumab [20, 21] and 20 patients by Ctx according to the discretion of the interdisciplinary tumor board or referring oncologist. Prior to detection of SMR, 45 of 104 patients had received ≥2 systemic anticancer therapies (Ctx or radioimmunotherapy) for either the primary tumor and/or the CRC-LM.

After diagnosis of SMR staging procedures were concordant to those mentioned above. Given that there are neither controlled trials nor established guidelines for the treatment of SMR, interdisciplinary decision making in individual patients considered extent of disease, performance status, comorbidity, patients’ preference and investigators as well as institutional experience. Primary resection of SMR was intended only in patients with localized single-site recurrences. When non-resectability or unfavorable tumor biology, in particular rapid progression was expected, Ctx was indicated with re-evaluation for secondary resectability at regular intervals. Tumor response to Ctx was measured using the Response Evaluation Criteria In Solid Tumors criteria and classified as complete response, partial response, stable disease or progressive disease [22]. Resection of SMR was performed according to established surgical operating procedures. Intraoperative ultrasound was used routinely in all patients scheduled for repeated liver resection to detect occult hepatic CRM. Cases with intraoperative open radiofrequency ablation of single liver lesions in addition to surgery were classified as incomplete (R1) resection. Median follow-up interval from time of SMR diagnosis to last observation was 28.0 (95 %CI, 19.4–37.4)months.

Statistical analysis

Statistical analysis was performed using the Statistical Computing Software R (Free statistical software R, version 2.12.2, www.r-project.org). Recurrence free survival (RFS) was calculated only for those patients who experienced R0/R1-resection of SMR. Cancer-specific survival (CSS) was calculated from the date SMR had been diagnosed on time to cancer-specific death using the R package survival. Median survival data have to be interpreted as time to 50 % at

Table 1 Clinicopathological data of primary tumor and first (liver-only) metastatic recurrence

Parameter	Patients (%) $N=104$
Age[a]	62.8 [56.5–67.6]
Gender	
Female	43 (41 %)
Male	61 (59 %)
Primary tumor	
Colon	55 (53 %)
Rectum[b]	49 (47 %)
Neoadjuvant radiochemotherapy	
Yes[c]	16 (15 %)
No	82 (85 %)
Resection status	
0	99 (95 %)
≥1	5 (5 %)
UICC stage	
≤1	5 (5 %)
2	19 (18 %)
3	24 (23 %)
4	56 (54 %)
Adjuvant systemic chemotherapy	34 (33 %)
Number of liver metastases[a]	2.0 [1.0–3.0]
Diameter of largest liver metastasis (cm)[a]	3.0 [2.0–5.0]
Preoperative systemic chemotherapy	
5FU	8 (8 %)
5FU+oxaliplatin	29 (28 %)
5FU+irinotecan	8 (8 %)
+ cetuximab	5 (5 %)
+ bevacizumab	7 (7 %)
Number of cycles[a]	4.0 [2.0–7.0]
More than one line	4 (9 %)
Type of resection[d]	
Minor	45 (43 %)
Major	59 (57 %)
2-stage with PVO	13 (13 %)
mT-stage [36]	
1	10 (10 %)
2	37 (36 %)
3	17 (16 %)
4	40 (38 %)
Fong score[37]	
0–2	64 (62 %)
3–5	40 (38 %)
Nordlinger score[38]	
0–2	25 (24 %)
3–4	65 (63 %)
≥5	14 (13 %)
Postoperative (pseudo-adjuvant) therapy	
5FU	3 (3 %)
5FU+oxaliplatin	11 (11 %)
5FU+irinotecan	6 (6 %)
+Cetuximab	2 (2 %)
+Bevacizumab	0 (0 %)
Radioimmunotherapy with 131I-labetuzumab	35 (34 %)
Number of cycles[a]	
Systemic chemotherapy	4.5 [3.0–8.0]
Radioimmunotherapy	1.0 [1.0–1.4]

UICC Union for International Cancer Control, *5FU* 5-fluorouracil, *EGFR* epidermal growth factor receptor, *VEGF* vascular endothelial growth factor, *PVO* portal vein occlusion

[a] Expressed as median [*IQR* interquantile range]

[b] Up to 16 cm from the anal verve measured by rigid rectoscopy

[c] One patient with synchronous liver metastases received systemic 5FU-based chemotherapy only

[d] Minor resection is defined as <hemihepatectomy

risk. Survival data was visualized using Kaplan–Meier plots and significance was calculated using the Cox Proportional Hazards Model. Significance for comparison between groups was calculated using Fisher's Exact Test for categorical variables or variables that were discretized (e.g., gender, tumor stage, type of therapy) and using the Wilcoxon Test for numeric variables (e.g., age, size of metastasis). p values<0.05 were considered significant.

Results

Pattern of recurrence

The liver was the predominant site of second metastatic recurrence ($n=49$). The second most common site was the lung ($n=18$). Other localizations of single-site recurrences were abdominal/retroperitoneal lymph nodes ($n=4$), locally in the small pelvis ($n=4$), peritoneal ($n=3$), cerebral ($n=2$) and osseous ($n=1$). Eleven patients developed simultaneous liver and lung recurrences. Other coincidental localizations included lung and brain ($n=3$), lung and abdominal/retroperitoneal lymph nodes ($n=2$) and other double and triple combinations in 7 additional patients. The pattern of SMR was not significantly different between those patients who initially had unilobar versus those who had bilobar CRC-LM ($p=0.554$).

Treatment of second metastatic recurrence

The treatment algorithm of SMR for the whole study cohort is shown in Fig. 1. Forty-two of 104 patients were scheduled for primary resection of SMR while 53 patients were determined as non-resectable and treated by palliative Ctx. Nine

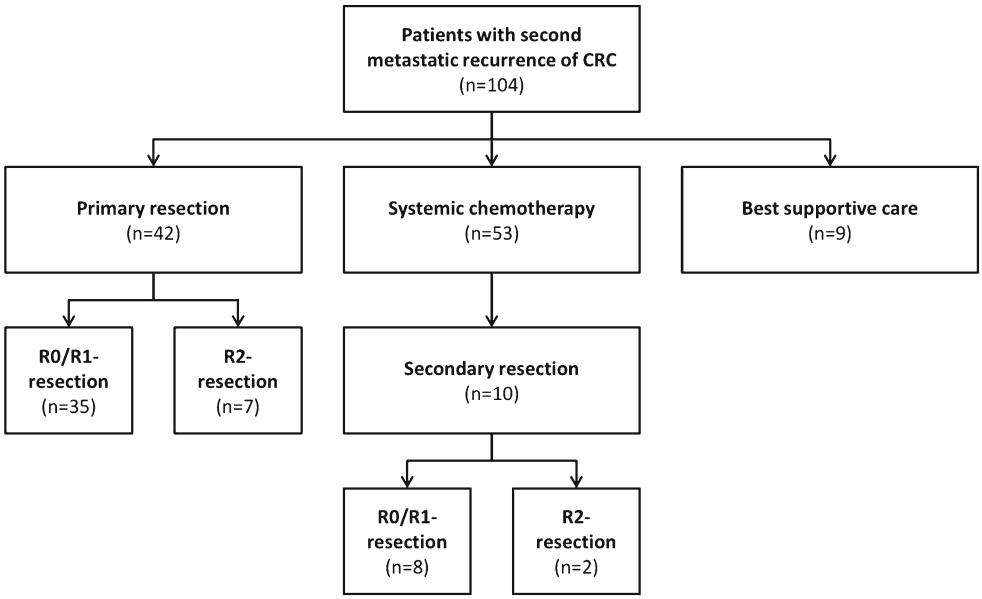

Fig. 1 Therapy algorithm for second metastatic recurrence. Primary and secondary R0/R1-resection could be achieved in 35 and 8 patients, respectively. The nine patients with R2-resection were postoperatively treated by palliative chemotherapy (n=6), radiotherapy (n=1) or chemotherapy with hyperthermia (n=1) while one patient denied further therapy. *CRC* colorectal cancer

patients denied any further therapy or the performance status was too poor for either surgery or Ctx. Therefore, these patients received best supportive care only.

Detailed treatment data for all patients except those treated by best supportive care are displayed in Table 2. In seven patients scheduled for resection of SMR intraoperative findings prevented macroscopically complete resection because of occult disseminated peritoneal carcinomatosis (n=2), extended lymph node metastases (n=2), unresectable progressive disease following portal vein ligation (n=1), inadequate remnant liver volume after previous extended hemihepatectomy and Ctx with oxaliplatin (n=1) and adjacence to vital cerebral structures (n=1). All these seven patients received palliative therapy. In detail, five patients were further treated by palliative Ctx, one patient with lymph node metastases requested Ctx with hyperthermia, and one patient suffering from cerebral metastasis received cerebral radiotherapy alone.

Of those 53 patients treated by Ctx, 19 had multi-site SMR and additional six patients had disseminated peritoneal, lymphatic, or osseous disease. Patients who received Ctx without either oxaliplatin or irinotecan were treated in the early study period. As a result of Ctx, three patients had complete radiographic remission of their metastases but developed third metastatic disease during follow-up (wait and watch strategy) localized at previous sites in all three patients. Partial response or at least stable disease was achieved in 16 patients. Of these 16 patients, 10 were scheduled for surgical exploration. Four of the remaining six patients had potentially resectable disease too, but three patients refused surgical re-intervention and 1 patient preferred brachytherapy of his residual metastases. In all ten patients scheduled for surgery, histopathologically confirmed R0-resection of targeted locoregional lesions could be achieved. Nevertheless, two cases were classified as incomplete (R2) resection because metastases at additional sites were not resected. In detail, one patient with hepatic and pulmonary SMR had divergent response to Ctx with stable liver metastases but slightly progressive pulmonary metastases. Based on good performance status and patients' request all pulmonary lesions were resected by bilateral thoracotomy. Postoperatively, the patient received Ctx and was alive as of the last observation. A second patient had pulmonary and cerebral metastases and experienced resection of cerebral metastases only as the lung metastases remained in stable disease status. However, this patient suffered from cerebral recurrence and died 22 months after surgery. The residuary 33 patients, classified as non-resectable for SMR, had progressive disease under continued Ctx and received up to five lines of palliative Ctx.

To identify differences in CRC biology and disease stage between the subgroups (primary resection, secondary resection, Ctx only) we performed pairwise comparisons for SMR-related parameters, in particular RFS (from previous liver resection to diagnosis of SMR) and number as well as largest diameter of SMR (Table 3). RFS and number of lesions were not statistically different distributed between the subgroups. The diameter of metastases was significantly greater in patients treated by Ctx only compared to those with primary resection of SMR (p=0.0465). Furthermore, metastatic affection of multiple sites was more often in patients treated by Ctx only compared to patients with primary or secondary resection (p<0.001).

Survival

RFS rates were calculated for patients with R0- and R1-status after resection of SMR. The 5-year RFS rates between R0 and R1 status were nearly identical with 22 versus 24 %,

Table 2 Data on treatment for second metastatic recurrence (n=95)

Parameter	Patients with primary resection (%) N=42	Patients with primary chemotherapy (%) N=53
Age[a]	62.9 [57–68.5]	65.3 [57.6–69.2]
Gender		
Female	16 (38 %)	22 (42 %)
Male	26 (62 %)	31 (58 %)
Side of recurrence		
Liver	31 (74 %)	14 (26 %)
Lung	5 (12 %)	13 (25 %)
Portal or retroperitoneal lymph nodes	1 (2 %)	3 (6 %)
Pelvic mass/local recurrence	3 (7 %)	1 (2 %)
Peritoneal carcinomatosis	1 (2 %)	2 (4 %)
Cerebral	1 (2 %)	–
Osseous	–	1 (2 %)
Lung + Liver	–	11 (21 %)
Lung + other	–	6 (11 %)
Other multiple sides	–	2 (4 %)
Number of metastases pretherapeutic[a]	1 [1.0–2.0]	4 [2.0–6.0]
Diameter of largest metastasis pretherapeutic (cm)[a]	1.9 [1.0–2.5]	2.5 [1.5–3.5]
Systemic 5FU-based chemotherapy (*first-line*)		
5FU	–	5 (9 %)
5FU+oxaliplatin	–	19 (36 %)
5FU+irinotecan	–	29 (55 %)
additional cetuximab	–	10 (19 %)
additional bevacizumab	–	18 (34 %)
Number of cycles[a]	–	5.0 [3.0–10.0]
Effect of systemic 5FU-based chemotherapy		
Progressive disease	–	34 (64 %)
Stable disease	–	11 (21 %)
Partial response	–	5 (9 %)
Complete response	–	3 (6 %)
Surgical Procedure		
Surgical exploration only	3 (7 %)	–
Surgical exploration + RFA liver	4 (10 %)	–
Non-anatomic liver resection	18 (43 %)	2 (20 %)
Bisegmentectomy	2 (5 %)	–
Bisegmentectomy + non-anatomic liver resection	–	1 (10 %)
Hemihepatectomy	3 (7 %)	–
Trisectorectomy	1 (2 %)	–
Rectal resection	3 (7 %)	–
Rectal extirpation + non-anatomic liver resection	–	1 (10 %)
Rectal extirpation + pulmonary wedge resection	–	1 (10 %)
Pulmonary wedge resection	5 (12 %)	3 (30 %)
Other	3 (7 %)	2 (20 %)
Resection status		
R0	26 (62 %)	8 (80 %)
R1	9 (21 %)	0 (0 %)
R2	7 (17 %)	2 (20 %)
Surgical morbidity	16 %	13 %
Surgical mortality	0 %	0 %
Postoperative treatment (*only R0/R1-resections*)		
None	16 (46 %)	4 (46 %)
Systemic 5FU-based chemotherapy	8 (23 %)	3 (38 %)
5FU alone	0 (0 %)	1 (13 %)
5FU + oxaliplatin	3 (9 %)	0 (0 %)
5FU + irinotecan	5 (14 %)	2 (25 %)
additional EGFR/VEGF-antibody	2 (6 %)	1 (13 %)
Number of cycles[a]	4.5 [2.8–6.5]	4.0 [2.5–4.5]
Radioimmunotherapy with 131I-labetuzumab	9 (26 %)	1 (13 %)
Number of cycles[a]	1.0 [1.0–2.0]	2.0 [2.0–2.0]
Radiotherapy	2 (6 %)	2 (25 %)

RFA radiofrequency ablation, *5FU* 5-fluorouracil, *EGFR* epidermal growth factor receptor, *VEGF* vascular endothelial growth factor

[a] Expressed as median [*IQR* interquantile range]

respectively (p=0.948, Fig. 2a). During follow-up, one patient with non-resectable intrahepatic relapse and three patients without evidence of recurrent disease died non-cancer related. For comparison of CSS rates between different oncological treatment procedures, all patients receiving best supportive care were excluded. Patients receiving potentially curative resection (R0/R1) of SMR had a 5-year survival rate of 38 % versus 10 % for patients with non-resectable malignancy continuously treated by palliative Ctx alone (p<0.001, Fig. 2b).

Discussion

During the last 10 years, treatment options in patients with metastatic colorectal cancer have been evolved by initiation of multidisciplinary therapeutic strategies. Most of these are using modern chemotherapeutic regimens including agents for targeted therapy as well as extended surgery to remove (residual) metastases. Thereby, the number of primarily or secondarily resected patients is increasing. Given that approximately two thirds of these patients experience relapse again, surgeons as well as medical oncologists

Table 3 Distribution of second metastatic recurrence related parameters between patients treated by primary surgery, secondary surgery and chemotherapy only

Parameter	Primary surgery (n=35)	Secondary surgery (n=8)	Chemotherapy only (n=52)
Number of metastases[a]	1.0 [1.0–2.0]	3.0 [2.0–6.5]	4.0 [2.0–6.0]
Diameter of largest metastasis (cm)[a]	1.9 [1.0–2.5]	2.5 [2.0–2.6]	2.0 [1.5–3.5]
Recurrence free survival in month[b]	7.9 [0.6–29.6]	9.4 [1.4–23.0]	6.8 [1.6–34.5]
Unilobar and bilobar liver metastases as first metastatic recurrence	20/15	4/4	28/24

[a]Expressed as median [*IQR* interquantile range]

[b]Expressed as median [95 %-CI]

are faced in clinical practice with a growing number of patients with SMR requesting further treatment. Therefore, data on what can be achieved in these patients by surgery and/or Ctx are needed.

Our single-center series of consecutive patients after R0-resection of CRC-LM has shown that repeated resection of SMR is feasible and safe in 40 % of patients. After re-resection of SMR patients showed a significantly longer CSS compared to non-resected patients treated by palliative Ctx alone.

Pattern of recurrence and previous oncological treatment

The pattern of SMR observed in our series was comparable to previous reports [8, 9, 23]. Stratifying patients according to the hepatic spread (unilobar versus bilobar) of initial CRC-LM, we could not observe the expected higher rate of intrahepatic SMR in the bilobar cohort. Repeated liver resection needed to be canceled only in one patient due to small remnant liver volume as reported. In contrast, in 10 of 28 patients with intrahepatic SMR scheduled for re-resection extended hemihepatectomies had been performed for initial CRC-LM. The postoperative course in all 28 patients was uneventful. In consequence, extended previous liver resections do not necessarily prohibit repeated resections for SMR as long as individual limitations, in particular liver tissue damage and involvement of vital anatomic structures are absent.

Treatment of second metastatic recurrence

There is very limited evidence on what can be recommended in patients with SMR. However, the goal of therapeutic intervention should be prolonged OS with acceptable quality of life and, if possible, without ongoing cytotoxic therapy. German guidelines [24] on the treatment of metastatic colorectal cancer do not include algorithms for patients with SMR after R0-resection of CRC-LM In contrast, the National Comprehensive Cancer Network guidelines mention that SMR limited to either liver or lung can be considered for re-resection in selected patients [25]. The crucial aspect of reasonable weighting treatment decisions is how to interpret the

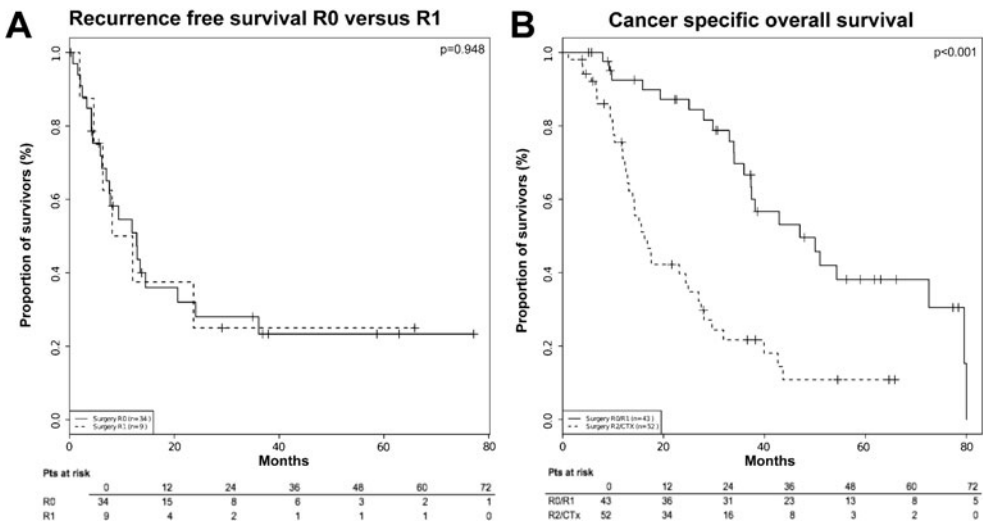

Fig. 2 Kaplan–Meier curve for recurrence free and cancer-specific overall survival. **a** Recurrence free survival for patients with R0 versus R1 resection of second metastatic recurrence (n=43). Five-year RFS rates for R0- and R1-resected patients were 22 and 24 % (p=0.948). **b** Overall cancer-specific survival for patients with R0/R1 resection versus R2-resection+palliative chemotherapy/palliative chemotherapy only for second metastatic disease (n=95). Five-year CSS rate was 38 % for R0/R1-resected patients versus 10 % for patients treated by palliative chemotherapy (p<0.001)

occurrence of SMR. Premature data from the SECA-trial evaluating the impact of liver transplantation in selected patients with unresectable CRC-LM showed that different from patients after resection of CRC-LM the majority of patients treated by liver transplantation developed extrahepatic recurrence [26]. These data support the hypothesis that to a certain extent occurrence of SMR more likely represents outgrowth of previously occult micrometastases instead of increasing aggressiveness. Therefore, when resection is the standard in initial CRC-LM, it would be consequent to aim for resection in SMR as well. Given that only 20 % of initial CRC-LM are considered resectable [3], our primary resection rate of 34 % in patients with SMR is encouraging. Resection rate and low morbidity, which has also been reported by Brachet et al. [27], further support multimodal treatment concepts including repeated surgery in patients suffering from SMR.

In the setting of initially unresectable CRC-LM Ctx-related conversion rates of 38–60 % to secondary resectability have been observed by using monoclonal EGFR/VEGF-antibodies in addition to Ctx [4, 28, 29]. In our study, secondary resection of SMR was performed in 15 % of patients initially treated with Ctx. Considering that four additional patients had resectable disease after Ctx, the percentage of resectable patients in this cohort even raised up to 23 %. However, monoclonal EGFR/VEGF-antibodies were introduced into clinical routine not until the second half period of the present study. We hypothesize that an even larger proportion of patients would qualify for secondary resection by using intensified Ctx protocols as investigated for example in the CELIM trial [8].

Although van der Pool et al. [30] found no difference in survival between patients with recurrent hepatic CRM treated by either RFA or liver resection, we classified patients sufficiently treated by RFA as R1 (n=5). A further four patients classified with R1-status had liver resections with the tumor being adjacent to remnant liver veins (n=2), resection of local recurrence limited by the sacrum (n=1) and resection of local peritoneal carcinomatosis (n=1). In all these patients, macroscopically complete resection was achieved. De Haas et al. [31] reported that survival following R1-liver resection is comparable to R0-resection. RFS in our nine patients classified as R1 was not significantly different compared to R0-resected patients. Therefore, we grouped patients with R0 and R1-resection together for CSS analysis and observed a significantly longer CSS compared to patients treated by palliative Ctx only. In concordance with Mise et al. [32] who evaluated resection in selected patients with single and multiple sites SMR, we consider a survival benefit when resection of SMR can be achieved.

Very recently, Hill et al. [33] proposed a scoring system to predict survival in patients with SMR based on three different parameters: CEA>200 ng/ml, >1 liver metastases and >5 cm liver metastases. Such scoring system would be very useful to stratify patients into different treatment concepts in particular primary resection versus preoperative chemotherapy. As we observed significant influence of treatment on survival, we advocate validating this initial experience in a larger independent patient cohort including treatment data.

It should be noted that the data of this retrospective study on patients in this advanced stage of disease with SMR are biased. Patients were not prospectively randomized into different treatment arms. The indication for the chemotherapy regimens was based on tumor biology (progression), toxicity and efficacy of previously applied therapies, introduction of innovative agents into clinical routine and physicians' discretion (multidisciplinary tumor board decision). However, in contrast to previous reports focusing on highly selected patients we present a consecutive series of patients with SMR. All patients have been treated in our center after introduction of advanced surgical techniques. The treatment decisions were consistently made by the same multidisciplinary team. Thereby, patients with resectable and non-resectable SMR were included and randomization could not be realized. Addressing disease aggressiveness, multiple site recurrences were significantly more frequent in the Ctx only group. However, although first-line trials suggest that multiple site recurrences have poorer survival compared to single-site recurrences [34] these data have not been confirmed in a well described patient cohort with SMR treated in a multimodality concept including resection. Pairwise comparisons between the study groups (Table 3) showed that parameters expressing more aggressive disease were mainly balanced. Therefore, selection bias considering patients with more favorable tumor biology or lower tumor load for primary resection seems to be unlikely. Recently, the meta-analysis of Gonzales et al. did not find a significant impairment of survival by previous liver resection for concomitant liver metastases compared to lung only metastases [35].

Conclusion

Surgical re-intervention is a feasible and safe treatment option in a remarkable number of patients with SMR following R0-resection of CRC-LM. Secondary resection after Ctx is possible in a remarkable proportion of patients initially deemed to be non-resectable. In our single-center series, patients who were treated within a multidisciplinary concept including R0/R1-resection of SMR had a significantly longer CSS compared to those who were treated by Ctx only. Therefore, all patients with SMR after R0-resection of CRC-LM should be discussed in a multidisciplinary team prior to any treatment onset. The possibility of repeated surgical intervention needs to be assessed by a surgeon experienced in oncological strategies as well as liver surgery.

Acknowledgments This work has been generated as a collaboration project of the Clinical Research Unit 179 (Biological basis of individual tumor response in patients with rectal cancer, subproject 5) and the Research Unit 942 (FOR942 BE 2552/4-1), both funded by the German Research Council (DFG).

Conflict of interests The authors declare that no conflicts of interest exist.

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