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ORIGINAL ARTICLE

The liver-first approach for synchronous colorectal liver metastases: more than a decade of experience in a single centre

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Abstract

Background: The feasibility of the liver-first approach for synchronous colorectal liver metastases (CRLM) has been established. We sought to assess the short-term and long-term outcomes for these patients.

Methods: Outcomes of patients who underwent a liver-first approach for CRLM between 2005 and 2015 were retrospectively evaluated from a prospective database.

Results: Of the 92 patients planned to undergo the liver-first strategy, the paradigm could be completed in 76.1%. Patients with concurrent extrahepatic disease failed significantly more often in completing the protocol (67% versus 21%; $p = 0.03$). Postoperative morbidity and mortality were 31.5% and 3.3% following liver resection and 30.9% and 0% after colorectal surgery. Of the 70 patients in whom the paradigm was completed, 36 patients (51.4%) developed recurrent disease after a median interval of 20.9 months. The median overall survival on an intention-to-treat basis was 33.1 months (3- and 5-year overall survival: 48.5% and 33.1%). Patients who were not able to complete their therapeutic paradigm had a significantly worse overall outcome ($p = 0.03$).

Conclusion: The liver-first approach is feasible with acceptable perioperative morbidity and mortality rates. Despite the considerable overall-survival-benefit, recurrence rates remain high. Future research should focus on providing selection tools to enable the optimal treatment sequence for each patient with synchronous CRLM.

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Introduction

Presentation of colorectal liver metastases (CRLM) at the time of diagnosis of the primary colorectal tumour occurs in almost 20% of all colorectal carcinoma patients.[1,2] For these patients with synchronous CRLM, resection of all proven disease is the only potential for cure.[3] Currently, there are different therapy regimens for these patients, encompassing both surgical and medical oncology components.[4,5] Overall, the three options for surgical resection are simultaneous resection of CRLM and the primary tumour, primary tumour-first resection or the liver-first approach.

While a substantial equipoise for the optimal treatment sequence remains when all patients with synchronous CRLM are considered together,[6] the selection of a certain pathway has become more patient-tailored.[5] This decision is based on factors such as the location of both primary and metastatic disease, the requirement of a neoadjuvant therapy regimen and certain patient-related factors.[7]

The liver-first approach was first described by Mentha *et al.* in 2008.[8] It is a staged approach in which the liver is operated on prior to the primary tumour and increasingly frequently preceded by induction chemotherapy.[9]

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Apart from the early application of systemic treatment, which provides a chance to evaluate response and thereby define tumour biology of the CRLM, the rationale behind the liver-first strategy is multiple-fold. The total treatment period in this paradigm is shortened, particularly for rectal primaries, since the obligatory post-radiation waiting period offers an interval for the performance of liver-directed surgery. An additional incentive for this approach is that CRLM are considered the main cause of death and that it is, therefore, important to eliminate these lesions first without running the risk of these growing beyond resectability. With the liver-first approach, treatment of the CRLM is not affected by possible complications after surgery of the primary tumour. Moreover, as a concurrent advantage, this strategy provides a certain window during which possibly latently present extrahepatic disease has a chance to declare itself.[10,11]

Data from our group published in 2011[12] showed that resection of hepatic metastases prior to resection of the primary colorectal tumour in a liver-first strategy is feasible and can be performed with acceptable morbidity and mortality. Therefore, in our centre, especially when the primary tumour requires a neoadjuvant treatment strategy that provides a window for the liver-first approach, this sequence of therapy is considered for all patients with synchronous CRLM.

Other groups have also reported their experiences and outcomes for the liver-first strategy for synchronous CRLM. Most authors reported the paradigm was feasible and had acceptable short-term outcomes.[13–15] However, most series contain relatively small patients numbers.[14–19] Moreover, the follow-up within these cohorts is often relatively short,[15,17–19] as also in our previous series.[12]

Furthermore, none of these studies provides robust data on long-term outcomes,[14,16] with regard to survival and other oncologic outcomes. Therefore, with the current study, we sought to assess not only the short-term outcomes for these patients with synchronous CRLM who were treated within the liver-first protocol, but importantly, the influence of this sequence in therapy on long-term outcomes.

Methods

Prospectively collected data on patients who underwent liver surgery from January 1st, 2005 to December 31st, 2015 were queried from the hepatectomy database at Maastricht University Medical Centre+ and retrospectively analysed. All patients with synchronous CRLM were identified. In 92 of these patients, a liver-first approach had been planned and these patients were the scope of the current study.

During preoperative assessment, patients were considered to have resectable disease if a resection with negative margins (R0) was anticipated for all known disease, located both intra- and extrahepatic. Only patients in whom an adequate future liver remnant (FLR) was expected, based on computed tomography (CT) volumetric analysis, were considered candidates for direct liver-directed surgery. The future liver remnant had to incorporate a minimum of two adjacent segments with sufficient vascular in- and outflow and adequate biliary drainage. If these criteria could not be initially met, patients were considered for a two-stage hepatectomy with or without portal vein embolization. Specifically, the FLR was calculated on a preoperative CT-scan and discussed at our multidisciplinary meeting. Here, the indication for PVE was set if the expected FLR was deemed insufficient to prevent postoperative liver failure. With an interval of between four and six weeks, a follow-up CT-scan was performed. Based on this scan the decision was made to continue with next phase of the liver-directed surgery.

In short, after patients were diagnosed with synchronous CRLM, they were referred to our tertiary referral centre (coordinated by the Surgical Oncologic Network of Limburg) and were subsequently presented and discussed in our biweekly multi-disciplinary oncology meeting. During this meeting treatment strategy was established in concordance with institutional guidelines previously described.[12] Concisely, all patients with rectal cancer underwent standard locoregional staging with T2-weighted magnetic resonance imaging (MRI), which in select cases was extended with an additional gadofosveset-enhanced imaging sequence for lymph node staging, in accordance with our institutional protocol described previously.[20] For patients with a primary tumour located in the colon, pre-operative staging was generally ascertained using a CT-scan. For more diagnostic information of their CRLM, a 4-phase CT-scan of the liver was performed. Specifically, in case small tumours were seen on the initial CT-scan, or if there was suspicion of the presence of such lesions, a MRI was performed. If patients had undergone a MRI-scan in their initial workup – the follow up imaging in establishing the response would also consist of an MRI-scan. According to our national guidelines[21] and the ESMO guideline 'Metastatic Colorectal Cancer',[22] all patients who are eligible for curative resection of their CRLM will undergo an FDG-PET to exclude irresectable extrahepatic disease.

Rather than treating all patients according to a strict and rigid protocol, the institution's policy is to provide each patient with a custom-made treatment regimen. In general, initial resectability of the CRLM was assessed. When the indication for preoperative (chemo-)radiation therapy on the primary rectal tumour was set (i.e. cT1-3N1 or cT3N0 with >5 mm extramural invasion; cT4 or cT3 with a distance to the mesorectal fascia $\leq$1 mm and/or cN2),[21] a window of time occurred in which liver surgery could be performed when awaiting the response of the rectal tumour. Since almost every patient with metastatic rectal cancer had locally advanced rectal tumours, (chemo-)radiation therapy in combination with the liver-first approach was considered to be the standard procedure. Patients with colon cancer and primarily technically R0-resectable CRLM were mostly treated with an upfront resection of their CRLM,

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especially when the metastases were limited in number and size. When the CRLM were potentially resectable, three cycles of CAPOX/FOLFOX in combination with bevacizumab were advised as an induction therapy. Response evaluation was performed with at least a 4-phase CT scan of the liver based on RECIST 1.1 criteria.[23] In case of response (≥30% decrease in the sum of diameters of the target lesions), leading to technically R0-resectable CRLM, patients were treated with the liver-first approach. In case of progressive disease (>20% increase in the sum of diameters of the target lesions or the appearance of new lesions), a switch in chemotherapy (e.g. after KRAS-typing) was considered and/or a palliative treatment protocol was chosen. In case of stable disease (neither sufficient shrinkage to qualify for response nor sufficient increase to qualify for progression), a case-by-case decision was made, based on the overall condition of the patient, the resectability of the CRLM and the possible advantages of SIRT or TACE. In selected patients, another three cycles of neo-adjuvant CAPOX/FOLFOX were prescribed, after which a second response evaluation was performed. The latest CT scan could not predate the operative date for more than six weeks.

Following surgery, all patients received postoperative care according to the ERAS-protocol.[24–26] Within this protocol, prophylactic heparin was routinely administered, based on patients' weight.

Data collection

Apart from standard demographic data (i.e. age and sex), the following data were collected for each patient: characteristics of the primary tumour (i.e. location and symptoms of the primary lesion and TNM-stage) as well as of the CRLM (i.e. distribution, number and size of lesions). Moreover, data concerning treatment-related variables were collected (i.e. peri-operative receipt of radiation and/or chemotherapy, details of hepatic surgery as well as data regarding the operation on the primary tumour). Furthermore, data regarding postoperative outcome (i.e. presence, type and severity of in-hospital or 90-day morbidity and postoperative mortality within 90 days of treatment) and data regarding disease recurrence and vital status were noted. Disease recurrence was defined as a lesion that was biopsy proven recurrent adenocarcinoma or a lesion that was deemed suspicious on cross-sectional imaging (e.g. PET-CT) in the setting of an elevated carcinoembryonic antigen (CEA) level.

Statistical analyses

All statistical analyses were performed using SPSS Version 22 for Mac. Summary statistics were obtained and presented as percentages or median values. Upon comparing categorical data, χ-square test, or if deemed appropriate, Fisher's exact test was used, while the Mann–Whitney U test was used to compare continuous data. Recurrence-free and overall survival analyses were performed using the non-parametric product limit method. Overall, a p-value less than 0.05 was considered significant.

Results

Patient and tumour characteristics

In the study period, 92 patients with synchronous CRLM from a colorectal primary tumour were treated according to the liver-first paradigm. The characteristics of these patients are detailed in Table 1.

The majority of patients were male (n = 70; 76.1%), while the overall median age at the time of diagnosis was 65 years [30–86]. Almost three-quarters of patients had a primary rectal tumour (n = 68; 73.9%). Nine patients reported no symptoms of their primary tumour (9.8%). In those with symptoms, the most common presenting symptom was rectal blood loss (n = 31; 33.6%), followed by changes in bowel habits (n = 26; 28.3%).

With regards to the CRLM, most patients had bilobar hepatic lesions (n = 51; 55.4%), while the median number of lesions was three [1–20].

At time of diagnosis, six patients (6.5%) had concurrent extrahepatic lesions. In all of these patients, the location of this extrahepatic disease was the lung.

Details of perioperative radiation and chemotherapy

In total, 59 patients (64.1%) received radiation therapy of their primary rectal tumour. Forty-three patients (46.7%) received a short-course of radiation therapy, of whom 40 patients (43.5%) also received multiple cycles of chemotherapy. Moreover, 16 patients (17.4%) underwent a long-course radiotherapy with a chemo-sensitizer (i.e. chemo-radiation therapy). Four of these patients (3.4%) received additional cycles of preoperative systemic chemotherapy (i.e. not as chemo-sensitizer).

Overall, all patients received chemotherapy sometime during the course of their treatment. The timing of this chemotherapy was preoperative only in 39 patients (42.4%), preoperative and during the interval between hepatic and colorectal surgery in 27 patients (29.3%) and preoperative and after completion of curative intent treatment in 21 patients (22.8%). All six patients (6.5%) in whom no resection of their CRLM was performed, received preoperative chemotherapy. Furthermore, all 16 patients (17.4%) in whom no resection of the primary tumour was undertaken received chemotherapy before commencement of the first operation, while seven of these patients (7.6%) also received chemotherapy during the surgical window. Moreover, one patient (1.1%) received interval and adjuvant chemotherapy, while another patient (1.1%) only received adjuvant chemotherapy. In three patients (3.3%), the exact timing of their chemotherapy was unknown.

Details of surgery

Details of liver-directed and primary tumour surgery are detailed in Table 2 and Fig. 1. Most patients (n = 79; 85.9%) underwent a laparotomy to resect their CRLM, while seven patients (7.6%) underwent a laparoscopic resection. Specifically, six patients (6.5%) underwent a non-therapeutic laparotomy at time of

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Table 1 Patients and tumour characteristics

Variable	No. of patients (%), n = 92
Patient characteristics	
Median age [range], y	65 [30–86]
Sex (male)	70 (76.1)
Primary tumour site	
Location of primary tumour	
Colon	24 (26.1)
Rectum	68 (73.9)
Symptoms caused by primary tumour	
None	9 (9.8)
Rectal blood loss	31 (33.6)
Changes in bowel habits	26 (28.3)
Bowel obstruction	8 (8.7)
Unknown	18 (19.6)
AJCC T-stage on pathology[a]	
ypT1/ypT2	9 (12.9)
ypT3/ypT4	44 (62.9)
Unknown	17 (24.1)
Lymph node status on pathology[a]	
ypN1/ypN2	27 (38.6)
ypN0	32 (45.7)
Unknown	11 (15.7)
Tumour grade (%)[b]	
1	18.3
2	78.4
3	3.3
Mutations (%)[b]	
KRAS	39.1
NRAS	0
Hepatic metastasis	
Size of largest metastasis (median [range]), cm	2.5 [0.4–12.0]
No. of metastasis (median [range])	3 [1–20]
Location (unilobular)	41 (44.6)
Concurrent extrahepatic Disease	
Presence of extrahepatic metastasis	6 (6.5)

[a] Excluding patients who did not undergo resection of their primary colorectal tumour (n = 22).
[b] Excluding unknown data.

Table 2 Details of surgical procedures

Variable	No. of patients (%), n = 92
Type of liver resection	
None	6 (6.5)
Single stage resection	
<Hemihepatectomy	60 (65.2)
Hemihepatectomy	19 (20.7)
Plus additional minor resection	8 (8.7)
Central hepatectomy	1 (1.1)
Two-stage resection	
<Hemihepatectomy followed by PVE and subsequent hemihepatectomy	5 (5.4)
Hemihepatectomy plus additional minor resection followed by PVE and subsequent metastasectomies	1 (1.1)
Ostomy formation during this procedure	3 (3.3)
Laparoscopic liver resection	7 (7.6)
Concomitant RFA	2 (2.2)
Type of colorectal resection	
None	24 (26.1)
Watch-and-wait policy	2 (2.2)
Extensive metastatic disease	16 (17.4)
Low anterior resection	34 (36.9)
Sigmoid resection	14 (15.2)
Abdominoperineal resection	10 (10.9)
Left hemicolectomy	4 (4.3)
Right hemicolectomy	3 (3.3)
Pelvic exenteration	1 (1.1)
Transanal endoscopic microsurgery	2 (2.2)
Ostomy formation during this procedure	18 (19.6)

intended liver resection. The majority of patients who did undergo curative-intent liver surgery for their CRLM underwent a minor liver resection, i.e. less than three segments (n = 60; 65.2%). In two patients (2.2%), radiofrequency ablation (RFA) was undertaken at time of liver surgery.

Furthermore, the details of the six patients (6.5%) who were treated within a two-stage protocol are also listed in Table 2.

Regarding the six patients with extrahepatic metastases at time of diagnosis (6.5%), four of these patients (4.3%) received chemotherapy only for their lung metastases, while two patients (2.2%) underwent resection. Specifically, these two patients underwent this surgery in the interval between liver-directed surgery and the expected resection of the primary tumour. However, on interval imaging, both of these patients and two of the patients who were treated with chemotherapy for their lung metastases were found to have widespread metastatic disease and were therefore not amenable to undergo resection of the primary tumour (n = 4; 4.3%).

After a median interval of four months after liver resection [range: 1–17], 68 patients (73.9%) underwent resection of their primary tumour. The type of resection is described in Table 2. Two patients (2.2%) were treated according to the watch-and-wait protocol.[27] These two patients had previously undergone minor liver resection for their CRLM. In both patients, viable tumour cells were found during pathologic examination of the CRLM-tumour samples.

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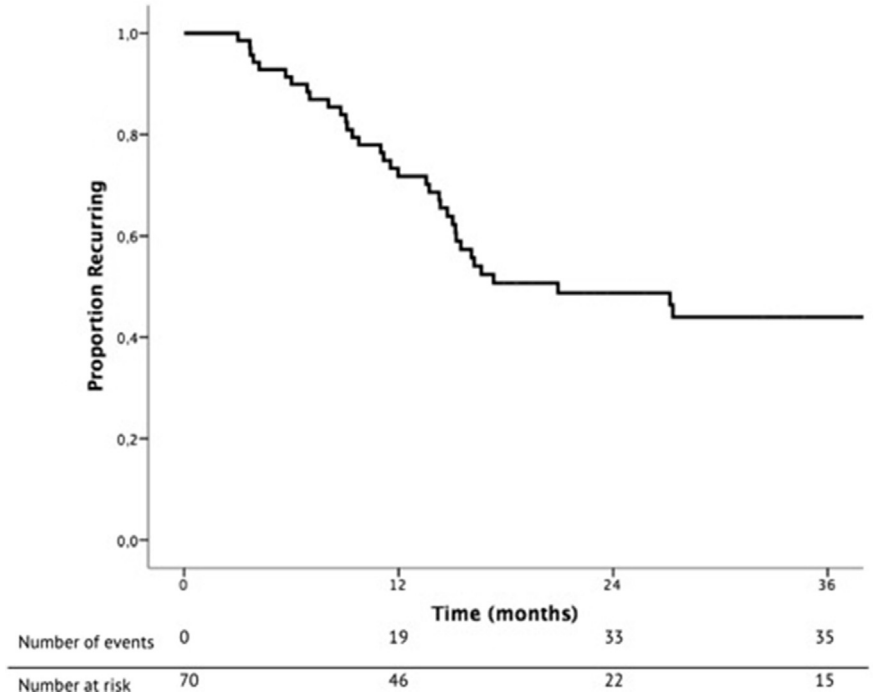

Figure 1 Recurrence-free survival of patients who underwent curative intent surgery for synchronous CRLM within the liver-first approach

The total proportion of patients completing the entire paradigm was 76.1% (n = 70). Upon comparing patients who completed the per-protocol treatment and patients who deviated from the protocol, no differences were observed with regard to patients' sex, location of the primary tumour or T-stage of the primary tumour (all $p > 0.05$). However, patients with extrahepatic disease at time of presentation less frequently completed the entire treatment paradigm (33% versus 79%; $p = 0.03$).

Postoperative and oncologic outcome

The specifics of the direct postoperative outcomes after liver-directed surgery are detailed in Table 3. While 29 patients (31.5%) developed complications, more than half of these (n = 17; 18.5%) developed major complications. Moreover, three patients (3.3%) died following liver-directed surgery.

One patient died on postoperative day 69 after the second stage of a two-stage hepatectomy during which a right hemihepatectomy was performed. The patient developed liver failure and was admitted to the ICU. Here, the patient developed multi-organ failure and subsequently succumbed.

The second patient passed away on postoperative day 14 after an open segmental resection of the liver. This patient had a history of cardiac disease and developed atrial fibrillation and progressive cardiac failure.

The third patient died of acute myocardial infarction on postoperative day 3 after extended left hemihepatectomy for a total of nine CRLM.

After surgery for the primary tumour, complications were reported in 21 out of the 68 patients who underwent surgery for their primary tumour (30.9%) within a 90-day-period. In 15 patients (22.1%) the occurrence of complications was unknown. Among those patients in whom complications were reported, 33.3% developed minor complications, while 66.7% developed major complications. The postoperative mortality following colorectal surgery was zero.

Table 3 Specifics of direct postoperative outcomes after liver-directed surgery

Variable	No. of patients (%), n = 92
Postoperative complications (any)	29 (31.5)
Minor (Clavien grade <3)	12 (13.0)
Major (Clavien grade ≥3)	17 (18.4)
Postoperative mortality (within 90 days)	3 (3.3)
Specific complications	
Intra-abdominal abscess	7 (7.6)
Liver insufficiency	5 (5.4)
Wound infection	4 (4.3)
Biloma/bile leakage	3 (3.3)
Acute myocardial infarction	3 (3.3)
Pneumonia	3 (3.3)
Iatrogenic bowel perforation	2 (2.2)
Multi-organ failure	2 (2.2)
Stroke	1 (1.1)
Other	6 (6.5)

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The median follow-up for all patients was 26 months. Of the 70 patients in whom the entire paradigm was completed, 36 patients (51.4%) developed recurrent disease. The median recurrence-free survival was 20.9 months. The 1- and 3-year recurrence-free survival were 76.1% and 42.2% respectively (Fig. 1). The pattern of recurrence was intrahepatic only in 9 patients (25%); extrahepatic only in four patients (11.1%) and both intrahepatic and extrahepatic in 23 patients (63.9%). The site of extrahepatic recurrence was lung in the majority of patients ($n = 17$; 47.2%), followed by extensive lymph node disease ($n = 9$; 25.0%) and peritoneal carcinomatosis ($n = 6$; 16.7%).

In total, six patients (6.5%) underwent repeat curative intent surgery for recurrent disease. One patient underwent a lobectomy of the left lung, while five patients underwent repeat curative intent liver surgery. Unfortunately, all of these six patients developed a new recurrence and none underwent a third curative intent surgery. The subsequent pattern of recurrence was intrahepatic only in one patient (16.7%) and extrahepatic only in three patients (50.0%), while two patients (33.3%) developed recurrent disease both within as well as outside of the liver.

The median overall survival for all 92 patients on an intention-to-treat basis was 33.1 months. The 3- and 5-year overall survival were 48.5% and 33.1% respectively (Fig. 2a). Patients who were not able to complete the therapeutic paradigm had a worse overall survival (median: 44.6 months versus 12.1 months; $p < 0.001$) (Fig. 2b). Moreover, at time of last follow-up, all of the patients who failed the protocol had died. Additionally, at time of last follow-up, seven patients were alive with disease (7.6%), while all other 29 patients (31.5%) who had developed recurrent disease had died.

The KRAS-status was available for only 36 patients (39.1%). Among this subgroup there were no statistically significant differences with regard to completion of the protocol (KRAS-mutation $n = 6$ (42.9%) versus wild-type $n = 8$ (57.1%); $p = 0.50$) nor for median overall survival (KRAS-mutation: 14.1 months [95% CI: 14.1–16.4] versus wild-type: 31.2 months [95% CI: 23.1–39.2]; $p = 0.08$).

Discussion

The current study describes a more than a decade experience with the liver-first approach for synchronous CRLM. We showed that this strategy could be completed in over 75% of patients. This is comparable to our previous report[12] and to other, smaller, series.[13–15] Moreover, two large systematic reviews independently reported a similar feasibility rate of 74%.[9,28] Among our patients, postoperative morbidity and mortality were 31.5% and 3.3% following liver resection and 30.9% and 0% after colorectal surgery, respectively. These complication rates are in line with a recent systematic review.[28] Furthermore, our results are comparable to those presented by other studies not included in this latter review.[16,29]

Specifically, the scope of the current study was to investigate the long-term, oncologic outcomes, following the liver-first approach. These outcomes can be divided in time to recurrence of the disease and time to decease of the patient (i.e. overall survival).

In our population, more than half of patients developed recurrent disease after a median recurrence-free survival of almost 21 months. The 1- and 3-year recurrence-free survival in our cohort were 76.1% and 42.2%, respectively. While statistics on recurrence following the liver-first strategy are relatively scarce, other studies show a wide variety of recurrence rates without clear differences within treatment protocols.[9,28] Straka *et al.*[17] reported an almost similar recurrence rate in their cohort of 32 patients. Conversely, while not presenting data on the recurrence-rate in their propensity score-matched outcomes analysis, Welsh *et al.*[30] did report a median disease-free survival of 36 months, which is better than for the patients in our study. However, none of the patients described in this study had concomitant extrahepatic disease at time of diagnosis. Furthermore, the 5-year disease-free survival in their cohort was 37%, which was comparable to the disease-free survival for patients who underwent a classical approach within the same study.[30] Labori *et al.* reported a median recurrence-free survival of only 13 months in their cohort of 45 patients,[13] which is notably shorter than the recurrence-free survival among our group of patients. Patients in this cohort seemed to have more extensive local disease at the primary site with more involved lymph nodes. Their tumour burden within the liver, however, seemed to be comparable. In line with this, Tanaka *et al.*[18] reported a 100% recurrence rate in their cohort of 10 patients with aggressive initially unresectable metastases, who underwent the liver-first approach. However, this group of patients is a highly selected population with a substantial tumour burden (also reflected by the low feasibility of 20%) and these results can therefore not be projected on a more general patient group with synchronous CRLM. Similarly, Okuno[31] *et al.* compared patients with a colorectal carcinoma and initially unresectable or not optimally resectable CRLM who underwent either a liver-first approach or a primary-first approach. They describe a recurrence-rate of 58.3% and a median recurrence-free survival of 10.5 months among 12 patients treated within a liver-first protocol. Although these outcomes are notably more dismal than those in our study, outcomes for patients treated with the primary-first approach in this study were similar. Therefore, overall, tumour biology and extent of the disease seem to be a more important prognostic factor for disease recurrence than the sequence in which the disease is operated.

While it has been shown that repeat curative intent surgery for recurrent metastatic disease for CRLM is feasible, safe and associated with a prolonged survival,[32–35] the overall survival for these patients remains an important aspect. On an intention-to-treat basis, the median overall survival for all 92 patients was 33.1 months, while the 3- and 5-year overall survival rates were 48.5%

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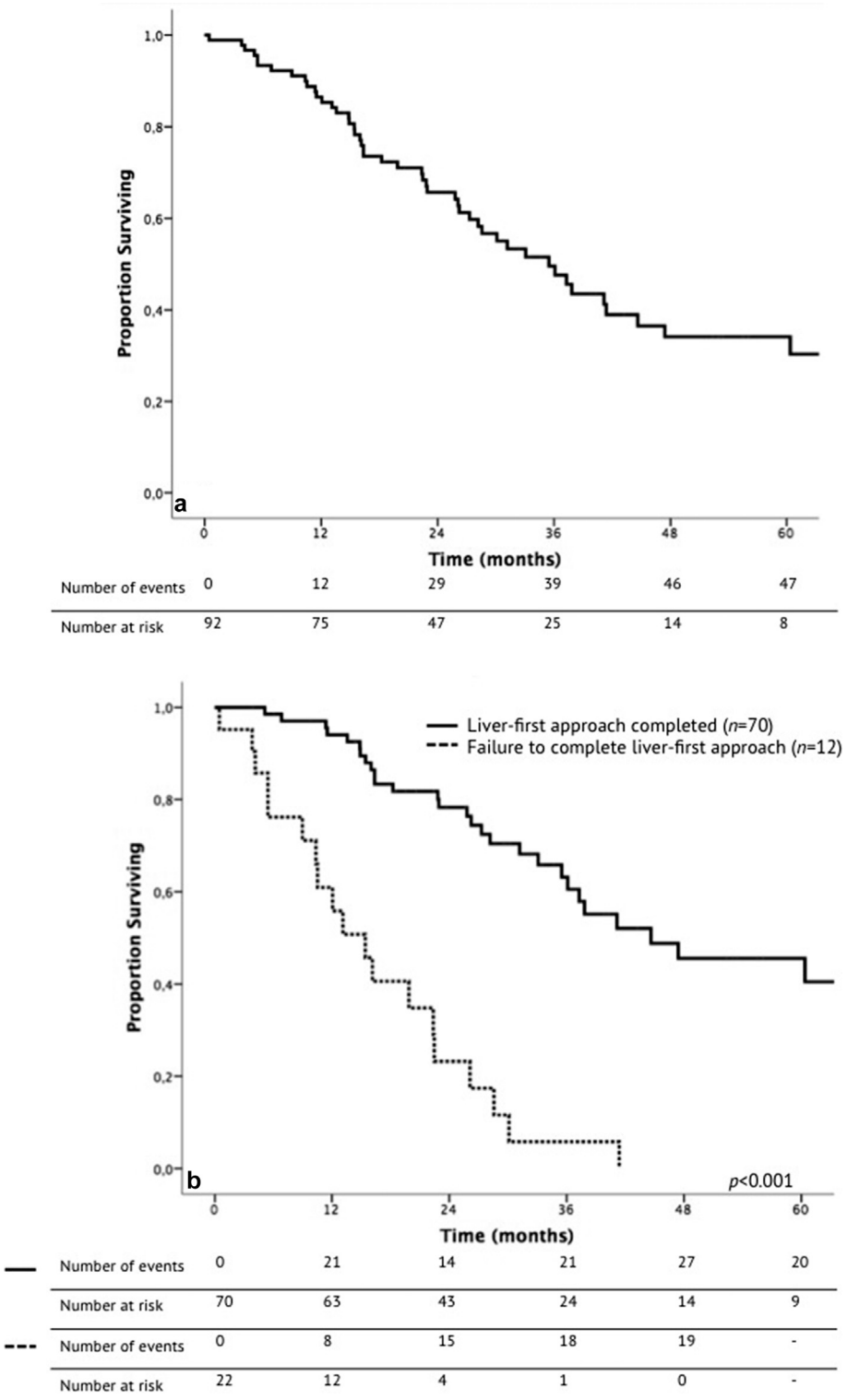

Figure 2 a Overall survival of patients who underwent curative intent surgery for synchronous CRLM within the liver-first approach on an intention-to-treat basis. b Overall survival of patients who underwent curative intent surgery for synchronous CRLM within the liver-first approach stratified by failure or completion of the approach

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and 33.1%, respectively. Notably, the overall survival for patients who completed the entire treatment-protocol was significantly better, with a median overall survival of almost 45 months. These data are overall comparable to the limited studies conducted by others.[13,16] Specifically, Wang *et al.*[29] reported a 1- and 3-year overall survival rate of 94.4% and 44.8%, respectively, with a median survival time of 30 months in a cohort of 16 patients. Notably, in a large population-based study on the prognosis of CRLM,[1] it was shown in multivariable analysis that the presence of synchronous CRLM is associated with a more dismal outcome compared to metachronous disease. Therefore, as only patients with synchronous CRLM are possible candidates for the liver-first approach, this cohort is always a select group within the total population of patients developing CRLM at some point during the course of their disease and the survival rates should, therefore, be viewed within this light.

Interestingly, studies on survival differences between the primary-first and liver-first approach have not shown differences in overall survival.[30,31] Moreover, in their systematic review of reports comparing different approaches for synchronous CRLM, Baltatzis *et al.*[36] reported a pooled 5-year survival fixed effect estimate of 44%, and found no evidence supporting any particular pathway. This group also included the simultaneous resection of all known disease, both primary and metastatic. Two other, large, studies had already reported no differences regarding both short-term as well as long-term outcomes upon comparing the three possible sequences.[5,37] More recently, Ableson *et al.*,[38] also reported that under appropriate clinical circumstances, simultaneous resection of all known disease could benefit select patients. Therefore, we propose that rather than favouring one of the treatment orders above another and establishing an optimal treatment sequence, the main focus should be on the selection of patients for each of the known treatment paradigms. Factors could include the local extensiveness of the disease and possible preoperative radiation therapy, the burden of the metastatic disease and other tumour-biology and patient related factors. Specifically, patients who present in an acute setting will never be able to be considered for the liver-first approach. Only by offering a tailor-made treatment plan for each patient, including both medical oncologic as well as surgical components, not only overall survival, but also disease-free survival can be obtained.

Additionally, the quest for the preferred treatment paradigm or for the best selection criteria for a certain approach remains a very current issue, particularly with the rising incidence of synchronous metastatic colorectal disease and synchronous CRLM. Van der Geest *et al.*[39] reported an increasing incidence of stage IV colorectal cancer patients in the Netherlands, even before the introduction of the Bowel Cancer Screening Program (BCSP). Specifically, the proportion of patients with metastatic liver disease at time of diagnosis of the primary tumour had increased. A possible explanation for this phenomenon proposed by these authors is a more accurate staging, owing to improved detection of metastatic disease due to an increased use and amended quality of radiologic imaging modalities, e.g. magnetic resonance imaging (MRI) of the liver. Moreover, with the widespread introduction of BCSPs,[40–43] the incidence of synchronous CRLM will likely, in the near future, only rise even more. Logan *et al.*[40] reported that after the first 1 million BCSP-tests in the United Kingdom, 3% of patients had Dukes D colorectal cancer, i.e. stage IV, metastatic disease. This latter group of patients are probably mostly asymptomatic, and therefore, these patients are the ideal candidates for establishing the preferred treatment strategy. Specifically, not only the sequence in which all disease should be surgically managed but also decisions regarding medical oncology components could potentially be established within this cohort.

The present study has several limitations associated with its retrospective nature. Moreover, although our study has one of the largest numbers of patients, the included number of patients is still relatively low. While this, on one hand, only stresses the highly selected nature of the cohort of patients with synchronous CRLM who were considered for this approach, the small sample size has statistical disadvantages. Furthermore, the KRAS-status was not known for the majority of patients in the current study. Therefore, very limited statistical inferences could be conducted with this parameter. This is a drawback, because of the known influence of the KRAS-mutation on both overall survival and local recurrence[44,45] and the possible association with failure to complete the liver-first approach. For future studies, this factor should definitely be further explored to assess its importance within the population with synchronous CRLM in general and those undergoing the liver-first approach in particular. Moreover, as our centre is a tertiary referral centre, all liver-directed surgery was performed at our centre, while most patients had their primary tumour surgery performed in their local clinic. The median interval between the liver directed surgery and the surgery on the primary tumour was four months. While this could be considered as rather long, it is in line with our role as a tertiary referral centre. After undergoing their liver-directed surgery, patients were discussed in a multidisciplinary meeting. And after discharge from our institute, patients are referred back to their home–institute where the surgery on their primary tumour is carried out.

In conclusion, this study underlines the feasibility of the liver-first paradigm in a larger cohort as well as the acceptable perioperative morbidity and mortality rates. This approach should, therefore, be standard of care when the primary tumour requires neoadjuvant treatment providing a window for the liver-first approach. In selected other patients, a multi-disciplinary approach is needed to determine the best, tailor-made, treatment strategy. Despite the considerable overall-survival-benefit of the liver-first approach, the disease recurrence-rates remain high. Future research should focus on providing selection tools to enable the optimal treatment sequence for each individual patient with synchronous CRLM.

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