Original article

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Resection of synchronous liver metastases between radiotherapy and definitive surgery for locally advanced rectal cancer: short-term surgical outcomes, overall survival and recurrence-free survival

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Abstract

Aim There is debate as to the correct treatment algorithm sequence for patients with locally advanced rectal cancer with liver metastases. The aim of the study was to assess safety, resectability and survival after a modified 'liver-first' approach.

Method This was a retrospective study of patients undergoing preoperative radiotherapy for the primary rectal tumour, followed by liver resection and, finally, resection of the primary tumour. Short-term surgical outcome, overall survival and recurrence-free survival are reported.

Results Between 2009 and 2013, 45 patients underwent liver resection after preoperative radiotherapy. Thirty-four patients (76%) received neoadjuvant chemotherapy, 24 (53%) concomitant chemotherapy during radiotherapy and 17 (43%) adjuvant chemotherapy. The median time interval from the last fraction of radiotherapy to liver resection and rectal surgery was 21 (range 7–116) and 60 (range 31–156) days, respectively. Rectal resection was performed in 42 patients but was not performed in one patient with complete response and two with progressive metastatic disease. After rectal surgery three patients did not proceed to a planned second stage liver ($n = 2$) or lung ($n = 1$) resection due to progressive disease. Clavien–Dindo ≥Grade III complications developed in 6.7% after liver resection and 19% after rectal resection. The median overall survival and recurrence-free survival in the patients who completed the treatment sequence ($n = 40$) were 49.7 and 13.0 months, respectively. Twenty of the 30 patients who developed recurrence underwent further treatment with curative intent.

Conclusion The modified liver-first approach is safe and efficient in patients with locally advanced rectal cancer and allows initial control of both the primary tumour and the liver metastases.

Keywords Locally advanced rectal cancer, synchronus colorectal liver metastases, liver-first approach

What does this paper add to the literature?
The optimal management of patients with locally advanced rectal cancer and synchronous liver metastases is controversial. This study is the first to show that liver resection in the time window between radiotherapy and rectal surgery is a safe and efficient alternative to the traditional liver-first approach.

Introduction

Anterior resection with total mesorectal excision remains the foundation for curative treatment of rectal cancer. If locally advanced, preoperative chemoradiotherapy is recommended for tumour downsizing followed by rectal resection 6–8 weeks after completion of

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radiotherapy [1,2]. Synchronous liver metastases occur in 15%–25% of patients with rectal cancer [3–5] and, if resectable, have generally been resected after the surgery for the primary tumour. This approach may allow liver metastases to progress and become unresectable.

Chemotherapy and the liver-first approach or simultaneous resection have been utilized to achieve initial control of liver metastases [6,7]. In centres using the liver-first approach, the treatment algorithm has been as follows: neoadjuvant chemotherapy, liver resection, chemoradiotherapy, rectal resection and adjuvant chemotherapy [8,9]. This treatment sequence may be improved by shortening the total treatment time from start to final rectal resection by utilizing the time period necessary for tumor downsizing after chemoradiotherapy. We have designed a modified liver-first approach: neoadjuvant chemotherapy, radiotherapy, liver resection, rectal resection and adjuvant chemotherapy. This strategy is in line with recent recommendations from a multidisciplinary international consensus [5]. The current study is the first to report safety, resectability rates and survival after a modified liver-first approach aiming for initial control of both the primary tumour and the liver metastases.

Method

This was a retrospective sudy of the patients who presented to the Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital (OUH), from July 2009 to December 2013 with locally advanced rectal cancer with liver metastases who had received preoperative local radiotherapy for their primary tumour and had then undergone liver resection with curative intent before their rectal resection. Primary rectal cancer was defined as adenocarcinoma located ≤ 15 cm from the anal verge by rigid rectoscopy. Tumours were considered locally advanced according to Norwegian guidelines: T4 or T3 with ≤ 3 mm distance from tumour or metastatic lymph node to the mesorectal fascia based on clinical examination and MRI [3]. Patient, tumour and treatment information was obtained from the hospital records. All patients underwent a baseline evaluation, including a medical history, physical examination and laboratory tests. CT of the chest and abdomen, multislice triple-phase CT of the liver and MRI of the pelvis were performed in all patients to determine disease stage and treatment strategy. In selected patients, liver-specific MRI of the liver or intra-operative ultrasound of the liver were also performed. Positron emission tomography (PET-CT) was not mandatory but was performed in selected patients. All patients were discussed in a multidisciplinary team (MDT) comprising hepatobiliary surgeons, colorectal surgeons, oncologists and radiologists. A treatment plan for the primary tumour and the metastases was decided, including the sequence of the treatment modalities. Data were collected up to 31 March 2016. The study was approved as a quality control assurance study by the Institutional Data Protection Officer for Research (2013/18143).

According to the Norwegian guidelines current at the time, patients with locally advanced rectal cancer received preoperative chemoradiotherapy (50 Gy $\times$ 2) with concomitant capecitabine or 5-fluorouracil. Frail patients received short-course radiotherapy (5 Gy $\times$ 5) [3]. The use of short-course radiotherapy was gradually introduced for patients with synchronous resectable liver metastases in the study period [10].

In this study, the long-course treatment was preferred in patients when downsizing was felt necessary to achieve a radical resection. If this was not a consideration, short-course radiotherapy was preferred [2].

Neoadjuvant chemotherapy for liver metastases was recommended on a case by case basis and was usually an oxaliplatin-based combination chemotherapy. Some patients with solitary small liver metastases were deemed resectable without initial chemotherapy. Generally, at least four cycles were given prior to MDT review of the subsequent CT but rarely were more than eight cycles given in total. These patients then received chemoradiotherapy (5 weeks) or short-course radiotherapy (1 week) at the Department of Oncology, OUH.

Patients were scheduled for liver surgery after completion of preoperative radiotherapy to the rectal primary and it was performed as open or laparoscopic and as a one- or two-stage procedure [11]. Resection of the rectal primary was performed at least 6 weeks after completion of adjuvant treatment. Patients with T4b tumours or involved mesorectal fascia, who needed a total mesorectal excision, were operated at the Norwegian Radium Hospital, OUH, whilst patients planned for standard total mesorectal excision were operated at the regional hospitals. Adjuvant chemotherapy was given if applicable.

Patients were followed up according to the national guidelines. CT of the liver/pelvis and chest and carcinoembryonic antigen measurements were obtained every 4 months for the first year and 6 monthly thereafter. Rigid sigmoidoscopy was performed every 6 months after anterior resection.

Descriptive statistics are expressed as median (range). The Mann–Whitney test was used for non-parametric data. The Kaplan–Meier method was used to estimate survival distributions. Recurrence-free survival (RFS) was estimated from the start of chemoradiotherapy until the detection of local or distant recurrence. Patients without recurrence were censored on 31 March 2016.

Overall survival (OS) was estimated from the start of chemoradiotherapy until death. Statistical analyses were performed in SPSS Version 18.0 for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

Forty-five patients with rectal cancer and synchronous liver metastases underwent liver resection after preoperative radiotherapy for the primary tumour. Patient and tumour characteristics are presented in Table 1. The median number of liver metastases was 2 (1–12). One patient had a small resectable lung lesion. All patients had clinical Stage T3 or T4 tumours. Neoadjuvant chemotherapy was given to 34 patients: most received combination therapy with oxaliplatin (Table 2). Eleven patients did not receive neoadjuvant chemotherapy.

Table 1 Patient, tumour and treatment characteristics.

Age, years, median (range)	62 (33–73)
Gender, *n* (%)	
Male	21 (47%)
Female	24 (53%)
Rectal cancer	
Stage at diagnosis	
T3	24
T4	21
N0	9
N1	13
N2	23
Radiological response*	
Complete	1†
Partial	35
Stable	1
Pathological T-stage	
ypT2	4
ypT3	36
ypT4	2
Pathological N-stage	
ypN0	19
ypN1	15
ypN2	8
Tumour differentiation	
High	4
Medium	34
Low	4
Liver metastases	
Number of lesions operated, median (range)	2 (1–12)
Size of largest lesion, cm, median (range)	2.4 (1.1–11.8)
Bilobar disease, *n* (%)	16 (35.6%)
Extrahepatic metastases (lung), *n* (%)	1 (2.2%)

*MRI not available after chemoradiotherapy in eight patients.
†One patient with complete response who did not undergo rectal surgery.

Table 2 Chemoradiotherapy and systemic chemotherapy.

Treatment	Number of patients (%)
Chemoradiation	45 (100)
2 Gy × 25 with capecitabine/5-FU	24 (53)
5 Gy × 5	21 (47)
Neoadjuvant systemic chemotherapy	
None	11 (25)
5-FU and oxaliplatin	27 (60)
5-FU and irinotecan*	3 (7)
Irionotecan	1 (2)
Two lines of combination chemotherapy*	3 (7)
Adjuvant chemotherapy	17† (43)

5-FU, 5-fluorouracil.
*Bevacizumab was given with irinotecan-based chemotherapy to four patients.
†17 of 40 patients who completed the whole treatment sequence.

These patients had easily resectable, solitary metastases and/or small, suspicious liver lesions on CT and radiotherapy was started while awaiting supplementary MRI liver or PET-CT to confirm the metastasis. All patients received preoperative radiotherapy consisting of either short-course radiotherapy (5 Gy × 5, $n = 21$) or long-course chemoradiotherapy (25 Gy × 2, $n = 24$). There was a drift towards increased use of short-course radiotherapy during the study period.

The median time interval from preoperative CT liver ($n = 45$) to liver surgery was 32 days (range 1–108 days). The median interval from preoperative liver-specific MRI ($n = 29$) to liver surgery was 47 days (range 6–228 days). Preoperative PET-CT was performed in six patients. Most patients, 36 of 37 evaluable patients, had radiological response with complete/partial response of the primary tumour, as shown in Table 1.

Liver resection was performed laparoscopically in 17 patients and by open surgery in 28 patients. Details on the surgical procedures and complications are given in Table 3. The median interval from the last fraction of radiotherapy to liver surgery was 21 days (range 7–116 days) and did not differ between patients undergoing short-course (median 18 days, range 7–116) and long-course radiotherapy (median 22 days, range 10–49) ($P = 0.333$). Three patients did not proceed to rectal resection, two due to progressive liver metastases and one with complete response to chemoradiotherapy on the rectal primary. Accordingly, 42 patients underwent a rectal resection, of whom eight were operated laparoscopically. In one patient both the liver and rectal resection were performed by the laparoscopic approach.

Table 3 Surgical procedures and complications in 45 patients undergoing liver resection and 42 patients undergoing rectal resection.

Surgical procedure	Number of patients (%)
Liver resection	
Wedge resections*	25 (55.6)
Segment resections	11 (24.4)
Right hemihepatectomy†	9 (20)
Complications	
Any grade	5 (11.1)
Biliary fistula (requiring percutaneous drainage)	2
Intra-abdominal infection (requiring percutaneous drainage)	1
Urinary infection	1
Pneumonia	1
Clavien III or IV	3 (6.7)
Reoperation	0
Rectal resection	
Low anterior resection	27
Anterior resection with end ostomy (Hartmann)‡	6
Abdominoperineal resection with end ostomy§	9
Complications	
Any grade	16 (38)
Wound infection	4
Urinary retention	5
Pulmonary embolism	2
Intra-abdominal infection	1
Anastomotic leak (requiring reoperation $n = 1$ or percutaneous drainage $n = 4$)	5
Necrotic stoma (requiring reoperation)	1
Parastomal abscess (requiring percutaneous drainage)	1
Intestinal obstruction (requiring reoperation)	1
Clavien III or IV	8 (19)
Reoperation	3

*Plus radiofrequency ablation in two patients.
†Plus additional minor resection in the left lobe in six patients (portal vein embolization performed in three of these patients).
‡24 had diverting stoma.
§Plus additonal sacral resection and cystectomy in one patient.

Details on the surgical rectal procedures and complications are given in Table 3. The median interval from the last fraction of radiotherapy to rectal surgery was 60 days (range 31–156 days). The median time interval from liver resection to rectal surgery was 37 days (range 10–126 days). The median interval from liver resection to rectal surgery in patients undergoing open and laparoscopic liver resection was 42 days (range 27–126 days) and 35 days (range 10–65 days) ($P = 0.03$), respectively. The median interval from the last fraction of radiotherapy to rectal surgery in patients undergoing short-course and long-course radiotherapy was 60 days (range 31–85 days) and 60 days (range 43–156 days) ($P = 0.567$), respectively. In six patients rectal surgery was performed > 10 weeks after the last fraction of radiotherapy due to administrative failure ($n = 2$), planned time interval between cessation of neoadjuvant chemotherapy to liver resection 6 weeks ($n = 1$), portal vein embolization (PVE) + two-stage liver resection ($n = 1$), PVE/two-stage liver resection/complications after liver resection ($n = 1$) and pulmonary embolism diagnosed during chemoradiotherapy ($n = 1$). Two patients planned for a second stage liver resection and one patient with synchronous liver and lung metastases did not proceed to the planned resections after rectal resection due to progressive liver metastases. Accordingly, 40 patients (89%) underwent curative resection of the primary and synchronous liver metastases and completed the treatment sequence initially planned at the MDT meeting. Of these 40 patients, postoperative chemotherapy was given in 17 patients (42.5%). Of the 24 patients receiving a loop ileostomy, 20 patients later had reversal of the stoma.

Morbidity after liver and rectal resection presented in five (11%) and 16 (38%) patients, respectively. Clavien–Dindo Grade 3 or higher complications presented in three (6.7%) patients after liver surgery and in eight (19%) patients after rectal surgery. There was no 90-day mortality. The median length of stay after liver and rectal resection was 6 days (range 1–31 days) and 8.5 days (range 4–22 days), respectively.

Median follow-up was 48 (range 6–85) months. During this period, 30/40 (75%) patients presented with recurrence (liver only, $n = 17$; lung only, $n = 5$; liver/lung, $n = 2$; liver/peritoneal carcinomatosis, $n = 2$; liver/para-aortal glands, $n = 2$; liver/local rectal recurrence, $n = 1$; liver/lung/para-aortal glands/local, $n = 1$). Twenty (67%) patients underwent a potentially curative treatment of the first recurrence (liver resection, $n = 12$; liver resection and radiofrequency ablation (RFA), $n = 2$; combined liver and omental resection and RFA, $n = 1$; RFA, $n = 1$; combined liver and lung resection, $n = 1$; liver resection and stereotactic radiotherapy pulmonary metastases, $n = 1$; lung resection, $n = 2$).

The median OS in all 45 patients was 48.4 [95% confidence interval (CI) 43.3–54.8] months (Fig. 1). The median OS and RFS in the 40 patients who completed the treatment sequence were 49.7 (95% CI: 45.2–57.1) months and 13.0 (95% CI: 16.0–30.3) months, respectively (Fig. 1).

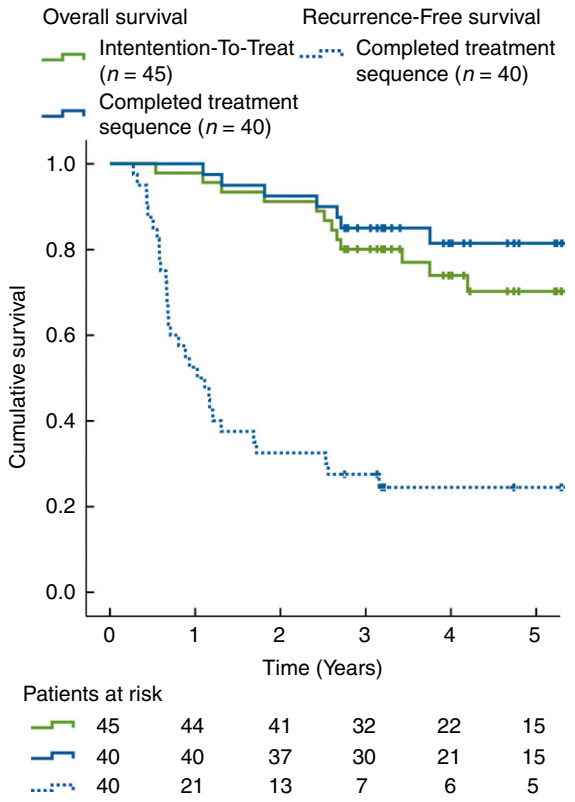

Figure 1 Overall survival and recurrence-free survival in patients treated with modified liver-first approach.

Discussion

The conventional approach to locally advanced rectal cancer with synchronous liver metastases has been to perform the rectal surgery before any liver resection [12]. The liver-first approach has been reported feasible and safe in several single-centre studies [13–19]. Since liver metastases are the main cause of death, a liver-first approach means that their elimination is not delayed by treatments directed at the primary tumour or the complications [20]. In the current study we used a modified liver-first approach and performed the liver resection in the time window between radiotherapy and rectal surgery. To our knowledge, no studies to date have evaluated the outcomes of such an approach [5]. The current study shows that the modified liver-first approach was feasible with oncological results in line with the traditional liver-first approach [13–19].

The treatment sequence completion rate after the modified liver-first approach was 89% compared to 73%–97% in similar studies [13–18]. The low complication rate of liver surgery partly explains the high completion rate. The modified liver-first approach may have several benefits over the traditional liver-first approach. First, initial and optimal control of both the liver metastases by chemotherapy and the primary rectal cancer by radiotherapy is achieved before curative surgery. Second, this strategy avoids a delay to chemoradiotherapy for rectal tumours in the case of complications after liver surgery. Third, early resection necessarily reduces the risk for local tumour progression during treatment of the liver metastases. Finally, the modified approach may allow a shortening of the overall treatment time in patients with synchronous disease. Two studies report a delay of about 4 months between liver and rectal surgery in patients undergoing the liver-first approach in which long-course radiotherapy was delivered after liver surgery [14,17]. In the study period our institution had significant concerns performing a liver resection at the same time as a major complex rectal resection, in line with a 2012 review of colorectal and liver surgeons in Great Britain [21]. Conversely, since 55% of the liver resections in the current study were minor wedge resections, simultaneous resection of the rectal cancer and liver metastases in these cases might have been an even more efficient treatment algorithm [7].

Probst *et al.* have shown that a time interval of at least 8 weeks between radiotherapy and rectal surgery results in increased pathological complete response and tumour downstaging, without increasing surgical complications [22]. The liver-first approach does not disadvantage the patient since the liver surgery occurs during a period of downstaging. The low complication rates of liver surgery and the potential benefits of laparoscopic surgery may add further value [23,24].

Logistical issues play an important role in this multimodal treatment and optimal planning is important. In line with recent recommendations from an international expert panel, short-course radiotherapy was given to 47% of the patients in the current study [5]. When rectal surgery is performed after an interval of 4–8 weeks, short-course radiotherapy has been shown to induce tumour downstaging [25]. When this is followed by chemotherapy, before surgery of the primary tumour and liver metastases in any order, has been shown to be a feasible and a potentially curative approach in patients with synchronous liver metastases from rectal cancer [10]. However, very locally advanced rectal cancer may require long-course chemoradiotherapy [26].

Thirty-four patients received neoadjuvant chemotherapy for their liver metastases. In those (n = 11) who did not, all had small, solitary liver lesions deemed initially easily resectable by the MDT. Oxaliplatin-based chemotherapy was preferred in line with the EORTC study and ESMO recommendations [2,27]. Only 43%

of the patients received postoperative chemotherapy, which is comparable to previous studies of locally advanced rectal cancer [28]. In the EORTC Intergroup trial 40 983 of patients with resectable colorectal liver (mostly metachronous) metastases receiving six cycles of FOLFOX before liver surgery and six cycles after liver surgery, 63% received postoperative chemotherapy [27]. This perioperative chemotherapy regimen demonstrated improved progression-free survival compared to surgery alone, but no overall survival benefit in long-term follow-up [29]. Nevertheless, chemotherapy has the advantage of efficacy on both the metastatic lesions and the primary tumour, and perioperative chemotherapy is currently recommended for curative treatment of rectal cancer with synchronous metastases [2,10].

Within a median of 13 months, 75% of the patients developed recurrence, and the intra-hepatic recurrence rate was high – 25/40 (63%) of those who completed the whole treatment sequence. However, treatment of the liver recurrence with curative intent was possible in more than 70% of these patients. Repeat hepatectomy is associated with long-term survival and possible cure [30,31]. The explanation for the high recurrence rate may be that this patient group already had adverse prognostic features: synchronous metastases and T3 or T4 primary tumours [32]. Furthermore, while CT was performed routinely in all patients prior to chemoradiotherapy and liver surgery, liver-specific MRI was only performed in 64.4% of the patients in this time period. A liver-specific MRI prior to preoperative chemotherapy for colorectal liver metastases has been shown to improve staging and reduce the need for a repeat hepatectomy [33]. Compared to CT, MRI may have a higher sensitivity for detecting small and uncertain lesions and has routinely been used in all patients evaluated for colorectal liver metastases in the authors' institution during the last 2 years [34].

Certain limitations of this study must be acknowledged. First, as in other reports of the liver-first approach, this was a retrospective study of patients treated at a single institution with all the inherent biases associated. There is no randomization and no control group, and although the results are comparable with published series they must be interpreted with caution. Second, quality of life is as important a marker of successful cancer treatment as OS and RFS. This issue was not evaluated with established instruments for assessment and should be addressed in future prospective trials. However, the authors wonder if quality of life is more dependent on the treatment modalities than their sequence. Third, even though current guidelines recommend upfront chemotherapy in patients with locally advanced rectal cancer and synchronous liver metastases, 25% of the patients in the current study did not receive neoadjuvant chemotherapy [35]. However, the guidelines also conclude that treatment must be individualized according to the patient, the extent of disease and whether it is primarily resectable or requires downsizing and/or downstaging. This is even more relevant where the number of metastases is limited and localized at sites that can be resected or otherwise ablated [35]. This supports the MDT decision not to offer neoadjuvant chemotherapy to the 11 patients with easily resectable, solitary liver metastases. Finally, where possible, patients should be included in prospective trials to determine the best treatment sequence in various tumour stages [36,37].

In conclusion, for patients with locally advanced rectal cancer and synchronous liver metastases, the modified liver-first approach was a safe and efficient alternative to the traditional liver-first approach. Compared to the 'classic' liver-first approach, the modified liver-first approach allows initial control of both the primary tumour and the liver metastases, and treatment is completed within a compact time frame.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

Author contributions

Study concept and design: KJL, MGG, BAB. Acquisition of data: KJL, MGG, KWB, AW, BR, SD, BE, BAB. Analysis and interpretation of data: All authors. Drafting of the work: KJL, MGG, KWB. Revising the work critically for important intellectual content: All authors. All authors have read and approved the final paper. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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