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Stage IV Colorectal Cancer: Outcomes Following the Liver-First Approach

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Background: To date, there is limited data on the liver-first approach in the management of colorectal liver metastases (CRLM). The aim of the study was to assess the outcomes of the liver-first approach for patients with synchronous CRLM in two tertiary referral centers.

Methods: Patients with stage IV colorectal cancer selected for the liver-first approach from January 2009 to December 2012 in two tertiary referral centers were included. Data collated included demographics, chemotherapy, operative findings, histo-pathological features, and survival.

Results: Thirty-seven patients with synchronous CRLM were considered for the liver-first approach. Twenty-five patients had rectal cancer. All patients underwent induction chemotherapy. Thirty patients underwent hepatic resections with no post-operative deaths. Following liver resection, five patients failed to proceed to colorectal resection and one patient had complete response to chemo-radiotherapy. Of the 25 patients that completed the liver-first approach, 13 patients had recurrent disease, of which 12 patients died. The overall 1- and 3-year survival rates were 65.9% and 30.4%, respectively.

Conclusion: The liver-first approach is a feasible strategy for patients with synchronous CRLM and may improve survival in selected patients. The selection of patients should be incorporated in a multidisciplinary approach to achieve the best possible outcomes.

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KEY WORDS: colorectal cancer; liver metastases; liver-first; reverse strategy and hepatectomy

INTRODUCTION

Approximately 25% of patients have synchronous colorectal cancer with liver metastases at the time of diagnosis [1], and these patients are thought to have a worse prognosis than those who develop metachronous disease [2,3]. The traditional management of patients with synchronous colorectal liver metastases (CRLM) is resection of the primary tumor, followed by hepatectomy if the liver metastases are resectable and subsequent adjuvant chemotherapy. Following the publication of the EORTC trial [2], many centers have changed their management pathways and advocate primary resection, followed by chemotherapy and then liver resection. The disadvantage of this approach is progression of the CRLM beyond resectability during treatment of the primary tumor, especially in the context of treatment delay secondary to the morbidity associated with primary resection [4] or adjuvant chemotherapy [5,6]. Although synchronous resection of the CRLM and primary tumor are associated with good outcomes, shorter hospital stay and reduced cost [7–10], this approach is not suitable for patients requiring major liver resection [11–13], elderly patients [14] and patients with locally advanced rectal cancer [15].

Recently, the "liver-first" approach, also known as the reverse strategy, which involves resection of the CRLM before the primary tumor, has been advocated. It was first proposed for rectal cancer patients with liver metastases who required chemo-radiotherapy prior to primary surgery [16]. This approach enabled control of the CRLM first, optimizing the chance of R0 liver resection, which may improve survival for these patients [17].

The aim of this study was to evaluate the feasibility and clinical outcomes of patients with synchronous CRLM treated with the "liver-first" approach in two tertiary referral hepatobiliary centers. The secondary aim included devising a management pathway for these patients.

PATIENTS AND METHODS

Patients

Patients presenting with synchronous CRLM undergoing hepatic resection with the primary tumor in situ from January 2009 to December 2012 were identified from two prospectively maintained databases. Collated data included patient demographics, tumor characteristics, surgical resection, and clinical outcome.

Multi-Disciplinary Approach

All patients enrolled into the study were discussed in a specialist multidisciplinary (MDT) meeting consisting of hepatobiliary surgeons, hepatologists, oncologists, radiologists and pathologists.

Pre-Operative Assessment and Neo-Adjuvant/Induction Treatment

Patients with resectable CRLM following neo-adjuvant chemotherapy or "potentially" resectable CRLM following successful induction

Conflict of interest: none.

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chemotherapy, with a resectable primary tumor were considered for the liver-first approach. Pre-operative radiological assessment included a computed tomography (CT) scan of the thorax, abdomen and pelvis and contrast enhanced magnetic resonance imaging (MRI) of the liver. In addition, all patients considered for neo-adjuvant or induction therapy underwent a positron emission tomography (PET).

Neo-adjuvant and induction chemotherapy consisted of an oxaliplatin-based chemotherapy regimen unless contraindicated, in which case patients received an irinotecan-based regimen. The addition of biological agents, such as cetuximab was considered in patients with *KRAS* wild-type tumors. The response to neo-adjuvant and induction therapy was assessed after three to six cycles of therapy with CT scan and MRI of the liver. Patients were then re-discussed at the MDT meeting and considered for surgery based on tumor response and extent of disease. Patients with resectable disease were scheduled for a liver resection, 4–6 weeks after their last cycle of chemotherapy.

Liver Resection

Liver resections were performed only if all CRLM could be resected with a clear resection margin that is with curative intent. Parenchymal transection was performed using the cavi-pulse ultrasonic surgical aspirator (CUSA). Intra-operative ultrasound was performed to confirm the findings of pre-operative imaging and to assist in surgical planning. Radiofrequency ablation (Nottingham) or microwave ablation (Liverpool) was used in selected patients in combination with liver resection. The number of hepatic (Couinaud's [18]) segments resected was determined by the procedure performed as stated in the Brisbane nomenclature [19]. Type of surgical procedure was dependent on the resection of all macroscopic disease and achieving a clear resection margin, while preserving sufficient remnant liver.

Colorectal Resection

Primary tumor resection was scheduled 4–8 weeks following liver resection, or after completion of chemo-radiotherapy for patients with locally advanced rectal cancer. All patients underwent re-staging with a CT scan and MRI to ensure there was no evidence of liver recurrence or distant metastases. Colorectal resection was performed according to accepted oncological standards, with complete meso-rectal excision for rectal cancers and lymph node dissection for colonic cancers.

Histology

Histopathological data of the resected liver specimen were collated. This included: tumor size in maximum diameter; tumor number; and status of resection margin. R0 resection was defined as no microscopic evidence of tumor at or within 1 mm of the margin.

Follow-Up

Patients were followed up in specialist hepatobiliary clinics. Following initial post-operative review at 1 month, all patients were examined in the outpatient clinic at 3, 6, 12, 18, and 24 months and annually thereafter. At each clinical review, carcino-embryonic antigen (CEA) levels were measured. All patients in this study had a minimum follow-up of 6 months following hepatic resection for CRLM.

Surveillance imaging included CT scan of the thorax, abdomen and pelvis. Patients underwent 6-monthly CT scan during the first two post-operative years, followed by annual CT scans thereafter. Liver MRI was used to characterize suspicious hepatic lesions demonstrated on CT. Development of symptoms of recurrence at any time-point prompted earlier review than scheduled.

Overall and disease-free survival was recorded, with disease-free survival being defined as the time from primary hepatic resection to the first documented disease recurrence on imaging. Overall survival was defined as the time interval between the date of commencement of neo-adjuvant/induction therapy and the date of death or most recent date of follow-up if the patient was still alive. Following detection of recurrent disease on surveillance imaging, all patients were discussed at the MDT meeting. Patients who had non-resectable disease were referred to the oncologists for consideration of palliative chemotherapy.

Statistical Analysis

Categorical data was presented as frequency and percentage. The Kaplan–Meier method was used to assess the actuarial survival and disease-free survival. Statistical analyses were performed using the SPSS for Windows™ version 16.0 (SPSS Inc, Chicago, IL), and statistical significance was taken at the 5% level.

RESULTS

Patient Demographics

During the study period, 37 patients with synchronous colorectal cancer and liver metastases were considered for the liver-first approach. Twenty-six patients were male and the median age at diagnosis was 65 years (range: 25–73 years). In the majority of patients, the site of the primary tumor was in the rectum (n = 25), and in the remaining patients the primary tumor was located in the colon [sigmoid (n = 7), descending (n = 2), ascending (n = 2) and transverse (n = 1)].

Neo-Adjuvant/Induction Therapy

All patients received either an oxaliplatin-based (n = 35) or irinotecan-based regimen (n = 2), with a range of 4–8 cycles. In addition, biological agents [cetuximab (n = 8)/bevacizumab (n = 1)] were administrated in nine patients. Seven patients failed to convert to resectability during induction chemotherapy, while 30 patients responded sufficiently to undergo liver resection. All seven patients that were not considered for liver resection had bilobar metastases, which remained static or progressed with induction chemotherapy and hence, were inoperable. One patient developed symptoms of obstruction due to the primary tumor during chemotherapy and required a de-functioning loop colostomy.

Liver Resection

A total of 30 patients underwent liver resection (Table I), with a morbidity rate of 40% (n = 12). According to the Clavien–Dindo classification there were four grade I complications (wound and cardiovascular complications), five grade II (pneumonia), three grade III (bile leak) and two grade IV (liver failure) complications. Thirteen patients underwent a hemi-hepatectomy or more radical resection, and one patient required an inferior vena cava resection. Two patients underwent microwave ablation in combination with liver resection. The majority of patients (n = 23) had multiple tumors [median = 5 (range: 2–13) and half of the patients that underwent liver resection had tumors that were >50 mm in maximum diameter (n = 15). Hence, in this study, the majority of patients (n = 27) had a high disease tumor burden i.e. multiple, bilobar metastases and large tumors. The R0 resection rate was 56.7% (n = 17; Table II).

Colorectal Resection

Following liver resection, 19 patients underwent chemo-radiotherapy for rectal cancer. Following liver resection, six patients did not subsequently undergo resection of the primary due to death from other medical cause (n = 2)/unfit for surgery (n = 1), disease progression

TABLE I. Clinical Data of 30 Patients That Underwent Liver Resection

Demographics	
Male:female	26:4
Age (years)[a]	65 (25–73)
Tumor characteristics	
Primary tumor location: rectum	21
Liver metastases	
Solitary metastasis	7
Size >5 cm	15
Hepatic resection (n = 30)	
Left hemi-hepatectomy (+ microwave ablation)	3 (1)
Right hemi-hepatectomy[b] (+ non-anatomical resection)	5 (2)
Left tri-sectionectomy	2
Right tri-sectionectomy	3
Left lateral sectionectomy (+ microwave ablation)	3 (1)
Segmental resection (+ non-anatomical resection)	5 (2)
Non-anatomical resection/metastectomy	9
Colorectal resection (n = 24)	
Abdomino-perineal resection[c]	7
Anterior resection	11
Sigmoid colectomy	1
Hartmann's procedure	1
Left hemi-colectomy	2
Right hemi-colectomy	2
R0 Resection margin	
Liver resection	17 (56.7%)
Colorectal surgery	22 (91.7%)

[a]Age presented as median (range).
[b]One patient had additional inferior vena cava resection.
[c]One patient had additional prostatectomy with ileal conduit urostomy and perineal flap.

(n = 2), or a complete response to chemo-radiotherapy (n = 1, Fig. 1). None of the three patients died because of complications secondary to the in situ primary tumor. The two patients that died of other medical causes while awaiting bowel surgery; one patient had multiple (n = 13) bilobar liver metastases and a R1 resection, while the other patient had a large solitary metastases with a R0 resection. One patient that underwent liver resection for bilobar metastases (n = 4) had a prolonged recovery with general deterioration and was deemed unfit for subsequent bowel surgery.

Following liver resection, there were two patients that demonstrated recurrence of liver metastases on CT prior to bowel resection. The recurrent disease was not suitable for further liver resection and was treated palliatively.

Of the 24 patients that underwent colorectal resection, anterior resection (n = 11) was the most common procedure performed, followed by abdomino-perineal resection (n = 7), right hemi-colectomy (n = 2), left hemi-colectomy (n = 2), sigmoid colectomy (n = 1) and Hartman's procedure (n = 1). The morbidity rate was 25% (n = 6) and there was one post-operative death. Based on the Clavien–Dindo classification, there were five grade I complications (wound and cardiovascular complications), two grade II (pneumonia), and one grade III complication (anastomotic leak). The overall R0 resection rate was 91.7% (n = 22).

TABLE II. Morbidity and Mortality Rates of Patients That Underwent Liver Resection and Colorectal Surgery in This Study

Post-operative morbidity and mortality	
Liver surgery (n = 30)	
Mortality	0
Morbidity	12 (40.0%)
Specific complications	
Bile leak	3 (10.0%)
Post-operative liver failure	2 (6.7%)
Hospital acquired pneumonia	5 (16.7%)
Cardiovascular complications	2 (6.7%)
Wound complications	2 (6.7%)
Colorectal surgery (n = 24)	
Mortality	1 (4.2%)
Morbidity	6 (25.0%)
Specific complications	
Anastomotic leak	1 (4.2%)
Hospital acquired pneumonia	2 (8.3%)
Cardiovascular complications	2 (8.3%)
Wound complications	3 (12.5%)

Outcomes

Of the 25 patients that completed the liver-first approach, 13 patients had recurrent disease at a median of 4 [1–7] months, of which 12 patients have subsequently died. The site of recurrence was liver (n = 5), lung (n = 3) or wide-spread metastases (n = 5). All patients with disease recurrence underwent palliative chemotherapy, and one patient had an additional percutaneous RFA. The other 12 patients remain disease-free after a median follow-up period of 12 months (range: 6–40 months).

The overall 1- and 3-year survival rates were 65.9% and 30.4%, respectively (Fig. 2). The median overall survival for patients who completed the reverse strategy was 12 months (range: 4–40 months), compared to 5 months (range: 3–8 months) in the seven patients who progressed on induction chemotherapy.

DISCUSSION

The use of induction chemotherapy and biological agents, as well as the introduction of the combined and reversed approaches has lead to an increase in the number of patients undergoing resection of synchronous CRLM [20]. The optimal surgical sequence for patients with synchronous CRLM however, remains controversial. The traditional staged approach is limited by the risk of disease progression during treatment of the primary tumor, and the combined approach is considered only suitable for patients with low liver disease burden. The liver-first approach involves resection of the CRLM first, followed by resection of the primary tumor with chemotherapy being used as a first line treatment before any surgery is undertaken. The rationale behind the reverse strategy is twofold: hepatectomy first allows control of the CRLM, optimizing the chance of curative liver resection, and subsequent resection of the primary tumor prevents loss of primary tumor-induced inhibition of the metastases, as demonstrated in pre-clinical studies [21–23].

Previous Studies

To date, only a few retrospective studies consisting of small cohorts of patients have been published. Mentha and co-workers [24] published the first series in 2006 consisting of 35 patients with synchronous resectable primary tumors and advanced CRLM. Verhoef et al. [25] later described their experience of 23 patients who had locally advanced rectal cancer and synchronous liver metastases, although no survival data was reported. More recently, De Jong and colleagues [26] reported their outcomes of 22 patients with CRLM from both colonic and rectal primaries. These studies suggested that this approach was a feasible option for patients with advanced liver disease.

Outcomes

In the present study, the 3-year survival rate for patients who completed the liver-first approach was 30.4%, which is comparable to the survival outcomes reported of 31–39% [20,24,26]. Studies have observed a poorer prognosis in patients with synchronous CRLM compared to patients with metachronous disease, especially in cases of rectal cancer [8,27,28]. In addition, not only do these patients have a worse prognosis from the outset, the majority of patients considered for

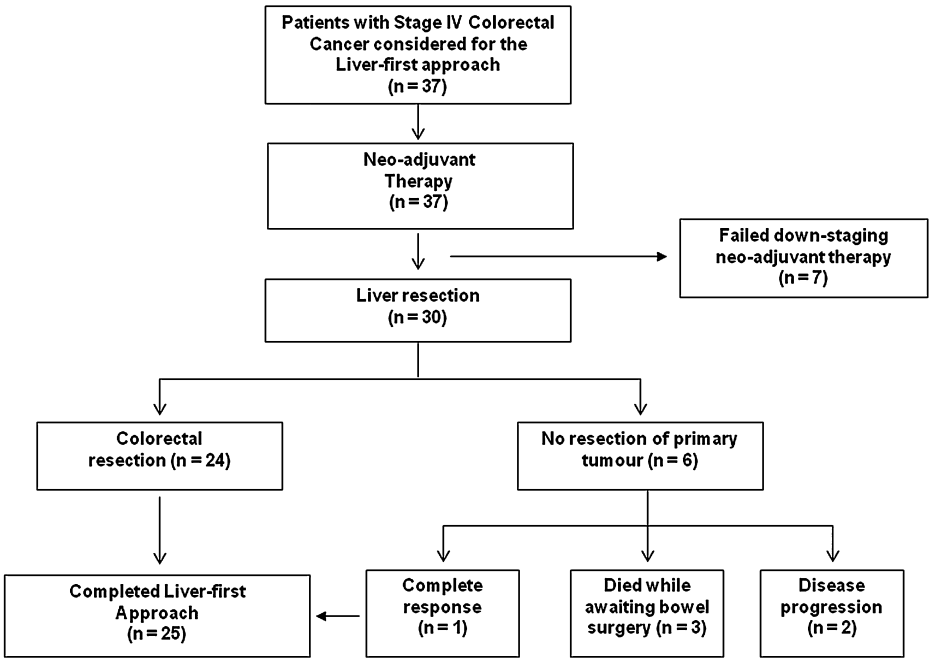

Fig. 1. Management algorithm of patients selected for the liver-first approach.

the liver-first approach have advanced liver metastases, another marker of a poorer outcome. Nevertheless, the survival outcomes reported were not significantly worse than those of patients with a lower burden of liver disease managed by the other surgical strategies. Brouquet et al. [20] compared the outcomes of 156 patients with synchronous CRLM managed by the traditional (n = 72); combined (n = 43); and liver-first (n = 27) approaches. The authors observed that the 5-year survival outcomes were not significantly different between the three groups (traditional = 48%, combined = 55%, reverse = 39%), although patients in the liver-first group had a significantly higher CRLM burden. Van der Poole and co-workers [29] also compared the outcomes of patients with synchronous CRLM managed by these three approaches. The authors performed simultaneous resections for patients with early rectal cancer and limited liver disease (n = 8), the liver-first approach for patients with advanced liver disease and/or locally advanced rectal cancer (n = 20), and compared the outcomes with patients managed by the traditional approach (n = 29). In the traditional, combined and liver-first groups, the 5-year survival rates were 28%, 73%, and 67%, respectively. This was despite patients in the liver-first group having a significantly higher median number of liver metastases. Both studies were limited by the presence of selection bias due to the significant difference in liver disease burden in the three groups. Brouquet et al. [20] did not report any selection criteria for allocating patients into the surgical groups. These results however, suggest that the outcome for patients treated with the liver-first approach with more extensive liver disease are comparable to the outcomes of patients treated with other approaches, indicating that the liver-first approach may be the most appropriate surgical sequence option for patients with advanced synchronous CRLM.

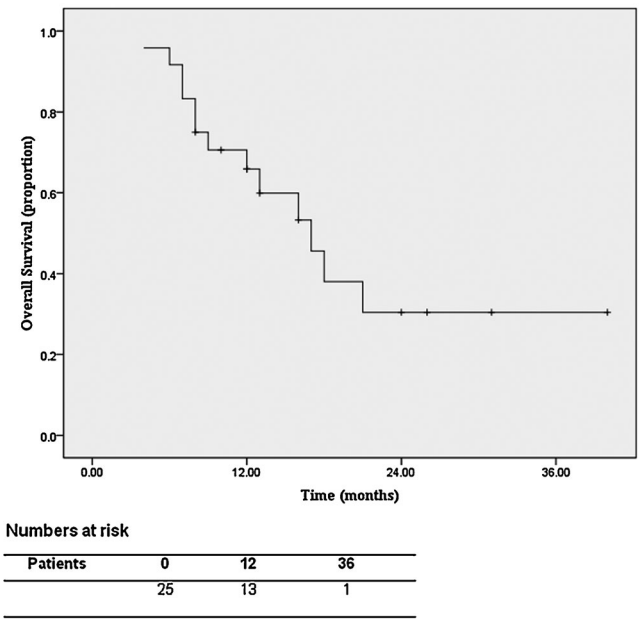

Fig. 2. Overall survival in patients that completed the liver-first approach.

Recurrence Rates

The current study observed a recurrence rate of 52% in patients who completed the liver-first approach. The recurrence rates reported in the literature ranged between 25% and 70% [20,24–26]. One possible explanation for the high rate of recurrence is that this group of patients have a higher liver disease burden, as well as more aggressive tumor biology. Due to the high risk of recurrence, it is important to have an appropriate surveillance program for these patients, and highlights the importance of a multi-disciplinary approach.

Limitations of the Reverse Strategy

One draw-back to the liver-first approach is the risk of complications related to the primary tumor which include obstruction, perforation, bleeding or pain [30,31]. It seems counterintuitive to some clinicians to

leave the primary tumor in situ, because of the potential morbidity secondary to the symptoms and/or de-functioning surgery which could result in considerable disruption to the induction chemotherapy regimen. However, the risks of complications are low; reported between 2.9% and 26% in patients developing symptoms from the primary tumor while on chemotherapy and underwent a diverting ostomy, without any additional morbidity or mortality [20,24,26]. In the present study, only one patient underwent a de-functioning loop colostomy during chemotherapy.

Failure to complete the reverse strategy limits the feasibility of this approach. The concern is that patients may undergo liver resection but fail to undergo primary resection because of disease progression, and such patients may have avoided a liver resection and undergone palliative chemotherapy alone. In the present series, 67% of patients completed the reverse strategy which is similar to the rates reported in previous studies (66–81%) [24–26]. Reasons for failure to complete this approach include disease progression in the liver or primary tumor, death from other co-morbidities while awaiting primary surgery and morbidity or mortality following liver resection. In the present series, there were no post-operative deaths and the morbidity rate of 40% was comparable to the rates of 11–37% reported in other studies following the liver-first approach as well as other larger series following hepatectomy for CRLM [32,33]. With the reverse strategy, there is a risk that an initially resectable primary tumor may progress to unresectability due to perforation or invasion into surrounding structures. However, progression of the primary tumor during induction chemotherapy is rare [30], and has only been described in one patient undergoing this approach [20]. Although there is a risk of failure to complete the liver-first approach, this aggressive approach is warranted in selected patients. Firstly, resection of the CRLM alone is associated with an increased quality of life compared with palliative chemotherapy [34], and secondly, a significant proportion of patients will complete the strategy and achieve better long-term survival compared to palliative chemotherapy alone.

Patient Selection

To allow better patient selection, it has been suggested that patients with stage IV colorectal cancer should undergo a period of neo-adjuvant/induction therapy as these patients have systematic disease, and treatment should be systemic from the beginning. Patients who experience tumor progression on chemotherapy should not undergo liver resection as it is associated with a poorer outcome [35]. In the current cohort, all patients received chemotherapy prior to surgery. Similarly, the groups of Mentha [24], Verhoef [25] and Brouquet [20] enrolled all their patients except one to chemotherapy prior surgery.

Following a period of induction chemotherapy, the treatment sequence should be determined based on response to chemotherapy and site of the primary tumor, emphasizing the importance of a specialist MDT approach. Patients with synchronous CRLM with rectal cancer that require chemo-radiotherapy, require a period of 8–12 weeks prior to their rectal surgery. This provides a window of opportunity to perform liver resection while awaiting rectal surgery. In these patients, the suggested treatment sequence would be neo-adjuvant or induction chemotherapy depending on the resectability of the CRLM, followed by chemo-radiotherapy for the rectal primary, liver resection and subsequent rectal primary resection. Another group of patients that may benefit from the reverse strategy are patients with asymptomatic (non-obstructive) colonic cancer that have extensive liver disease that require down-staging (Fig. 3). Following down-staging of liver disease with systemic chemotherapy, patients can undergo a liver resection, followed by subsequent colonic resection.

Some clinicians may argue that the traditional approach allows patients with more aggressive liver disease to "declare themselves" following their colorectal surgery, and hence, these patients would not benefit from liver resection. However, the risk of this approach is that these patients may have disease progression while awaiting surgery for the CRLM following primary surgery.

CONCLUSION

Patients with synchronous CRLM are known to have a worse prognosis, and historically would have only been offered a palliative management approach. The emphasis in the management of this complex patient group should be a "chemotherapy-first" and not "liver-first" approach, which is the most appropriate treatment sequence in

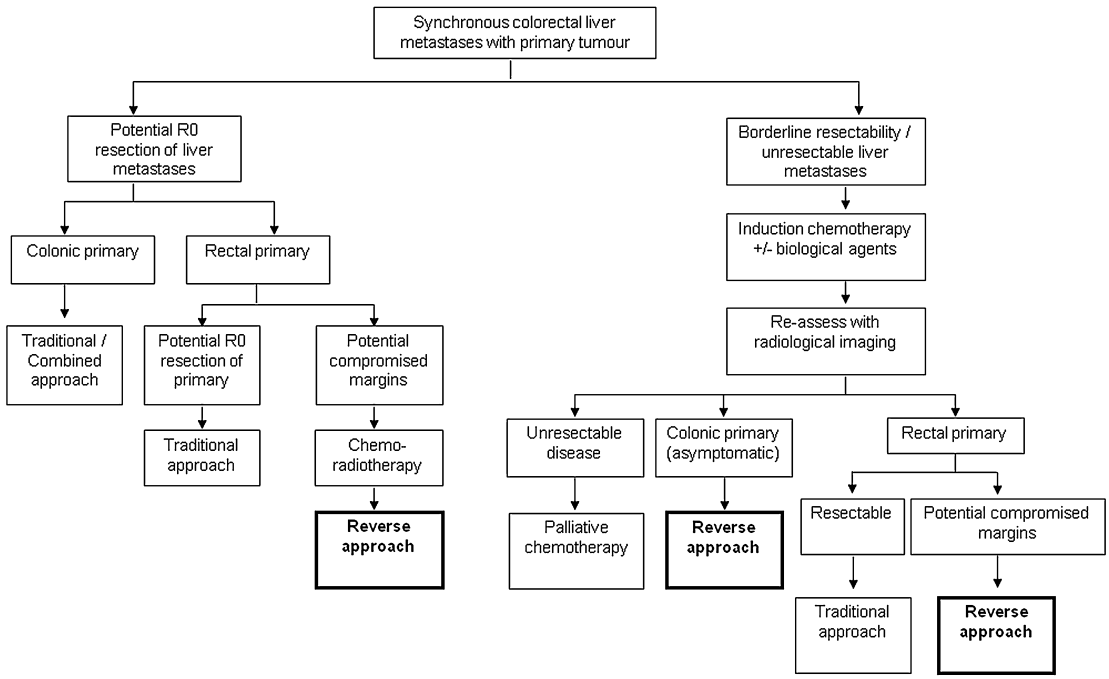

Fig. 3. Suggested management algorithm for patients with synchronous rectal cancer/asymptomatic colonic tumor and liver metastases.

patients with stage IV colorectal cancer; a systemic disease. Patients should be managed by a staged onco-surgical approach and the exact surgical sequence should be dictated by the location and response of the tumors to induction therapy. The reverse strategy can be considered for patients with: (a) early stage rectal cancer and extensive liver disease; (b) locally advanced rectal cancer with limited/extensive liver disease; or (c) asymptomatic colonic cancer with extensive liver disease. The present study shows that improved survival can be achieved in selected patients with synchronous CRLM managed by this approach. Patient selection is crucial, and should be managed by specialist MDT with an interest in metastatic colorectal cancer.

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