

## REVIEW ARTICLE

# A systematic review of a liver-first approach in patients with colorectal cancer and synchronous colorectal liver metastases

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## Abstract

**Background:** Since the liver metastases rather than the colorectal cancer itself is the main determinant of patient's survival, the 'Liver-First Approach (LFA)' with upfront chemotherapy followed by a hepatic resection of colorectal liver metastases (CLM) and finally a colorectal cancer resection was proposed. The aim of this review was to analyse the evidence for LFA in patients with colorectal cancer and synchronous CLM.

**Methods:** A literature search of databases (MEDLINE and EMBASE) to identify published studies of LFA in patients with colorectal cancer and synchronous CLM was undertaken focussing on the peri-operative regimens of LFA and survival outcomes.

**Results:** Three observational studies and one retrospective cohort study were included for review. A total of 121 patients with colorectal cancer and synchronous CLM were selected for LFA. Pre-operative chemotherapy was used in 99% of patients. One hundred and twelve of the initial 121 patients (93%) underwent a hepatic resection of CLM. In total, 60% had a major liver resection and the R0 resection rate was 93%. Post-operative morbidity and mortality after the hepatic resection were 20% and 1%, respectively. Ultimately, 89 of the initial 121 (74%) patients underwent a colorectal cancer resection. Post-operative morbidity and mortality after a colorectal resection were 50% and 6%, respectively. The median overall survival was 40 months (range 19–50) with a recurrence rate of 52%.

**Conclusions:** Current evidence suggests that LFA is safe and feasible in selected patients with colorectal cancer and synchronous CLM. Future studies are required to further define patient selection criteria for LFA and the exact role of LFA in the management of synchronous CLM.

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## Introduction

Colorectal cancer is the third most common cancer worldwide.<sup>1</sup> Up to 25% of patients have synchronous colorectal liver metastases (CLM) at presentation<sup>2,3</sup> and such synchronous presentation has been associated with poor survival outcomes.<sup>4–6</sup> Nevertheless, surgical resection of all tumour sites is considered the only curative therapy enabling long-term survival.<sup>4–6</sup> The traditional surgical strategy for patients with resectable synchronous CLM is a two-stage approach that includes colorectal cancer resection followed by chemotherapy and delayed hepatic resection of the CLM. One disadvantage of this approach includes disease progression of CLM

between the colorectal and hepatic surgery rendering the CLM unresectable.<sup>7</sup> This is of particular concern in patients who develop post-operative complications after colorectal cancer resection, precluding the administration of chemotherapy and hepatic resection of CLM.<sup>8</sup> In the last decade, simultaneous resection of colorectal cancer and CLM has been increasingly used in selected patients with comparable peri-operative morbidity and mortality as well as survival outcomes.<sup>9,10</sup> This approach however is associated with increased post-operative complications when a major hepatic resection of CLM is performed.<sup>9</sup> The benefit of peri-operative chemotherapy in patients undergoing a hepatic resection of CLM has been increasingly apparent. Indeed a recent multicentre

randomized controlled trial of 5-fluorouracil (5-FU) monotherapy demonstrated an increased disease-free survival and a trend towards increased overall survival compared with a hepatic resection of CLM alone.<sup>11</sup> With the introduction of several effective systematic cytotoxic and targeted agents, recent studies have also demonstrated an improved response rate and survival outcomes in patients with metastatic colorectal cancer.<sup>12</sup> In patients with synchronous CLM, the optimal sequence of colorectal cancer resection, hepatic resection of CLM and systematic chemotherapy has not been clearly defined and remains controversial. Since the proposal that liver metastases rather than the colorectal primary may be the most common cause of a patient's death, Mentha *et al.*<sup>7</sup> described the 'Liver-First Approach (LFA)' with chemotherapy given upfront followed by hepatic resection of CLM and finally colorectal cancer resection. This systematic review has been undertaken to assess the published evidence for the safety and feasibility of LFA in patients with synchronous CLM.

## Methods

### Literature search strategy

A search was undertaken of MEDLINE (1966 to July 2012) and EMBASE (January 1974 to July 2012) databases. The search terms *colorectal cancer or colorectal neoplasm; liver metastases or hepatic metastases; hepatectomy or liver resection or hepatic resection; liver-first or reverse approach* were used. These terms were mapped to MEDLINE Subject Headings (MESH) terms as well as being searched for as text items. Reference lists from relevant articles were searched for other potentially relevant studies.

### Study selection

The study evaluation was performed by two reviewers (V.L. and J.L.). After the initial search, reviews, case reports, conference abstract, non-human studies or case series including less than 10 patients completing the LFA were excluded. Abstracts of the remaining studies were retrieved and then reviewed for relevance. The full text of the selected articles was thoroughly reviewed. Studies from which a decision could not be made based upon the abstract were also reviewed. Those studies which described the use of the LFA with curative intent in patients with colorectal cancer and synchronous CLM were included for analysis. Studies that adopted a hybrid approach combining liver resection with ablation techniques, or two-stage hepatectomy, or resection of extra-hepatic metastases with the aim of expanding the criteria for resection of CLM, were also included for review. Only studies reporting both short- and long-term outcomes of LFA were included. When multiple publications were identified from the same or overlapping patient series, only the most complete or recent publication was included. Study methodology quality was assessed according to the Newcastle–Ottawa scale.<sup>13</sup> A score of four or more was required for inclusion.

### Data extraction and critical appraisal

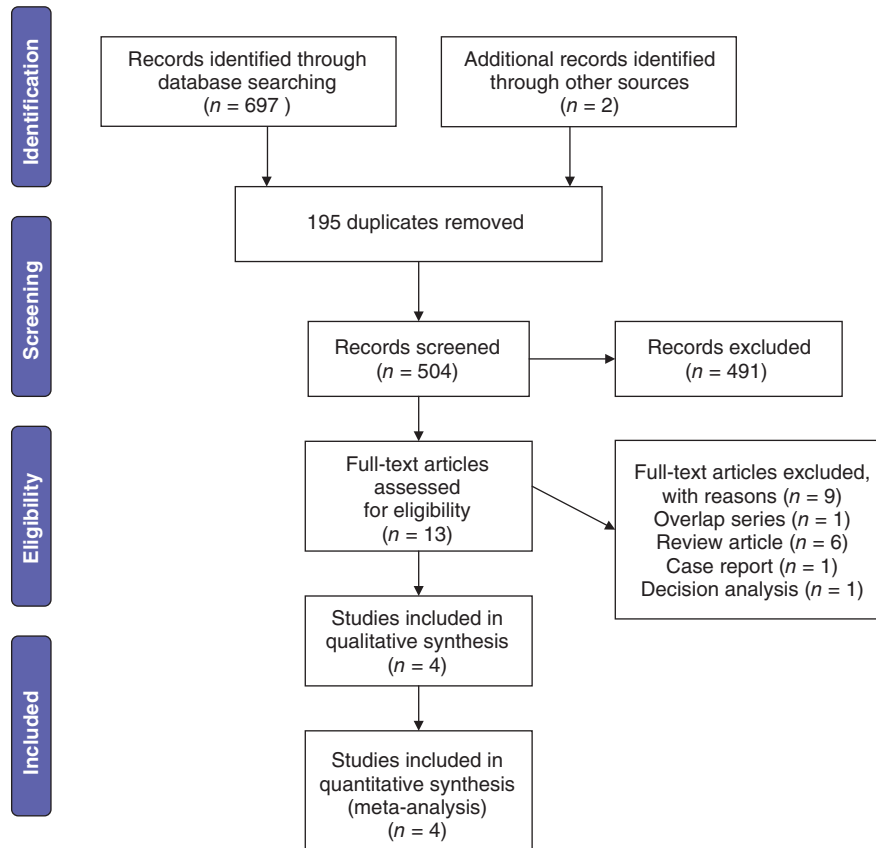
Two reviewers (V.L. and J.L.) independently appraised each article using predefined criteria. Data extracted included the methodol-

ogy, quality criteria, the setting of the use of peri-operative chemotherapy, the response to chemotherapy, the proportion of R0 resections, the overall survival (OS); the morbidity and mortality of this multimodality approach. Discrepancies were resolved by consensus. A major hepatectomy was defined as a resection of three or more Couinaud segments. Owing to the lack of a control group and the heterogeneity present amongst the selected studies, a meta-analysis could not be carried out. According to PRISMA guidelines,<sup>14</sup> a systematic review was performed without a comparator group by full tabulation of the results. The level of evidence of each article was scored according to the Hierarchy of Evidence table.<sup>15</sup>

## Results

The literature search using the above-described strategy identified 697 studies. Duplicated studies, non-human studies, review articles, case report and conference abstract were excluded. The manuscripts of the 13 remaining articles were reviewed. Nine articles not fulfilling the inclusion criteria were excluded. The remaining 4 studies were individually reviewed (Fig. 1). No meta-analyses or randomized control trials were identified.

This review comprised of 3 observational studies (level IV evidence) and 1 retrospective cohort (level III evidence) study. Overall, 121 patients with synchronous colorectal cancer and CLM were selected for the LFA.<sup>16–19</sup> Two studies with overlapping patient series<sup>7,20</sup> were excluded as well as a case report.<sup>21</sup> Selection criteria for the LFA were reported in 4 studies and none of these studies used the same criteria (Table 1).<sup>16–19</sup> One study considered all patients with primary rectal cancer with synchronous CLM<sup>19</sup> whereas another study included only patients with locally advanced rectal cancer with synchronous CLM.<sup>17</sup> Three of the four studies included patients with both colon or rectal cancer<sup>16,18,19</sup> while one study included rectal cancer only.<sup>17</sup> Three studies reported the proportion of rectal and colon cancer primary sites (Table 2) with a total of 70/86 (81%, range 68–100%) patients having primary rectal cancer. Three studies reported the proportion of patients with colonic symptoms, and a total of 39/40 (98%) were symptomatic at the time of presentation.<sup>16,17,19</sup> Two studies defined the criteria of resectability of CLM<sup>16,19</sup> according to a previous consensus conference of the surgical management of CLM.<sup>22</sup> All four studies used modern pre-operative chemotherapy (Oxaliplatin or Irinotecan-based regimens ± bevacizumab and/or cetuximab) with a total of 99% (120/121) of patients treated.<sup>16–19</sup> However, the dosage and duration of the pre-operative chemotherapy regimens were not uniform. One study also included pelvic radiation in the pre-operative chemotherapy phase before hepatic resection of CLM.<sup>19</sup> The rate of response of CLM to pre-operative chemotherapy was reported in only one study with a complete response rate of 1/22, a partial response rate of 15/22 and a stable response rate of 6/22.<sup>17</sup> All four studies reported colonic complications during pre-operative chemotherapy but only 6/120 (5%) (range, 3–10%)



**Figure 1** Flow chart showing the search strategy used to identify studies

patients required an emergency colorectal cancer resection with no mortality.<sup>16–19</sup> Overall, one patient died of fungal sepsis during the pre-operative chemotherapy phase.<sup>16</sup>

The surgical characteristics and peri-operative outcomes of the first stage (hepatic resection of CLM) of LFA are depicted in Table 3. Two studies reported the proportion of concomitant colorectal resection with a value of 7/31 and 1/22, respectively, in each study.<sup>16,17</sup> A liver resection was performed in all four studies with a total of 112/121 (93%, range 83–100%) patients undergoing a liver resection.<sup>16,17</sup> The R0 resection rate and proportion of major liver resections were reported in three studies with a total of 62/67 (93%, range 85–100%) and 40/67 (60%, range 32–89%) patients, respectively.<sup>17–19</sup> Post-operative morbidity was reported in 3 studies with a total morbidity rate of 13/64 (20%) (range, 9–27%).<sup>17–19</sup> Overall, there was one peri-operative mortality after the first stage of LFA.<sup>19</sup> Interval chemotherapy  $\pm$  pelvic radiation was reported in three studies with a total of 39/68 (57%, range 18–100%) patients receiving such treatment.<sup>17–19</sup> The interval duration between the first and second stage of LFA was reported in two studies with a median interval duration of 4 weeks and 3 months, respectively, in each study.<sup>17,19</sup>

Thirty of the initial 121 (25%) patients did not progress to the second stage of LFA. Interval disease progression (26/30) was the

main reason followed by disappearing primary (2/30) and death before the second stage of LFA (2/30). The surgical characteristics and peri-operative outcomes of the second stage (colorectal cancer resection) of the LFA are depicted in Table 4. Eighty-nine of the initial 121 (74%) patients ultimately underwent a colorectal cancer resection. Post-operative morbidity was reported in two studies with a rate of 1/30 and 8/16, respectively.<sup>16,19</sup> Post-operative mortality was reported in 3 studies and there was one [1/62(2%)] post-operative death.<sup>16,17,19</sup>

Overall, 91 of the initial 121 (75%) patients completed both stages of the LFA including 89 patients who underwent a colorectal cancer resection and 2 patients with disappearing rectal cancer primary after peri-operative chemoradiation. The survival outcomes after completion of LFA are depicted in Table 4. The follow-up time was reported in two studies with a median follow-up of 18 and 25 months, respectively.<sup>17,18</sup> Survival outcomes were reported in all four studies. The median OS of patients who completed both stages of the LFA was reported in all 4 studies with values of 19, 36, 44 and 50 months, respectively.<sup>16–19</sup> The recurrence rate was reported in all four studies with a total of 47/91 (52%) (range, 13–70%) patients suffering recurrence.<sup>16–19</sup> Three-year OS post-completion of the LFA was reported in all 4 studies with values of 41%, 60%, 79% and 89% respectively.<sup>16–19</sup>

**Table 1** Setting of the studies reporting the results of the liver-first approach (LFA) in patients with synchronous colorectal liver metastases including the selection criteria of LFA

Reference	Year of publication	Country	Setting	Study period	Selection criteria of 'LFA'
Mentha <sup>16</sup>	2008	Switzerland	Prospective observational study	1998–2007	<ul style="list-style-type: none"> <li>Advanced synchronous colorectal liver metastases<sup>a</sup></li> <li>Age &lt;70</li> <li>Performance status &lt;2</li> <li>Non-occlusive primary tumour</li> <li>At least two liver segments without metastases</li> <li>No or resectable extrahepatic disease</li> <li>Clinical risk score &gt;3</li> </ul>
Verhoef <sup>17</sup>	2009	Netherlands	Retrospective observational study	2003–2007	<ul style="list-style-type: none"> <li>Synchronous liver metastases</li> <li>Locally advanced rectal cancer and where it is defined as:               <ol style="list-style-type: none"> <li>tumour &gt;5 cm at colonoscopy or MRI (clinically large T3); or</li> <li>clinically fixed tumor or with ingrowth in adjacent organ on MRI (T4); or</li> <li>N + tumor (lymph node &gt;8 mm on CT or MRI)</li> </ol> </li> </ul>
Brouquet <sup>18</sup>	2010	United States	Retrospective cohort study	1992–2009	<ul style="list-style-type: none"> <li>Synchronous colorectal liver metastases</li> <li>Criteria not specifically stated but liver resection is planned as soon as the disease was considered resectable, typically after 3 to 5 cycles of preoperative chemotherapy</li> </ul>
De Jong <sup>19</sup>	2011	Netherlands	Retrospective Observational study	2005–2010	<ul style="list-style-type: none"> <li>Synchronous colorectal liver metastases</li> <li>Liver remnant post resection includes at least two adjacent liver segments as well as sufficient vascular inflow and outflow and adequate biliary drainage</li> <li>All patients with a primary rectal cancer were considered for the liver-first approach</li> <li>Patients with colorectal cancer located in the colon were selected on a case-to-case basis</li> </ul>

<sup>a</sup>Criteria of 'Advanced Synchronous Colorectal Liver metastases' was not clearly defined.

whereas 5-year OS post-completion of LFA was reported in 3 studies with the value of 31%, 39% and 89%, respectively.<sup>16–18</sup>

## Discussion

This systematic review demonstrates that LFA in selected patients with synchronous colorectal cancer and CLM is associated with low peri-operative morbidity and mortality and acceptable survival outcomes. The 3-year OS ranged from 41% to 89% whereas the 5-year OS was 31% to 89%. These outcomes are comparable with those of a hepatic resection in selected patients with resectable CLM after the colorectal cancer resection.<sup>4–6</sup> Although the LFA has been discussed widely among hepatobiliary surgeons in international and regional hepatobiliary surgery conferences,<sup>23,24</sup> only four surgical series with a total of 91 patients who completed the LFA were identified and thus the results should be interpreted with caution.

Although the value of a hepatic resection for CLM has never been demonstrated in a prospective randomized controlled trial, numerous surgical series have demonstrated the possibility of long-term survival. Additionally, no other treatment apart from a liver resection has shown a survival plateau. Recently, a number of case series describing 10-year actual survivors after a liver resection of CLM have also been published.<sup>5,6</sup> These results support liver resection as the standard practice as well as the only curative treatment for CLM.

In this systematic review, there were no uniform patient selection criteria for the LFA and it is a significant limitation to the critical evaluation of outcomes of this approach. The majority of the selected patients who had rectal cancer [70/86 (81%) and 39/80 (49%)] had colonic symptoms at the time of presentation. Two of the 4 studies made reference to the recent consensus conference CLM resectability criteria as part of the patient selection criteria. It was unclear whether the remaining two studies included patients with definitely resectable, borderline resectable or unresectable CLM or a combination of these three. Pre-operative chemotherapy with oxaliplatin- or irinotecan-based regimens with bevacizumab and/or cetuximab were administered in 120/121 (99%) of patients and appeared to be an integral part of the LFA. This was followed by a hepatic resection in 112/121 (93%) of patients and ultimately colorectal cancer resection in 89/121 (74%) of patients. Thirty out of 121 (25%) patients did not complete all stages of the LFA with disease progression being the most common reason.

The timing and sequence of therapeutic interventions in patients presenting with synchronous CLM has not been clearly defined and the decision whether to go 'Bowel-First', 'Simultaneous' or 'Liver-First' remains controversial.<sup>25</sup> For patients presenting with severe symptoms related to the intact colorectal cancer, the decision to resect the colorectal cancer first is straightforward.<sup>26</sup> However, the intact colorectal cancer is asymptomatic in the majority of patients. The traditional 'Bowel First' approach is

**Table 2** Patient characteristics, systemic chemotherapy and response to treatment

Reference	Total patients selected initially for 'Liver-first Approach'	Rectal Primary <i>n</i> (%)	Colonic symptoms at the time of presentation <i>n</i> (%)	Preoperative chemotherapy <i>n</i> (%)	Chemotherapy regimens	Radiological response rate of chemotherapy <sup>a</sup> <i>n</i> (%)	Colonic complications during chemotherapy <i>n</i> (%)
Mentha <sup>16</sup>	35	NR	0 (0)	35 (100)	Oxaliplatin, Irinotecan, 5-FU, leucovorin ± bevacizumab and/or cetuximab	NR	1/35 <sup>b</sup> (3)
Verhoef <sup>17</sup>	23	23 (100)	23 (100)	22 (96)	5-FU/Capecitabine, Oxaliplatin or Irinotecan ± bevacizumab	16/22 (73)	1/22 <sup>c</sup> (5)
Brouquet <sup>18</sup>	41	28 (68)	NR	41 (100)	5-FU, Oxaliplatin or Irinotecan ± bevacizumab and/or cetuximab	NR	2/41 <sup>d</sup> (5)
De Jong <sup>19</sup>	22	19 (86)	16 (73)	22 (100)	<ul style="list-style-type: none"> <li>• Non-locally advanced rectal cancer: Short course pelvic radiation (5X5 Gy) + 3 cycles of oxaliplatin ± bevacizumab</li> <li>• Locally advanced rectal cancer(T3-4, N1-2): Long course pelvic radiation (28 fractions of 1.8 Gy radication) with capecitabine + 2 cycles of oxaliplatin ± bevacizumab</li> </ul>	NR	2/22 <sup>e</sup> (10)
Total percentage		70/86 (81)	39/80 (49)	120/121 (99)			6/120 (5)
Range		68–100	0–100%				3–10
Total	121						

<sup>a</sup>Complete or partial response.

<sup>b</sup>Colonic occlusion requiring an emergency Hartmann's procedure.

<sup>c</sup>Caecal perforation requiring an emergency colectomy.

<sup>d</sup>Symptomatic requiring an emergency colostomy.

**Table 3** Surgical characteristics and peri-operative outcomes of a liver resection stage of the liver-first approach (LFA)

Reference	Number of patients underwent liver resection <i>n</i> (%)	Synchronous liver and bowel resections <i>n</i> (%)	R0 resection <i>n</i> (%)	Major liver resection <i>n</i> (%)	Perioperative Morbidity <i>n</i> (%)	Perioperative Mortality <i>n</i> (%)	Interval chemotherapy ± radiation <i>n</i> (%)
Mentha <sup>16</sup>	31/35 (89)	7 (23)	NR	NR	5 (16)	0	NR
Verhoef <sup>17</sup>	19/23 (83)	1 (5)	19 (100)	6 (32)	2 (9)	0	19 (100)
Brouquet <sup>18</sup>	41/41 (100)	NR	23/27 <sup>a</sup> (85)	24/27 <sup>a</sup> (89)	NR	1/27 <sup>a</sup> (4)	16/27 <sup>a</sup> (59)
De Jong <sup>19</sup>	21/22 (95)	NR	20 (95)	10 (48)	6 (27)	0	4 (18)
Total Percentage	112/121 (93)		62/67 (93)	40/67 (60)	13/64 (20)	1/91 (1)	39/68 (57)

<sup>a</sup>Twenty-seven of the initial 41 patients completed both liver and bowel resection; R0 and major liver resection rates and peri-operative outcomes were reported in these 27 patients.

a two-stage procedure that includes colorectal cancer resection followed by delayed hepatic resection of CLM. Arguments for an initial colorectal cancer resection in these patients include: (i) if the tumour obstructs, bleeds or perforates, emergency surgery is required, which is associated with a higher peri-operative morbidity and mortality; and<sup>27</sup> (ii) the interval time period between a

colorectal resection and hepatic resection may allow occult systematic disease to become detectable.<sup>28</sup> Patients with disease progression rendering the disease unresectable can thus be spared the peri-operative morbidity and mortality of futile hepatic surgery.

Several arguments however have been posited against upfront colorectal resection: (i) over the past decade, peri-operative

**Table 4** Surgical characteristics and peri-operative outcomes of bowel resection stage of the liver-first approach (LFA); and survival outcomes after completion of LFA

Reference	Patients underwent bowel resection n (%)	Bowel Resection		Survival Outcomes in patients who completed both hepatic and bowel resection stages of the LFA					
		Perioperative morbidity n (%)	Perioperative mortality n (%)	Number of patients completed both stages of LFA	Median Follow-up (months)	Median OS (months)	Recurrence rate n (%)	3-year OS (%)	5-year OS (%)
Mentha <sup>16</sup>	30/35 (86)	1/30 (3)	0	30	NR	44	20/30 (68%)	60	31
Verhoef <sup>17</sup>	16/23 (70)	NR	0	16	18	19	2/16 (13%)	89	89
Brouquet <sup>18</sup>	27/41 (66)	NR	NR	27	25	50	19/27 (70%)	79	39
De Jong <sup>19</sup>	16/22 <sup>a</sup> (73)	8/16 (50)	1/16 (6)	18 <sup>b</sup>	NR	36	6/18 (33%)	41	NR
Total Percentage	89/121 (74)			91/121 (75)			47/91 (52%)		
Range							13–70		

<sup>a</sup>Excluding two patients who had a complete response of the rectal cancer after chemoradiation.

<sup>b</sup>Survival outcomes included two patients who had a complete response of rectal cancer after chemoradiation and no bowel resection was thus performed.

OS, overall survival.

chemotherapy followed by a hepatic resection is increasingly performed in patients with resectable CLM. In a randomized controlled study, 5-FU-based peri-operative chemotherapy followed by a hepatic resection was associated with increased disease-free survival and a trend towards increased overall survival when compared with a hepatic resection alone.<sup>11</sup> Furthermore, modern chemotherapy regimens using a combination of 5-FU plus oxaliplatin and/or irinotecan has produced even better response rates with a partial response rate up to 50% and a median survival approaching 2 years in patients with unresectable metastatic colorectal cancer.<sup>29,30</sup> The addition of biological agents such as bevacizumab and cetuximab has been shown to further improve the response rate;<sup>31,32</sup> (ii) in patients with intact colorectal cancer and synchronous CLM, it has been shown that pre-operative chemotherapy with oxaliplatin- and/or irinotecan-based regimens induced a major histological response of 70% in colorectal cancer. Such a response was also significantly correlated with a response of the corresponding CLM; (iii) recent studies demonstrated that colorectal cancer resection in patients with metastatic colorectal cancer was associated with a significantly higher 30-day mortality of 10% when compared with a colorectal cancer resection in the non-metastatic setting;<sup>33,34</sup> (iv) the potential colonic complications of leaving the colorectal cancer intact may have been overstated. The rate of surgical intervention for colonic complications was only 20% in one review of 255 patients with metastatic colorectal cancer treated primarily with 5-FU.<sup>27</sup> Poultsides *et al.*<sup>27</sup> published the Memorial Sloan-Kettering Cancer Centre experience of 233 patients with metastatic colorectal cancer with an intact primary tumour. The incidence of colonic complications was 7% with the use of modern oxaliplatin- or irinotecan-based chemotherapy. A recent multi-institutional NSABP Trial C-10 prospectively followed 86 patients with asymptomatic colon cancer and unresectable metastases. All patients were treated with

infusional 5-FU, leucovorin and oxaliplatin (mFOLFOX6) combined with bevacizumab. The incidence of a significant colonic complication was 12/86 (14%) with 10 patients requiring surgery (8 for an obstruction, 1 for perforation and 1 for abdominal pain) and 2 patients died with symptoms of colon cancer;<sup>35</sup> (v) even if patients develop symptoms related to advanced colorectal cancer, endoscopic treatment has been increasingly used. One systematic review demonstrated that self-expanding metallic stents were safe and effective for relieving malignant colorectal obstruction with a median clinical success rate of 92%.<sup>36</sup> Endoscopic ablative therapies might also be useful in controlling haemorrhagic symptoms;<sup>37</sup> (vi) an anastomotic leak after colorectal resection is not uncommon. The rate of an anastomotic leak after a rectal resection in particular was up to 12%, with a morbidity rate of up to 50%. Such complications could lead to a delay or even cancellation of both hepatic surgery and chemotherapy. One study also demonstrated that up to 50% of patients did not undergo further optimal post-operative chemotherapy treatment because of post-operative complications after rectal surgery; (vii) metastatic disease rather than primary colorectal cancer has been proposed to be the main determinant of patient survival and thus treatment of the CLM should be the first priority.<sup>7,17</sup> One systematic review also demonstrated that downstaging chemotherapy could convert 22.5% of patients with initially unresectable CLM into 'resectable'.<sup>38</sup> On this basis many argue that modern chemotherapy should be administered first and not delayed by the colorectal cancer resection, especially if surgical complications occur.<sup>25</sup> All these findings lend support to the LFA with upfront modern chemotherapy followed by hepatic resection in patients with synchronous asymptomatic colorectal cancer and CLM. This conclusion is further supported by a decision analysis demonstrating that the optimal management in patients with colorectal cancer and synchronous resectable CLM should be upfront systemic chemotherapy.<sup>39</sup>



The majority of patients in this review of LFA received up-front chemotherapy. Although peri-operative chemotherapy (both before and after liver resection) is associated with improved oncological outcomes, it appears to come at the cost of increased post-operative morbidity.<sup>11</sup> However, given that no high-quality study compares pre- and post-operative chemotherapy to post-operative chemotherapy alone, the optimal sequence of liver surgery, colonic resection and systemic chemotherapy in synchronous CLM is as yet unresolved. Consideration should be given in particular to liver damage owing to chemotherapy in the form of steohepatitis (associated with irinotecan exposure) and sinusoidal injury (linked to oxaliplatin administration). This may increase the risk of liver failure after a resection, particularly if extended in nature. A liver first approach, prior to systemic treatment, circumvents these issues and may reduce the risks of post-operative surgical complications.

In the past decade, a simultaneous colorectal cancer resection and hepatic resection of CLM has been increasingly performed. Brouquet *et al.*<sup>18</sup> compared the 'Bowel First', 'Simultaneous' and 'Liver First' approaches in the management of 156 consecutive patients with colorectal cancer and synchronous CLM and found an equivalent peri-operative morbidity and mortality as well as survival outcome among all three strategies. One systematic review comparing simultaneous and staged resection for synchronous CLM also demonstrated the safety and efficacy of the simultaneous approach in selected patients with comparable oncological outcomes and fewer overall complications.<sup>10</sup> The major limitation of this review was that all the included studies were retrospective. In addition, the patients who underwent simultaneous colorectal and hepatic resection were more likely to have a right-sided primary tumour, fewer and smaller synchronous CLM and were more likely to require a minor hepatic resection. Nevertheless, if a simultaneous resection can be performed without added morbidity and mortality, the potential benefits of one surgical procedure over two are clear with a shorter total hospital stay and thus less financial costs.<sup>40</sup>

In this study, a pooled analysis was conducted where the data from observational studies were combined as if it were derived from a single sample. The application of any formal meta-analytic methods, particularly simple pooling, to observational studies has been controversial.<sup>41</sup> Although combining data by meta-analytic methods is preferable, it was not feasible in this study.<sup>42</sup> It must be acknowledged that the studies in this review each include a small number of patients and that there is considerable heterogeneity evident in their design. Nevertheless, pooling of data provides an indication of real-world outcomes, but its results must be interpreted with caution.

In conclusion, this systematic review demonstrated that LFA is safe and feasible in selected patients with colorectal cancer and synchronous CLM and is associated with acceptable peri-operative and survival outcomes. The experience of LFA is in its infancy and future prospective controlled studies are required to further define the patient selection criteria for LFA and the exact role of LFA in the management of synchronous CLM.

#### Conflicts of interest

None declared.

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