

The Liver-First Approach to the Management of Colorectal Cancer With Synchronous Hepatic Metastases

A Systematic Review

Santhalingam Jegatheeswaran, MRCS; James M. Mason, DPhil; Helen C. Hancock, PhD; Ajith K. Siriwardena, MD, FRCS

Importance: To our knowledge, this is the first systematic review of the liver-first approach to the management of patients with colorectal cancer with synchronous liver metastases.

Objective: To review current evidence for the liver-first approach to the management of patients with colorectal cancer with synchronous liver metastases.

Evidence Review: PubMed, EMBASE, the Science Citation Index, the Social Sciences Citation Index, Conference Proceedings Citation Index, and the Derwent Innovations Index were searched for the period from January 2000 to May 2012 using terms describing colorectal cancer, liver metastases, and surgery. A predefined protocol for data extraction was used to retrieve data on the design of each study including demographic profile, distribution of primary and hepatic metastatic disease, management of chemotherapy, surgery, the sequence of intervention, disease progression, the numbers completing treatment algorithm, and outcome and survival.

Findings: The literature search identified 417 articles,

of which 4 cohort study reports described the liver-first approach and reported survival data. There was good agreement between studies on the sequence of treatment using the liver-first approach. The preferred algorithm was systemic chemotherapy, followed by liver resection, then chemoradiotherapy for those patients with rectal lesions, and colorectal resection as the last operative step. Two protocols provided further adjuvant chemotherapy after colorectal resection. Of 121 patients starting treatment, 90 (74%) completed the specified treatment protocol. Disease progression during the protocol period occurred in 23 patients (19%). There was wide variation in survival despite apparently similar protocols.

Conclusions and Relevance: The liver-first approach for patients with colorectal cancer with synchronous liver metastases is possible but is associated with a wide range of survival outcomes, despite protocol similarities between studies. There is a need for a well-designed clinical trial comparing this liver-first approach with the classic (bowel-first) approach.

JAMA Surg. 2013;148(4):385-391

THE LIVER IS THE MOST COMMON site of metastasis for patients with colorectal cancer.¹ About 14% to 18% of patients with colorectal cancer have liver metastases at presentation, and another one-third will subsequently develop it.^{1,2} Patients who present with metastatic liver disease at a time

at the time of the index presentation with their colorectal cancer (which is termed *synchronous metastasis*) is more complex. These patients represent individuals with less favorable cancer biology who are thus less likely to become long-term survivors.² The classic management of these patients comprised surgical resection of the colorectal primary tumor, adjuvant chemotherapy, and then liver resection as a subsequent operation.^{3,4} The rationale for this classic approach was that the colorectal primary tumor was the usual source of symptoms (with some of these, such as partial obstruction or bleeding, necessitating early surgery). The primary tumor was thought to be the likely source of subsequent metastasis and thus should be removed first, and the recovery period after bowel resection created a natural selection “window” by which patients who

See Invited Critique at end of article

point remote from the treatment of the primary disease (which is termed *metachronous disease*) are logically managed by treatment directed at this new metastatic disease.

In contrast, the management of patients who present with liver metastases

Author Affiliations:
Hepatobiliary Surgery Unit, Manchester Royal Infirmary, Manchester (Drs Jegatheeswaran and Siriwardena), Durham Clinical Trials Unit, School of Medicine and Health, Durham University and Wolfson Research Institute, Stockton-on-Tees (Drs Mason and Hancock), England.

went on to develop progressive disease were excluded from undergoing liver resection.⁴

This classic approach has been increasingly questioned. First, advances in surgical technique and, in particular, the ability to perform liver and bowel resections with relatively little operative blood loss, coupled with advances in anesthesia and perioperative care, have made the synchronous approach an option.⁵ In the synchronous approach, the liver metastases and colorectal primary tumor are resected as a single stage.⁶ This approach has the advantage of removing all of the macroscopic cancer during a single operation. The disadvantages are that the morbidity of complex liver resection, combined with major bowel resection, is likely to be considerable, and there is some evidence that the combined strategy has a negative effect on progression-free survival.⁶

An alternative paradigm for the management of patients with synchronous colorectal cancer and liver metastatic disease is the reverse or so-called liver-first approach.⁷ This modern policy has evolved as a result of the increasing complexity of care of primary colorectal cancer, with evidence supporting preoperative chemoradiotherapy for rectal cancer, together with the development of colonic stenting, which has allowed palliation of symptoms such as partial obstruction without surgery so that patients can be candidates for systemic chemotherapy at an early stage in their treatment course.^{8,9} Another cited advantage of the reverse strategy (but one that remains in question) is the view that it is the liver metastatic disease, rather than the primary cancer, that gives rise to systemic metastatic disease.¹⁰ The scientific support for this currently popular concept is relatively limited, and there is counterevidence to suggest that it is the in situ primary tumor that produces systemic effects promoting angiogenesis in the liver parenchyma and thus favoring further metastasis.¹¹ Nonetheless, a clear attraction of the reverse strategy is the option to give systemic chemotherapy as a first step early in the treatment course. Current evidence indicates that colorectal cancer is a chemosensitive disease, and thus there is a logic to early systemic treatment (in conjunction with endoscopic stent palliation and radiotherapy for symptomatic rectal lesions).^{8,12} Following systemic chemotherapy, the liver resection is undertaken as the first operative intervention with the reasoning being that it is the burden of liver disease that is the likeliest course of subsequent metastasis.⁸ Colorectal cancer resection is reserved as the second operative step, and for selected patients with rectal tumors (who have a complete endoscopic and radiologic response to chemoradiotherapy), there may then be the option to avoid pelvic surgery altogether.¹³

As with many aspects of modern hepatic surgery, there is no randomized trial evidence to support or refute this line of management, but an increasing number of cohort reports have accrued on the feasibility and outcome of the liver-first approach.^{7,10,14-17} Currently published reports of the liver-first strategy are all single-center clinical cohorts.^{7,10,14-17} Pooling of data from these reports potentially allows for a better understanding of variations in protocol in the use of the term *liver-first* and

a collective overview of case mix, outcome, and survival. Thus, the aim of the present study is to undertake a systematic review of survival reports of patients receiving the liver-first approach to surgery for colorectal cancer with synchronous hepatic metastases. The review sought to identify common procedural elements in treatment protocols and to identify sources of heterogeneity in outcomes.

METHODS

LITERATURE SEARCH STRATEGY

MEDLINE and EMBASE databases were searched for the period from January 2000 to May 2012 using MeSH (Medical Subject Headings) and the key words “colorectal neoplasms,” “liver neoplasms,” and “synchron*.” Boolean operators were used to ensure that variations in key words were captured in the search. Combining these searches and excluding non-English language publications identified 347 potentially relevant unique citations. A separate search was performed using the Web of Knowledge (version 5.5), including the Science Citation Index, the Social Sciences Citation Index, the Conference Proceedings Citation Index, and the Derwent Innovations Index using colorectal cancer, synchronous liver metastases, and surgery as topics. Limiting this search to the English language yielded 317 unique citations. These 2 sets of abstracts were downloaded, and duplicates were excluded to identify 417 unique articles. Publications that did not contain details of procedure-related outcomes for patients undergoing the liver-first approach to the treatment of synchronous colorectal liver metastases were excluded (n=411). Six studies reported outcomes from the liver-first surgical strategy for synchronous colorectal liver metastases. Two of these studies were excluded—one provided no procedure-specific data,¹⁷ and the other report was an initial description of the liver-first strategy⁷ by a group whose subsequent report (with overlapping patient data between studies) is included in this review.¹⁴

Four publications were identified as meeting the inclusion criteria of this review, providing demographic and clinical outcome data on patients with synchronous colorectal hepatic metastases and primary colorectal tumors treated by the liver-first approach. These articles constitute the study population.^{10,14-16} (**Figure 1**). The Cochrane database of systematic reviews was then cross-checked to ensure that no similar systematic reviews had been undertaken.

STUDY ELIGIBILITY AND QUALITY ASSESSMENT

Studies describing the procedural approach to liver-first surgery and providing original, patient-level data on survival after the liver-first approach for synchronous colorectal liver metastases were included.

DATA EXTRACTION AND REPORTING

A predefined protocol for data extraction was used to retrieve data on the design of each study, including demographic profile, primary and hepatic metastatic disease distribution, chemotherapy, surgical interventions, the sequence of intervention, disease progression, numbers completing treatment algorithm, and outcome and survival.

Survival data for each cohort were extracted from each study report. Three articles^{10,14,16} provided Kaplan-Meier survival analyses. These plots were enlarged onto an A4-page format, and the timing of individual events (death or censoring) extracted graphi-

cally. Further explanations about mortality in the early post-operative period were retrieved from the text to support this method. One article¹⁵ provided individual survival data for each patient. Finally, one study¹⁶ limited survival data to those patients completing the liver-first strategy, and the pooled survival data only included 27 of the 41 patients.

ANALYSIS

The principal outcome was an analysis of survival data. Survival and status (diseased or not) data were entered into the SPSS statistical software package (SPSS version 19.0 for Windows; SPSS Inc) and analyzed using the Kaplan-Meier method. The intention was to perform an individual patient reanalysis of survival from the included studies; however, the heterogeneity of cohort survival findings precluded this.

RESULTS

COLLECTIVE PROTOCOL OVERVIEW

All liver-first protocols administered neoadjuvant chemotherapy as the first intervention (**Table 1**), using conventional oxaliplatin-based or irinotecan hydrochloride-based chemotherapy regimens augmented by biological agents, such as bevacizumab, from the time of availability of these latter agents. Liver resection was the first operative step (and the second intervention). Chemoradiotherapy was administered after liver resection in those patients with rectal primary tumors. Two protocols provided further adjuvant oxaliplatin- or irinotecan-based chemotherapy after resection of the primary tumor (Table 1). Two protocols addressed the phenomenon of patients with a primary tumor that resolved after adjuvant chemotherapy by the adoption of a watch and wait policy.

CASE VOLUME AND SITE

The total number of patients who received the liver-first approach to treatment was 121, of whom 90 (74%) completed the full protocol of their respective unit (Table 1). Of these 121 patients, 23 (19%) experienced disease progression during the protocol period (Table 1). The extent and distribution of disease are shown in **Table 2**, including 83 cases of rectal primary cancer and 33 cases of colon primary cancer, with the site of the primary tumor being unreported in 5 cases.

CHEMOTHERAPY STRATEGIES

Conventional colorectal cancer-directed systemic chemotherapy using oxaliplatin- or irinotecan-based regimens was used in all 4 protocols, with the supplementation of bevacizumab when this agent became available (**Table 3**). Between 3 and 6 cycles of chemotherapy were administered. Data on the delay to liver resection were provided in 2 studies only (Table 3). No studies provided data on any potential influence of chemotherapy on the liver parenchyma. Chemoradiotherapy for rectal tumors was administered after liver resection, and 2 protocols used further adjuvant oxaliplatin- or

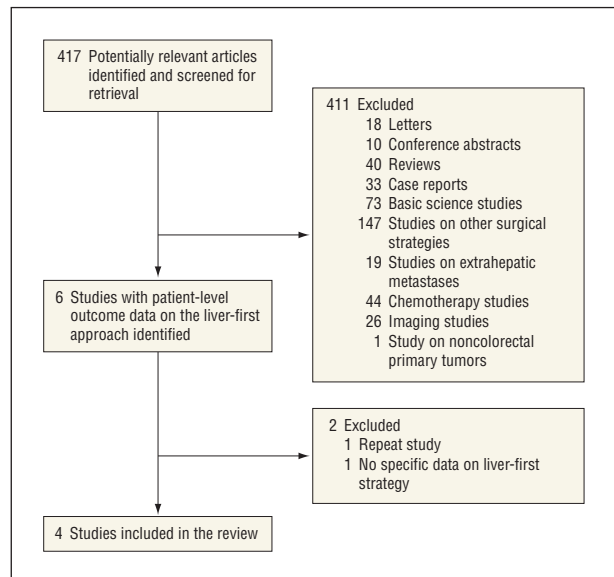


Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart of the studies identified and screened in the systematic review. Two studies were excluded for either being a repeat study⁷ or having no specific data on the liver-first strategy.¹⁷ Four studies^{10,14-16} were reviewed.

irinotecan-based chemotherapy after resection of the primary tumor.

LIVER RESECTION

Among the studies providing data on the hepatic burden of metastases, all report multiple lesions, with a majority of patients having bilobar disease (Table 2). Of the 121 patients in the starting cohort, 96 (79%) reached the stage of liver resection, with disease progression or death during chemotherapy being the principal causes of failure to proceed to liver resection (**Table 4**). One patient with liver metastases at the outset of the protocol did not undergo liver resection because the lesions disappeared after neoadjuvant chemotherapy. For 67 patients, there was information on whether the liver resection was categorized as major (>3 segments), and of these 67 patients, 43 (64%) underwent major liver resection. The liver disease burden for 11 of the 96 patients (11%) required a 2-stage hepatectomy.

COLORECTAL CANCER RESECTION

Of the 121 patients in the starting cohort, 91 (75%) underwent colorectal cancer resection (**Table 5**). The procedure was undertaken synchronously, with 8 patients undergoing only 1 stage of a 2-stage liver resection strategy. The median delay from liver resection to colorectal resection was 4 weeks in 2 studies and 12 weeks in 1 study, and 1 study did not provide data on delay to liver resection.

PATTERNS OF DISEASE RECURRENCE AND SURVIVAL

Of the original 121 patients, 73 (60%) developed either progressive or recurrent disease (the timing of recur-

Table 1. Protocol Design of Liver-First Strategies

Study	Inclusion Period	Intervention				No. of Patients		Disease Progression During Protocol, No. (%) of Patients
		First	Second	Third	Fourth	Starting Protocol	Completing Protocol	
Mentha et al, ¹⁴ 2008	1998-2007	Neoadjuvant chemotherapy	Liver resection	Resection of colorectal primary tumor with or without neoadjuvant radiotherapy (for T3N1 rectal cancers)	Adjuvant chemotherapy	35	30 ^a	3 (9) ^b
Verhoef et al, ¹⁵ 2009	2003-2007	Neoadjuvant chemotherapy	Liver resection	Chemoradiotherapy	Resection of rectal primary tumor	23	17	6 (26)
Brouquet et al, ¹⁶ 2010	1992-2009	Neoadjuvant chemotherapy	Liver resection	Chemoradiotherapy	Resection of colorectal primary tumor	41	27	10 (24) ^c
de Jong et al, ¹⁰ 2011	2005-2010	Neoadjuvant chemotherapy/chemoradiation	Liver resection	Chemoradiotherapy	Resection of colorectal primary tumor with or without adjuvant chemotherapy ^d	22	16 ^e	4 (18)

^aSeven patients underwent synchronous liver and bowel resection.

^bOne patient died of sepsis during chemotherapy, and 1 patient had liver metastases that disappeared after chemotherapy.

^cTwo patients had a complete response of the primary tumor. One patient died after liver resection.

^dPatients with colonic (as opposed to rectal) tumors underwent adjuvant chemotherapy after bowel resection.

^eTwo patients did not have colorectal resection because they experienced a complete clinical response to chemotherapy.

Table 2. Extent and Distribution of Disease at Commencement of Liver-First Protocol

Study	Total No. of Patients	Site of Primary Tumor (Rectum/Colon), No. of Patients	N1 Status of Primary Tumor, No. (%) of Patients	Liver Lesions, Median (Range), No.	Bilobar Liver Metastases, No. (%) of Patients
Mentha et al, ¹⁴ 2008	35	13/17 ^a	NA	6 (1-21)	NA
Verhoef et al, ¹⁵ 2009	23	23/0	13 (57) had a clinical response, but 3 (13) had pathological stage of disease ^b	9 patients had >3 lesions	12 (52)
Brouquet et al, ¹⁶ 2010	41	28/13	17 (41)	3 (1-10) ^c	27 (66)
de Jong et al, ¹⁰ 2011	22	19/3	6 (38)	2 (1-7)	12 (55)

Abbreviation: NA, not applicable.

^aData are provided only for the 30 patients who completed the program.

^bRefers to the difference in nodal positivity comparing clinical assessment to resection histology.

^cData are provided only for patients who underwent a liver resection.

rence in relation to the study protocol is defined in 3 studies). The survival experience of each cohort varies considerably and is shown in **Figure 2**. It is possible to abstract individual patient survival from published figures and tables. However, without a firm understanding of the variables causing such differences in survival and without patient-level data on these covariates, reanalysis of the survival data was not attempted. Similarly, because 3 of the studies did not provide outcome data categorized by the anatomical site of the primary tumor, survival by location of primary tumor is not analyzed.

COMMENT

To our knowledge, this is the first systematic review of the liver-first approach for the treatment of patients presenting with colorectal cancer with synchronous liver metastases. Data on the demographics, disease, and interventions of participants have been summarized, and survival data pooled to provide an overview of treatment protocols and clinical management with this new strategy.

Table 3. Chemotherapy Strategy

Study	Neoadjuvant Protocol	Type of Chemotherapy	Cycles of Neoadjuvant Chemotherapy	Delay to Liver Surgery, wk	Place of Adjuvant Chemotherapy in Protocol
Mentha et al, ¹⁴ 2008	OCFL	Bevacizumab after 2006	3-6	3	2-3 courses as final step
Verhoef et al, ¹⁵ 2009	OxCap or 5-FU (20 patients); iri + 5-FU (2 patients)	Bevacizumab (8 patients)	Median, 5 (range, 2-10)	Median, 5 (range, 2-11)	A median of 4 wk (range, 2-9 wk) after liver resection as chemoXRT
Brouquet et al, ¹⁶ 2010	Oxaliplatin (33 patients); iri (6 patients); 5-FU (2 patients)	Bevacizumab (33 patients)	3-5	NA	ChemoXRT after liver resection (16 patients)
de Jong et al, ¹⁰ 2011	Oxaliplatin	Bevacizumab (10 patients)	6	NA	Adjuvant oxaliplatin after bowel resection (9 patients)

Abbreviation: chemoXRT, chemoradiotherapy; iri + 5-FU, irinotecan hydrochloride plus 5-fluorouracil; NA, not applicable; OCFL, oxaliplatin combined with iri and 5-FU/leucovorin calcium; OxCap, oxaliplatin plus capecitabine combination chemotherapy.

As is particularly the case with emerging interventional approaches (and the varying terminology they introduce), it is possible that the search may not have captured all reports of the liver-first approach. Studies presented only in abstract form would not be captured, and reports not providing clinical outcome data were excluded according to our protocol.

Accepting these potential limitations, we identified a pooled cohort of 121 patients from 4 separate reports^{10,14-16} who underwent the liver-first approach to treatment. The first point that is highlighted in this systematic review is the similarity between the 4 reports^{10,14-16} in terms of their liver-first protocols (Table 1). There is a common sequence comprising neoadjuvant systemic chemotherapy, liver resection, chemoradiotherapy for rectal tumors, colorectal resection, and (in 2 protocols) adjuvant chemotherapy. For future reports, it may be more accurate to use the term *chemotherapy-first* because the rationale is to provide early systemic treatment. In relation to chemotherapy, post-liver resection treatment could be regarded as neoadjuvant for the colorectal component of disease, and “true” adjuvant intervention is given after surgical treatment of both liver disease and bowel disease. Future reports might usefully provide further data on time lines for treatment, as it would appear that compliance with the full protocol may take a considerable amount of time. Despite this, 90 patients (74%) completed the protocol. Of the initial 121 patients, 23 (19%) experienced disease progression. Pooled data highlight the relatively prolonged recruitment period of each study; although this probably reflects the infrequent use of this approach until the first decade of the 21st century, it may also reflect the infrequency with which this approach can be applied. Only the report by de Jong et al¹⁰ provides denominator data on all patients undergoing liver resection in their respective units during the study period.

In terms of patient selection for application of the liver-first strategy, contemporary criteria are likely to include fluorodeoxyglucose positron emission tomography in staging, potentially providing more information on extrahepatic metastatic disease in this patient population.¹⁸ Information on pulmonary metastatic disease was

Table 4. Liver Resection Strategy

Study	Liver Resection, No. (%) of Patients	Ratio of Major (≥3) Segments to Minor Resection	2-Step Hepatectomy, No. of Patients
Mentha et al, ¹⁴ 2008	31 (89)	NA	10
Verhoef et al, ¹⁵ 2009	20 (87) ^a	10:10	0
Brouquet et al, ¹⁶ 2010	27 (66)	24:3	0 ^b
de Jong et al, ¹⁰ 2011	21 (95)	9:11	1

Abbreviation: NA, not applicable.

^aOne patient proceeded directly to liver resection without prior neoadjuvant chemotherapy.

^bIf 2-step hepatectomy was required at this center, patients underwent resection of their colorectal primary tumor at the time of the lesser of the 2 resections.

provided only by Mentha et al,¹⁴ with 3 of their 35 patients (8.5%) having lung lesions. Accurate staging is critical because the available evidence indicates that an appreciable proportion of patients in this study¹⁴ who presented with synchronous disease had advanced disease, as confirmed by the nodal status of the primary tumor and by the number and distribution of colorectal hepatic metastases (Table 2).

Modern colon cancer-directed chemotherapy was used in all the reports, with biological agents (such as bevacizumab) being used when they became available (Table 3). This pattern of use of chemotherapy may restrict the ability to compare the present data with data from early cohorts of the classic approach. For example, although de Haas and colleagues⁶ provide survival data on a cohort of 173 patients treated with the classic approach of primary colorectal resection with adjuvant chemotherapy followed by liver resection, they provide no information on choice of chemotherapy regimen, and with a recruitment period from 1990 to 2006, the agents that are used today were likely unavailable. Nonetheless, for their cohort, they report a 3-year overall survival rate of

Table 5. Colorectal Resection Strategy

Study	Total No. of Patients	No. (%) of Patients			Interval From Liver to Colonic Surgery, wk	Rectal XRT
		Colorectal Resection	Synchronous Liver/Bowel Resection			
Mentha et al, ¹⁴ 2008	35	31 (89)	7 (23)		4-8 (and after rectal XRT)	50 Gy if T3 or N1 rectal disease
Verhoef et al, ¹⁵ 2009	23	17 (74)	1 (4)		Median delay of 4 wk (range, 2-9 wk) from liver resection to ChemoXRT; median of 9 wk (range, 1-15 wk) to surgery	50 Gy in long course for 18 patients treated with capecitabine; 50 Gy in short course for 1 patient
Brouquet et al, ¹⁶ 2010	41	27 (66)	NA ^a		Not reported	NA
de Jong et al, ¹⁰ 2011	22	16 (72)	NA		Median, 12 (range, 4-44)	Long course for 13 patients; short-course chemoXRT for 8 patients ^b

Abbreviations: ChemoXRT, chemoradiotherapy; XRT, radiotherapy.

^aPatients undergoing synchronous resection are reported separately in this study.

^bRadiotherapy also used for nonrectal tumors.

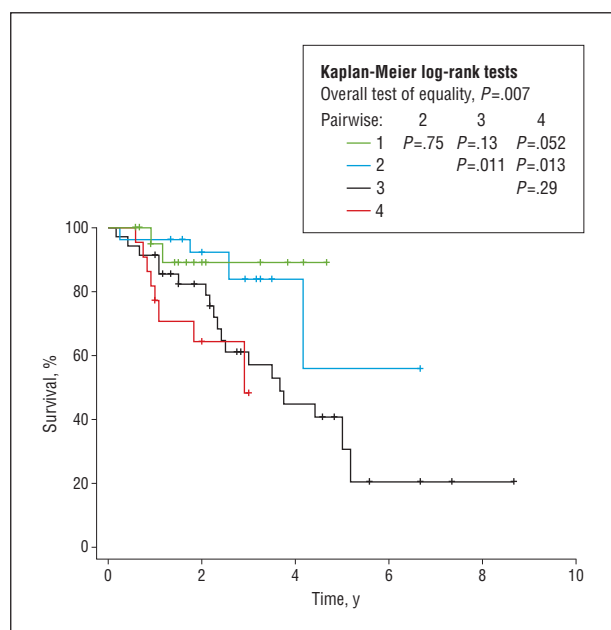


Figure 2. Survival analysis using the Kaplan-Meier method. The number 1 indicates the study by Verhoef et al¹⁵; 2, the study by Brouquet et al¹⁶; 3, the study by Mentha et al¹⁴; and 4, the study by de Jong et al.¹⁰

70.3% (similar to our pooled cohort) and a 3-year disease-free survival rate of 26.1%.⁶

The patients included in our review had relatively advanced diseases from the outset, as seen by the median number of liver lesions and the proportion with bilobar disease (Table 2). With an unfavorable prognosis, there may be an advantage in commencing systemic chemotherapy within a short period after the establishment of a diagnosis rather than waiting for recovery from colorectal cancer resection. The period of chemotherapy can also be used to modify the future remnant liver after resection by portal vein embolization.¹⁹ Following neoadjuvant chemotherapy, the first operative intervention was liver resection in all protocols, with 99 of 121 patients progressing to hepatectomy. Further details on delay to

resection, management of radiologically resolving lesions, and histological effects of chemotherapy on liver parenchyma are required.

A theoretical disadvantage of the liver-first approach is the delay to chemoradiotherapy for rectal tumors. Despite this, 91 of the 121 patients (75%) in the starting cohort underwent colorectal cancer resection (Table 5). A potential advantage of the liver-first approach is that a small number of patients (4 of 121) had a complete response to treatment, with resolution of the primary tumor, and thus did not require colorectal resection. This option for observation is clearly not available with the classic approach.

The variation in survival rates among the 4 different reports^{10,14-16} of the liver-first strategy is a striking observation gained by pooling data (Figure 2). Some of this apparent variation may be a reflection of the small sample size of the cohorts. However, from an oncological perspective, all of the patients included had colorectal cancer with synchronous liver metastases and received similar oncological and surgical treatment. The study by Verhoef et al¹⁵ demonstrated the best survival data, and their report includes only patients with locally advanced rectal cancer. This wide variation in survival between apparently similar treatment protocols for patients with apparently similarly staged diseases makes comparison with classic treatment protocols (colorectal surgery first, chemotherapy, and liver surgery as the last intervention) difficult.

In summary, to our knowledge, we report the first systematic review of outcomes for patients with synchronous colorectal cancer and liver metastases managed by the liver-first approach. The 4 studies^{10,14-16} reported herein show a high level of consistency in their protocols. The liver-first approach takes advantage of modern stenting and chemoradiotherapy approaches for rectal cancer and has the principal theoretical benefit of early systemic treatment of a disease with a systemic distribution. The evidence presented herein suggests a position of scientific equipoise and the need for evidence from a robust randomized controlled trial comparing liver-first and classical approaches that use clearly defined protocols.

Accepted for Publication: October 4, 2012.

Correspondence: Ajith K. Siriwardena, MD, FRCS, Hepatobiliary Surgery Unit, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL, England (ajith.siriwardena@cmft.nhs.uk).

Author Contributions: Study concept and design: Mason, Hancock, and Siriwardena. Acquisition of data: Jegatheeswaran and Siriwardena. Analysis and interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: Mason, Hancock, and Siriwardena. Statistical analysis: All authors. Study supervision: Mason and Siriwardena.

Conflict of Interest Disclosures: None reported.

REFERENCES

1. Leporrier J, Maurel J, Chiche L, Bara S, Segol P, Launoy G. A population-based study of the incidence, management and prognosis of hepatic metastases from colorectal cancer. *Br J Surg*. 2006;93(4):465-474.
2. Manfredi S, Lepage C, Hatem C, Coatmeur O, Faivre J, Bouveir AM. Epidemiology and management of colorectal liver metastases from colorectal cancer. *Ann Surg*. 2006;244(2):254-259.
3. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. *Br J Surg*. 1990;77(11):1241-1246.
4. Bismuth H, Castaing D, Traynor O. Surgery for synchronous hepatic metastases of colorectal cancer. *Scand J Gastroenterol Suppl*. 1988;149:144-149.
5. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg*. 1999;230(3):309-318, discussion 318-321.
6. de Haas RJ, Adam R, Wicherts DA, et al. Comparison of simultaneous or de-layed liver surgery for limited synchronous colorectal metastases. *Br J Surg*. 2010;97(8):1279-1289.
7. Mentha G, Majno PE, Andres A, Rubbia-Brandt L, Morel P, Roth AD. Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. *Br J Surg*. 2006;93(7):872-878.
8. Rödel C. Radiotherapy: Preoperative chemoradiotherapy for rectal cancer. *Nat Rev Clin Oncol*. 2010;7(3):129-130.
9. Dionigi G, Villa F, Rovera F, et al. Colonic stenting for malignant disease: review of literature. *Surg Oncol*. 2007;16(suppl 1):S153-S155.
10. de Jong MC, van Dam RM, Maas M, et al. The liver-first approach for synchronous colorectal liver metastasis: a 5-year single-centre experience. *HPB (Oxford)*. 2011;13(10):745-752.
11. van der Wal GE, Gouw ASH, Kamps JAAM, et al. Angiogenesis in synchronous and metachronous colorectal liver metastases: the liver as a permissive soil. *Ann Surg*. 2012;255(1):86-94.
12. Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med*. 2009;360(14):1408-1417.
13. Dalton RS, Velineni R, Osborne ME, et al. A single-centre experience of chemoradiotherapy for rectal cancer: is there potential for nonoperative management? *Colorectal Dis*. 2012;14(5):567-571.
14. Mentha G, Roth AD, Terraz S, et al. 'Liver first' approach in the treatment of colorectal cancer with synchronous liver metastases. *Dig Surg*. 2008;25(6):430-435.
15. Verhoef C, van der Pool AE, Nuyttens JJ, Planting AS, Eggermont AM, de Wilt JH. The "liver-first approach" for patients with locally advanced rectal cancer and synchronous liver metastases. *Dis Colon Rectum*. 2009;52(1):23-30.
16. Brouquet A, Mortenson MM, Vauthey JN, et al. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: classic, combined or reverse strategy? *J Am Coll Surg*. 2010;210(6):934-941.
17. van der Pool AE, de Wilt JH, Lalmahomed ZS, Eggermont AM, Ijzermans JN, Verhoef C. Optimizing the outcome of surgery in patients with rectal cancer and synchronous liver metastases. *Br J Surg*. 2010;97(3):383-390.
18. NHS; National Institute for Health and Clinical Excellence. Colorectal cancer: the diagnosis and management of colorectal cancer. <http://www.NICE.org.uk/nicemedia/live/13597/56998/56998.pdf>. Accessed June 14, 2012.
19. Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. *N Engl J Med*. 2007;356(15):1545-1559.