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Synchronous primary colorectal and liver metastasis: impact of operative approach on clinical outcomes and hospital charges

Aslam Ejaz[1,2], Eugene Semenov[1], Gaya Spolverato[1], Yuhree Kim[1], Dylan Tanner[1], John Hundt[1] & Timothy M. Pawlik[1]

[1]Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA and [2]Department of Surgery, University of Illinois Hospital and Health Sciences Center, Chicago, IL, USA

Abstract

Objectives: The management of patients with colorectal cancer (CRC) and synchronous colorectal liver metastasis (CLM) remains controversial. The present study was conducted in order to assess the clinical and economic impacts of managing synchronous CLM with a staged versus a simultaneous surgery approach.

Methods: A total of 224 patients treated for synchronous CLM during 1990–2012 were identified in the Johns Hopkins Hospital liver database. Data on clinicopathological features, perioperative outcomes and total hospital charges (inflation-adjusted) were collected and analysed.

Results: Overall, 113 (50.4%) patients underwent staged surgery and 111 (49.6%) were submitted to a simultaneous CRC and liver operation. At surgery, liver-directed therapy included hepatectomy (75.0%) or combined resection and ablation (25.0%). Perioperative morbidity (30.0%) and mortality (1.3%) did not differ between groups (both $P > 0.05$). Median total length of hospitalization was longer in the staged (13 days) than the simultaneous (7 days) surgery group ($P < 0.001$). Median total hospital charges were higher among patients undergoing staged surgery (US$61 938) than among those undergoing a simultaneous operation (US$34 114) ($P < 0.01$). Median (simultaneous, 32.4 months versus staged, 39.6 months; $P = 0.65$) and 5-year (simultaneous, 27% versus staged, 29%; $P = 0.60$) overall survival were similar between groups.

Conclusions: Patients with synchronous CLM managed with either simultaneous or staged surgery have comparable perioperative and longterm outcomes. However, patients treated with simultaneous surgery spent an average of 6 days fewer in hospital, resulting in a reduction of median hospital charges of US$27 824 (55.1%). When appropriate and technically feasible, the simultaneous surgery approach to synchronous CLM should be preferred.

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Correspondence

Timothy M. Pawlik, Department of Surgery, Johns Hopkins Hospital, 600 North Wolfe Street, Blalock 688, Baltimore, MD 21287, USA. Tel: + 1 410 502 2387. Fax: + 1 410 502 2388. E-mail: tpawlik1@jhmi.edu

Introduction

Colorectal cancer (CRC) is the third most common cancer in the USA and almost one in 20 persons is diagnosed with the disease at some point in life.[1] It is expected that over 140 000 new cases of CRC will have been diagnosed in 2013 and that they will result in over 50 000 deaths.[1] Although the use of surveillance colonoscopy and other diagnostic techniques has significantly increased over time, nearly one in four patients will have metastatic disease at the time of presentation, with the liver being the most common site of spread.[2–5] Complete surgical resection provides the best hope for longterm survival, but only approximately 20% of patients with colorectal liver metastasis (CLM) are eligible for curative intent resection.[6] With improvements in operative technique, as well as the advent and use of modern chemotherapy and liver-directed

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therapies, 5-year survival is estimated to range from 40% to 58% in surgically resected patients with CLM.[7–10]

The optimal surgical management of patients with CRC and synchronous CLM remains controversial. Complete surgical resection with negative margins of both the primary and metastatic tumours provides the best option for longterm survival. A topic of debate, however, is the timing and sequence of operations. Traditionally, many patients with resectable disease have undergone two separate staged operations: initial colorectal resection of the primary tumour, followed by hepatic resection for the metastatic disease at a later date (colorectal-first approach). More recently, patients have been submitted to a reversed staged approach in order to address the hepatic tumour burden first (liver-first approach) and to prevent any delays in liver-directed and systemic therapies.[5,11] Finally, in patients with resectable liver metastases at the time of diagnosis, several institutions have advocated for a single operation addressing both the primary colorectal and metastatic liver tumours (simultaneous approach).[12–14] The potential benefits of a simultaneous approach include a single operation and anaesthetic administration, as well as perhaps a shorter overall hospital stay. The simultaneous performance of colorectal and liver resections, however, increases the complexity of the procedure. Furthermore, this potential for increased complexity and greater length of operation has raised concerns that the associated morbidity and mortality may be higher with the simultaneous approach.[12–14]

In addition to the potential differences in morbidity, there may be economic differences associated with a simultaneous versus a staged approach to synchronous CLM. The increasing cost of health care in the USA and worldwide necessitates a comprehensive evaluation of the financial impact of treatment decisions in addition to standard clinical outcomes. As such, several investigators have performed cost comparison analyses for various gynaecological,[15] orthopaedic,[16,17] vascular[18] and general surgical[19,20] operations, among others. The comparison of the economic impacts associated with, respectively, a simultaneous versus a staged approach in patients with synchronous CLM remains less well studied. Thus, the present authors aimed to define the perioperative and longterm outcomes of patients undergoing surgical resection for synchronous CLM. Specifically, the present study sought to compare the economic impacts of a simultaneous versus a staged approach for patients with resectable synchronous CLM using actual hospital charges at the study institution.

Materials and methods

All patients submitted to liver resection for synchronous CLM at Johns Hopkins Hospital between 1990 and 2012 were identified through a structured query of the liver database. Patients were categorized based on operative approach: simultaneous (combined colorectal/liver resection) and staged (either colorectal- or liver-first approaches). Patients with synchronous CLM who underwent a staged approach in which the initial colorectal resection was performed at an outside hospital and the subsequent liver operation at Johns Hopkins Hospital were included in the study cohort. Patients who underwent only an ablative procedure without concurrent hepatic resection were excluded from analysis.

Standard clinicopathological data were collected on characteristics including age, sex and comorbidities. Treatment data were collected and included estimated operative blood loss, operative time, and the type and timing of perioperative chemotherapy and/or radiation if applicable. Tumour characteristics were reported based on the tumour–node–metastasis (TNM) staging system. Perioperative complications were recorded according to the Clavien–Dindo classification system, in which a major complication is classified as of Grade III or higher.[21] Perioperative 90-day mortality[22] and time to recurrence, if applicable, were calculated from the date of liver resection and based on the date of last follow-up. The Johns Hopkins University Institutional Review Board approved the study.

Economic analysis

An economic comparison analysis was performed based on all charges assessed during the index hospitalization(s). Total charges were tabulated based on all hospital services provided, including room and board, surgical and anaesthesia services, medications, laboratory and radiology services, physical/occupational/speech therapy, and other miscellaneous charges. Charges were administered and calculated based on a fixed internal hospital fee to allow for a direct comparison between treatment strategies.[23] For patients who underwent a staged colorectal resection at an outside institution, total charges were imputed based on average charges assessed for all patients submitted to an equivalent colorectal resection over the past 5 years at the study institution. All values were inflation-adjusted and expressed in 2012 US dollars.

Statistical analysis

Discrete variables were described as medians with interquartile ranges (IQRs). Categorical variables were noted as totals and frequencies. Univariate comparisons were assessed using the chi-squared or analysis of variance tests as appropriate. Univariate and multivariate logistic regression models were constructed to determine the association of relevant clinicopathological and operative factors (extent of hepatectomy) with perioperative complications. Univariate and multivariate regression models were constructed to assess the impacts of different clinicopathological and treatment factors on overall inflation-adjusted hospital charges. The most parsimonious models were created using a stepwise approach that included factors that were of clinical importance or were statistically significant on univariate analysis. Overall survival time was calculated from the date of the index liver resection to the date of death. Survival adjusted for censoring was calculated using the Kaplan–Meier method and median survival was compared using the log-rank test. All analyses were carried out using

STATA Version 12.0 (StataCorp LP, College Station, TX, USA). A *P*-value of <0.05 (two-tailed) was considered to indicate statistical significance.

Results

Description of cohort

Between 1990 and 2012, 224 patients with synchronous CLM underwent hepatic resection at Johns Hopkins Hospital. Among these patients, 111 (49.6%) were managed with a simultaneous approach, 105 (46.9%) patients underwent a colorectal-first approach and very few ($n = 8$, 3.6%) were treated with a liver-first approach (Table 1). The median patient age was 57 years (IQR: 49–67 years) and the majority of patients were male ($n = 137$, 61.2%). Most patients had a primary colonic tumour ($n = 154$, 68.8%), and about a third of patients ($n = 70$, 31.3%) had a primary rectal tumour. At the time of colorectal resection, patients most commonly underwent a hemi-colectomy ($n = 102$, 45.5%) or low anterior resection ($n = 58$, 25.9%). On pathology, median colorectal tumour size was 4 cm (IQR: 3–5 cm). Most patients had a colorectal tumour that penetrated through the muscularis propria (T3 tumours: $n = 154$, 72.3%) and nodal metastases were common (>N1: $n = 155$, 71.8%). The colorectal margin status was microscopically negative (R0) in the overwhelming majority of patients ($n = 161$, 97.6%).

In terms of metastatic liver disease, most patients ($n = 145$, 65.3%) had unilobular disease with an average tumour burden of two metastases (IQR: 1–4 tumours). The median size of the largest metastatic liver lesion was 2.5 cm (IQR: 1.5–4.5 cm). At the time of surgery, hepatic resection involved either a minor (less than four Couinaud segments resected) or major (four or more Couinaud segments resected) hepatectomy. An R0 hepatic resection was achieved in the majority of patients ($n = 192$, 85.7%). Of note, nearly a quarter of patients ($n = 55$, 24.6%) underwent concurrent ablation therapy in addition to surgical resection.

Several clinicopathological and operative characteristics differed between patients undergoing a simultaneous versus a staged approach. Rectal tumours were more common in patients undergoing a staged operation (colorectal-first: $n = 36$, 34.3%; liver-first: $n = 6$, 75.0%) compared with patients undergoing a simultaneous resection ($n = 28$, 25.2%) ($P = 0.009$). In addition, receipt of neoadjuvant therapy was more common among patients undergoing a liver-first approach ($n = 7$, 87.5%) than among those undergoing either a colorectal-first ($n = 18$, 17.1%) or simultaneous ($n = 43$, 38.7%) approach ($P \leq 0.001$). At the time of hepatic resection, patients undergoing a staged operation were also more likely to undergo a major hepatic resection ($n = 58$, 51.3%) than were patients submitted to a simultaneous approach ($n = 26$, 23.4%) ($P < 0.001$). The use of concurrent ablation therapy in addition to surgical resection was comparable, however, among patients undergoing a staged ($n = 33$, 29.2%) versus a simultaneous ($n = 22$, 19.8%) approach ($P = 0.14$).

Short- and longterm outcomes

Among the entire cohort, 67 patients experienced a perioperative complication after either the colorectal, hepatic or simultaneous operation, giving a perioperative complication incidence of 29.9% (Table 2). The overall incidence of complications did not differ according to operative approach (simultaneous, $n = 28$, 25.2%; colorectal-first, $n = 34$, 32.4%; liver-first, $n = 5$, 62.5%; $P = 0.06$). In the staged approach group, complications after hepatic resection were more common: 11 patients (9.7%) experienced a perioperative complication after colorectal resection, and 32 patients (28.3%) experienced a perioperative complication after liver resection. The incidence of complications after hepatic resection remained similar between the two groups after stratifying by minor (simultaneous, $n = 21$, 24.7% versus staged, $n = 16$, 29.1%; $P = 0.57$) and major (simultaneous, $n = 7$, 26.9% versus staged, $n = 16$, 27.6%) hepatectomy (Table 3). Furthermore, the incidence of major complications (Grade III or higher) was similar among those undergoing a minor (simultaneous, $n = 14$, 16.5% versus staged, $n = 8$, 14.5%; $P = 0.76$) or major (simultaneous, $n = 6$, 23.1% versus staged, $n = 7$, 12.1%; $P = 0.20$) hepatectomy. After multivariable analysis, operative approach (simultaneous versus staged) was not associated with an increased risk for complications [odds ratio (OR) 0.80, 95% confidence interval (CI) 0.44–1.45; $P = 0.46$]. In fact, only patients undergoing a concurrent ablative procedure along with resection were at higher risk for complications (OR 2.02, 95% CI 1.05–3.89; $P = 0.04$) (Table 4).

The median total hospital length of stay (LoS) among the entire cohort was 11 days (IQR: 7–14 days). Total LoS was shorter in the simultaneous surgery than in the staged surgery cohort [simultaneous, 7 days (IQR: 5–9 days); colorectal-first, 13 days (IQR: 12–15 days); liver-first, 10 days (IQR: 9–12 days); $P < 0.001$] (Fig. 1). Perioperative 90-day mortality occurred in three patients and rates did not differ between groups; two patients (1.8%) in the staged cohort died after hepatic resection and one patient (0.9%) died after simultaneous resection ($P = 0.21$).

After a median follow-up of 14 months (IQR: 3–39 months), tumour recurrence occurred in 56% of patients. Among these, 3% experienced a recurrence at the primary tumour location, 58% had intrahepatic recurrence, 19% had extrahepatic recurrence, and 20% of patients experienced both intra- and extrahepatic recurrence. Median time to recurrence was 25.9 months (95% CI 22.1–32.2 months) and did not differ between the simultaneous and staged groups [simultaneous, 25.9 months (95% CI 20.0–32.4 months) versus staged, 25.2 months (95% CI 20.7–35.4 months); $P = 0.68$]. Median overall survival among the cohort was 33.4 months (95% CI 26.0–42.2 months) and was similarly equivalent between the two groups [simultaneous, 32.4 months (95% CI 23.9–41.4 months) versus staged, 39.6 months (95% CI 25.2–46.2 months); $P = 0.60$] (Fig. 2). Overall rates of 1-, 3- and 5-year survival were 88.9%, 47.3% and 27.8%, respectively. Rates of 1-, 3- and 5-year recurrence-free survival were 83.6%, 37.6% and

Table 1 Clinicopathological characteristics of cohort

	Total (n = 224)	Simultaneous (n = 111)	Colorectal first (n = 105)	Liver first (n = 8)	P-value
Age, years, median (IQR)	57 (49–67)	57 (47–69)	59 (51–65)	54 (47–55)	0.73
Male gender, *n* (%)	137 (61.2%)	66 (59.5%)	68 (64.8%)	3 (37.5%)	0.27
Preoperative chemotherapy, *n* (%)	68 (30.4%)	43 (38.7%)	18 (17.1%)	7 (87.5%)	<0.001
Preoperative radiotherapy, *n* (%)	14 (6.3%)	5 (4.5%)	9 (8.6%)	0	0.35
Location of primary tumour, *n* (%)					0.009
Colon	154 (68.8%)	83 (74.8%)	69 (65.7%)	2 (25.0%)	
Rectum	70 (31.2%)	28 (25.2%)	36 (34.3%)	6 (75.0%)	
Colorectal resection, *n* (%)					0.004
Hemi-colectomy	102 (45.6%)	64 (57.6%)	38 (36.2%)	0	
Sigmoidectomy	39 (17.4%)	15 (13.5%)	22 (21.0%)	2 (25.0%)	
Low anterior resection	58 (25.9%)	20 (18.0%)	32 (30.5%)	6 (75.0%)	
Abdominoperineal resection	15 (6.7%)	8 (7.2%)	7 (6.7%)	0	
Subtotal/total	4 (1.8%)	2 (1.8%)	2 (1.9%)	0	
Size of colorectal tumour, cm, median (IQR)	4 (3–5)	4 (3–5)	4 (3–6)	3 (1–3)	<0.001
T-stage, *n* (%)					0.21
T1	5 (2.4%)	3 (2.7%)	2 (2.1%)	0	
T2	22 (10.3%)	16 (14.4%)	5 (5.3%)	1 (12.5%)	
T3	154 (72.3%)	72 (64.9%)	75 (79.8%)	7 (87.5%)	
T4	32 (15.0%)	20 (18.0%)	12 (12.8%)	0	
N-stage, *n* (%)					0.73
N0	61 (28.2%)	29 (26.6%)	31 (31.3%)	1 (12.5%)	
N1	89 (41.2%)	47 (43.1%)	37 (37.4%)	5 (62.5%)	
N2	65 (30.1%)	32 (29.4%)	31 (31.3%)	2 (25.0%)	
N3	1 (0.5%)	1 (0.9%)	0	0	
R0 colorectal resection, *n* (%)	161 (98.2%)	100 (98.0%)	55 (98.2%)	8 (100%)	0.52
Liver metastasis location, *n* (%)					0.54
Unilateral	145 (65.3%)	74 (67.9%)	67 (63.8%)	4 (50.0%)	
Bilateral	77 (34.7%)	35 (32.1%)	38 (36.2%)	4 (50.0%)	
Liver metastases, *n*, median (IQR)	2 (1–4)	2 (1–4)	2 (1–4)	4 (2–4)	0.72
Liver-directed therapy, *n* (%)					0.18
Resection only	165 (74.3%)	85 (78.0%)	76 (72.4%)	4 (50.0%)	
Resection + ablation	55 (24.8%)	22 (20.2%)	29 (27.6%)	4 (50.0%)	
Type of liver resection, *n* (%)					0.009
Wedge resection	126 (56.3%)	76 (68.5%)	46 (43.8%)	4 (50.0%)	
Hemi-hepatectomy	71 (31.7%)	25 (22.5%)	43 (41.0%)	3 (37.5%)	
Extended hemi-hepatectomy	27 (12.1%)	10 (9.0%)	16 (15.2%)	1 (12.5%)	
R0 liver resection, *n* (%)	192 (85.7%)	94 (84.7%)	91 (86.7%)	7 (87.5%)	0.91
Extrahepatic metastasis, *n* (%)	35 (15.7%)	21 (19.1%)	14 (13.3%)	0	0.54

IQR, interquartile range.

20.3%, respectively. There was no difference in 5-year overall (simultaneous, 27.0% versus staged, 29.0%) or recurrence-free (simultaneous, 19.1% versus staged, 21.6%) survival based on the surgical approach to synchronous CLM (both $P > 0.05$) (Fig. 2).

Comparison of hospital charges for simultaneous versus staged surgery

Mean ± standard deviation (SD) total hospital charges among the entire cohort were US$48 151 ± 24 948. Patients undergoing a simultaneous operation had overall lower total mean charges

Table 2 Perioperative outcomes after colorectal and liver resection

	Total (n = 224)	Simultaneous (n = 111)	Colorectal first (n = 105)	Liver first (n = 8)	P-value
Complications after colorectal resection, n (%)	11 (49.6%)	–	9 (8.6%)	2 (0.3%)	<0.001
Grades I and II	4 (36.4%)	–	3 (33.3%)	1 (50.0%)	0.66
Grades III and IV	7 (63.6%)	–	6 (66.7%)	1 (50.0%)	
90-day mortality after colorectal resection, n (%)	3 (1.3%)	–	0	0	0.21
LoS after colorectal resection, days, median (IQR)	4 (0–7.5)	–	7.5 (7.5–7.5)	6 (5–7)	<0.001
ICU LoS after colorectal resection, days, median (IQR)	0 (0–0)	–	0 (0–0)	2 (2–3)	<0.001
Complications after liver resection, n (%)	60 (26.8%)	28 (25.2%)	28 (26.7%)	4 (50.0%)	0.31
Grades I and II	22 (38.6%)	7 (25.9%)	12 (46.2%)	3 (75.0%)	0.10
Grades III and IV	35 (61.4%)	20 (74.1%)	14 (53.9%)	1 (25.0%)	
90-day mortality after liver resection, n (%)	3 (1.3%)	1 (0.9%)	2 (1.9%)	0	0.07
LoS after liver resection, days, median (IQR)	3 (0–5)	7 (5–9)	5 (4–6)	5 (4–6)	<0.001
ICU LoS after liver resection, days, median (IQR)	0 (0–1)	2 (2–3)	1 (1–2)	2 (1–3)	0.04
Total LoS, days, median (IQR)	11 (7–14)	7 (5–9)	13 (12–15)	10 (9–12)	<0.001
Total ICU LoS, days, median (IQR)	1 (0–1)	2 (2–3)	2 (2–3)	2 (1–3)	0.10
Recurrence, n (%)	125 (55.8%)	57 (51.4%)	63 (60.0%)	5 (62.5%)	0.41

LoS, length of stay, IQR, interquartile range; ICU, intensive care unit.

Table 3 Complications after minor and major hepatectomy for colorectal liver metastasis

	Simultaneous (n = 111)	Staged (n = 113)	P-value
Minor hepatectomy (<4 segments), n (%)			
Total (n = 140)	85	55	
No complication	64 (75.3%)	39 (70.9%)	
Overall complications after liver surgery	21 (24.7%)	16 (29.1%)	0.57
Grades I and II	7 (8.2%)	8 (14.5%)	0.24
Grades III and IV	14 (16.5%)	8 (14.5%)	0.76
Mortality within 90 days	0	0	
Major hepatectomy (≥4 segments), n (%)			
Total (n = 84)	26	58	
No complication	19 (73.1%)	42 (72.4%)	
Overall complications after liver surgery	7 (26.9%)	16 (27.6%)	0.95
Grades I and II	0	7 (12.1%)	0.06
Grades III and IV	6 (23.1%)	7 (12.1%)	0.20
Mortality within 90 days	1 (3.8%)	2 (3.4%)	0.93

(US$34 114 ± 24 765) compared with patients undergoing staged operations (US$61 938 ± 15 807). The difference in charges between a simultaneous and a staged approach represented an average saving of US$27 824 per patient (Fig. 3a). Among patients undergoing staged operations, total charges were higher for the hospitalization following colorectal resection (colorectal charges, US$32 293 versus hepatic charges, US$29 331; P = 0.001). Total hospital charges also varied significantly according to the type and extent of colorectal (right/left hemi-colectomy, US$28 632 versus low anterior resection, US$35 144 versus sigmoid, US$33 123; P = 0.004) resection. In a subset analysis examining only patients with colon cancer lesions (i.e. excluding all patients with rectal tumours), a similar difference in charges was noted. Specifically, among patients with colon cancer, the total charges associated with a simultaneous approach were US$36 144, whereas charges for a staged approach were US$61 931 ($P$ < 0.001). An additional subset analysis of only patients treated in the era of 'modern' chemotherapy (2000 to the present) was then performed, which similarly demonstrated a difference in total charges (simultaneous surgery, US$38 199 versus staged surgery, US$63 018; P < 0.001).

Several clinicopathological and operative factors were associated with higher overall mean charges. Specifically, mean total

Table 4 Univariate and multivariate analysis of factors associated with complications

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.00	0.98–1.02	0.78	NA	–	–
Female gender	1.09	0.61–1.96	0.77	NA	–	–
Rectal tumour	0.82	0.44–1.54	0.54	NA	–	–
>2 liver lesions	1.12	0.62–2.01	0.70	NA	–	–
Bilateral disease	1.42	0.78–2.57	0.25	NA	–	–
Simultaneous operation	0.64	0.36–1.14	0.13	0.80	0.44–1.45	0.46
Major hepatic resection	0.90	0.50–1.63	0.74	NA	–	–
Colorectal tumour size	0.91	0.77–1.09	0.31	NA	–	–
T-stage						
T1	Ref			NA	–	–
T2	1.5	0.14–16.27	0.74			
T3	1.81	0.20–16.64	0.60			
T4	1.82	0.18–18.41	0.61			
Extrahepatic metastasis	0.53	0.22–1.29	0.16	0.59	0.24–1.46	0.25
Liver tumour size	1.07	0.97–1.18	0.16	1.07	0.97–1.19	0.18
Liver-directed therapy						
Resection alone	Ref					
Resection + ablation	1.98	1.05–3.74	0.04	2.02	1.05–3.89	0.04

OR, odds ratio; 95% CI, 95% confidence interval; NA, not applicable.

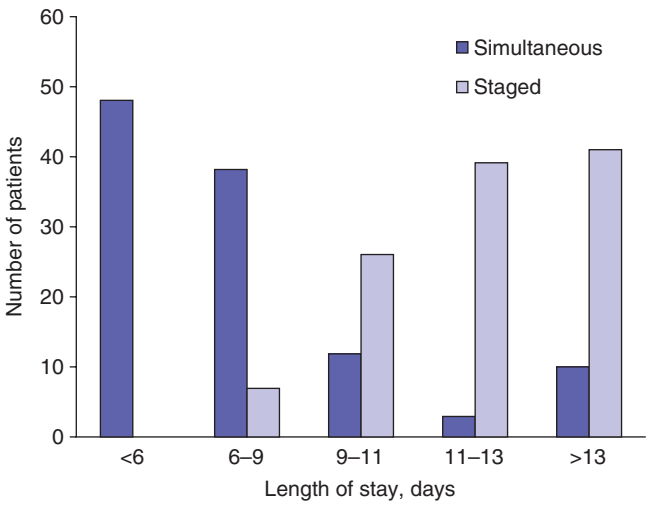

Figure 1 Distribution of length of stay in the simultaneous and staged surgery cohorts

charges were higher in patients with bilateral hepatic disease (bilateral disease, US$53 103 versus unilateral disease, US$45 761; $P = 0.04$), as well as among those patients undergoing combined resection and ablation (with ablation, US$56 999 versus resection alone, US$45 536; $P = 0.003$). In addition, charges were higher among patients undergoing a major hepatectomy (major hepatectomy, US$54 510 versus minor hepatectomy, US$44 335; $P = 0.003$) (Fig. 3a). On multivariate analysis, although tumour location (unilateral versus bilateral) was not associated with overall mean charge, combined resection plus ablation (ΔUS$11 989; $P = 0.003$) and major hepatectomy (ΔUS$12 020; $P < 0.001$) remained associated with a higher charge. In addition, although the occurrence of a perioperative complication increased charges in both cohorts, mean charges were significantly higher in patients who experienced a complication in the staged cohort (simultaneous surgery, US$55 309 versus staged surgery, US$69 413; $P < 0.001$). After adjusting for the extent of hepatic resection and incidence of complications, charges remained higher (ΔUS$25 176; $P < 0.001$) in the staged surgery cohort. The higher charges in the staged surgery group were largely driven by the increased LoS; each additional hospital day resulted in an average increase of US$3581 ($P < 0.001$) in total charges. Interestingly, after adjusting for total LoS, charges remained higher in patients submitted to a staged approach (Fig. 3b).

Discussion

Improved screening efforts have resulted in the earlier diagnosis of patients with CRC in the USA.[24] Along with the declines in the incidence of and mortality rates in CRC over the last several decades, improved treatment strategies for CRC have emerged.[24] Over a quarter of all patients with CRC will still present, however, with synchronous CLM at the time of diagnosis and only one in five will be eligible for curative intent resection.[2–5] Complete

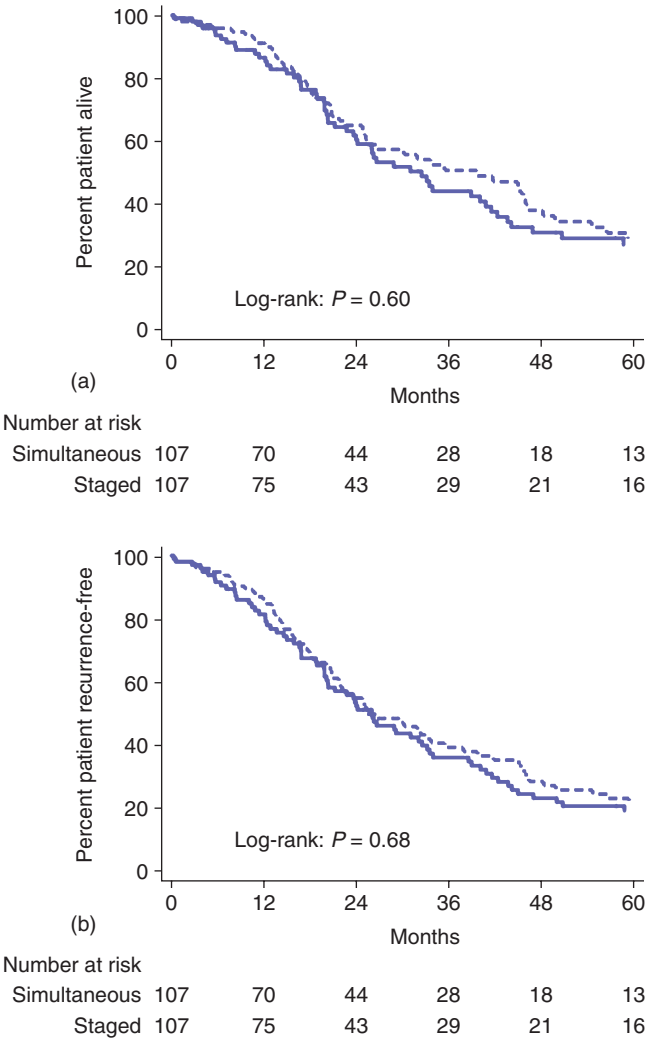

Figure 2 Kaplan–Meier curves for (a) overall survival, stratified by operative approach and (b) recurrence-free survival, stratified by operative approach

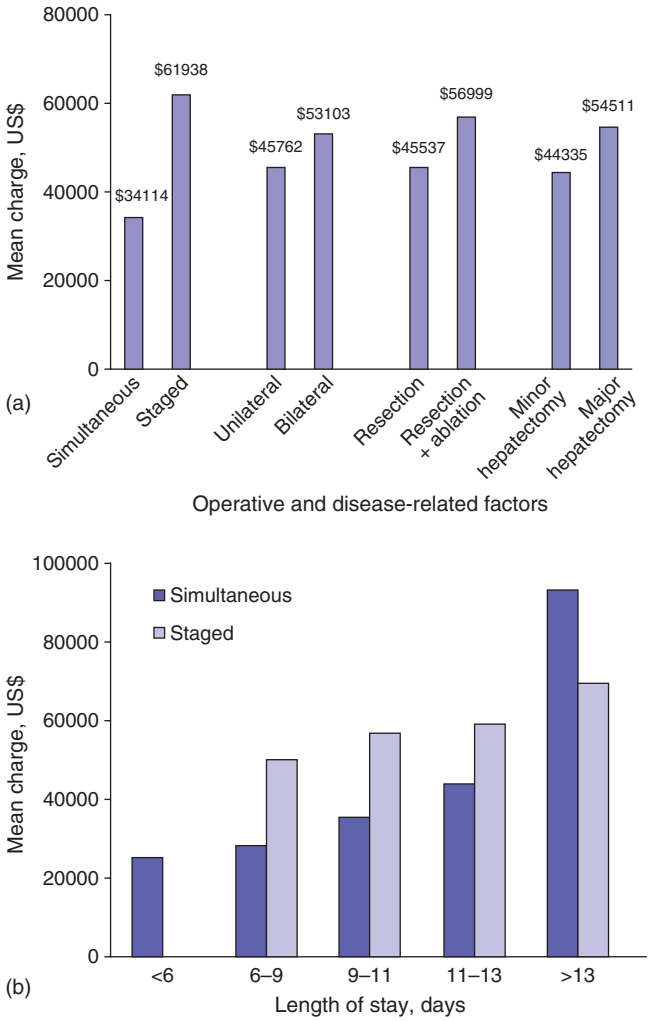

Figure 3 Comparisons of total mean charges by (a) various operative and disease-related factors and (b) length of stay stratified by operative approach. All comparisons are statistically significant ($P < 0.05$)

surgical excision of CLM represents the best chance for longterm recurrence-free and overall survival.[7–10] Whether patients with synchronous CLM are best treated with a staged or a simultaneous approach has been a long-debated topic. Although some surgeons prefer a staged approach, other groups have argued for a simultaneous approach in view of improvements in surgical technique and postoperative care.[12–14] In fact, the present centre previously reported outcomes in a multi-institution cohort of 1004 patients with synchronous CLM and noted no difference in short- or longterm outcomes among patients undergoing a simultaneous procedure in comparison with patients submitted to a staged approach.[13] The current study expands on this previous work by focusing on results from a single institution. In this way, the effects of potential heterogeneity on clinical outcomes at the many different centres included in the previous study were avoided. Perhaps, more importantly – unlike in the previous work – the present study evaluated the economic impact of the simultaneous versus staged approaches to synchronous CLM. Patients undergoing a simultaneous resection for synchronous CLM were noted to have rates of perioperative morbidity and mortality, as well as longterm overall and disease-free survival, comparable with those in patients undergoing staged surgery. Furthermore, patients undergoing a simultaneous operation spent, on average, 6 days fewer in hospital and had an associated average lower hospital charge of US$27 824 per patient compared with patients who underwent staged surgery.

Several previous studies have demonstrated that a simultaneous approach to synchronous CLM can have outcomes comparable with those of the classic staged approach.[12–14] Data from the current study corroborate that simultaneous surgery in patients

with synchronous CLM is both safe and effective. Patients submitted to either a simultaneous or a staged approach had similar rates of perioperative morbidity and 90-day mortality. Although patients in the simultaneous surgery cohort were more likely to have undergone a minor hepatectomy than patients in the staged surgery cohort, the incidence of complications remained similar between the two groups even after adjusting for the extent of hepatectomy (Table 3). More importantly, the incidence of major complications that caused a deviation from the standard postoperative course was equivalent in both groups. In fact, only patients undergoing a combined resection and ablative procedure had a higher risk for the occurrence of a complication. Specifically, patients undergoing a concomitant ablation were approximately twice as likely to experience a perioperative complication. Although the reasons for this finding are undoubtedly multifactorial, they may relate to the fact that patients who underwent resection and ablation had more extensive disease in the liver and thus represented cases of increased complexity. With regard to longterm outcomes, patients undergoing a simultaneous operation had overall and recurrence-free survival rates similar to those of patients undergoing staged surgery. Specifically, median survival was 32.4 months in the simultaneous surgery cohort and 39.6 months in the staged surgery cohort ($P = 0.65$). Collectively, the data would strongly suggest that the simultaneous resection of synchronous CLM at the time of resection of the primary colorectal lesion is both safe and as effective as staged surgery.

The approach, timing and sequence of operations in patients with synchronous CLM do need to be tailored based on patient-, surgeon- and hospital-specific factors. In particular, patients with locally advanced rectal cancer may benefit from a staged liver-first approach.[11,25] As these patients are often treated with neoadjuvant chemotherapy, a liver-first approach may prevent a delay in hepatic resection. In the current cohort, all of the patients who underwent a liver-first approach had a primary rectal tumour and many received neoadjuvant chemotherapy. In fact, on multivariate analysis, the only factor associated with a higher likelihood of receiving neoadjuvant chemotherapy was a rectal primary tumour site (OR 2.46, 95% CI 2.34–3.53; $P = 0.004$); other patient and pathological factors, such as age, sex, race, and number and size of hepatic lesions, were not associated with receipt of neoadjuvant chemotherapy. Patients with a rectal tumour, those with a large burden of liver disease requiring two-stage hepatectomy, and perhaps some patients with marginal performance status, may be better served by a staged approach. Most patients, however, can seemingly be managed with a simultaneous surgery approach. As noted herein, even patients who undergo a major hepatic resection simultaneously with a colorectal procedure did not have a higher incidence of complications, including major morbidity. Patients who underwent a simultaneous approach also had a significantly shorter total LoS in the hospital. In addition, in patients submitted to a 'classic' staged approach, hepatectomy for CLM was delayed by an average of 4.8 months (IQR: 3–8 months). Although it is difficult to ascribe an oncological impact to this delay, any delay in the definitive management of CLM – especially one that may not be necessary – is probably best avoided. As such, although the surgical plan should be specific to each patient, a simultaneous surgery approach to the treatment of synchronous CLM seems to be preferable based on comparable morbidity, mortality and a shorter total LoS for the patient.

One of the main objectives of the current study was to define the potential savings to be derived from the use of a simultaneous versus a staged surgery approach to synchronous CLM. Cost comparison analyses of alternative treatment strategies are crucial in an era of escalating health care expenditures. Several methods are possible when evaluating the economic impact of treatment. In the only other published study to compare the economic impacts of simultaneous and staged resection, respectively, in patients with synchronous CLM, Abbott *et al.* utilized Medicare reimbursement data to estimate cost differences between the operative approaches.[14] The authors found that a simultaneous approach resulted in approximately 17.1% lower costs compared with a staged approach.[14] The use of Medicare reimbursement data, however, is problematic as they pertain to a specific segment of the population who are covered by one national insurance plan. As such, the current study sought to further analyse the economic impact of a simultaneous versus staged approach. Specifically, the present study is unique in that it utilized actual hospital charges based on fixed internal fees to determine the economic impact of treatment. On average, total hospital charges for patients undergoing a simultaneous operation resulted in savings of US$27 824 per patient and were 55.1% lower than the average cost of a staged surgery approach. Perhaps as expected, increasing extent of disease (bilateral versus unilateral metastatic disease), as well as the complexity of the colorectal (low anterior resection versus right hemi-colectomy) and hepatic (major versus minor hepatectomy) resection resulted in higher overall total charges (Fig. 3). Furthermore, the incidence of any perioperative complications resulted in higher total charges. After controlling for these factors, however, the main driving factor for the higher charges among patients in the staged surgery cohort was found to refer to the increased total hospital LoS. Patients in the staged surgery group spent an average of 13 total days in hospital, whereas those in the simultaneous surgery group spent an average of 7 total days in hospital. At an average charge of US$3581 per day, prolonged overall LoS in the staged surgery group was a main driver of increased charges. Interestingly, after adjusting for LoS and extent of hepatectomy and colectomy, total charges remained higher in the staged approach group. The most likely cause of the increased marginal charge above the charges associated with each hospital stay were the added charges associated with a second hospitalization, and reflected additional laboratory, radiology, medication and other miscellaneous charges incurred during a second stay. In sum, a single simultaneous operation in patients with synchronous CLM was noted to cut the total hospital charges for the treatment of synchronous CLM by over half of the charge for two separate staged operations.

There are several limitations to consider when interpreting these data. As with all retrospective analyses, selection bias was a possibility. A subset of patients who underwent a staged approach underwent the initial colorectal procedure at an outside hospital and the exact charge data for the procedure at the outside institution were not available. To account for this, charges for the colorectal procedure were input using the average charges assessed for all patients undergoing an equivalent colorectal resection over the past 5 years at the study institution. Given the large overall difference found between a simultaneous and staged approach, the potential difference between actual and inputted data is likely to have had minimal impact on the overall economic benefit noted for the simultaneous approach. Although the present analyses utilized hospital charges as opposed to estimating the actual costs of treatment, all hospital charges were derived from a single institution and were based on fixed internal fees for each service provided. Thus, the comparative economic benefit observed with a simultaneous approach should not be affected by the use of charge rather than cost data from this institution. Lastly, data on perioperative morbidity for those colorectal cases performed at an outside institution among patients in the staged approach group were also not available. Given that the present study showed comparable rates of morbidity between the staged and simultaneous groups, these missing data would actually have led to an underestimation of complications associated with a staged approach and – if anything – provide further support for a simultaneous approach to surgery.

In conclusion, patients with synchronous CLM managed with either a simultaneous or staged approach had comparable perioperative and longterm outcomes. Patients treated with a simultaneous approach spent an average of 6 days fewer in hospital. In turn, a simultaneous approach resulted in a reduction in median charges of US$27 824, or 55.1% per patient. Therefore, when appropriate and technically feasible, the simultaneous surgery approach to synchronous CLM should be preferred as it is safe and effective, and provides for substantial economic savings.

Conflicts of interest

None declared.

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