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Early and long-term outcomes of patients undergoing liver resection and diaphragm excision for advanced colorectal liver metastases

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ABSTRACT

INTRODUCTION At present, liver resection offers the best long-term outcome and only chance for cure in patients with colorectal liver metastases. However, there are no large series that report the early and long-term outcomes of patients who require simultaneous diaphragm excision. This study was designed to investigate these patients.

PATIENTS AND METHODS A total of 285 consecutive liver resections were performed over a 10-year period. Of these, 258 had liver resections alone and 27 underwent liver resection and simultaneous diaphragm excision. Data were collected prospectively and analysed retrospectively. Pre-operative assessment was standardised. The outcomes between the two groups were compared.

RESULTS There was no difference in age, hospital stay or intra-operative blood loss. The diaphragm was histologically involved in four out of 27 resections. As a result, the cancer involved resection margin incidence was greater in the liver resection and diaphragm excision group (14.8% versus 3.9%; $P = 0.12$). The median tumour size was also different between the two groups (60 mm versus 30 mm; $P = 0.001$). The liver and diaphragm resection group had a greater peri-operative complication rate (44.4% versus 21.3%; $P = 0.02$) and mortality (7.4% versus 1.6%; $P = 0.25$). Overall and disease-free survival was significantly worse in the group who underwent simultaneous diaphragm excision and liver resection ($P = 0.04$ and $P = 0.005$, respectively). Diaphragm invasion was found to be an independent predictor of poor overall outcome ($P = 0.02$).

CONCLUSIONS Liver resection and simultaneous diaphragm excision have a greater incidence of peri-operative morbidity and mortality and a significantly worse long-term outcome compared with liver resection alone. However, these data suggest that liver resection in the presence of diaphragm invasion may still offer a favourable outcome compared with chemotherapy treatment alone. Therefore, we believe that diaphragm involvement by tumour should not be a contra-indication to hepatectomy.

KEYWORDS

Colorectal liver metastases – Liver resection – Diaphragm excision – Hepatectomy

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Colorectal carcinoma is common in the Western world.[1,2] Approximately 50% of patients diagnosed with the disease develop liver metastases.[3,4] Currently, for patients with colorectal liver metastases, liver resection offers the only potential chance for cure.[1,2] However, the proportion of patients with colorectal liver metastases eligible for liver resection remains low (20–30%),[5,6] although there has been a steady increase over the past 10–15 years,[1–4] largely due to improvements in pre-operative assessment and selection and the use of neo-adjuvant chemotherapy.

Studies have reported factors that influence early and long-term survival.[7–10] Over the past 10 years in our unit, it was felt that diaphragm invasion and subsequent diaphragm excision at the time of liver resection predicted an adverse outcome. To the authors' knowledge there have not been any reports in the literature focusing on diaphragm excision with liver resection for colorectal liver metastases.

Therefore, this study was undertaken to compare those patients who had liver resection and diaphragm excision with those who had liver resection alone, for colorectal liver metastases.

Patients and Methods

A total of 285 consecutive completed liver resections for colorectal liver metastases in a single unit over a 10-year period (September 1996 to November 2006) were studied. Of these, 27 patients underwent liver resection and diaphragm excision simultaneously and 258 underwent liver resection

Table 1 Peri-operative findings and overall outcomes

	Liver resection with diaphragm excision (n = 27)	Liver resection alone (n = 258)	P-value
Male:female	3.2:1	1.5:1	
Median age (years)	67.4 (47–78.2)	66.2 (34–85.4)	0.43
ASA			
1	4	51	
2	14	142	
3/4	4	32	
Not recorded	5	33	
Median intra-operative blood loss (ml)	202 (0–2100)	200 (0–2500)	0.34
Median hospital stay (days)	12 (6–47)	10 (5–53)	0.1
Neo-adjuvant chemotherapy			
Yes (%)	25 (92.6%)	228 (88.4%)	0.44
No	2	30	
Cancer-involved resection margins			
R1 or R2 (%)	4 (14.8%)	10 (3.9%)	0.12
R0	23	248	
Median maximum tumour size (mm)	60 (15–130)	30 (3–165)	0.001
Peri-operative morbidity	12 (44.4%)	55 (21.3%)	0.019
Peri-operative mortality	2 (7.4%)	4 (1.6%)	0.25
Median disease-free survival (months)	12 (0.5–60)	19 (0.5–115)	0.005
Median overall survival (months)	21.5 (0.5–82)	29.5 (0.5–115)	0.04

Value ranges are given in parentheses.

alone. Data were prospectively collected and retrospectively analysed. The two groups were compared.

Pre-operative assessment was standardised for each patient using computerised tomography (CT) of the chest, abdomen and pelvis, magnetic resonance imaging (MRI) of the liver and serum carcino-embryonic antigen (CEA). Operative assessment always included intra-operative ultrasound scanning (Terason, CA, USA).

In our unit, since 1996, all patients with colorectal liver metastases have been treated with 6–8 cycles (depending on response) of neo-adjuvant chemotherapy as standard for synchronous and early (< 2 years) metachronous colorectal liver metastases. Patients with late (> 2 years) metachronous colorectal liver metastases only received neo-adjuvant chemotherapy if their tumours were considered borderline for resection at pre-operative assessment. Neo-adjuvant chemotherapy included 5-fluorouracil during the early years of the study and, more recently, included either oxaliplatin or irinotecan.

Objective data were recorded including intra-operative blood loss, rate and volume of blood transfusion, morbidity, hospital stay, and overall and disease-free survival. Peri-operative mortality was defined as death before discharge from hospital or within 30 days of resection. Meticulous follow-up of all patients to recurrence or death was carried out by a dedicated data clerk.

Statistical analyses including chi-squared, t-tests, Fisher's Exact test, log ranking and Cox regression were performed using the Patient Management & Analysis System 2004 statistics software.[11] P-values less than 0.05 were considered to be significant. The median follow up period was 34 months.

Results

Liver resection alone

Overall, 258 consecutive patients underwent liver resection for colorectal liver metastases over 10 years. Patients' details are outlined in Table 1. The median age was 66.2 years, the median hospital stay was 10 days and the median intra-operative blood loss was 200 ml. Of patients, 88.4% received neo-adjuvant chemotherapy.

The cancer-involved resection margin rate (CIRM) was 3.9% and the median maximum tumour size was 30 mm. Table 2 shows the number and distribution of colorectal liver metastases.

Table 2 Number and distribution of colorectal liver metastases

	Liver resection with diaphragm excision (n = 27)	Liver resection alone (n = 258)
Single metastasis	14 (51.9%)	119 (46.1%)
2 metastases	5 (18.5%)	59 (22.9%)
3 metastases	3 (11.1%)	34 (13.2%)
4 metastases	2 (7.4%)	15 (5.8%)
> 4 metastases	2 (7.4%)	20 (7.8%)
Complete response to neo-adjuvant chemotherapy	1	11
Bilateral metastases	3 (11.1%)	51 (19.8%)

There were 55 complications in 48 patients (21.3%; Table 3) and there were four peri-operative deaths (1.6%). The 1-, 3- and 5-year disease-free survival rates were 74.8%, 50.7% and 42.8%, respectively, and the 1-, 3- and 5-year overall survival rates were 92.6%, 74.2% and 62%, respectively (Table 4).

Liver resection with diaphragm excision

Twenty-seven consecutive patients underwent liver resection with diaphragm excision for colorectal liver metastases over the 10-year period studied. Table 1 outlines the patients' details and peri-operative findings. The median age was 67.4 years (P = 0.43), the median hospital stay was 12 days (P = 0.1), and the median intra-operative blood loss was 202 ml (P = 0.34). Of patients, 92.6% received neo-adjuvant chemotherapy (P = 0.44).

The CIRM was 14.8% (P = 0.12) and the median maximum tumour size was 60 mm (P = 0.001). Of the 27 resected diaphragms, only four were found to be involved by tumour on histological examination. CIRM occurred at the site of liver transection in all patients, not the diaphragmatic aspect.

There were 12 complications in nine patients (44.4%; P = 0.02; Table 3) and there were two peri-operative deaths (7.4%; P = 0.25). The 1- and 3-year disease-free survival rates were 57.4% and 22.1%, respectively (P = 0.005), and the 1-, 3- and 5-year overall survival rates were 71.5%, 40.4% and 19.6%, respectively (P = 0.04; Table 4).

Univariate and multivariate analyses carried out to identify independent predictors of outcome. Diaphragm invasion was found to be an independent predictor of poor outcome (Tables 5 and 6).

Figures 1 and 2 demonstrate the overall and disease-free survival curves using the Kaplan–Meier technique.

Table 3 Peri-operative complications

Complication	Liver resection with diaphragm excision	Liver resection alone
Bile leak	0	12
Wound infection	2	7
Respiratory failure	1	5
Upper GI bleed	0	2
Delayed pneumothorax	1	2
Hepatic insufficiency	2	3
Sub-phrenic collection	0	4
Acute renal failure	1	1
Cardiac complications		
Atrial fibrillation	1	7
Myocardial infarction	0	1
Pulmonary oedema	2	1
Heart block	0	1
Bradycardia requiring pacing	0	1
Pleural effusion	0	1
Pneumonia	2	7
Total	**12 (44.4%)**	**55 (21.3%)**

P = 0.02

Discussion

Complications following high-risk surgery have been shown to correlate with mortality in large population-based studies.[12–14] The data in this article have shown that the peri-

Table 4 Overall and disease-free survival

Years post resection	Liver resection with diaphragm excision (SE%)	Liver resection alone (SE%)
	Overall Survival (%)	
1	71.5 (9)	92.6 (1.6)
3	40.4 (10)	74.2 (3)
5	19.6 (10)	62 (4)
	Disease-free survival (%)	
1	57.4 (11)	74.8 (3)
3	22.1 (12)	50.7 (3.7)
5	–	42.8 (5)

SE%, standard error %.

Table 5 Univariate predictors of overall survival of liver resection for colorectal cancer metastases (log ranking test)

	Status	Overall survival
Dukes' stage of primary tumour	A	0.21
	B	
	C	
ASA	1	0.74
	2	
	3	
Resection margin	R1 & R2	0.006
	R0	
Diaphragm invasion	Yes	0.02
	No	
Pre-operative serum CEA	< 100 ng/ml	0.0001
	> 100 ng/ml	
Systemic recurrence (following resection)	No	0.005
	Yes	
Tumour size	< 5 cm	0.009
	> 5 cm	
Pre-operative chemotherapy	No	0.74
	Yes	

Table 6 Multivariate predictors of overall survival using Cox regression method

	P-value
Post resection systemic recurrence	0.009
Macroscopic diaphragm invasion	0.04
Number of positive nodes	0.17
CEA > 100 ng/ml	0.21

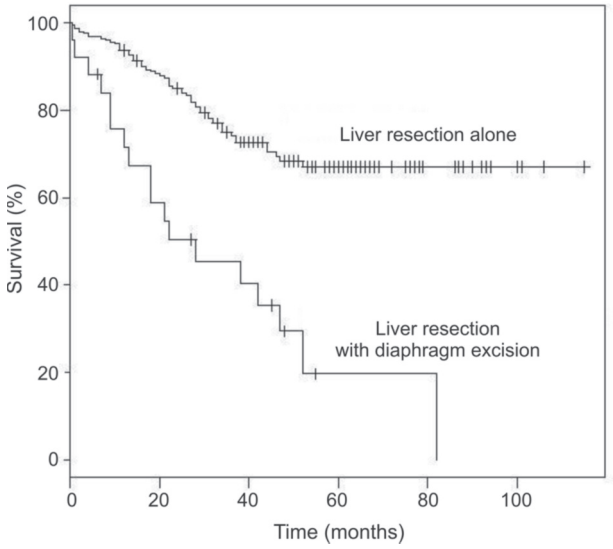

Figure 1 Overall survival in the two groups (Kaplan–Meier survival curve ($P = 0.04$).

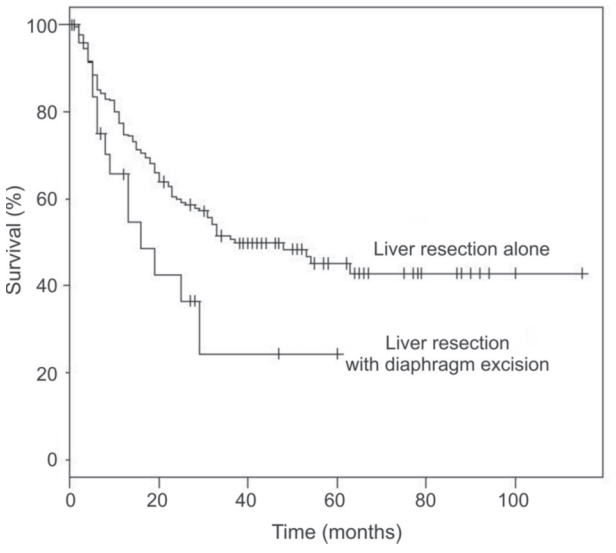

Figure 2 Disease-free survival in the two groups (Kaplan–Meier survival curve ($P = 0.005$).

operative complication rate in patients undergoing liver resection and diaphragm excision was significantly greater than those undergoing liver resection alone. This was reflected in the substantially increased peri-operative mortality in this group, even though this did not achieve significance.

There was an increase in respiratory complications in the group who had simultaneous diaphragm excisions. This can be explained as excision of part of the diaphragm will likely increase the risk of respiratory-related complications. However, there did not appear to be an increase in delayed pneumothoracies or pleural effusions, which one may expect in patients undergoing diaphragm excision.

The poorer morbidity and mortality in this group are due, in part, to the greater volume of tissue required to be resected. The significantly larger tumour size likely reflects more advanced stage of disease which results in resections that are technically more challenging, which itself is reflected by the substantially increased incidence of CIRM.

The high overall and disease-free survival of the patients who underwent liver resection alone can be explained as this was a select group. Those who underwent simultaneous liver resection and diaphragm excision were analysed separately. The overall and disease-free survival of the entire consecutive series were 46.1% and 27.9%, respectively (data not included here).[15] However, these survival

data are also higher than much of the literature, which may have been influenced by the standard policy of neo-adjuvant chemotherapy given for synchronous and early metachronous tumours.

The policy to treat all synchronous and early (< 2 years) metachronous tumours with neo-adjuvant chemotherapy may have influenced the outcome of patients with diaphragm invasion. The role of neo-adjuvant chemotherapy in the treatment of multiple colorectal metastases, or metastases with potentially threatened resection margins has been demonstrated in retrospective studies.[16–19] However, its role in patients with resectable disease has not yet been established. Chemotherapy is commonly used in conjunction with surgery to down-size tumours previously judged inoperable.[2–4,16] The French association series, and more recent data from the EPOC phase III trials, have suggested that survival after liver resection can be improved in patients treated with neo-adjuvant chemotherapy followed by liver resection.[16,18,20]

Of patients who had simultaneous liver resection and diaphragm excision, 85.2% did not have tumour involved in the diaphragm. It may be, therefore, that the significantly poorer outcome is due, in part, to a less favourable biology in addition to advanced stage of disease. The increased CIRM and significantly increased tumour size in this group would support this. It is also a concern that diaphragm invasion represents a possible breach of Glisson's capsule by the tumour and, therefore, potential peritoneal involvement.[21] These factors may explain the finding that diaphragm invasion is an independent predictor of poor overall outcome.

Outcomes following treatment of metastatic colorectal cancer with chemotherapy alone has improved over the years from a median survival of 12 months with 5-fluorourocil alone[22] to 24 months with the addition of irinotecan- and oxaliplatin-based chemotherapy and more recently the introduction of targeted monoclonal antibodies raised against epidermal growth factor (EGFR) such as bevacizumab (Avastin) and cetuximab (Erbitux).[25–26] However, while patients with diaphragm involvement appear to have a less favourable outcome than those with no diaphragm involvement, these data suggest that liver resections in patients with diaphragm invasion by tumour may still have a more favourable outcome than treatment with chemotherapy alone. In addition, even if the diaphragm appears involved intra-operatively, in the majority of cases there is no microscopic invasion. Therefore, surgeons should be encouraged to complete liver resections if diaphragm invasion is apparent either on pre-operative imaging or during the intra-operative setting.

Conclusions

Liver resection and simultaneous diaphragm excision have a greater incidence of peri-operative morbidity and mortality and a significantly worse long-term outcome compared with liver resection alone. However, these data suggest that patients who undergo liver resection in the presence of diaphragm invasion may still have a favourable outcome compared with chemotherapy alone and so diaphragm involvement by tumour should not be a contra-indication to hepatectomy.

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