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ORIGINAL ARTICLE

Influence of Hepatic Parenchymal Histology on Outcome Following Right Hepatic Trisectionectomy

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Abstract
Background Histological abnormalities in the non-tumour-bearing liver (NTBL) may influence outcome following hepatectomy. Effects will be most pertinent following right trisectionectomy but have yet to be specifically examined in this context. This study aimed to investigate the influence of perioperative factors, including NTBL histology, on outcome following right trisectionectomy.
Methods Pathological review of the NTBL of 103 consecutive patients undergoing right trisectionectomy between January 2003 and December 2009 was performed using established criteria for steatosis, non-alcoholic steatohepatitis (NASH), sinusoidal injury (SI), fibrosis and cholestasis. Perioperative and pathological factors were correlated with post-operative outcome (morbidity, major morbidity, hepatic insufficiency and mortality).
Results Morbidity, hepatic insufficiency and major morbidity occurred in 37.9 %, 14.6 % and 22.3 % of cases, respectively. Ninety-day mortality rate was 5.8 %. NASH (P=0.007) and perioperative blood transfusion (P=0.001) were independently associated with hepatic insufficiency following trisectionectomy. NASH (P=0.028), perioperative transfusion (P=0.016), diabetes mellitus (P=0.047) and coronary artery disease (P=0.036) were independently associated with major morbidity. Steatosis, SI, fibrosis and cholestasis in the NTBL demonstrated no association with any adverse outcome.
Conclusion NASH, but not steatosis or SI, is associated with adverse outcome following right trisectionectomy and caution must be exerted when considering major hepatectomy in patients with NASH.

Keywords Hepatectomy · Trisectionectomy · Liver histology · Morbidity · Mortality

Introduction

Right hepatic trisectionectomy (resection of segments 4–8±1),[1] the most extensive liver resection, was first described in 1952,[2] enabling potentially curative resection of large or multifocal tumours that largely spare the left lateral bisegment. The procedure is associated with greater risks of bleeding and post-operative hepatic dysfunction than those experienced with segmentectomy and hemihepatectomy, primarily due to the volume of liver resected. Volumetric analysis demonstrated that the native right trisectionectomy future liver remnant (FLR, segments 1–3) represents on average 18 % (maximum 30 %) of total liver volume (TLV),[3] with an additional variable contribution to remnant volume provided by tumour-associated compensatory hypertrophy. The risks of right trisectionectomy remain considerable, with recent series reporting associated

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morbidity rates of approximately 40 % and 90-day mortality rates of 6.0–8.0 %.[4–6]

The identification of factors associated with adverse outcome following right trisectionectomy is essential if post-operative outcomes are to be further improved. Of studies examining risk factors for adverse outcome following trisectionectomy,[4–8] several have included right-sided resections incorporating incomplete excision of segment 4 (extended right hepatectomy[1]),[5,8] whilst others have reported combined analyses of left and right trisectionectomy.[6,7] Indeed, to date, only Halazun et al. have reported a risk factor analysis solely for patients undergoing right trisectionectomy.[4] Analyses have also varied significantly in the covariates and outcomes assessed, producing discordant results.

Recent data from series incorporating less extensive hepatic resections have raised concerns that histological abnormalities in the non-tumour-bearing liver (NTBL) may prejudice function of the FLR, predisposing it to hepatic failure and death.[9–12] This led some observers to suggest that a 30 % minimum FLR should be maintained in patients with histologically abnormal livers,[5,13] though data to support this cutoff are lacking. Whilst effects of parenchymal abnormalities upon outcome will be most pertinent following right trisectionectomy, given that the predicted FLR is generally considerably smaller than the proposed 30 % cutoff,[3] their association with outcome has yet to be examined specifically in this context. The aim of this study, therefore, was to report the results of right trisectionectomy at our centre and conduct a comprehensive analysis of perioperative variables, including NTBL histology, to identify factors associated with adverse post-operative outcome.

Patients and Methods

All patients undergoing right hepatic trisectionectomy between January 2003 and December 2009 were identified from our institution's prospectively maintained database. These data were analysed retrospectively, with additional information gathered from medical records. Staging protocol prior to hepatectomy included contrast-enhanced spiral computerised tomography of the chest, abdomen and pelvis using an iodinated contrast agent and gadolinium-enhanced magnetic resonance imaging of the liver. Neither volumetry nor portal vein embolisation (PVE) was used. The criteria for acceptance for surgery were: anatomically resectable hepatic disease on cross-sectional imaging, absence of distant metastases (barring resectable colorectal lung metastases) and fitness for major surgery. Patients presenting with obstructive jaundice underwent preoperative endoscopic and/or percutaneous biliary drainage.

All resections were carried out under low central venous pressure conditions. Inflow and outflow control was achieved extra-hepatically before parenchymal dissection. The liver parenchyma was dissected using a Sonoca ultrasonic dissector (Söring Medical, Quickborn, Germany), with haemostasis achieved using diathermy, argon beam coagulation and suturing. If necessary, intermittent clamping of the portal triad (Pringle manoeuvre) was performed during parenchymal dissection, with periods of occlusion of up to 10 min alternating with 5-min release intervals.

The following data, available preoperatively, were recorded: age; gender; comorbidity; body mass index (BMI); haematology and biochemistry results; tumour type, number and size; preoperative biliary drainage and use of chemotherapy within 6 months of hepatectomy. The following perioperative variables were recorded: resection of additional hepatic tissue (caudate lobe resection, extra-anatomical or incontiguous segment 2/3 resection), performance of synchronous extra-hepatic procedures (biliary reconstruction, vascular reconstruction, and others), use of the Pringle manoeuvre, blood loss and perioperative blood transfusion.

Histological Assessment of the Non-Tumour-Bearing Liver

Histology of the NTBL remote from the resected lesions(s) was assessed in a blinded fashion by two pathologists with hepatobiliary expertise. Steatosis was estimated as the percentage of involved hepatocytes and categorised as follows: 0, absent; 1, mild (<30 % of hepatocytes); 2, moderate (30–60 % of hepatocytes); and 3, severe (>60 % of hepatocytes).[10] Non-alcoholic steatohepatitis (NASH) was graded as defined by Kleiner et al.[14] based on a composite score derived from steatosis (score 0=5 %; 1=5–33 %; 2=>33–66 %; 3=>66 %), lobular inflammation (score 0=no foci; 1=<2 foci; 2=2–4 foci; 3=>4 four foci per ×200 field), and ballooning (score 0=none; 1=few ballooned cells; 2=prominent ballooning). As previously,[12] steatohepatitis was defined as a score of 4 or greater. Having identified NASH, cases of simple steatosis (i.e., without necro-inflammatory activity) were identified.

Sinusoidal injury (SI) was scored using an established grading system of sinusoidal dilation: 0, absent; 1, mild (centriolobular involvement limited to one-third of the lobular area); 2, moderate (centrilobular involvement extending into two-thirds of the lobular area); 3, severe (complete lobular involvement).[15] Peliosis was also noted. Fibrosis was scored according to the Metavir score: 0=absent; 1=portal fibrosis without septa; 2=portal fibrosis with few septa; 3=numerous septa without cirrhosis; 4=cirrhosis.[16] Cholestasis was scored semiquantitatively as previously: 0=absent, 1=mild, 2=moderate, 3=severe.[17]

Outcomes

Postoperative outcome measures were morbidity, hepatic insufficiency, major morbidity (Clavien grades III–V complications,[18] i.e., requiring surgical, endoscopic or radiological intervention,

High Dependency Unit/Intensive Care Unit management or resulting in death) and mortality. Morbidity and mortality were defined as occurring within 90 days of surgery. As previously,[5,19] hepatic insufficiency was defined as post-operative peak serum total bilirubin >120 μmol/L (7.0 mg/dL).

Statistical Analysis

Correlations between preoperative variables and NTBL histology were determined using the Chi-squared or Kruskal-Wallis tests as appropriate. Binary logistic regression analyses were used to examine the association of variables with perioperative transfusion requirement and adverse post-operative outcomes. Multivariable analyses were performed using a stepwise binary logistic regression model, including all variables with $P<0.10$ on univariable analysis. Statistical significance was defined as $P<0.05$. Statistical analyses were performed using Statistical Package for the Social Sciences 16.0® (SPSS, Chicago, IL, USA).

Results

A total of 103 consecutive patients underwent right trisectionectomy over the study period. Preoperative variables for these patients are shown in Table 1. Forty patients (38.8 %) received chemotherapy within the 6 months prior to liver resection. 5-Fluorouracil (5-FU) and leucovorin (LV) alone were used in 13 cases (12.6 %), 5-FU/LV plus oxaliplatin in 24 cases (23.3 %), and other regimes in three cases (2.9 %). All oxaliplatin-based chemotherapy was a short course (median 6 cycles, range 2–8 cycles). Only one patient received irinotecan and bevacizumab was not used.

Twenty patients (19.4 %) had resection of additional hepatic tissue (five caudate resections, 15 incontiguous or non-anatomical segment 2/3 resections). Twenty-four patients (23.3 %) had a synchronous extra-hepatic, intra-abdominal procedure performed: 16 patients (15.5 %) underwent biliary reconstruction and 11 patients (10.7 %) underwent other intra-abdominal procedures, including four (3.9 %) portal vein or vena caval resections.

Histological Abnormalities in the Non-Tumour-Bearing Liver

NASH (Kleiner score ≥4) was present in nine patients (8.7 %). Steatosis without concomitant inflammatory activity (simple steatosis) was identified in 43 cases (41.7 %), with ≥30 % steatosis in five cases (4.9 %). Sinusoidal dilatation was present in 32 patients (31.1 %), with ten (9.7 %) having moderate to severe (grade 2–3) dilatation. Peliosis was identified in nine cases (8.7 %). Fibrosis was present in 36 patients (35.0 %), with seven (6.8 %) having grade 2–3 fibrosis. No patient had cirrhosis. Cholestasis was present in 27 cases (26.2 %).

Preoperative oxaliplatin-based chemotherapy was the only factor significantly associated with SI in the NTBL ($P=0.017$). 5-FU/LV chemotherapy was not associated with any histological abnormality. BMI >25 was the only factor significantly associated with steatosis ($P=0.004$) and with NASH in the NTBL ($P=0.033$). Diabetes mellitus showed no significant association with any histological abnormality. No association was seen between histological abnormalities and preoperative liver function tests.

Operative Blood Loss and Transfusion Requirement

Median operative duration was 300 min (range 130–660 min) and median operative blood loss, 600 mL (range 100–7,000 mL). Thirty-seven patients (35.9 %) received a perioperative blood transfusion with a mean perioperative transfusion requirement of 1.6 U (median 0 U, range 0–14 U). The mean Pringle duration for patients who had the manoeuvre performed was 20 min. Analysis of perioperative factors revealed that resection of cholangiocarcinoma ($P=0.001$, HR 7.49, 95 % CI 2.30–24.43) and SI in the NTBL ($P=0.011$, HR 3.76, 95 % CI 1.35–10.50) were the only factors independently associated with perioperative transfusion requirement.

Morbidity and Mortality Following Trisectionectomy

Postoperative morbidity occurred in 39 patients (37.9 %), with a total of 55 events recorded (Table 2) and multiple complications developing in 14 patients (13.6 %). Hepatic insufficiency developed in 15 patients (14.6 %). Major complications occurred in 23 cases (22.3 %). In-hospital mortality was 5.8 % ($n=6$, Table 3), with no other deaths within 90 days of surgery. Three of these patients (2.9 %) died within 30 days of surgery.

Risk Factor Analysis

Results of univariable analyses for associations of perioperative variables with adverse post-operative outcomes following right trisectionectomy are shown in Tables 4 and 5. Results of multivariable analyses are shown in Table 6. Hypertension and transfusion requirements were the only variables associated with morbidity on univariable analysis, with significance for both variables maintained on multivariable analysis ($P=0.044$ and $P=0.003$). For hepatic insufficiency, BMI >25, tumour size, presence of NASH and transfusion requirement were associated on univariable analysis, with NASH ($P=0.007$) and transfusion requirement ($P=0.001$) maintaining significance on multivariable analysis.

Table 1 Pre-operative variables in patients undergoing right trisectionectomy

Variable	Median (range)	*n* (%)
Age	58 (18–84)	
Gender (male:female)	59:44	
Comorbid disease		39 (37.9 %)
Hypertension		21 (20.4 %)
Coronary artery disease		10 (9.7 %)
Pulmonary disease		8 (7.8 %)
Diabetes		7 (6.8 %)
Body mass index	26 (20–35)	
Histology of hepatic disease		
Colorectal metastases		66 (64.1 %)
Cholangiocarcinoma		17 (16.5 %)
Neuroendocrine metastases		7 (6.8 %)
Gallbladder carcinoma		5 (4.9 %)
Hepatocellular carcinoma		3 (2.9 %)
Benign disease		5 (4.9 %)
Number of tumours	2 (1–20)	
Maximum tumour diametre (mm)	50 (4–170)	
Preoperative chemotherapy		40 (38.8 %)
5-Fluorouracil/leucovorin (5-FU/LV)		13 (12.6 %)
5-FU/LV/oxaliplatin		24 (23.3 %)
Other		3 (2.9 %)
Preoperative biliary drainage		12 (11.7 %)
Laboratory variables		
Haemoglobin (g/dL)	13.4 (9.5–16.6)	
Leucocyte count ($\times 10^9$/L)	7.2 (3.1–15.1)	
Serum bilirubin (μmol/L)	10 (2–403)	
Serum albumin (g/L)	42 (28–48)	
Serum creatinine (μmol/L)	80 (51–303)	

Table 2 Post-operative morbidity following right trisectionectomy

Morbidity	*n* (%)
Overall morbidity	39 (37.9 %)
Hepatic insufficiency	15
Renal failure	8
Lower respiratory tract infection	7
Intra-abdominal abscess	6
Bile leak/biloma	5
Bleeding duodenal ulcer	3
Wound infection	2
Myocardial infarction	2
Perforated duodenal ulcer	1
Post-operative intra-abdominal bleeding	1
Gastrointestinal anastomotic leak	1
Bowel obstruction	1
Pulmonary embolism	1
Cardiac arrhythmia	1
Cerebrovascular event	1
Major morbidity	23 (22.3 %)

For major (Clavien grades III–V) complications, comorbidity, coronary artery disease, pulmonary disease, diabetes mellitus, BMI >25, NASH and operative blood loss were significantly associated on univariable analysis, with perioperative transfusion requirement demonstrating a borderline significant association (P=0.053). On multivariable analysis, coronary artery disease (P=0.036), diabetes mellitus (P=0.047), NASH (P=0.028) and transfusion requirement (P=0.016) were independently associated with major morbidity following right trisectionectomy. Comorbidity, pulmonary disease and diabetes mellitus were also associated with mortality following right trisectionectomy on univariable analysis, with NASH demonstrating a borderline significant association with this outcome (P=0.050). Diabetes mellitus was the only factor independently associated with mortality (P<0.001).

When outcome analyses for steatosis, SI, fibrosis and cholestasis were repeated to compare patients with more severe (grade 2/3) injury to those with grade 1/2 injury or grade 1 (uninjured) NTBL, no univariable association

Table 3 Summary of deaths and perioperative risk factors in patients undergoing right trisectionectomy

Age	Gender	Diagnosis	Comorbid disease	Operation	NTBL histology	Transfusion (U)	Cause of death	Survival (days)
43	Female	CC	BP, DM	RTS	NASH, SI	4	MOF	19
58	Male	CLM	DM	RTS + seg2/3	NASH	0	Sepsis	11
62	Male	CLM	BP, CAD	RTS	Normal	2	MOF	18
68	Male	CLM	None	RTS + seg2/3	SI	2	Perf DU, MOF	33
75	Male	NET	Pulm, DM	RTS	Steatosis	0	MOF	43
77	Male	CC	Pulm, CAD, DM	RTS	SI	0	Sepsis, MOF	80

NTBL non tumour-bearing liver, *CC* cholangiocarcinoma, *BP* hypertension, *DM* diabetes mellitus, *RTS* right trisectionectomy, *NASH* non-alcoholic steatohepatitis, *SI* sinusoidal injury, *MOF* multi-organ failure, *CLM* colorectal liver metastases, *seg 2/3* additional segment 2/3 resection, *CAD* coronary artery disease, *Perf DU* perforated duodenal ulcer, *NET* neuroendocrine tumour, *Pulm* pulmonary disease

with any adverse outcome was noted, confirming that even more severe forms of these NTBL injuries did not prejudice outcome. In particular, steatosis >30 % was not associated with any adverse outcome when compared to either steatosis <30 % or non-steatotic NTBL.

Discussion

Although the rates of mortality (5.8 %) and morbidity (37.9 %) following right trisectionectomy in the current series are amongst the lowest reported,[4–6] identification of factors

Table 4 Univariable analyses of risk factors for morbidity and hepatic insufficiency following right trisectionectomy

Variable	Patients (n=103)	Morbidity (n=39)		Hepatic insufficiency (n=15)	
		Hazard ratio (95 % CI)	P	Hazard ratio (95 % CI)	P
Age: <65/≥65 years	78/25	2.17 (0.87–5.41)	0.098	1.70 (0.52–5.55)	0.38
Gender: male/female	59/44	0.89 (0.40–2.00)	0.79	0.88 (0.29–2.68)	0.82
Comorbidity (any): yes/no	39/64	2.09 (0.92–4.75)	0.078	1.53 (0.51–4.62)	0.45
Hypertension: yes/no	21/82	2.72 (1.02–7.23)	0.046	2.25 (0.68–7.49)	0.19
Coronary artery disease: yes/no	10/93	2.73 (0.72–10.36)	0.14	1.54 (0.29–8.06)	0.61
Pulmonary disease: yes/no	8/95	2.99 (0.67–13.29)	0.15	0.83 (0.09–7.24)	0.86
Diabetes mellitus: yes/no	7/96	2.32 (0.49–10.99)	0.29	2.55 (0.45–14.56)	0.29
Body mass index: <25/≥25	49/54	1.81 (0.81–4.08)	0.15	4.38 (1.16–16.61)	0.030
Tumour diametre: ≤50/>50 mm	54/49	0.91 (0.41–2.03)	0.82	0.23 (0.06–0.87)	0.030
Pre-operative chemotherapy: yes/no	40/63	0.57 (0.25–1.32)	0.19	0.76 (0.24–2.40)	0.64
Oxaliplatin chemotherapy: yes/no	24/79	0.78 (0.47–1.28)	0.32	0.68 (0.31–1.49)	0.33
Pre-operative biliary drainage: yes/no	12/91	1.76 (0.52–5.89)	0.36	3.64 (0.94–14.11)	0.062
Non-tumour-bearing liver histology					
NASH: present/absent	9/94	2.21 (0.56–8.77)	0.26	6.04 (1.41–25.93)	0.016
Steatosis[a] : present/absent	43/60	0.75 (0.32–1.75)	0.50	0.40 (0.10–1.63)	0.20
Sinusoidal dilatation: present/absent	32/71	0.98 (0.41–2.31)	0.96	1.13 (0.35–3.62)	0.84
Fibrosis: present/absent	36/67	0.89 (0.39–2.06)	0.79	1.29 (0.42–3.96)	0.66
Cholestasis: present/absent	27/76	0.77 (0.31–1.93)	0.57	0.67 (0.17–2.57)	0.56
Intraoperative variables					
Additional liver resected: yes/no	20/83	2.40 (0.89–6.47)	0.08	1.64 (0.46–5.80)	0.45
Blood loss (litres): <1,500 ml/≥1,500 ml	86/17	2.10 (0.73–6.00)	0.17	3.17 (0.92–10.88)	0.067
Blood transfusion: yes/no	37/66	3.73 (1.55–8.94)	0.003	6.00 (1.85–19.47)	0.003

NASH non-alcoholic steatohepatitis

[a] Steatosis in the absence of necro-inflammatory activity (i.e., excluding patients with NASH). Results for the following non-significant variables (all P>0.10) are not shown: cerebrovascular disease, renal disease, diagnosis (cholangiocarcinoma/other), number of tumours (12/≥2), preoperative cholangitis, International Normalised Ratio, leucocyte count, serum bilirubin, serum creatinine, serum albumin, caudate resection, segment 2/3 resection, synchronous intraabdominal procedure, biliary reconstruction, vascular reconstruction and use of Pringle manoeuvre

Table 5 Univariable analyses of risk factors for major morbidity and mortality following right trisectionectomy

Variable	Patients (n=103)	Major morbidity (n=23)		Mortality (n=6)	
		Hazard ratio (95 % CI)	P	Hazard ratio (95 % CI)	P
Age: <65/≥65 years	78/25	1.98 (0.72–5.44)	0.19	3.41 (0.64–18.10)	0.15
Gender: male/female	59/44	0.65 (0.25–1.71)	0.39	0.25 (0.03–2.23)	0.22
Comorbidity (any): yes/no	39/64	3.42 (1.31–8.95)	0.012	9.27 (1.04–82.55)	0.046
Hypertension: yes/no	21/82	2.06 (0.72–5.95)	0.18	2.05 (0.35–12.05)	0.43
Coronary artery disease: yes/no	10/93	4.17 (1.09–15.95)	0.037	5.56 (0.88–35.20)	0.068
Pulmonary disease: yes/no	8/95	7.13 (1.56–32.62)	0.011	7.58 (1.15–50.08)	0.035
Diabetes mellitus: yes/no	7/96	5.40 (1.11–26.21)	0.036	62.67 (8.07–484.78)	<0.001
Body mass index: <25/≥25	49/54	3.29 (1.18–9.22)	0.023	4.90 (0.55–43.49)	0.15
Tumour diametre: ≤50/>50 mm	54/49	0.64 (0.25–1.65)	0.36	0.53 (0.09–3.04)	0.48
Pre-operative chemotherapy: yes/no	40/63	0.62 (0.23–1.68)	0.35	0.78 (0.14–4.45)	0.78
Oxaliplatin chemotherapy: yes/no	24/79	0.94 (0.54–1.65)	0.84	1.31 (0.54–3.15)	0.55
Pre-operative biliary drainage: yes/no	12/91	2.90 (0.82–10.19)	0.098	4.35 (0.71–26.83)	0.11
Non-tumour-bearing liver histology					
NASH: present/absent	9/94	5.28 (1.29–21.65)	0.021	6.43 (1.00–41.44)	0.050
Steatosis[a]: present/absent	43/60	0.94 (0.33–2.63)	0.90	1.20 (0.16–8.86)	0.86
Sinusoidal dilatation: present/absent	32/71	1.24 (0.47–3.32)	0.66	2.35 (0.45–12.31)	0.31
Fibrosis: present/absent	36/67	1.26 (0.49–3.29)	0.63	0.35 (0.04–3.16)	0.35
Cholestasis: present/absent	27/76	0.99 (0.35–2.85)	0.99	0.55 (0.06–4.90)	0.59
Intraoperative variables					
Additional liver resected: yes/no	20/83	2.26 (0.78–6.56)	0.14	2.19 (0.37–12.92)	0.39
Blood loss (L): <1,500 ml/≥1,500 ml	86/17	3.06 (1.01–9.28)	0.048	1.01 (0.11–9.26)	0.99
Blood transfusion: yes/no	37/66	2.58 (0.99–6.71)	0.053	2.35 (0.45–12.31)	0.31

NASH non-alcoholic steatohepatitis

[a] Steatosis in the absence of necro-inflammatory activity (i.e., excluding patients with NASH). Results for the following non-significant variables (all P>0.10) are not shown: cerebrovascular disease, renal disease, diagnosis (cholangiocarcinoma/other), number of tumours (1–2/≥2), preoperative cholangitis, International Normalised Ratio, leucocyte count, serum bilirubin, serum creatinine, serum albumin, caudate resection, segment 2/3 resection, synchronous intra-abdominal procedure, biliary reconstruction, vascular reconstruction and use of Pringle manoeuvre

associated with adverse outcome may allow results to be further improved. Risk factor analyses performed to date have varied significantly in the covariates assessed, with no study performing a comprehensive assessment of hepatic parenchymal histology, and have largely limited outcomes to morbidity and/or mortality, with inconclusive results.[4,6,7,20] Identification of factors associated with mortality is limited by the infrequency of this outcome and the consequent risk of type II statistical error. The current study, therefore, also assessed major morbidity and hepatic insufficiency (using a cutoff

Table 6 Multivariable analyses of risk factors for adverse outcome following right trisectionectomy

Risk factor	Morbidity		Hepatic insufficiency		Major morbidity		Mortality	
	Hazard ratio (95 % CI)	P	Hazard ratio (95 % CI)	P	Hazard ratio (95 % CI)	P	Hazard ratio (95 % CI)	P
Hypertension	2.88 (1.03–8.07)	0.044						
Coronary artery disease					4.78 (1.11–20.57)	0.036		
Diabetes mellitus					6.38 (1.03–39.71)	0.047	97.11 (8.24–1144.29)	<0.001
NASH			12.01 (1.96–73.74)	0.007	6.02 (1.21–30.00)	0.028		
Blood transfusion	3.86 (1.58–9.48)	0.003	14.49 (3.21–65.42)	0.001	3.92 (1.29–11.88)	0.016		

NASH non-alcoholic steatohepatitis

recently shown to accurately predict liver-related death and overall mortality following major hepatectomy in non-cirrhotic patients).[19]

Studies of the influence of hepatic parenchymal abnormalities upon outcome following liver resection have largely focused upon NAFLD and SI. NAFLD describes a pathological spectrum progressing from simple steatosis, through NASH (steatosis with concomitant necro-inflammatory activity), to cirrhosis.[21,22] Steatosis is closely associated with the metabolic syndrome (obesity, diabetes, dyslipidaemia, hypertension), affecting up to 30 % of the general population and up to 75 % of obese individuals.[23] Between 10 % and 30 % of individuals with steatosis develop NASH, with this transition likely requiring a 'second-hit' involving oxidative stress, with irinotecan identified as one candidate stressor.[12,17]

Vauthey et al. provided the only significant outcome data on NASH to date,[12] finding NASH to be associated with significantly higher overall mortality and mortality from liver failure following major hepatectomy. In line with these data, we found NASH to be independently associated with both hepatic insufficiency and major morbidity following right trisectionectomy. Of note, whilst Vauthey et al. found NASH to be closely linked to irinotecan use, only one patient in the current study received this agent, suggesting that NASH also influences outcome in irinotecan-naïve populations.

Several studies have demonstrated steatosis to be associated with morbidity following major liver resection,[9,10,24] with a recent meta-analysis confirming this association for both mild (<30 %) and severe (≥30 %) steatosis.[25] This latter analysis also significantly correlated severe steatosis and mortality following hepatectomy, although no individual series has demonstrated this. Crucially, however, none of these studies distinguished steatohepatitis from simple steatosis, and so, by default, included cases of NASH in their diagnosis of 'steatosis'. Recognising the distinction of NASH from simple steatosis, Vauthey analysed these abnormalities in defined groups and demonstrated that, in contrast to NASH, even severe simple steatosis was associated with neither morbidity nor mortality following hepatectomy.[12] The current study agrees with these data, demonstrating that steatosis without necroinflammatory activity, regardless of severity, showed no association with adverse outcome following right trisectionectomy.

Following the initial report of Rubbia-Brandt et al.,[15] subsequent studies have noted SI in 19–52 % of oxaliplatin-treated patients undergoing hepatic resection,[11,12,26–28] with severity of SI reflecting treatment duration.[29,30] Although no study has demonstrated increased mortality in patients with oxaliplatin-related SI, Nakano et al.[11] noted an association with increased morbidity following major hepatectomy. More recently, Soubrane et al. reported SI to be independently associated with hepatic dysfunction (though not liver failure or death) following hepatectomy.[31] These studies employed long-course oxaliplatin regimes (mean 9 and 8.4 cycles, respectively), however, and reported more severe forms of SI than studies using short-course treatment. By contrast, available data do not support an association between short-course oxaliplatin-associated SI and adverse outcome following hepatectomy, with morbidity at most minimally increased.[12,26,28,32] In line with these data, the current study found that even following right trisectionectomy, neither short-course oxaliplatin nor associated SI showed any association with adverse outcome.

Whilst 20 % TLV is widely accepted as the minimum FLR in patients with normal hepatic histology,[5,13] there is little evidence to support the 30 % FLR cutoff proposed for patients with abnormal liver parenchyma. The current study, employing a population undergoing the most extensive liver resection, whom volumetric analysis has shown will largely have an FLR considerably smaller than 30 %,[3] suggests that the 30 % cutoff should not be applied to all NTBL histological abnormalities. Whilst data do support a larger FLR for patients with NASH, this study suggests that right trisectionectomy may be safely performed in patients with both steatosis and short-course oxaliplatin-associated SI.

In relation to other risk factors, as previously,[4–6,8,20] perioperative blood transfusion was associated with adverse outcome, showing independent correlations with morbidity, hepatic insufficiency and major morbidity. Large volume blood loss increases the probability of post-operative hepatic compromise, whilst blood transfusion exerts immunosuppressive effects that may predispose infective complications[33] and impairs liver regeneration.[34] Whilst SI was not associated with adverse outcome following right trisectionectomy, it was independently associated with transfusion requirement. Similarly, patients with more severe forms of SI were previously found to have greater transfusion requirements.[26] These associations are not unexpected given the proangiogenic, haemorrhagic nature of SI.[35]

Patient comorbidity was the final factor independently associated with adverse outcome following right trisectionectomy. Similarly, Wei et al.[8] previously reported comorbidity to independently predict mortality following extended hepatectomy. Diabetes mellitus was also previously associated with poor outcome following major hepatic resection.[36,37] Whilst this association was partly attributed to the presence of NAFLD in diabetics, correlations in the present study were independent of hepatic histology. Diabetes also impairs the hepatic regenerative response,[38] and these effects, along with immune response alterations, may explain associations with outcome. Further studies are needed to confirm this finding, however, given the small number of diabetics in the current study.

In summary, NASH, but not steatosis, in the NTBL and patient comorbidity are independently associated with adverse outcome following right trisectionectomy. SI, although not

itself associated with adverse outcome, was independently associated with transfusion requirement, the third independent predictor of major morbidity following trisectionectomy. These data suggest that, in addition to meticulous operative technique and careful patient selection in terms of general physiological status, greater efforts are necessary to identify histological abnormalities in the NTBL of patients who are candidates for trisectionectomy and to adapt treatment strategy accordingly.

Preoperative volumetry was not performed at our centre at the time of the current study and FLR data were consequently not available for our patients. Nevertheless the mortality rate in this study is marginally lower than a recent series employing preoperative volumetric analysis.[5] Further volumetric analyses are needed, however, to confirm the findings of this study and to definitively determine the safe FLR for individual NTBL histological abnormalities. In the case of NASH, this is likely in excess of 30 %. Equally important is the ability to sensitively and specifically detect NTBL abnormalities preoperatively in order that these data may be combined with volumetry to predict perioperative risk.

Regarding SI, short-course oxaliplatin-associated injury can be detected preoperatively with super-paramagnetic iron-oxide-enhanced MRI,[39] whilst CT volumetric assessment of increased splenic size may accurately predict higher grades of SI.[40] Potentially, therefore, these techniques may enable the preoperative identification of patients at risk of developing severe SI, with its associated risks of portal hypertension and intra-operative bleeding and, potentially, regimen alteration to address this risk. Whist bevacizumab co-administration has been convincingly demonstrated to reduce oxaliplatin-induced SI,[41] translation of this effect into reduced intraoperative bleeding remains to be confirmed.

Whilst available data support a larger FLR in patients with NASH, at present, there is no widely available, reliable, non-invasive method to distinguish this type of NAFLD from simple steatosis. Although current CT and MRI technologies are able to identify hepatic steatosis, with MRI detecting levels as low as 3 %, they are currently unable to reliably distinguish NASH from steatosis.[42] Liver biopsy is regarded as the 'gold standard' technique to allow this distinction but involves risks to the patient and is associated with significant sampling error (as histological changes are often not uniformly distributed), as well as intra- and inter-observer scoring variability.[43] A number of novel, non-invasive imaging techniques and biomarker-based approaches that may allow the distinction of NASH from steatosis to be accurately and safely determined are, therefore, currently under investigation.[44,45]

Accurate diagnosis of NASH and subsequent volumetry will likely result in increasing recourse to PVE in patients with a predicted inadequate FLR, though it remains to be demonstrated whether the efficacy of PVE shown for other chronic liver diseases also applies to patients with NASH.[46] An alternative approach that has recently been advocated is to attempt to reverse NAFLD prior to undertaking hepatic resection.[47] There is now significant evidence supporting NAFLD reversal, with both lifestyle modification and pharmacological treatments (including insulin sensitisers and vitamin E) shown to yield improvements in liver histology.[48,49] Thiazolidinediones, for example, were associated with improvements in both steatosis and necro-inflammation in a recent meta-analysis.[48] The efficacy of these strategies in the context of liver resection, however, given the relatively short time window available for intervention, as well as their influence upon post-hepatectomy liver function, remains to be determined.

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