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ORIGINAL ARTICLE

Critical review of the prognostic significance of pathological variables in patients undergoing resection for colorectal liver metastases

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Abstract

Objective: The aim of this study was to identify prognostic factors, particularly pathological variables, that influence disease-free and overall survival following resection for colorectal liver metastases (CRLM).

Methods: Patients undergoing CRLM resection from January 2005 to December 2011 were included. Data analysed included information on demographics, laboratory results, operative findings, histopathological features and survival.

Results: A total of 259 patients were included. Of these, 138 (53.3%) patients developed recurrent disease, of which 95 died. The median length of follow-up in the remaining patients was 28 months (range: 12–96 months). There were significant associations between recurrence and higher tumour number ($P = 0.002$), presence of perineural invasion ($P = 0.009$) and positive margin (R1) resection ($P = 0.002$). Multivariate analysis showed all three prognostic factors to be independent predictors of disease-free survival. Significantly poorer overall survival after hepatic resection for CRLM was observed in patients undergoing hemi-hepatectomy or more radical resection ($P = 0.021$), patients with a higher number of tumours ($P = 0.024$) and patients with perineural invasion ($P < 0.001$). Multivariate analysis showed perineural invasion to be the only independent predictor of overall survival.

Conclusions: The presence of perineural invasion, multiple tumours and an R1 margin were associated with recurrent disease. Perineural invasion was also an independent prognostic factor with respect to overall survival.

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Introduction

Hepatic resection has become the treatment of choice in resectable colorectal liver metastases (CRLM) and is associated with longterm survival in these patients. Around 25% of patients have synchronous liver metastases at presentation and a further 20% subsequently develop metachronous liver disease, usually within 2 years of the resection of the primary tumour.[1,2] Despite the variability in the selection criteria of patients with CRLM for hepatic resection, 5-year survival rates of up to 58% have been reported.[1,3,4]

Several clinicopathological features have been identified as prognostic factors. These include the size of the largest hepatic metastasis, the number of hepatic metastases, the distribution of hepatic tumours, the extent of hepatic resection, preoperative expression of C-reactive protein (CRP) and neutrophil-to-lymphocyte ratio (NLR), and the status of the resection margin.[5–9] Various hepatobiliary units have proposed prognostic scoring systems to stratify patients into risk categories for clinical management.[5,10] In patients with primary liver tumours such as those of cholangiocarcinoma and hepatocellular carcinoma, lymphatic, vascular and perineural invasion are well-established pathological variables that influence overall survival following hepatic resection.[11–13] To date, data on the prognostic implications of vascular, biliary, perineural and lymphatic invasion in patients with CRLM are limited. In addition to clinical scoring systems, these histopathological features may potentially be useful in selecting patients for adjuvant therapy and clinical trials.

The aim of the current study was to analyse the impact of pathological variables, in particular biliary, vascular, perineural and lymphatic invasion, on outcomes in patients after potentially curative hepatic resection for CRLM.

Materials and methods

Patients

Patients with CRLM undergoing hepatic resection at Nottingham University Hospitals National Health Service (NHS) Trust, Nottingham, UK, during the 7-year period from January 2005 to December 2011 were identified from a prospectively maintained database. All patients who underwent primary hepatic resection with curative intent were included in the analysis. Prior to any treatment, patients were discussed at a specialist multidisciplinary (MDT) meeting that included hepatobiliary surgeons, hepatologists, oncologists, radiologists and pathologists. Preoperative radiological assessment included a computed tomography (CT) scans of the thorax, abdomen and pelvis and magnetic resonance imaging (MRI) of the liver. Patients considered for neoadjuvant chemotherapy and patients with indeterminate lesions, in particular lung nodules, underwent positron emission tomography (PET).

A subgroup of patients were given neoadjuvant oxaliplatin-based chemotherapy prior to liver resection. If this was unsuitable, an irinotecan-based regimen was administered. Following this, patients underwent reassessment prior to resection. According to the unit's protocol, all patients were offered adjuvant chemotherapy following liver resection unless they had undergone chemotherapy adjuvant to bowel resection within 12 months of the primary hepatic resection.

Collated data included information on patient demographics, laboratory analyses, type of surgical resection, histopathology analysis and clinical outcomes.

Surgery

Parenchymal transection was performed using the Cavi-Pulse Ultrasonic Surgical Aspirator (CUSA). Intraoperative ultrasound was performed to confirm the findings of preoperative imaging and to assist in surgical planning. The number of hepatic (Couinaud[14]) segments resected was determined by the procedure to be performed according to the Brisbane nomenclature.[15] The type of surgical procedure was selected with the aim of achieving the resection of all macroscopic disease, clear resection margins and the preservation of sufficient remnant liver. The extent of hepatic resection was used to classify study patients into two groups according to whether the resection represented a lesser procedure than hemi-hepatectomy, or a hemi-hepatectomy or more radical resection.

Follow-up

Patients were followed up in specialist hepatobiliary clinics. Following the initial postoperative review at 1 month, all patients were examined in the outpatient clinic at 3, 6, 12, 18 and 24 months and annually thereafter. At each clinical review, carcinoembryonic antigen (CEA) levels were measured. All patients in this study underwent a minimum follow-up of 1 year following hepatic resection for CRLM.

Surveillance imaging included CT of the thorax, abdomen and pelvis. Patients underwent 6-monthly CT scans during the first 2 years postoperatively, followed by annual CT scans thereafter. Liver MRI was used to characterize suspicious hepatic lesions demonstrated on CT. The development of symptoms suspicious of recurrence at any time-point prompted an earlier than scheduled review.

Following the detection of recurrence on surveillance imaging, patients with unresectable disease were referred to the oncologist and patients who were suitable for further surgery were submitted to liver and/or lung resection within an average of 4 weeks. Overall and disease-free survival data were recorded; disease-free survival was defined as the time from primary hepatic resection to the first documented disease recurrence on imaging. Overall survival was defined as the time between the dates of primary hepatic resection and death or most recent follow-up if the patient was still alive.

Histopathological analysis

Histopathological data for the resected liver specimen were collated. These included: tumour size (maximum diameter); tumour number, and the status of the resection margin. A negative margin (R0) resection was defined by no microscopic evidence of tumour at or within 1 mm of the margin. In addition, lymphatic, perineural, biliary and vascular invasion were determined in haematoxylin and eosin (H&E)-stained sections (Fig. 1).

Biliary invasion was defined by the presence of adenocarcinoma cells infiltrating through part of or completely replacing the bile duct epithelium in the large, medium-sized or small intrahepatic bile ducts (Fig. 1b–d). Perineural invasion was defined as tumour cells within any layer of the nerve sheath or tumour in the perineural space (Fig. 1d). Lymphatic invasion was defined by the presence of adenocarcinoma cells within the lumen of the lymphatic space (Fig. 1e). The presence of vascular invasion was defined by adenocarcinoma cells within the lumen of the vascular channel (Fig. 1f).

In this study, all histopathological parameters in hepatic resection specimens of CRLM were reviewed by a specialist hepatobiliary histopathologist (AMZ).

Statistical analysis

Categorical data were presented as frequencies and proportions (%). The median and range were used to describe continuous

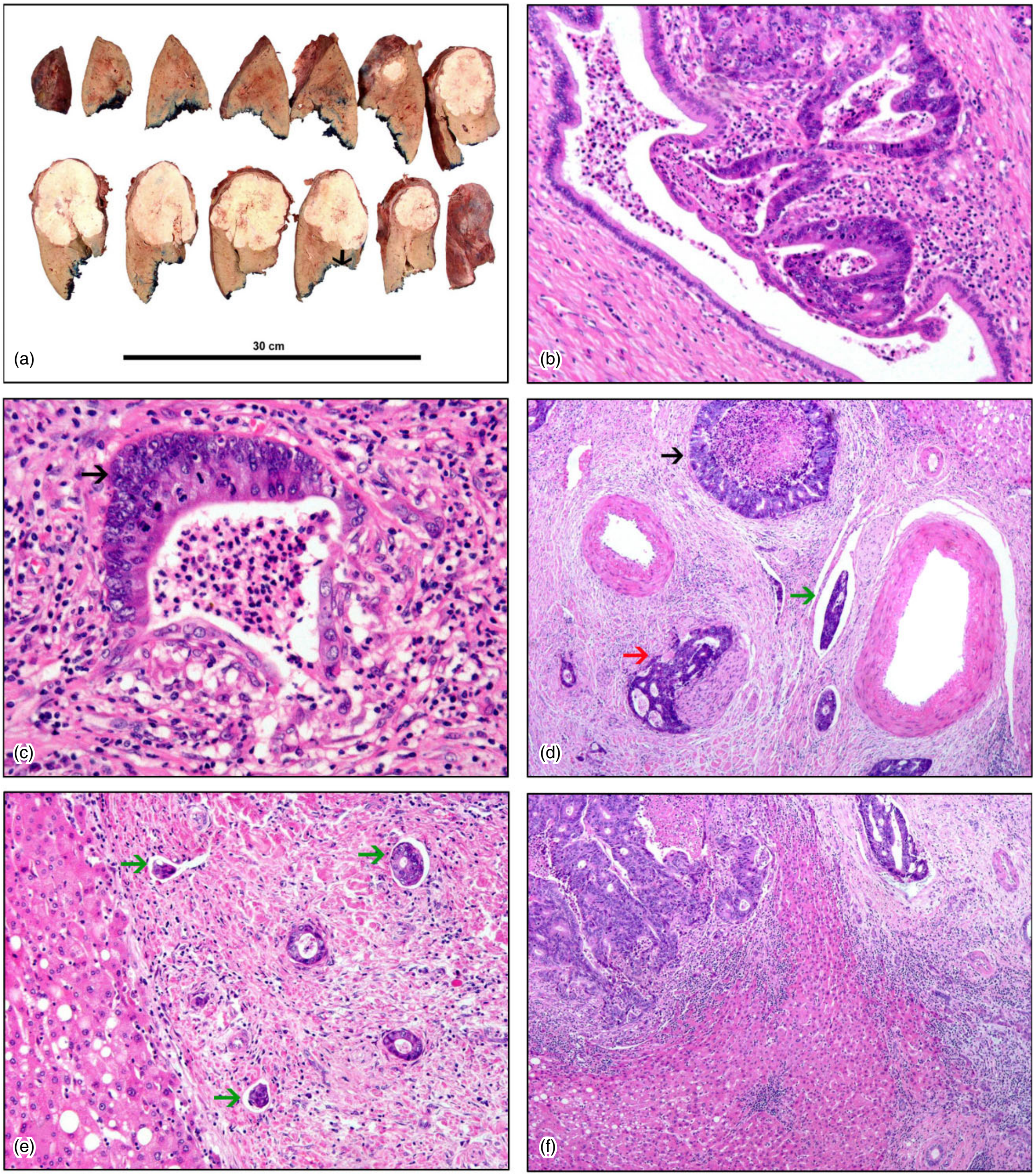


Figure 1 (a) Gross specimen of hepatic resection showing a single tumour nodule. The distance between the front of the tumour and the margin of excision is marked with an arrowhead. Histopathology shows: (b) early invasion of the biliary epithelium by metastatic adenocarcinoma; (c) invasion of the biliary epithelium of a medium-sized duct by metastatic adenocarcinoma (arrowhead); (d) complete replacement of the biliary epithelium by adenocarcinoma (black arrowhead) with perineural invasion (red arrowhead) and adenocarcinoma cells within vascular spaces (green arrowhead); (e) multiple lymphatic spaces containing metastatic adenocarcinoma cells (green arrowheads), and (f) metastatic adenocarcinoma within the lumen of a blood vessel (top right). [Haematoxylin and eosin stain; original magnification (b) ×20, (c) ×20, (d) ×10, (e) ×10, (f) ×10]

data. Categorical data were analysed using Pearson's chi-squared test. The Kaplan–Meier method was used to assess actuarial and disease-free survival. Univariate analysis was performed to assess for any significant difference in clinicopathological characteristics that influenced disease recurrence and survival following hepatic resection. Multivariate analysis was performed using Cox regression (stepwise forward model) for variables significant on univariate analysis. Statistical analyses were performed using SPSS for Windows Version 16.0 (SPSS, Inc., Chicago, IL, USA). Statistical significance was set at the 5% level.

Results

Patient demographics, surgical procedures and pathological data

During the study period, 261 patients underwent primary hepatic resection for CRLM. Two patients died postoperatively. Data for these two patients were removed from further analyses. Eleven patients underwent induction chemotherapy prior to liver resection. Two patients submitted to staged liver resections and three patients underwent portal vein embolization. A total of 138 (53.3%) patients developed recurrent disease; 95 of these patients died. The median length of follow-up in the remaining patients was 28 months (range: 12–96 months).

Prognostic factors influencing disease recurrence and overall survival

Multivariate analysis identified three independent predictors of disease-free survival (Table 1): tumour number; perineural invasion, and resection margin. The presence of perineural invasion was the only independent predictor of poorer overall survival on multivariate analysis (Table 2).

Impact of perineural invasion on survival

Patients with perineural invasion were found to have a significantly higher likelihood of lymphatic ($P < 0.001$), vascular ($P = 0.003$) or biliary ($P < 0.001$) invasion compared with patients who did not exhibit perineural invasion (Table 3). Patients with perineural invasion were more likely to undergo a hemi-hepatectomy or more radical resection ($P = 0.029$).

Median disease-free and overall survival in patients with perineural invasion were 12 months and 21 months, respectively. Five-year disease-free survival in patients without perineural invasion was 43.1% ($P = 0.009$) (Fig. 2). Five-year overall survival in patients without perineural invasion was 48.0% ($P < 0.001$) (Fig. 3). None of the patients with perineural invasion survived to 5 years.

Discussion

Hepatic resection for CRLM has consistently achieved good longterm disease-free and overall survival based on absence of recurrence[16,17] and thus offers outcomes that stand in stark contrast to those in patients with unresectable disease.[18] The present series demonstrates that tumour number, resection margin and perineural invasion significantly influenced outcome.

Number of metastases

Various studies have shown tumour number to significantly influence survival outcomes,[7,8,19] although other authors have not demonstrated this finding.[1,5,7,20] In the present series, patients with multiple metastases had poorer disease-free survival, but this variable did not influence overall survival. The fact that tumour number has been inconsistently identified suggests that other factors, such as tumour biology, may influence outcomes in CRLM patients depending on their tumour burden at presentation.

Resection margin

Some authors have observed that resection margin and margin width did not correlate significantly with survival following resection for CRLM,[21] whereas others have shown margin status to be a predictor of survival outcome.[22,23] A recent meta-analysis[24] demonstrated that a margin of ≥ 1 cm confers a survival benefit compared with a margin of < 1 cm. In the present cohort, tumour at the resection margin was a predictor of poorer disease-free survival, but not overall survival. These differences suggest that only a selected group of CRLM patients undergoing resection are influenced by an R0 margin, especially in the era of systemic chemotherapy, which represents an important avenue of treatment in the multimodal approach to therapy in these patients.[25–27]

Intrahepatic invasion

Few studies have investigated the incidence of intrahepatic invasion,[28–34] and the exact definitions, types and methods of detection in CRLM specimens have not been described. Sasaki *et al.*[32] defined portal vein, hepatic vein and bile duct invasion as cancer cells invading the lumen of an artery or vein or bile duct branches within the liver, and lymphatic invasion as cancer cells involving the luminal structures in the portal area lined by endothelial cells. Korita *et al.*[34] defined lymphatic invasion as the presence of tumour cells within vessels that showed immunoreactivity for D2-40 monoclonal antibody, but did not define other forms of intrahepatic invasion. By contrast, the present study defined vascular, biliary, lymphatic and perineural invasion, as well as the methods used to detect the presence of tumour cells in their respective channels.

A limited number of studies have assessed the influence of vascular invasion on outcomes in patients with CRLM.[27,29–31,34] Although improved survival has been observed in patients without portal vein invasion compared with patients with portal vein invasion,[35] the sample sizes referred to elsewhere were small, leading to significant heterogeneity.[27,29,31,32] Similarly, few studies have reported outcomes in patients with hepatic vein invasion in CRLM specimens,[29,31,32] the influence of which remains to be

Table 1 Statistical analysis of prognostic factors with respect to disease-free survival

Demographic, clinical and pathological factors	Survival, months, median (range)	Univariate analysis	Multivariate analysis	Risk ratio (95% CI)
Demographic factors		0.059		
Age				
<65 years (n = 82)	14 (3–82)			
≥65 years (n = 177)	18 (3–96)			
Gender		0.771		
Male (n = 166)	18 (3–96)			
Female (n = 93)	15 (3–84)			
Presentation		0.704		
Synchronous (n = 105)	18 (3–79)			
Metachronous (n = 154)	16 (3–96)			
Extent of surgery				
Less than hemi-hepatectomy (n = 136)	18 (3–84)	0.336		
Hemi-hepatectomy or more (n = 123)	15 (3–96)			
Pathological factors				
Largest tumour size		0.110		
<5 cm (n = 173)	18 (3–84)			
≥5 cm (n = 86)	14 (3–96)			
Number of metastases		0.002	0.018	0.655 (0.461–0.930)
Solitary (n = 127)	21 (3–96)			
Multiple (n = 132)	12 (3–84)			
Lymphatic invasion		0.942		
Positive (n = 42)	14 (3–96)			
Negative (n = 217)	17 (3–84)			
Vascular invasion		0.441		
Positive (n = 115)	15 (3–96)			
Negative (n = 144)	18 (3–84)			
Perineural invasion		0.009	0.007	2.346 (1.256–4.382)
Positive (n = 13)	6 (3–52)			
Negative (n = 246)	18 (3–96)			
Biliary invasion		0.451		
Positive (n = 94)	18 (3–96)			
Negative (n = 165)	16 (3–84)			
Resection margin (R0)		0.002	0.018	0.618 (0.414–0.922)
R0 (n = 205)	18 (3–96)			
R1 (n = 54)	10 (3–69)			

95% CI, 95% confidence interval

determined.[35] A recent meta-analysis of five studies that assessed outcomes in CRLM patients with biliary invasion[29,31–33,36] showed no correlation between the presence of biliary invasion and overall survival.[35] A meta-analysis of two studies evaluating the impact of lymphatic invasion on outcomes in CRLM patients[32,34] demonstrated lymphatic invasion to be associated with significantly poorer survival.[35] In the present study, vascular, lymphatic and biliary invasion in CRLM patients did not significantly influence survival outcome. Similarly, Bockhorn *et al.*[37] observed that the presence of vascular invasion or lymphatic infiltration in isolation did not significantly influence survival, but the presence of both in combination resulted in significantly poorer survival than in patients without vascular and lymphatic invasion.

Perineural invasion

Leibig *et al.*[38] showed perineural infiltration to be a predictor of survival in patients undergoing surgery for colorectal cancer. Although perineural invasion has been observed in 12–17% of

Table 2 Statistical analysis of prognostic factors with respect to overall survival

Demographic, clinical and pathological factors	Survival, months, median (range)	Univariate analysis	Multivariate analysis	Risk ratio (95% CI)
Demographic factors		0.718		
Age				
<65 years (*n* = 82)	24 (5–82)			
≥65 years (*n* = 177)	27 (4–96)			
Gender		0.709		
Male (*n* = 166)	25 (4–96)			
Female (*n* = 93)	27 (4–84)			
Presentation		0.964		
Synchronous (*n* = 105)	28 (7–79)			
Metachronous (*n* = 154)	25 (4–96)			
Extent of surgery				
Less than hemi-hepatectomy (*n* = 136)	24 (7–84)	0.021	0.119	1.410 (0.916–2.170)
Hemi-hepatectomy or more (*n* = 123)	27 (4–96)			
Pathological factors				
Largest tumour size		0.263		
<5 cm (*n* = 173)	27 (9–84)			
≥5 cm (*n* = 86)	24 (4–96)			
Number of metastases		0.024	0.103	0.705 (0.463–1.073)
Solitary (*n* = 127)	27 (4–96)			
Multiple (*n* = 132)	25 (6–84)			
Lymphatic invasion		0.730		
Positive (*n* = 42)	24 (4–96)			
Negative (*n* = 217)	25 (4–84)			
Vascular invasion		0.612		
Positive (*n* = 115)	24 (4–96)			
Negative (*n* = 144)	28 (5–84)			
Perineural invasion		<0.001	<0.001	3.152 (1.636–6.074)
Positive (*n* = 13)	19 (6–56)			
Negative (*n* = 246)	26 (4–96)			
Biliary invasion		0.901		
Positive (*n* = 94)	24 (4–96)			
Negative (*n* = 165)	26 (4–84)			
Resection margin (R0)		0.087		
R0 (*n* = 205)	27 (4–96)			
R1 (*n* = 54)	20 (4–69)			

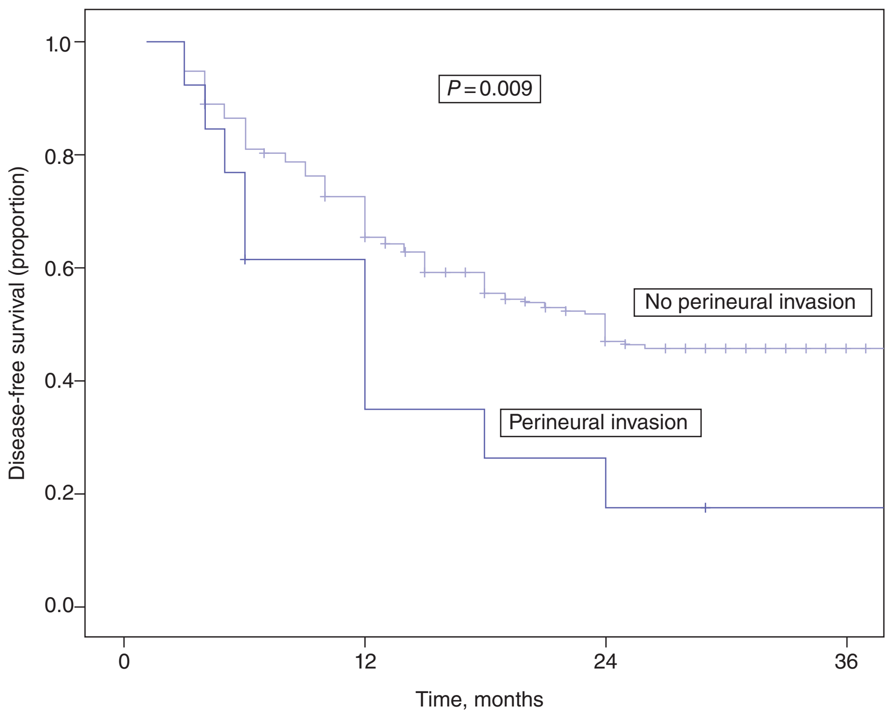
95% CI, 95% confidence interval

patients undergoing hepatic resection for CRLM,[28,29,33] it has been reported not to significantly influence survival.[28,33] In the present cohort, 5% of patients had perineural invasion and achieved significantly poorer disease-free and overall survival. In addition, the presence of perineural invasion was significantly associated with lymphatic, vascular and biliary invasion. These results demonstrate that this subgroup of patients is more likely to have aggressive tumour biology resulting in intrahepatic invasion of the tumour. This may account for the significantly higher number of major liver resections required to achieve clear margins in this group of patients.

Although it was retrospective in nature, the present study defined each histopathological feature of intrahepatic invasion and the methods used for its detection. The presence of perineural invasion following resection of CRLM was an independent predictor of a poorer outcome. The association of perineural invasion with other features of intrahepatic invasion is likely to reflect more aggressive disease and hence a poorer outcome.

Table 3 Demographic, clinical and pathological factors in patients with and without perineural invasion

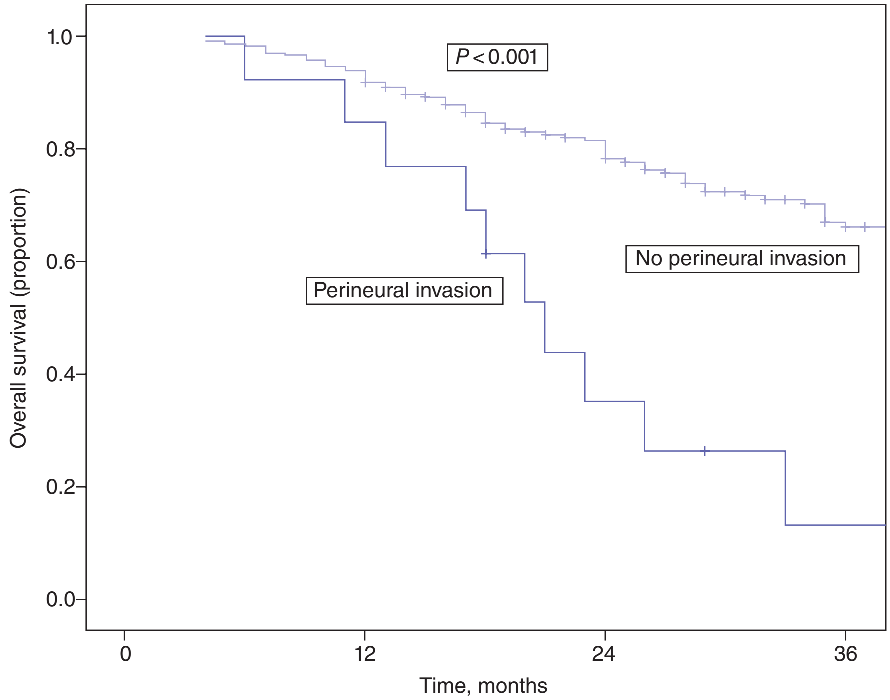
Demographic, clinical and pathological factors	Patients with perineural invasion (*n* = 13), *n*	Patients without perineural invasion (*n* = 246), *n*	*P*-value
Demographic factors			
Age ≥65 years	6	171	0.078
Male gender	9	157	0.692
Synchronous presentation	3	102	0.188
Extent of surgery			
Hemi-hepatectomy or more	10	113	0.029
Pathological factors			
Largest tumour size ≥5 cm	7	79	0.105
Solitary hepatic metastases	4	123	0.172
Lymphatic invasion	7	35	<0.001
Vascular invasion	11	104	0.003
Biliary invasion	11	83	<0.001
Resection margin	12	193	0.231



Numbers at risk

Time, months	0	12	36
Patients with perineural invasion (*n* = 13)	13	7	1
Patients without perineural invasion (*n* = 246)	246	175	51

Figure 2 Disease-free survival in patients with and without perineural invasion



Numbers at risk

Time, months	0	12	36
Patients with perineural invasion (*n* = 13)	13	11	1
Patients without perineural invasion (*n* = 246)	246	231	82

Figure 3 Overall survival in patients with and without perineural invasion

Conflicts of interest

None declared.

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