Original article

Treatment of recurrent intrahepatic cholangiocarcinoma

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Background: **The aims of this study were to evaluate risk factors for recurrence following hepatectomy with curative intent for intrahepatic cholangiocarcinoma (ICC), and predictors of survival after intrahepatic recurrence.**

Methods: **All patients with ICC who underwent liver resection between January 1997 and August 2011 in a single centre were analysed retrospectively. Clinicopathological factors likely to influence recurrence and postrecurrence survival were assessed by univariable and multivariable analysis.**

Results: **A total of 87 patients were analysed. R0 resection was achieved in 65 patients (75 per cent). Eighty-three patients survived more than 1 month after resection. Median survival was 33 months, with 1-, 3- and 5-year actuarial survival rates of 79, 47 and 31 per cent respectively. Recurrence occurred in 45 (54 per cent) of the 83 patients, most frequently in the liver (25 patients). Satellite nodules (odds ratio (OR) 8·17, 95 per cent confidence interval 1·38 to 48·53; $P = 0·021$), hilar lymph node metastases (OR 5·24, 1·07 to 25·75; $P = 0·041$) and perineural invasion (OR 9·68, 1·07 to 87·54; $P = 0·043$) were identified as independent risk factors for recurrence. Repeat hepatectomy ($P = 0·003$) and intra-arterial yttrium-90 radiotherapy ($P = 0·048$) were associated with longer survival after intrahepatic recurrence.**

Conclusion: **Satellite nodules, hilar lymph node metastases and perineural invasion are risk factors for recurrence following resection with curative intent for ICC. Repeat hepatectomy and labelled yttrium-90 radiotherapy may improve survival after intrahepatic recurrence.**

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Introduction

Intrahepatic cholangiocarcinoma (ICC) is a rare malignant liver tumour that accounts for 5–10 per cent of primary liver carcinomas[1]. In recent years, the incidence of ICC has increased significantly in Western countries[2,3]. Resection remains the only potentially curative treatment for these tumours, whilst chemotherapy can achieve a partial response or stabilize the disease in patients with unresectable disease[4,5]. As there are no specific early symptoms for ICC, it is usually diagnosed at an advanced stage when surgery is difficult or impossible. This accounts for the wide range in resectability rates (19–74 per cent) and the high incidence of recurrence[6,7].

Recurrence occurs most often during the first year after liver resection, most frequently in the remnant liver[8]. Ercolani and colleagues[9] showed recently that aggressive multimodal treatment of ICC and its recurrence is associated with a 5-year survival rate of 48 per cent. An increased understanding of risk factors for recurrence is therefore essential to permit early diagnosis at a stage when repeat hepatectomy or other treatments are still possible[10]. For several years, the present authors have taken an aggressive stance on the treatment of primary ICC, including extended hepatectomy and *ex situ* liver resection. A similarly aggressive approach to hepatic and localized recurrence has been adopted, combining repeat resection with intra-arterial yttrium-90 radiotherapy, with or without systemic chemotherapy.

The aim of this study was to retrospectively analyse outcomes after primary liver resection for ICC, specifically considering risk factors for recurrence. In addition, the study aimed to identify factors that may improve survival after recurrence, with particular focus on intrahepatic recurrence.

Methods

A retrospective analysis was undertaken of all partial hepatectomies for ICC performed with curative intent at a tertiary hepatobiliary surgery referral centre between 1 January 1997 and 31 August 2011. Only mass-forming type ICCs, as defined by the Liver Cancer Study Group of Japan[11], were included and analysed. Patients with hilar bile duct cholangiocarcinoma, periductal infiltrating type, intraductal growth type cholangiocarcinoma and gallbladder carcinoma were excluded, as were patients with ICC who underwent orthotopic liver transplantation.

Data were collected on demographics (age, sex, body mass index (BMI)), postoperative chemotherapy, surgical variables, length of hospital stay, morbidity, and follow-up including disease recurrence and death. Liver failure was defined by the '50–50' criteria on postoperative day 5 (serum bilirubin level above 50 μmol/l and prothrombin time less than 50 per cent)[12]. Perioperative mortality was defined as death during the initial hospital stay or within 30 days of surgery if the patient had been discharged. The study was approved by the institutional review board.

Surgery

All liver resections were performed as open procedures by senior hepatic surgeons. Resections were categorized according to the International Hepato-Pancreato-Biliary Association classification for liver resections (Brisbane 2000)[13]: resection of two, three or four, or five or more segments was defined as minor, major and extended hepatectomy respectively. *Ex situ* liver resection was performed occasionally, if deemed necessary.

Macroscopically radical hepatectomy (R0 and R1) was defined as absence of peritoneal extension, absence of bulky lymph nodes in the coeliac or para-aortic area, and absence of tumour residue in the remnant liver.

Follow-up protocol

After resection, all patients were followed up every 3 months by clinical examination and computed tomography for the first 2 years, and every 6 months thereafter. Follow-up data were obtained at routine clinic visits, or via personal contact. The end of follow-up was set between 1 August 2011 and 1 November 2011, or at time of death.

Recurrence

When recurrence of ICC was diagnosed, the treatment strategy was agreed by a multidisciplinary team comprising a liver surgeon, radiologist and oncologist. Patients with general recurrence received systemic chemotherapy. The drug regimen for chemotherapy was gemcitabine or gemcitabine plus oxaliplatin (GEMOX) when applicable. For intrahepatic or localized recurrences, the feasibility of repeat hepatectomy was evaluated first. For unresectable intrahepatic recurrences, labelled yttrium-90 radiotherapy or systemic chemotherapy, or a combination of both treatments, was indicated if the patient's general status allowed this.

The regimen of yttrium-90 radiotherapy (a pure β emitter that does not require isolation after treatment) consisted of two stages of arteriography[14]. The first stage was performed to achieve mapping of the hepatic artery, to embolize extrahepatic branches of the hepatic artery, and to inject ^{99m}Tc-labelled albumin macroaggregates in order to quantify hepatopulmonary shunts. In the second stage, a single injection of yttrium-90 (TheraSphere®; MDS Nordion, Ottawa, Canada) was given in a dose of 120 ± 20 Gy (1 GBq corresponds to 50 Gy for a target mass of 1 kg)[15]. The correct dose for the target volume was calculated according to the individual body surface area, and adjusted to tumour volume and lung shunting fraction.

Statistical analysis

Eighteen factors with a possible influence on recurrence after partial hepatic resection with curative intent for ICC were tested in univariable analysis and, if appropriate, in multivariable analysis. Quantitative variables are expressed as mean(s.d.) or median, and compared using Student's *t* test or the Wilcoxon test, as appropriate. Qualitative variables are expressed as numbers with percentages, and compared with the χ^2 or Fisher's exact test, as appropriate. All variables with $P < 0{\cdot}100$ on univariable analysis, as well as variables believed to influence recurrence, were studied in a multiple logistic regression model. $P < 0{\cdot}050$ was considered statistically significant. R statistical software version 2.15.1 (http://www.r-project.org/) was used.

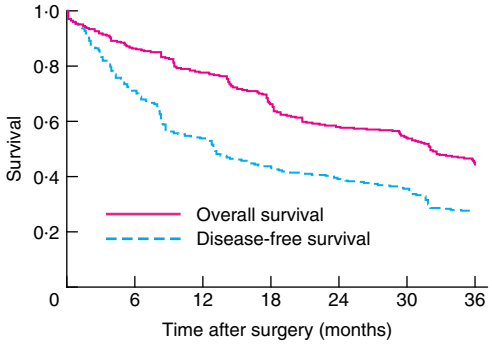
Cumulative survival rates were estimated by the Kaplan–Meier method. Overall survival was calculated from the day of surgery to the date of death or end of follow-up. Disease-free survival was calculated using the date of death or recurrence as the time of the terminal event. Survival after recurrence was calculated from the date of recurrence to the date of death or end of follow-up. Survival curves were compared with the log rank test.

Results

Demographic and operative data

During the study period, 87 patients underwent liver resection with curative intent for ICC (68 men and

19 women). Mean age at the time of resection was 66(9) years. Hepatectomies were classified as minor, major or extended in 21 (24 per cent), 47 (54 per cent) and 19 (22 per cent) patients respectively. No patient had hilar invasion or needed to undergo biliary or vascular resection. One patient had an *ex situ* liver resection for a large tumour invading the three hepatic veins. Left extended hepatectomy was performed with reconstruction of the right hepatic vein followed by autotransplantation of the remaining segments, VI and VII. Complete tumour removal (R0 resection) was achieved in 65 patients (75 per cent). Perioperative mortality and morbidity rates were 5 per cent (4 patients) and 48 per cent (42) respectively. The most frequent complications were bile leaks (17 patients, 20 per cent), infectious complications including pneumonia (14 patients, 16 per cent) and liver failure (9 patients, 10 per cent). Mean duration of hospital stay was 16(15) (median 11, range 5–91) days.



No. at risk

Overall survival	87	74	66	52	41	35	28
Disease-free survival	87	61	46	34	30	24	18

Fig. 1 Overall and disease-free survival after partial liver resection with curative intent for intrahepatic cholangiocarcinoma

Survival and recurrence rates

All 87 patients were included in the survival analysis. Mean follow-up was 30(27) (range 0–145) months. Overall median survival was 33 months, with 1-, 3- and 5-year actuarial survival rates of 79, 47 and 31 per cent respectively. Median disease-free survival was 13 months, with 1-, 3- and 5-year actuarial survival rates of 54, 28 and 19 per cent respectively (*Fig. 1*). The patient who

Table 1 Univariable and multivariable analysis of clinicopathological factors and recurrence of intrahepatic cholangiocarcinoma following partial hepatectomy with curative intent

	Recurrence*			Multivariable analysis	
	Yes ($n = 45$)	No ($n = 38$)	P‡	Odds ratio†	P¶
Sex ratio (F : M)	9 : 36	9 : 29	0·890	1·33 (0·34, 5·12)	0·683
Age (years)			0·143	0·40 (0·09, 1·78)	0·228
≥ 60	32 (71)	33 (87)			
< 60	13 (29)	5 (13)			
Body mass index (kg/m^2)			0·948		
≥ 25	31 (69)	25 (66)			
< 25	14 (31)	13 (34)			
Clinical symptoms	34 (76)	28 (74)	0·954		
Portal vein embolization	5 (11)	4 (11)	1·000§		
Neoadjuvant chemotherapy	4 (9)	7 (18)	0·342		
Pedicular clamping (Pringle)	38 (84)	33 (87)	0·997		
Blood transfusion	14 (31)	10 (26)	0·813		
Major hepatectomy	37 (82)	26 (68)	0·227		
Postoperative morbidity	24 (53)	14 (37)	0·200		
Tumour size > 5 cm	31 (69)	25 (66)	0·948	0·64 (0·19, 2·13)	0·467
Satellite nodules	12 (27)	2 (5)	0·021	8·17 (1·38, 48·53)	0·021
Microvascular invasion	20 (44)	11 (29)	0·220		
Perineural infiltration	13 (29)	1 (3)	0·004	9·68 (1·07, 87·54)	0·043
Positive hilar lymph node	13 (29)	3 (8)	0·033	5·24 (1·07, 25·75)	0·041
Macrovascular invasion	7 (16)	3 (8)	0·332§		
Complete tumour resection			0·775		
R0	32 (71)	29 (76)			
R1	13 (29)	9 (24)			
Adjuvant chemotherapy	7 (16)	3 (8)	0·332	3·34 (0·68, 16·40)	0·138

Values in parentheses are *percentages and †95 per cent confidence intervals. ‡χ^2 test, except §Fisher's exact test; ¶multiple logistic regression analysis.

Table 2 Clinicopathological factors and 3-year survival after recurrence of intrahepatic cholangiocarcinoma following partial hepatectomy with curative intent

	3-year survival after recurrence		
	Yes ($n = 5$)	No ($n = 40$)	P*
Sex ratio (F : M)	0 : 5	9 : 31	0·566
Age (years)			0·617
≥ 60	3 (60)	29 (73)	
< 60	2 (40)	11 (28)	
Body mass index (kg/m^2)			0·166
≥ 25	2 (40)	29 (73)	
< 25	3 (60)	11 (28)	
Major hepatectomy	3 (60)	34 (85)	0·211
Tumour size > 5 cm	1 (20)	30 (75)	0·027
Satellite nodules	0 (0)	12 (30)	0·303
Microvascular invasion	2 (40)	18 (45)	1·000
Perineural infiltration	3 (60)	10 (25)	0·136
Positive hilar lymph node	1 (20)	12 (30)	1·000
R1 resection	2 (40)	11 (28)	0·617
Adjuvant chemotherapy	1 (20)	6 (15)	0·571
Haemochromatosis	1 (20)	7 (18)	1·000
Cirrhosis	0 (0)	13 (33)	0·301
Cirrhosis and/or haemochromatosis	1 (20)	18 (45)	0·378
Surgery for recurrence	4 (80)	3 (8)	0·001
Chemotherapy for recurrence	2 (40)	20 (50)	1·000
Yttrium-90	2 (40)	4 (10)	0·125

Values in parentheses are percentages. *Fisher's exact test.

underwent *ex vivo* extended hepatectomy was still alive after 20 months of follow-up.

Recurrence occurred in 45 (54 per cent) of the 83 patients who were still alive after the postoperative period. Median time to recurrence was 8 (range 1–54) months. Patients with recurrence were divided into three groups: liver only (25 patients); localized extrahepatic (2 patients: 1 adrenal and 1 peritoneal metastasis); and general (including general lymph node, lung and bone metastases, either associated or not associated with intrahepatic localization; 18 patients). In the latter group of 18 patients, five had liver metastases (liver and lung metastases, 2; liver and distant lymph node metastases, 2; liver metastases associated with multicentric spread of secondaries, 1) and the remaining 13 patients had extrahepatic metastases only (diffuse lymph node metastases alone, 7; lymph node and lung metastases, 3; lymph node and bone metastases, 1; lymph node metastasis and diffuse spread, 2). Median survival after recurrence was 13 (range 0–115) months.

Risk factors for recurrence

Of the 18 variables assessed by univariable analysis, intrahepatic satellite nodules ($P = 0·021$), lymph node metastases in the hepatoduodenal ligament ($P = 0·033$) and perineural invasion ($P = 0·004$) were significantly related to recurrence (*Table 1*). On multivariable analysis,

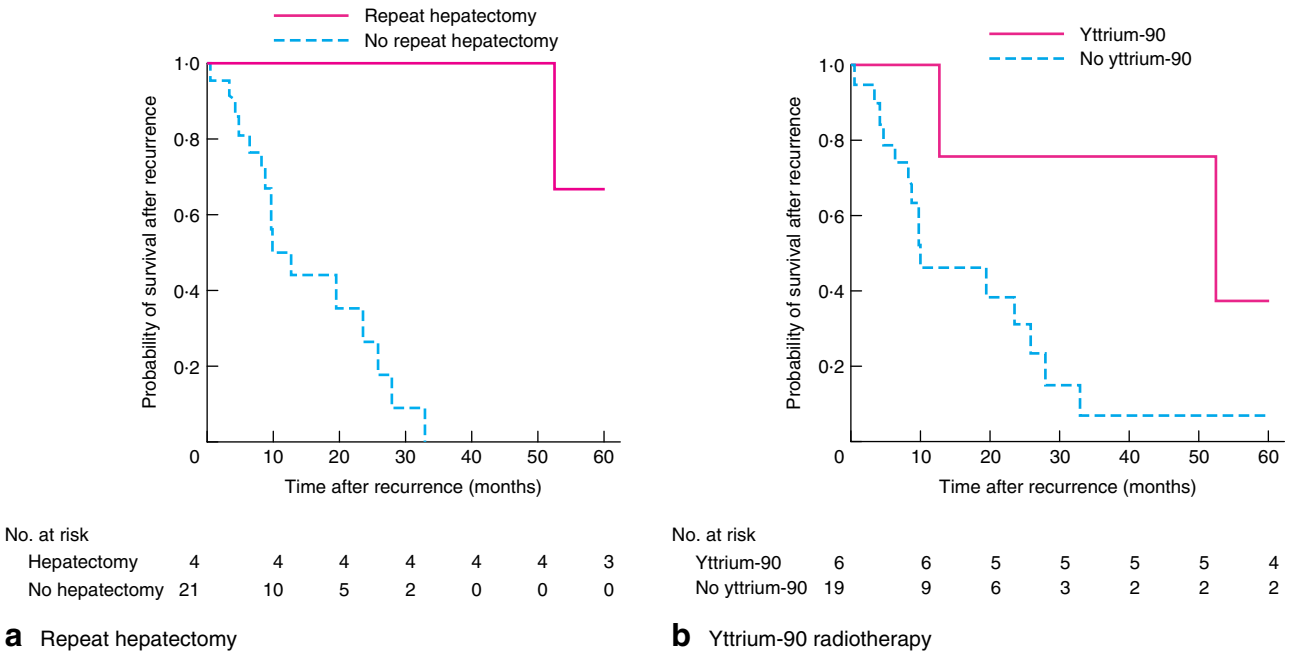


Fig. 2 Survival after intrahepatic recurrence following partial liver resection with curative intent for intrahepatic cholangiocarcinoma, according to **a** repeat hepatectomy or **b** use of labelled intra-arterial yttrium-90 radiotherapy. **a** $P = 0·003$, **b** $P = 0·048$ (log rank test)

intrahepatic satellite nodules (odds ratio (OR) 8·17, 95 per cent confidence interval 1·38 to 48·53; $P = 0·021$), perineural invasion (OR 9·68, 1·07 to 87·54; $P = 0·043$) and lymph node metastases (OR 5·24, 1·07 to 25·75; $P = 0·041$) remained significant independent risk factors for recurrence.

Factors influencing survival after recurrence

In univariable analysis, primary tumour size of 5 cm or less ($P = 0·027$) and resection if possible ($P = 0·001$) were significantly associated with increased 3-year survival after recurrence (*Table 2*).

Factors influencing survival after intrahepatic recurrence

Of the 25 patients who had intrahepatic recurrence only, 11 had no treatment and 14 underwent systemic chemotherapy, repeat hepatectomy, yttrium-90 radiotherapy, or a combination of these three treatments. Univariable analysis showed that repeat hepatectomy ($P = 0·003$) and yttrium-90 radiotherapy ($P = 0·048$) were significantly associated with increased survival rate after recurrence (*Fig. 2*). The effect of postrecurrence chemotherapy was not statistically significant ($P = 0·350$).

Discussion

Despite partial hepatectomy with curative intent, ICC is still associated with poor prognosis owing to a high rate of recurrence, especially during the first year after liver resection[1,8]. This study of 87 patients who underwent potentially curative liver resection showed that recurrence occurred in half of the patients, frequently during the first year and usually only in the remnant liver. If recurrence was isolated (hepatic, adrenal or peritoneal), repeat surgery was associated with significantly improved survival. Moreover, patients with unresectable recurrence who underwent intra-arterial yttrium-90 radiotherapy had better survival than patients who received chemotherapy, a finding that has not been reported to date.

Primary hepatectomy should be performed with curative intent, and extensive surgery is justified in ICC. However, long-term overall and recurrence-free survival remain disappointing[8,16], and an improved understanding of risk factors for recurrence is necessary to identify high-risk individuals. Lymph node metastases have previously been reported as almost universally associated with early recurrence following surgery for ICC[17,18], a finding recently confirmed by the Association Française de Chirurgie – Intrahépatic Cholangiocarcinoma (AFC-IHCC) 2009 study group[19]. The results of the present study were in line with recent reports[20,21], and showed that satellite nodules and perineural invasion are also independent risk factors for recurrence. These data strongly suggest that lymphadenectomy should always be performed to ensure correct staging, and that patients at higher risk of recurrence should be monitored closely to detect recurrence early enough for resection to be possible. Moreover, for this high risk group it would seem beneficial to provide preventive chemotherapy after curative hepatectomy. A prospective study of this approach (ClinicalTrials.gov identifier NCT0113377) is currently ongoing, with the aim to reduce the relapse rate.

No clear management strategy is currently available if recurrence occurs, especially for patients with localized intrahepatic ICC recurrence. Few studies have evaluated the impact of aggressive treatment such as repeat hepatectomy, radiofrequency ablation or chemotherapy on survival following recurrence of ICC[22–24]. Consistent with these preliminary data, the present analysis shows that repeat hepatectomy for intrahepatic recurrence may improve patient survival. In this series, one patient who underwent repeat hepatectomy with chemotherapy after surgery was still alive 115 months after recurrence. However, repeat liver resection should be carried out only if it is possible to leave sufficient parenchyma and perform macroscopic curative resection.

For patients who have unresectable recurrent disease in the liver, transarterial radioembolization using yttrium-90 permits the delivery of a high radiation dose to the target tumour and a low radiation dose to adjacent parenchyma. Yttrium-90 radioembolization has been used primarily in patients with unresectable hepatocellular carcinoma (HCC)[25,26]. Sangro *et al.*[27] recently demonstrated that yttrium-90 radioembolization was associated with increased survival in patients with HCC. One advantage of arterial radioembolization is the fact that cancer cells are supplied preferentially by arterial blood, whereas healthy hepatocytes receive primarily portal venous blood. Moreover, yttrium-90 can be used in patients with large lesions or portal vein thrombosis. Regarding ICC, yttrium-90 has been used only for unresectable primary tumours[28,29]. Saxena and co-workers[29] reported a partial response or stabilization of disease in 74 per cent of treated patients and concluded that yttrium-90 was a safe and efficacious treatment. Yttrium-90 can also be used to downstage tumours before curative resection[30]. In the present study, only a small number of patients were included, but the analysis showed the effectiveness of yttrium-90 for intrahepatic recurrence of ICC, and a

significant increase in survival was observed in this setting. Yttrium-90 may therefore represent a new weapon in the treatment of intrahepatic ICC recurrence. Of course, these results are based on only a small sample size and further investigations in future studies are needed. Equally, it must be kept in mind that, despite the systematic follow-up protocol, small recurrences (notably those that were not indicated before surgery by cancer antigen 19-9) may have remained undetected, creating a bias.

These results confirm that the factors exerting the greatest influence on risk of recurrence after liver resection for ICC are hilar lymph node metastasis, perineural invasion and intrahepatic satellite nodules. The presence of these factors can be used to define a high-risk group of patients in whom closer monitoring is warranted. In selected patients with intrahepatic recurrence, aggressive multimodal management including repeat hepatectomy and/or yttrium-90 radiotherapy, with or without systemic chemotherapy, may prolong patient survival.

Disclosure

The authors declare no conflict of interest.

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Snapshot Quiz

Answer

Snapshot Quiz 12/21

Adenocarcinoma. Histopathological assessment identified an ulcerated dermal nodule comprising moderately differentiated adenocarcinoma. Immunohistochemistry confirmed cutaneous metastasis from the rectosigmoid primary. Cutaneous metastases from colorectal tumours are rare and suggest disseminated disease. Unresolving skin lesions after cancer treatment merit a high index of suspicion; early specialist referral, wide excision biopsy and multidisciplinary discussion are indicated.