Original article

Early *versus* late recurrence of intrahepatic cholangiocarcinoma after resection with curative intent

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Background: **The objective of this study was to investigate the characteristics, treatment and prognosis of early *versus* late recurrence of intrahepatic cholangiocarcinoma (ICC) after hepatic resection.**

Methods: **Patients who underwent resection with curative intent for ICC were identified from a multi-institutional database. Data on clinicopathological characteristics, initial operative details, timing and sites of recurrence, recurrence management and long-term outcomes were analysed.**

Results: **A total of 933 patients were included. With a median follow-up of 22 months, 685 patients (73·4 per cent) experienced recurrence of ICC; 406 of these (59·3 per cent) developed only intrahepatic disease recurrence. The optimal cutoff value to differentiate early (540 patients, 78·8 per cent) *versus* late (145, 21·2 per cent) recurrence was defined as 24 months. Patients with early recurrence had extrahepatic disease more often (44·1 per cent *versus* 28·3 per cent in those with late recurrence; $P < 0·001$), whereas late recurrence was more often only intrahepatic (71·7 per cent *versus* 55·9 per cent for early recurrence; $P < 0·001$). From time of recurrence, overall survival was worse among patients who had early *versus* late recurrence (median 10 *versus* 18 months respectively; $P = 0·029$). In multivariable analysis, tumour characteristics including tumour size, number of lesions and satellite lesions were associated with an increased risk of early intrahepatic recurrence. In contrast, only the presence of liver cirrhosis was independently associated with an increased likelihood of late intrahepatic recurrence (hazard ratio 1·99, 95 per cent c.i. 1·11 to 3·56; $P = 0·019$).**

Conclusion: **Early and late recurrence after curative resection for ICC are associated with different risk factors and prognosis. Data on the timing of recurrence may inform decisions about the degree of postoperative surveillance, as well as help counsel patients with regard to their risk of recurrence.**

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Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver tumour after hepatocellular carcinoma (HCC), accounting for 10–15 per cent of all primary liver cancers[1,2]. Although relatively rare, ICC is a fatal malignancy, which often has a more aggressive tumour biology than HCC[3]. In fact, among patients who present with advanced and/or metastatic disease, the overall 5-year survival rate is dismal at just 5–10 per cent[4]. For the 20–40 per cent of patients with ICC who present with operable disease, surgical resection remains the only potentially curative treatment option for ICC[5,6]. Even after resection with curative intent, the 5-year survival rate is still only

20–35 per cent[4,7]. The main reason for the poor long-term oncological outcomes relates to the incidence of recurrence, which can be as high as 54–71 per cent[7–9].

Several studies have investigated the risk factors, as well as the management, associated with recurrent ICC after resection with curative intent[7–9]. The risk of recurrence has generally been associated with biological factors indicative of tumour aggressiveness, as well as technical factors such as a positive surgical margin[7–9]. In addition, similar to HCC, the majority of ICC recurrences after hepatic resection occur in the liver remnant[7,8,10]. In patients with HCC, the aetiology of recurrences has been attributed to either intrahepatic metastasis from the initial tumour or a *de novo* tumour[10,11]. In clinical practice, the differentiation between a recurrence and development of a *de novo* tumour can be challenging and relies largely on genetic or molecular studies of the clonal origin of the tumours[12,13]. Early recurrence after resection of HCC has been associated with certain tumour pathological characteristics, whereas late recurrence has been related to underlying liver disease[14–17]. In turn, early recurrence is more likely to be 'recurrent' disease, whereas late recurrence is more often a representation of a metachronous second primary lesion[14–17].

Although early *versus* late recurrence has been examined extensively among patients with HCC, the topic has been poorly studied in those with ICC. Data on risk factors, patterns of recurrence, and outcomes in patients with early *versus* late recurrence may have important implications for postoperative surveillance and adjuvant therapy, as well as management of the recurrence[10,17]. The objective of the present study was to define the risk factors, treatment and prognosis of patients with early *versus* late recurrence of ICC after surgery with curative intent. In addition, the implications of early *versus* late recurrence on long-term outcomes among patients with ICC were characterized.

Methods

Patients undergoing hepatic resection with curative intent for ICC from 1990 to 2016 at one of 14 major hepatobiliary centres in North America, Europe, Australia and Asia were included in the study. Patients with extrahepatic metastasis at the time of surgery and those undergoing palliative resection, ablation only or intra-arterial therapy only were excluded. Additionally, patients who were lost to follow-up, those who did not have detailed information regarding site of recurrence, and patients who died within 30 days of surgery were excluded. All patients were diagnosed with histologically confirmed ICC. The Institutional Review Boards of each participating institution approved the study.

Data collection and follow-up

Demographic and clinicopathological variables were collected for each patient. Liver cirrhosis was diagnosed based on histological examination of pathological specimens. Tumour size, number and morphology, vascular, perineural, biliary and adjacent organ invasion, lymph node metastasis and histological grade were also documented based on final pathology reports. Data on tumour stage were collected according to the AJCC seventh edition staging system[18]. Patients were followed regularly after surgery with assessment of serum carbohydrate antigen 19-9, carcinoembryonic antigen levels, and abdominal CT or MRI.

Recurrence was defined as suspicious imaging findings or biopsy-proven tumour. Sites of recurrence were categorized as intrahepatic, extrahepatic, or both intrahepatic and extrahepatic. Overall survival (OS) and recurrence-free survival were calculated from the date of surgery. OS after the first recurrence was calculated from the date of recurrence and was used to compare the outcome of patients with early and late recurrence.

Treatment of recurrence

When tumour recurrence was diagnosed, the therapeutic strategy was evaluated based on tumour location, number of tumours, general patient condition and liver function. Treatment with curative intent, including surgical re-resection, ablation or both, was considered for patients with only intrahepatic recurrence. Other treatments were individualized for patients with advanced recurrent disease, and included intra-arterial therapy, chemotherapy and radiotherapy, depending on disease extent and the patient's performance status.

Statistical analysis

Continuous variables are expressed as median (i.q.r.) and compared with Student's *t* test or the Mann–Whitney *U* test. Categorical variables are expressed as numbers and percentages, and compared with the χ^2 test or Fisher's exact test. Kaplan–Meier curves with log rank tests were used to compare survival. Univariable and multivariable logistic regression models were used to determine factors associated with 'any site' and intrahepatic-only recurrence. Hazard ratios (HRs) and 95 per cent confidence intervals were estimated by means of multivariable analysis. Variables with a *P* value of less than 0·100 in univariable analysis were entered into the multivariable model. A two-tailed *P* value greater than 0·050 was considered statistically significant. Statistical analysis was performed using SPSS® 22.0 (IBM, Armonk, New York, USA).

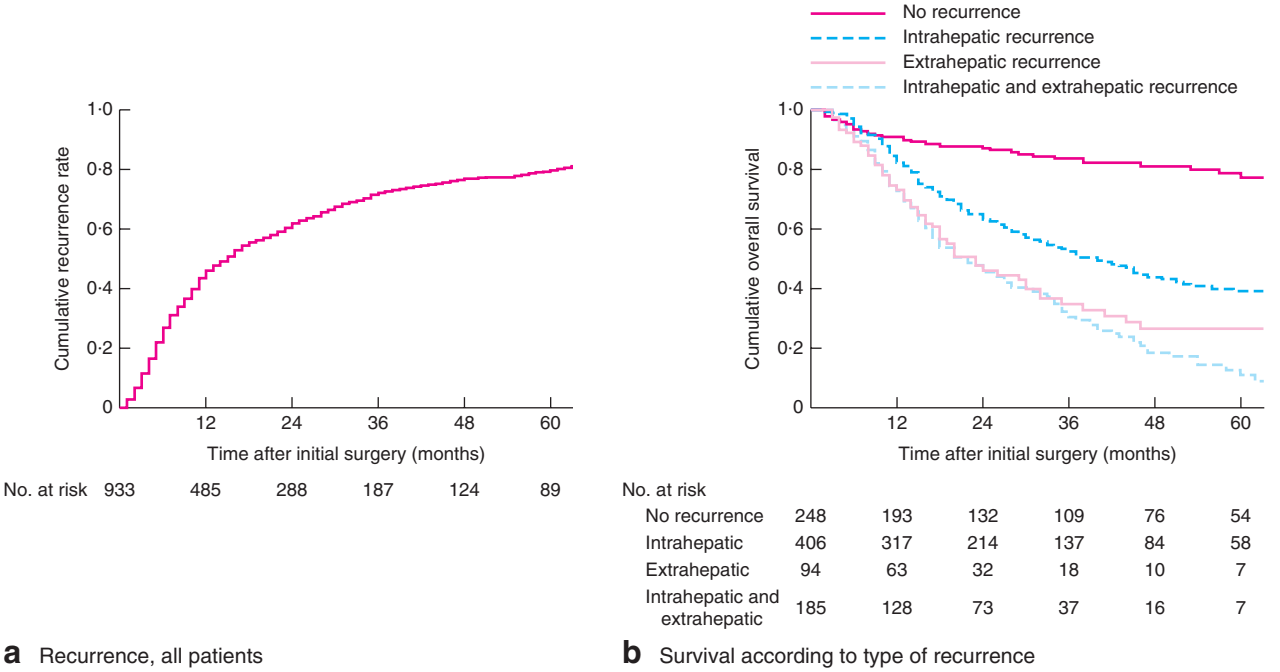

Fig. 1 **a** Cumulative recurrence among patients with intrahepatic cholangiocarcinoma (ICC) who underwent surgery with curative intent. **b** Overall survival of patients according to type of recurrence after initial surgery for ICC. $P < 0{\cdot}001$ (log rank test)

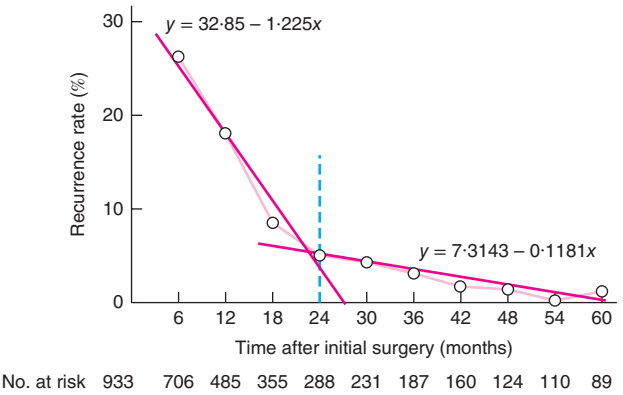

Fig. 2 Determination of the optimal cutoff value for early and late recurrence of intrahepatic cholangiocarcinoma (ICC). Recurrence was divided into two periods according to the slope of the curves identified with linear regression. The function of the two lines was $y = 32{\cdot}85 - 1{\cdot}225x$ and $y = 7{\cdot}3143 - 0{\cdot}1181x$ respectively. The intercept value of the two lines was 23 months; 24 months was thus defined as the optimal cutoff value to differentiate early and late recurrence of ICC

Results

A total of 1142 patients were identified from the 14 institutions. Thirty-two patients were excluded because of extrahepatic metastasis at the time of surgery, palliative resection, ablation alone or intra-arterial therapy alone. A further 89 patients were lost to follow-up, did not have detailed information regarding site of recurrence (30 patients) or died within 30 days of surgery (58; in-hospital death rate 5·1 per cent) and were therefore excluded. A total 933 patients undergoing curative resection for ICC were included in the analysed cohort.

With a median follow-up of 22 months, 440 patients (47·2 per cent) had died. Cumulative 1-, 3- and 5-year OS rates were 82, 53 and 41 per cent respectively. Of these 440 patients, 397 (90·2 per cent) died from tumour recurrence and 43 (9·8 per cent) from other causes. Some 292 patients (31·3 per cent) were alive at last follow-up with tumour recurrence. The cumulative recurrence rate at 1, 3 and 5 years was 44, 65 and 70 per cent respectively (*Fig. 1a*). In total, 685 patients (73·4 per cent) developed recurrence, of whom 406 (59·3 per cent) had intrahepatic disease only, 94 (13·7 per cent) had extrahepatic disease only, and 185 (27·0 per cent) had both intrahepatic and extrahepatic disease. The lungs, distal lymph nodes and peritoneum were the most common sites of extrahepatic recurrence (23·7, 24·7 and 16·1 per cent respectively).

Patients with no postoperative recurrence had a better survival than those who developed ICC recurrence ($P < 0{\cdot}001$) (*Fig. 1b*). Notably, patients who had recurrent intrahepatic disease alone had a longer median OS than

Table 1 Clinical and pathological characteristics of patients with early *versus* late recurrence following initial surgery for intrahepatic cholangiocarcinoma

	Early recurrence ($n = 540$)	Late recurrence ($n = 145$)	P†
Age (years)*	58 (49–68)	61 (54–67)	0·139‡
Men	313 (58·0)	74 (51·0)	0·129
BMI (kg/m^2)*	25·3 (22·3–28·0)	25·2 (22·2–28·0)	0·889‡
Liver cirrhosis	62 (11·5)	31 (21·4)	0·002
Carbohydrate antigen 19-9 (units/ml)*	53·8 (16·0–272·3)	33·0 (11·2–90·0)	0·878‡
Carcinoembryonic antigen (ng/ml)*	2·4 (1·3–4·3)	2·2 (1·5–3·6)	0·911‡
Tumour size (cm)*	6·5 (4·8–9·0)	6·0 (3·8–8·0)	0·019‡
Multiple lesions (≥ 2)	120 (22·2)	16 (11·0)	0·002
Bilobar tumour	102 (18·9)	21 (14·5)	0·272
Vascular invasion			
Macro	65 (12·0)	13 (9·0)	0·377
Micro	155 (28·7)	29 (20·0)	0·044
Perineural invasion	87 (16·1)	20 (13·8)	0·604
Direct invasion of adjacent organs	47 (8·7)	8 (5·5)	0·300
Biliary invasion	76 (14·1)	17 (11·7)	0·571
Satellite lesions	152 (28·1)	20 (13·8)	< 0·001
AJCC tumour category			0·056
T1–2	413 (76·5)	114 (78·6)	
T3–4	101 (18·7)	16 (11·0)	
Missing	26 (4·8)	15 (10·3)	
AJCC node category			0·009
N0	284 (52·6)	77 (53·1)	
N1–2	117 (21·7)	17 (11·7)	
Nx	139 (25·7)	51 (35·2)	
Histological grade			0·263
Well to moderately differentiated	422 (78·1)	117 (80·7)	
Poorly to undifferentiated	100 (18·5)	20 (13·8)	
Missing	18 (3·3)	8 (5·5)	
Morphological type			0·147
Mass-forming	428 (78·2)	106 (73·1)	
Papillary	13 (2·4)	8 (5·5)	
Periductal infiltrating	24 (4·4)	6 (4·1)	
Mass-forming + periductal infiltrating	52 (9·6)	9 (6·2)	
Missing	23 (4·3)	16 (11·0)	
Resection procedure			0·557
Minor	220 (40·7)	63 (43·4)	
Major	320 (59·3)	82 (56·6)	
R0 resection	472 (87·4)	130 (89·7)	0·566
Margin distance (mm)			0·013
< 1	68 (12·6)	15 (10·3)	
1–4	197 (36·5)	41 (28·3)	
5–9	115 (21·3)	27 (18·6)	
≥ 10	126 (23·3)	53 (36·6)	
Missing	34 (6·3)	9 (6·2)	
Major vascular resection	61 (11·3)	15 (10·3)	0·882
Bile duct resection	99 (18·3)	22 (15·2)	0·462
Lymphadenectomy	269 (49·8)	69 (47·6)	0·634
Intraoperative blood loss (ml)*	450 (200–800)	400 (200–600)	0·405‡
Duration of surgery (min)*	200 (120–310)	205 (120–355)	0·773‡
Adjuvant chemo/radiotherapy	197 (36·5)	48 (33·1)	0·294
Postoperative complications	189 (35·0)	53 (36·6)	0·729

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †χ^2 or Fisher's exact test, except ‡Student's t test or Mann–Whitney U test.

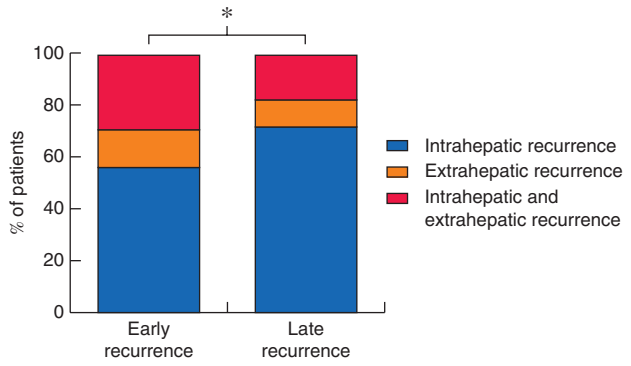

Fig. 3 Sites of recurrence in patients who had early or late recurrence following surgery with curative intent for intrahepatic cholangiocarcinoma. *$P = 0{\cdot}003$ (χ^2 test)

those with only extrahepatic recurrent disease (40 *versus* 23 months respectively; $P = 0{\cdot}003$), as well as patients who developed both intrahepatic and extrahepatic disease (40 *versus* 22 months; $P < 0{\cdot}001$) (*Fig. 1b*).

Optimal cutoff value for early and late recurrence

To determine the optimal cutoff value to distinguish between early and late recurrence, recurrence was evaluated at 6-month time points. Twenty-four months was defined as the optimal cutoff value, as explained in *Fig. 2*.

Clinicopathological data and outcomes after recurrence were analysed and compared between the early and late recurrence groups.

Outcomes following early and late recurrence at any site

The time duration from the date of initial hepatic surgery to tumour recurrence was documented among the 685 patients with recurrence. A total of 540 patients (78·8 per cent) who developed recurrence within 24 months were defined as having early recurrence, and 145 (21·2 per cent) who had recurrence 24 months or more after first hepatic surgery were defined as having late recurrence. Although many of the clinicopathological and operative data from the time of initial surgery were comparable between the two groups, liver cirrhosis was more common among patients who experienced a late *versus* an early recurrence ($P = 0{\cdot}002$) (*Table 1*). Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection were the two most common causes of liver cirrhosis: 73 (78 per cent) of the 93 patients with liver cirrhosis who developed recurrence had hepatitis. Early recurrence occurred more commonly in patients with tumours that had more aggressive biological

Table 2 Risk factors for early and late recurrence of intrahepatic cholangiocarcinoma at any site

	Early recurrence ($n = 540$)			Late recurrence ($n = 145$)		
		Multivariable analysis			Multivariable analysis	
	Univariable *P*	Hazard ratio	*P*	Univariable *P*	Hazard ratio	*P*
Sex (M : F)	0·256			0·336		
Liver cirrhosis	0·008	0·81 (0·52, 1·19)	0·252	0·029	1·89 (1·09, 3·26)	0·023
Tumour size (cm)	< 0·001			0·244		
≤ 5		1·00 (reference)				
5–10		1·67 (1·02, 2·90)	0·038			
≥ 10		2·12 (1·49, 3·04)	< 0·001			
Multiple tumours	< 0·001	1·18 (0·72, 1·93)	0·507	1·000		
Bilobar disease	0·304			0·459		
Macrovascular invasion	0·084	1·19 (0·74, 2·21)	0·447	0·756		
Microvascular invasion	0·018	1·34 (0·86, 2·14)	0·189	0·702		
Perineural invasion	0·084	1·08 (0·67, 1·74)	0·816	0·419		
Biliary invasion	0·468			0·866		
Direct invasion of adjacent organs	0·002	1·71 (0·73, 4·16)	0·252	0·156		
Satellite lesions	< 0·001	2·0 (1·32, 3·15)	0·002	0·640		
Poorly differentiation to undifferentiated	0·023	1·13 (0·70, 1·68)	0·678	0·637		
AJCC tumour category	0·008			0·871		
T1–2		1·00 (reference)				
T3–4		1·0 (0·64, 1·66)	0·944			
AJCC node category	< 0·001			0·379		
N0		1·00 (reference)				
N1		1·3 (1·01, 1·63)	0·028			
Adjuvant chemo/radiotherapy	< 0·001	0·67 (0·46, 0·97)	0·029	0·022	0·7 (0·4, 1·2)	0·218

Values in parentheses are 95 per cent confidence intervals.

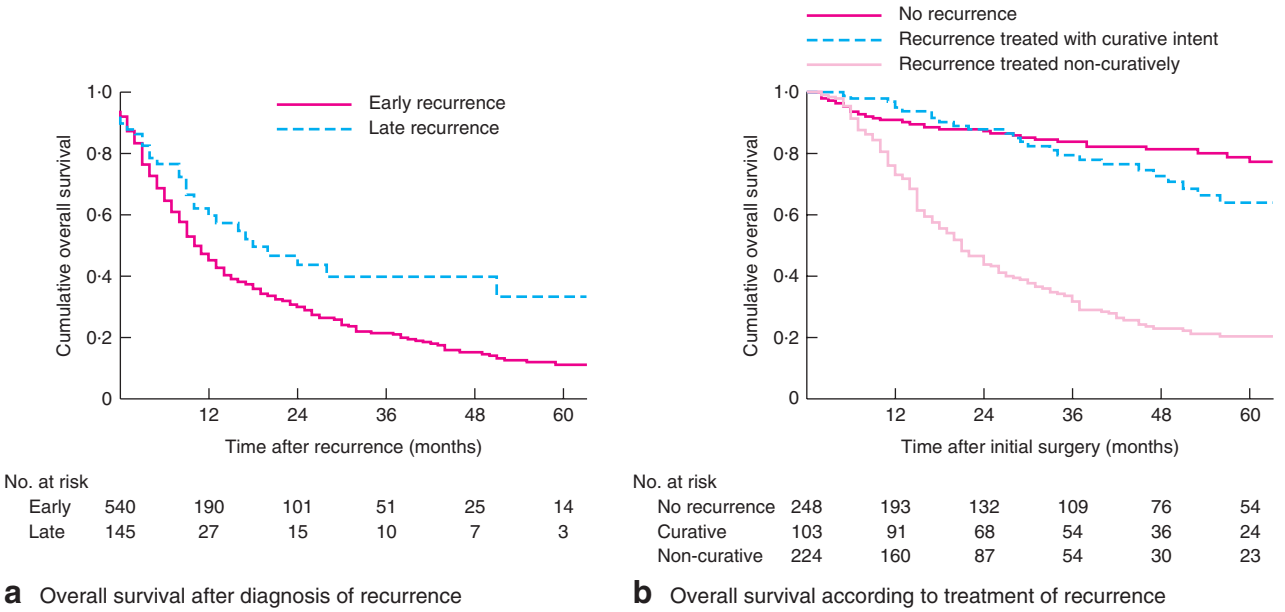

Fig. 4 Overall survival **a** from date of diagnosis of recurrence stratified by early *versus* late recurrence and **b** following initial surgery for intrahepatic cholangiocarcinoma (ICC) in patients with no recurrence, patients with recurrence of ICC treated with curative intent and those with recurrence treated non-curatively. **a** $P = 0{\cdot}029$, **b** $P < 0{\cdot}001$ (log rank test)

features, including larger size ($P = 0{\cdot}019$), multiple lesions ($P = 0{\cdot}002$), and the presence of microvascular invasion ($P = 0{\cdot}044$) or satellite lesions ($P < 0{\cdot}001$). Although the type and extent of surgery were no different between the two groups, more patients with early recurrence had a narrow surgical margin than those with late recurrence (margin less than 1 cm: 70·4 *versus* 57·2 per cent respectively; $P = 0{\cdot}003$).

Intrahepatic-only recurrence was more common in patients who had a late recurrence (104 (71·7 per cent) *versus* 302 (55·9 per cent) in those with early recurrence; $P < 0{\cdot}001$), whereas extrahepatic recurrence was more common in patients with an early recurrence (238 (44·1 per cent) *versus* 41 (28·3 per cent) with a late recurrence; $P < 0{\cdot}001$) (*Fig. 3*).

Factors associated with early recurrence after initial hepatectomy were investigated among all 933 patients in the analysed cohort. Factors related to late recurrence were investigated among the 393 patients who were free of recurrence in the first 24 months after the index operation. Tumour characteristics, including increasing tumour size, satellite lesions and lymph node metastasis, were associated with an increased likelihood of early recurrence, whereas adjuvant chemo/radiotherapy was associated with a decreased risk of early recurrence (*Table 2*). In contrast, only the presence of liver cirrhosis was independently associated with an increased risk of late recurrence.

Following recurrence, median OS was lower among patients who developed early recurrence than in those with late recurrence (10 *versus* 18 months respectively; $P = 0{\cdot}029$) (*Fig. 4a*).

Risk factors and outcome after early and late intrahepatic-only recurrence

For intrahepatic-only recurrence, tumour size, number of tumours and satellite lesions were independent risk factors for early intrahepatic recurrence (*Table 3*). Liver cirrhosis was the only independent risk factor for late recurrence. Of the 406 patients who had an intrahepatic recurrence, 327 (80·5 per cent) had treatment for the recurrent disease (274 with early and 53 with late intrahepatic recurrence). One-quarter of patients (70 of 274, 25·5 per cent) with early intrahepatic recurrence had treatment with curative intent (surgical resection, 61; ablation, 9), whereas 62 per cent (33 of 53) of those with late intrahepatic recurrence underwent potentially curative therapy (surgical resection, 20; ablation, 13) ($P < 0{\cdot}001$).

Median OS after resection and ablation were comparable (124 months *versus* median not reached for ablation; $P = 0{\cdot}543$). Palliative treatments including repeat intra-arterial therapy and systemic chemotherapy were undertaken in 74·5 per cent (204 of 274) of patients with early intrahepatic recurrence and 38 per cent (20 of 53) of those with late intrahepatic recurrence.

Table 3 Risk factors for early and late intrahepatic-only recurrence of intrahepatic cholangiocarcinoma

	Early recurrence ($n = 302$)			Late recurrence ($n = 104$)	
		Multivariable analysis		Univariable analysis	
	Univariable *P*	Hazard ratio	*P*	Hazard ratio	*P*
Sex (M : F)	0·529				0·171
Liver cirrhosis	0·063	0·84 (0·53, 1·27)	0·337	1·99 (1·11, 3·56)	0·019
Tumour size (cm)	< 0·001				0·436
≤ 5		1·00 (reference)			
5–10		1·58 (0·92, 2·72)	0·105		
≥ 10		1·87 (1·34, 2·81)	0·001		
Multiple tumours	< 0·001	1·62 (1·03, 2·72)	0·052		0·644
Bilobar disease	0·726				0·429
Macrovascular invasion	0·985				0·834
Microvascular invasion	0·064	1·09 (0·74, 1·73)	0·632		0·223
Perineural invasion	0·095	1·16 (0·69, 1·87)	0·577		0·767
Biliary invasion	0·895				0·320
Direct invasion of adjacent organs	0·037	1·58 (0·56, 4·24)	0·367		0·457
Satellite lesions	< 0·001	1·85 (1·22, 3·13)	0·008		1·000
Poorly differentiated to undifferentiated	0·166				0·725
R1 margin	0·069	1·33 (0·74, 2·30)	0·476		0·633
AJCC tumour category	0·116				0·352
T1–2					
T3–4					
AJCC node category	0·001		0·469		1·000
N0		1·00 (reference)			
N1		1·14 (0·93, 1·32)			
Adjuvant chemo/radiotherapy	0·008	0·66 (0·52, 1·11)	0·142		0·311

Values in parentheses are 95 per cent confidence intervals.

From the time of ICC recurrence, patients with early intrahepatic disease tended to have a worse OS than those with late intrahepatic disease (median 13 *versus* 24 months respectively; $P = 0·190$). However, subsequent OS following curative treatment of the recurrence was no different in early and late recurrence groups (median OS 51 *versus* 55 months respectively; $P = 0·654$). Following treatment with curative intent of the recurrence (103 of 327 patients: 70 of 274 with early and 33 of 53 with late intrahepatic recurrence), 1-, 3- and 5-year OS rates were 94·8, 79·5 and 63·7 per cent respectively, comparable to rates in the 248 patients who had no recurrence (91·1, 83·7 and 77·1 per cent respectively) ($P = 0·270$) (*Fig. 4b*). Of note, patients with intrahepatic recurrence who did not undergo treatment with curative intent (224 of 327: 204 with early and 20 with late intrahepatic recurrence) had worse long-term outcomes (1-, 3- and 5-year OS rates of 73·1, 31·5 and 20·1 per cent respectively; $P < 0·001$).

Discussion

Even when surgical resection with curative intent is performed, the prognosis of patients with ICC is poor owing to a high incidence of recurrence, which may occur early or late. The optimal time point to differentiate early *versus* late recurrence of ICC had not been defined previously. Based on a large international cohort of patients with ICC, 2 years was defined empirically as an optimal cutoff to distinguish early *versus* late recurrence. In particular, early recurrence was associated with tumour-specific factors such as large multiple tumours with microvascular invasion and lymph nodes metastasis. In contrast, late recurrence was related more to the underlying non-tumorous liver parenchyma, in particular the presence of cirrhosis. Although only genetic and molecular studies of clonal origin can definitively differentiate a recurrence from a second primary, the present study strongly suggests that early recurrence of ICC is most likely a recurrence of the initial tumour, whereas late recurrence is probably a second primary cancer and potentially related to the background liver. These findings are important, as the data strongly suggest that surveillance needs to be focused more intensely on the first 2 years after resection of ICC, especially among patients with certain clinical features. The data also provide prognostic information to help counsel patients and potentially guide adjuvant treatment planning.

In the present study, the time course of recurrence after surgical resection of initial tumours was analysed empirically and the majority of recurrences were noted to occur within 24 months, with the rate of recurrence

declining after this time point. Of note, early recurrence was strongly associated with tumour characteristics including lesion size and the presence of satellite lesions. Given the short time to recurrence, disease that recurs within 24 months may be a consequence of intrahepatic metastasis, microsatellite lesions or even occult residual disease that was present at the time of the first operation. As such, special attention should be paid to patients with multiple large tumours and satellite lesions during the preoperative evaluation interval. Although improvement in accuracy of imaging modalities can help identify tumours and metastatic lesions, as many as one-third of patients have occult metastatic or locally advanced disease[5,19]. Of note, although not associated with early intrahepatic-only recurrence, lymph node metastasis was associated with early any-site recurrence. Moreover, patients who recurred early were more likely to present with extrahepatic recurrence. In turn, patients who experienced an early recurrence had a worse long-term outcome than those with a late recurrence[20]. Similarly, early recurrence of HCC and colorectal liver metastasis after initial hepatectomy have been associated with worse long-term outcomes[16,21,22]. As such, adjuvant therapy following resection of ICC should be considered to decrease the probability of tumour recurrence after surgical resection[23,24]. Further, it has been reported[25] that use of chemotherapy is associated with a survival benefit for patients with ICC and nodal metastasis and advanced tumour stage.

Although tumour factors were associated with early recurrence, underlying liver cirrhosis was the only factor associated with late recurrence. Previous studies[7–9] noted that recurrence following resection of ICC with curative intent was associated with liver cirrhosis, as well as tumour characteristics. However, none of these studies specifically examined the timing of recurrence relative to the pattern of recurrent disease or time of recurrence. The present study not only identified liver cirrhosis as a cause of intrahepatic-only recurrence, but also noted that it was associated specifically with a late timing of recurrence. In addition, many of the patients who experienced a late recurrence in the setting of cirrhosis also had hepatitis. These data strongly imply that the late 'recurrence' of ICC may instead be the development of a second primary tumour. Cirrhosis, secondary to HBV and HCV infection, primary biliary disease, alcoholic and non-alcoholic steatohepatitis, can be associated with an increased risk of ICC development[26–30]. Hepatocytes and cholangiocytes have the same progenitor cell, and therefore both HBV and HCV may induce carcinogenesis in the two cell types by a similar mechanism[27,28]. It has previously been proposed[31] to classify ICC as 'conventional' (without underlying liver disease) or 'unconventional' (developing in a background of non-biliary chronic liver disease and cirrhosis). As liver cirrhosis is not so common in patients with ICC as in those with HCC, other factors may account for the development of metachronous recurrent disease in patients with 'conventional' ICC. Further studies on the molecular signatures of late recurrent disease are needed to help classify recurrent ICC[32].

A subset of patients with intrahepatic recurrence underwent repeated attempts at curative therapy. Among this subset of patients, surgical resection and ablation were both employed. It has been noted previously[20] that local management, such as surgery, transarterial chemoembolization and radiofrequency ablation, are effective in selected patients with localized intrahepatic and extrahepatic recurrence. Similarly, in the present study, the 5-year OS rate of patients treated with curative intent for their recurrence was 63·7 per cent, which was not statistically different from that of 77·1 per cent among patients who never experienced a recurrence. Similar good outcomes for treatment of recurrent HCC have been published previously[16]. Moreover, retreatment with curative intent of patients who experienced early recurrence achieved postrecurrence survival comparable with that of patients who developed late recurrence, and curative treatments should be considered for patients with tumour recurrence within even 2 years of initial first surgery.

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