



Factors of Early Recurrence After Resection for Intrahepatic Cholangiocarcinoma

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Abstract

Background Two-thirds of patients undergoing liver resection for intrahepatic cholangiocarcinoma experience recurrence after surgery. Our aim was to identify factors associated with early recurrence after resection for intrahepatic cholangiocarcinoma.

Methods Patients with intrahepatic cholangiocarcinoma undergoing curative intent resection (complete resection and lymphadenectomy) were included in two centers between 2005 and 2021 and were divided into three groups: early recurrence (< 12 months after resection), delayed recurrence (> 12 months), and no recurrence. Patients experiencing early (< 90 days) postoperative mortality were excluded.

Results Among 120 included patients, 44 (36.7%) experienced early recurrence, 24 (20.0%) experienced delayed recurrence, and 52 (43.3%) did not experience recurrence after a median follow-up of 59 months (IQR: 26–113). The median recurrence-free survival was 16 months (95% CI: 9.6–22.4). Median overall survival was 55 months (95% CI: 45.7–64.3), while it was 25 months for patients with early recurrence ($p < 0.001$). Patients with early recurrence had significantly larger tumors (59.1% of tumors > 70 mm in early vs. 58.3% in delayed vs. 26.9% in no recurrence group, $p = 0.002$), multiple lesions (65.9% vs. 29.2% vs. 11.5%, $p < 0.001$), and positive lymph nodes (N +) (38.6% vs. 37.5% vs. 11.5%, $p = 0.005$). In multivariable analysis, presence of multiple lesions (OR: 9.324; 95% CI: 3.051–28.489; $p < 0.001$) and positive lymph nodes (OR: 3.307. 95% CI: 1.001–11.011. $p = 0.05$) were associated with early recurrence.

Conclusion Early recurrence after curative resection of intrahepatic cholangiocarcinoma is frequent and is associated with the presence of multiple lesions and positive lymph nodes, raising the question of surgery's futility in this context.

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Introduction

Intrahepatic cholangiocarcinoma (ICC) represents 20% of all biliary malignancies which are the second most frequent primary liver tumors [1]. Incidence of ICC has increased during the past decades [2]. ICC prognosis is poor as it is most usually diagnosed at an advanced stage due to absence of symptoms and rare development on pre-existing chronic liver disease. As a consequence, complete surgical resection (with negative surgical margins) and regional lymphadenectomy [3] are feasible for only 30% of patients

[4]. Moreover, postoperative morbidity and mortality after ICC resection are high usually due the extension of the resected liver volume, given the large diameter of the tumors, and the frequent underestimation of biliary and vascular extension necessitating reconstruction [5].

So far, no neoadjuvant chemotherapy protocol has demonstrated any benefit on recurrence and overall-free survival for initially resectable ICC [6]. Moreover, despite complete resection and administration of adjuvant capecitabine [7], two-thirds of ICC patients will experience disease recurrence [8], with more than 60% representing local liver recurrences and more than 50% occurring within the first 12 months [9]. Since modern chemotherapy protocols in advanced ICC provide a median overall survival of 12 months [10], the question of surgery's futility should be raised when disease recurrence occurs within 12 months after a curative intent surgery.

The aim of the present study was to identify factors associated with early recurrence after complete surgical resection of ICC.

Methods

Study population

All consecutive patients who underwent curative intent surgical resection of ICC from January 2005 to May 2021 at Beaujon Hospital, Clichy, France and Cochin Hospital, Paris, France were retrieved from prospectively maintained databases.

Patients with ICC considered as initially resectable after a complete preoperative evaluation including both multiphase CT-scan and magnetic resonance imaging (MRI) were selected. Resectability was evaluated and validated in a multidisciplinary board meeting and was defined as the possibility to perform a negative margin resection while preserving an adequate future liver remnant. All patients undergoing a curative intent surgery with associated lymphadenectomy were finally included. Patients with macroscopic positive resection margins, without associated lymphadenectomy or experiencing early postoperative mortality (< 90 days) were excluded from the analysis. This study was approved by the institutional review board and conducted in accordance with the Declaration of Helsinki.

Surgical technique, postoperative outcomes and histological analysis

All operative procedures were performed by at least one senior liver surgeon. Liver resection was either performed by laparotomy or laparoscopy. Parenchymal transection

was performed using the ultrasonic dissector (Thunderbeat®, Olympus Co, Tokyo, Japan) when performed under laparoscopy and the Cavitron Ultrasonic Surgical Aspirator (CUSA®) when performed under laparotomy. Pringle maneuver and hepatic pedicle clamping were not routinely performed but were used in cases of liver parenchymotomy bleeding. Extent of liver resection was defined according to the Brisbane classification of liver resection [11] and major hepatectomy was defined as a resection of 3 or more contiguous segments. All patients underwent a lymphadenectomy of the hepatoduodenal ligament and coeliac region. Patients who did not undergo lymphadenectomy were excluded from the analysis.

Operative time, intraoperative blood loss and transfusion were recorded. Postoperative morbidity and mortality were evaluated within 90 days after surgery using the Dindo-Clavien classification [12] with severe complications defined as a grade 3 or more. Postoperative liver failure rate and postoperative bile leak were defined according to the International Study Group of Liver Surgery [13, 14]. Tumor classification was described according to the TNM-AJCC-UICC classification [15] and ICC with more than one lesion or satellite nodules was considered as multiple lesions (T2 stage tumor). On histological analysis, R0 resection margin was defined as a margin of at least 1 mm distance from the tumor, while R1 as a distance of less than 1 mm or in case of direct microscopic invasion. R2 patients, defined by macroscopical invasion of the resection margins, were excluded from the analysis.

Follow-up and definition of recurrence

Patients were followed up according to national French surveillance protocols [15], including physical examination, liver function tests and CA 19–9 testing and finally multiphase thorax/abdominal/pelvic computed tomography (CT), performed every 3 months for 2 years and every 6 months for the following 3 years.

Adjuvant chemotherapy was considered for all patients and was decided after a multidisciplinary board meeting. Until February 2014, gemcitabine + oxaliplatin were administered for 6 months to all patients as part of the PRODIGE 12-accord 18-unicancer GI trial [16]. Since the results of the BILCAP study, launched in 2019 [3], patients received capecitabine for 6 months.

Disease recurrence was defined as an intrahepatic or extrahepatic lesion being suspicious on cross-sectional imaging. Time to recurrence was defined as the time separating the operation and first imaging revealing a new lesion. Early recurrence was defined as any recurrence occurring within 12 months after liver resection [17]. Disease recurrence was either treated by chemotherapy alone or combined with surgery or radiofrequency ablation

when accessible to complete resection, or by best supportive care in case of advanced metastatic disease. Finally, overall survival (OS) defined from the time of surgery to the time of death or most recent follow-up was calculated.

Study Design and statistical analysis

Patients were divided into three groups according to presence or absence of recurrence and timing of recurrence: patients who had no recurrence (NoR Group), patients experiencing early recurrence (ER Group) and patients with delayed recurrence (DR Group).

All data analyses were performed using SPSS 23.0 statistical software (SPSS, Inc., Chicago, IL, USA). Categorical variables were compared using χ^2 test or Fischer's exact test when appropriate. Continuous data are expressed as mean \pm standard deviation (SD) or medians with interquartile range (IQR) and were compared using the Mann–Whitney test or Kruskal–Wallis test as appropriate. A *p* value of less than 0.05 was considered as statistically significant. Multivariable analysis by multinomial logistic regression was performed to determine independent clinical risk factors for early recurrence and death within 12 months after surgery.

Results

Study population

From January 2005 to May 2021, 190 consecutive patients operated for ICC were considered for inclusion. Among all 190 selected patients, 43 (22.6%) without lymphadenectomy and 6 (3.2%) with incomplete resection macroscopically (R2) were excluded. Twenty-one patients (11.1%) experiencing early (< 90 days) postoperative death were also excluded from the study. Therefore, the selected population included 120 ICC patients with complete surgical resection and lymphadenectomy (Fig. 1). Among these patients, 52 (43.3%) did not experience any recurrence (NoR), while 44 (36.7%) experienced early recurrence (ER) and 24 (20.0%) experienced delayed recurrence (DR).

Baseline characteristics, intraoperative and postoperative data

The distribution of patient baseline characteristics, intraoperative and postoperative data are presented in Tables 1 and 2. Among the 120 patients selected, 66 (55.0%) patients were female and mean age was 63.0 ± 11.5 years. Overall, 93 (77.5%) patients underwent a major liver resection. Patients with ER underwent more frequently a

major liver resection than those without (61.5% vs. 90.9% vs. 87.5% in the NoR, ER and DR groups, respectively, *p* = 0.001). However, no difference was found between groups regarding postoperative complications (Table 2). After resection, 41 patients (34.2%) received adjuvant chemotherapy with ER and DR patients receiving more frequently adjuvant chemotherapy compared with the NoR group (21.1% vs. 40.9% vs. 50.0% in NoR, ER and DR groups, respectively, *p* = 0.028).

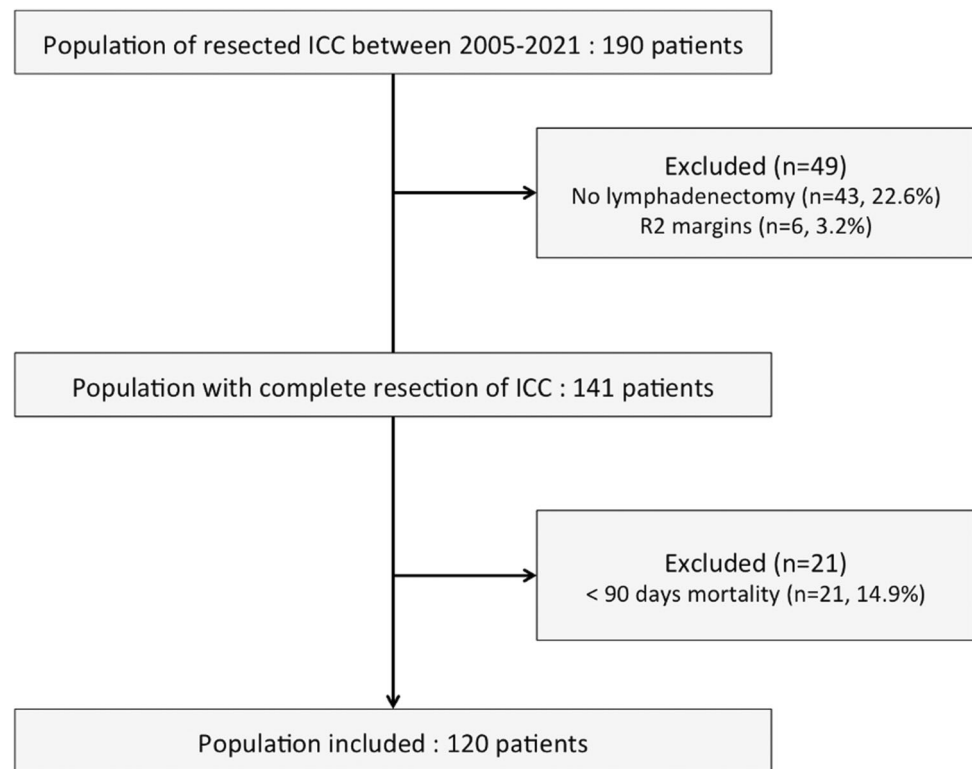
Histological findings

Mean tumor size was 65.5 ± 38.2 mm, 32 (26.7%) patients had positive lymph nodes, and 95 (79.2%) had R0 margin on final pathological examination. Patients with recurrence had significantly larger tumors (with 26.9% of tumors > 70 mm in the NoR group, 59.1% in the ER group and 58.3% in the DR group, *p* = 0.002), more frequently multiple lesions (11.5% vs. 65.9% vs. 29.2% in the NoR, ER and DR groups, respectively, *p* < 0.001) and more frequently associated with positive lymph node status (11.5% vs. 38.6% vs. 37.5% in the NoR, ER and DR groups, respectively, *p* = 0.005). Histological findings are described in Table 3.

Disease recurrence analysis, prognostic factors and long-term outcomes

After a median follow-up of 59 months (IC 95% 61.5–96.4), 68 patients experienced disease recurrence, while 80.9% of these patients developed disease recurrence within 24 months after resection. Median time to recurrence was 7.3 months (IQR 4–9) in the ER group and 29.2 months (IQR 18–43) in the DR group. Recurrence patterns and treatment according to the delay of recurrence are described in Table 4. Both ER and DR groups had similar disease recurrence patterns, principally characterized by exclusive intrahepatic recurrence (34.1% and 37.5%, respectively, *p* = 0.412) and followed by exclusive extrahepatic recurrence (25.0% and 20.8%, respectively, *p* = 0.973) or both intra- and extrahepatic recurrence (29.5% and 16.7%, respectively, *p* = 0.394). Disease recurrence was most frequently treated by chemotherapy alone (52.3% in the ER vs. 45.8% in the DR group, *p* = 0.569), combination of chemotherapy and surgery (15.9% vs. 4.2% in the ER and DR group, respectively, *p* = 0.569) or best supportive care (15.9% vs. 12.5% in the ER and DR group, respectively, *p* = 0.569) due to extensive metastatic disease.

Median DFS was 16 months (95% CI 9.6–22.4) and median OS was 55 months (95% CI 45.7–64.3) in the whole population. Median OS was significantly shorter in the ER group (25 months (95% CI 13.0–36.9)) compared

Fig. 1 Flowchart of patients operated for intrahepatic cholangiocarcinoma**Table 1** Baseline characteristics

Variables	No recurrence (NoR) (n = 52)	Early recurrence (ER) (n = 44)	Delayed recurrence (DR) (n = 24)	p value
Male sex	22 (42.3%)	19 (43.2%)	13 (54.2%)	0.599
Mean age (years)	65.1 (± 11.6)	59.7 (± 11.2)	64.7 (± 10.9)	0.758
ASA [†] score ≤ 2	40 (76.9%)	40 (90.9%)	23 (95.8%)	0.004
BMI (kg/m ²)	25.9 (± 5.64)	24.7 (± 3.39)	24.5 (± 4.16)	0.002
Cardiovascular disease	6 (11.5%)	4 (9.1%)	8 (33.3%)	0.018
Cirrhosis	4 (7.7%)	3 (6.8%)	2 (8.3%)	0.972
Diabetes	9 (17.3%)	5 (11.4%)	3 (12.5%)	0.684
Dyslipidaemia	20 (38.5%)	9 (20.5%)	5 (20.8%)	0.098
Hypertension	26 (50.0%)	20 (45.5%)	10 (41.7%)	0.779
Metabolic syndrome	15 (28.8%)	7 (15.9%)	2 (8.3%)	0.130
Tumor-related symptoms	30 (57.7%)	25 (56.8%)	17 (70.8%)	0.478
Preoperative Biliary drainage	9 (17.3%)	5 (11.4%)	5 (20.8%)	0.550
Endoscopic	9 (100%)	5 (100%)	4 (80%)	
Percutaneous	0 (0%)	0 (0%)	1 (20%)	
Portal vein embolization	7 (13.5%)	5 (11.4%)	3 (12.5%)	0.953
Radioembolization	1 (1.9%)	1 (2.3%)	0 (0%)	0.753

[†]ASA American society of anesthesiologists; BMI Body mass index

with the other groups (73 months (95% CI 51.7–94.3)) ($p < 0.001$). ER patients who died within 12 months after surgery (18.4%) had T4 stage tumors in 22.2% and positive lymph nodes in 55.5% of the cases. Disease recurrence for

ER patients was short (median DFS 3.44 ± 1.3 months) and mostly extrahepatic (66.7%).

On multivariable analysis, among the different clinical and pathological variables analyzed as potential prognostic

Table 2 Intraoperative and postoperative data

Variables	No recurrence (NoR) (n = 52)	Early recurrence (ER) (n = 44)	Delayed recurrence (DR) (n = 24)	p value
Major liver resection	32 (61.5%)	40 (90.9%)	21 (87.5%)	0.001
Number of resected segments	3.52 (± 1.65)	4.29 (± 1.25)	4.21 (± 1.79)	0.007
Hepaticojejunostomy	11 (21.2%)	10 (22.7%)	6 (25.0%)	0.932
Laparoscopy	3 (5.8%)	0 (0.0%)	0 (0.0%)	0.134
Duration of clamping (min)	20.2 (± 24.2)	28.7 (± 25.7)	31.1 (± 28.1)	0.447
Estimated blood loss (ml)	537 (± 472)	602 (± 399)	656 (± 429)	0.388
Transfusion	10 (19.2%)	9 (20.5%)	3 (12.5%)	0.695
Associated procedure [†]	3 (5.8%)	11 (25.0%)	3 (12.5%)	0.026
Associated vascular resection	7 (13.5%)	6 (13.6%)	2 (8.3%)	0.788
Arterial	0 (0%)	1 (16.7%)	0 (0%)	
Venous	7 (100%)	5 (83.3%)	2 (100%)	
Duration of surgery (min)	306 (± 107)	354 (± 118)	357 (± 125)	0.349
CCI [‡]	24.2 (± 22.3)	24.7 (± 19.8)	21.2 (± 18.3)	0.840
Clavien-Dindo				0.699
0	12 (23.1%)	10 (22.7%)	6 (25.0%)	
I	10 (19.2%)	4 (9.1%)	7 (29.2%)	
II	14 (26.9%)	13 (29.5%)	6 (25.0%)	
IIIA	4 (7.7%)	6 (13.6%)	1 (4.2%)	
IIIB	5 (9.6%)	1 (2.3%)	0 (0%)	
IV	7 (13.5%)	10 (22.7%)	4 (16.7%)	
Postoperative bleeding	5 (9.6%)	4 (9.1%)	1 (4.2%)	0.708
Grade B or C postoperative liver failure [§]	20 (38.5%)	10 (22.7%)	6 (25.0%)	0.205
50–50 criteria	3 (5.8%)	2 (4.5%)	0 (0%)	0.498
Grade B or C bile leak [§]	10 (19.2%)	13 (29.5%)	5 (20.8%)	0.467
Cardiac complication	1 (1.9%)	1 (2.3%)	1 (4.2%)	0.832
Pulmonary complication	5 (9.6%)	8 (18.2%)	3 (12.5%)	0.465
Infectious complication	16 (30.8%)	11 (25.0%)	6 (25.0%)	0.782
Reintervention	6 (11.5%)	4 (9.1%)	1 (4.2%)	0.585
Duration of hospital stay (days)	17.6 (± 16.1)	16.9 (± 12.6)	16.3 (± 10.1)	0.613
Duration of ICU stay (days)	5.4 (± 14.8)	6.21 (± 8.8)	5.0 (± 7.66)	0.695
Adjuvant chemotherapy	11 (21.2%)	18 (40.9%)	12 (50.0%)	0.028

[†]Associated procedures: diaphragmatic resection, surrenal resection, duodenal resection, peritoneal resection

[‡]CCI Charlson comorbidity index

[§]According to ISGLS classification

factors of disease recurrence, factors associated with ER were satellite lesions (OR: 9.324; 95% CI: 3.051–28.489; $p < 0.001$) and lymph node involvement (OR: 3.307. 95% CI: 1.001–11.011. $p = 0.05$) (Table 5). Moreover, lymph node involvement was the only predictor of death within 12 months following surgery (OR = 12.700; 95% CI: 1.801–89.552; $p = 0.011$) (Table 6).

Discussion

Despite optimal treatment including both complete surgical excision and adjuvant chemotherapy, prognosis of patients with ICC remains poor, due to high rate of disease recurrence [18]. The present series shows that 36.7% of patients undergoing curative intent surgery experienced ER and not surprisingly this latter was associated with dismal prognosis. Previous studies have established a 24-month cutoff after resection to differentiate early and delayed recurrence [19]. However, this cutoff described empirically is based

Table 3 Tumor characteristics on pathological evaluation

Variables	No recurrence (NoR) (<i>n</i> = 52)	Early recurrence (ER) (<i>n</i> = 44)	Delayed recurrence (DR) (<i>n</i> = 24)	<i>p</i> value
Maximal tumor size (mm)	50.2 (± 33.4)	77.3 (± 37.1)	76.5 (± 40.0)	0.303
Tumor > 70 mm	14 (26.9%)	26 (59.1%)	14 (58.3%)	0.002
Multiple lesions	6 (11.5%)	29 (65.9%)	7 (29.2%)	< 0.001
Stem cell component	3 (5.8%)	3 (6.8%)	1 (4.2%)	0.842
Tumor differentiation				0.078
Well-moderate	44 (84.6%)	33 (75.0%)	21 (87.5%)	
Poor	4 (7.7%)	9 (20.5%)	1 (4.2%)	
Mass forming	44 (84.6%)	40 (90.9%)	19 (79.2%)	0.397
Hepatocolangiocarcinoma	5 (9.6%)	3 (6.8%)	2 (8.3%)	0.872
Margins				0.243
R0	42 (80.8%)	38 (86.4%)	17 (70.8%)	
R1	10 (19.2%)	6 (13.6%)	7 (29.2%)	
TNM status				
pT1a	15 (28.8%)	5 (11.4%)	5 (20.8%)	0.058
pT1b	16 (30.8%)	15 (34.1%)	9 (37.5%)	0.902
pT2	8 (15.4%)	15 (34.1%)	5 (20.8%)	0.157
pT3	6 (11.5%)	7 (15.9%)	4 (16.7%)	0.854
pT4	0 (0%)	2 (4.5%)	1 (4.2%)	0.339
<i>N</i> classification				
pN1/2	6 (11.5%)	17 (38.6%)	9 (37.5%)	0.005

Table 4 Recurrence patterns and treatment according to time of recurrence

Variables	Early recurrence (ER) (<i>n</i> = 44)	Delayed recurrence (DR) (<i>n</i> = 24)	<i>p</i> value
Exclusive intrahepatic recurrence	15 (34.1%)	9 (37.5%)	0.412
Exclusive extrahepatic recurrence	11 (25.0%)	5 (20.8%)	0.973
Lung	4 (36.4%)	3 (60.0%)	
Bone	2 (18.3%)	0 (0%)	
Peritoneal	5 (45.5%)	2 (40.0%)	
Lymph nodes	4 (36.4%)	2 (40.0%)	
Others	0 (0%)	1 (20.0%)	
Intra and Extra hepatic recurrence	13 (29.5%)	4 (16.7%)	0.394
Lung	7 (53.8%)	3 (75.0%)	
Bone	1 (7.7%)	0 (14.3%)	
Peritoneal	4 (30.8%)	1 (25.0%)	
Lymph nodes	3 (23.1%)	2 (50.0%)	
Recurrence treatment			0.569
Chemotherapy alone	23 (52.3%)	11 (45.8%)	
Surgery or RFA	0 (0%)	2 (8.3%)	
Chemotherapy + Surgery or RFA [†]	7 (15.9%)	1 (4.2%)	
Others [‡]	7 (15.9%)	7 (29.2%)	
Best supportive care	7 (15.9%)	3 (12.5%)	

[†]RFA Radiofrequency ablation[‡]Other type of recurrence treatment: radiotherapy, radioembolization, immunotherapy

Table 5 Multivariable analysis of the factors associated with early recurrence

Variables	OR	<i>p</i> value	95% CI
Adjuvant chemotherapy	2.022	0.188	0.709–5.763
Tumor size > 70 mm	2.174	0.139	0.778–6.079
Multiple lesion tumors	9.324	< 0.001	3.051–28.489
Positive lymph node status	3.307	0.050	1.001–11.011

on the definition employed in the setting of HCC [20] and aims to discriminate disease recurrence related to tumor characteristics or de novo tumor development related to underlying liver disease, i.e., cirrhosis. In the case of ICC, disease recurrence after 24 months is rare, and most patients will experience recurrence within the first 2 years after surgery. Indeed, a recent study of Wang et al. [17] determined that the optimal cutoff time point to define early and delayed recurrence in ICC after curative resection was 12 months. In our study, we used the same cutoff in order to investigate the futility of surgery in the setting of ICC. We thus observed that 82.6% of patients experienced disease recurrence within 24 months after surgical resection and ER patients within a median interval time of 6 months.

In this study, patients who experienced ER had more aggressive tumors, as evidenced by the rate of poor differentiation and presence of multinodularity, as well as the higher rate of adjuvant chemotherapy administered to these patients. Moreover, patients with ER had larger tumors compared with NoR patients although not statistically larger than DR patients. Indeed, large ICCs are more frequently associated with satellite lesions [21, 22]. Multifocal tumors were described in the present series as the presence of multiple confluent lesions or satellite lesions. Multifocal ICC lesions are associated with poorer prognosis [17, 19] as is the case of multiple hepatocellular carcinomas, associated with more frequent tumor recurrence, whatever the type of multifocality (satellite nodules or multiple lesions) [23]. In our study, presence of multiple lesions was independently associated with ER and is thus related with a greater liver tumor burden [24].

Table 6 Multivariable analysis of the factors associated with death within 12 months after resection

Variables	OR	<i>p</i> value	95% CI
Adjuvant chemotherapy	0.176	0.133	0.018–1.694
Tumor size > 70 mm	0.974	0.977	0.154–6.166
Multiple lesion tumors	0.602	0.624	0.079–4.586
Positive lymph nodes status	12.700	0.011	1.801–89.552

Our results also confirmed that more than 30% of patients with ER presented exclusive intrahepatic disease recurrence [8]. On the other hand, patients with multiple lesions presented more frequently extrahepatic recurrence, which raises the possibility that satellite nodules could be equivalent to early stage intrahepatic synchronous metastases. In TNM-UICC-AJCC classification [15], multifocal disease only classified the primitive lesion as T2. Multiple lesions however seem associated with tumor aggressiveness, and as a consequence with poorer prognosis. It could be more clinically accurate to define multiple ICC as metastatic, such as for hilar cholangiocarcinomas [15], but this should be evaluated with a comparative study evaluating oncological outcomes between those patients and extrahepatic metastatic patients treated with chemotherapy only.

Just as the presence of multiple tumors is a strong determinant of survival, presence of positive lymph nodes, reported in 45–65% of patients with ICC, has a significant prognostic impact [25] and is a well-known factor associated with the development of extrahepatic metastases and low survival [26]. Indeed, in our study, we observed that positive lymph node status was independently associated with early disease recurrence (OR: 3.883, 95% CI: 1.115–13.523, *p* = 0.033) and death (OR: 9.189; 95% CI: 1.516–55.689; *p* = 0.016) within 12 months after surgery. Thus, presence of both multiple tumors and positive lymph node status may question the futility of surgery for these patients and indicate a neoadjuvant chemotherapy. In our study, patients who died within 12 months had more extrahepatic recurrence (66.7%). However, one of the main limitations in the preoperative diagnosis of lymph node invasion is the low diagnostic accuracy of MRI, CT-scan and PET-scan imaging [27, 28], usually necessitating hepatic pedicle lymphadenectomy in order to ensure precise lymph node staging.

Our results suggest that, given the importance of lymph node status and multiple lesion tumors on disease prognosis [25, 29] as well as their potential impact on OS [30, 31], it may be preferable to consider performing lymph node dissection and frozen section analysis before any liver resection is performed. If presence of positive lymph nodes is confirmed, interruption of surgery should be considered and a neoadjuvant (or palliation) treatment should be initiated in order to select the best candidates for a future curative liver resection according to treatment response. Indeed, however, no randomized study has been conducted yet, the rationale of neoadjuvant chemotherapy with a downstaging intent exists in ICC, including systemic and transarterial therapies [32].

The limitations of our study are its retrospective nature covering a long period, during which surgical techniques and imaging modalities have evolved. Moreover, it can

imply time lead bias regarding follow-up and management protocols, especially in regards to chemotherapy regimens, which have evolved throughout the study period. Nevertheless, it was performed by two high-volume tertiary French centers following common practices. Finally, the present study failed to assess some preoperative patient-related factors, such as CA 19–9 level, which could have impacted ICC prognosis.

In conclusion, one-third of patients with ICC undergoing curative intent surgery experienced disease recurrence within 12 months (ER). ER was associated with the presence of multiple lesion tumors and positive lymph nodes. Given the poor prognosis of this group of patients, futility of extended liver resections should be put in question. Neoadjuvant or palliation treatment may be of interest and should be considered in these situations.

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Declarations

Conflict of interest The authors have no conflict of interest to declare.

Consent to publish This study has not been previously published elsewhere. All authors actively contributed to this work and gave their final approval before submission.

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