World J Surg (2019) 43:1105–1116
https://doi.org/10.1007/s00268-018-04876-x

ORIGINAL SCIENTIFIC REPORT

Surgical Resection for Recurrent Intrahepatic Cholangiocarcinoma

Fabian Bartsch[1] · Markus Paschold[1] · Janine Baumgart[1] · Maria Hoppe-Lotichius[1] · Stefan Heinrich[1] · Hauke Lang[1]

Published online: 6 December 2018

Abstract

Background Although after R0 resection of intrahepatic cholangiocarcinoma (ICC) recurrence is frequent, most guidelines do not address strategies for this. The aim of this study was to analyze the outcome of repeated resection and to determine criteria when repeated resection is reasonable.

Methods Between 2008 and 2016, we consecutively collected all cases of ICC (n = 176) in a prospective database and further analyzed them with a focus on tumor recurrence, its surgical treatment, overall survival and recurrence-free survival.

Results Overall, a total of 22 explorations were performed for recurrent ICC in 17 patients. Resection rate was 18 repeated resections in 13 patients. Three patients underwent repeated resection twice and one patient three times. Recurrence was solitary in 7 patients and multifocal in 11 re-resected cases. Median overall survival (OS) of patients who underwent repeated resection was 65.2 months (interquartile range 37–126.5) with a 5-year OS rate of 62%, calculated from primary resection. Patients who underwent repeated resections had a significant better OS compared to those receiving chemotherapy, transarterial chemoembolization, selective internal radiotherapy, radiofrequency ablation or best supportive care ($p < 0.001$).

Conclusion Repeated resection of recurrent ICC is reasonable and associated with an improved survival. Re-exploration should be considered as long as resection is technically possible.

Introduction

The incidence of intrahepatic cholangiocarcinoma (ICC) has increased over the past decades [1, 2]. Complete resection still provides the only chance of cure, but it is often difficult to achieve due to the extent of the disease at diagnosis. However, in experienced centers a large proportion of patients may undergo potentially curative surgery [3].

Many patients develop disease recurrence (40–76%) after curative surgery within a median period of 18 months [4–6]. Risk factors for disease recurrence are tumor size, positive lymph node status or resection margin and microvascular invasion [7–9]. Although recurrence is frequent, there is hardly any data about the patterns of recurrence.

Since ICC is a rare malignancy, treatment guidelines for ICC therapy have a low level of evidence. The more guidelines for the treatment of recurrence are particularly difficult to establish. While surgical resection is not clearly recommended for recurrent ICC in current guidelines, this approach has been reported as safe and feasible in selected

✉ Hauke Lang
hauke.lang@unimedizin-mainz.de

[1] Department of General, Visceral and Transplant Surgery, University Medical Center of the Johannes Gutenberg-University Mainz, Langenbeckstraße 1, 55131 Mainz, Germany

patients and should be considered [7, 8, 10–13]. The European Association for the Study of the Liver (EASL) guidelines at least mention the possibility of surgical therapy in a small subset of cases [14].

Our policy is to offer surgical therapy for recurrent ICC if a R0 resection of all visible lesions appears possible. We herein report our experience with repeated surgery for recurrent ICC. In particular, this manuscript aims at stratifying treatment for recurrent ICC trying to identify prognostic factors for favorable outcome after surgical therapy of disease recurrence.

Methods

Between January 2008 and December 2016, data from all consecutive patients who underwent surgical exploration at the University Hospital of Mainz for ICC were identified from our prospective institutional database. Patients with mixed hepatocellular–cholangiocellular carcinomas, distal, perihilar and gallbladder carcinomas were excluded. Data were analyzed with special regard to patterns of recurrence, treatment of recurrence and outcome after surgical therapy. Follow-up after primary resection was carried out every 3 months after primary surgery. At least every 6 months, a computed tomography (CT) was performed. If patients underwent imaging externally, magnetic resonance tomography or positron emission tomography (PET)—CT—was accepted as well. After primary resection, adjuvant therapy was no standard procedure at our center due to lacking data at the time the study was conducted.

Surgical therapy and outcome

All cases were discussed with a liver surgeon, oncologist and radiologist preoperatively during our interdisciplinary tumor conference. Surgical therapy for recurrence was considered adequate, if the patients had a sufficient state of health, a tolerable size and function of the future liver remnant and sufficient remaining vascular structures. Preferentially, solitary tumors were candidates, but also multifocal tumors underwent repeated resection in selected cases. Time to recurrence had to exceed at least 3 months. Performance of repeated resection was independent from the initial extent of resection(s). Even extrahepatic recurrence may be a reasonable target for resection in unifocal cases. Cases of simultaneous intra- and extrahepatic recurrences were no candidates for surgery.

The type of surgery, histological results, morbidity, mortality, overall survival and recurrence-free survival were analyzed. Morbidity was classified using the Dindo–Clavien classification [15]. Mortality was defined as in-hospital mortality. As for primary resection, even after repeated resection for recurrence no adjuvant therapy was performed because of the before-mentioned reason.

Follow-up and definition of disease recurrence

After curative resection, all patients had regular surveillance with ultrasound examinations and either magnetic resonance imaging or computed tomography 3 months after surgery and every 6 months thereafter. Tumor recurrence was assumed, whenever new soft tissue lesions appeared during follow-up, and the radiological criteria for recurrence were fulfilled, or a tumor marker increase was documented. A histological proof of disease recurrence was not generally required.

After surgery for tumor recurrence, follow-up was continued as for primary surgery.

Statistics

Statistical analysis was performed with SPSS 23 (SPSS Inc., released 2014, IBM SPSS Statistics for Windows, Version 23.0, IBM Armonk, NY, USA: IBM Corp). For survival analyses, we used the Kaplan–Meier method and the logrank test for statistical comparison. Overall and recurrence-free survivals were calculated from the day of re-resection until the respective event according to Punt et al. [16]. Categorical data were analyzed with cross-tabulation and Chi-square test. p values < 0.05 were considered significant.

Results

During the period of analysis, a total of 176 patients with ICC underwent explorative laparotomy at our department. Of these, 127 (72.2%) patients underwent resections with curative intent (Fig. 1).

Patterns and treatment of tumor recurrence

The median follow-up of this analysis was 16.6 months (IQR 6.1–31.5). During this period, 77 patients (60.6%) developed tumor recurrence.

Surgical exploration for recurrent ICC was performed in 17 patients with 9 of them having the first liver resection in our center and additional 8 patients who were admitted for disease recurrence after primary resections at other centers.

Characteristics of patients and the primary resection are presented in Table 1.

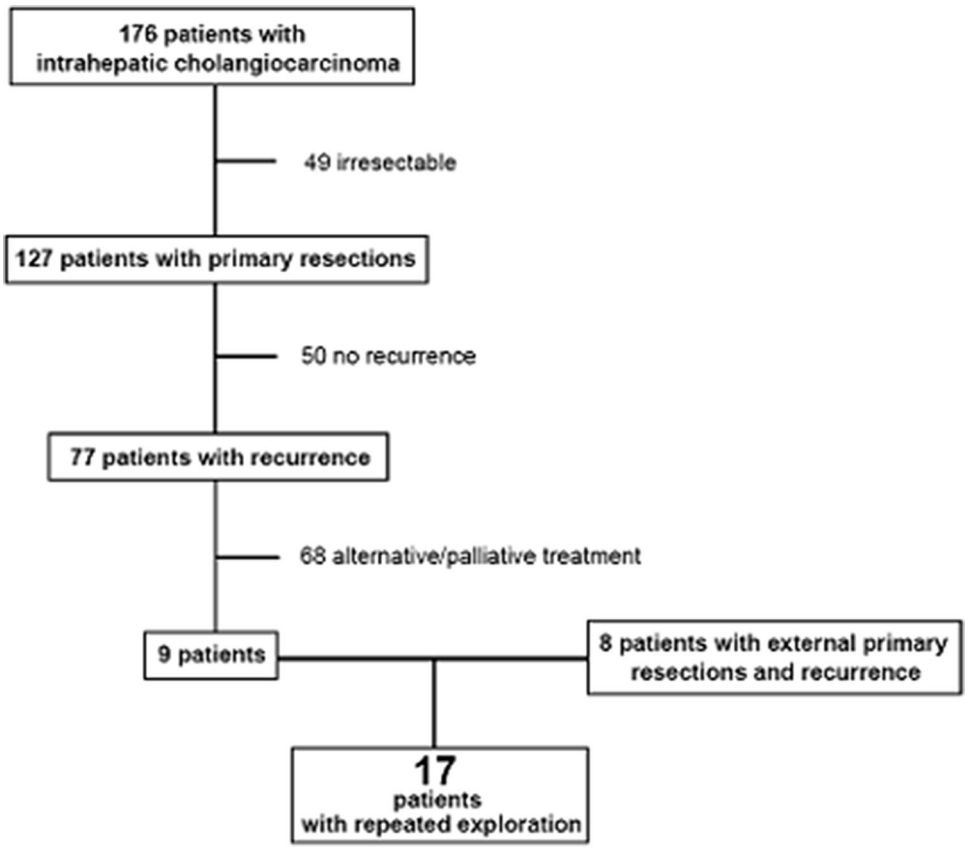


Fig. 1 Flow diagram for all explorations with primary and repeated resections of ICC

Patterns of recurrence

Detailed patterns of recurrences and conducted therapies are found in Table 2. Isolated recurrence in the liver was most common, and patients underwent a variety of different treatments. Our decision tree is shown in Fig. 2. One reason that more than 75% (25/33) of those patients were no candidates for repeated resection was diffuse multifocal spread. There was no definitive number of nodules leading to resign from surgery, but if multifocality had an excessive number or also centrally located nodules, repeated resection was not considered an option. Also, advanced centrally located recurrence requiring a too extended resection was a reason to step back from surgery.

In patients with extrahepatic recurrence, only two patients underwent potential curative treatment. One patient was a candidate for repeated resection of isolated tumor recurrences in interaortocaval lymph nodes, while another underwent ablation of a singular lung metastasis (Table 2).

All patients with simultaneous intra-plus extrahepatic recurrence underwent palliative chemotherapy.

Surgical treatment of recurrences

Surgical therapy was intended in 17 patients with recurrent ICC. Initial resections had been major ($n = 4$) or extended ($n = 6$) hepatectomy and minor resections/segmentectomies ($n = 7$) of the primary ICC (Table 3). Lymph node status at primary surgery was negative in 12, positive in 3 and not known in 2 patients.

Only an exploration was performed in four patients (23.5%) due to the intraoperative detection of peritoneal carcinomatosis ($n = 2$), multifocal disease ($n = 1$) and a complex infiltration of the hepatoduodenal ligament ($n = 1$). These findings had not been detected in the preoperative radiological workup.

Surgical treatment of intrahepatic recurrences

Out of the remaining patients, 12 had intrahepatic recurrence only and underwent a total of 17 re-resections with curative intent. There were 8 patients having 1 re-resection, three patients with two re-resections and one patient who underwent three re-resections. Minor liver resection was performed 14 times. In two patients, liver resection had to be extended with additional partial resection of the diaphragm. In addition, the vena cava inferior had to be

Table 1 Patients characteristics of primary surgery

Groups	All *n* = 176	Repeated resection[a] *n* = 7 + (6)	No recurrence *n* = 50	Recurrence Ø rep. res. *n* = 70	External primary *n* = 8
Gender, female/male	86/90	5/2	23/27	38/32	7/1
Age, median [IQR]	63.7 [55.9–72.9]	68.8 [61.3–75.8]	63.7 [56.3–69.8]	63.7 [54.8–73.7]	65.9 [59.1–69.9]
Primary resection					
Right trisectionectomy	22	2 + (2)	9	11	2
Left trisectionectomy	17	–	5	12	–
Right hepatectomy	22	(1)	9	13	2
Left hepatectomy	15	(2)	5	10	2
Mesohepatectomy (≥ three central segments)	7	1	2	4	–
ALPPS	6	1	2	3	–
Monosegmentectomy	7	–	2	2	–
Bisegmentectomy	21	1 + (1)	11	9	2
Resection of three liver sg.	8	2	4	5	–
Atypic/wedge resection	2	–	1	1	–
Irresectable	49	–	–	–	–
Histology (TNM 8th Ed.)					[b]
T-status					
T1a	19	–	10	9	–
T1b	23	2 + (3)	11	10	3
T2	51	5 + (2)	16	30	2
T3	12	(1)	6	6	1
T4	22	–	7	15	1
N-status					
N0	74	5 + (5)	29	40	6
N1	38	2	14	22	–
NX	15	(1)	7	8	1
R-status					
R0	108	6 + (5)	44	58	6
R1	17	1	4	12	–
R2	–	(1)	–	–	1
Rx	2		2	0	–
Grading					
G1	2	–	1	1	–
G2	75	4 + (6)	30	45	7
G3	41	3	16	22	–
G4	1	–	1	0	–
Preoperative chemotherapy	8		2	1	–

[a]Number in brackets is patients with external primary resection

[b]The histology of one patient who underwent primary resection externally is not known

partially resected and reconstructed with a Goretex patch in one patient.

Adjuvant systemic chemotherapy was not applied after resection of recurrent ICC.

Surgical treatment of extrahepatic recurrence

One patient had isolated extrahepatic recurrence of interaortocaval lymph nodes und underwent repeated

Table 2 Patterns and therapy of recurrence

Therapy of recurrence	Intrahepatic only $n = 33$ (42.8%)	Extrahepatic only $n = 21$ (27.3%)	Intra + extrahepatic $n = 23$ (29.9%)
Repeated exploration	16[a]	1	–
Chemotherapy	18	11	23
TACE	3	–	–
RFA/IRE (ablation)	3	1	–
SIRT	1	–	–
Best supportive care	–	8	–

TACE transarterial chemoebolization, *RFA* radiofrequency ablation, *IRE* irreversible electroporation, *SIRT* selective internal radiotherapy

[a]Including 8 external primary resections

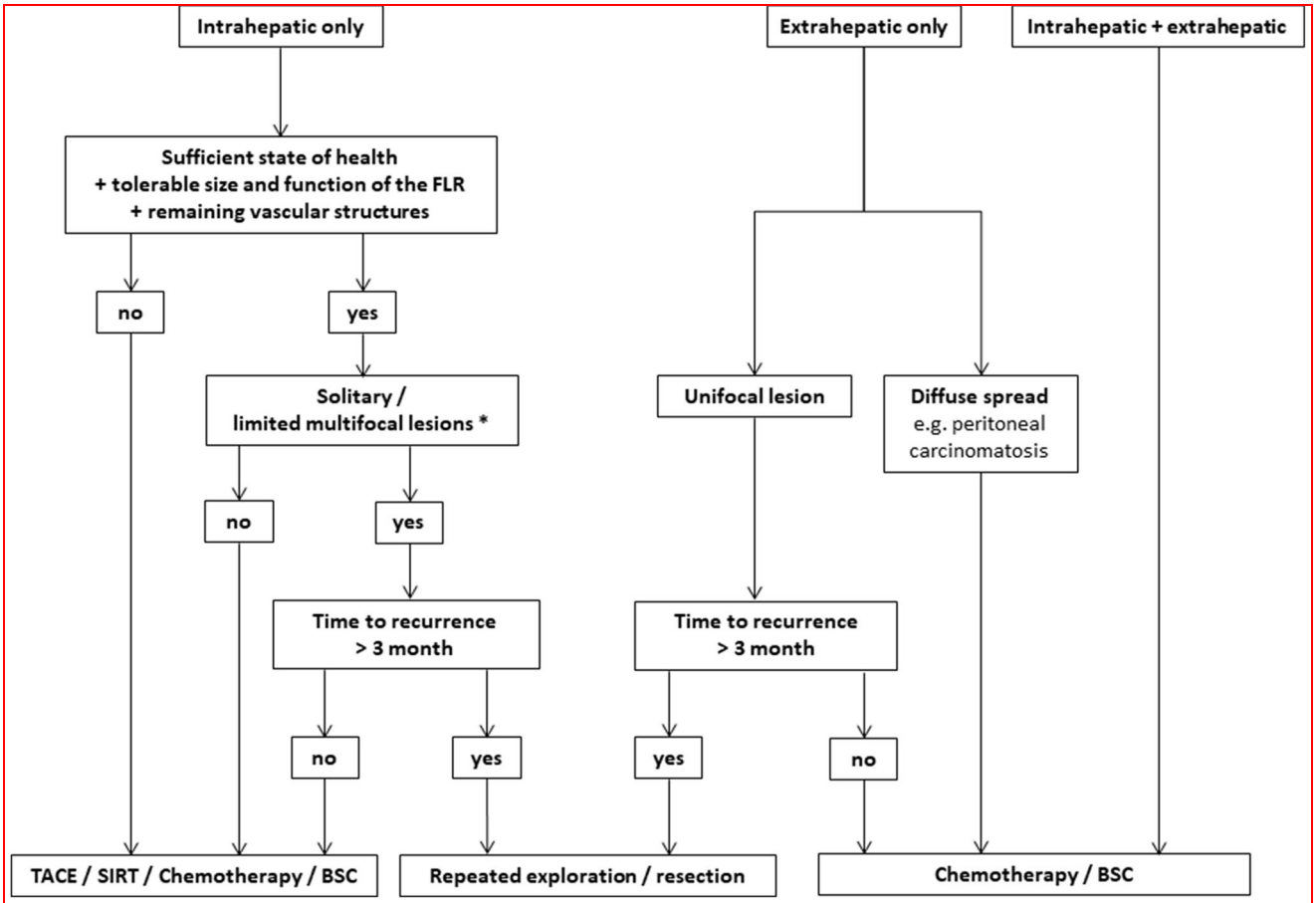


Fig. 2 Decision tree for the treatment of different locations of recurrence. *There is no definitive number of nodules leading to resign from surgery, but if multifocality had an excessive number or also centrally located nodules, repeated resection is no option

resection with curative intent. No adjuvant systemic chemotherapy was applied after resection as well.

Histological factors at primary resection influencing resectability of recurrence

Comparing different histological parameters at primary resection between the 13 patients who underwent repeated resection of recurrence and all patients with recurrence who were no candidates for repeated surgery ($n = 68$), only the R-status showed a statistically significant influence on the chance of repeated resection ($p = 0.019$), while the *N*-status ($p = 0.401$) and other factors like T-status ($p = 0.290$), L-status, V-status, Pn-status, grading ($p = 0.958$), UICC-grade ($p = 0.509$), tumor size of the biggest nodule (< 5 cm vs. 5–10 cm vs. > 10 cm;

Table 3 Repeated resections for recurrence of ICC

Pat. #	# of resection	Resection	Histology/reason irresectable	TNMR	Months until recurrence	Therapy recurrence or palliative	OS in months	Patient alive
1	Primary	Bisegmentectomy (ext.)	8 cm, solitary	T1 Nx M0 G2 R0	11	Rep. expl.	42.4	No
1	1st rep.	Bisegmentectomy	6 cm, solitary	R0	7	Rep. expl.		
1	2nd rep.	Monosegmentectomy	5 cm, multifocal	R0	8	Rep. expl.		
1	3rd rep.	Atypic resection	Solitary	R0	4	Chemotherapy		
2	Primary	Bisegmentectomy	7.5 cm, multifocal	T3 N1 (1/2) M0 G3 R1	7	Rep. expl.	12	No
2	1st rep.	Exploration	Peritoneal carcinomatosis	Irresectable	–	BSC		
3	Primary	Multiple atypic resections	6.2 cm, solitary	T1 N0 (0/4) M0 G3	27	Rep. expl.	69.9	No
3	1st rep.	Monosegmentectomy	Multifocal	R0	20	Chemotherapy		
4	Primary	ALPPS (right trisectionectomy)	7.5 cm, multifocal	T3 N0 (0/3) M0 G2 R0	15	Rep. expl.	83.7	Yes
4	1st rep.	Monosegmentectomy	Multifocal	R0	No	–		
5	Primary	Right trisectionectomy (ext.)	Solitary	T1 N0 (0/4) M0 G2 R2	36	Rep. expl.	47.9	No
5	1st rep.	Monosegmentectomy	Multifocal	R0	5	BSC		
6	Primary	Right hepatectomy (ext.)	5.1 cm, multifocal	T3 N0 (0/1) M0 G2 R0	14	Rep. expl.	46.3	Yes
6	1st rep.	Exploration	Infil. hepatoduod. ligament	Irresectable	–	Chemotherapy		
7	Primary	Right trisectionectomy (ext.)	Not available	T2 N0 M0 G2 R0	166	Rep. expl.	192	Yes
7	1st rep.	Atypic resection	Solitary	R0	No	–		
8	Primary	Trisegmentectomy	0.6 cm, multifocal	T2 N0 (0/9) M0 G2 R0	3	Rep. expl.	29.5	Yes
8	1st rep.	Bisegmentectomy	1.5 cm, multifocal	R0	12	Rep. expl.		
8	2nd rep.	Bisegmentectomy	Multifocal	R0	3	Chemotherapy		
9	Primary	Mesohepatectomy	5.7 cm, multifocal	T1 N0 (0/11) M0 G2 R0	8	Rep. expl.	31.5	Yes
9	1st rep.	Monosegmentectomy	Solitary	R0	7	Chemotherapy		
10	Primary	Right trisectionectomy	10.2 cm, solitary	T2 N1 (2/3) M0 G3 R0	2	Rep. expl.	20.2	No
10	1st rep.	Atypic resections	Multifocal	R0	3	Chemotherapy		
11	Primary	Bisegmentectomy (ext.)	Not available	Not available	11	Rep. expl.	14	No
11	1st rep.	Exploration	Advanced multifocality	irresectable	–	Chemotherapy		
12	Primary	Left hepatectomy (ext.)	Not known	T1 N0 (0/1) M0 G2 R0	7	Rep. expl.	13	No
12	1st rep.	Atypic resection	Multifocal	R0	3	Chemotherapy		
13	Primary	Bisegmentectomy	4.8 cm, solitary	T1 N1 (3/19) M0 G3 R0	15	Rep. expl.	61	No
13	1st rep.	Res. of interaortocaval LN	Multifocal (2 LN)	R0	7	Chemotherapy		
14	Primary	Right trisectionectomy	8.5 cm, multifocal	T2 N0 (0/6) M0 G2 R0	23	Rep. expl.	28.6	Yes
14	1st rep.	Atypic resection	1.8 cm, solitary	R0	4	Watchful waiting		

Table 3 continued

Pat. #	# of resection	Resection	Histology/reason irresectable	TNMR	Months until recurrence	Therapy recurrence or palliative	OS in months	Patient alive
15	Primary	Left hepatectomy (ext.)	Not known	T3 N0 (0/3) M0 G2 R0	19	Rep. expl.	47.3	Yes
15	1st rep.	Bisegmentectomy (ext.)	Solitary	R0	22	Rep. expl.		
15	2nd rep.	Monosegmentectomy	2.3 cm, solitary	R0	No	–		
16	Primary	Right hepatectomy (ext.)	4 cm, multifocal	T2 N0 (0/2) M0 G2 R0	6	Rep. expl.	62.2	Yes
16	1st rep.	Monosegmentectomy (ext.)	1.1 cm, multifocal	R0	9	Rep. expl.		
16	2nd rep.	Monosegmentectomy	2.5 cm, multifocal	R0	13	RFA		
17	Primary	Bisegmentectomy	4.3 cm, solitary	T1 N0 (0/5) M0 G2 R0	6	Rep. expl.	18.2	Yes
17	1st rep.	Exploration	Peritoneal carcinomatosis	Irresectable	–	Chemotherapy		

TNMR, TNMR stage of TNM classification; OS, overall survival; Rep., repeated exploration; (ext.), external resection; Rep. expl., repeated exploration; BSC, best supportive care; RFA, radio frequency ablation

$p = 0.408$) and focality (solitary vs. multifocal; $p = 0.984$) did not.

Histological results

ICC recurrence was confirmed in all patients. Tumor recurrence was solitary in 7 and multifocal in 11 specimens, with a median number of two nodules (range 1–5). R0 resection was achieved in 16 resections with two R1 resections.

Morbidity and mortality

After repeated resection, there were 4 patients having complications of grade III or IVa. There were bile leakage/intraabdominal abscesses in 3 cases, requiring drain placement (Dindo grade IIIa). One patient required packing and ICU therapy due to diffuse bleeding, and depacking was performed 2 days later (Dindo grade IVa). No patient died during the hospital stay.

Survival analysis of tumor recurrence

Median follow-up after first repeated exploration was 30.4 months (range 11.7–83.7). The median recurrence-free survival after initial surgical therapy of ICC primary ($n = 18$) was 11 months (range 2–166 months). The time until repeated recurrence after resection of ICC recurrence was 7 months (median, range 3–22 months).

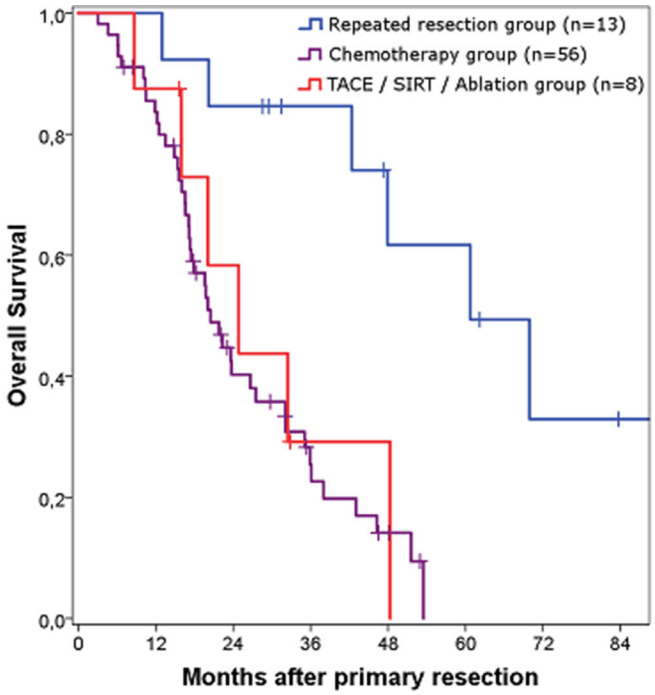
At the time of this analysis, seven patients were still alive and three patients (23.1%) are free of recurrence at 68.7, 26 and 6.3 months after the last repeated resection, respectively, and at 83.7, 192 and 47.3 months after primary resection. The median overall survival for patients who underwent potentially curative surgery for ICC recurrence calculated from the resection of primary ICC was 65.2 months (range 13–192) with consecutive 1-, 3- and 5-year overall survival rates of 100%, 85% and 62%, respectively.

Patients with surgical therapy of disease recurrence had a significantly better median overall survival than the entire cohort of patients with ICC calculated from the day of primary surgery ($p = 0.002$). Considering all patients with recurrent disease, patients who underwent surgical therapy had superior overall survival compared to patients who had alternative treatments (Fig. 3, $p < 0.001$). In patients with isolated intrahepatic recurrence the repeated resection group also had a favorable overall survival compared to patients who were no candidates for surgery and underwent chemotherapy (Fig. 4, $p = 0.003$).

Comparing the repeated resection group with patients who had no recurrence ($n = 50$), no statistical differences in overall survival could be shown (Fig. 5, $p = 0.941$).

Risk factors for repeated disease recurrence after surgical therapy of recurrent ICC

We did not observe a significant difference between patients with solitary and multifocal recurrences regarding overall survival ($p = 0.430$). Similarly, no significant difference could be found for recurrence-free survival after resection of solitary or multifocal recurrences ($p = 0.452$). Solitary or multifocal recurrence was no risk factor for repeated recurrence ($p = 0.512$) as well as R0 versus R1



number at risk	0	12	24	36	48	60	72	84
Repeated res. group	13	10	8	4	3	3	1	1
Chemotherapy group	56	44	18	8	4	0	0	0
TACE/SIRT/Ablation grp.	8	7	4	1	1	0	0	0

Fig. 3 Comparison of Kaplan–Meier analyses of overall survival for different treatment strategies in patients with recurrent ICC. Repeated resection group versus chemotherapy ($p < 0.001$); repeated resection group versus TACE/SIRT/ablation ($p = 0.011$). Survival was calculated from the day of primary resection

resection ($p = 0.584$) or morbidity after repeated resection ($p = 0.512$).

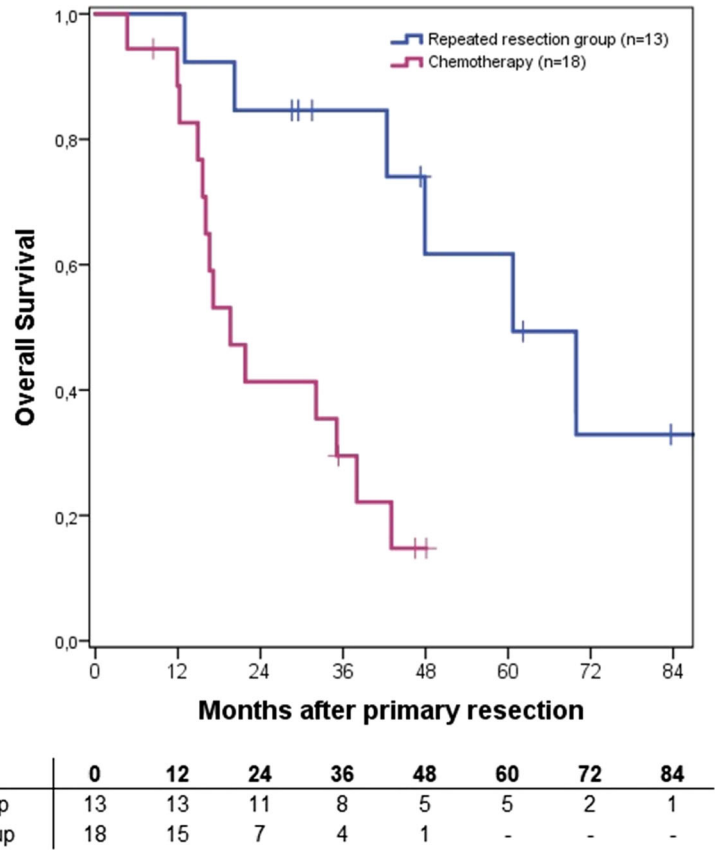
Discussion

Currently, chemotherapy is the common treatment of disease recurrence of ICC after resection [14, 17, 18]. As for other malignant diseases, surgery, TACE, SIRT or percutaneous tumor ablation could probably be potential treatment alternatives for intrahepatic tumor recurrence. However, outcome data on these techniques are scarce in the literature. As we follow an aggressive policy for the treatment of recurrent ICC, a large proportion of patients had local therapies including surgery.

Here, we report on 17 patients with ICC tumor recurrences, who underwent repeated exploration. Thirteen patients had repeated resection for recurrent disease, three of them had two and one even 3 repeated hepatectomies for recurrent ICC. The survival of these patients was superior to patients in whom recurrence had been treated by chemotherapy, interventional treatment or best supportive care, only. Furthermore, patients who underwent surgery for disease recurrence revealed an even better overall survival as the entire group of patients who underwent surgery for primary ICC. This is clearly a strong indicator for biological selection because ICC tending to recur intrahepatic only, amenable for repeated surgery, seems to be less aggressive than those leading to diffuse spread.

Surgery for recurrent ICC has been reported from a number of groups, but the sample size was mostly very limited [3–8, 11–13, 19–23] (Table 4).

In our series, more than 60% of patients presented with tumor relapse after potentially curative resection after a median of 7.4 months (range 1–68 months) which is comparable to the literature [4–7, 12, 20, 21, 24]. Only selected patients with tumor recurrences were candidates for repeated exploration in our study. Reasons to refrain from surgery were a future liver remnant that was too small, limitations of future liver function, or a critical general state of health. Patients with isolated extrahepatic tumor recurrences might also be candidates for repeated resection in very selected cases. We report one patient who received resection for isolated tumor recurrences in the interaortocaval lymph nodes who survived 46 months after repeated resection. Studies analyzing therapy for extrahepatic recurrences are lacking, but isolated cases are seldom reported [5, 22]. Lymphadenectomy of the hepatoduodenal ligament at primary resection was performed standardly in our center. Most patients who



number at risk	0	12	24	36	48	60	72	84
Repeated res. group	13	13	11	8	5	5	2	1
Chemotherapy group	18	15	7	4	1	-	-	-

Fig. 4 Comparison of Kaplan–Meier analyses of overall survival of the repeated resection group and patients with intrahepatic recurrence only who underwent chemotherapy ($p = 0.003$). Survival was calculated from the day of primary resection

underwent repeated resection had negative lymph node status at primary resection ($n = 10$) with two lymph node positive patients and one with unknown status.

Median time to first recurrence of the repeated resection group ($n = 13$) was 15 months (range 2–166), while all patients who were no candidates for surgery had a median of 7.2 (range 2–68). Statistically no significance is reached ($p = 0.326$). Nevertheless, the larger time to recurrence seems to be an expression of a positive tumor biology of the repeated resection group, whereby three patients had a time to recurrence equal or below 7 months.

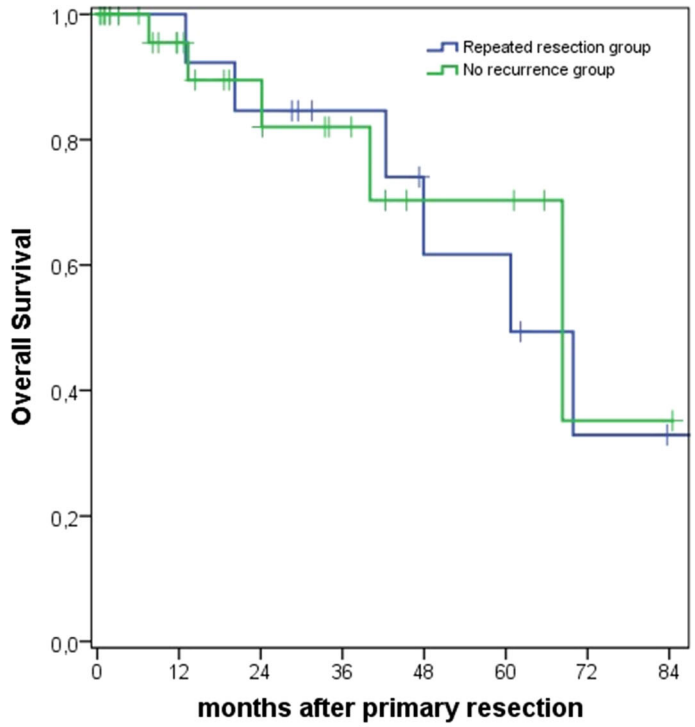
Risk factors for repeated recurrence after repeated surgical recurrence resection are not mentioned in the literature yet. Our analysis in an admittedly very limited number of patients showed that neither the R-status, morbidity after repeated resection nor focality of recurrence are risk factors for repeated recurrence.

In cases of isolated intrahepatic recurrence, TACE, SIRT or ablation are treatment alternatives to surgery. These interventional procedures were used ($n = 8$) in our series if we considered surgery not reasonable, i.e., in small, centrally located nodules, which would have required the resection of a larger liver volume.

In a multicenter analysis, Spolverato et al. [7] analyzed 563 patients who underwent curative intended hepatic resection over a 23-year period. Of these, 41 patients underwent repeated liver resection, with or without additional ablation for disease recurrence. They reported only modest benefit in median survival for patients who underwent repeated surgery over those who had percutaneous ablation or intra-arterial therapy. In contrast, Zhang et al. [11] reported a survival benefit of repeated resection ($n = 32$) over thermal ablation ($n = 77$) in tumors above 3 cm. The authors noted that the inclusion criteria for resection or ablation differed. Comparable to Zhang, we also found a significant benefit of repeated resections over chemotherapy or intervention (TACE/SIRT/ablation) (Fig. 3).

Regarding the incidence of major complications, Zhang reported a significantly higher morbidity in the hepatic resection group (in 15/32 patients) compared to local ablation. This is in contrast to our results, since we found a low rate of morbidity ($\geq$ grade III) in 22% (4/18).

Our patients did not undergo adjuvant chemotherapy after resection of primary or recurrent ICC due to the lack of data at the time of clinical presentation. Three patients were included in the ACTICCA trial after primary resection. After first results of the BILCAP trial [25] were presented, adjuvant chemotherapy with capecitabine became standard treatment, at least at our center. From our



number at risk	0	12	24	36	48	60	72	84
Repeated res. group	13	13	11	8	5	5	2	1
No recurrence group	42	23	16	11	5	5	1	1

Fig. 5 Comparison of Kaplan–Meier analyses of overall survival of the repeated resection group versus patients who had no recurrence ($p = 0.941$). Survival was calculated from the day of primary resection

point of view, patients with repeated resection (and/or ablation) for recurrent ICC should be advised by an oncologist and offered adjuvant treatment. Particularly, those patients who did not undergo adjuvant chemotherapy after primary resection or with short time to recurrence what indicates an obviously more aggressive tumor biology might benefit most. However, these suggestions are difficult to discuss because there are no data available on this particular topic yet.

Data on preoperative/neoadjuvant chemotherapy for ICC are scarce as well. Buettner and colleagues showed in a retrospective multicenter study that 5.9% of 1057 patients who underwent liver resection for ICC received preoperative chemotherapy [26]. These patients had more likely advanced disease compared to patients who did not undergo preoperative chemotherapy, but the overall and disease-free survivals were comparable. These findings were endorsed by Le Roy et al. [27]. In our cohort, only one patient who underwent repeated resection for recurrent ICC received preoperative chemotherapy ahead primary surgery (patient number 14 of Table 4) and due to the small number further statistical analysis was not reasonable. In advanced and borderline resectable ICC, preoperative chemotherapy can stabilize or even downsize the disease and lead to later resection. This approach might be used in recurrent ICC as well. Three patients underwent chemotherapy ahead of repeated resection with time to de novo recurrence of 20, 3 and 3 months, respectively. Further studies of preoperative and adjuvant chemotherapy are necessary to show possible benefits and their impact in the future.

Due to the small number of patients and study design, we cannot prove that surgery is superior to chemotherapy for recurrences of ICC. However, we demonstrate that the natural history of disease recurrence is as variable as that of the primary disease, and that repeated surgery in this subgroup of patients results in favorable outcome. We would consider patients candidates for surgical therapy, if the disease is limited to the liver and surgery can be offered with acceptable morbidity irrespective of the extent of primary surgery. A long interval between primary tumor surgery and diagnosis of recurrence appears advantageous because of a favorable tumor biology, but the shortest time until repeated resection was 3 months. We did not consider patients with disease-free interval < 3 months for surgical therapy. Chemotherapy can still be offered in case of recurrence after surgery, when a local therapy does not appear reasonable. However, neoadjuvant chemotherapy might also be beneficial prior to surgery for recurrent disease in selected cases.

Table 4 Literature overview

Author (reference)	Year	# of resections	Cases of rep. resection	Focality of 1st recurrence	Kaplan–Meier analysis of survival benefit
Yamamoto [6]	2001	123	4	ncd	na
Sotiropoulos [19]	2005	–	3	ncd	na
Konstadoulakis [3]	2008	54	7[a]	sol. + multi.	na
Choi [4]	2009	64	3	ncd	na
Lang [5]	2009	83	4	sol. + multi.	na
Ohtsuka [23]	2009	57	9	ncd	na
Ercolani [20]	2010	72	6	ncd	na
Kamphues [22]	2010	107	7	ncd	na
Sulpice [21]	2012	87	4	ncd	na
Zhang [11]	2013	1372	32	sol. + multi.	na[b]
Doussot [12]	2015	188	12	ncd	na
Souche [8]	2015	125	12	sol. only	Significant
Takahashi [13]	2015	70	12	sol. + multi.	Significant[d]
Spolverato [7]	2016	563	41[a]	sol. + multi.	na[c]
Bartsch (presented)		127	18	sol. + multi.	Significant

Ref., reference; rep., repeated; ncd, not clearly defined; na, not analyzed; sol., solitary, multi., multifocal

[a]With or without additional ablation, all patients underwent adjuvant chemotherapy

[b]Study designed for comparison of ablation with repeated resection

[c]Survival was compared through median survival after treatment

[d]For survival analysis, patients with gallbladder carcinoma, perihilar and distal cholangiocarcinoma were included

In conclusion, an aggressive surgical approach for recurrent ICC achieved reasonable overall survival. However, the optimal criteria for patient selection need to be defined. So far, the indication for surgery for recurrent disease has remained individual and should be taken after interdisciplinary discussion in specialized centers in order to guarantee low morbidity. In guidelines, repeated surgery should be mentioned as treatment option.

Compliance with ethical standards

Conflict of interest There are no conflicts to declare or financial relationships to disclose.

References

1. Patel T (2002) Worldwide trends in mortality from biliary tract malignancies. BMC Cancer 2:10
2. Khan SA, Taylor-Robinson SD, Toledano MB, Beck A, Elliott P, Thomas HC (2002) Changing international trends in mortality rates for liver, biliary and pancreatic tumours. J Hepatol 37(6):806–813
3. Konstadoulakis MM, Roayaie S, Gomatos IP, Labow D, Fiel MI, Miller CM et al (2008) Fifteen-year, single-center experience with the surgical management of intrahepatic cholangiocarcinoma: operative results and long-term outcome. Surgery 143(3):366–374
4. Choi SB, Kim KS, Choi JY, Park SW, Choi JS, Lee WJ et al (2009) The prognosis and survival outcome of intrahepatic cholangiocarcinoma following surgical resection: association of lymph node metastasis and lymph node dissection with survival. Ann Surg Oncol 16(11):3048–3056
5. Lang H, Sotiropoulos GC, Sgourakis G, Schmitz KJ, Paul A, Hilgard P et al (2009) Operations for intrahepatic cholangiocarcinoma: single-institution experience of 158 patients. J Am Coll Surg 208(2):218–228
6. Yamamoto M, Takasaki K, Otsubo T, Katsuragawa H, Katagiri S (2001) Recurrence after surgical resection of intrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Surg 8(2):154–157
7. Spolverato G, Kim Y, Alexandrescu S, Marques HP, Lamelas J, Aldrighetti L et al (2016) Management and outcomes of patients with recurrent intrahepatic cholangiocarcinoma following previous curative-intent surgical resection. Ann Surg Oncol 23(1):235–243
8. Souche R, Addeo P, Oussoultzoglou E, Herrero A, Rosso E, Navarro F et al (2015) First and repeat liver resection for primary and recurrent intrahepatic cholangiocarcinoma. Am J Surg 212:221–229
9. Bartsch F, Baumgart J, Hoppe-Lotichius M, Schmidtmann I, Heinrich S, Lang H (2018) Visceral infiltration of intrahepatic cholangiocarcinoma is most prognostic after curative resection—retrospective cohort study of 102 consecutive liver resections from a single center. Int J Surg 55:193–200
10. Khan SA, Davidson BR, Goldin RD, Heaton N, Karani J, Pereira SP et al (2012) Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. Gut 61(12):1657–1669
11. Zhang SJ, Hu P, Wang N, Shen Q, Sun AX, Kuang M et al (2013) Thermal ablation versus repeated hepatic resection for recurrent intrahepatic cholangiocarcinoma. Ann Surg Oncol 20(11):3596–3602
12. Doussot A, Groot-Koerkamp B, Wiggers JK, Chou J, Gonen M, DeMatteo RP et al (2015) Outcomes after resection of

intrahepatic cholangiocarcinoma: external validation and comparison of prognostic models. J Am Coll Surg 221(2):452–461
13. Takahashi Y, Ebata T, Yokoyama Y, Igami T, Sugawara G, Mizuno T et al (2015) Surgery for recurrent biliary tract cancer: a single-center experience with 74 consecutive resections. Ann Surg 262(1):121–129
14. Bridgewater J, Galle PR, Khan SA, Llovet JM, Park JW, Patel T et al (2014) Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol 60(6):1268–1289
15. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD et al (2009) The Clavien–Dindo classification of surgical complications: five-year experience. Ann Surg 250(2):187–196
16. Punt CJ, Buyse M, Kohne CH, Hohenberger P, Labianca R, Schmoll HJ et al (2007) Endpoints in adjuvant treatment trials: a systematic review of the literature in colon cancer and proposed definitions for future trials. J Natl Cancer Inst 99(13):998–1003
17. Benavides M, Anton A, Gallego J, Gomez MA, Jimenez-Gordo A, La Casta A et al (2015) Biliary tract cancers: SEOM clinical guidelines. Clin Transl Oncol 17(12):982–987
18. Alvaro D, Cannizzaro R, Labianca R, Valvo F, Farinati F, Italian Society of Gastroenterology (SIGE) et al (2010) Cholangiocarcinoma: a position paper by the Italian Society of Gastroenterology (SIGE), the Italian Association of Hospital Gastroenterology (AIGO), the Italian Association of Medical Oncology (AIOM) and the Italian Association of Oncological Radiotherapy (AIRO). Dig Liver Dis 42(12):831–838
19. Sotiropoulos GC, Lang H, Broelsch CE (2005) Surgical management of recurrent intrahepatic cholangiocellular carcinoma after liver resection. Surgery 137(6):669–670
20. Ercolani G, Vetrone G, Grazi GL, Aramaki O, Cescon M, Ravaioli M et al (2010) Intrahepatic cholangiocarcinoma: primary liver resection and aggressive multimodal treatment of recurrence significantly prolong survival. Ann Surg 252(1):107–114
21. Sulpice L, Rayar M, Boucher E, Pracht M, Meunier B, Boudjema K (2012) Treatment of recurrent intrahepatic cholangiocarcinoma. Br J Surg 99(12):1711–1717
22. Kamphues C, Seehofer D, Eisele RM, Denecke T, Pratschke J, Neumann UP et al (2010) Recurrent intrahepatic cholangiocarcinoma: single-center experience using repeated hepatectomy and radiofrequency ablation. J Hepatobiliary Pancreat Sci 17(4):509–515
23. Ohtsuka M, Kimura F, Shimizu H, Yoshidome H, Kato A, Yoshitomi H et al (2009) Significance of repeated resection for recurrent intrahepatic cholangiocarcinoma. Hepatogastroenterology 56(89):1–5
24. Hyder O, Hatzaras I, Sotiropoulos GC, Paul A, Alexandrescu S, Marques H et al (2013) Recurrence after operative management of intrahepatic cholangiocarcinoma. Surgery 153(6):811–818
25. Primrose JN, Fox R, Palmer DH, Prasad R, Mirza D, Anthoney DA, et al (2017) Adjuvant capecitabine for biliary tract cancer: The BILCAP randomized study. ASCO 2017; Abstract 4006
26. Buettner S, Koerkamp BG, Ejaz A, Buisman FE, Kim Y, Margonis GA et al (2017) The effect of preoperative chemotherapy treatment in surgically treated intrahepatic cholangiocarcinoma patients—a multi-institutional analysis. J Surg Oncol 115(3):312–318
27. Le Roy B, Gelli M, Pittau G, Allard MA, Pereira B, Serji B et al (2017) Neoadjuvant chemotherapy for initially unresectable intrahepatic cholangiocarcinoma. Br J Surg 105:839–847