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Clinical outcome after resection of early-stage hilar cholangiocarcinoma

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ABSTRACT

Background: Liver transplantation in patients with unresectable early-stage (<3 cm, node negative) hilar cholangiocarcinoma has been recently reported to be associated with longer survival compared to liver resection and therefore suggested as potential treatment option also in resectable disease. Here, we investigated the outcome of resection in early-stage tumours as the standard of care in an experienced European centre.

Methods: Patients with de novo resectable hilar cholangiocarcinomas who underwent liver resection between mid-2009 and December 2017 were classified as early-stage (<3 cm and node negative) or later-stage tumours (≥3 cm and/or node positive), and were investigated with respect to clinical outcome.

Results: Fifty-six patients were analyzed of whom 17 had early-stage tumours and 39 had later-stage tumours. The sex ratio (m:f) was 30:26. The median age was 65 years (range 33–80). The median follow-up was 17.0 months (range 0.7–92.4). 5-year overall survival (OS) rates were 82% in patients with early-stage tumours and 23% in patients with later-stage tumours, respectively. Median OS was 89.9 months and 27.6 months, respectively (HR 0.25 (95% CI 0.08–0.84), $P = 0.024$).

Conclusions: In an experienced European centre, 5-year survival rates after liver resection for early-stage hilar cholangiocarcinoma are comparable with reported outcomes after transplantation. The results of this study question the value of liver transplantation in this setting, especially with respect to the shortage of transplantable organs worldwide.

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Introduction

Cholangiocarcinoma is a malignant tumour of the biliary tree with the liver hilum being the most common tumour location. Its incidence is approximately 2/100,000 individuals in a Western society [1,2]. Patients with hilar cholangiocarcinoma usually present with painless jaundice and require interventional drainage. Unfortunately, most patients are unresectable at the time of diagnosis due to locally advanced or metastatic disease [3]. In patients with resectable disease, surgical resection is the gold standard of treatment [4]. However, resection is technically challenging as dissection along vital structures such as the hepatic artery and the portal vein is required, as well as a biliodigestive anastomosis. In addition, postoperative morbidity is substantial with a reported rate of up to 60% even in experienced centres [5]. Prognosis of hilar cholangiocarcinoma is usually poor but 5-year overall survival (OS) rates of 20–45% can be achieved in experienced centres [3,5–7].

Until now, tumour differentiation, resection margin status and lymph node status have been reported as clinically relevant prognosticators [5]. Additional pathological factors associated with prognosis include perineural and lymphovascular invasion [8,9].

The Mayo Clinic has previously reported their landmark data on liver transplantation following preoperative chemoradiation in patients with unresectable hilar cholangiocarcinoma [10,11]. After 319 patients treated per protocol and 199 patients who underwent transplantation the 5-year OS rate at the Mayo Clinic was 56% in patients with de novo cholangiocarcinoma [12]. In a recent multicentre study by Ethun et al., liver transplantation after

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neoadjuvant chemoradiation was investigated as a potentially curative treatment approach in patients with unresectable hilar cholangiocarcinoma and compared to patients with tumours who underwent resection (5-year OS 64% (transplant) versus 18% (resection), $P < 0.001$). In patients with de novo cholangiocarcinoma, the authors reported a 5-year OS for transplant patients with unresectable tumours of 54% versus 29% for resection patients with early-stage tumours (<3 cm radial diameter, node negative disease). The authors therefore concluded that these results warrant prospective investigation of transplantation in patients with resectable disease [13].

To address the question of treatment options for early-stage resectable hilar cholangiocarcinoma, we investigated clinical outcome in patients with histologically confirmed tumours <3 cm and N0-status who underwent liver resection in curative intent in an experienced European centre and who would have met the inclusion criteria for transplantation reported by Ethun et al. [13].

Material and methods

Consecutive patients who underwent resection of de novo resectable hilar cholangiocarcinoma in curative intent at the Aintree University Hospital between mid-2009 and 2017 were enrolled. Patients with intrahepatic cholangiocarcinoma were excluded. None of the patients had primary sclerosing cholangitis (PSC). Clinical data were obtained from a prospectively maintained database. The study was approved by the institutional review board. Patients were classified as having early-stage tumours (solitary <3 cm radial diameter and node negative upon histological examination) or later-stage tumours (≥3 cm and/or node positive). Patient groups were compared with respect to OS. Other factors analyzed were age, sex, ASA grade, tumour stage, tumour grade, node stage, presence of lymphatic vessel or perineural invasion, resection margin, presence of preoperative biliary drainage, classification according to Bismuth-Corlette, type of resection and portal vein resection [14]. All patients were assessed at the local multidisciplinary tumour board and underwent preoperative contrast-enhanced multiphase CT of chest, abdomen and pelvis,

Table 1
Patient and tumour characteristics.

Variable	Early-stage tumour n = 17	Later-stage tumour n = 39	*P* value
Age, years	63.8 (10.5)	63.1 (11.4)	0.80
Sex ratio (M:F)	8:9	22:17	0.57
ASA			0.59
1	6	18	
2	6	14	
3	5	7	
Tumour grade			0.48
G1	3	10	
G2	8	21	
G3	6	8	
Tumour classification			0.19
T1	1	7	
T2	14	26	
T3	1	6	
T4	1	0	
Node classification			<0.001
N0	17	16	
N1	0	23	
R status			0.14
R0	16	29	
R1	1	10	
Tumour size (mm)	20 (8–29)	35 (10–65)	<0.001
Bismuth-Corlette classification			0.89
I	0	0	
II	3	8	
III	12	25	
IV	2	6	
Lymphovascular invasion			1.00
Present	8	18	
Absent	9	21	
Perineural invasion			1.00
Present	15	33	
Absent	2	6	
Preoperative biliary drainage			0.16
Yes	17	33	
No	0	6	
Liver resection			0.72
Yes	13	32	
No	4	7	
Type of resection			0.69
Radical bile duct resection	4	7	
Left hemihepatectomy, seg 1 + EHBD	4	8	
Right hemihepatectomy, seg 1 + EHBD	1	5	
Left trisectionectomy, seg 1 + EHBD	3	12	
Right trisectionectomy, seg 1 + EHBD	5	7	
Portal vein resection			0.54
Yes	7	12	
No	10	27	

and staging laparoscopy for disease assessment and to exclude peritoneal disease prior to the tumour resection. Additionally, MRI of the liver was performed in 40 patients and PET-CT in one patient. Biliodigestive reconstruction was performed with an end-to-side Roux-en-Y anastomosis. Postoperative morbidity and mortality within the first 90 days after surgery was documented using the Clavien-Dindo classification [15].

Follow-up

Patients were followed up every 6 months after the operation with clinical investigation, blood test including CEA and CA19-9 levels and contrast-enhanced multiphase CT of chest, abdomen and pelvis for the first 2 years, and once a year thereafter.

Statistical analysis

Normally distributed continuous values were presented as mean (±standard deviation) and compared using the Student's *t*-test, otherwise as median (range) and compared using the Mann-Whitney *U* test. Categorical variables were compared using chi-square test. OS was defined as time from surgery to death, or censored at the time of the last follow-up. Fur survival analysis, Kaplan-Meier curves were created and compared using the log rank test. In addition, Cox regression analyses were performed. *P* values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS 24.0 (IBM, Armonk, NY, USA).

Results

Fifty-six of 60 eligible patients were analyzed. In the remaining four patients, available information on tumour size or node status was insufficient to characterize the tumour as early or later-stage, thus they were therefore not included in this study. The sex ratio (m:f) was 30:26. The median age was 65 years (range 33–80). The median follow-up was 17.0 months (range 0.7–92.4). Of 56 patients, 17 had a tumour <3 cm and a node negative status while 39 patients had a tumour ≥3 cm and/or node positive status. Patient demographics are given in Table 1.

The median OS for the whole cohort was 33.5 months (95% CI 15.8–51.3). The median OS in patients with early-stage tumours was significantly longer compared to patients with later-stage tumours (89.9 vs. 27.6 months, HR 0.25 (95% CI 0.08–0.84), $P = 0.024$). The 1-, 3- and 5-year OS rates were 82% versus 76%, 82% versus 38%, and 82% versus 23%, respectively (Fig. 1). The only other variable that was associated with OS in univariable Cox regression analysis was node status (HR 3.33, $P = 0.003$) (Table 2). As patients were grouped into early-stage and later-stage tumours with respect to node status, these two variables were not included into a multivariable Cox regression analysis.

Postoperative mortality within 90 days was 7 of 56 patients, this was not significantly different in patients with early-stage or later-stage tumours (0 of 17 versus 7 of 39, $P = 0.09$), respectively. Postoperative complications are given in Table 3. Postoperative morbidity within 90 days was also not significantly different between the groups (11 of 17 versus 23 of 39, $P = 0.77$).

Discussion

This study investigated the clinical outcome after resection of hilar cholangiocarcinoma in patients with early-stage tumours. Unsurprisingly, overall survival was significantly longer compared to patients with later-stage tumours. Moreover, 5-year OS in patients with early-stage tumours treated at our centre (82%) was substantially higher compared to patients with early-stage tumours who underwent resection (29%) as reported in the recent multi-

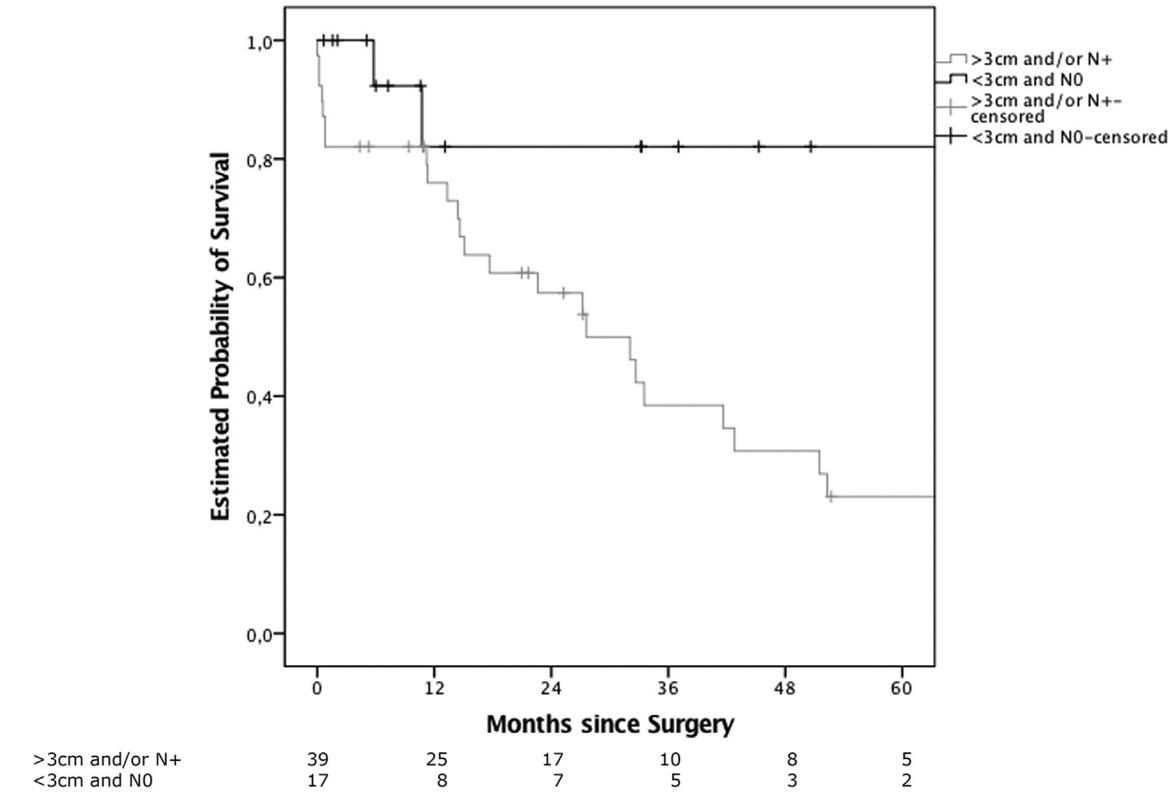

Fig. 1. OS according to tumour size and lymph node status (<3 cm and node negative vs. ≥3 cm and/or node positive, log rank P = 0.015).

Table 2
Univariable and multivariable Cox regression analyses of factors associated with OS.

Variable	Univariable	
	HR (95% CI)	*P* value
Age		0.59
>70 years	0.78 (0.31, 1.93)	
≤70 years	1 (Reference)	
Sex		0.48
Female	1.30 (0.63, 2.68)	
Male	1 (Reference)	
ASA		0.97
3	1.02 (0.41, 2.53)	
1, 2	1 (Reference)	
Tumour grade		0.05
G3	2.24 (0.99, 5.08)	
G1, G2	1 (Reference)	
Tumour classification		0.23
T3, T4	1.74 (0.70, 4.35)	
T1, T2	1 (Reference)	
Node classification		0.003
N1	3.33 (1.51, 7.31)	
N0	1 (Reference)	
R status		0.13
R1	2.06 (0.81, 5.21)	
R0	1 (Reference)	
Lymphovascular invasion		0.62
Present	1.22 (0.56, 2.69)	
Absent	1 (Reference)	
Perineural invasion		0.17
Present	2.80 (0.65, 11.95)	
Absent	1 (Reference)	
Preoperative biliary drainage		0.74
Yes	1.23 (0.37, 4.11)	
No	1 (Reference)	
Liver resection		0.09
Yes	0.40 (0.14, 1.14)	
No	1 (Reference)	
Portal vein resection		0.24
Yes	1.58 (0.73, 3.40)	
No	1 (Reference)	
Early-stage tumour		0.024
Yes	0.25 (0.08, 0.84)	
No	1 (Reference)	

centre study [13].

Ethun et al. presented a retrospective multi-centre study investigating 232 patients, of whom 41 underwent liver transplantation after completing neoadjuvant chemoradiation according to the Mayo protocol for unresectable disease between 2000 and 2015 [10,13]. The other 191 patients had resectable disease and underwent liver resection in curative intent. They found that patients who underwent liver transplantation had a significantly longer OS compared to patients who underwent liver resection for resectable disease (5-year OS 64% versus 18%, $P < 0.001$). When comparing a subgroup of non-PSC patients with tumours <3 cm in size and node negative status who underwent liver resection the difference in survival was still statistically different (5-year OS 54% versus 29%, $P = 0.03$). The authors therefore concluded that liver transplantation for unresectable tumours (<3 cm and node negative) is superior to resection in patients with resectable hilar cholangiocarcinoma and may be a viable treatment option also in patients with resectable tumours warranting prospective studies. However, these conclusions must be considered with caution.

The 5-year OS rate in patients with resectable early-stage tumours (histologically confirmed <3 cm and node negative) who underwent liver resection was only 29% and therefore less than half that reported in our series (82%). This is especially remarkable as this is a favorable group with low volume disease and 29% survival at five years is similar to that reported for all patients (including bulky node positive disease) who undergo resection with 5-year OS rates between 20 and 45% as previously reported by our group and other experienced centres [3,5–7]. Also Dr. Nagino, an experienced hepatobiliary surgeon from the Nagoya University Graduate School of Medicine in Japan, addressed this fact in his comment to the study by Ethun et al. and raises strong concerns regarding the use of transplantation in this setting [16].

One possible explanation for this striking difference in 5-year OS could be the number of procedures performed at the investigated institutions in the earlier study. Over a period of 15 years, 191 liver resections were performed in ten different centres, which means that in average less than two resections were performed per centre per year. In contrast, approximately seven resections per year were performed at our centre. This volume difference may be one of the reasons why 5-year OS was dramatically better in our centre compared to 5-year OS in the study reported by Ethun et al.

Another issue that questions the clinical value of liver transplantation in patients with resectable early-stage hilar cholangiocarcinoma is the fact that accurate patient selection according to the proposed criteria is currently not feasible. At present, preoperative assessment of tumour size and especially node status cannot be ensured. This is despite the fact that all patients undergo preoperative imaging including CT and MRI scans and staging laparoscopy to rule out peritoneal disease. PET-CT has limited clinical value in staging of patients with cholangiocarcinoma with a sensitivity for detecting lymph node metastases ranging from 42 to 76% and does therefore not robustly contribute to identifying patients who met the criteria for liver transplantation [17–19] This limitation in preoperative staging meant that in the presented unresectable cohort seven of 41 patients who underwent transplantation actually had occult nodal disease and an unreported number of patients had tumours up to 5 cm in size. Unfortunately, the authors did not report the 5-year OS of patients with histologically proven early-stage tumours who underwent liver transplantation. Classification of early-stage versus later-stage tumours in our study was performed based on postoperative histological examination.

Another fact that raises concerns regarding the results presented by Ethun et al. is the definition of resectability and subsequent patient selection. In our experience, patients with early-stage tumours (<3 cm and node negative) who underwent liver transplantation are rarely unresectable. The question remains how big the fraction of resectable patients was who were deemed unresectable. If resectable, these patients should have rather undergone liver resection. Moreover, Ethun et al. reported that in their resection group 15 of 52 patients with early-stage tumours had a Bismuth-Corlette type IV tumour, which is a higher rate compared to our study (2 of 17) [13]. This higher rate may have also contributed to the higher R1 resection rate (30%) and the lower 5-year OS rate in their study.

Finally, there are differences in patient characteristics between patients who underwent transplantation and those who underwent resection in the study of Ethun et al., which not only refers to the fact that transplantation patients were deemed unresectable and resection patients resectable. Patients in the resection group were significantly older, had a higher bilirubin and a lower R0 resection rate compared to transplant patients. All these differences may have an influence on the 5-year OS rates in the two groups [13].

The worldwide shortage of donor organs is another issue that has to be recognized when discussing treatment modalities for early-stage resectable hilar cholangiocarcinoma. Therefore, adding this early-stage disease as an indication for liver transplantation has to be questioned when liver resection can be safely performed with excellent clinical outcome in experienced centres. Also Dr. Rosen from the Mayo Clinic raised concerns regarding

Table 3
Postoperative complications before 90 days after surgery according to Clavien-Dindo classification.

Type of complications	Number of complications
Grade 2	
Sepsis requiring IV antibiotics	36
Bile leak without IR drainage	12
Ascites (medically managed)	7
Acute coronary syndrome	3
Thromboembolic event	3
Grade 3a	
Abdominal abscess with IR drainage	7
Bile leak with IR drainage	5
Grade 3b	
Repeat laparotomy	2
Grade 4	
Multi-organ dysfunction syndrome	8

transplantation in patients with resectable disease in a comment to the study of Ethun et al. mainly because of the small difference in 5-year OS in the intention-to-treat populations, which in his opinion does not justify the use of donor livers [12,13]. Moreover, Dr. Rosen and colleagues addressed the role of transplantation compared to resection in patients with de novo hilar cholangiocarcinoma and found no difference in survival in a subgroup of patients with node negative disease concluding that resection is the treatment of choice in patients with resectable disease [20].

At the moment, liver transplantation for resectable hilar cholangiocarcinoma in a multidisciplinary treatment approach is an experimental concept and should only be offered to patients in prospective clinical studies. The French TRANSPHIL randomised-controlled trial is currently recruiting patients and should therefore be supported to clarify the clinical value of this concept (clinicaltrials.gov identifier NCT02232932). With respect to unresectable disease, the Mayo clinic reported a 5-year OS rate of 56% in patients with de novo cholangiocarcinoma and 76% in patients with PSC-related cholangiocarcinoma [12]. These data suggest that the latter patients may benefit more from transplantation than patients with de novo disease.

Finally, patients with node positive disease who undergo liver resection still have poor survival rates. The BILCAP study has shown that adjuvant chemotherapy with capecitabine improves clinical outcome [21]. Nevertheless, new multimodal treatment concepts are urgently needed to improve survival in this patient population.

However, our study has limitations that have to be considered. One is the retrospective design of the study. Another limitation that needs to be acknowledged is the patient number. Furthermore, we understand that cross-study comparisons have to be considered with caution. Also, we acknowledge that there are some differences between patients in the present study and those reported by Ethun et al. In our study, 12 of 17 patients with early-stage tumours were ASA 1-2, while in the study by Ethun et al. only 15 of 45 patients were ASA 1-2. Moreover, in our study 16 of 17 patients had an R0 resection, while only 39 of 56 patients in the study by Ethun et al. had an R0 resection. Especially, the latter fact may be related to the higher rate of Bismuth-Corlette type IV tumours and partially explain the lower 5-year OS rate in the previous study [13].

Conclusions

This study investigating patients with hilar cholangiocarcinoma shows that resection of early-stage tumours (<3 cm and node negative) is associated with excellent 5-year survival in an experienced centre. The results of this study support the clinical value of liver resection in these patients. With respect to the shortage of organs for transplantation worldwide, liver transplantation may not be treatment of choice in this favorable patient group with low volume disease.

Conflicts of interest

The authors declare no conflict of interest.

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