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REVIEW

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Diagnostic and surgical approaches in hilar cholangiocarcinoma

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Abstract Hilar cholangiocarcinoma is a rare tumor. Surgery remains the only treatment to prolong survival. There is a correlation between the extent of diagnostic work-up and the achieved resection rates. Moreover, diagnostic work-up may contribute to an improvement of the surgical technique. Due to the perihilar fibrosis, the extent of the central lesion may be overestimated, which may lead to exclude the patient from potentially curative surgery. En bloc resection is requested to achieve tumor-free resection margins. The prognosis of the patients treated with surgery is strongly influenced by negative resection margins. According to our experience, 5-year survival of 78/111 patients with tumor resection (resection rate 71%) has been 30%. Forty-eight percent of the patients with curative en bloc resection of tumor and liver survived for more than 5 years. Perioperative mortality was 5.1%. The available data are supposed to reflect the results of centers with high caseload and not the general situation.

Keywords Hilar cholangiocarcinoma · Diagnostic approach · Surgery · Resection · Prognosis

Introduction

Hilar cholangiocarcinoma (hilCC) was described to be a particular entity of biliary carcinomas by G. Klatskin in 1965 [1]. With an estimated incidence of 1:250,000, the number of patients is low and, therefore, experience with this disease is limited. The number of patients included in retrospective analyses exceeds 100 only in a few specialized centers [2–8]. In addition, prospective studies are not available.

The histomorphological features of the hilCC are identical with other extra- and intrahepatic bile duct carcinomas. Particular localization leads to early clinical symptoms. The early clinical manifestation of this tumor contributes to better prognosis compared to intrahepatic cholangiocarcinoma, even though a different tumor biology may not be excluded. HilCC usually demonstrates a tendency of intramural growth, perineural, and perifocal lymphatic infiltration. Moreover, the adjacent liver parenchyma may be infiltrated. On the other hand, lymph nodes are involved in only 30 to 40% and distant metastases are observed in only 10% of the patients at the time of surgery [4, 9–12]. Due to the particular localization of this tumor and its propensity to infiltrate the hilar region, hilCC remains a challenge for surgeons, internists, and radiologists.

Course of hilar cholangiocarcinoma

Without treatment, survival of patients with hilCCs ranges between 4 and 8 months. Palliative biliary drainage by stents or prostheses appears to confer a survival benefit of only a few months [13–20] (Table 1). Endoscopically placed plastic stents or metallic stents result in comparable survival. Plastic stents may be changed if occluded, whereas the patency of metallic stents persists over a longer period but these stents cannot be changed. The benefit of brachytherapy in hilCC is uncertain [15, 21]. Photodynamic treatment, however, may be an option for patients with surgically unresectable tumors [19, 20].

Surgery remains as the only life-prolonging and potentially lifesaving approach. Even patients with palliative resection benefit from surgery compared to those without resection. In patients treated at our institution, the following general experience exists (Fig. 1): Survival—mean and median—is increased by a factor of 5 in patients with palliative surgery compared to patients without specific surgical treatment, and increases only moderately in patients with curative resection compared to palliative resection. In any study, patient selection appears to play a role. Survival of patients without any surgery may be restricted to 1 or 2 months due to their poor condition. In comparison, those patients with explorative surgery but also without specific surgical treatment may survive for 6 months since their condition is better. The problem of patient selection will be repeatedly encountered during the discussion of diagnostic work-up and surgical treatment.

Diagnostic work-up

The elevation of alkaline phosphatase indicates an unilateral biliary obstruction. Most patients are recognized to suffer from hilCC when serum bilirubin and alkaline phosphatase are increased. Ultrasonography, endoscopic retrograde cholangiography (ERC), percutaneous transhepatic cholangiography (PTC), and magnetic resonance imaging (MRI) are used to delineate the site and longitudinal extension of the obstruction. In addition, MRI and computerized tomography (CT) scans remain as the principal approaches to visualize peripheral tumor growth.

According to radiological and medical studies, imaging procedures are extremely reliable to assess the longitudinal and peripheral tumor growth [22–27]. The accuracy of CT and MRI to depict the peripheral extent of the tumor has been shown to reach 100%, and the accuracy of ERC, PTC, and MR cholangiography (MRC) ranges between 80 and 100%. A fundamental drawback of radiological studies is that diagnostic procedures are usually compared with one another and not with the gold standard, which is the surgical specimen [24, 26–28].

The surgical experience differs considerably from the results of radiological and medical studies. The problem is reflected by a remarkable number of patients who are deemed unresectable due to misleading preoperative information. Remarkably, high resection rates seem to correlate with the extent and quality of the diagnostic work-up. In this work-up, PTC remains a central issue [29–31]. Whereas PTC particularly in Japan delineates single segmental biliary branches, we have restricted PTC to the right and the left part of the biliary system by one puncture each. Only in exceptional cases are the right anterior and posterior trunk visualized separately.

Based on this approach, we have compared localization and extent of the hilCC determined by ERC, MRC, and PTC with the surgical specimens of 59 patients by a retrospective, blinded analysis [32]. According to this study, ERC was capable of depicting the biliary system in less than 50% of the cases. Moreover, MRC was significantly inferior to PTC. Regarding all available data resulting from ERC, MRC, and PTC, the classification according to Bismuth and Corlette was correctly predicted in only 31 of 59 patients (Table 2). Even if the classification according to Bismuth and Corlette was unprecise (particularly between the types III and IV), it was possible to define the strategy before surgery. In 48 of 59 cases, the predicted operation was performed [33]. Overestimation of the tumor extent was the most common mistake during diagnostic work-up. R0 resection and survival, however, were not significantly worse in patients with overestimated lesions compared to correctly assessed tumors [32]. It would have been fatal if overinterpretation of the real situation had led to the exclusion of these patients from surgery. It is obvious that tumor infiltration may be mimicked by sludge formation or stromal proliferation, which leads to overinterpretation of tumor extent.

A hilar stricture that cannot be explained by reliable data from the patient's history must be regarded as malignant. Even in specialized centers, the true disease behind a negative biopsy may be a malignoma [34]. In our experience, brush cytology in 40 patients with hilCC was positive in only ten patients. This result appears to reflect the clinical reality. Therefore, the resection has to be performed even if

Table 1 Survival in palliatively treated patients with hilar cholangiocarcinoma

Author and year	Number of patients	Palliation	Survival
Cheng et al. [13]	36	Wallstent	4.5 months, median
Gerhards et al. [14]	41	Endoprosthesis	9 months, median
Golfieri et al. [15]	20	Percutaneous transhepatic drainage (PTD) + brachytherapy	7.5 months, mean
		PTD	1.7 months, mean
Figueras et al. [16]	48	Endoprosthesis/stent	6 months, mean
Kaiho et al. [17]	21	Metallic stent	4.9 months mean
Schima et al. [18]	41	Wallstent	4.3 months, mean
Wiedmann et al. [19]	23	Photodynamic treatment	0.3 months, mean
Ortner et al. [20]	20	Photodynamic treatment	16.4 months, median

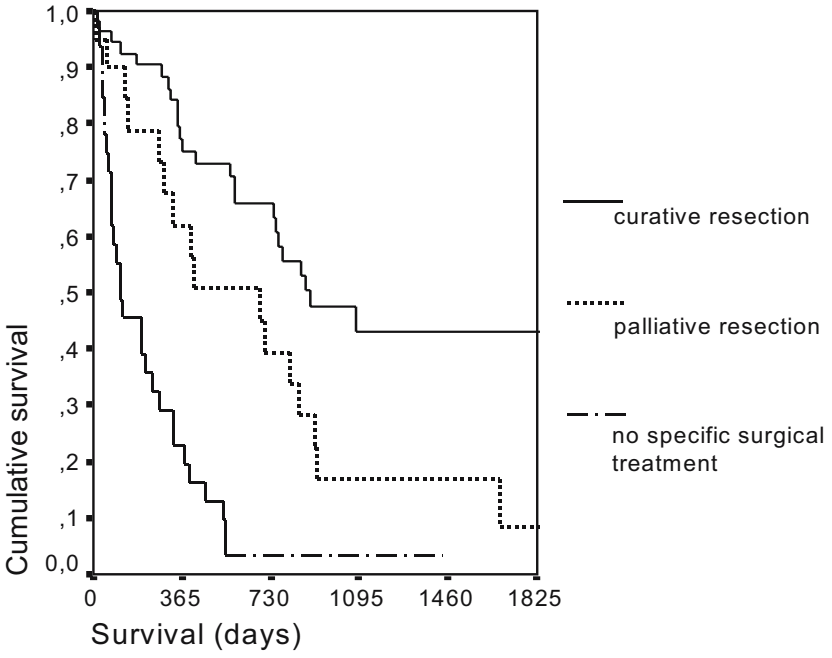

Fig. 1 Survival (Kaplan–Meier) of patients with hilar cholangiocarcinoma following curative resection (n=57), palliative resection (n=21), and without specific treatment (patients without surgery and after exploration; n=33). The difference between the patients are highly significant: patients after surgery vs no surgery p<0.0001, curative vs palliative surgery p=0.02, and palliative surgery vs no surgery p=0.0008

the results of a biopsy or of a cytological test are negative. The general rule has to be applied that malignant growth can never be excluded by a negative test. As a consequence, the rate of benign strictures in patients resected for suspicious hilar obstruction is around 15% [35].

In contrast to numerous radiological publications [22, 23, 26, 27], the peripheral tumor growth cannot be reliably assessed. A small hilCC, even if infiltrating the adjacent parenchyma, may remain invisible in CT or MRI. In our experience, the preoperative CT scan or the MRI is important for two reasons: to exclude distant metastases including intrahepatic metastases and to assess the size of the two liver lobes, which is important for surgical decisions.

Table 2 Accuracy of preoperative assessment of the tumor type according to Bismuth and Corlette in 59 patients with hilar cholangiocarcinoma

Preoperative assessment	Assessment of the surgical specimen				
	I	II	IIIa	IIIb	IV
I	2	2	3	1	
II		1	1		
IIIa		1	12		2
IIIb				10	
IV		1	9	8	6

Thirty-one patients have been correctly assessed. In 19 and 9 patients, respectively, the tumor was over- and underestimated

Hilar anatomy and surgical principles

Peculiarities and difficulties of the surgical approach in hilCC result from hilar anatomy and the distinct features of this tumor. The bifurcation of the bile duct is located ventrally and slightly craniad to the portal bifurcation. In most patients, the right hepatic artery crosses behind the common duct caudad to the bifurcation. The ventral aspect of the biliary bifurcation is partially covered by the parenchyma of segment 4b. The left hepatic duct runs for about 2 cm outside the parenchyma to reach the region of the left lateral segments at the ligamentum teres. The right hepatic duct is extremely short—if developed at all. After less than 5 mm, the right duct divides into two main trunks for the anterior (5 and 8) and posterior (6 and 7) segments, respectively. The branching of the right duct may be irregular. The connective tissue that surrounds the intraparenchymal ducts and vessels forms a fibrous plate at the bile duct bifurcation, the so-called hilar plate. The hilar plate is clearly visible after resection of the bile duct bifurcation, including short portions of the right and left main ducts. In this situation the openings of the bile ducts encased in connective tissue form a horseshoe-like, ventrocranially convex bow. Behind this bow the right branches of the portal vein and the hepatic artery (or arteries) enters the liver parenchyma. The bile duct(s) to the first segment is visible in the dorsal portion of the resected field and slightly to the left but usually within and very close to the portal bifurcation. The bile duct(s) to the caudate lobe are extremely short. This close contact may be a reason for the frequent tumor infiltration of the 1st segment, the portal vein, and the hepatic artery [36, 37].

Due to this close contact with important hilar structures, a local resection of hilCC—even in type I—results frequently in an oncologically insufficient situation. Limited resection is usually inadequate neglecting ductal and periductal growth, lymphatic and perineural involvement, and parenchymal infiltration. The required radicality may only be achieved by en bloc resection of the hilar tumor and a part of the adjacent liver. As local recurrence is the main reason for failure of surgical treatment, the principal resection of the portal vein at its bifurcation may be advisable [8, 36, 38].

The obvious benefit resulting from the en bloc approach consists in a higher rate of tumor-free bile duct margins. En bloc resection per se failed to be of prognostic importance in the absence of negative margins. Nevertheless, positive periductal lymphatic and neural structures, as well as positive parenchymal margins, are highly probable to be influential on tumor relapse [8, 12]. Unfortunately, pathomorphological studies—including the work-up of our own surgical specimens—usually focus on tumor-free bile ducts. Clear bile ducts, clear periductal structures, and parenchymal margins are best reached by a right trisegmentectomy. From the oncological point of view aiming at wide margins and to perform a no-touch resection, this approach is the most preferable one and it is also relatively easy. In any case, the caudate lobe has to be resected. An R0 resection without removal of the caudate lobe is virtually impossible.

In accordance to this, type IIIa and type IV tumors are preferably resected by right trisegmentectomy or right hepatectomy. According to our experience, in type IIIb tumors, and also in many type IV tumors, the left hepatectomy is the safer approach because a higher volume of parenchyma is left behind. Long-lasting biliary occlusion leads to atrophy of the affected lobe, i. e. in type IIIb tumors the atrophy of the left lobe. The preoperative decompression of the occluded duct and particularly the additional occlusion of the portal vein of the hemiliver to be resected enable the parenchyma to regenerate [39–41]. Nevertheless, we prefer to preserve a sufficient portion of the right lobe in compromised patients instead of relying on the questionable functional capacity of the left lateral segments [39]. A long-term biliary decompression and a portal vein occlusion were not performed in any of our 69 en bloc resections.

Liver function of patients with high bilirubin levels may be compromised regardless of the size of the liver. In these patients external or internal biliary decompression aiming at recompensation of the liver function has been performed. Results of randomized studies are controversial [42]. Three of our four patients who died perioperatively had serum bilirubin levels that exceeded 20 mg%.

In general, hilCC is deemed unresectable if the tumor is reaching the segmental bile duct branches on both sides, if there are distant metastases, and probably if lymph nodes beyond the gastroduodenal ligament are involved. With regard to the involvement of the bile ducts, it should be stressed once again that assessment of resectability is rather unreliable due to hilar sclerosis during surgery and tumor extent is frequently overestimated in preoperative work-up.

Results

The survival of patients with hilCC clearly depends on:

1. Whether it is feasible to perform a resection (resection rate)
2. How the resection is performed (hilar resection vs en bloc resection, R0 resection)
3. Biological predictors of survival

In discussing these issues we face a principal concern: The data from the literature are difficult to compare because patient selection may vary from center to center and surgery is performed applying different principles. In addition to this, only retrospective studies are available.

In our experience the respective median survival of curatively resected patients vs patients with palliative resection vs patients without any specific surgery was 897 vs 686 vs 117 days ($p<0.0001$). To reach a high resection rate appears, therefore, to be an important goal (Table 3). According to publications from Asian countries, a comprehensive preoperative diagnostic work-up and a more aggressive attitude toward resection have contributed to reaching this goal [4–7, 29, 48]. The difference in surgical approach is impressively demonstrated in a recently published comparison of an American and a Japanese center [31]. Surgery was performed in 80% of the Nagoya patients, while in comparison, only 25% of the patients in the Lahey Clinic were considered to be resectable. Survival of the resectable patients was comparable in the two institutions, as was survival in unresectable patients indicating similar tumor biology. Patient selection also did not play a big role. The attitude toward resection

Table 3 Resection rate and rate of curative resections in patients with hilar cholangiocarcinoma

Author and year	Number of patients	Resection rate	Curative resections
Jarnagin et al. [43]	225	36%	78%
Launois et al. [44]	552	32%	–
Lee et al. [5]	151	85%	–
Neuhaus et al. [8]	133	–	60%
Nimura et al. [30]	177	80%	70%
Puhalla et al. [45]	88	42%	33%
Tsao et al. [31]	100 (Lahey)	25%	7/25
	155 (Nagoya)	79%	96/122
Uchiyama et al. [46]	57	58%	64%
Yi et al. [47]	197	61%	41%
Own Results	99	71%	75%

led to higher resection rates, because the surgical specimens in Japan demonstrated more advanced tumors than in the US.

En bloc resection of tumor and liver results in superior survival compared to hilar resection [5, 6, 49]. Whereas the 5-year survival of patients with hilar resection ranges between 0 and 10%, it reaches 25 to 30% after en bloc resection. This difference is particularly evident in type I and type II tumors (0 vs 55%) [44]. Most data suggest that the hospital mortality after en bloc resection is not higher compared to hilar resection. In high-volume centers, it ranges between 5 and 15% [4, 49, 50] and may be only marginally lower in patients with hilar resection (3%) [49]. Postoperative morbidity is generally reported to be high. It may exceed 70% [51]. Anastomotic or parenchymal biliary leaks leading to infectious complications are the major sources. In our experience, morbidity was 53%. The rate of biliary complications reached 30%.

In numerous multivariate analyses, R0 resection is reported to be the most important prognostic parameter [2, 4, 10–12, 31, 45, 50]. Lymph node involvement, and in some reports, tumor grading are prognostic predictors [4, 10–12, 31, 43]. Comparable to numerous tumor entities, positive lymph nodes are supposed to indicate a poor prognosis, whereas their surgical dissection has limited influence on survival. Even meticulous studies concerning the features of lymph node involvement are incapable of demonstrating the benefit resulting from lymph node dissection [3].

Vascular resection, in particular the resection of the portal vein, may be influential on survival. Portal vein resection has usually been performed in advanced disease to achieve oncological radicality [36, 38, 52]. Due to more advanced disease, the results might be worse, but in many studies survival is not hampered by portal vein resection. This led to the idea to perform a principal portal vein resection, and in selected patients, 5-year survival has been reported to exceed 70% [8].

A summary of the results in our patients is given in Table 4. Resection rate was 71%, the rate of curative resection 73%, and the hospital mortality 5.1%. The 5-year survival of all 111 patients who presented at our institution was 22%; in surgically treated patients it was 30%. After en bloc resection, the 5-year survival was 48% for patients with R0 (n=53) and 62% in patients with R0/N0 situation (n=43). When an R0 and N0 situation existed, all surgical approaches were comparable. According to the multivariate analysis, only lymph node involvement proved to be of prognostic impact (p=0.001; risk ratio, 3.4; confidence interval, 1.67–6.57).

Conclusions

Prognosis of patients with hilCC who are not candidates for surgery is dismal. Even if the minority of patients with hilCC may be cured, only surgically treated patients achieve a chance of long-term survival. As long as other

Table 4 Univariate analysis of potentially prognostic factors of survival in 69 patients with en bloc resection (Kaplan–Meier, significance according to log-rank test)

	Number of patients	Median survival (days)	Survival (%)		p value
			1 year	5 years	
T classification					
T1/2	21	858	68	23	
T3	48	746	68	36	0.73
Lymph node involvement					
N0	49	1,670	78	47	
N1/2	20	358	48	0	0.0003
Grading					
G1/2	47	873	69	45	
G3/G4	21	583	68	0	0.31
Bile duct margin					
R0	56	873	74	48	
R1/2	13	287	46	0	0.001
Surgical approach					
Right trisegmentectomy	12	746	64	21	*
Right hepatectomy	22	813	75	44	
Left hepatectomy	35	766	67	34	
Vascular resection					
Yes	24	746	59	41	
No	45	813	74	29	0.84
N0/vascular resection	14	1,881	83	62	
N0/R0	43	1,881	86	61	

*Significance (p value) comparing surgical approaches: right trisegmentectomy vs right hepatectomy: 0.95, left vs right hepatectomy: 0.89, comparison of all modes of resection: 0.96

forms of treatment remain ineffective, the primary option in the treatment of patients with hilCC remains to be surgery.

- According to numerous reports, there is a correlation between preoperative diagnostic work-up and resection rate. Moreover, preoperative work-up may help to decide upon the surgical strategy and to avoid intraoperative traumatization of the hilar region. Improvements of surgical technique are supposed to contribute to the recently increased survival following surgery.
- In most multivariate analyses, positive histologic margins remain an important predictor of survival. Compared to hilar tumor resection, the rate of R0 situations may be substantially increased by resection of the hilar tumor and major parts of the liver. Multivariate analyses failed to demonstrate that liver resection independent of negative margins contributed to improved survival.
- Resection of the caudate lobe is generally advisable, whereas the survival benefit of vascular resection is not supported by conclusive data. The available studies indicate that the extent of lymph node dissection has likely no influence on survival.
- Perioperative mortality and morbidity after isolated bile duct resection and major liver resection are comparable in centers with high caseload.
- The outcome in patients with hilCC is strongly influenced by biological factors. In our patients, negative lymph nodes are the most potent predictor of survival.

Diagnostic work-up, decisions upon surgery, surgical procedure, and postoperative treatment in patients with hilCC require particular experience and routine, which are dependent on the surgical volume. The studies available in the literature have been exclusively performed in centers with high volume. The general results in the treatment of hilCC are supposed to be different from these.

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