ORIGINAL RESEARCH

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Correlation analysis of preoperative magnetic resonance cholangiopancreatography and prognosis in hilar cholangiocarcinoma

Abstract

Purpose: To determine the presence and extent of preoperative biliary obstructions, using magnetic resonance cholangiopancreatography (MRCP), and to determine the clinicopathological consequences of these obstructions in a group of 83 patients with hilar cholangiocarcinoma (HC).

Methods: Fifty-five HC patients with biliary obstruction and 28 HC patients without biliary obstruction were included in the study. The associations between biliary obstruction (assessed using MRCP) and clinicopathological characteristics were analysed.

Results: Patients with biliary obstruction had a higher liver function and serum carbohydrate antigen than those without biliary obstruction. The Bismuth-Corlette classification, tumour stage and lymph node metastasis were identified as independent relative factors of biliary obstruction, while differentiation and biliary obstruction were identified as independent factors of overall survival. Furthermore, the size of the tumour, differentiation and biliary obstruction were independent prognostic indicators of disease-free survival for HC patients.

Conclusions: The presence and extent of preoperative biliary obstruction, measured by MRCP, was associated with aggressive clinicopathological features and indicated poor prognosis in HC patients.

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Hilar cholangiocarcinoma (HC) is one of the most common primary tumours of the biliary tract and accounts for 2% of all human malignancies [1]. The highest incidence of HC in the world is in southeast Asia and China. According to the results of epidemiological studies in China, the incidence of HC in residents aged 35–74 years in Shanghai (one of the largest cities in China) is 0.58/100,000. Hilar cholangiocarcinoma is often a fatal tumour, with a poor prognosis due to difficulties in diagnosing this disease at an early stage. The hilar cholangiocarcinoma lies in the core part of the biliary system and can easily occlude the bile ducts [2]. The development of biliary obstruction may contribute to poor outcomes, delays in treatment, decreased quality of life and increased mortality, leading to poor survival [3].

Magnetic resonance cholangiopancreatography (MRCP) has been increasingly used for HC since it allows for the easier identification of a tumour's extent for staging purposes and better visualisation of the biliary tree. Magnetic resonance cholangiopancreatography has demonstrated similar efficacies to endoscopic cholangiopancreatography (ERCP) in identifying the anatomic extension of HC tumours but with fewer complications [4]. In diagnosing biliary obstruction, MRCP has a sensitivity and a specificity of 97% and 98%, respectively. Furthermore, MRCP has been deemed a promising test for diagnosing biliary obstruction in HC patients.

The present study investigated the relationships between preoperative biliary obstruction (as measured by MRCP) and clinicopathological characteristics, and evaluated the correlation with overall survival (OS) and disease-free survival (DFS) in HC patients.

Materials and methods

Patients and information collection

Our study was conducted in accordance with the code of ethics of the world medical association (Helsinki Declaration) and was approved by the ethics committee of our hospital (Nankai Hospital, China). Each participant signed an informed consent form before participating.

Patients with HC who underwent curative surgery in a hospital between April 2009 and December 2013 were included in the study. The eligibility criteria for the present study were as follows: 1) patients histologically proven to have HC; 2) patients without distant metastasis or peritoneal dissemination confirmed during the operation; 3) patients who were not subjected to radiation, chemical, or biological treatment before potentially curative surgery was performed; 4) patients whose adjuvant chemotherapy or radiotherapy was not routinely administered, that is, if a patient's

pathology revealed a high degree of malignancy, chemotherapy was given when necessary, while radiotherapy was given when R0 resection was performed; 5) patients with available and complete follow-up data; and 6) HC patients who were preoperatively assessed with MRCP. The MRCP findings were consistent with the ERCP findings and final diagnoses. Staging was based all examinations, including ERCP and MRCP.

MRI examination method and detection index

An MRCP scan was performed for patients using a 3.0T magnetic resonance imaging (MRI) system (MR750; GE Healthcare; Milwaukee, WI, USA). Fasting and water prohibition was performed at four hours before scanning. These patients were in the supine position, and a body coil and respiratory gating were used for the FSE heavy T2WI scan (TR: 6,000 ms/TE: 200 ms).

MRI image analysis

Intrahepatic biliary obstruction was defined as a diameter of the grade I-II branches of the intrahepatic bile duct >5 mm. The tumour stage classification was determined after the operation, according to the American Joint Committee on Cancer's tumour size, lymph nodes affected and metastases (AJCC TNM) staging, measured maximum tumour diameter, Bismuth-Corlette grading, pathological grading and lymph node metastasis.

Follow-up

After treatment, all patients were followed every 3–6 months for two years and subsequently every year until September 2017 (or until death). Clinical examinations, serum carbohydrate antigen (CA19-9) level measurements, liver function tests, and hepatic ultrasonography were performed during each patient visit. If recurrence was suspected, further assessments, such as abdominal computed tomography or MRCP, were performed to arrive at a definitive diagnosis.

Statistical analysis

Chi-square test was performed to examine the relationship between the status of the biliary obstruction and the clinicopathological characteristics. The multivariate analysis was conducted through logistic regression. The univariate analysis for survival was performed using the Kaplan–Meier method and compared by the log-rank test. Factors with potential importance on the univariate analysis were included in the multivariate analysis. The multivariate analysis for OS was performed using the Cox proportional hazards model.

with the forward step procedure, and the hazard ratio (HR) was generated. For all analyses, $P < 0.05$ was considered statistically significant. All statistical analyses were carried out using SPSS software 18.0 [5].

Results

Patient characteristics

A total of 83 HC patients met the inclusion criteria for the present study. No patients were lost to follow-up. The median age of these patients was 58.34 years old (range: 30–79 years old). Among these 83 HC patients, 55 patients presented with biliary obstruction, while 28 patients had no biliary obstruction. The presence and different degrees of biliary obstruction determined by MRCP (Figure 1). The clinicopathological characteristics of these patients are presented in Table 1. Of the 85 patients, 14 (16.9%) were in stage T1, 21 (25.3%) in T2 and 48 (57.8%) in T3.

TABLE 1. Clinicopathological characteristics of hilar cholangiocarcinoma patients

Variables	Cases (%)
Gender	
Male	61 (73.5%)
Female	22 (26.5%)
Age (years)	
≤60	47 (56.6%)
>60	36 (43.4%)
Size of tumour (cm)	
≤4	52 (62.7%)
>4	31 (37.3%)
Bismuth-Corlette classification	
Type I-II	29 (34.9%)
Type III	31 (37.3%)
Type IV	2 (27.7%)
Differentiation	
Well/moderate	27 (32.5%)
Poor	56 (67.5%)
Tumour stage	
T1	14 (16.9%)
T2	21 (25.3%)
T3	48 (57.8%)
Lymph node metastasis	
No	36 (43.4%)
Yes	47 (56.6%)
Biliary obstruction	
No	55 (66.3%)
Yes	28 (33.7%)

FIGURE 1. The biliary obstruction examined by MRCP:

(A) HC patients without biliary obstruction examined by MRCP; (B) HC patients with mild biliary obstruction examined by MRCP; (C) HC patients with moderate biliary obstruction examined by MRCP; (D) HC patients with severe biliary obstruction examined by MRCP. Abbreviations: HC, hilar cholangiocarcinoma; MRCP, magnetic resonance cholangiopancreatography

Liver function and serum CA19-9 in HC patients

Liver function and serum CA19-9 tests were preoperatively performed for all HC patients. Aspartate transaminase, alanine aminotransferase, γ -glutamyl transpeptidase and total bilirubin were significantly higher in patients with biliary obstruction compared with patients without biliary obstruction (aspartate transaminase: 39.23 ± 6.78 vs. 23.68 ± 5.67 , alanine aminotransferase: 36.37 ± 7.98 vs. 17.34 ± 10.23 , γ -glutamyl transpeptidase: 43.35 ± 12.34 vs. 27.65 ± 11.78 and total bilirubin: 20.73 ± 6.59 vs. 11.67 ± 7.53 ; $P < 0.05$). Moreover, it was found that patients with biliary obstruction had higher CA19-9 levels compared with patients without biliary obstruction (CA19-9: 120.21 ± 47.38 vs. 87.76 ± 32.57 ; $P < 0.05$).

Associations between the status of biliary obstruction and clinical pathological characteristics

The status of the biliary obstruction was assessed according to the previously reported standard for biliary obstruction [8]. The status of the biliary obstruction was analysed in terms of gender, age, tumour size, location, differentiation, Bismuth-Corlette classification, tumour stage and lymph node metastasis. The Bismuth-Corlette classification (HR=1.588, $P=0.019$), tumour stage (HR=1.534, $P=0.011$) and lymph node metastasis (HR=2.649, $P < 0.001$) were identified as independent relative factors for the status of the biliary obstruction (Table 2). Furthermore, it was found that Bismuth-Corlette classification type IV, T3 stage and the presence of lymph node metastasis were associated with biliary obstruction in HC patients.

Survival analysis for HC patients

The Kaplan-Meier method and the Cox proportional hazard regression model were used to analyse OS and DFS. The univariate analysis revealed that there was a significant relationship between OS and Bismuth-Corlette classification, differentiation, tumour stage, lymph node metastasis and biliary obstruction ($P < 0.05$). Furthermore, differentiation (HR=2.094, $P=0.023$) and biliary obstruction (HR=2.654, $P=0.014$) were identified as independent factors of OS through the multivariate analysis (Table 3). Moreover, HC patients with biliary obstruction had shorter OS compared with patients without biliary obstruction (Figure 2A).

TABLE 2. Relationships between preoperative biliary obstruction and clinicopathological factors

Variables	Status of biliary obstruction		Univariate p value	Multivariate	
	Yes	No		HR value	p value
Gender			0.406		
Male	19	42			
Female	9	13			
Age (years)			0.689		
≤ 60	15	32			
> 60	13	23			
Size of tumour (cm)			0.029		
≤ 4	13	39			
> 4	15	16			
Bismuth-Corlette classification			0.020	1.588	0.019
Type I-II	6	23			
Type III	9	22			
Type IV	13	10			
Differentiation			0.296	2.537	0.134
Well/moderate	7	20			
Poor	21	35			
Tumour stage			0.014	1.534	0.011
T1	1	13			
T2	5	16			
T3	22	26			
Lymph node metastasis			< 0.001	2.649	< 0.001
No	3	33			
Yes	25	22			

TABLE 3. Univariate and multivariate analysis of factors influencing overall survival

Variables	Five-year survival rate (%)	Univariate analysis		Multivariate analysis	
		χ^2 value	p value	HR value	p value
Gender		1.568	0.211		
Male	27.9				
Female	45.5				
Age (years)		1.888	0.169		
≤60	23.4				
>60	44.4				
Size of tumour (cm)		3.706	0.054		
≤4	40.4				
>4	22.6				
Bismuth-Corlette classification		7.565	0.023	1.003	0.988
Type I-II	51.7				
Type III	30.4				
Type IV	25.8				
Differentiation		10.652	0.001	2.094	0.023
Well/moderate	55.6				
Poor	21.4				
Tumour stage		8.733	0.013	1.278	0.255
T1	57.1				
T2	28.6				
T3	25				
Lymph node metastasis		6.146	0.013	0.991	0.979
No	47.2				
Yes	21.3				
Biliary obstruction		22.374	<0.001	2.654	0.014
No	45.5				
Yes	10.7				

The univariate analysis revealed that tumour size, differentiation, tumour stage, lymph node metastasis and biliary obstruction were correlated with DFS ($P<0.05$). The Cox analysis revealed that tumour size ($HR=1.769$, $P=0.046$), differentiation ($HR=2.033$, $P=0.031$) and biliary obstruction ($HR=3.140$, $P<0.001$) were independent prognostic indicators of DFS for HC patients (Table 4). Patients without biliary obstruction had longer DFS compared with patients with biliary obstruction (Figure 2B).

The prognostic value of the degree of biliary obstruction was determined in the 28 HC patients with biliary obstruction. Based on the diameter of the obstruction of the bile duct, the biliary obstruction was classified as mild, moderate, or severe. The log-rank test revealed that there was a significant difference in OS and DFS among the different degrees of biliary obstruction ($P<0.05$). The HC patients with severe biliary obstruction had the shortest OS and DFS (Figure 3).

Discussion

Magnetic resonance cholangiopancreatography is a novel technique for biliary duct imaging. The MRCP technique is heavily based on T2-weighted images, in which the bile presents a very high signal intensity compared with the lower intensity background. As previously reported, MRCP is especially useful in detecting biliary tract neoplasms [6]. It has advantages over ERCP in the diagnosis of biliary duct cancer as it is non-invasive, can visualise ducts proximal to the obstruction, can better visualisation of the mass, and does not require the use of an intravenous contrast agent [7]. Furthermore, MRCP can help in accurately determining the status of the biliary ductal system in patients with malignant obstruction by identifying the exact site of obstruction and length of obstruction [8]. Various studies have shown that the sensitivity of MRCP for detecting biliary obstruction is approximately 95% [9]. In the present study, MRCP was preoperatively used to determine the status of the biliary obstruction and degree of biliary obstruction. The results revealed that 55 HC patients had no biliary obstruction while 28 HC patients had biliary obstructions. Based on the diameter of the obstruction, the 28 HC patients were further divided into three groups: eight HC patients were considered to have mild biliary obstructions; 10 HC patients were considered to have moderate biliary obstructions; and 10 HC patients were considered to have severe biliary obstruction.

FIGURE 2. Survival curve of hilar cholangiocarcinoma (HC) patients according to the status of the biliary obstruction:

(A) overall survival curve of HC patients according to the status of the biliary obstruction (yes or no); (B) disease-free survival curve of HC patients according to the status of biliary obstruction (yes or no).

FIGURE 3. The survival curve of hilar cholangiocarcinoma (HC) patients according to the degree of biliary obstruction:

(A) the overall survival curve of the 28 HC patients with biliary obstruction, according to the degree of biliary obstruction (mild, moderate, or severe); (B) the disease-free survival curve of the 28 HC patients with biliary obstruction, according to the degree of biliary obstruction (mild, moderate or severe).

TABLE 4. Univariate and multivariate analysis of factors influencing DFS

Variables	Three-year disease-free rate (%)	Univariate analysis		Multivariate analysis	
		χ^2 value	p value	HR value	p value
Gender		0.009	0.926		
Male	56.5				
Female	60.3				
Age (years)		0.568	0.451		
≤60	56.1				
>60	58.8				
Size of tumour (cm)		6.515	0.011	1.769	0.046
≤4	65.3				
>4	44.9				
Bismuth-Corlette classification		5.113	0.078		
Type I-II	72.4				
Type III	55.6				
Type IV	43.5				
Differentiation		9.349	0.002	2.033	0.031
Well/moderate	77.8				
Poor	46.4				
Tumour stage		11.238	0.004	1.338	0.17
T1	67.1				
T2	56.4				
T3	46.5				
Lymph node metastasis		2.698	0.1		
No	78.8				
Yes	40.3				
Biliary obstruction		27.398	<0.001	3.14	<0.001
No	76				
Yes	24.4				

Biliary obstruction is common among biliary tract and pancreatic diseases. Obstruction can be induced by benign or malignant diseases, which are difficult to differentiate. Cholangiocarcinoma, carcinoma gall bladder and secondary deposits account for the majority of malignant biliary obstructions [10]. Increased CA19-9 levels, thicker bile duct wall and regional lymphadenopathy, the cholangiographic appearance of an abrupt cut-off, and the separation of the biliary ductal system often suggests a malignant obstruction. A study revealed the association of elevated bilirubin levels of >8.4 mg% and serum CA19-9 levels of >100 U/L with malignant biliary obstruction [11]. It has been reported previously that MRCP performed better than CT in differentiating the malignant causes of biliary obstruction [12]. The stage of the malignant biliary obstruction was based on the Bismuth-Corlette classification. This classification categorises a tumour according to its location and extent of bile duct involvement [13].

In the present study, the differences in liver function and CA19-9 level in HC patients with and without biliary obstruction were analysed, and it was found that patients with biliary obstruction had significantly higher liver function and CA19-9 levels compared with patients without biliary obstruction. These results suggest that patients with biliary obstruction have greater liver function damage and present a more aggressive molecular biology. The Bismuth-Corlette classification, tumour stage and lymph node metastasis were also identified as independent relative factors of the status of biliary obstruction and Bismuth-Corlette classification type IV was associated with biliary obstruction in HC patients. These findings indicate that biliary obstruction is associated with more aggressive pathological features in the progression of HC.

The predictive value of biliary obstruction in HC patients was also investigated in the present study. Previously, De Jong et al. [14] found that the histologic depth of invasion tended to be associated with worse long-term outcome in HC. To assess the prognostic value of biliary obstruction in HC patients, patient survival was analysed using OS and DFS. The present results identified biliary obstruction as an independent factor for OS and DFS. Patients with biliary obstruction presented with shorter OS and DFS compared with patients without biliary obstruction, indicating that patients with biliary obstruction may be a high-risk group with poor survival. Furthermore, the prognostic value of the degree of biliary obstruction in HC patients was determined, and it was found that patients with severe biliary obstruction had the shortest OS and DFS. These findings suggest that the degree of biliary obstruction affects the prognosis of HC patients and that HC patients

with severe biliary obstruction may require more aggressive additional postoperative systemic therapy.

The present study had some limitations. First, the sample size was limited. Second, in China, many patients with cholangiocarcinoma present with biliary obstruction and were not suitable for surgery. In our trial, we only included those patients who were willing to undergo surgery; therefore, not all patients with HC were enrolled in our study. Thirdly, there were no specific data concerning the pathological examination; thus, this requires further research.

In conclusion, biliary obstructions, assessed by MRCP, were found to be associated with poor outcome in HC patients.

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