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RAPID COMMUNICATION

Preoperative evaluation with T-staging system for hilar cholangiocarcinoma

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Abstract

AIM: To investigate the clinical value of T-staging system in the preoperative assessment of hilar cholangiocarcinoma.

METHODS: From March 1993 to January 2006, 85 patients who had cholangiocarcinoma diagnosed by operative tissue-biopsy were placed into one of three stages based on the new T-staging system, and it was evaluated the resectability and survival correlated with T-staging.

RESULTS: The likelihood of resection and achieving tumor-free margin decreased progressively with increasing T stage ($P < 0.05$). The cumulative 1-year survival rates of T1, T2 and T3 patients were 71.8%, 50.8% and 12.9% respectively, and the cumulative 3-year survival rate was 34.4%, 18.2% and 0% respectively; the survival of different stage patients differed markedly ($P < 0.001$). Median survival in the hepatic resection group was greater than in the group that did not undergo hepatic resection (28 mo *vs* 18 mo; $P < 0.05$). The overall accuracy for combined MRCP and color Doppler Ultrasonagraphy detecting disease was higher than that of combined using CT and color Doppler Ultrasonagraphy (91.4% *vs* 68%; $P < 0.05$). And it was also higher in detecting port vein involvement (90% *vs* 54.5%; $P < 0.05$).

CONCLUSION: The proposed staging system for hilar cholangiocarcinoma can accurately predict resectability, the likelihood of metastatic disease, and survival. A concomitant partial hepatectomy would help to attain curative resection and the possibility of long-term survival. MRCP/MRA coupled with color Doppler Ultrasonagraphy was necessary for preoperative evaluation of hilar cholangiocarcinoma.

Key words: Hilar cholangiocarcinoma; Preoperative staging; Survival rate; Surgical treatment

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INTRODUCTION

Cholangiocarcinoma is an adenocarcinoma that arises from the bile duct epithelium and is the second most common primary hepatobiliary cancer, however, cholangiocarcinoma remains a relatively rare disease, accounting for < 2% of all human malignancies[1-3]. Although the entire biliary tree is potentially at risk, hilar cholangiocarcinoma which involved the biliary confluence or the right or left hepatic ducts are most common and account for 40%-60% of all cases[4]. In most instances, the prognosis of hilar cholangiocarcinoma is very poor, with an overall 5-years survival rate of only 1%[5]. At present, surgical resection of early detected tumors is still the optimal treatment method for hilar cholangiocarcinoma[6,7]. Therefore, precise preoperative imaging evaluation including classification and staging of tumor is crucial for planning treatment and assessing prognosis.

Currently, the modified Bismuth-Corlette system and American Joint Committee on Cancer (AJCC) systems are still commonly used in evaluation of hilar cholangiocarcinoma in China, but both of them are failure to identify patients who are operative candidates or to provide prognostic information[5,8,9]. It is possible that the AJCC or Bismuth-Corlette systems has been misused by a

generation of medical oncologists and surgeons who have used staging systems based on postoperative evaluation of the tumor to guide the preoperative, intraoperative, and even postoperative management[9,10].

In an attempt to improve the preoperative clinical and prognostic usefulness of stag system, the organizational structure of the hepatobiliary program at Memorial Sloan-Kettering Cancer Center (MSKCC) have proposed a new T staging that takes into consideration both vascular involvement by local tumor extension and the presence or absence of liver atrophy (Table 1)[11]. This proposed T staging system is predictive of resectability, of the likelihood of nodal or distant metastases, and of overall survival[11]. In this study, we used the proposed T staging system, based on imaging data, to stratifies 85 patients hilar cholangiocarcinoma into one of three stages and evaluate the resectability or survival correlated with T-staging. We also want to find the correlation between the T staging and nodal or distant metastases. In addition, in our study, biliary resections coupled with in-continuity hepatic resection has been proposed, to attain radical resection.

Table 1 Revised preoperative T staging system for patients with hilar cholangiocarcinoma

T Stage	Description
T1	Tumor involving biliary confluence ± unilateral extension to 2° biliary radicles No liver atrophy or portal vein involvement
T2	Tumor involving biliary confluence ± unilateral extension to 2° biliary radicles with ipsilateral portal vein involvement ± ipsilateral hepatic lobar atrophy No main portal vein involvement
T3	Tumor involving biliary confluence + bilateral extension to 2° biliary radicles; OR unilateral extension to 2° biliary radicles with controlateral portal vein involvement; OR unilateral extension to 2° biliary radicles with controlateral hepatic lobar atrophy; ralateral hepatic lobar atrophy; phy; OR main or bilateral portal venous involvement

MATERIALS AND METHODS

Data selection

Data was collected from a database of Hepatobiliary Surgery of the Second Affiliated Hospital of SUN Yat-sen University From March 1993 through January 2006, 85 patients of hilar cholangiocarcinoma underwent laparotomy and diagnosed by tissue-biopsy were retrospectively analyzed in this study. There were 45 men and 40 women and their mean age was 63.5 (median, 65; range, 42-81) years. Follow-up was defined as the number of months between the operation date and the date of death or, if the patient was alive, the end dates of the study period (December 31, 2006). Preoperative baseline examinations were electrocardiogram (ECG), sternite, prothrombin time (PT), hepatic and renal function test. All of 85 patients presented with hilar cholangiocarcinoma had more than one kind of image examinations. Ultrasound (US) or duplex ultrasonography (DUS) coupled with tomographic (CT) scanning were performed on 25 patients; duplex ultrasonography coupled with magnetic resonance cholangiopancreatography (MRCP) was performed on 35 patients; ultrasound, CT coupled with ERCP was performed on 11 patients; ultrasound, CT coupled with MRCP was performed on 14 patients.

T-staging

Tumors were restaged retrospectively using revised preoperative T staging system based on preoperative imaging examinations (Table 1). This staging system, a modification of a previously reported scheme[12], classifies tumors according to three factors related to local tumor extent: the location and extent of bile duct involvement (according to the Bismuth-Corlette system)[13,14], the presence or absence of portal venous invasion, and the presence or absence of hepatic lobar atrophy. The survival data was then compared among the stages. T staging correlated with respectability, Ro resection (margins negative), and the incidence of metastatic disease were reviewed.

Surgical strategies

All 85 patients in this study were treated with laparotomy, the type of therapeutic procedures depended on tumor expansion and clinical conditions of patients. If the tumor was resectable, surgery was the first choice of treatment for patients in good clinical conditions. The two types of operations were: (1) local resection of the bile duct alone; (2) extrahepatic biliary resection with in-continuity hepatic resection. In patients with non-resectable tumors or bad clinical conditions, palliative procedure using endoscopic transpapillary and/or percutaneous transhepatic biliary drainage was performed. In this study the survival of all patients undergoing resection of hilar cholangiocarcinomas by either extrahepatic biliary resection alone or by extrahepatic biliary resection with in-continuity hepatic resection were reviewed.

Statistical analysis

All data were analyzed with SPSS 11.5 statistical package. Cumulative overall survival was calculated by the Kaplan-Meier method using the log rank test with T staging. The correlation between T staging and respectability, Ro resection or the incidence of metastatic disease were analyzed using the χ^2 test. Significance was accepted with 95% confidence.

RESULTS

Proposed T-staging system

The follow-up time of all patients was more than 3 mo. Eighty five patients were staged according to the proposed preoperative clinical system, as described above Table 1. Thirty nine patients had tumor involvement of the biliary confluence (with or without unilateral extension to second-order biliary radicles), no portal vein involvement, and no lobar atrophy and were therefore classified as having T1 tumors. Fifteen patients had T2 lesions because of ipsilateral portal vein involvement or ipsilateral lobar atrophy; or both findings. Thirty one patients had T3 tumors because of biliary extent alone, or main portal vein involvement, or metastatic disease.

Table 2 Resectability, incidence of margins negative and metastatic disease after staging by T stage

T Stage	Operative modus			Margins		Metastatic disease	
	Resected	Drainage	Biopsy	Negative	Positive	Negative	Positive
T1 (n = 39)	29 (74.4)	8 (20.5)	2 (5.1)	22 (75.9)	7 (24.1)	24 (61.5)	15 (38.5)
T2 (n = 15)	9 (60.0)	4 (26.7)	2 (13.3)	3 (33.3)	6 (66.7)	7 (46.7)	8 (53.3)
T3 (n = 31)	2 (6.5)	15 (48.4)	14 (45.1)	0 (0)	2 (100)	9 (30.0)	22 (70.0)
χ^2 value		35.5		8.8		7.3	
P value		0.000		0.012		0.026	

The percentages indicate the proportion of patients within each stage grouping or of the total number of patients. Metastatic disease refers to metastases to N2-level lymph nodes or to distant sites. Median survival was calculated for all patients, including those who died perioperatively.

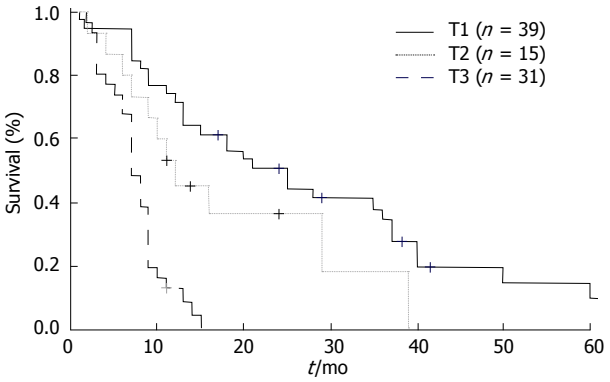

Figure 1 Kaplan-Meier survival analysis stratified by T stage. T stages seemed to be correlated with the survival time (χ^2 = 37.65, P < 0.001), and the survival time decreased progressively with increasing T staging. The cumulative 1-year survival rates of T1, T2 and T3 patients were 71.8%, 50.8% and 12.9%, respectively, and the cumulative 3-year survival rate was 34.4%,18.2% and 0%, respectively, the survival of different stage patients differed markedly (P < 0.001).

The clinical and survival-related factors associated with T stage are detailed in Table 2. Resectability and the likelihood of achieving an R0 resection both decreased progressively with increasing T stage (P < 0.05). A similar proportion of patients with T1 (74.4%) and T2 (60.0%) tumors underwent resection with curative intent. Two patients with T3 tumors (6.5%) were also underwent resection ,but both couldn't achieved R0 resection. In addition, metastatic disease to N2-level lymph nodes or to distant sites (i.e., metastatic disease that contraindicated resection) correlated with increasing T stage (P < 0.05).

Survival analysis

Kaplan-Meier estimate for survival depending on T stages was shown in Figure 1, it showed that T stages seemed to be correlated with the survival time (χ^2 = 37.65, P < 0.001), and the survival time decreased progressively with increasing T staging. The cumulative 1-year survival rates of T1, T2 and T3 patients were 71.8%, 50.8% and 12.9% respectively, and the cumulative 3-years survival rate was 34.4%, 18.2% and 0% respectively; the survival of different stage patients differed markedly (P < 0.001).

In patients with T1 lesions, 12 patients undergoing extrahepatic biliary resections alone and 17 patients underwent in-continuity hepatic resection (Table 3). This is in contrast to patients with T2 lesions, all of patient required a concomitant partial hepatectomy and 3 (33%) of whom required a portal vein resection and reconstruction.

Table 3 Margins negative, complication, operative mortality and survival based on in-continuity hepatic resection

Hepatic resection	n	Margins		Operative mortality, n (%)	Median survival, mo
		Negative, n (%)	Complication, n (%)		
In-continuity Hepatic Resection	28	21 (75)	16 (57)	3 (11)	28
No Hepatic Resection	12	4 (33)	4 (33)	1 (8)	18

Forty of 85 patients underwent resection, 28 (70%) had a concomitant partial hepatectomy, and negative histological margins were attained 75% of the time. The performance of a partial hepatectomy was predictive of a negative histological margin in this series. Median survival in the hepatic resection group was greater than in the group that did not undergo hepatic resection (28 *vs* 18 mo; P < 0.05). And the incident rate of complication and operative mortality in two groups were not different (P > 0.05).

Preoperative imaging evaluation

Most patients were diagnosed after at least a partial radiographic evaluation had been completed, usually consisting in ultrasonography, in a computed tomographic (CT) scan and in some form of direct cholangiography such as ERCP. After referral, further evaluation of tumor extent within the biliary tree and assessment of possible vascular involvement or metastatic disease were performed with MRCP or duplex ultrasonography, which are currently the preferred studies. Some patients who could not be diagnosed preoperatively were considered to have laparotomy for exploration. Altogether, 85 patients had the final diagnosis of hilar cholangiocarcinoma via pathologic diagnosis. The consistent rate with pathological findings of US or duplex ultrasonography coupled with CT, or with MRCP, or with CT and ERCP, or with CT and MRCP was 68% (17/25), 91.4% (32/35), 90.9% (10/11) and 100% (14/14) respectively. And the consistent rate of US combined with CT was significant lower than other combined examinations (P < 0.05). The final diagnosis rate of tumor infiltrated portal vein for duplex ultrasonography combined with MRCP/MRA, duplex ultrasonography combined with CT were 90% (19/21), 54.5% (6/11) respectively. The overall accuracy for combined MRCP and color Doppler Ultrasonagraphy detecting disease and

port vein involvement was higher than that of combined using CT and color Doppler Ultrasonagraphy ($P < 0.05$).

DISCUSSION

Currently, the only curative option for patients with cholangiocarcinoma is aggressive surgical resection. Many authors advocate that patients with suspected cholangiocarcinoma should be considered for operative resection and postoperative adjuvant therapy even if microscopically clear resection margins can not be achieved[15-17]. Therefore, precise preoperative imaging evaluation and staging of tumor are crucial for planning treatment and assessing prognosis.

Great effort has been expended to develop staging systems that are of greater prognostic utility to the surgeon and can be used to guide not only preoperative treatment, but also intra- and postoperative management of patients with cholangiocarcinoma[8,18-20]. There are currently 3 main staging systems utilized for patients with hilar cholangiocarcinomas: AJCC, Bismuth-Corlette, and Blumgart[9]. The AJCC tumor-node-metastasis (TNM) staging system is only applicable to patients who have undergone resection[4]. The Bismuth-Corlette system describes the tumors in terms of their anatomic location. Typically, it has been used to guide treatment (particularly resection), yet it does little to identify patients who are operative candidates or to impart prognostic information[11,12]. The modifications proposed, by Blumgart (Table 1) not only provide anatomic information about the local extent of the tumor but also better stratify patients who are candidates for surgical exploration by taking into account parenchymal characteristics of the liver.

In this study, we retrospectively reviewed 85 patients with cholangiocarcinoma who underwent resection and restaged them into the T-staging system. We have demonstrated the correlation between resectability or R0 resection or survival time and T stage, in 85 patients with hilar cholangiocarcinoma. Resectability and the likelihood of achieving an R0 resection both decreased progressively with increasing T stage. Patients with T1 and T2 have a chance of R0 resection; T3 stage tumors usually have no chance for resection. In our data, a similar proportion of patients with T1 (74.4%) and T2 (60.0%) tumors underwent resection with curative intent. Two patients with T3 tumors (6.5%) also underwent resection, but both couldn't achieve R0 resection. Kaplan-Meier analysis revealed that T-staging seemed to correlate with survival time, and the 1, 3-years accumulative survival time decreased with increasing T stage. The media survival time of patients with T1 stage was significantly higher than that of patients with T2 or T3 stage. In addition, metastatic disease to N2-level lymph nodes or to distant sites (i.e., metastatic disease that contraindicated resection) correlated with increasing T stage. In order to improve operative resectability and curability, hepatic resection has been applied to the treatment for hilar cholangiocar cinoma[21-23]. Whereas, several authors reported that the extent of hepatic resection was closely associated with the occurrence of postoperative complications, such as liver failure, sepsis, and anastomosis leakage[22,24-27]. In this study, we demonstrated a significant survival benefit in those patients who were able to undergo extrahepatic biliary resections coupled with in-continuity hepatic resection as compared with those undergoing to extrahepatic biliary resections alone. Hepatic resection did not increase the incurrence of complication and operative mortality in this series; this results also were supported by Miyazaki *et al*[28]. In our experience, the segments I and Ⅳ resection for hilar cholangiocarcinoma have the benefit of preserving enough hepatic mass for the patient to tolerate surgical stress as compared with major hepatic resection.

Early detection and accurate staging are crucial for planning treatment and improving survival rate of hilar cholangiocarcinomas. Noninvasive methods like magnetic resonance cholangiopancreatography or magnetic resonance angiography (MRCP/MRA) and Doppler ultrasound have been proposed by Jarnagin[29]. In our data analysis, duplex ultrasonography and magnetic resonance cholangiopancreatography have been successful when compared with any other combination of examinations. Ultrasonagraphy detecting disease and port vein involvement was 91.4% and 90%.and was higher than that of combined using CT and color Doppler Ultrasonagraphy. Duplex ultrasonography is noninvasive, and a skilled operator can identify the site of biliary obstruction, as well as the presence or absence of portal venous involvement. The efficacy of MRCP/MRA as a noninvasive means of acquiring reliable and precise information about the anatomy of both the intrahepatic and the extrahepatic biliary tree, as well as the level of tumor involvement, and the presence of nodal or distant metastases, has been well documented and has all but replaced percutaneous and endoscopic cholangiography[30-32].

In conclusion, the T-staging system correlates with respectability, RO resection and overall accumulative survival. Patients with hilar cholangiocarcinoma in T1 and T2 stage have the chance of curative resection, in-continuity hepatic resection, and it is necessary to achieve this with lower complications. Duplex ultrasonography and MRCP/MRA are essential for a preoperative assessment of hilar cholangiocarcinoma.

COMMENTS

Background

Cholangiocarcinoma is a malignancy with poor prognosis, and the best result still comes from surgical resection. However, in many of patients who underwent laparotomy the tumors are found not respectable. Therefore, a precise preoperative evaluation system seems to be particularly important. Whereas, currently the modified Bismuth-Corlette system and American Joint Committee on Cancer (AJCC) systems are still commonly used in evaluation of hilar cholangiocarcinoma in China, but both of them failed to identify patients who are operative candidates or to provide prognostic information.

Research frontiers

This current study retrospectively analyzes 85 patients with cholangiocarcinoma who underwent surgery using the T-staging system, and evaluates whether the resectability or survival correlated with T-staging. We also wanted to find the correlation between the T staging and nodal or distant metastases. Additionally, in our study, biliary resections coupled with in-continuity hepatic resection has been proposed to attain radical resection.

Innovations and breakthroughs

In our data, a similar proportion of patients with T1 (74.4%) and T2 (60.0%) tumors underwent resection with curative intent. Hepatic resection has been applied to the treatment for hilar cholangiocarcinoma, and achieved higher median survival than in the group that did not undergo hepatic resection (28 *vs* 18 mo; $P < 0.05$). In our study, the segments I and IV resection for hilar cholangiocarcinoma have the benefit of preserving enough hepatic mass for the patient to tolerate surgical stress as compared with major hepatic resection. In our data analysis, duplex ultrasonography and magnetic resonance cholangiopancreatography are chosen over any other combination of examinations.

Applications

This study provided important reference as regard to the preoperative assessment for patients with halir cholangiocarcinoma. In conclusion, the T-staging system correlates with resectability, RO resection and overall accumulative survival. Patients with hilar cholangiocarcinoma in T1 and T2 stages have the chance of curative resection, and in-continuity hepatic resection is necessary to achieve this with lower complications. Duplex ultrasonography and MRCP/MRA are necessary for a preoperative assessment of hilar cholangiocarcinoma.

Terminology

In current study, revised preoperative T staging systems were used to preoperatively evaluate the status of patients with hilar cholangiocarcinoma, and it described as follows: T1, Tumor involving biliary confluence ± unilateral extension to 2° biliary radicles, No liver atrophy or portal vein involvement. T2, Tumor involving biliary confluence ± unilateral extension to 2° biliary radicles with ipsilateral portal vein involvement ± ipsilateral hepatic lobar atrophy, No main portal vein involvement T3, Tumor involving biliary confluence + bilateral extension to 2° biliary radicles; OR unilateral extension to 2° biliary radicles with controlateral portal vein involvement; OR unilateral extension to 2° biliary radicles with controlateral hepatic lobar atrophy; OR main or bilateral portal venous involvement.

Peer review

The manuscript retrospectively analyzes 85 patients with cholangiocarcinoma who underwent surgery using the T-staging system. The results show resectability, tumor-free margin resection and cumulative survival of patients decrease with increasing T stage. The study also suggests that MRCP/MRA coupled with Doppler Ultrasonagraphy provides better preoperative evaluation of hilar cholangiocarcinoma. The paper is well written and more importantly it does provide important reference as regard to the preoperative assessment for patient with halir cholangiocarcinoma.

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