Original Article
Preoperative serum CA19-9 levels is an independent prognostic factor in patients with resected hilar cholangiocarcinoma

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Abstract: To investigate the appropriate cutoff point of CA19-9 for prognosis and other potential prognostic factors that may affect survival of patients with hilar cholangiocarcinoma (HC) after radical surgery. 168 patients who had undergone radical surgery for hilar cholangiocarcinoma and resultant macroscopic curative resection (R0 and R1) were discreetly selected for analyses. Categorized versions were used in univariate model to determine the appropriate cutoff point of CA19-9. CA19-9 and other clinicopathologic factors were analyzed for influence on survival by univariate and multivariate methods. The strongest univariate predictor among the categorized preoperative CA19-9 measures was CA19-9 less than 150 IU/L (P = 0.000). In univariate analysis, tumor size, Bismuth-Corlette classification, portal vein invasion, Lymph node metastasis, resection margin and preoperative CA19-9 levels were identified as significant prognostic factors. In multivariable analysis, lymph node metastasis, resection margin and preoperative CA19-9 levels were independent prognostic factors. our results demonstrated that preoperative CA19-9 levels was also an independent prognostic factor for hilar cholangiocarcinoma, and the most discriminative cutoff point of CA19-9 for prognosis proved to be at 150 U/ml.

Keywords: Hilar cholangiocarcinoma, CA19-9, cutoff point, lymph node metastasis, resection margin

Introduction

Cholangiocarcinoma may develop anywhere in the biliary tree from the ampulla of Vater to the peripheral intrahepatic ducts; however, the most frequent site of involvement is the biliary confluence at the hilus of the liver, accounting for 40%-60% of cases [1]. Aggressive surgical resection including right or left hemihepatectomy extending to segment 1 has been recognized as standard treatment option for hilar cholangiocarcinoma (HC) [2, 3]. However, achieving histologically negative margin (R0) resection remains difficult, although this may offer the only chance for cure and long-term survival.

In HC, vascular invasion, nodes metastases, serum level of total bilirubin, resection margin and postresection radiotherapy has been reported to affect postoperative outcome. However, CA19-9, an important serum marker for HC, its value for prognosis has not been explored in detail.

CA19-9 is a carbohydrate tumor-associated antigen originally isolated from a human colorectal cancer cell line by Koprowski et al [4, 5] in 1979. The monoclonal antibody 1116NS19-9 reacts with the sialylated Lewis[ab] blood group substance. In western countries, approximately 5% of the population is lewis[a-b-]; these individuals cannot increase their serum CA19-9 levels [6]. Since the development of the radioimmunometric assay by Del Villano et al in 1983, CA19-9 has been used for the diagnosis, prognosis, and monitoring of pancreatic cancer, cholangiocarcinoma, gastric cancer and other digestive

Table 1. Demographics and clinical characteristics of 168 patients

Characteristics	Value
Age (in years)	57.3 (33-77)
Gender (male/female)	96/72
Bismuth-Corlette classification	
I	18
II	18
III (a/b)	12/30
IV	90
Histopathologic type	
Well	9
Moderate	153
Poor	6
AJCC (6th)	
I A	9
I B	39
II A	69
II B	45
III	6
IV	0
Survival time (in months) median (range)	38.0 (6-75)

system tumors [7]. However high levels of CA 19-9 can be caused by benign obstructive jaundice or cholangitis. Since the presenting symptom in over 90% of HC is progressive obstructive jaundice, it's difficult to determine how high a CA19-9 needs to be in order to indicate if a cancer is present. Therefore, CA19-9 is more likely to be suitable as a prognostic factor for HC. Of the studies relating to prognostic implication in HC, three groups have demonstrated a significant difference in survival when a high cutoff level (1000 ng/ml [8], 100 ng/mL [9]) is used to compare groups. At lower cutoff values (> 37 ng/mL) two studies found no significant association with survival [10, 11]. The conflicting evidence within these studies is likely to be related to the non-standardized cutoff values used in the analyses and no study has investigated the most discriminative cutoff point for prognosis.

In the present study, we analyzed patients who underwent curative resection for HC. First, we aimed to determine whether preoperative CA19-9 levels increased in parallel with patients' pathological stage, and then we used categorized versions in univariate model to determine the most discriminative cutoff point of CA19-9 for prognosis. CA19-9 and other clinicopathologic factors were analyzed for influence on survival by univariate and multivariate methods.

Materials and methods

Ethics principle

The study protocol is conformed to the ethical guidelines of the Declaration of Helsinki, and was reviewed and approved by the Ethical Committee of the Eastern Hepatobiliary Surgery Hospital of the Second Military Medical University. Statement of informed consent was obtained from all participants after full explanation of the procedure.

Study population

From January 2008 to December 2013, 168 patients underwent radical surgery for HC at the Eastern Hepatobiliary Surgery Hospital of the Second Military Medical University (Shanghai, China). This study included 96 males and 72 females, with the mean age of 57.4 years (range, 33-77 years). The extent of the tumor along the bile duct was classified according to the modified Bismuth-Corlette classification and the result of this classification was as follows: 18 type I (10.7%), 18 type II (10.7%), 12 type III a (7.1%), 30 type III b (17.9%), and 90 type IV (53.6%). About 9, 39, 69, 45 and 6 cases were staged by AJCC staging classification of extrahepatic cholangiocarcinoma (sixth edition) [12] into stages I A, I B, II A, II B, and III, respectively, and all patients were considered as candidates for curative surgery (**Table 1**). Of those patients who underwent a potentially curatively resection, 27 required portal vein resection and 15 had a hepatic artery resection. All patients had a regional lymphadenectomy (hepatoduodenal, retroduodenal and celiac axis lymph node stations), and caudate lobe was removed in almost all partial hepatectomy (**Table 2**).

Initial log-rank tests were performed to determine the predictive value of categorized versions of the preoperative serum CA19-9 levels. The following clinicopathologic factors were analyzed by comparing subgroups divided according to each variable: age (< 60, ≥ 60 years), gender, tumor size (< 2.5, ≥ 2.5 cm), differentiation, bismuth type, stage, lymph node metastasis, perineural invasion, portal vein invasion, hepatic artery invasion, liver invasion, resection margin, serum level of total bilirubin (< 10 mg/dL, ≥ 10 mg/dL), preoperative biliary

Table 2. Type of surgical procedure

	Patients	PV resection	HA resection
CBD excision	45	3	6
Partial hepatectomy	123		
Plus lobus quadratus excision	6		
Left hemihepatectomy	18	3	3
Left hemihepatectomy with caudate lobectomy	75	15	6
Right hemihepatectomy	3		
Right hemihepatectomy with caudate lobectomy	21	6	

CBD: common bile duct; PV: portal vein; HA: hepatic artery.

Table 3. Preoperative CA19-9 level as a predictor of pathologic stage

Stage	No. of patients	Median preoperative CA19-9 (U/mL)
I A	9	15
I B	39	57
II A	69	125
II B	45	222
III	6	281.5

Table 4. Preoperative CA19-9 levels as a predictor of survival

Preoperative CA19-9 (U/mL)	Median survival time (months)	No. of patients	Univariate P
< 37	41	45	0.364
≥ 37	38	123	
< 100	41	78	0.076
≥ 100	25	90	
< 150	44	93	0.001
≥ 150	22	75	
< 200	42	99	0.003
≥ 200	22	69	
< 400	40	120	0.010
≥ 400	22	48	
< 600	40	132	0.050
≥ 600	25	36	
< 800	40	141	0.247
≥ 800	27	27	

follow up. Differences in the survival curves were analyzed using a log-rank test. A multivariate analysis was performed using a Cox regression model including variables, which have a P value by a log-rank test being < 0.05, as covariates of the final model. Statistical analysis was performed using SPSS Statistics 16.0 software (SPSS Inc., Chicago, IL). The presence of a statistically significant difference was denoted by P < 0.05.

Results

There were no postoperative deaths among the 168 patients. Overall, the 1-, 3-, and the 5-year survival rates were 89.3%, 53.6%, and 28.6%, respectively.

Preoperative CA19-9 was strongly associated with pathologic stage (**Table 3**), the median preoperative CA19-9 values increased with increasing stage. Similarly, the median preoperative CA19-9 levels were lower for patients with negative lymph nodes compared with positive nodes (78 vs 228 U/mL, respectively; nonparametric P = 0.048) and for patients with tumor size < 2.5 cm versus tumor size ≥ 2.5 cm (76 vs 253 U/mL, respectively; nonparametric P = 0.041).

drainage and postresection radiotherapy. Based on the results of the univariate analysis, a multivariate analysis was performed.

Statistical analysis

The Kaplan-Meier method was used to estimate survival which was measured from time of presentation to Eastern Hepatobiliary Surgery Hospital to the date of death or date of last

To determine the predictive value of preoperative CA19-9 values, categorized versions of it were used in univariate model. The most discriminative cutoff point for prognosis proved to be at CA19-9 levels of 150 U/ml, although dichotomization with a broad range of CA19-9 levels, between 150 and 600 U/mL, gave significantly discriminative log-rank P values (**Table 4**). Patients with CA19-9 levels of 150 U/mL or less had a much better survival than
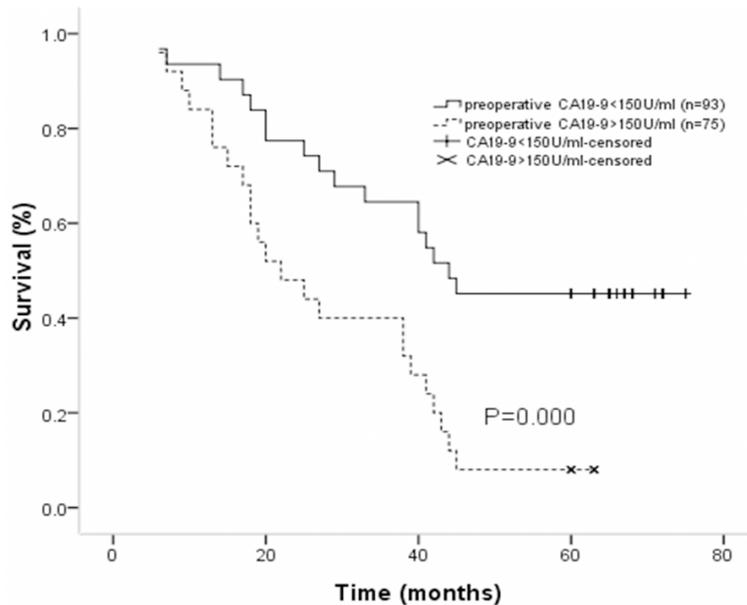
Figure 1. Patients with preoperative CA19-9 levels of less than 150 U/ml have an improved survival compared with patients with preoperative CA19-9 levels of more than 150 U/ml.

CA19-9 has not been gained widespread use in biliary tract cancer. At first, some studies have demonstrated that elevated serum concentrations of CA19-9 have good sensitivity and specificity for diagnosis of cholangiocarcinoma in patients with primary sclerosing cholangitis [14]. And then, several studies investigated the value of CA19-9 for diagnosis in patients with a cholangiocarcinoma without primary sclerosing cholangitis [15, 16]. The results showed the sensitivity of a CA19-9 levels > 100 U/mL in diagnosing cholangiocarcinoma was 53%, One study showed a 100% sensitivity and specificity using CEA > 5.2 ng/mL and CA 19-9 > 180 U/mL [17].

patients with CA19-9 levels above 150 U/mL (P = 0.000, **Figure 1**).

In the univariate analysis of other clinicopathologic factors, tumor size (P = 0.007), Bismuth-Corlette Classification (P = 0.032), lymph node metastasis (P < 0.001), portal vein invasion (P = 0.013) and resection margin (P = 0.018) were identified as statistically-significant prognostic factors (**Table 5**). Multivariate analysis with a stepwise regression model identified preoperative CA19-9 levels (odds ratio: 2.234, P = 0.020), lymph node metastasis (odds ratio: 3.489, P < 0.001) and resection margin (odds ratio: 2.317, P = 0.048) as independent prognostic factors for survival (**Table 6**). Patients without lymph node metastasis or with negative resection margin also had a better survival than patients with lymph node metastasis (**Figure 2**) or positive resection margin (**Figure 3**).

Discussion

CA19-9 is a widely used diagnostic and prognostic biochemical marker in patients with pancreatic cancer. Cristina RF. et al have demonstrated perioperative CA19-9 levels can predict stage and survival in patients with respectable pancreatic adenocarcinoma [13]. However,

CA19-9 has been reported to correlate with burden of disease [18, 19]. To our knowledge there are no studies on the relationship between preoperative CA19-9 levels and postresection pathologic stage in HC. Our results demonstrated that preoperative CA19-9 levels correspond with postresection pathologic stage. Higher CA19-9 values should raise the suspicion of a more extensive tumor burden. Karachristos A. et al [20] investigated the association between preoperative CA19-9 levels and pathologic stage on pancreatic cancer. The results indicated that for those patients with low CA19-9 values and respectable lesion on preoperative imaging, the utility and need for laparoscopy to detect unsuspected metastases may be diminished. However, a high CA19-9 value may justify laparoscopy even if the lesion appears respectable for cure on preoperative imaging [13]. Our study demonstrated this conclusion is also suitable to HC.

So far, it is still undefined whether CA19-9 is useful for predicting survival in cholangiocarcinoma. Use different cutoff points of CA19-9 in univariate analysis showed opposite results on survival. Three previous studies on pancreatic cancer have shown that the median of pretreatment CA19-9 levels can serve as a valuable cutoff point for predicting overall survival [21-23]. One study on unresectable biliary tract

Table 5. Univariate analysis of potential predictors of survival

Variable	Number of patients (%)	Median survival time (months)	Five year survival rate (%) 5 years	P value
Age (y)				
< 60	90 (54)	38	40.0	0.079
≥ 60	78 (46)	27	15.4	
Gender				
Male	96 (57)	29	25.0	0.426
Female	72 (43)	41	33.3	
Tumor size (cm)				
< 2.5	105 (63)	41	40.0	0.007
≥ 2.5	63 (37)	22	9.5	
Differentiation				
Well, moderate	162 (96)	38	29.6	0.206
Poor	6 (4)	7	0.0	
Bismuth-Corlette Classification				
I, II	39 (23)	–	53.8	0.032
III a, III b, IV	129 (77)	29	20.9	
Lymph node metastasis				
Present	51 (30)	20	5.9	< 0.001
Absent	108 (70)	42	38.5	
Perineural invasion				
Present	66 (39)	27	22.7	0.275
Absent	102 (61)	41	32.4	
Portal vein invasion				
Present	51 (30)	27	5.9	0.013
Absent	117 (70)	41	38.5	
Hepatic artery invasion				
Present	36 (21)	25	16.7	0.149
Absent	132 (79)	40	31.8	
Liver invasion				
Present	45 (27)	33	6.7	0.134
Absent	123 (73)	39	36.6	
Resection margin				
R0	141 (84)	40	34.0	0.018
R1	27 (16)	17	0.0	
Total bilirubin (mg/dl)				
< 10	72 (43)	39	33.3	0.436
≥ 10	96 (57)	33	25.0	
Preoperative biliary drainage				
Performed	51 (30)	40	23.1	0.210
Not performed	117 (70)	29	41.2	
Postresection radiotherapy				
Performed	66 (39)	40	38.2	0.284
Not performed	102 (61)	38	13.6	

cancer has suggested that patients with CA19-9 levels above the median of 300 U/mL had a nearly 3-fold risk for early death as compared with patients with CA19-9 levels ≤ 300 U/mL [24]. Cristina RF. et al [13] used categorized versions of CA19-9 to determine the most discriminative cutoff point and have demonstrated the strongest univariate predictor among

Table 6. Multivariate analysis of potential predictors of survival

Variable	Odds Ratio	95% Ratio	P
Tumor size	1.129	0.557-2.287	0.737
Bismuth-Corlette Classification	1.697	0.687-4.195	0.252
Lymph node metastasis	3.489	1.739-7.001	< 0.001
Portal vein invasion	0.928	0.431-1.999	0.848
Resection margin	2.317	1.007-5.334	0.048
Preoperative CA19-9 levels	2.234	1.135-4.399	0.020
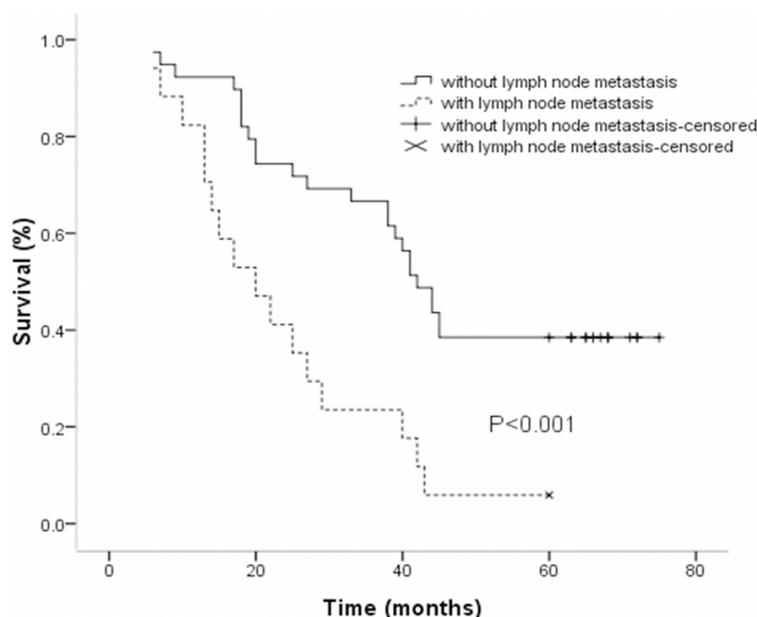
Figure 2. Patients without lymph node metastasis have an improved survival compared with patients with lymph node metastasis.

ic variables in univariate analysis as well as preoperative serum CA19-9. The final three factors predictive of survival in the multivariate model included preoperative serum CA19-9 (P = 0.020), lymph node metastasis (P < 0.001) and resection margin (P = 0.048).

Lymph node metastasis has been identified as an important factor for prognosis in patients with HC, even the lymph node micrometastasis which cannot be detected by conventional haematoxylin & eosin (HE) staining at the time of surgical resection has an adverse impact on the outcome in HC [25]. Our study showed the median preoperative CA19-9 levels were significantly lower for patients with negative lymph nodes compared with positive nodes. This result indicated high preoperative CA19-9 levels were strongly associated with metastasis.

the categorized preoperative CA19-9 measures was CA19-9 less than 1,000 U/mL. However, there is no standardized CA19-9 cutoff point for prognosis in patients with cholangiocarcinoma, therefore, we decided to use categorized versions in univariate model to investigate the most discriminative cutoff point of preoperative CA19-9 levels for prognosis in patients with HC. Lower preoperative CA19-9 values correlated not only with a lower pathologic stage, but also with an increased postresection survival. In the current study, we found an increase in median survival time of 44 months versus 22 months if the preoperative CA19-9 value was less than 150 U/mL (P = 0.01). Based on these results, we can deduce that patients with a higher preoperative CA19-9 level are more likely to have a higher tumor burden and reduced chances of survival.

A multivariate survival model was fit using all statistically-significant clinical and demograph-

Complete resection of the macroscopic tumor is the therapeutic gold standard for HC; curative (R0) resection is defined as histological evidence of cancer-free surgical margins. Ductal margin status is an established prognostic factor in patients with hilar cholangiocarcinoma who have undergone resection, the prognosis of patients with positive ductal margins is generally considered to be poor [26-29]. The anatomic features of the hepatic hilus often make it easy for HC to invade major vessels, such as those hepatic artery and portal vein. Therefore, HC occasionally requires combined vascular resection and reconstruction to obtain negative resection margin due to involvement of hilar vasculatures. In our study, the portal vein resection included 21 wedge resection and 6 bifurcation resection and reconstruction, 15 patients had undergone hepatic artery resection, and 6 of them had common hepatic artery resection without reconstruction. All these patients obtained negative resection margin.
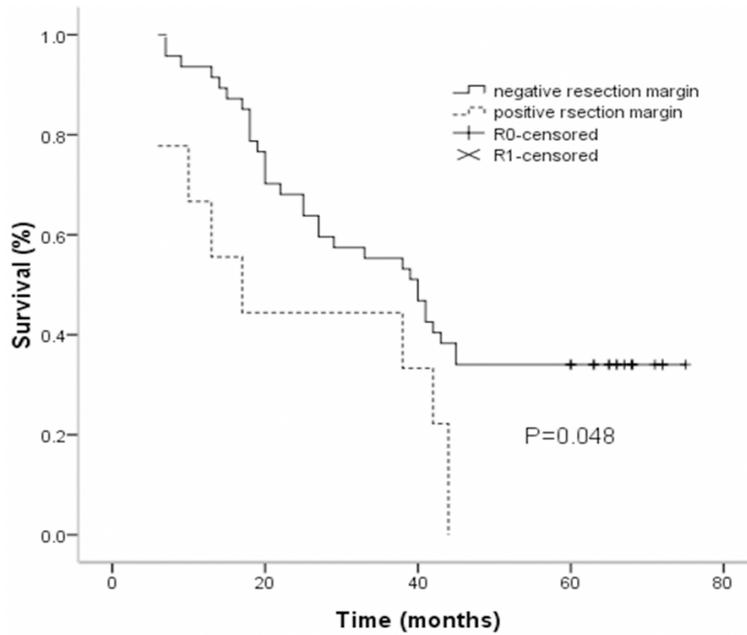
Figure 3. Patients with negative resection margin have an improved survival compared with patients with positive resection margin.

We demonstrated the median survival time of R0 and R1 group is 44, 17 months, respectively ($P = 0.018$).

Does postresection radiotherapy benefit survival or not, it still remains controversial. Several studies demonstrated postresection radiotherapy can improve prognosis in patients with HC after radical surgery [30, 31]. Other studies showed in R0 resected patients, external beam radiation with or without intraoperative radiotherapy and intraluminal radiotherapy (brachytherapy) have shown no survival benefits [32, 33]. On the other hand, adjuvant radiotherapy can benefit patients with positive resection margins (5-year survival 14% versus 34%) [34-36]. Our results showed there was no significant difference between survival rates in postresection radiotherapy group and surgery alone group ($P = 0.284$). What caused so many studies concluded that postresection radiotherapy can benefit survival in patients with HC? Attila N. et al [37] had indicated that in many of those retrospective reports, patients who have undergone radiotherapy, and are expected to have good outcomes, have been compared with patients with advanced stage disease who did not receive radiotherapy. Therefore, several studies drew this conclusion that patients receiving postresection radiother-

apy have survived longer than control group. One previous prospective study had carried out at the Johns Hopkins Hospital stratified patients on the basis of pathologic stage and extent of resection in order to objectively assess the radiotherapy benefit. The result suggested postresection radiotherapy had no effect on overall survival in curative resection group and palliative resection group [38].

From the results of the current study, preoperative serum CA19-9, lymph node metastasis and resection margin are identified as the independent prognostic factor. Furthermore, we determined preoperative CA19-9 can predict pathologic stage and the most discriminative cutoff point of CA19-9 levels for prognosis in patients with resected HC was 150 U/mL. Incorporation of CA19-9 levels may help to stage patients more accurately for entrance into laparoscopy exploration and predict survival in patients with resected HC.

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Disclosure of conflict of interest

None.

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