

TUMOR MARKERS AS A DIAGNOSTIC KEY FOR HILAR CHOLANGIOCARCINOMA

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Abstract

Objective: Hilar cholangiocarcinoma is the fourth most common gastrointestinal malignancy. CA19-9 and CEA are helpful devices in the management of gastrointestinal malignancies and belong to clinical routine in surgical oncology. But the validity of these parameters in terms of tumor extension and prognosis of bile duct malignancies still remains unclear.

Methods: From 1998 to 2008, we obtained preoperative CA19-9 and CEA serum levels in 136 patients with hilar cholangiocarcinoma. We correlated tumor stage, resectability rate and survival with preoperative CA 19-9 and CEA serum levels.

Results: CA19-9 (UICC I: 253 ± 561 U/ml; UICC II: 742 ± 1572 U/ml; UICC III: 906 ± 1708 U/ml; UICC IV: 1707 ± 3053 U/ml) and CEA levels (UICC I: 2.9 ± 3.8 U/ml; UICC II: 4.6 ± 6.5 U/ml; UICC III: 18.1 ± 29.6 U/ml; UICC IV: 22.7 ± 53.9 U/ml) increase significantly with rising tumor stage. Patients with preoperative serum levels of CA19-9 (>1000 U/ml) and CEA (>14.4 ng/ml) showed a significant poorer resectability rate and survival than patients with lower CA19-9 and CEA serum levels respectively.

Conclusion: CA19-9 and CEA serum levels are associated with the tumor stage. If preoperatively obtained CA19-9 and CEA serum levels are highly elevated patients have an even worse survival and the frequency of irresectability is significantly higher.

Key words: bile duct cancer, CA19-9, CEA, hilar cholangiocarcinoma, Klatskin-tumor, tumor staging

INTRODUCTION

Hilar cholangiocarcinoma is a primary cancer of the bile ducts located at the hilar bifurcation [1]. According to the proximal tumor extension the hilar cholangiocarcinoma is classified by Bismuth-Corlette [2]. It is quite a rare malignant tumor (yearly incidence of 2-4 out of 100,000 patients), but nevertheless the fourth most common gastrointestinal malignancy [3]. Previous studies report that the 5-year survival rate after curative resection was between 28-40% [4].

The resectability rate of patients operated for hilar cholangiocarcinoma is 61% at our institution and

therefore comparable to recently published investigations [5]. Hilar cholangiocarcinoma arises from malignant transformation of cholangiocytes, the epithelial cells that line the biliary ducts. Risk factors that have been associated with the development of cholangiocarcinoma are age ≥ 65 years, primary sclerosing cholangitis (PSC), hepatobiliary flukes (*Opisthorchis viverrini*, *Chlonorchis sinensis*), Caroli disease, choledochal cysts, bile duct adenoma, biliary papillomatosis, chronic intraductal stones, liver cirrhosis, surgical biliary/enteric drainage procedures as well as chemicals/agents like thorotrast, dioxin or vinyl chloride [6].

The diagnosis of hilar cholangiocarcinoma is still challenging because tumor masses are often not visible by using computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound. In the case of extended disease dual-modality PET/CT imaging has a high specificity in detection of lymph node and distant metastasis of hilar cholangiocarcinoma [7].

Endoscopic approaches like the endoscopic retrograde cholangiopancreticography (ERCP) are at least useful to identify strictures in the bile ducts, but they do not clearly distinguish between benign or malignant dignity of the lesions. In a previous study we were able to demonstrate that 10% of the patients operated in our clinic for hilar bile duct strictures showed benign conditions after histopathologic diagnosis in terms of a Klatskin-mimicking lesion [8]. Other authors also report 9% up to 15% of Klatskin-mimicking lesions in patients operated for suspected hilar cholangiocarcinoma [9, 10].

Serum tumormarkers like CA19-9 and CEA are helpful keys in the diagnosis and therapy monitoring of gastrointestinal malignancies and belong to the clinical routine today [11, 12]. CA19-9 is a glycolipid synthesized by biliary duct, pancreatic, gastric, colonic, endometrial and salivary epithelial cells [13]. CA19-9 has an important role in the management of hepatobiliary and pancreatic malignancies. Palliative chemotherapy is monitored by CA19-9 serum levels and curative surgery can be followed up with normalized amounts of CA19-9. Nevertheless the validity of this parameter remains unclear and there is an ongoing discussion about the value of CA19-9 for bile duct malignancies. For example, CA 19-9 blood levels are

dependent on the Lewis phenotype of red blood cells [14]. It has been shown that 7% of the population is Lewis negative and even in the presence of a malignant tumor these individuals are CA 19-9 negative [15]. It also has to be mentioned that benign diseases of the hepatobiliary tract like Mirizzi syndrome, autoimmune pancreatitis, benign biliary strictures due to primary sclerosing cholangitis, as well as pancreatic exocrine dysfunction, are frequently associated with elevated CA 19-9 levels [16, 17, 18, 19].

CEA is an important tumor marker for colorectal and other carcinomas like gastric, gallbladder, breast, urinary tract, and lung carcinoma. CEA is a cell membrane associated glycoprotein and shows a differential expression pattern in normal and cancerous tissues [20]. CEA is a commonly used tumor marker and belongs to clinical routine for patients with suspected gastrointestinal malignancies. It has been suggested that CEA may also play a role in cholangiocarcinoma screening [12].

Authors report that tumor markers like CA19-9 and CEA have a certain threshold concentration that can predict malignancy. CA19-9 serum concentrations >1000U/ml indicate most likely malignant tumors. In the case of CEA a malignant tumor is most likely if serum levels are four times higher than the reference serum value of 3.6 ng/ml at our institution [21]. Complete resection of hilar cholangiocarcinoma plus additional liver resection with hilar lymph node dissection offers the only curative treatment. The resectability rate of patients operated for hilar cholangiocarcinoma is 61% at our institution and therefore comparable to most recently published investigations [3, 22]. In many cases, complete resection is technically challenging or even impossible, because of the tumor's proximity to the hepatic artery and portal vein and frequent extended liver and vascular invasion [23]. In a highly selected group of patients liver transplantation may offer a curative treatment option for hilar cholangiocarcinoma [24, 25, 26]. In case of irresectable hilar cholangiocarcinoma our group and Todoroki and coworkers previously reported, that, intraoperative radiotherapy (IORT) of the tumor significantly improves patients' survival in comparison to palliative surgery alone [27, 28, 29].

The aim of this study was to evaluate if the amount of CA19-9 and CEA correlates with the tumor stage according to UICC and if the aforementioned cut off concentrations of CA19-9 (>1000U/ml) and CEA (>14.4ng/ml) correlate with patients' survival and tumor resectability rate.

MATERIAL

From 1998 to 2008, 136 patients were operated for hilar cholangiocarcinoma proven by histopathology and preoperative CA19-9 and CEA serum levels were obtained from all patients. These 136 patients (81 males and 55 females) had a mean age of 61.8 ± 11.2 years.

METHODS AND STATISTICS

After operation we received the pathological report including the tumor-node-metastasis system (TNM) re-

sults and staged the tumor into the International Union against Cancer (UICC) 6th edition [30]. We correlated the UICC tumor stages with the amount of the preoperative CA19-9 and CEA serum levels. CA19-9 ≥ 37 U/ml and CEA ≥ 3.6 ng/ml were considered as elevated.

As mentioned above, the tumor markers CA19-9 and CEA are supposed to have a certain threshold concentration that can probably predict malignancy. Therefore we correlated survival after operation in months in patients providing tumor markers higher and lower than 1000U/ml for CA19-9 and 14.4ng/ml for CEA respectively and subdivided them in two groups. Two groups A are defined as CA19-9 ≤ 1000 U/ml and CEA ≤ 14.4 ng/ml. Two groups B are defined as CA19-9 >1000 U/ml and CEA > 14.4 ng/ml, respectively.

Preoperative diagnostic work-up included initial ultrasound, contrast enhanced spiral CT, MRCP, chest x-ray and in cases of equivocal findings thoracic CT, selective use of PET scanning and endoscopic ultrasound and invasive cholangiography. Preoperative biliary drainage has been performed through ERCP in most cases or via Percutaneous transhepatic biliary drainage (PTBD). Liver function, haematological tests, nutritional status and the serum tumor markers CA19-9 and CEA were determined. As per our protocol, the standard initial evaluation addressed the exclusion of extrahepatic liver disease and the determination of operability/operative risk. Liver resection was considered as the first line of treatment. Criteria for partial hepatectomy included anatomically resectable disease and adequate reserve liver function. Curative intended tumor resection was undertaken whenever feasible. Non-resectability was defined intraoperatively in case of metastatic disease (bilateral liver metastasis, peritoneal carcinosis, and lymph node infiltration outside the liver hilum) and/or major infiltration of bilateral liver lobes, hepatic artery, portal vein and/or remnant liver function judged as insufficient due to poor quality of the liver parenchyma. Suspicious abdominal lymph nodes were removed and analysed by histopathology in each case. If peritoneal spread was confirmed by histopathology of the frozen section, only explorative laparotomy was performed. In case of non-resectability a decision was made between the complementary forms of therapy like endoscopic, radiation therapy or operative palliation.

Results are presented as mean \pm standard deviation as well as median with range or interquartile range (IQR). Survival in the different groups was compared with the Wilcoxon test. Tumor markers in tumor stages II to IV were compared with tumor stage I. P-values were established performing the Wilcoxon test. Significance was defined as a p-value of < 0.05 . Analyses were performed in SAS 9.2.

RESULTS

The preoperatively obtained CA19-9 and CEA serum levels of the 136 patients suffering from hilar cholangiocarcinoma were correlated with the 6th edition of UICC tumor stages (30). Patients' survival and tumor resectability rate.

CA19-9

Out of 136 patients, 109 (80%) show elevated CA19-9 serum levels (≥ 37 U/ml). With rising tumor stages, we detect increasing mean CA19-9 serum levels and a higher percentage of CA19-9 positive patients (≥ 37 U/ml) (Table 1). The preoperative CA19-9 serum levels are significantly higher in tumor stage II-IV compared with stage I: UICC I vs. UICC II ($p = 0.0472$); UICC I vs. UICC III ($p = 0.0187$); UICC I vs. UICC IV ($p = 0.0004$). In addition we correlated patients' survival with their preoperatively estimated CA19-9 levels. Group B is defined by a CA19-9 level >1000 U/ml and associated with poorer survival compared to Group A (median survival of 8 versus 13

months). We also observed a significant higher rate of irresectable tumor masses in Group B than in Group A (64% versus 30%) (Table 2).

CEA

In contrast to CA19-9 only 55 (40%) out of the 136 patients showed elevated CEA serum levels (≥ 3.6 ng/ml) prior to operation. The following results of CEA are in line with the results of CA19-9. We observe increasing CEA serum levels with rising tumor stages. Also, the percentage of patients with elevated CEA (≥ 3.6 ng/ml) serum levels increased with higher tumor stages (Table 3). Preoperative achieved CEA serum levels are significantly higher for tumor stages

Table 1. UICC stages in correlation with CA19-9 serum levels (median and mean) and rate of elevated CA19-9 serum levels in patients with hilar cholangiocarcinoma.

Variable	N=	N (elevated)=	Median CA19-9 levels(range) [U/ml]	Mean \pm standard deviation CA19-9 levels [U/ml]
UICC I	26	15 (58%)	70 (range: 0.8-2730)	253 \pm 561
UICC II	64	51 (80%)	146 (range:0.3-8566)	742 \pm 1572
UICC III	17	16 (94%)	255 (range:1-5879)	906 \pm 1708
UICC IV	29	27 (93%)	428 (range:16-13500)	1707 \pm 3053
Total	136	109 (80%)	173 (range:0.3-13500)	874 \pm 1910

(Data are means \pm standard deviations, median and range)

Table 2. Rate of patients with preoperative elevated tumor marker CA19-9. Mean and median survival of patients with CA19-9 serum levels ≤ 1000 U/ml (Group A) vs. >1000 U/ml (Group B) in months. Rate of nonresectable tumor masses in Group A and Group B.

Variable	Group A (CA19-9 ≤ 1000 U/ml)	Group B (CA19-9 >1000 U/ml)	p-value
N=	111	25	
CA19-9 (U/ml) (Mean/ \pm)	208 \pm 247	3864 \pm 2999	0.00002
CA19-9 (U/ml) (Median/range)	119 (0.3-1000)	2960 (1009-13500)	
Mean survival (Months/ \pm)	23 \pm 25	12 \pm 22	>0.05
Median survival (Months/IQR)	13 (3 to 38)	8 (1 to 9)	
Nonresectable	27 (30%)	16 (64%)	0.0006

(Data are means \pm standard deviations ,median and range or IQR respectively, p-value established by wilcoxon-test)

Table 3. UICC stages in correlation with preoperative CEA serum levels (median and mean) and rate of elevated CEA serum levels in patients with hilar cholangiocarcinoma.

Variable	N=	N (elevated)=	Median CEA levels(range) [ng/ml]	Mean CEA levels \pm standard deviation [ng/ml]
UICC I	26	5 (19%)	1.7 (range:0-15.8)	2.9 \pm 3.8
UICC II	64	24 (38%)	2.8 (range:0.9-37.3)	4.6 \pm 6.5
UICC III	17	8 (47%)	3.5 (range:1.1-94)	18.1 \pm 29.6
UICC IV	29	18 (62%)	5.3 (range:0-250)	22.7 \pm 53.9
Total	136	55 (40%)	3 (range:0-250)	9.9 \pm 27.8

(Data are means \pm standard deviations, median and range)

Table 4. Rate of patients with preoperative elevated tumor marker CA19-9. Mean and median survival of patients with CEA serum levels ≤ 14.4 ng/ml (Group A) vs. CEA >14.4 ng/ml (Group B) in months. Rate of nonresectable tumor masses in Group A and Group B.

Variable	Group A (CEA ≤ 14.4 ng/ml)	Group B (CEA >14.4 ng/ml)	p-value
N=	119	17	
CEA (Mean/ \pm)	3.3 \pm 2.6	56 \pm 62	0.0004
CEA (ng/ml) (Mean/range)	2.4 (0-14)	8.1 (0.5-60)	
Mean survival (Months/ \pm)	22 \pm 26	14 \pm 17	>0.05
Median survival (Months/IQR)	11 (2 to 35)	8 (3 to 15)	
Nonresectable	35 (29%)	9 (53%)	0.008

(Data are means \pm standard deviations, median and range or IQR respectively, p-value established by wilcoxon-test)

II-IV compared to stage I: UICC I vs. UICC II ($p = 0.0124$); UICC I vs. UICC III ($p = 0.0033$); UICC I vs. UICC IV ($p = 0.0083$). Patients belonging to Group B (CEA >14.4 ng/ml) are associated with a poorer survival than patients in Group A (median survival of 8 versus 11 months). Patients belonging to Group B have a significantly higher incidence of irresectable tumor masses than Group A (53% versus 29%) (Table 4).

DISCUSSION

R0 resection is the only curative treatment resulting in survival benefit for patients suffering from hilar cholangiocarcinoma patients, but it is associated with a high perioperative morbidity up to 76% and a mortality up to 19% [3, 29]. Accurate primary tumour staging is indispensable, especially to exclude patients unsuitable for oncologic surgery. We demonstrate that the preoperative established CA19-9 and CEA serum level especially in hilar cholangiocarcinoma can be a useful key to characterise the tumor. A blood sample for tumormarkers prior to operation can even determine the estimated resectability rate. It is evident that CA 19-9 and CEA play an important role in monitoring disease progression in hepatobiliary malignancies. Regarding the hilar cholangiocarcinoma this investigation shows, that the amount of CA19-9 and CEA in preoperatively obtained blood samples correlates positively with the current UICC tumor stages. Furthermore we could demonstrate that the amount of CA19-9 and CEA has a significant correlation to the rate of irresectable tumor masses. The results of the present study indicate that strongly increased amounts of preoperatively obtained CA19-9 (>1000 U/ml) and CEA (>14.4 ng/ml) levels are significantly associated with an even worse survival in patients suffering from hilar cholangiocarcinoma. Patients having negative tumor markers cannot be evaluated by CA19-9 or CEA as a diagnostic or prognostic parameter. In our collective 109 (80 %) out of 136 patients with a proven malignancy had elevated CA19-9 serum levels (≥ 37 U/ml), but only 55 (40 %) out of these 136 patients presented elevated CEA serum levels. There-

fore the value of CA19-9 seems to be higher with a greater reliability and predictive value than CEA. The results of the present study suggest that prognostic information might be obtained from CA19-9 and CEA serum levels before an operative approach for hilar cholangiocarcinoma. Preoperatively obtained CA19-9 serum levels >1000 U/ml and CEA serum levels >14.4 ng/ml are associated with a nonresectability rate of 64% and 53% respectively in comparison to patients with lower preoperative CA19-9 and CEA serum levels respectively. But only 30% (CA19-9 ≤ 1000 U/ml) and 29% (CEA ≤ 14.4 ng/ml) respectively of the patients in group A had non-resectable tumor masses. The preoperatively analyzed CA19-9 and CEA levels give the clinician a prognostic and diagnostic device and might be one of the tools to define the optimal treatment option for the hilar cholangiocarcinoma.

In addition, a preoperative risk stratification, established by CA19-9 and CEA serum levels supplies a potential prognostic tool that may be of use in company with postoperative tumor histology by separating patients (CA19-9 >1000 U/ml/ CEA >14.4 ng/ml) in a high risk group. These results might be helpful for further oncological management and patient selection in the light of neoadjuvant and adjuvant therapy for hilar cholangiocarcinoma.

So we conclude that the preoperative determination of the CA 19-9 and CEA serum values is a helpful device in the diagnostic and prognostic armamentarium for hilar cholangiocarcinoma. It has to be emphasized that like most diagnostic tests it is only helpful if positive. This study demonstrates that the amount of serum CA19-9 and CEA is one of the diagnostic tools to estimate resectability rate in correlation to the tumor stage of hilar cholangiocarcinoma. As shown by this analysis CA19-9 seems to be the more reliable tumor marker compared to CEA for preoperative stratification of patients suffering from hilar cholangiocarcinoma in the light of future adjuvant or neoadjuvant treatment. However additional diagnostic tests are needed to achieve an even more appropriate preoperative estimation of the tumor stage and resectability in hilar cholangiocarcinoma in the future.

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