# Prognostic Relevance of Carbohydrate Antigen 19-9 Levels in Patients with Advanced Biliary Tract Cancer

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## Abstract

**Serum carbohydrate antigen 19-9 (CA 19-9) has been identified as biochemical marker for biliary tract cancer (BTC). The purpose of this study was to evaluate its value as a treatment response marker and its value as a prognostic parameter in patients with unresectable BTC. We analyzed 70 patients with BTC treated with chemotherapy. CA 19-9 levels before and after two treatment courses were analyzed with respect to their effect on treatment response. Patients were categorized into two subgroups according to biliary stenting: patients without endoscopic intervention or biliary drainage (non-stent subgroup) and patients with endoluminal stenting (stent subgroup). Pretreatment CA 19-9 levels were prognostic with respect to overall survival for the entire study population. Patients with CA 19-9 levels above the median of 300 units/mL had a nearly 3-fold risk for early death (hazard ratio, 2.92; 95% confidence interval, 1.51-5.64; adjusted $P = 0.002$) as compared with patients with CA 19-9 levels ≤300 units/mL. An association between CA 19-9 and therapeutic response was observed in the non-stent subgroup ($P = 0.001$) only. Furthermore, the decrease of CA 19-9 levels after treatment was predictive for improved survival in the non-stent subgroup (adjusted $P = 0.018$) but not in the stent subgroup. Our results indicate that pretreatment CA 19-9 levels and CA 19-9 decrease after chemotherapy are of prognostic relevance in patients with BTC.** (Cancer Epidemiol Biomarkers Prev 2007;16(10):2097–100)

## Introduction

Biliary tract cancer (BTC) is a heterogeneous tumor entity comprising intrahepatic mass-forming type cholangiocarcinoma, perihilar Klatskin tumors, extrahepatic cholangiocarcinoma (also called intraductal growth type), and gallbladder cancer. More than 50% of patients are diagnosed at an advanced stage and need palliative treatment with chemotherapy and/or biliary drainage, both of which showing benefits over no therapy or best supportive care (1-3).

Combined with radiologic findings, serum levels of carbohydrate antigen 19-9 (CA 19-9) are widely used as a marker for BTC, especially to assess treatment response. CA 19-9, the sialylated Lewis blood group antigen defined by the monoclonal antibody 1116 NS 19-9, is produced by many cell types including gastric and colon epithelia as well as pancreatic and biliary ductal cells. It is found in high concentrations in normal pancreatic juice and bile. Serum levels in healthy individuals are extremely low (4). For patients without either cholangitis or cholestasis, a CA 19-9 cutoff value of ≥37 units/mL showed a sensitivity of 73% and a specificity of 63% for BTC (5). Levels can be slightly elevated in pancreatitis and other benign gastrointestinal disorders and markedly elevated in benign biliary tract disease especially in the presence of cholangitis or cholestasis and also in adenocarcinoma of nonbiliary origin (6-8). Using a cutoff value of ≥37 units/mL in the presence of either cholangitis or cholestasis, the specificity decreases to 42%. In patients with cholestasis or cholangitis, a cutoff value of ≥300 units/mL increased the specificity (87%) but reduced sensitivity (41%; ref. 5). Patients with malignant bile duct obstruction who need biliary drainage often suffer from recurrent acute or chronic cholangitis resulting in elevated CA 19-9 levels (9). This prompted us to evaluate the prognostic relevance of CA 19-9 in patients with advanced BTC with or without biliary intervention and its value as a marker for response prediction after chemotherapy.

## Materials and Methods

**Patients.** Between June 1998 and June 2005, 75 patients with histologically or cytologically proven unresectable BTC were treated at our institution, with at least two treatment courses of various chemotherapy regimens. The chemotherapy regimens were 5-fluorouracil or gemcitabine based, often in combination with cisplatin or oxaliplatin. For 70 patients, CA 19-9 levels at the beginning of treatment and during the follow-up examinations were available and could be analyzed retrospectively. The cutoff date for data analysis was December 21, 2005. The baseline characteristics of the study population are given in Table 1. The treatment response was measured by computed tomography, magnetic resonance imaging,

Received 2/19/07; revised 6/20/07; accepted 8/1/07.

**Note:** J. Harder and O. Kummer contributed equally to this work.

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doi:10.1158/1055-9965.EPI-07-0155

**Table 1. Patient baseline characteristics**

| | Overall | Non-stent group | Stent group |
|---|---|---|---|
| *N* | 70 | 43 | 27 |
| Male, *n* (%) | 33 (47) | 21 (49) | 12 (44) |
| Female, *n* (%) | 37 (53) | 22 (51) | 15 (56) |
| Median age (y) | 62 | 63 | 62 |
| Median CA 19-9 (units/mL) | 293 | 134 | 412 |
| Tumor grading,* *n* (%) | | | |
| 1 | 2 (3) | 1 (2) | 1 (4) |
| 2 | 49 (76) | 34 (79) | 15 (65) |
| 3 | 14 (20) | 8 (19) | 6 (27) |
| 4 | 1 (1) | 0 | 1 (4) |
| Tumor stage,† *n* (%) | | | |
| II | 11 (16) | 6 (14) | 5 (22) |
| III | 16 (24) | 11 (26) | 5 (19) |
| IV | 43 (60) | 26 (60) | 17 (59) |
| Median survival (mo) | 16.1 | 16.0 | 16.1 |
| BTC, *n* (%) | | | |
| Gallbladder | 16 (23) | 9 (21) | 7 (26) |
| Intrahepatic | 33 (47) | 29 (67) | 4 (15) |
| Extrahepatic | 21 (30) | 5 (12) | 16 (59) |
| Treatment response, *n* (%) | | | |
| Partial response | 14 (20) | 10 (23) | 4 (15) |
| Stable disease | 30 (43) | 18 (42) | 12 (44) |
| Progressive disease | 26 (37) | 15 (35) | 11 (41) |

*In four patients, grading could not be determined.
†According to American Joint Committee on Cancer/Unio Internationale Contra Cancrum classification 2002.

or ultrasound according to the standard WHO (1979) criteria.

Patients were categorized into two subgroups: the endoluminal stent subgroup ($n = 27$) and patients without biliary intervention, the non-stent subgroup ($n = 43$). In each subgroup, CA 19-9 was measured at two distinct time points before treatment and after two treatment courses 10 weeks later.

The CA 19-9 levels were measured as part of the routine staging procedures using a commercially available chemoluminescence immunoassay (Elecsys 1010, Roche Diagnostics GmbH) with a reference range of 0 to 20 units/mL. The method of analyzing CA 19-9 did not change over the study period and was done according to good laboratory practice (ISO 9001: 2000 certified by the German Technical Inspection Authority) and continuously validated by an independent external institution. Overall survival time was measured from the time of histologic diagnosis.

**Statistical Analyses.** Data are presented as medians for continuous data and absolute and relative frequencies for categorical data. Comparison of marker values between the different response groups was done by nonparametric Kruskall-Wallis tests. Survival probabilities were estimated by the Kaplan-Meier method. The prognostic relevance of marker values and clinical characteristics for survival was assessed by multivariable Cox's proportional hazards regression model using sex, age, grade, stage, and whether stenting had been done as adjusting variables. Results of the Cox models are presented as relative risk ratios with 95% confidence intervals together with the $P$ values from Wald's tests. All tests of significance were two sided and $P < 0.05$ was considered statistically significant. Statistical analysis was done using SAS version 8 (SAS Institute).

## Results

The median age of the study population was 62 years (range, 32-81 years); 37 patients were female and 33 male. Gallbladder cancer was diagnosed in 23% (21% non-stent subgroup versus 26% stent subgroup), intrahepatic cholangiocarcinoma in 47% (67% versus 15%), and extrahepatic BTC in 30% (12% versus 59%). The imbalance in the

**Table 2. Median baseline CA 19-9 levels and their median absolute change after chemotherapy in all 70 patients and in stent subgroups according to treatment response**

| | Progressive disease | Stable disease | Partial response | *P* |
|---|---|---|---|---|
| Baseline CA 19-9 (units/mL) | | | | |
| All patients | 236 | 415 | 123 | n.s. |
| Stent group | 932 | 2,091 | 187 | n.s. |
| Non-stent group | 131 | 415 | 123 | n.s. |
| CA 19-9 difference | | | | |
| All patients | +4 | −35 | −66 | n.s. |
| Stent group | −173 | −220 | −99 | n.s. |
| Non-stent group | +276 | −25 | −66 | 0.001 |

Abbreviation: n.s., not significant ($P > 0.05$).

**Table 3. Results of a multivariate Cox survival analysis for the prognostic effect of pretreatment CA 19-9 dichotomized at the median value of 300 units/mL**

| Characteristic | Relative risk (95% confidence interval) | *P* |
|---|---|---|
| CA 19-9 >300 units/mL | 2.92 (1.51-5.64) | 0.002 |
| Stage IV vs II/III | 0.72 (0.40-1.28) | 0.265 |
| Grade 1/2 vs 3/4 | 1.12 (0.56-2.25) | 0.748 |
| Male sex | 0.81 (0.47-1.40) | 0.445 |
| Stent | 0.74 (0.39-1.39) | 0.344 |
| Age >62 y | 0.88 (0.52-1.51) | 0.641 |

NOTE: All patients, $N = 70$.

latter group is explained by the fact that extrahepatic cancer is more likely to cause obstructive jaundice and cholangitis than intrahepatic tumors. Therefore, a large proportion of patients with extrahepatic BTC required bile duct stenting as palliative procedure. The tumor grade was well balanced between the groups (Table 1). The median CA 19-9 level before treatment was 293 units/mL (range, 4.9-257,100), 134 units/mL (range, 4.9-257,100) in the non-stent subgroup versus 412 units/mL (range, 5.6-39,270) in the stent subgroup. Tumor response to chemotherapy was also well balanced: partial response occurred in 20% for the entire study population, in 23% for the non-stent versus 15% for the stent subgroup; stable disease was observed in 43%, with 42% in the stent versus 44% in the non-stent subgroup; and progressive disease was seen in 37%, with 35% in the stent versus 41% in the non-stent subgroup. After two courses of treatment, CA 19-9 median level in the entire study population irrespective of treatment response was 226 units/mL (range, 6.1-70,893), 143 units/mL (range, 7.0-70,893) in the non-stent and 270 units/mL (range, 6.1-9,215) in the stent subgroup. The median baseline CA 19-9 level of patients responding to chemotherapy was 123 units/mL for the entire group, 187 units/mL in the stent and 123 units/mL in the non-stent subgroup. After treatment, median CA 19-9 level was 57 units/mL for all patients responding to chemotherapy, 88 units/mL in the stent and 57 units/mL in the non-stent subgroup. Radiologic response after two treatment courses was associated with a decrease in CA 19-9 levels in the non-stent subgroup ($P = 0.001$) but not in the stent subgroup [$P > 0.05$ (not significant); Table 2]. The median overall survival time from diagnosis was 16.1 months with no significant difference between the non-stent and the stent subgroups (16.0 in the non-stent versus 16.1 in the stent subgroup). At the time of data analysis, 10 patients were alive and 60 patients had died. Fifty-one patients died of end-stage BTC. In nine patients, death was tumor associated. The cause of death in these patients was obstructive jaundice and cholangiosepsis (four patients), duodenal perforation (two patients), neutropenic sepsis due to chemotherapy (one patient), intracranial bleeding with known cerebellar metastasis (one patient), and pneumonia with known pulmonary metastasis and chronic obstructive pulmonary disease (one patient). With exception of the latter, there had been no non-tumor-related deaths. There was a significant association between CA 19-9 level at diagnosis and overall survival for the entire study population ($P = 0.0023$). Furthermore, the decrease of the CA 19-9 level in patients responding to chemotherapy was predictive for improved survival overall ($P = 0.003$). This could also be shown in the non-stent subgroup ($P = 0.001$) but not in the stent group ($P > 0.05$, not significant). Table 3 presents the results of multivariate analyses of all patients for pretreatment CA 19-9 levels dichotomized at the median of 300 units/mL. Patients with CA 19-9 ≤300 units/mL have an adjusted hazard ratio of 2.92 (95% confidence interval, 1.51-5.64; $P = 0.002$) for better survival as compared with those with CA 19-9 >300 units/mL. The median survival in patients with pretreatment CA 19-9 <300 units/mL was 23.5 months as compared with 13.4 months in those with CA 19-9 >300 units/mL (Fig. 1).

## Discussion

CA 19-9 is a widely used diagnostic and prognostic biochemical marker in patients with pancreatic cancer. In addition, several studies support the value of this tumor marker in combination with radiologic findings for predicting treatment response and overall survival. Despite its widespread use in patients with BTC, there are no published data available for this tumor entity. Therefore, it is still undefined whether CA 19-9 is useful for predicting survival and assessing treatment response in these patients. Three previous studies on pancreatic cancer have shown that the median of pretreatment CA 19-9 levels can serve as a valuable cutoff for predicting overall survival (10-12). Therefore, we decided to use the median CA 19-9 level at diagnosis as cutoff in our study on BTC.

Chemotherapy is often used with palliative intention in patients with BTC, but no standard regimen has been defined to date. Our data indicate that pretreatment CA 19-9 levels predict prognosis in patients with advanced BTC (Fig. 1). Furthermore, the CA 19-9 levels after chemotherapy correlate with radiologic response and prognosis in the subgroup of patients not treated by biliary stenting. There is no such correlation in the subgroup of patients treated with endoluminal stents. This may be

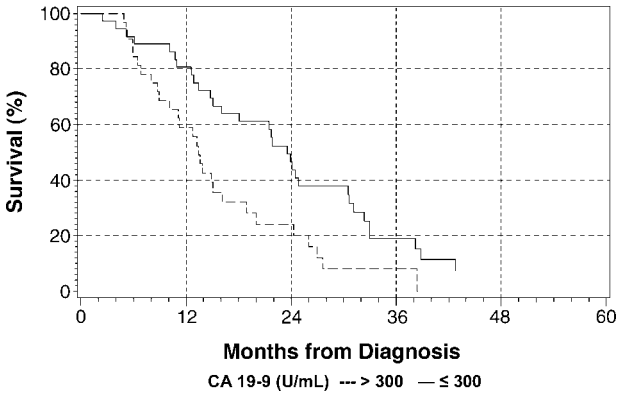


**Figure 1.** Kaplan-Meier survival estimates of the entire study population ($n = 70$), dichotomized in patients with pretreatment CA 19-9 levels below or above the median value of 300 units/mL.

explained by the fact that patients treated with biliary stents had tumor-associated biliary obstruction with or without cholangitis. Cholestasis or cholangitis is associated with increased serum CA 19-9 levels irrespective of the underlying disease (6-8). Accordingly, studies on the sensitivity and specificity of CA 19-9 as tumor marker for cholangiocarcinoma in patients with primary sclerosing cholangitis showed that a high cutoff level is necessary to discriminate benign from malignant disease because of the frequent presence of cholangitis (13, 14). In primary sclerosing cholangitis patients, persistently elevated or increasing serum CA 19-9 levels do not predict the development of BTC (15). Similarly, Patel et al. (16) reported in patients without primary sclerosing cholangitis that a CA 19-9 level of >100 units/mL achieved only a sensitivity of 53% to discriminate BTC from benign bile duct strictures. Therefore, some patients with biliary stenting have increasing CA 19-9 levels despite a response to chemotherapy whereas others have decreasing levels due to resolution of cholangitis in spite of tumor progression. Stent occlusion and cholangitis are frequent complications in patients with BTC, resulting in non-BTC-related increase of CA 19-9 levels. Markers for inflammation like C-reactive protein or erythrocyte sedimentation rate, to distinguish cholangitis from tumor progression, are of little help because they are frequently increased in malignancies (17). On the other hand, the good correlation of CA 19-9 levels in patients without cholestasis and biliary stenting is well explained. In these patients, the CA 19-9 levels solely reflect tumor burden.

Our data show that CA 19-9 levels are associated with radiologic treatment response in patients without prior biliary intervention. Furthermore, baseline CA 19-9 levels have prognostic relevance in all patients with nonresectable BTC (Fig. 1). Patients with CA 19-9 levels below our cutoff of 300 units/mL have a better survival than those with higher levels.

We recommend the use of CA 19-9 as a tumor marker in patients with BTC without cholangitis or prior biliary stenting for monitoring treatment response and as a prognostic indicator for all patients with BTC treated with chemotherapy.

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*Cancer Epidemiol Biomarkers Prev* 2007;16:2097-2100.