

## **THE VALUE OF TUMOUR ASSOCIATED ANTIGEN CA 19-9 IN DIAGNOSING MALIGNANT AND BENIGN BILIARY STRICTURES**

*Departments of Intenal Medicine\*, Clinical Pathology\*\*\**

*Faculty of Medicine, and General Surgery\*\*,*

*University, Egypt*

### **Abstract**

The diagnosis of cholangiocarcinoma is often difficult, making management approaches problematic. A reliable serum tumor marker for cholangiocarcinoma would be a useful additional diagnostic test. Previous studies have demonstrated that elevated serum concentrations of CA 19-9, a tumor-associated antigen, have good sensitivity and specificity for cholangiocarcinoma in patients with primary sclerosing cholangitis. However, the value of this tumor marker for cholangiocarcinoma unassociated with primary sclerosing cholangitis is unclear. Thus, the aims of this study were to determine the usefulness of a serum CA 19-9 determination in the diagnosis of de novo cholangiocarcinoma.

*Methods:* We measured serum CA 19-9 concentrations in patients with cholangiocarcinoma (n=25), nonmalignant liver disease (n=30), and benign bile duct strictures (n=15). serum CA 19-9 concentrations were measured by a direct chemiluminometric technology.

*Results:* The sensitivity of a CA 19-9 value > 100U/ml in diagnosing cholangiocarcinoma was 53%. When compared with the nonmalignant liver disease and the benign bile duct stricture groups, the true negative rates were 76% and 92%, respectively. Patients with unresectable cholangiocarcinoma had significantly greater mean CA 19-9 concentrations compared to patients with resectable cholangiocarcinoma.

*Conclusions:* These data suggest that the serum CA 19-9 determination is a useful addition to the available tests for the differential diagnosis of cholangiocarcinoma.

---

## Introduction

Cholangiocarcinoma is a malignant tumor arising from bile duct epithelium. Unlike most human cancers, a tissue diagnosis of cholangiocarcinoma is often extremely difficult because of tumor location, size, and desmoplastic characteristics. Percutaneous fine needle aspiration is frequently not possible because many of these tumors are located in the liver hilum and large vascular structures. Furthermore, tumor masses are often not even identifiable by CT, ultrasound, or magnetic resonance imaging. Endoscopic approaches are also of limited usefulness in tissue diagnosis because of the desmoplastic nature of these cancers. Indeed, bile cytology obtained at endoscopic retrograde cholangiography (ERCP) has a sensitivity of only 30-50% (Harell et al, 1981, Cohan et al, 1985, Dessa et al, 1991 and Davidson et al, 1992), endobiliary brush cytology of 50-66% (Foutch et al, 1990 and Kurzawinski et al, 1992), and endoscopic transpapillary biopsy of 35-86% for detecting cholangiocarcinoma (Rusing et al, 1994, Pugliese et al, 1995 and Massanori et al, 1996). Because of

the problems in obtaining a diagnostic tissue diagnosis, treatment and management decisions for patients with biliary stricture that may be malignant are problematic.

Diagnostic adjuncts for cholangiocarcinoma, such as a serum marker, would be useful for the clinical management of this disease. CA 19-9 determinations are useful for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis (PSC). The sensitivity and specificity for CA 19-9 value > 100 U/ml for cholangiocarcinoma in PSC was 89% and 86%, respectively (Nichols et al 1993). Ramage et al, 1995 found the sensitivity to be as high as 86% when using CA 19-9 and carcinoembryonic antigen in combination in patients with cholangiocarcinoma superimposed on PSC. Although widely used as a tumor marker (Ritts et al, 1984, Jalanko et al, 1984, Yoshikawa et al, 1985 and Andriulli et al, 1986), the clinical value of serum CA 19-9 determinations in the diagnosis of cholangiocarcinoma in the absence of PSC is unknown.

to  
tio  
  
two  
199  
Univ  
Unit  
to fu  
ment  
gethe  
abdom  
(Duric  
ing an  
tained  
nation]  
  
This  
with ch  
tients w

**Aim Of Work :**

The objective of this study was to determine the clinical usefulness of CA 19-9 values for de nova cholangiocarcinoma. Our specific aims were to address the following questions: 1) What are the serum CA 19-9 value in patients with cholangiocarcinoma, benign bile duct strictures, and nonmalignant end-stage liver diseases? 2) Are elevated CA 19-9 levels in patients with cholangiocarcinoma related to tumor stage or liver dysfunction, or both.

**Patients and Methods**

The study was carried on between May 1997 and September 1999, at Benha and Ein Shams University Hospitals (Endoscopy Units). All patients were subjected to full clinical, laboratory assessments (CBC, ESR, LFT, KFT, together with CA 19-9 estimation), abdominal U/S studies and ERCP (During which endobiliary brushing and papillary biopsies were obtained for histopathological examination).

This study included 25 patients with cholangiocarcinoma, 30 patients with nonmalignant liver dis-

ease, and 15 patients with benign biliary strictures. Of the 25 patients with cholangiocarcinoma, the diagnosis was established by surgical biopsy in 14 patients, endoscopic biopsies and brushings in 11 patients.

The benign bile duct stricture group consisted of 15 patients. The median duration of follow-up in those patients was 15 months. They had benign-appearing strictures with negative endoscopic brushings and biopsies; none of these patients developed metastasis, stricture progression, or died during their follow-up.

The other control group consisted of 30 patients with nonmalignant liver diseases, previously diagnosed, from multiple causes including viral hepatitis (C and B) (n=20), cryptogenic cirrhosis (n=6) and autoimmune hepatitis (n=4).

Blood sample was withdrawn from each patient, about 5 mL placed into plain tube, serum was separated and stored at -70°C until measured (for LFT, KFT and CA 19-9 determinations) and 3 mL placed on tube containing

EDTA for CBC and ESR measurements.

Total bilirubin in serum was determined by a method of Jendrassik and Grof, 1938. (Normal range: up to 1 mg/dl).

AST (Aspartate aminotransferase) in serum was done by a colorimetric method of Reitman and Frankel, 1957. (Normal range: up to 17 U/L).

ALP (Alkaline phosphatase) in serum was done by a colorimetric method of kind and king, 1954. (Normal range: 60-170 U/L).

CA 19-9 in serum was determined using Chiron Diagnostics ACS 180 (automated chemiluminescence system) by a sandwich immunoassay using direct chemil-

uminometric technology which used two purified monoclonal mouse antibodies specific for CA 19-9 (Kricka, 1991).

This assay measured CA 19-9 concentration up to 600 U/ml with a minimum detectable concentration of 0.42 u/ml. Serum samples with levels greater than 600 u/ml were diluted for an accurate determinations (normal range 0-37 u/ml).

#### Statistics :

The results were expressed as mean values  $\pm$  SE. Statistical significance in mean values was evaluated by the Student's t test. The relationship between CA 19-9 level and total bilirubin, alkaline phosphatase, and AST were determined by linear regression analysis.

Table 1. Patients Characteristics in the Three Groups.

Characteristics	Cholangiocarcinoma	Nonmalignant Liver disease	Benign Bile duct stricture
Number of Patients	25	30	15
Sex (M:F)	15:10	12:18	5:10
Total bilirubin (mg/dl)	7.0 (9.5)*	3.4 (6.6)*	1.9 (2.1)*
AST (U/L)	88 (84)+*	136 (325)+*	70 (56)+*
ALP (U/L)	803 (474)*	394 (426)*	837 (942)*
CA 19-9 (U/ml)	7.999 (40.486)	76 (148)	44 (45)

Results are mean with SD in parentheses.

ALP = alkaline phosphatase.

+\*P < 0.01 = Significant.

### Results

The mean ages of the patients with cholangiocarcinoma, nonmalignant liver disease, and benign bile duct strictures were similar. However, the mean total serum bilirubin and serum alkaline phosphatase values were significantly higher in patients with cholangiocarcinoma, compared to the other two groups ( $P < 0.01$ ). In contrast, the serum AST values were significantly higher in the nonmalignant liver disease group than the other two groups ( $P < 0.01$ ). Thus, the patients with cholangiocarcinoma had a more marked cholestatic profile than the other two groups of patients (Table 1).

The mean CA 19-9 concentration was significantly greater in the cholangiocarcinoma group than in the nonmalignant liver disease group and the benign biliary strictures group (Fig. 1). Table 1 shows the mean serum CA 19-9

concentration in patients with cholangiocarcinoma was 7.999 U/ml (range 7-386.000 U/ml) in comparison with 44 U/ml (range 7-870 U/ml) in the benign biliary stricture group. Of the 25 patients with cholangiocarcinoma, 13 (53%) had concentrations exceeding 100 U/ml. Using a CA 19-9 concentration of 100 U/ml, the true negative rate of a CA 19-9 for cholangiocarcinoma is 76% when assessed using as the control group patients with nonmalignant liver disease and the 92% when evaluated using the benign bile duct stricture group.

If the reference value was increase to 200 U/ml, the true negative rate increases from 76% to 93% using the nonmalignant liver disease group as the control group, as compared with the combined benign bile duct stricture group where the true negative rate only increases from 92% to 97%.

**Table 2.** Correlation between CA 19-9 concentrations and T. Bilirubin, ALP and AST in patients with cholangiocarcinoma.

CA 19-9	T. bilirubin	ALP	AST.
7.999 (40.486)	7.0 (9.5)	803 (747)	88 (84)
	$r = 0.057$	$r = 0.147$	$r = 0.027$
	N.S.	N.S.	N.S.

N S = Non significant

ALP = Alkaline Phosphatase