Digestive Diseases and Sciences, Vol. 50, No. 9 (September 2005), pp. 1734–1740 (© 2005)
DOI: 10.1007/s10620-005-2927-8

The Value of Serum CA 19-9 in Predicting Cholangiocarcinomas in Patients with Primary Sclerosing Cholangitis

CYNTHIA LEVY, MD,* JAMES LYMP, PhD,† PAUL ANGULO, MD,‡ GREGORY J. GORES, MD,‡ NICHOLAS LARUSSO, MD,‡ and KEITH D. LINDOR, MD‡

CA 19-9 has been used with questionable accuracy to aid diagnosis of cholangiocarcinoma complicating primary sclerosing cholangitis. We aimed to characterize the test properties of CA 19-9 and of a change in CA 19-9 over time in predicting cholangiocarcinoma. Charts of 208 patients were reviewed. Fourteen patients had cholangiocarcinoma. Median CA 19-9 was higher with cholangiocarcinoma (15 vs. 290 U/ml, $p < 0.0001$). A cutoff of 129 U/ml provided: sensitivity 78.6%, specificity 98.5%, adjusted positive predictive value 56.6% and negative predictive value 99.4%. The median change over time was 664 U/ml in cholangiocarcinoma compared to 6.7 U/ml in primary sclerosing cholangitis alone ($p < 0.0001$). A cutoff of 63.2 U/ml for change in CA 19-9 provided: sensitivity 90%, specificity 98% and positive predictive value 42%. Only 2 patients with cholangiocarcinoma were the candidates for curative therapy. In conclusion, the positive predictive value of an elevated CA 19-9 was 56.6%; only advanced cases were detected by this method.

KEY WORDS: primary sclerosing cholangitis; cholangiocarcinoma; biliary tract malignancy; carbohydrate 19-9.

Cholangiocarcinoma is the second most common primary biliary tumor, after gallbladder cancer. Originally coined by the International Association for the Study of the Liver to describe intrahepatic bile duct tumors, the term "cholangiocarcinoma" is now used to refer to tumors arising from both intra- and extra-hepatic bile ducts. It is estimated that in the United States the incidence rate of intrahepatic cholangiocarcinoma, which represent about 25% of all types of cholangiocarcinomas (1), increased from 0.13 per 100,000 in 1973 to 0.67 per 100,000 in 1997 (2). Similarly, mortality rates increased from 0.07 per 100,000 in 1973 to 0.69 per 100,000 in 1997.

Primary sclerosing cholangitis (PSC), with or without chronic ulcerative colitis (CUC), is one of the strongest risk factors for cholangiocarcinoma with a lifetime risk of 5–15% (3). However, the prevalence of cholangiocarcinoma in autopsies or liver specimens of patients undergoing liver transplantation for PSC is as high as 41%, indicating that the usually quoted figures may underestimate the true prevalence of this cancer (4, 5). It is estimated that the annual incidence of cholangiocarcinoma in PSC is 0.5–1% (5).

Age, gender, stage and/or duration of disease, anatomic distribution of the stricturing process (intra- vs. extrahepatic) and presence or absence of inflammatory bowel disease can not predict development of cholangiocarcinoma in this population (4, 6). There is some evidence that cholangiocarcinoma is more frequent in smokers (7) and in those with CUC associated with colonic dysplasia or neoplasia (8). Both benign and malignant strictures

Manuscript received September 1, 2004; accepted January 12, 2005.

From the *Division of Gastroenterology, Hepatology and Nutrition, University of Florida, Gainesville, †Biostatistics at Mayo Clinic Rochester, Minnesota, and ‡Gastroenterology and Hepatology at Mayo Clinic Rochester, Minnesota.

Cynthia Levy was at Mayo Clinic Rochester at the time this research was conducted and manuscript was written.

Address for reprint requests: Keith D Lindor, Division of Gastroenterology and Hepatology at Mayo Clinic Rochester, 200 1st St SW, Rochester, Minnesota 55905; lindor.keith@mayo.edu.

may have the same radiographic and endoscopic appearance, and the histologic diagnosis from endoscopic specimens has a sensitivity of only 30–80% (9–11). Cholangiocarcinoma may be the initial presentation of PSC and approximately 5% of all cholangiocarcinomas are multifocal (1).

Despite recent discoveries in the field of molecular biology, such as the frequent inactivation of tumor suppressor genes (p53, APC, smad 4, bcl2, p16), the finding of mutations in oncogenes (k ras, c myc, c erb 2, c neu), and chromosomal aneuploidy detected in up to 25% of cases, there is no established clinical role for such tests as of yet (12).

Serum tumor markers have been used to aid diagnosis, but with a controversial role. There is no tumor marker considered specific for cholangiocarcinoma. Serum levels of CA 19-9 are elevated (above 35 U/ml) in a variety of diseases, including malignant (hepatocellular carcinoma, cholangiocarcinoma) and non-malignant conditions such as alcoholic liver disease, primary sclerosing cholangitis, ascending cholangitis, primary biliary cirrhosis, chronic hepatitis B and C, autoimmune hepatitis as well as acute and chronic pancreatitis (13).

Previous studies have demonstrated that high CA 19-9 correlates with the risk of developing cholangiocarcinoma in patients with (10, 14–16) or without PSC (17). However, other investigators have questioned the utility of this tumor marker in predicting development of cholangiocarcinoma or other pancreaticobiliary tumors due to a high false-positivity rate (11, 18, 19). The aim of this study was to evaluate CA 19-9 test properties, particularly positive and negative predictive values, and the receiver operating characteristic (ROC) curve.

PATIENTS AND METHODS

After approval of the study protocol by the Mayo Institutional Review Board in concordance with the ethical guidelines of the 1975 Declaration of Helsinki, data from 504 consecutive patients with PSC evaluated between 8/1/1997 and 2/1/2002 were retrospectively reviewed. This cutoff date was chosen because the study was started in August 2002, and the investigators estimated that by going back approximately 5 years we would have included a reasonably large number of patients. We allowed 6 months (2/1/2002 to 8/1/2002) for follow-up of the last patient included. Subjects were identified using a computerized medical index of diagnosis. Information was obtained from chart review of consenting patients only. An established diagnosis of PSC by radiographic criteria on endoscopic retrograde cholangiopancreatogram (ERCP), percutaneous transhepatic cholangiogram (PTC) or magnetic resonance cholangiopancreatogram (MRCP) was required for every study participant. Patients with a history compatible with secondary sclerosing cholangitis and those who had PSC but who had undergone orthotopic liver transplantation prior to 8/1/1997 were excluded from the study.

In each case, the diagnosis of cholangiocarcinoma was based on histopathologic evidence from either brush cytology/biopsies obtained at the time of ERCP or PTC, or from specimens obtained at surgery or autopsy.

CA 19-9 levels were obtained at the time of routine visits for standard care of PSC. Each analysis of CA 19-9 was recorded, along with the closest measurement of serum aspartate aminotransferase, total and direct bilirubin and alkaline phosphatase levels. Similarly, each ERCP, PTC or MRCP was recorded.

Follow-up was censored at the time of death, diagnosis of cholangiocarcinoma or liver transplantation.

Spearman's rank correlation was used as a measure of association between CA 19-9 and serum alkaline phosphatase, total bilirubin and aspartate aminotransferase levels. Wilcoxon rank sum tests were used to compare serum CA 19-9 in patients with benign and malignant dominant strictures, as well as to compare changes in CA 19-9 in patients with and without cholangiocarcinoma. Results are reported as medians, with interquartile range (IQR) shown in parenthesis. A receiver operator characteristic curve (ROC) was built based on a single measurement of CA 19-9 per patient (the one closest to the diagnosis of cholangiocarcinoma for cases, or closest to the date of last follow-up for controls). Results are shown with 95% confidence intervals (CI). Based on the ROC curve, a cutoff value was designated for the CA 19-9 to maximize the average of sensitivity and specificity. The positive and negative predictive values were calculated assuming the prevalence of cholangiocarcinoma observed in our population (2.58%) and a second set was calculated assuming the expected prevalence of 1%.

RESULTS

Of the 504 patients, 296 were excluded due to wrong diagnosis noted upon chart review ($n = 38$), no cholangiogram available for review ($n = 25$), normal cholangiogram ($n = 18$), evidence of tumor on initial presentation ($n = 4$), previous liver transplantation ($n = 125$) or because there was no CA 19-9 measurement available ($n = 86$). Patients with at least one measurement were included.

A total of 208 patients were followed for a mean of 2.6 years (range 0–5.23 years), comprising 540.8 patient-years. An average of 3.8 CA 19-9 measurements was obtained per patient. Fourteen patients (6.7%) had cholangiocarcinoma. Table 1 shows the clinical characteristics of

TABLE 1. CHARACTERISTICS OF PATIENTS WITH AND WITHOUT CHOLANGIOCARCINOMA

	PSC without CC (n = *194*)	*PSC with CC* (n = *14*)
Duration of PSC* (year)	10.2 (5.7–13.2)	7.4 (2.1–15.5)
Age (year)	53 (48–63)	56 (48–63)
Gender (%) Male	60.6	62.5

Note. Continuous variables represented as median (interquartile range), where interquartile range represents values for the 1st and 3rd quartiles in each group. PSC: primary sclerosing cholangitis; CC: cholangiocarcinoma.
*Known duration of disease.

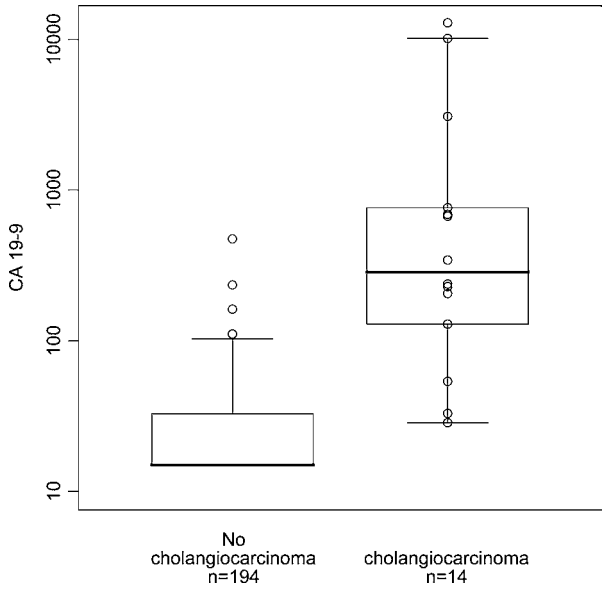

Fig 1. Median CA 19-9 values in patients with PSC without cholangiocarcinoma compared to those with cholangiocarcinoma (15 U/ml vs. 290 U/ml, $p < 0.0001$). The box plots show the median values and the first and third quartiles in each group (interquartile range-IQR). The T bars represent the rest of the data with a maximum of 1.5 times the inter-quartile range.

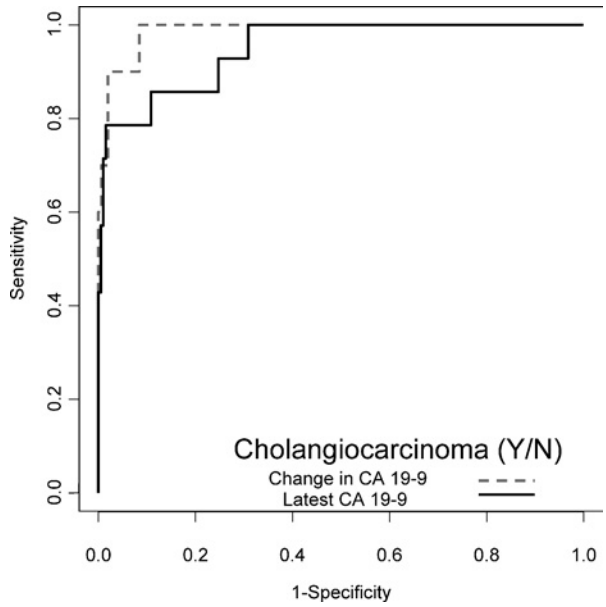

Fig 2. Receiver operator characteristic (ROC) curves for CA 19-9 and change in CA 19-9. The area under the curve (AUC) for the overall group is 0.9492 (95% CI: 0.895, 1.000). The AUC for a change in CA 19-9 > 63.2 is 0.958 (95% CI: 0.969, 1.000).

patients with and without cholangiocarcinoma. Age, gender and duration of PSC were not significantly different between the two groups. Median CA 19-9 was 15 U/ml (IQR 15–33) in patients with PSC alone and 290 U/ml (IQR 148–744) in those with cholangiocarcinoma ($p < 0.0001$, Figure 1).

Weak but statistically significant correlation was found between CA 19-9 and serum liver biochemistries: aspartate aminotransferase $r = 0.26$, $p = 0.0002$; alkaline phosphatase $r = 0.15$, $p = 0.03$; total bilirubin $r = 0.28$, $p < 0.0001$; and direct bilirubin $r = 0.34$, $p < 0.0001$.

Test Properties

By plotting sensitivity of CA 19-9 against 1-specificity for each possible cut-point, an ROC curve was created (Figure 2). The area under the curve (AUC) was 0.949 (95% CI 0.895, 1.000), which suggests that CA 19-9 can accurately distinguish patients with cholangiocarcinoma from those without it.

Using the ROC curve, we determined a cutoff value for CA 19-9 that would maximize the average of sensitivity and specificity: 129 U/ml. With such a cutoff value the following test properties were calculated: sensitivity 78.6%, specificity 98.5%, positive predictive value 78.6%, negative predictive value 98.4% and accuracy 97.1%. Table 2 compares these properties to the ones we would have obtained had we used other cutoff values for CA 19-9 frequently reported in the literature: 100 and 200 U/ml. Also, because this is not a case control study, we used Bayesian statistics to adjust the post-test probability (positive predictive value) according to the pre-test probability (prevalence) of cholangiocarcinoma in our population. Table 3 shows the adjusted post-test probability of having cholangiocarcinoma if the CA 19-9 is greater than 129 U/ml using various pre-test probabilities. In our population, the annual incidence of cholangiocarcinoma was 2.5% and this value was used as pre-test probability. Given the fact that cholangiocarcinoma is relatively rare and has poor prognosis, its incidence approaches its prevalence.

Changes Over Time

Of the 208 patients, 164 had two or more measurements of CA 19-9 performed at variable intervals of time during the follow-up period. The median change in CA 19-9 was 6.7 U/ml (IQR 0–24) in patients with PSC alone and 664 U/ml (IQR 347–2919) in those with PSC and cholangiocarcinoma ($p < 0.0001$), as illustrated in Figure 3. An ROC curve was created and the AUC was 0.987 (95% CI 0.969, 1.000—Figure 2). A cutoff value of 63.2 U/L (for change in CA 19-9 over time) was identified, with sensitivity of 90%, specificity of 98% and positive predictive value 42%. There was no improvement in predictive values when change in CA 19-9 >65 U/ml was combined with CA 19-9 >129 U/ml.

TABLE 2. CA 19-9 TEST PROPERTIES WITH DIFFERENT CUTOFF VALUES

	100 U/ml	*129 U/ml*	*200 U/ml*
True positives	11	11	10
False negatives	3	3	4
False positives	5	3	2
True negatives	189	191	192
Sensitivity (%, 95% CI)	78.6 (49.2–95.3)	78.6 (49.2–95.3)	71.4 (41.9–91.6)
Specificity (%, 95% CI)	97.4 (94.1–99.2)	98.5 (95.5–99.7)	99 (96.3–99.9)
PPV (%, 95% CI)	43.9 (26.2–79.6)	78.6 (49.2–95.3)	64 (38.3–100)
NPV (%, 95% CI)	99.4 (98.9–100)	99.4 (98.9–100)	99.3 (98.7–99.8)
Accuracy (%, 95% CI)	96.2 (92.6–98.3)	97.1 (93.9–98.9)	97.1 (93.8–98.9)

Note. PPV: positive predictive value; NPV: negative predictive value.

Discriminating Between Benign and Malignant Strictures

A total of 198 ERCPs, 43 MRCPs and 38 PTCs were available for 131 patients. Forty-eight patients had dominant strictures, of which 12 (25%) were malignant and 36 (75%) were benign. Median CA 19-9 was 15 U/ml (IQR 15–43) in patients with PSC and a benign dominant stricture and 453 U/ml (IQR 94–839) in those with PSC and a malignant dominant stricture ($p < 0.0001$). This is shown in Figure 4.

Outcomes of Patients with Cholangiocarcinoma

Table 4 summarizes the outcomes of 14 patients with cholangiocarcinoma. Of note, only two patients were suitable candidates for intervention with the intent to cure: patient A had orthotopic liver transplantation and patient B had an en-bloc resection. Median survival in this group was 91 days (IQR 27 to 280 days). The CA 19-9 value at the time of diagnosis of cholangiocarcinoma is also shown in Table 4. Interestingly, the two patients who were amenable to treatment had normal CA 19-9 values at the time of their diagnosis, indicating that CA 19-9 did not perform well as a screening test.

DISCUSSION

The use of CA 19-9 as a screening tool for cholangiocarcinoma in patients with PSC is a widespread, yet controversial, practice among gastroenterologists. In this historical cohort study, CA 19-9 distinguished between isolated PSC and PSC complicated by cholangiocarcinoma with an accuracy of 97.1%. It separated benign from malignant dominant strictures.

A few limitations deserve comments. First, the study was carried out in a referral center. Clinicians tend to see more complex cases in tertiary centers, possibly with a higher rate of malignancies. Despite that, we only observed 14 cases of cholangiocarcinoma. Although we acknowledge the small number of events, we also understand this is the largest reported cohort of patients with PSC followed for cholangiocarcinoma. Second, only patients who had a serum CA 19-9 available were included, possibly translating into a selection bias. However, it is impossible to predict the direction of the selection bias in the present study. Many physicians order serum CA 19-9 as a screening for cholangiocarcinoma regardless of

TABLE 3. ADJUSTED POSITIVE PREDICTIVE VALUE (POST-TEST PROBABILITY) ACCORDING TO PRE-TEST PROBABILITY OF CHOLANGIOCARCINOMA

Pre-test probability	*Pre-test odds*	*Pre-test odds*	*Post-test probability*
0.025	0.0256	1.34	0.566
0.01	0.01	0.524	0.344
0.005	0.005	0.262	0.207

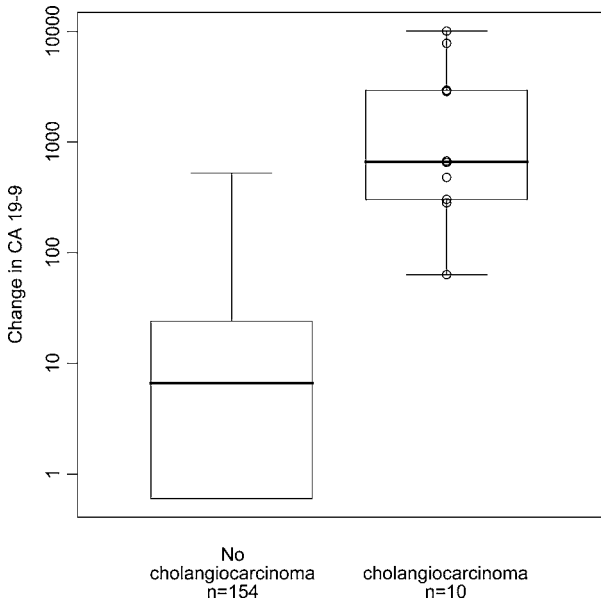

Fig 3. Median changes in serum CA 19-9 over time with PSC alone in comparison to those with PSC and cholangiocarcinoma (6.7 U/ml vs. 664 U/ml, $p < 0.0001$).

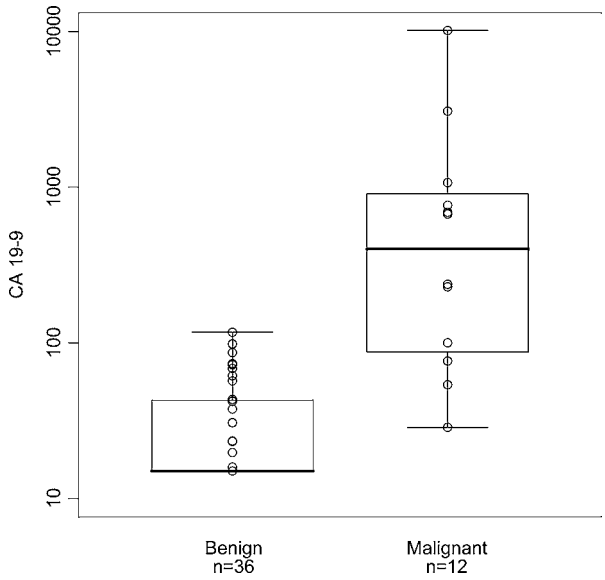

Fig 4. Serum CA 19-9 values for patients with PSC and dominant strictures. Median CA 19-9 value is shown for benign and malignant strictures (15 U/ml vs. 453 U/ml, $p < 0.0001$).

the clinical presentation. Finally, because this is a retrospective study, participants were followed for different lengths of time and had a different number of CA 19-9 measurements during their follow-up. After adjusting for the different periods of follow-up (using persons-years as the denominator), the observed annual incidence of cancer was 2.5%. Such incidence is 2.5 to 5 times higher than expected. Using prior odds of 2.5%, the calculated positive predictive value is 56.6%. Therefore, in this tertiary center, a CA 19-9 value >129 U/ml had a positive predictive value of 56% in detecting cholangiocarcinoma arising in patients with PSC. This may not be reproducible in populations with lower prevalence of cholangiocarcinoma. For example, if the prevalence were 1%, the positive predictive value would have been approximately 34%!

Previous studies assessing the test properties of CA 19-9 characteristically involved a much smaller sample size (11, 14–16). Nichols *et al.* analyzed the serum of 28 patients with PSC alone and 9 patients with PSC and cholangiocarcinoma and found a sensitivity of 89% and specificity of 86% for a CA 19-9 >100 U/ml for detecting cancer (14). However, most of the patients with cholangiocarcinoma were known to have advanced disease and regional metastasis at the time CA 19-9 was measured. Ramage *et al*. conducted a retrospective study involving 74 patients with PSC, 15 with associated cholangiocarcinoma. In that study, a value >200 U/ml had sensitivity and specificity of 60 and 90%, respectively, in differentiating PSC versus PSC with cholangiocarcinoma (15). The authors were interested in the value of an index combining CEA (carcinoembryonic antigen) and CA 19-9 [CA 19-9 + (CEA × 40)]. They found that an index >400 had 100% specificity and positive predictive value, but only 66% sensitivity. This finding has not been confirmed by other investigators (16) and was not the aim of our study, as most patients did not have a CEA measured. Chalasani *et al.* performed a case-control study involving 26 patients with PSC and cholangiocarcinoma and 87 patients with PSC but no cholangiocarcinoma. A CA 19-9 >100 U/ml had a sensitivity of 75% and specificity of 80% in diagnosing cholangiocarcinoma. The investigators did not address the positive and negative predictive values of CA 19-9. In that study, risk factors for cholangiocarcinoma in patients with PSC were evaluated, and alcohol consumption was positively associated with the development of cancer, with an odds ratio of 2.95 (95% CI 1.04, 8.3).

Siqueira *et al.* revisited this controversy by comparing the yield of serum tumor markers (CA 19-9 and

TABLE 4. OUTCOMES OF PATIENTS WITH CHOLANGIOCARCINOMA

Patient	*CA 19-9**	*Diagnosis*	*OLT*	*Resection*	*Survival (days)*	*Status*
A	32.9	Cytology	Yes	No	168	Dead
B	28.6	Laparoscopy	No	Yes	589	Alive
C	762	Biopsy	No	No	280	Dead
D	3,074	Biopsy	No	No	18	Dead
E	53.7	Cytology	No	No	112	Alive
F	342	Cytology	No	No	280	Dead
G	688	Biopsy	No	No	112	Dead
H	228	Biopsy	No	No	15	Dead
I	129	Laparoscopy	No	No	50	Dead
J	10,123	Laparoscopy	No	No	70	Dead
K	205	Biopsy	No	No	30	Dead
L	237	Cytology	No	No	70	Dead
M	669	Cytology	No	No	280	Dead
N	12,886	Fine needle aspiration	No	No	15	Dead

Note. OLT: orthotopic liver transplantation.
*CA 19-9 at the time of diagnosis, in U/ml.

CEA) to that of brush cytology and concluded that the combination of a positive cytology or abnormal CA 19-9 (>180 U/ml) provided the best sensitivity (87.5%) and specificity (97.3%) (9). Predictive values of CA 19-9 were not discussed in the article.

Levels of CA19-9 show a positive correlation with the bilirubin level or with other markers of cholestasis in patients with obstructive jaundice, making it difficult to interpret an elevated CA19-9 in this setting (20). Cholestasis may enhance expression and/or passage of the marker from bile to blood. In fact, even intrahepatic cholestasis has been associated with increased expression of CA 19-9 in cirrhotics (21) and that may explain the significant correlations found between CA 19-9 and alkaline phosphatase as well as total and direct bilirubin in the present study.

We found that a change in CA 19-9 over time greater than 63.2 U/ml also had a high sensitivity and specificity in detecting cholangiocarcinoma in patients with PSC, but with a low positive predictive value of 42%. Therefore, this index (change in CA 19-9) can not be used alone to predict development of cholangiocarcinoma. Although intuitively one could use this in combination with an elevated CA 19-9 to aid in the decision making process, in this study the positive predictive value of the two measurements combined was not better than that of a CA 19-9 >129 U/ml.

We believe that despite being an accurate test to diagnose cholangiocarcinoma, CA 19-9 is not a good screening tool in that setting. An ideal screening test must 1) have high sensitivity and specificity, 2) be simple and safe to perform, 3) be acceptable to both patients and physicians, 4) have low cost and 5) effective early treatment should be available (22). This last requirement is now met with liver transplantation or with surgical resection. Finally, the outcome of treating the disease must be better if it is found by screening than when it is discovered later. The data shown here argue against CA 19-9 as a screening tool, since only 2 of the 14 patients were candidates for further treatment, and these two patients had normal CA 19-9 values. Thus, CA 19-9 only identified patients with advanced, unresectable cholangiocarcinoma. These results need to be validated in an independent set of patients.

In conclusion, patients with primary sclerosing cholangitis with and without cholangiocarcinoma are clinically indistinguishable and, in that setting, serum CA 19-9 appears to be indicated in patients with dominant strictures, as it can help differentiate between benign and malignant strictures. However, CA 19-9 seems to identify only patients with advanced cholangiocarcinoma who are not suitable candidates for curative procedures. Further studies are needed assessing other diagnostic methods such as detection of bile duct dysplasia in order to find patients who may be helped by early intervention.

ACKNOWLEDGMENTS

The authors are indebted to the Mayo Clinic General Clinical Research Center (GCRC) for their guidance regarding protocol development, data abstraction and management as well as statistical support.

REFERENCES

1. Khan SA, Davidson BR, Goldin R, Pereira SP, Rosenberg WM, Taylor-Robinson SD, Thillainayagam AV, Thomas HC, Thursz MR, Wasan H: Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. Gut 51(Suppl 6):VI1–VI9, 2002
2. Patel T: Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. Hepatology 33(6):1353–1357, 2001
3. Chapman RW: Risk factors for biliary tract carcinogenesis. Ann Oncol 10(Suppl 4):308–311, 1999
4. Rosen CB, Nagorney DM, Wiesner RH, Coffey RJ, Jr, LaRusso NF: Cholangiocarcinoma complicating primary sclerosing cholangitis. Ann Surg 213(1):21–25, 1991
5. Broome U, Olsson R, Loof L, Bodemar G, Hultcrantz R, Danielsson A, Prytz H, Sandberg-Gertzen H, Wallerstedt S, Lindberg G: Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. Gut 38(4):610–615, 1996
6. Aadland E, Schrumpf E, Fausa O, Elgjo K, Heilo A, Aakhus T, Gjone E: Primary sclerosing cholangitis: A long-term follow-up study. Scand J Gastroenterol 22(6):655–664, 1987
7. Bergquist A, Glaumann H, Persson B, Broome U: Risk factors and clinical presentation of hepatobiliary carcinoma in patients with primary sclerosing cholangitis: A case-control study. Hepatology 27(2):311–316, 1998
8. Broome U, Lofberg R, Veress B, Eriksson LS: Primary sclerosing cholangitis and ulcerative colitis: Evidence for increased neoplastic potential. Hepatology 22(5):1404–1408, 1995
9. Siqueira E, Schoen RE, Silverman W, Martin J, Rabinovitz M, Weissfeld JL, Abu-Elmaagd K, Madariaga JR, Slivka A, Martini J: Detecting cholangiocarcinoma in patients with primary sclerosing cholangitis. Gastrointest Endosc 56(1):40–47, 2002
10. Rogers SA, Podolsky DK: Predicting cholangiocarcinoma in patients with primary sclerosing cholangitis: An analysis of the serological marker CA 19-9. Hepatology 19(2):543–545, 1994
11. Fisher A, Theise ND, Min A, Mor E, Emre S, Pearl A, Schwartz ME, Miller CM, Sheiner PA: CA19-9 does not predict cholangiocarcinoma in patients with primary sclerosing cholangitis undergoing liver transplantation. Liver Transpl Surg 1(2):94–98, 1995
12. Reeves ME, DeMatteo RP: Genes and viruses in hepatobiliary neoplasia. Semin Surg Oncol 19(2):84–93, 2000
13. Maestranzi S, Przemioslo R, Mitchell H, Sherwood RA: The effect of benign and malignant liver disease on the tumour markers CA19-9 and CEA. Ann Clin Biochem 35(Pt 1):99–103, 1998
14. Nichols JC, Gores GJ, LaRusso NF, Wiesner RH, Nagorney DM, Ritts RE, Jr.: Diagnostic role of serum CA 19-9 for cholangiocarcinoma in patients with primary sclerosing cholangitis. Mayo Clin Proc 68(9):874–879, 1993
15. Ramage JK, Donaghy A, Farrant JM, Iorns R, Williams R: Serum tumor markers for the diagnosis of cholangiocarcinoma in primary sclerosing cholangitis. Gastroenterology 108(3):865–869, 1995

16. Chalasani N, Baluyut A, Ismail A, Zaman A, Sood G, Ghalib R, McCashland TM, Reddy KR, Zervos X, Anbari MA, Hoen H: Cholangiocarcinoma in patients with primary sclerosing cholangitis: A multicenter case-control study. Hepatology 31(1):7–11, 2000
17. Patel AH, Harnois DM, Klee GG, LaRusso NF, Gores GJ: The utility of CA 19-9 in the diagnoses of cholangiocarcinoma in patients without primary sclerosing cholangitis. Am J Gastroenterol 95(1):204–207, 2000
18. Bjornsson E, Kilander A, Olsson R: CA 19-9 and CEA are unreliable markers for cholangiocarcinoma in patients with primary sclerosing cholangitis. Liver 19(6):501–508, 1999
19. Hultcrantz R, Olsson R, Danielsson A, Jarnerot G, Loof L, Ryden BO, Wahren B, Broome U: A 3-year prospective study on serum tumor markers used for detecting cholangiocarcinoma in patients with primary sclerosing cholangitis. J Hepatol 30(4):669–673, 1999
20. Mann DV, Edwards R, Ho S, Lau WY, Glazer G: Elevated tumour marker CA19-9: Clinical interpretation and influence of obstructive jaundice. Eur J Surg Oncol 26(5):474–479, 2000
21. Giannini E, Borro P, Botta F, Chiarbonello B, Fasoli A, Malfatti F, Romagnoli P, Testa E, Risso D, Lantieri PB, Antonucci A, Boccato M, Milone S, Testa R: Cholestasis is the main determinant of abnormal CA 19-9 levels in patients with liver cirrhosis. Int J Biol Markers 15(3):226–230, 2000
22. Fletcher R, Fletcher S, Wagner E: Clinical Epidemiology: The Essenctials. Third ed. Philadelphia: Williams & Williams, 1996.