REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Title:
Title: Endoscopic retrograde cholangiopancreatography and carbohydrate antigen 19-9 in the differential diagnosis of biliary strictures

Authors:
Lisset Barroso Marquez, Lissette Chao González, Marcia Samada Suárez, Harlim Rodríguez Rodríguez, Yunia Tusen Toledo, Kenia Valenzuela Aguilera, Teresita Pérez González

DOI: 10.17235/reed.2021.7711/2020
Link: PubMed (Epub ahead of print)

Please cite this article as:
Barroso Marquez Lisset, Chao González Lissette, Samada Suárez Marcia, Rodríguez Rodríguez Harlim , Tusen Toledo Yunia, Valenzuela Aguilera Kenia, Pérez González Teresita. Title: Endoscopic retrograde cholangiopancreatography and carbohydrate antigen 19-9 in the differential diagnosis of biliary strictures . Rev Esp Enferm Dig 2021. doi: 10.17235/reed.2021.7711/2020.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Accepted Article

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

OR 7711

Endoscopic retrograde cholangiopancreatography and carbohydrate antigen 19-9 in the differential diagnosis of biliary strictures

Lisset Barroso Márquez[1], Lissette Chao González[1], Marcia Samada Suarez[1], Harlim Rodríguez Rodríguez[2], Yunia Tusen Toledo[3], Kenya Valenzuela Aguilera[1], Teresita Pérez González[2].

[1]Centro de Investigaciones Médico Quirúrgicas. La Habana. Cuba.

[2.]Hospital General Docente "Iván Portuondo". San Antonio de los Baños. Artemisa. Cuba

[3.] Centro de Investigaciones Clínicas. La Habana. Cuba.

Correspondence: lisetbaromar77@gmail.com

ABSTRACT

Introduction

Bile duct strictures include a wide spectrum of benign or malignant diseases. Objective: To determine the usefulness of endoscopic retrograde cholangiopancreatography (ERCP) and circulating carbohydrate antigen19-9 (CA 19-9) in the differential diagnosis of biliary strictures.

Method

We used an observational, prospective and cross-sectional study in 75 patients with biliary stricture diagnosed by ERCP between October 2018-January 2020. The variables were: type of biliary stricture diagnosed by ERCP, biliary cytology and CA 19-9 levels. For the statistical analysis, descriptive statistic was used according to the type of variable. The relationship among them was performed using Pearson's chi-square and Fisher's exact probability tests, assuming the differences as significant when $p < 0.05$. The cut-off point for CA 19-9 was calculated using the ROC curve and the Cohen's Kappa index was used to measure concordance between diagnostic methods. Results: Cytology was positive in 51 (68%) patients with biliary stenosis. The mean age was 63 years. Acute cholangitis predominated in malignant strictures (93.7%). There was agreement between the cytology and the cut-off value calculated for CA 19-9 of 85.4U / ml, with Kappa agreement index = 0.332 ($p = 0.004$); as well as between ERCP and

cytology with Kappa concordance index = 0.701 (p <0.001). Conclusions: A serum CA 19-9 value higher than 85.4 U / ml is highly related to neoplastic biliary stenosis.

Keywords

Biliary stricture, endoscopic retrograde cholangiopancreatography, biliary cytology, carbohydrate antigen 19-9 (CA 19-9).

List of abbreviations

ERCP: endoscopic retrograde cholangiopancreatography; CA 19-9: carbohydrate antigen 19-9

INTRODUCTION

Bile duct stenosis is a frequent indication for an endoscopic retrograde cholangiopancreatography (ERCP). Benign strictures are mainly iatrogenic and inflammatory in origin, while malignant ones are related to biliopancreatic tumors (1).

Neoplastic biliary strictures are mainly due to tumors of the pancreatic head and cholangiocarcinomas. Pancreatic cancer is the second leading cause of digestive tract tumor disease (1-2). Currently, there is an increase in intrahepatic cholangiocarcinoma incidence and a decrease in the perihilar and distal malignancies. Although, they have a poor prognosis worldwide (1, 3).

The differential diagnosis of biliary stenosis from the clinical point of view is not always possible, since there are not pathognomonic clinical signs that define it. It is published that jaundice, abdominal pain, and weight loss could suggest malignancy. In contrast, an asymptomatic clinical course may be related to benign stenosis. Using analytical methods, only elevation of cholestasis enzymes can be found. Although, liver cytolysis is frequently found as well (1,4-5).

The development achieved in recent years in diagnostic techniques such as multiphasic computed tomography, magnetic resonance imaging, and endoscopic ultrasound has contributed to the differentiation between benign and neoplastic strictures. ERCP is commonly used as a minimally invasive technique to drain the bile duct using a prothesis and to obtain a

Accepted Article

pathological sample by brushing the bile duct (1,6-9).

Besides, it has been reported that the serum quantification of tumor markers can contribute to the diagnosis (7,10-11).

Carbohydrate antigen 19-9 (CA 19-9) is used for the diagnosis and monitoring of neoplastic biliopancreatic diseases, particularly cholangiocarcinoma and adenocarcinoma of the pancreas. Serum levels higher than 37 U / ml have a sensitivity of 74% for malignant biliary pathology, although they present a low specificity. However, circulating CA 19-9 levels is considered the preferred choice over other evaluated markers (11).

The objective of this work was to determine the usefulness of ERCP and CA 19-9 in the differential diagnosis of biliary strictures.

MATERIAL AND METHODS

A descriptive, prospective and cross-sectional study was carried out in a group of patients with biliary stenosis diagnosed by ERCP at CIMEQ hospital in the period between October 2018 and January 2020.

All patients with biliary stricture of undetermined etiology diagnosed by ERCP were included. Patients with biliary stricture with a highly probable benign etiology, such as after liver transplantation or after cholecystectomy, were excluded. Those who did not give their informed consent to participate in the study were also excluded.

The sample consisted of 75 patients with biliary stricture, 34 (45.3%) women and 41 (54.7%) men, with a mean age of 63.7 ± 12.8 years, (range 30-84).

In all cases, ERCP with bile duct brushing was performed for cytological study. Clinical manifestations, liver enzyme results, and CA 19-9 levels were collected from the patients' medical records.

All ERCPs were performed by two endoscopists with more than 10 years of experience, who jointly reported the radiological images. The cytologies were analyzed by two pathologists with more than 30 years of experience.

Two study groups were formed according to the results of the biliary cytology obtained by ERCP. The pathology was defined as neoplastic when the cytology was positive and benign if

Accepted Article

the cytology for malignancy was negative.

Types of biliary stricture diagnosed by ERCP:

• Benign biliary stricture: stricture with a long transition zone, not abrupt with a smooth narrowing, and concentric (12).

• Malignant biliary stricture: stricture with a length greater than 14 mm, irregular or asymmetric appearance (12).

To estimate the sample size, OpenEpi version 3 was used with the data: population size n = 75, frequency of the response factor p = 50%. Confidence interval: d = 5%. The estimated sample size was 72.

The data were processed by the SPSS statistical package. Version 25.0 on Windows. Descriptive statistic (percentages, means and standard deviations) was used according to the type of variable. The relationship between the variables was performed using Pearson's chi-square and Fisher's exact probability tests, denoting differences as significant when $p < 0.05$. The cut-off point in this sample was calculated using a ROC curve to compare the agreement of Ca 19-9 with conventional cytology.

The consistency between the results of the diagnosis by cytology and CA 19-9 and by cytology and ERCP was determined using Cohen's Kappa index. It was interpreted according to Landis and Cosh, in order to measure the strength of agreement between the methods.

This research was approved by the Ethics Committee of the center where the study was carried out and the ethical bases of research in human beings corresponding to the Declaration of Helsinki were respected (13).

RESULTS

Of the 75 patients who underwent ERCP with bile duct brushing, the cytological diagnosis of malignant biliary stricture prevailed in 51 (68.0%) patients (Fig. 1).

Mean age and gender behaved similarly in both groups without significant differences between them, with a slight predominance of male patients (Table 1).

Regarding the clinical manifestations, of the 75 patients evaluated, the combination of abdominal pain plus jaundice was the most frequent in 32 patients, 11 (34.4%) with benign

Accepted Article

biliary stricture and 21 (65.6%) with malignant disease. Cholangitis was observed in 15 patients (93.7%) with malignant biliary stenosis and it was the only variable of the clinical manifestations that had significant differences between both groups (p = 0.01). The mean values of GGT (723.7U / L) and FAL (1017.5U / L) predominated in the malignant stenosis group without significant differences among the laboratory values evaluated. (Table 1)

CA 19-9 levels higher than 37 U / ml was more frequent in the malignant stenosis group (Table 1).

The cut-off point of CA 19-9 levels was calculated with the data obtained (Fig. 2), when the reference value of this marker was used (> 37 U / ml) the result was not significant and the Kappa concordance index was low. However, for the value 85.47 U / ml, the Kappa index was 0.332 with a significance of 0.004 (Table 2).

The relationship between the type of biliary stricture diagnosed by ERCP and cytology is shown in Table 3. Of the 51 patients with positive cytology, 50 (98%) had an endoscopic appearance of malignant stricture. Therefore, it was found that the cholangiographic image by ERCP and cytology are concordant for the differential diagnosis of biliary stenosis, the Kappa index was 0.701 with a significance of p <0.001.

Discussion

The objective of the study was to determine a possible cut-off point in the serum determination of the tumor marker CA 19-9 to differentiate between benign and neoplastic biliary strictures (14-15).

Tumor markers are molecules (generally glycoproteins) that may be elevated in the presence of cancer, either as a reaction of the host to the tumor or as a product of the tumor itself. Their serum concentration depends on the biological variability of the patient and they are detected in different body fluids. Its existence reflects tumor growth or activity and allows to know the presence, evolution or therapeutic response of a malignant tumor (16).

Various authors have evaluated the usefulness of the circulating tumor marker CA 19-9 in the differential diagnosis of biliary strictures. So far, the results found are disappointing, since low rates of sensitivity and specificity are reported for the standardized reference value of 37 U / ml. It is known that CA 19-9 is elevated in cholestasis and cholangitis. For this reason, several

Accepted Article

studies have focused on clarifying the use of this marker and finding the appropriate cut-off values for each study population (16-18).

In this study, it has been found that a serum CA 19-9 value higher than 85.4 U / ml is highly related to neoplastic biliary stricture.

In our work, there is a higher proportion of neoplastic stenosis because patients with post-transplant and postsurgical stenosis, which are the fundamental causes of benign stenosis. These patients were excluded from the study. In contrast, previous Cuban authors have reported a higher frequency of benign biliary stricture (15, 17, 19-20).

In this series, there was a predominance of acute cholangitis as a form of presentation of malignant biliary stricture. There were not differences in known clinical manifestations such as jaundice or abdominal pain.

The results of this investigation are similar to those reported in the literature. There was not concordance between cytology and CA 19-9 with the standardized values (more than 37 U / ml). However, cytology was consistent with the calculated cut-off value higher than 85.4 U / ml in CA 19-9 molecule.

In Cuba, ERCP, together with the cytological study of biliary stricture, continues to be the most widely used method for the differential diagnosis of biliary strictures.

The appearance of ERCP cholangiography is insufficient to provide the definitive diagnosis of biliary stricture, so the study of tissue samples is required to confirm the diagnosis. A CA 19-9 value higher than 85.4 U / ml can help to differentiate between benign and neoplastic biliary strictures.

REFERENCES

1. Arvanitakis V, Fernández M. Early diagnosis and management of malignant biliary obstruction: A review on current recomendations and guidelines. Clinical and expermimental gastroenterology 2019;12:415-32.https://doi.org/10.2147/CEG.S195714
2. Saurí T, Tabernero Caturla J (dir), Maraculla T (dir). Tesis caracterización molecular de los tumores de vías biliares. Tamara Saurí Nadal. [Tesis doctoral en Internet]. [Barcelona]: Universidad Autónoma de Barcelona;2019.

Accepted Article

3. Banales J, Marin J,Lamarca A, et al.Cholangiocarcinoma 2020: thenext horizon in mechanisms andmanagement. Gastroenterology & Hepatology.http:// doi.org/10.1038/s41575-020-0310-z.
4. Singh A, Gelrud A, Agarwal B, et al. Biliary strictures and approach. Gastroenterol Rep 2015; 3(1):22-31.http:// doi: 10.1093/gastro/gou072. Epub 2014 Oct 28.
5. Dumonceau J, Delhaye M, Charette N and Farina A. Challenging biliary strictures: pathophysiological features, differential diagnosis, diagnostic algorithms, and new clinically relevant biomarkers- part 1.Therapeutic Advances in Gastroenterology 2020; 13:1-27
6. Fairchild A, Eric J, Hohenwalter E, Gipson M, et al. Appropriateness criteria radiologic management of biliary obstruction. Journal of the American College of Radiology 2019;16:196-213.https://doi:10.1016/j.jacr.2019.02.020
7. Castrillón G y Gómez D. Obstrucción maligna de la vía biliar: hallazgos imagenológicos usuales y recientes. Rev. Colomb. Radiol 2015;26(4):4317-27.https://pesquisa.bvsalud.org/portal/resource/pt/biblio-987874
8. Dorrell R, Pawa S, Zhou Y, et al. The Diagnostic Dilemma of Malignant Biliary Strictures. Diagnostics 2020;10:337.https://doi:10.3390/diagnostics10050337.
9. Moya E, Salmerón A, Medina P, et al.Estenosis biliares. Claves para el diagnóstico diferencial. Radiología 2016;58:786
10. Navaneethan U, Hasan M, Lourdusamy V, Njei B, Varadarajulu S, Hawes R. Single-operator cholangioscopy and targeted biopsies in the diagnosis of indeterminate biliary strictures: a systematic review. Gastrointest. Endosc 2015; 82(4): 608–14. http://doi: 10.1016/j.gie.2015.04.030
11. Medina G, Saccá F, Louis C. Ictericia obstructiva benigna y maligna: utilidad del CA 19-9. Rev Gen 2016;70(2):54-60.
12. Zamalloa H, Valdivia M, Vargas G, et al. Experiencia con la colangiografía retrógrada endoscópica como procedimiento diagnóstico y terapeútico. Hospital Nacional Arzobispo Loayza de Lima. 2004. https://pesquisa.bvsalud.org/portal/resource/pt/lil-484270

Accepted Article

13. World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects adopted by the 59th WMA General Assembly. Seoul. October 2008.
14. Montes de Oca M, Laureano L, Noa G, et al. Tumores malignos biliopancreáticos: diagnóstico y terapéutica mediante colangiopancreatografía retrógrada endoscópica. Archivo Médico de Camagüey2013;17(2):150-161. http://www.redalyc.org/articulo.oa?id=211129316007
15. Brizuela R, Ruiz J, Martínez R, et al. Tratamiento endoscópico de las afecciones obstructivas no litiásicas de la vía biliar principal; resultados en una serie de 1455 casos. Endoscopia 2010;22(4):171-7. http://www.elsevier.es
16. Hermida I, Sánchez E, Cordero R, et al. Marcadores tumorales. Rev Clin Med Fam 2016;9(1):31-42.
17. Jans B, Talma M, Almonacid M, et al. Rendimiento diagnóstico del marcador tumoral CA 19-9 en la diferenciación entre patología bilio-pancreática benigna y maligna.Rev Chil Cir 2013;65(4):307-314.
18. Tsen A, Barbara M, Rosenkranz L.Dilemma of elevated CA 19-9 in biliary pathology. Pancreatology 2018;18:862-867. https://doi.org/10.1016/j.pan.2018.09.004
19. Chao L, Barroso L, Tusen Y, et al. Cirugía endoscópica biliopancreática. Resultados de 10 años en el CIMEQ. Invest Medicoquirur 2015;7(1):91-110.
20. Experiencia en el tratamiento endoscópico de la obstrucción de la Vía Biliar Principal. Brizuela Quintanilla RA y Fábregas Rodríguez C. Rev Cubana Med Milit 2003;32(2):81-7)

Accepted Article

Table 1. Characteristics of patients with biliary strictures according to cytology test.

Variables	Malignant	Benign	p
Female/Male(n=75)	22/29	12/12	0,578
Age (years, mean±SD)	63,8 ± 12,2	63,6±14,3	0,966

Clinical manifestations			
Jaundice (n=25)	15(42,8%)	10(28,5%)	0,294
Jaundice + abdominal pain (n=32)	21(65,6%)	11(34,4%)	0,704
Acute Cholangitis (n=16)	15(93,7%)	1(6,2%)	**0,015**
Liver enzimes (n=75)			
AST (U/L)	125,0±101,3	109,1±69,4	0,489
ALT(U/L)	154,2± 163,5	101,6±55,5	0,130
GGT(U/L)	723,7± 659,3	459,5±365,0	0,071
ALP (U/L)	1017,5± 1362,1	686,4±515,0	0,254
TBIL (µmol/L)	191,2± 138,8	177,2±153,9	0,694
Tumor biomarker			
CA 19,9 >37 U/ml (n=53)	39 (73,6%)	14(26,4%)	0,108
CA 19-9 >85, 4 U/ml (n=46)	37 (80,4%)	9(19,6%)	**0,004**

AST, aspartate aminotransferase, ALT, alanine aminotransferase, GGT: γ-glutamyl transpeptidase, ALP: Alkaline phosphatase, TBIL: Total bilirubin, CA 19-9: carbohydrate antigen 19-9

Table 2. Relationship between biliary cytology and CA 19-9 level higher than 85,4U/ml

Cytology	CA 19-9 higher than 85,4 U/ml			
	Positive		Negative	
	n	**%**	**n**	**%**
Positive n=51	37	72,6	14	27,4
Negative n=24	9	37,5	15	62,5

Kappa Concordance Index = 0,332 (p=0,004)

Table 3. Relationship between biliary stricture type by ERCP and biliary cytology

Biliary cytology	Biliary stricture			
	Malignant		Benign	
	n	**%**	**n**	**%**
Positive n=51	50	98,0	1	2,0
Negative n=24	8	33,3	16	66,7

Accepted Article

Kappa Concordance Index = 0,701 (p<0,001)

ERCP: Endoscopic retrograde cholangiopancreatography

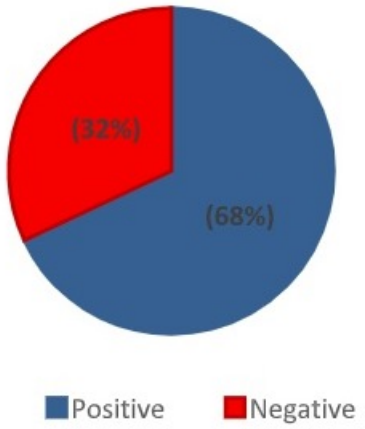
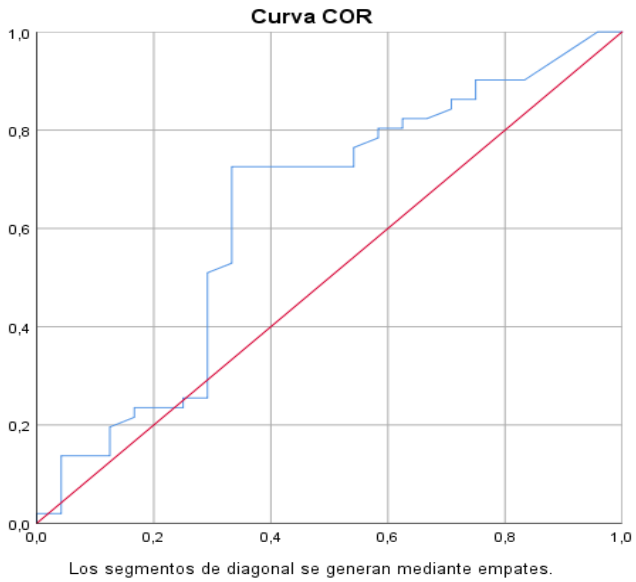


Figure 1. Incidence of biliary stricture according to cytology test.



Accepted Article

REVISTA ESPAÑOLA DE
ENFERMEDADES DIGESTIVAS
The Spanish Journal of Gastroenterology

Figure 2. CA 19-9 cut off according to receiver operator characteristic curve (ROC)

Area under curve (AUC) =0,630

Cutt off = 85,4750

Accepted Article