

Diagnostic Accuracy of tumor marker CA 19-9 in patients with Cholangiocarcinoma taking ERCP as gold standard test”

AFTAB HAIDER ALVI¹, AIJAZ ZEESHAN KHAN CHACHAR², ABDUL KAFI³, ABDUL FAROOQ⁴, SAJJAD ALI⁵, SAJJAD ALI⁶

¹Associate Professor, Fatima Memorial Hospital, Shadman, Lahore.

²Senior Registrar, Fatima Memorial Hospital, Shadman, Lahore.

³Consultant Gastroenterologist, Afghanistan.

⁴Post graduate trainee, Gastroenterology,

⁵Internist, Obesity Medicine and Infectious Diseases Physician, Sultan Bin Abdul Aziz Humanitarian City, Riyadh Saudi Arabia

⁶Consultant Physician, Eastern Maine Medical center, USA

Correspondence to: Dr. Aijaz Zeeshan Khan Chachar, Email: dr_ajaz84@hotmail.com

ABSTRACT

Background: Majority of the cases of Cholangiocarcinoma at presentation are unresectable, it's diagnosis at an early stage is pivotal but generally difficult due to lack of easy availability of confirmatory test at the moment in our country. Endoscopic Retrograde Cholangiopancreatography (ERCP) is not only helpful in reaching the diagnosis

Aim: To find out the diagnostic accuracy of tumour marker CA 19-9, in suspected patients of Cholangiocarcinoma taking ERCP as gold standard test

Methods: This cross sectional study was conducted in general and private clinics of Department of Gastroenterology of the Fatima Memorial Hospital Lahore from, October 21, 2014 to April 20, 2015. Sampling technique used was probability purposive sampling.

Results: A total of 150 suspected patients of cholangiocarcinoma were included in the study in which 61 (40.7%) were male and 89(59.3%) were female with total mean age of 56.32±14.13 years. Among the studied patients, 88(58.7%) were found positive for malignant stricture on ERCP and CBD brushing cytology. Sensitivity, specificity and accuracy of the tumour marker CA 19-9 was 53.4%, 66.1% and 58% respectively.

Conclusions: CA 19-9 is a very important tumor marker in making diagnosis of cholangiocarcinoma and in our country due to lack of easy access/availability to invasive diagnostic methods like endoscopic ultrasonography (EUS) and fine needle aspiration (FNA) of the tumor. It should be used as routine early diagnostic modality in suspected cases of Cholangiocarcinoma.

Keywords: Cholangiocarcinoma, Cancer antigen (CA) 19-9, ERCP, biliary brushing and cytology

INTRODUCTION

Cholangiocarcinoma is known to be an aggressive and devastating epithelial tumor of the bile ducts that usually observed as locally advanced or metastatic disease carrying extremely poor prognosis.¹ Cholangiocarcinoma (CCA) includes diverse group of malignancies that can take origin from the canals of Hering to the main bile duct. CCA are considered to be the uncommon tumors accounting almost 3% of gastrointestinal tumors with overall incidence of less than 2100,000². When discussing about liver malignancies, CCAs are the second most common tumor and Hepatocellular carcinoma (HCC) is still on top in liver malignancy. About 20% of the deaths from hepatobiliary cancers are considered to be from CCAs, accounting for 13% of the total cancer mortality worldwide. Studies conducted in last few years have revealed that incidence of CCA is alarmingly rising mostly in Western countries^{2,3}. Regarding the fatality of CCA, it is known to be the one of the most fatal cancer albeit with early diagnosis and advances in therapeutic options, 1- year mortality has reduced alot over time but still the 5-year survival is still very low which is around 10%⁴. The definite and the best available option for patients having CCA is surgical resection which is considered as curative option. Despite higher incidence of resectibility of CCAs, which is reported in literature as 65%, curative resection rates were unfortunately as low as 50%⁵. It is very unfortunate that two-thirds of CCAs are clinically silent and are only diagnosed in their unresectable stages⁶. Since most of the

cases are unresectable during presentation, its diagnosis at an early stage is of most significance but generally difficult due to lack of easily available confirmatory test at the moment in our setup. Radiologically, usually ultrasonography (USG) abdomen, is the most common modality used for screening purposes during routine practice.

Endoscopic Retrograde Cholangiopancreatography (ERCP) is not only used for diagnosis but also therapeutic purposes in most of the advanced unresectable cases. It has got a sensitivity of 74% and specificity of 70% in diagnosis of cholangiocarcinoma. It has been used as a gold standard test in diagnosis of cholangiocarcinoma in literature.⁷ Biliary Brushing cytology is a technique performed during ERCP for obtaining a tissue sample from an indeterminate biliary stricture with sensitivity of 52%, specificity of 100%⁸. Cancer antigen (CA) 19-9 is the most commonly used tumor marker in diagnosis of CC in our hospitals, due to its easy availability and low cost compared to other invasive and expensive investigations like computed tomography (CT) scan and ERCP. According to one study in literature, sensitivity of CA 19-9 is 67.5% and specificity is 86.8%⁹. Keeping in view the above facts, it is very important to find out the diagnostic value of CA 19-9 in diagnosis of cholangiocarcinoma in our setup.

Operational definitions:

ERCP: ERCP was considered as positive for Cholangiocarcinoma when both of the following were present:

- Cholangiography done during ERCP indicate common bile duct (CBD) stricture with diameter of <6 mm, length of >1cm, irregular margins and asymmetry
- Biliary Brushing taken during ERCP show malignant cells on cytology

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Suspected patients of cholangiocarcinoma: All patients were considered suspected patients of CCA if total Bilirubin was >1 mg/dl, Alkaline Phosphatase was >147 international units/liter (IU/L), USG abdomen showed CBD stricture of <6mm in diameter with proximal dilatation.

PATIENTS AND METHODS

This Cross Sectional study was conducted in the Department of Gastroenterology of the Fatima Memorial Hospital Lahore. All patients presenting to general and private outdoor clinics were enrolled and included in it. Study was completed in six months, from Oct 21, 2014 to Apr 20, 2015. Non-probability consecutive sampling techniques was used. It was estimated as 150 cases using 95% confidence level, with an expected sensitivity as 75% with 13% margin of error, specificity 80% with 12% margin of error taking a percentage of Cholangiocarcinoma as 85% cases

Inclusion criteria: All patients with following features were included in the study:

- Age of 18-90 years and either sex.
- Cholangiocarcinoma suspected patients as per operational definitions.
- Cholangiocarcinoma only confined to CBD and right and left hepatic ducts from where brushing is possible, assessed on ultrasonography (USG) abdomen.

Exclusion criteria:

- Biliary obstruction due to stone (Based on USG abdomen findings).
- Hepatocellular carcinoma (HCC) with metastasis in CBD based on history and USG findings.
- CBD stricture due to any previous surgical intervention (iatrogenic), or trauma in the history.

Data collection: After approval from ethical committee, 150 patients with provisional diagnosis of CCA fulfilling inclusion and exclusion criteria were selected as per operational definitions. Informed & written consent was taken from every patient. Demographic details such as age, sex and address were recorded. ERCP was performed under fluoroscopic guidance and cholangiography evaluated for CBD stricture. The stricture was brushed by using standard 8 French wire-guided biliary cytology brush, one pass and multiple to-and-fro movements across the stricture. The cellular material adherent to the brush was directly transferred to glass slides. The specimens were sent immediately to the laboratory of the hospital where they were evaluated by a histopathologist. Cytology results were recorded as positive or negative for atypical cells. The specimens with atypical cells were considered as positive for cholangiocarcinoma as per operational definitions and those negative for atypical cells were considered as negative for cholangiocarcinoma. CA 19-9 level of all patients were evaluated and levels >100 IU/ml were labeled as positive for cholangiocarcinoma while those with a level ≤ 100 were considered as negative for cholangiocarcinoma. The data were collected by researcher himself. A formal Proforma was designed and used for data collection.

Statistical analysis: The collected data was analyzed statistically by using SPSS version 17. Quantitative variables like age, CA 19-9, Bilirubin and Alkaline Phosphatase were presented in form of mean \pm S. D Qualitative variables like gender, CA 19-9, ERCP findings and presence or absence of malignant cells in BBC were presented in form of frequency and percentages. 2 X 2 table was formulated. Sensitivity,

specificity, positive predictive value (PPV) and negative predictive value (NPV) were assessed for CA 19-9.

RESULTS

A total of 150 patients were enrolled to determine the diagnostic significance of CA 19-9 in diagnosis of cholangiocarcinoma patients considering ERCP and CBD brushing as a gold standard test, in a tertiary care hospital.

Age distribution of the patients was done in Table No. 1, where most of the patients were recorded between 45-65 years of age i.e. 90(60%), 28(18.6%) were below 45 years, while the remaining 32(21.3%) above 65 years, mean and Standard deviation SD was recorded 56.33 ± 14.13 . While recording gender distribution, females were present in majority i.e. 89(59.3%) and 61(40.7%) were males (Table 1).

Table 1 shows malignant stricture distribution among different age groups. A total of 88 patients (58.7%) were found to have malignant stricture on ERCP with a positive result on cytology for malignant cells. Most of these patients were between 45 and 65 years of age i.e. 59(67%). Among other age groups 27(30.7%) were >65 years while the rest 2(2.3%) were of age <45 years. The mean and sd was recorded 62.17 ± 10.44 .

Among 150 patients included in the study 88 were found to have malignant CBD strictures. Out of above 88 patients 50(56.8%) were female which constituted 56.1% of total female patients, while the remaining 38(43.2%) were male which constituted 62.3% of the total male patient (Tables 1).

While recording malignant strictures among the male patients it was found that most of the patients were of age 45-65 years i.e. 29(76.3%). The rest were of age above 65 i.e. 9(23.7%). There was no patient with malignant CBD stricture below 45 years of age. Mean and sd recorded for this group was 61.16 ± 9.29 (Table 1).

While recording malignant strictures among female pnts it was found that most of the patients were of age 45-65 years i.e. 30(60%). Among the rest 18(36%) were of age above 65 while remaining 2(4%) were below 45 years of age. Mean and sd recorded for this group was 62.94 ± 11.26 (Table 1).

While recording the ERCP finding I found that most of the malignant CBD strictures were in distal CBD i.e. 28(31.8%), while the second most common type according to location in biliary tract was in mid CBD i.e. 18(20.5%). The third most common type was involving proximal CBD and Common Hepatic Duct (CHD) i.e. 12(13.6%) (Table 2).

Table 2 also recorded frequency of different types of Kalatskin tumour (Hilar/perihilar cholangiocarcinoma) according to Bismuth-Corlette classification among the patients with malignant CBD stricture. Overall Klatskin tumour was present among 16(18.2%) patients. Among these the most common type was type I involving common hepatic duct (CHD) only 9(56.2%). Among the other types type IIIA (involving the CHD and right hepatic duct) was present in 1(6.25%) while type IV (involving the CHD and right and left hepatic ducts) was present in 6(37.5%). Sensitivity of CA 19-9 was calculated in table 3. According to our study taking ERCP (stricture of extrahepatic biliary tree of >1cm with irregular margins), and positive cytology of biliary brushing as gold standard, it turned out to be 53.4% which is in accordance with the other studies done in literature. The p value was calculated to be <0.05 which is statistically significant. Specificity of CA 19-9 was calculated to be 66.1% which is again in accordance with the literature and even better. This indicates its significance in our setup (Table 3).

Table 1: Age & gender distribution with malignant stricture in males & females

Age in years	Frequency (Percentage)			
	Overall Distribution	Malignant Stricture	Malignant CBD stricture (Males)	Malignant CBD stricture (Females)
18-25	4(2.7)	1(1.1)	0(0)	1(2)
26-35	11(7.3)	0(0)	0(0)	0(0)
36-45	19(12.7)	2(2.3)	0(0)	3(6)
46-55	32(21.3)	21(23.9)	14(36.8)	7(14)
56-65	52(34.7)	36(40.9)	15(39.5)	18(36)
66-75	24(16)	21(23.9)	6(15.8)	15(30)
76-90	8(5.3)	6(6.8)	3(7.9)	3(6)
Total	150(100)	88(100)	38(100)	50(100)
Mean ± SD	56.33 ± 14.13	62.17 ± 10.44	61.16 ± 9.29	

Table 2: Malignant Stricture Distribution, According to CBD location and site (n=88)

CBD location	n	%age
Whole CBD	2	2.3
CBD plus CHD	12	13.6
Common Hepatic Duct (CHD)	9	10.2
CHD plus Right or left Hepatic duct	7	7.9
Distal CBD	28	31.8
Middle and Distal CBD	4	4.5
Proximal CBD	3	3.4
Middle and Proximal CBD	2	2.3
Middle CBD	18	20.5
Right and left HD	3	3.4
Total	88	100
Site		
CHD (Type I)	9	56.2
CHD plus Rt HD (Type IIIA)	1	6.2
CHD plus Right and left HD (Type IV)	6	37.5
Total	16	100

Table 3: Cross tabulation

	Positive Malignancy ERCP Cytology	for on and	Negative Malignancy ERCP Cytology	for on and
Positive CA 19-9	47		21	
Negative CA 19-9	41		41	
Totals	88		62	

P<0.05 (Statistically Significant)

Diagnostic Measures	Numerical Measures
Sensitivity	53.4%
Specificity	66.1%
NPV	50%
PPV	69.1%

DISCUSSION

The diagnosis of cholangiocarcinoma has been a challenge for many decades due to unavailability of a confirmatory standard test and is still a clinical challenge for the clinicians. Most of the physicians rely mainly on either the radiological tests like USG and CT scan, or tumor markers easily available like CA 19-9 for diagnosis of cholangiocarcinoma. Tumor markers, CA19-9 and carcinoembryonic antigen (CEA) are successful markers to differentiate malignant from benign causes in cases of obstructive jaundice¹⁰. ERCP is another diagnostic and therapeutic test available in most of the tertiary care hospitals, which is used for diagnosis and palliative treatment of cholangiocarcinoma patients.

In this study we have used the opportunity of ERCP to take brushing of CBD for cytological analysis to confirm the diagnosis of cholangiocarcinoma as is done in many other parts of the world.^{11,12} Its the only available confirmatory test in our country. The other confirmatory test used in other parts of the world is fine needle aspiration (FNA) obtained during endoscopic ultrasonography (EUS),^{11,12} which is not easily

available in most tertiary hospitals of our country. In parallel, biliary stent cytology can provide additional opportunity for diagnosis when prior sampling is inconclusive, but is not useful when there is a need for an immediate diagnosis^{14,2}. Despite a very high specificity, sensitivity of cytologic methods remains generally low and variable. Sensitivity of biliary brushing and cytology (BBC) is reported to range from less than 30% to over 80% with median of 50%, while its specificity is reported greater than 80% up to 100% with median of 98%, according to different reviews¹³⁻¹⁷.

According to our study most of our patients with Cholangiocarcinoma were aged between 45 and 65 (Mean age was 56.33). This is relatively younger age group compared to that studied before by Hassan E. M and his colleagues, where the mean age of the selected patients with CBD stricture was 64.33 years¹⁸. According to our study Cholangiocarcinoma patients were typically older than those with benign strictures of the CBD (Mean age 56.33 compared to 48.03 years). Sixth decade is the age of presentation in most of our patients with cholangiocarcinoma, which is younger than that studied by Shaib and El-Serag, 2004¹⁹ who stated that CC mostly present in 7th decade of life. But his statement that CCA rarely occur before age 40 is true for our study too. Similarly another study done by M Aljiffry and his colleagues the average age at presentation for intrahepatic CC is the seventh decade of life with a male to female ratio of 1.5. Similarly 65% of extra hepatic CCA present in the seventh decade of life²⁰.

Most of our patients were female i.e. 89(59.3%) out of which 50(56.2%) were found to have cholangiocarcinoma, while among the male patients 61(40.7%), 38(62.3%) were found to have malignant CBD strictures which shows no statistical difference (P=0.455). This is in contrary to a study done by Hassan E. M and his colleagues, who had included more male patients in their study i.e. 39 out of 60 patients. However, males were commoner in malignant groups and equal in non malignant group with no statistical difference (p= 0.138).¹⁸ According to our study in CC group, the ratio of male: female was 1:1.25. This was lower than that reported before e.. 1.5:1^{19,21} and ranged 0.6-1.8: 1 in Parkin et al series²². Since CA 19-9 is cheaper compared to other investigations like CT scan, magnetic resonance imaging (MRI) and invasive investigation like ERCP; and since it is noninvasive, we have tried to find out its significance in this regard. Two thirds of are extrahepatic while the remaining third is intrahepatic. In this study we have included only the patients with suspected extrahepatic cholangiocarcinoma with complaints of obstructive jaundice. Among the different types of extrahepatic CCA the distal CBD were the most common site involved which is according to the studies done before in the literature²³.

According to this study serum CA 19-9 value >100 U/ml has a sensitivity and specificity for diagnosis of CC of 53.4% and 66.1% respectively which is lower than that

recorded by Gores, G.J., 2000, in patients with primary sclerosing cholangitis; which was approximately 75% and 80%, respectively²⁴. This difference is because he has studied this in patients with primary sclerosing cholangitis (PSC). In patient without PSC the sensitivity of CA 19-9 according to studies done by Patel AH, Harnois DM, Klee GG, et al, and Levy C, Lymp J, Angulo P, et al.; is 53% at a cut-off value of >100 U/L^{25,26}. This is almost exactly the same finding as in our study which also included the patients without PSC. On the contrary according to the same study the NPV at the same cutoff of CA 19-9 was ranging between 76 and 92% which is much higher than that we have studied i.e. 50%²⁵. According to another small study reporting a sensitivity of 89% and specificity of 86% for a serum CA 19-9 level greater than 100 U/mL in diagnosing cholangiocarcinoma.²⁷

CONCLUSION

Most of the patients with cholangiocarcinoma present during 6th decade of life. The difference in incidence of cholangiocarcinoma between male and female patients was not statistically significant with a p value of 0.455. As a screening test CA 19-9 is an excellent test available locally in our setup for the diagnosis of cholangiocarcinoma. According to our study its sensitivity came out to be 53.4% with a specificity of 66.1% and a PPV of 69.1% and NPV of 50% with p-value of <0.05 which is statistically significant.

Limitations: Our study was single centre with relatively smaller sample size, so results cannot be generalized to whole population.

Recommendations: CA 19-9 is an excellent indirect tool easily available for screening to make the early diagnosis of cholangiocarcinoma as it is cheap, inexpensive and non invasive way to guide us for making further decisions which makes Physician/Gastroenterologist to improvise at earlier stages in making diagnosis and helping in formulating the treatment plan for cholangiocarcinoma. Taking all these factors in mind, further multicentre studies with the help government and with larger sample size are still required to come up with some local recommendations for this devastating disease and prevent the misery which patients & family go through having this disease diagnosed at later stages. It is the need of the day to create awareness among general population and for general practitioners through electronic media, print media and arranging seminars and symposia about the disease and its early diagnosis and so as to prevent the complications related with this disease.

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