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The Diagnostic Worth of Serum CA19-9 and CEA Levels in Anicteric Patients with Thick Walled Gallbladder

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Abstract

Introduction: Gallbladder carcinoma (GBC) is the most common malignancy of the biliary tract, accounting for 80–95% of biliary tract cancers.1 GBC affects over 140 000 patients worldwide and over100 000 die each year from this aggressive disease.2 The value of CEA (carcinoembryonic antigen) and/or CA19-9 (Carbohydrate antigen) in the prognosis of gallbladder cancer has been previously reported.4, 8 However, their role in evaluation of thick walled gall bladder where, GBC is a suspect, is still largely wanting. We decided to audit our records, in order to address this issue of finding the significance of CA19-9 and CEA, as diagnostic marker in patients with thick walled gall bladder with a high index of suspicion of GBC, the lesion being resectable on imaging.

Method: A cross sectional analysis of 48 anicteric patients with thick walled gall bladder was done from January 2017 to January 2018. Tumour markers viz. CA19-9, CEA were recorded preoperatively along with other patient characteristics and then correlated with the final histopathological diagnosis. Statistical analysis was done using SPSS VERSION 21.

Results: 48 patients of anicteric thick walled gall bladder (on imaging) were taken up for surgery. Mean age in this study was 53 years. Male: Female ratio was 11:37. There were 15 patients of gall bladder cancer while the other 33 turned out to have a benign pathology on final biopsy (6 Xanthogranulomatous cholecystitis and 27 cases of chronic cholecystitis). Presence of regional lymphadenopathy ($p<0.001$) and suspicion of abdominal metastasis ($p=0.008$) were found to have statistical association with presence of cancer and with CA19-9 level above 35U/ml. CEA level>5ng/ml, was found in only 4(8.3%) patients, 3(6.2%) of these patients had cancer while 1(2.1%) had an inflammatory gall bladder ($p=0.049$), the value just attaining significant association

with the presence of cancer. On multivariate analysis no independent predictor could be identified. The sensitivity and specificity of preoperative CA19-9 was 24.24% and 22.22% in predicting cancer in this study while CEA failed to demonstrate any predictive significance.

Conclusion: In anicteric patients with thick walled gallbladder and suspicion of gallbladder malignancy, Serum CA19-9 and CEA levels alone have low predictive significance. Their role as tumour marker however increases in the presence of CECT findings of regional lymphadenopathy, locally advanced or metastatic disease.

Keywords: Thick walled gallbladder, Gallbladder cancer, CA19-9, CEA.

Introduction: Gallbladder carcinoma (GBC) is the most common malignancy of the biliary tract, accounting for 80–95% of biliary tract cancers.[1] GBC affects over 140 000 patients worldwide and over100 000 die each year from this aggressive disease.[2]

1.2Carbohydrate antigen 19-9 (CA19-9) is a mucinous protein that can be elevated in patients with pancreatic, gastric, and bile duct cancers.[3,4] CEA and CA19-9 are currently used as prognostic markers in gastric and pancreatic cancer[5]. The value of CEA and/or CA19-9 in the prognosis of GBC has been previously reported.[4,6] However, their role in evaluation of thick walled gall bladder where, GBC is a suspect, is still largely wanting. We decided to audit our records, in order to address this issue of finding the significance of CA19-9 and CEA, in improving the diagnostic accuracy in patients with thick walled gall bladder with a high index of suspicion of GBC, the lesion being resectable on imaging,

Aim: To evaluate the significance of CA 19-9 and CEA in predicting gall bladder cancer in cases of thick walled gallbladder without jaundice.

Materials and Methods: A cross sectional analysis of 48 anicteric patients with thick walled gall bladder was done from January 2017 to January 2018. Tumour markers viz. CA19-9, CEA were recorded preoperatively along with other patient characteristics and then correlated with the final histopathological diagnosis. For statistical analysis the patient characteristics were compared with- (1) cancer and (2) inflammatory (no-cancer) group, based on final biopsy. For statistical analysis, continuous variables were transformed into categorical variables. The univariate analysis was done using the Chi-square test. P value <0.05 was considered statistically significant. The variables that were found significant on univariate analysis were subsequently analyzed by multivariate analysis using a multiple logistic regression model. Statistical analysis was done using SPSS VERSION 21.

4.1

Results: 48 patients of anicteric thick walled gall bladder (on imaging) were taken up for surgery. The patient parameters are described in table 1.

Table1: Patient characteristics in cancer and benign (non-cancer) group with associations: Applied χ^2 test/ Fisher exact test as appropriate for significance.

Variable		Cancer group n=15	% of n=15	Benign /Inflammatory (non-cancer:- Xanthogranulomatous and chronic cholecystitis) n=33	% of n=33	Total N=48 (%)	p-value Chi-square test
Age	25 - 50 years	8	53.3	11	33.3	19(39.6)	
	51 - 60 years	6	40.0	15	45.5	21(43.8)	
	>60 years	1	6.7	7	21.2	8(16.7)	0.298
Sex	Male	2	13.3	9	27.3	11(22.9)	0.287
	Female	13	86.7	24	72.7	37(77.1)	
Pain	Present	13	86.7	28	84.8	41(85.4)	0.869
Past History of Jaundice	Present	5	33.3	9	27.3	14(29.2)	0.669
Loss of weight	Present	4	26.7	5	15.2	9(18.8)	0.343
Mass	Count	4	26.7	1	3.0	5(10.4)	0.013
Diabetes	Present	2	13.3	4	12.1	6(12.5)	0.906
Obesity		0	0	1	3.0	1(2.1)	0.496
Diffuse wall thickness	Present	1	6.7	5	15.2	6(12.5)	0.410
Irregular wall thickness	Present	14	93.3	28	84.8	42(87.5)	0.410

CBD stones	Present	2	13.3	7	21.2	9(18.8)	0.517
CECT suspicion of metastasis	Present	3	20.2	0	0	3(6.2)	0.008
CECT evidence of regional lymph node	Present	12	80	6	18.2	18(37.5)	<0.001
CA19-9	>=35	7	46.7	6	18.2	13(27.1)	0.040
	< 35	8	53.3	27	81.8	35(72.9)	
CEA	>=5	3	20.0	1	3.0	4(8.3)	0.049
	<5	12	80	32	97	44(91.7)	
Survival	>6 months	3	20	33	100	36(75)	<0.001
	<=6 months	12	80	0	0	12(25)	
Final Histopat-hology	Cancer	15	31.2	33	68.7	48(100)	Referance category cancer.

Mean age in this study was 53 years. Male: Female ratio was 11:37. There were 15 patients of gall bladder cancer while the other 33 turned out to have a benign pathology (6 Xanthogranulomatous cholecystitis and 27 cases of chronic cholecystitis). The most common presenting symptom was upper abdominal pain (85.4%) while symptoms suggesting potential malignancy like loss of weight and abdominal mass was present in 9(18.8%) and 5(10.4%) patients respectively. Past history of jaundice was present in 14(29.2%) patients. Diabetes was present in 6(12.5%) patients and one (2.1%) patient was obese (BMI>30). Abdominal imaging was suggestive of, irregular thick walled gall bladder in 42(87.5%) cases while 6 patients had diffuse thick walled gall bladder

(12.5%). Gall bladder stones were reported in 37(77.1%) cases and concomitant CBD stone was reported in 9(18.8%) patients. None of the patients had any family history of malignancy. With the exception of presence of abdominal mass (p=0.013), none of the above-mentioned variables displayed any statistically significant association with the occurrence of cancer.All these patients underwent CECT/MRCP abdomen, where the abdominal sonography findings were corroborated with additional finding related to evidence of abdominal lymphadenopathy, metastasis and local extent of the disease. Presence of regional lymphadenopathy was reported in 12(80%) patients that were finally diagnosed to have gallbladder cancer, while only 6/33(18.2%) of the non-malignant patient demonstrated this finding, showing regional lymphadenopathy to have a strong statistical association with the presence of cancer (p<0.001). Suspicion of abdominal metastasis was noted in 3(20%)patients that had gallbladder carcinoma on final pathology, and this finding also had significant statistical association (p=0.008) with cancer occurrence. CA19-9 level above 35U/ml, was seen in 13(27.1%) patients, of these 7(14.5%) were finally found to have cancer while the other 6(12.5%) had benign pathology (p=0.040).Similarly CEA level>5ng/ml, was found in only 4(8.3%) patients, 3(6.2%) of these patients had cancer while 1(2.1%) had an inflammatory gall bladder (p=0.049), the value just attaining significant association. Survival of less than, or beyond 6 months, after surgery, demonstratedstatistical association (p<0.001) on univariate analysis. On applying multiple logistic regression analysis on the variables found to be significant on univariate analysis, none of the variables turned out to behave as an independent predictor.We then further analyzed the CA19-9 levels as the dependent variable against other variables (table 2), and found that with the exception of abdominal mass and suspicion of metastasis on imaging, the other factors which demonstrated significant association remained the same that is (1) presence of regional lymphadenopathy on imaging, (2) cancer on final histopathology, (3) survival after surgery.Table 2. CA19-9 levels with Associations: Applied $\chi 2$ test/ Fisher exact test as appropriate for significance.

S no.	Variable	Subcategory	CA 19-9<35ng/ml N=35	CA 19-9 >35ng/ml N=15	Frequency N=48(%)	p-value
1.	Age	25 to 50yrs	15 (42.9%)	4(30.8%)	19(39.6%)	0.666
		51 to 60yrs	15(42.9%)	6(46.2%)	21(43.8%)	
		>60yrs	5(14.3%)	3(23.1%)	8(16.7%)	
2.	Sex	Male	8(22.9)	3(23.1)	11(22.9%)	0.987
		Female	27(77.1)	10(76.9)	37(77.1%)	
3.	Loss of weight	History present	5(14.3%)	4(30.8%)	9(18.8%)	0.194
4.	Mass in Rt. hypochondrium	Present	3(8.6%)	2(15.4%)	5(10.4%)	0.492

5.	Pain	History Present	28(80.0%)	13(100%)	41(85.4%)	0.081
6.	Previous history of jaundice	Present	9(25.7%)	5(38.5%)	14(29.2%)	0.388
7.	Diabetes	Present	5(14.3)	1(7.7%)	6(12.5%)	0.539
8.	Obesity	Present	1(2.9%)	0	1(2.1%)	0.538
9.	CBD stones	Present	8(22.9%)	1(7.7%)	9(18.8%)	0.232
11.	Diffuse wall thickness on imaging	Present	7(20.0%)	3(23.1%)	10(20.8%)	0.816
10.	Irregular wall thickness on imaging	Present	15(42.9%)	10(76.9%)	25(52.1%)	0.036
12.	Enlarged regional nodes on imaging	Present	10(28.6%)	8(61.5%)	18(37.5%)	0.036
13.	Suspicion of abdominal metastasis on imaging	Present	1(2.9%)	2(15.4%)	3(6.2%)	0.111
14.	Final Histopathology	Cancer	8(22.9%)	7(53.8%)	15(31.2%)	0.002
		Xanthogranulomatous cholecystitis	2(5.7%)	4(30.8%)	6(12.5%)	
		Chronic cholecystitis	25(71.4%)	2(15.45%)	27(56.2%)	
15.	Survival	>6M	29(82.9%)	7(53.8%)	36(75.0%)	0.005
		6 months or less	6(17.1%)	6(46.2%)	12(25.0%)	

As before on further analyzing these variables by multiple logistic regression analysis no factor was found to reach statistical significance to act as an independent predictor. CEA on the other hand failed to show any association of significance.

The Receiver operator character curve (ROC) for CA19-9 is presented in figure 1. Area under the curve 0.695 was found statistically significant (p=0.032) with the best cut off value suggested for diagnosis of malignancy in the non-jaundiced patients of thick walled gallbladder to be 23.61U/ml rather than 35U/ml as is being used by many centers and by us as well. The sensitivity (24%) and specificity (22%) of this marker however was quite low for early diagnosis of gallbladder cancer patients with a

positive predictive value (PPV) of 53% and an even lower negative predictive value (NPV) of 7.4% only.

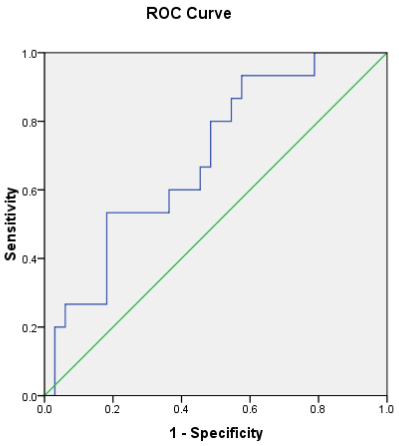

Figure 1: Receiver operator character curve for CA19-9 in cancer patients. Area under the Curve=0.695, 95%CI=0.540-0.850, p=0.032 standard error0.079. Best suggested cut off 23.61u/ml.

Discussion

Patients with symptomatic gall stone disease with thick walled gallbladder, without jaundice, often raise the doubt of malignancy in the endemic belt of northern India (incidence of gallbladder cancer in northern india-8.9/100,000 per year), more so in the elderly age group as was seen in this study where the mean age was 53yrs.

The study results show that CA19-9 level>35U/ml and CEA >5ng/ml can be used as tumour marker for carcinoma gallbladder, however they were also raised in patients with non-malignant pathology of the gallbladder like Xanthogranulomatous cholecystitis.[7,8]

According to the observations, CA19-9 along with imaging results especially presence of regional lymphadenopathy or increased tumour load as evidenced by metastasis can provide reasonable association in predicting potential malignancy in patients with thick walled gallbladder and no jaundice. The results also show that CA19-9 alone has very little clinical utility in detecting early, localized gallbladder cancer.[9]

Although The roc curve does show acceptable result in terms of sensitivity to diagnose malignancy, however, if cases of diagnostic dilemma like that of Xanthogranulomatous cholecystitis were added to the group of all benign lesion, the diagnostic predictive value of CA 19-9 decreased, hence it would be appropriate to say that in patients where preoperative suspicion of malignancy vs. Xanthogranulomatous Cholecystitis is high, CA19-9 at best can only be of supportive value and not a diagnosis predicting marker. The combined use of CEA and CA19-9 has been shown to be superior to either one alone as a prognostic marker for patients with pancreatic cancer.[10, 11] On the same lines when we analyzed our data we found that CEA levels did not add much to the diagnostic value of CA19-9.[6] Literature supports that CA19-9 elevation is more marked in advanced carcinoma gall bladder cases[12], which may be due to the increased tumour burden. However, in smaller resectable lesions the value of CA19-9 may not be elevated to levels diagnostic of malignancy as also seen in our study where the best value suggested for good sensitivity in roc curve was 26.61U/ml instead of the standard 35U/ml. This reduction in the cut-off value will increase the sensitivity of the test but on the flip side it will add to the false positive cases as well.[13]

ROC curve for Sr.CEA levels showed 50%area under the curve and hence was statistically not considered for further analysis. Survival in the malignancy group did show a significant p-value on correlation with preoperative Sr.CA19-9 thus indicating that those with cancer and raised CA19-9 have an increased tumour load and hence a smaller survival period. Although literature shows correlation between high serum levels of CA19-9 as a bad prognostic marker in patients with advanced disease however the jury is still out on its relevance in

resectable, low tumour load cases.

Conclusion

In anicteric patients with thick walled gallbladder and suspicion of gallbladder malignancy, Serum CA19-9 and CEA levels alone have low predictive significance. Their role as tumour marker however increases in the presence of CECT findings of regional lymphadenopathy, locally advanced or metastatic disease.

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