Prognostic Value of CA19-9 and CA242 in Gallbladder Cancer - An Exploratory Study

Akash Agarwal[1], Vandana Tiwari[2], Swati Kumari[3], Nuzhat Husain[4]

ABSTRACT

Introduction: There are, at present, no biomarkers to predict to prognosis of Gallbladder cancer. We conducted a prospective exploratory study to evaluate the role to serum CA 19-9 and CA 242 as prognostic markers.

Material and Methods: We enrolled consecutive patients for this study and CA 19-9 and 242 were estimated from venous samples. Association of these markers with clinical variables and median overall survival (OS) difference between patients who has raised versus normal levels of these markers was determined.

Results: Sixty-two patients were enrolled for this study. Forty-four (71%) patients had elevated CA19-9. Thirty-nine (62.9%) patients had an raised CA242 levels. CA 19-9 was found to be significantly associated with the presence of jaundice (p=0.038) and advanced stage (p=0.009). Median OS of patients who had elevated CA 19-9 was 5.73 months compared to 8.33 months in patients who had normal CA 19-9. The difference was not statistically different (p= 0.15). Median OS for patients who had elevated CA 242 was 5.53 months, which was inferior to those who had normal levels (9.1 months). This difference approached, but was not statistically significant (p=0.055).

Conclusion: This is the first study to show association between CA 19-9 and stage of disease in GBC. At present, CA 19-9 and CA 242 cannot be recommended as prognostic markers. However, role of CA 242 needs to be examined in a larger cohort of patients of GBC to establish its usefulness.

Keywords: CA19-9, CA242, Gallbladder Cancer

INTRODUCTION

Gallbladder cancer (GBC) is the most common malignant lesion of the biliary tract. It is one of the commonest malignancies among women in North India with an age-standardized rate of 8.0 per 100,000 females in Dew Delhi during the period 2003-2007.[1]

Gallbladder cancer has a dismal prognosis with a median survival of 2-4 months in patients with unresectable disease and a 1-year survival of less than 5%.[2] Even with the use of modern combination chemotherapy, the median progression free survival is only about eight months and median overall survival is 11.7 months.[3]

Tumor markers are antigens and bioactive substances produced by tumor cells due to abnormal expression of correlated genes. They are either not produced or only minimally produced, in normal tissues, and can be detected in tissues, body fluids or excreta of patients with cancer. Tumor markers are used for diagnosis, prognosis and to detect recurrences in a variety of cancers. They provide rapid results with acceptable reliability and minimum cost and pain to patients.

The prognosis of GBC depends on multiple variables- stage of disease, lymph node status and cellular differentiation.[4,5] Very little evidence exists on the use of tumor markers for prognostication in GBC.

Elevated carbohdrate antigen 19-9 (CA 19-9) has been shown to be associated with poorer prognosis in pancreatic adenocarcinomas.[6] Similarly, CA 242 has been shown to determine prognosis in pancreatic cancer and had better association than CA 19-9 levels.[7] As gallbladder and pancreas share the same embryonic origin, it is expected that the tumor markers in pancreatic cancer may be useful in GBC also.

Though commonly used, the role of CA 19-9 in the diagnosis of GBC is still uncertain. It has poor sensitivity and specificity-17% and 67% respectively.[8] For prognosis, scant data is available. In one study, elevated pre-operative CA 19-9 levels have been found to a prognostic factor for poor survival in resected biliary malignancies.[9] However, this study has a small number of GBC and only included patients who underwent surgery.

Carbohydrate Antigen 242 (CA 242), like CA 19-9 is also a sialiated carbohydrate antigen and has been used as a tumor marker for pancreatic cancer. CA242 has been shown to have better sensitivity and specificity 64% and 83% respectively when compared to CA 19-9 in the diagnosis of GBC.[8] CA 242 has not been studied yet as a prognostic factor in GBC.

At present, there is lack of informative biomarkers to prognosticate gallbladder cancer and to predict response to treatment. We, thus, conducted this exploratory study for quantitative evaluation of CA 19-9 and CA 242 as prognostic markers in GBC.

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MATERIAL AND METHODS

A prospective observational study was conducted over a period of two years at our hospital. All patients with gallbladder cancer with ECOG performance status of 0-2 were enrolled in this study. Patents who were suffering from a second malignancy and those who were unwilling to participate were excluded.

Sixty two patients were planned for enrolment in this study. All the participants of the study underwent a standardized interview using a questionnaire on medical history, family history, demographic profile, and lifestyle habits. For female patients, information on marital status, age at first pregnancy, number of pregnancies and number of childbirths, age of menarche and menopause (if menopausal) was additionally recorded.

Five ml venous blood was collected form the study subjects at start of enrolment. Serum was islolated and processed as per manufactirer's instructions. CA 19-9 was measured by Chemiluminescence immunoassay and values >35U/ml were considered as positive while values <=35U/ml were negative. CA 242 was measured by ELISA (United Biolink Inc.). Values >20 U/ml were considered as positive while values <=20 U/ml were negative. All the enrolled patients were followed up from date of registration using the hospital records and telephonic interview. Patients were followed up for for a minimum of 6 months after the end of enrolment. The research was approved by the Institutional Ethics Committee.

STATISTICAL ANALYSIS

Association was studied using Chi-square test. Survival was analyzed using the Kaplan-Meier method and compared by log-rank analysis. P-values were considered significant at < 0.05 level. (2-sided). All analyses were performed using the SPSS statistical analysis software, version 15.0 (SPSS, Chicago, IL, USA).

RESULTS

A total of 62 patients were enrolled for this study. The majority of patients were females (42 vesus 20 males); a male: female ratio of 1:2.1. The median age of patients was 55 years (range 30-85 years).

Gallstones were present in 32 (51.6%) patients. Thirty two patients (51.6%) had obstructive jaundice. Majority of patients had stage IV disease (82.3%). Most patients had an

Variable		Number (percentage)
Age: (Median, range) years		55(30-85)
Sex	Male	20(32.3%)
	Female	42(67.7%)
Gallstones	Present	32 (51.6%)
	Absent	30 (48.4%)
Jaundice	Present	32 (51.6%)
	Absent	30 (48.4%)
Performance status (WHO -ECOG)	0	3 (4.8%)
	1	42 (67.7%)
	2	12 (19.4%)
	3	5 (8.1%)
Stage (TNM)	1	0 (0)
	2	2 (3.2%)
	3	9 (14.5%)
	4	51 (82.3%)

Table-1: Demographic and Clinical Profile

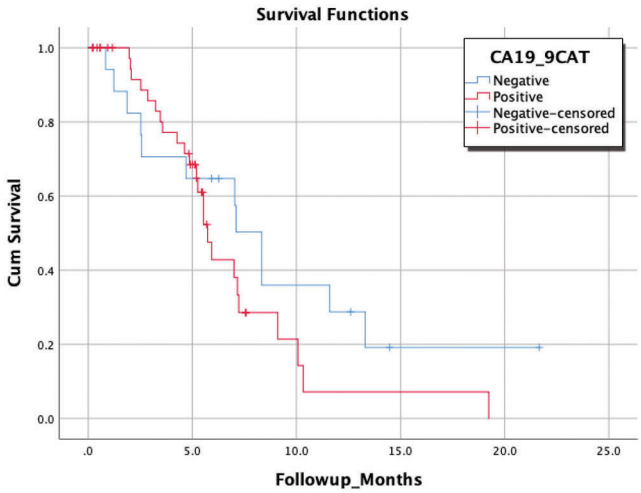

Figure-1: Overall Survival in GBC patients and serum CA 19-9 levels

	CA 19-9			CA 242		
Characteristics	**Elevated**	**Normal**	**p value**	**Elevated**	**Normal**	**p value**
Jaundice						
Present	26	6	**0.038 ***	22	10	0.263
Absent	18	12		17	13	
Gallstones						
Present	19	11	0.200	18	13	0.467
Absent	25	7		22	9	
Sex						
Male	17	3	0.093	12	7	
Female	27	15		27	17	
Stage						
II	0	2	**0.009 ***	0	2	0.412
III	4	5		5	4	
IV	40	11		34	17	

Table-2: Univariate analysis of association between CA 19-9, CA 242 and clinical features

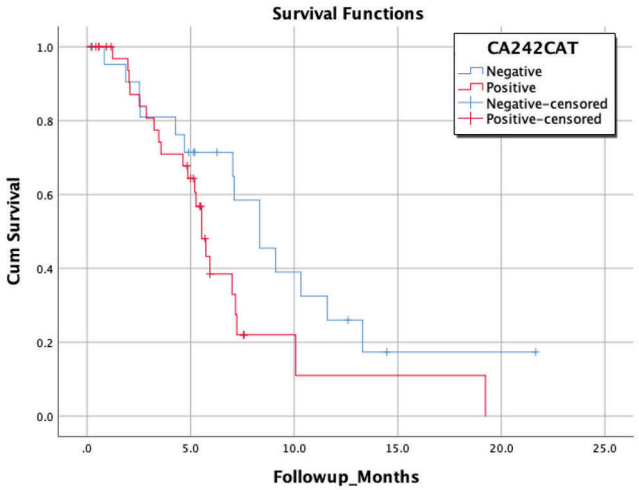

Figure-2: Overall Survival in GBC patients and serum CA 242 levels

ECOG performance status of 1 (67%). Table-1 displays the demographic and clinical distribution of study subjects.

Forty four (71%) patients had CA19-9 greater than 35U/ml. The median value of CA19-9 was 171U/ml (range 0-299150U/ml). The median value of CA242 was 40.88 U/ml (range: 0.17-35556 U/ml) and 39 (62.9%) patients had an elevated CA242.

High serum levels of CA 19.9 were significantly associated with stage IV disease (p=0.009) and presence of jaundice (p=0.038). However, there was no significant association of Ca 19-9 with presence of gallstones and sex of the patient. There was no significant association of CA 242 with any of the evaluated clinical factor (Table 2).

Median follow up was 5.1 months. The minimum follow up was 0.2 months and the maximum follow up was 21.7 months. Thirty six (58.1%) patients died during follow up. Ten (16%) patients were alive at the end of the study.

Survival was compared for patients who had elevated versus those who did not have elevated tumor markers. The survival of patients who had CA 19-9 greater than 35 IU was 5.73 months (95% CI: 5.04- 6.42 months) which was lesser than 8.33 months (95% CI: 6.07-10.59 months) in patients who had normal CA 19-9. The difference however, was not not statistically different (p= 0.15)(Figure 1).

Similarly, the survival for patients who had elevated CA 242 was 5.53 months (95% CI: 4.88-6.18 months) which was inferior to those who had normal levels which was 9.1 months (95%CI: 6.08-12.11 months). This difference approached, but was not statistically significant.(p=0.055) (figure 2)

DISCUSSION

Tumor markers have been used in many cancers, for diagnosis, prognosis and for detecting recurrences. Though clinical prognostic factors like nodal staus, stage and differentiation are known, very little data is available on the usefulness of serum tumor markers for the purpose of prognosis in GBC.

Although CA 19-9 has been evaluated as a diagnostic marker for GBC, it's utility is limited by low sensitivity and specificity.[8] Previous reports show that Se. CA 19-9 is elevated in about 60% of patients in biliary tract cancers. However, these figures are limited to studies which evaluated resectable patients and included all biliar cancers, not only those with GBC.[10] Similar to published results, we found that 71% patients of GBC had elevated Se. CA 19-9.

Similarly, CA242 has also been studied for diagnostic purposes, but its utlility has been limited. In the same study, it was found that Ca 242 was elevated in 64% of the patients.[8] CA 242 was elevated in 39% of our patients. Here, prevalence of raised CA 242 is not in conformity to the reported literature. Though we could not find any association with levels of CA 242 and stage of disease, difference in stage of patients in the two studies may be a reason for the difference in results.

Currently, there is no literature to report an association of elevated Se CA 19-9 with stage of GBC. We found that elevated CA 19-9 was significantly associated with stage IV disease. Jaundice and CA 19-9 have been shown to be associated.[11] This is also evident in our study where we found significantly elevated levels of CA 19-9 in patients with jaundice. However, the interpretation and relevance of this elevation remains unclear, especially for diagnostic purposes.

We did not find any association of Ca 242 with any of the baseline characteristics including stage, presence of jaundice, gallstones and sex of the patient.

CA 19-9 has been studied as a prognostic marker in resectable GBC where it has shown to be of statistically significant benefit.[9,12,13] However, it has not been evaluated before in prognostication of advanced/ metastaic disease status except in one study which inculded all biliary tract malignancies.[14] In this study, there were about 25% GBC patients and the analysis was not done for these patients separately. In our study, we could not find any significant association between the presence of elevated levels of CA 19-9 and survival. Thus, we would not recommend CA 19-9 estimation for this purpose.

Pancreas and the biliary systen have similar embyonic origin. Tumor markers which have been shown to be useful in pancreatic cancer have been shown to be of use for biliary malignancies as well. CA 242 has been shown to be of prognostic significance in pancreatic cancer.[15,16] However, very little literature exists about the utility of CA 242 in GBC. Most of the existing literature evaluates the diagnostic utility of this biomarker to differenciate it from benign condition of GBC.[8,17,18] The use of CA 242 has not been reported as yet. Though we could not find a statistically significant prognostic value of CA 242, it aproached statistical significance. Given the small number of patients and limitations of this study, as discussed later, it seems worthwhile to evaluate this marker in context of a lager study.

This study was carried out in one of the highest incidence areas in the world. The majority of the patients included were of advanced disease, which reflects the true distribution of the disease. This is also the first instance where these tumor

markers have been evaluated for prognostic purpose in GBC patients who not necessarily underwent surgery. The findings of this research are encouraging especially with respect to the use of CA 242 as a prognostic marker.

Our study has a few limitations as well. The distribution of patients is skewed towards advanced disease, with very few patients of localized disease. This is primarily due to very few patients who present with early and localized disease. Also, a large number of patients 16 (26%) were censored due to loss to follow up. This can be an important factor in arriving at the present results. However, this problem of censoring is inherent to most clinical studes done outside a clinical trial setup, albeit, to a lesser extent.

CONCLUSION

Gallbladder cancer remains as one of the important cancers in North India. There is lack of imformative biomarkers which could help in determining the prognosis of these patients. We have, for the first time, demonstrated that elevated CA 19-9 is associated with increased stage of the disease. This exploratory study also shows that there might be a role of serum biomarkers in determining the prognosis of GBC, especially Se. CA 242. Though at present, the use of these tumor markers cannot be suggested, definitive results can be expected when a larger cohort of GBC patients of various stages are evaluated in a larger prospective study. Also, the role of these serum markers should be investigated to predict response to surgery and chemotherapy and for monitoring recurrence.

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