



CA19.9 & CEA AS PROGNOSTIC TUMOR MARKERS IN CARCINOMA GALLBLADDER - AN OBSERVATIONAL STUDY

Oncology

Ashwani Anshu*	Pg. Trainee, Department Of General Surgery, G.s.v.m. Medical College, Kanpur *Corresponding Author
Gulab Dhar Yadav	Professor, Department Of General Surgery, G.s.v.m. Medical College, Kanpur
Ramendra Kumar Jauhari	Professor, Department Of General Surgery, G.s.v.m. Medical College, Kanpur
Priyesh Shukla	Assistant Professor, Department Of General Surgery, G.s.v.m. Medical College, Kanpur

ABSTRACT

Introduction: Gallbladder cancer (GBC) has been documented since the 17th century, with increasing incidence over time. Despite advancements, GBC remains highly fatal due to its asymptomatic progression and limited understanding of its origins. Gallbladder cancer is the 25th most common cancer globally, with significant gender and regional variations. In India, the incidence is notably higher in the north compared to the south. Risk factors identified by the Indian Council of Medical Research (ICMR) include age, gender, ethnicity, gallstones, chronic inflammation, genetics, and lifestyle. Improved imaging and tumor markers like CEA and CA19-9 are crucial for better diagnosis and prognosis. **Objective:** To investigate the epidemiology and clinical presentation of gallbladder carcinoma, to assess the levels of tumor markers CA19.9 and CEA in relation to different stages of gallbladder carcinoma and to examine the relationship between tumor markers CA19.9 and CEA in predicting the prognosis of patients with gallbladder carcinoma who have undergone resection. **Methods:** This prospective study was conducted at GSVM Medical College, Kanpur, from January 1, 2023, to June 30, 2024, on patients suspected or diagnosed with gallbladder carcinoma or mass lesions. Patients aged between 18 to 70 years, patients suspected or diagnosed with gallbladder carcinoma or mass lesions, and patients who provided informed consent. **Results:** Predominantly in patients under 60 years (43.3%), with a higher prevalence in females (73.3%). The most common symptoms were a lump abdomen (80%) and pain abdomen (55%). The body of the gallbladder was the most common site (65%), with dilated CBD in 30% of cases. Adenocarcinoma was the most common subtype (90%). Raised CA19-9 and CEA levels were effective in diagnosing gallbladder carcinoma with sensitivities of 63.6% and 54.5%, respectively. CA19-9 was superior in predicting tumour burden and recurrence. Significant reductions in CA19-9 levels were observed one-week post-surgery, while CEA levels significantly decreased one-month post-surgery. **Conclusion:** Raised CA19-9 and CEA levels are useful for initial screening and prognostication of gallbladder carcinoma. CA19-9 is particularly effective in predicting tumor burden and recurrence. Tumor resection significantly reduces these markers, indicating a positive response to surgery. These markers, combined with cytohistology, can enhance diagnostic accuracy and patient outcomes.

KEYWORDS

Gallbladder Cancer; Adenocarcinoma; Lump Abdomen; Pain Abdomen; markers

INTRODUCTION

The first reports of gall bladder cancer date back to the 17th century. Over time, both the incidence of gall stones and gall bladder carcinoma have grown. Globally, the overall incidence varies between 0.11/100000 and 10.6/100000 across various cancer registries.¹ With only roughly a 32% 5-year survival probability for lesions limited to the innermost layer of gallbladder and one-year survival rate for invasion of further layers of gallbladder is only 10%, hence, the prognosis is not good.² Several factors rooting for gallbladder cancer (GBC) have been discovered by the Indian Council of Medical Research (ICMR), including age, gender, ethnicity, gallstones, chronic inflammation, genetics, gallbladder polyps, and lifestyle.³

CA19.9 and CEA are tumor markers that can be elevated in various cancers, including Gallbladder carcinoma. Previous studies have found that raised levels of CA19.9 and CEA have in gall bladder carcinoma has prognostic relevance. Patients with pancreatic, stomach, and bile duct malignancies may have higher levels of the mucinous protein carbohydrate antigen 19-9 (CA19-9).⁴ Tumour marker carcinoembryonic antigen (CEA) is a protein-polysaccharide complex present in normal embryonic gut, biliary system and pancreas as well as gastrointestinal cancer. The sensitivity and specificity of CEA for bile duct tumors are low, even though a raised CEA may indicate the presence of several tumor types.⁵ The cut-off values in these investigations ranged from CEA - 4 IU/mL to CA 19-9 - 10 to 20 IU/mL.⁶ The management of GBC typically involves surgical resection in the early stages, but the prognosis varies. Understanding the role of CA19.9 and CEA can aid in the management by providing insights into the likelihood of metastasis and recurrence, which is crucial for determining the course of treatment and follow-up. However, there has been very less studies for evaluation of the ability for diagnosis by these makers individually or when combined. Hence, we performed a study to evaluate the specificity and sensitivity of CA19-9 and CEA in diagnosing Gall bladder cancer.

Aim & Objectives

This study aims to determine –

1. Epidemiology & Clinical presentation of Carcinoma Gall bladder and various methods of Diagnosis.
2. Level of Tumor markers CEA and CA19.9 in different stages of Carcinoma Gall bladder.
3. Relation of Tumor markers CEA and CA19.9 in predicting prognosis of patients with GB carcinoma who underwent resection.

MATERIAL & METHODS

This is a prospective study conducted on patients suspected or diagnosed with CA GB or GB mass lesions, in the “Department of General Surgery” at “GSVM Medical College, Kanpur” spanning from 1 Jan 2023 to 30 June 2024, after obtaining Ethical approval from the institute.

Sample Selection

Inclusion Criteria-

1. Age between 18 to 70 years.
2. Patients suspected or diagnosed with CA GB or GB mass lesions.
3. Patients who provide informed consent for participation in the study.

Exclusion Criteria-

1. Age below 18 years or above 70 years.
2. Patients with severe comorbidities, including uncontrolled hypertension (HTN), Diabetes mellitus (DM), or immunocompromised status.
3. Patients with hemodynamic instability.
4. Patients with other concomitant malignancies.
5. Pregnant women.
6. Patients who do not provide informed consent.

Sampling: 60 Study participants were taken during the period.

Data Collection Methods -

Starting with a pre-surgery evaluation which included taking a detailed history, physical examination, baseline investigations such as CBC,

LFT, KFT, RBS, PT/INR, BT/CT, serum electrolytes, chest X-ray, and ECG to establish the patient's overall health status then imaging and staging procedures using USG, CECT abdomen, PET-CT, and MRI to determine the extent of the disease ,CA19.9 and CEA also measured before surgery. Eligible patients then proceeded to surgical intervention, where the GB mass lesion was resected. Post-operative evaluations included measuring CA19.9 and CEA levels again to assess the effectiveness of the surgical intervention in reducing these tumor markers. Lastly, patients were subjected to a structured follow-up regimen to monitor for any signs of recurrence or progression of the disease, which involved regular follow-up visits and repeat imaging studies as necessary.

Statistical Analysis -

To summarize the distribution(demography) and clinical characteristics of the study population, we used Descriptive statistics, presenting the data through means, medians, frequencies, and percentages. Comparative analysis involved comparing pre- and post-surgery levels of CA19.9 and CEA using paired t-tests or Wilcoxon signed-rank tests for non-parametric data, to determine the statistical significance of changes in tumor marker levels. All data analyses were carried out using SPSS or another appropriate statistical software package, with statistically significant p-value was considered to be less than 0.05 .

Observation And Results -

- Majority of studied cases were of age above 60 years (43.3%) followed by 41 to 50 years (25.0%), 51 to 60 years (23.3%) least were below 40 years (8.3%) with mean age 56.05±10.8 years.
- The distribution of the studied cases based on their age showed that most of the cases were females (73.3%) followed by males (26.7%).
- The chief complaints in studied cases showed that the majority of the cases had lump in the abdomen (80.0%) followed by pain abdomen (55.0%) and jaundice (35.0%).
- The distribution of the studied cases based on the location of mass showed that 65.0% had a mass in the body followed by the neck (18.3%),liver, and GB stump (13.3%), and fundus (3.3%).
- The distribution of the studied cases based on the wall thickness of the gall bladder showed that wall thickness >4mm was found in most of the cases (68.3%) followed by increased thickness (28.3%) and post-cholecystectomy (3.3%).
- The distribution of the studied cases based on CBD dilatation showed that CBD was dilated in 30.0% of cases and was normal in 70.0% of cases.
- The findings of histopathology showed that 15.0% had adenocarcinoma of GB followed by squamous cell carcinoma of GB (1.7%) and Keratinising squamous cell carcinoma in 1.7% cases, resection could not be done in rest 81.7% cases.
- The distribution of the cases based on their TNM clinical staging showed that in T stage T3 was in most of the cases (40.0%), in N stage N2 was in the majority (48.3%) followed by N1 (30.0%) and in M stage M1 was in majority (50.0%) followed by M2 (43.3%).
- The below table exhibits the comparison of tumor markers at different follow-ups and it was found that CA19.9 was significantly reduced from preoperative (2185.4±2557) to postoperative 1 week (628.6±814) and further reduced significantly after one month of surgery (204.7±443). CEA was 59.01±41.4 preoperatively which was reduced significantly to 34.8±29.5 after 1 week postoperatively and 12.7±13.5 after one month postoperatively (p<0.05).

Table 1: Details Of The Patients Based On Tumor Markers In Different Intervals

Tumor marker	Patients (%)	CA 19.9	CEA
Pre-Operative	60	2185.4±2557	59.01±41.4
Post-Operative (1 week)	7	628.6±814	34.8±29.5
Post-Operative (1 month)	8	204.7±443	12.7±13.5
p-value		<0.001	<0.001

- The below table in studied patients displays that diagnostic accuracy was highest after 1-month for both markers with 86.4% accuracy and 72.7% sensitivity and 94% specificity for CA19.9 & 92% for CEA.

Table 2: Comparison between histopathological diagnosis with CA19.9 & CEA in pre-operative & post operative period.

Calculated value	Preoperatively		1-week postop		1-month postop	
	CA19.9	CEA	CA19.9	CEA	CA19.9	CEA
Cut off	274	22.0	5.14	0.88	6.0	0.60
Sensitivity	63.6%	54.5%	63.6%	63.6%	72.7%	72.7%
Specificity	23.1%	19.4%	92.0%	91.0%	94.0%	92.0%
Diagnostic accuracy	30.2%	28.6%	81.8%	81.8%	86.4%	86.4%

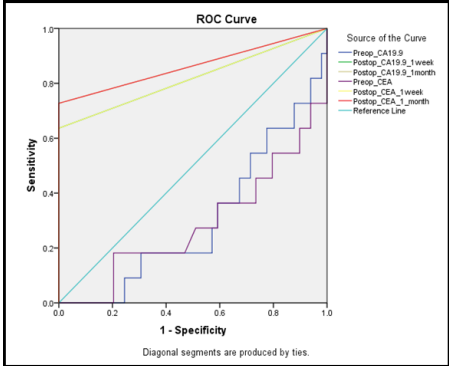


Figure 1: Comparison between histopathological diagnosis with CA19.9 & CEA in pre-operative period & post-operative period.

DISCUSSION –

Although it is usually seen as a rare disease, gallbladder cancer is responsible for 80% to 95% of all biliary tract cancer cases, making it the most frequent bile tract cancer. Early detection is crucial since this cancer spreads quietly and can be lethal if detected too late. Tumor markers are created by cancerous tumors or by the host's reaction to cancer and can be found in blood or tissue. These indicators can be applied to response monitoring, diagnosis, and screening. An oncofetal antigen called CEA is linked to tumor cells' plasma membranes. It is elevated in breast, stomach, lung, and colon cancers. Moreover, it is elevated in a few benign diseases such as cirrhosis, pancreatitis, and inflammatory bowel disease. Gastric cancer, pancreatic cancer, colon cancer, and lung cancer are all addressed by CA 19-9.⁷ In several malignancies, including colorectal, pancreatic, liver, and stomach, tumor markers CEA, CA 19-9, are being used for diagnosis, prognosis, and recurrence detection.⁸

Age

In this study, a major portion of the cases were of the age above 60 years (43.3%) followed by 41 to 50 years (25.0%), 51 to 60 years (23.3%) least below 40 years (8.3%) with mean age 56.05±10.8 years with females' predominance (73.3%). Our findings were comparable with the findings of Agrawal S et al⁹ who stated that the study's patient population was 55.6 years old on average (range: 30-80 years old). There were 18.3% and 81.7% females.

Chief Complaints

In the present study based on chief complaints, it was found that the majority of the cases had lump in the abdomen (80.0%) followed by pain abdomen (55.0%) and jaundice (35.0%). Our findings were consistent with the findings of Jiwani MS et al¹⁰ has listed each symptom separately, in which yellowish discoloration of skin and sclera (jaundice) , right upper quadrant pain, fever ,nausea, vomiting, clay colored stools, dark colored urine, lump in the abdomen, weight loss, etc. are common symptoms which was comparable to the present study.

Location Of Mass

In this study, it was found that 65.0% had a mass in the body followed by the neck (18.3%), liver, GB stump (13.3%), and fundus (3.3%). Wall thickness >4mm was found in most of the cases (68.3%) followed by increased thickness (28.3%) and post-cholecystectomy (3.3%). CBD was dilated in 30.0% of cases and was normal in 70.0% of cases. El-Sayed Darwish et al¹¹ described that patients with thickness of gallbladder wall ≥4mm had significantly increased risk for difficult cholecystectomy (p=0.037).

FNAC findings

In the present study, FNAC findings show that the majority of the cases had Adenocarcinoma of gall bladder (90.0%) followed by mild

dysplasia (1.7%) and normal 8.3% cases whereas histopathological findings depicted that 81.7% cases were benign or normal and 15.0% had adenocarcinoma of GB followed by squamous cell carcinoma of GB (1.7%) and Keratinising squamous cell carcinoma in 1.7% cases. Our findings were correlated with **Chandra S et al**¹² who reported that Ten of these 13 cases—or 76.9%—had recurrent FNAC diagnoses of adenocarcinoma.

TNM Staging

It was found that in T stage T3 was in most of the cases (40.0%), in N stage N2 was in the majority (48.3%) followed by N1 (30.0%) and in M stage M1 was in the majority (50.0%) followed by M2 (43.3%). 13.3% required resection whereas 86.7% did not require resection. **Agrawal et al**⁹ reported that T3 was in the majority (54.9%) cases followed by T4 (22.5%), in N stage N1 was in the majority 45.1% followed by N2 in 32.4%. M1 stage was in 62.0% of cases followed by M0 in 38.0% and patients who could undergo curative resection were only 11 out of 71 patients (15.5%).

Tumor Markers

In this study, it was found that CA19.9 was significantly reduced from preoperative (2185.4±2557) to postoperative 1 week (628.6±814) and further reduced significantly after one month of surgery (204.7±443). CEA was 59.01±41.4 preoperatively which was reduced significantly to 34.8±29.5 after 1 week postoperatively and 12.7±13.5 after one month postoperatively ($p < 0.05$). **Sachan A et al**¹³ reported that In terms of predicting the metastatic disease, a cutoff value of 72 IU/ml for CA19-9 had 52% sensitivity, 80% specificity and 0.674 area under the ROC curve (AUC). In contrast, a cutoff value of 5 ng/ml for CEA had 51% sensitivity, 72% specificity, and an AUC of 0.628 for the detection of disease with metastasis.

Strengths Of The Study

The strength of this study is that we included a complete spectrum of gall bladder cancer patients to derive the importance of the tumour marker.

Limitations Of The Study

The main shortcoming of this study was the small sample size and inability to correlate with TNM staging of tumors as many patients were either referred to the higher center or left after initial diagnosis. As cases of only Carcinoma GB was taken, so specificity was seen on higher side.

CONCLUSION

This study was conducted in G.S.V.M. Medical college, Kanpur which comes under North Indian Gangetic belt which is considered prone to development of Carcinoma Gall Bladder. Its Incidence was seen mostly in Age >60 years with preponderance of Female sex. Although there are too many cases of this disease in this belt, yet due to lack of awareness, mostly patients present late with most common presentation being Lump Abdomen followed by Pain Abdomen. Most common location of mass was Body of GB with dilated CBD found in only 30% cases with most common Histological Subtype found to be Adenocarcinoma.

In our study, it was found that Increased CA19-9 and CEA was helpful in diagnosing Gall bladder carcinoma with good sensitivity [CA19.9 – 63.6% & CEA – 54.5%] with CA19-9 being overall superior than CEA in predicting tumour burden, metastasis and recurrence. Patients with increased CA 19-9 levels may be a candidate for metastatic workup and for adjuvant chemotherapy post resection.

Also it was found that there was significant reduction in levels of CA19.9, 1 week following surgery whereas significant reduction in CEA was found about 1 month following resection. This indicates a positive response to the surgical intervention. Thus, it can be concluded that raised serum CA 19-9 and serum CEA (combined) may act as a good adjunct for initial screening of suspected cases of Carcinoma GB which can be further investigated with help of histopathology for confirmation.

REFERENCES

1. National Cancer Registry Programme: first all India Report 2001- 2002.summary of specific sites. New Delhi: Indian Council of Medical Research, 2004; 225-227.
2. Panwar A, Mahajan P, Galodha S, Negi S, Thakur A. Role of CEA and CA19-9 in Predicting Metastasis, Operability and Resectability in Patients of Carcinoma Gall Bladder. East African Scholars Journal of Medical Sciences. 2020;3(11):394-398
3. Indian Council of Medical Research. Review of Published Data. In: Consensus Document for Management of Gallbladder Cancer. 2014;14-36.

4. Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. Eur J Surg Oncol 2007;33:266-270.
5. Grunnet M, Mau-Sørensen M. Serum tumor markers in bile duct cancer—a review. Biomarkers 2014;19:437-443.
6. Wang Y, Feng F. Combined detection tumor markers for diagnosis and prognosis of gallbladder cancer. World J Gastroenterol. 2014;20:4085-4092.
7. Daniel WC, Stewart S. Tumor markers. In: Burtis CA, Ashwood ER, editors. Teitz textbook of clinical chemistry. 3rd edn. Philadelphia: Saunders Elsevier; 1999. pp. 733-7.
8. Zhang D, Yu M, Xu T, Xiong B. Predictive value of serum CEA, CA19-9 and CA125 in diagnosis of colorectal liver metastasis in Chinese population. Hepatogastroenterology. 2013;60:1297-1301.
9. Agrawal S, Gupta A, Gupta S, Goyal B, Siddeek RAT, Rajput D, Chauhan U, Kishore S, Gupta M, Kant R. Role of carbohydrate antigen 19-9, carcinoembryonic antigen, and carbohydrate antigen 125 as the predictors of resectability and survival in the patients of Carcinoma Gall Bladder. J Carcinog. 2020 Jun 27;19:4.
10. Jiwani MS, Banode PJ, Kharche AD, Jiwani AA, Vaidhya SV. Role of Magnetic Resonance Cholangiopancreatography in Cases of Obstructive Jaundice in Correlation with Ultrasonography. IJRSMS 2016;2(2):70-84
11. El-sayed Darwish AEF, El-Banna AM and Salem A. Assessment of perioperative predictors of difficult laparoscopic cholecystectomy. Al-Azhar Med. J. Surgery. 2022;51(1):13-30
12. Chandra S, Chandra H, Shukla SK, Sahu S. Fine-needle aspiration cytology of gallbladder with an attempt of cytomorphological classification. Cytojournal. 2019;22:16:1.
13. Sachan A, Saluja SS, Nekarakanti PK, Nimisha, Mahajan B, Nag HH, Mishra PK. Raised CA19-9 and CEA have prognostic relevance in gallbladder carcinoma. BMC Cancer. 2020 Aug 31;20(1):826.