

Evaluation of Postoperative Serum CA19-9 in Hepatobiliary and Pancreatic Malignancies

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1. Abstract

1.1. Introduction: CA 19-9 serves as an important tumor marker in diagnosis of digestive system malignancies and high preoperative levels of CA 19-9 have been found to correlate with patient outcomes. Study on serum CA 19-9 levels pre and postoperative hepatobiliary and pancreatic malignancies is not available in literature. Therefore, this study was planned to determine value of serum CA 19-9 in the diagnosis and follow up of the malignancies and also to correlate the change in preoperative and postoperative serum levels of CA 19-9 with the surgical resection limit.

1.2. Materials and Methods: This prospective observational study was carried out at Department of General Surgery, PGIMER Chandigarh in 31 patients. Statistical comparison between pre and postoperative values were carried out using chi-square test with statistically significant p values.

1.3. Results: The post-operative decrease in the levels of CA 19-9 ranges from 24 U/ml to 174 U/ml. The mean postoperative levels of serum CA19-9 were 87.6 U/ml for carcinoma pancreas group. Maximum and minimum drop in CA 19-9 levels was seen in carcinoma head of pancreas cases and duodena adenocarcinoma group respectively. Mean difference of CA19-9 with SD in Ca head of pancreas, carcinoma gallbladder and Distal CBD cholangiocarcinoma was 789.09 + 207.95 U/ml, 388 + 163.17 U/ml and 124.5 + 56.47 respectively at 95% CI with statistically significant p-value (0.00, 0.006 and 0.02).

1.4. Conclusion: Serial measurement of this tumor marker can be done in patients to assess response to therapy who undergo curative surgical resection

2. Introduction

Malignancies of digestive system can be diagnosed and monitored by role of several tumor markers. CA19-9 is a carbohydrate antigen produced against a human colorectal carcinoma cell line which was originally identified by a murine monoclonal antibody [1]. It is a glycoprotein with high-molecular-weight which is normally synthesized and expressed not only in pancreatic and biliary ductal cells but also in gastric, colon, endometrial and salivary epithelial cells. CA19-9 which is also referred to as sialyl Lewis-x is expressed on the surface of cancer cells as a glycolipid and as an O-linked glycoprotein [2]. In small amounts, it is present in serum and in several benign gastrointestinal disorders, this antigen is overexpressed [1,2]. CA19-9 serum levels have not only been used for diagnosis of tumor recurrence but also valuation of resectability, preoperative staging, and prediction of pancreatobiliary cancers [3-8]. As it is related to Lewis blood group antigens, this antigen is expressed in patients with blood group Le (a-B+) or Le (a + B-). In order to produce the antigen epitope, enzyme 1,4-ucosyl transferase is required which is deficient in 5-10% of population. As a result, Le (a-B-) phenotype is manifested, and thus use of CA19-9 as a universally applicable biomarker is limited. Elevation in CA 19-9 level correlates with degree of tumor differentiation as well as the extent of tumor mass [9]. In patients with pancreatic carcinoma elevated levels of CA 19-9 have been related to poor prognosis and lesions which are unresectable [10]. The sensitivities of CA 19-9 in diagnosis of pancreatic adenocarcinoma is around 70-80% with specificity around 80-90% [11,12]. CA 19-9 value 100U/ml implying unlikely resectable pancreatic malignancy. Low preoper-

ative value of CA 19-9 is associated with improved median survival when compared to elevated preoperative pancreatic cancer CA 19-9 values. Determination of this anti gen can provide important information about preoperative staging, prognosis and evaluation of the response to treatment and recurrence in case of pancreatic malignancy. Increased levels of CA 19-9 are associated with malignancies of biliary tract [13]. High preoperative levels of CA 19-9 have been found correlate with adverse patient outcome. Abnormally elevated CA 19-9 levels are also found associated with malignant condition of the digestive tract namely the stomach, colon and rectum. Sensitivity of CA 19-9 is found to be around 50% with a high positive predictive value [14-17]. Abnormally elevated pre operative CA 19-9 levels are associated with advance stage of disease in digestive tract malignancies and are associated with poor prognosis [18]. CA 19-9 when used along with CEA levels is a highly sensitive indicator for response to treatment in colon cancer and monitoring for colon cancer metastasis. In gall bladder cancer, CA 19-9 level is a fairly good test in discrimination from benign disease of gall bladder. CA19-9 levels are significantly high in malignant with both the sensitivity and specificity observed about 80% [19,20]. When used judiciously with other tumor marker like CEA, the information provided is significant. Role of CA 19-9 also lies in evaluating treatment response and anticipating the onset of recurrences of a disease whenever used judiciously taking into account other dimensions of the medical condition. But to the best of our knowledge, study on serum CA 19-9 levels pre and postoperative hepatobiliary and pancreatic malignancies is not available in literature. Therefore, this study has been planned to determine value of serum CA 19-9 in the diagnosis and follow up of the malignancies and correlate the change in preoperative and post operative serum levels of CA 19-9 with the surgical resection limit.

3. Materials and Methods

This prospective observational study was carried out at Department of General Surgery, PGIMER Chandigarh. Serum Levels of CA19-9 of all suspected and diagnosed cases of hepatobiliary and pancreatic malignancies were determined at the time of admission in 31 patients. CA19-9 levels were determined at Gastro Biochemistry section in Department of Gastroenterology, PGIMER, Chandigarh. Upper limit of normal for CA19-9 was 37 IU/ml. All subjects had confirmed diagnosis and clinical stages determined by standard appropriate instrumental tests including radiological, clinical, histopathological and operative findings. CA19-9 levels were measured again after 7 days after a curative surgery was performed. Values obtained were compared with pre operative values for analysis of significance.

3.1. Inclusion Criteria

- I. All patients diagnosed with hepatobiliary and pancreatic malignancies.
- II. Both Sex
- III. Age >18 to <80 Years
- IV. Patients giving a valid informed consent.

3.2. Exclusion Criteria

- I. Patients who refused to give consent
- II. Cases proven to be benign in the course of evaluation and treatment.
- III. Patients with non resectable tumor.

3.3. Statistical Analysis

Data was summarized and expressed as mean, median, sensitivities and positive predictive values where ever indicated. Statistical comparisons between preoperative and postoperative values were carried out using chi-square test, a paired t- test with statistically significant p value <0.05. All statistical calculations were done by using standard statistical programs (SPSS 10.01, SPS, Inc, Chicago, IL).

4. Results

4.1. Demographic Characteristics

Thirty-one patients fulfilling inclusion criteria were included in the study. 22 were males while 9 females. Their mean age was 56.29 years. Maximum age was 80 years and the minimum 24 years. Mean body mass index (BMI) was 23.5kg/m² with a standard deviation of 2.7 (range 17.3-28.6) (Table 1). The mean age of patients of carcinoma head of pancreas was 56.09 years. The male to female ratio was 4.5:1. The mean age of patients of cholangiocarcinoma was 62, with a M: F ratio of 3:2 while the mean age of patients of carcinoma gall bladder was 51.5 years with a M: F ratio 1:1. A 24 years' male was included in the study with HCC. Serum Ca19-9 level was raised in all malignancies arising from the head of pancreas that were included in the study.

8 out of 11 cases had serum CA19-9 levels greater than 1000 U/ml while 3 had significantly elevated serum CA19-9 levels but less than 1000 U/ml. The post-operative decrease in the levels of CA 19-9 ranges from 24 U/ml to 174 U/ml. During the postoperative period mean levels of serum CA19-9 were 87.6 U/ml for carcinoma pancreas group. The drop was statistically significant at a p-value <0.01 (Table 2). (Table 3) shows comparison of pre-operative and postoperative serum CA 19-9 levels in different hepatobiliary malignancies. Maximum drop in CA 19-9 levels was seen in the carcinoma head of pancreas cases and minimum in duodenal adenocarcinoma group. A single case of hepatocellular carcinoma and intrahepatic cholangiocarcinoma was included in the study and had normal CA19-9 level.

Table 1: Demographic profile

		Mean± SD
No. of patients	31	
Age (years)	24-80	56.29± 11.07
M:F ratio	22:09	
BMI(Kg/m2)	17.3-28.6	56.29± 11.07

Table 2: Levels of CA 19-9 in carcinoma head of pancreas patients

	Pre-operative CA19-9 U/ml	Post- operative CA19-9 U/ml
1	>1000	68
2	>1000	58
3	>1000	72
4	>1000	72
5	>1000	72
6	>1000	112
7	>1000	144
8	>1000	174
9	680	24
10	560	48
11	560	58

Table 3: Pre-operative and Post- operative levels in different hepatobiliary malignancies.

	Mean ±SD Preoperative CA 19-9 (U/ml)	Mean ±SD Postoperative CA 19-9 (U/ml)
Duodenal adenocarcinoma (n=4)		
Carcinoma head of pancreas (n=11)	871.8±220.7	87.6±39.7
Carcinoma gall bladder (n=6)	380±160.9	29.5±8.6
Hilar cholangiocarcinoma (n=3)	206±81	24±6.1
Distal common bile duct cholangiocarcinoma (n=5)	94±47	23±12
Duodenal adenocarcinoma (n=4)	21.5±4.55	15.5±7.8
Intrahepatic Cholangiocarcinoma (n=1)	8	8
Hepatocellular carcinoma (n=1)	8	8

4.2. Paired Difference of Serum CA19-9

The mean difference of CA19-9 in Ca head of pancreas was 789.09 U/ml, with a SD of 207.95 U/ml at 95% CI. Statistically significant p-value 0.00 was calculated (Table 4). For carcinoma gallbladder, the mean difference in CA19-9 was 388U/ml with a SD of 163.17 U/ml at 95% CI and significant p-value of 0.006. Mean difference of CA19-9 in Distal CBD cholangiocarcinoma was 124.5U/ml, with a SD of 56.47 U/ml at 95% CI. The p-value observed was

0.02, which is statistically significant. Mean CA19-9 levels in the case of hilar cholangiocarcinoma (p-value of 0.06) and duodenal adenocarcinoma (p-value0.09) showed no statistical significance. As the study included single cases of intrahepatic cholangiocarcinoma and hepatocellular carcinoma, statistical comparison between preoperative and post-operative levels of CA19-9 could not be done. Moreover, both disease entities had a normal CA19-9 levels preoperatively.

Table 4: Paired difference in CA19-9 level

	Paired Difference				
	Mean	Std. Deviation	95% Confidence Interval of the Difference		Significant
			Lower	Upper	
Ca head of pancreas	785.091	207.951	645.388	924.794	0
Ca gall bladder	388	163.17	185.397	590.603	0.006
Distal CBD cholangiocarcinoma	124.5	56.477	34.632	214.368	0.022
Hilarchoangiocarcano ma	181.333	80.903	-19.641	382.308	0.06
Duodenal adenocarcinoma	7	1.414	-5.706	19.706	0.09
Intrahepatic cholangiocarcinoma	8	8	-	-	-
Hepatocellular carcinoma	8	8	-	-	-

5. Discussion

In this study, 8 out of 11 cases of carcinoma pancreas had serum CA19-9 levels greater than 1000 U/ml while 3 had significantly elevated serum CA19-9 levels but less than 1000 U/ml. All patients with carcinoma pancreas included in the study were surgically resectable. After an R0 resection, the mean postoperative levels of serum CA19-9 were 87.6 U/ml for carcinoma pancreas group. In one of the leading studies prognostic impacts of CA 19-9 was evaluated in 176 patients by Ferrone et al [21]. In this study patients who had bilirubin levels <2 mg/dl, perioperative levels of this marker were measured in those patients. Based on preoperative concentration of CA 19-9, patients were separated on the basis of poor and good outcome which was best described at 1000 U/ml. It was also well-thought-out that this essential biomarker should be included as a measure of evaluation in prognostic nomograms. As per this study, elevated CA 19-9 levels, >1000 U/ml, strongly indicated advanced disease and they recommended diagnostic laparoscopy in such cases, although the lesion on preoperative imaging looked resectable. Duffy et al. [22] after a systematic review of various articles came to the conclusion that CA 19-9 levels correlate with overall survival in patients with resectable pancreatic cancer, presurgical and post resection cases. For risk stratification, other factors also need to be taken into consideration as raised CA 19-9 levels in pretreatment cases were related to adverse patient outcome in advanced disease. Therefore, they recommended use of imaging in conjunction with CA 19-9 levels in monitoring therapy after the surgical resection.

Present study included 9 cases of cholangiocarcinoma, 3 hilar cholangiocarcinoma who underwent hepatic resection and hepaticojejunostomy, 5 distal CBD cholangiocarcinoma who underwent pancreaticoduodenectomy and 1 case of intrahepatic cholangiocarcinoma who underwent hepatic resection. R0 resection was achieved in all cases. Serum CA19-9 levels were found to be high in all hilar cholangiocarcinoma patients (n=3), the mean being 206 U/ml. In cases of hilar cholangiocarcinoma there was no significant drop in postoperative serum CA19-9 levels. However, in distal CBD cholangiocarcinoma, serum CA19-9 levels were abnormal but not more than 100 U/ml, the mean was 92 U/ml.

Postoperative drop in serum values of Ca19-9 was significant at a p-values of 0.02. There was a single case of intrahepatic cholangiocarcinoma in present study; the preoperative serum CA19-9 was normal, and continued to remain normal postoperatively. Statistical significance post-surgery in CA19-9 could not be tested for intrahepatic cholangiocarcinoma. In a study done by Cai et al [23] 168 patients with hilar cholangiocarcinoma (HC) after radical surgery were investigated. In view of potential prognostic factors, the appropriate cutoff point of CA19-9 that would affect the survival of patients was determined in this study. Univariate and multivariate methods were used for analyzing CA19-9 and other clinicopathologic factors for influence on survival. Results highlighted that among the categorized preoperative cases, CA19-9 levels less than 150 IU/L (P=0.000) were measured as the strongest univariate predictor. Yoo et al [24] analysed perioperative CA19-9 in 74 cases of intrahepatic cholangiocarcinoma who underwent surgical resection. They found that in intrahepatic cholangiocarcinoma (ICC) patients treated with surgical resection, change in CA19-9 levels after surgery was an important prognostic factor for foretelling survival. It was also concluded that these levels should be measured in patients amenable to attempted curative resection. Postoperatively, shorter survival outcome was seen in patients who did not have regularized CA19-9 levels. Even if radiographic evidence of disease was absent, a continued or alternative therapy was suggested in such patients.

In present study we observed that mean value of serum CA19-9 in carcinoma gallbladder was 380 U/ml. All underwent an R0 resection at extended cholecystectomy. A significant drop in postoperative serum CA19-9 values with a p-values of <0.01 was observed in our study. Preoperative serum CA19-9 was normal in a case of hepatocellular carcinoma which underwent a curative hepatectomy and the drop in postoperative CA19-9 was not significant in that case. Kankonkar et al [25] observed 225 cases of GI tract cancer, 22 of which were carcinoma gall bladder. In their study, for the detection of gall bladder cancer they determined the sensitivity of three tumor markers which included CA 19-9, CEA and alpha feto protein (AFP) and found that CA 19-9 was the most sensitive among them at 100% sensitivity. It was also noticed that with ad-

vancing stage of disease, serum concentration of AFP and CEA showed no increase as seen in CA 19-9 levels. Their study also showed a very high level of preoperative CA19-9 >1000U/ml and much higher in advanced disease. They concluded that a combination of CT (or US) and serum CA19-9 is not only a noninvasive approach but also cost-effective and reasonable in establishing the diagnosis of gall bladder cancer. The limitation of this study is a smaller number of cases. Long term follow up of patients in terms of prognosis and outcome was not done due to time limit set for completion of the study.

6. Conclusion

CA19-9 is a subtle marker in diagnosing pancreatic, gall bladder and cholangiocarcinoma. Serial measurement of this tumor marker can be done in patients to assess their response to therapy who undergo curative surgical resection.

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