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UTILITY OF CA 19-9 AND CEA IN DETERMINING RESECTABILITY OF PANCREATIC CANCER

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ABSTRACT

Background: Pancreatic cancer considered as a ‘silent killer’ is usually diagnosed at the late stage of its course. Therefore, the accurate determination of its resectability is the most important contribution to reduce needless surgery to a minimum.

Objective: The aim of the study was to assess the utility of serum CA 19-9, CEA in determining resectability of pancreatic cancer.

Methods: This was a prospective observational study among purposively selected 54 patients diagnosed as pancreatic cancer in Dhaka Medical College Hospital (DMCH) from 1st July 2016 to 31st June 2017. The patients were evaluated by history, physical examination and investigations. The patients were considered to have potentially resectable tumour after assessment. The patients were undergoing surgery for potential tumour resection at the operation theater. Statistical analyses of the results were obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences.

Results: This study shows 59.26% (32) patients were in >60 years age group. 62.96% (34) patients were male out of total 54 patients. 98.15% (53) patient had jaundice, 96.30% (52) had weight loss. There was no significant association between CA 19-9, CEA with age, sex and clinical features. Out of the 54 patients, 45 patients were resectable pancreatic carcinoma and 9 patients was unresectable. In this study sensitivity was 88.9%, specificity was 55.6%, PPV was 90.9% and NPV was 50% for CA 19-9. In CEA, sensitivity 77.78%, specificity was

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55.56%, PPV was 89.74% and NPV was 33.33%. **Conclusion:** The study revealed that lower level of CA 19-9 and CEA can be utilized to determine resectability in patients with pancreatic carcinoma with a good positive predictive value.

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INTRODUCTION

Pancreatic cancer is one of the most aggressive human malignancies. It represents the fourth most frequent cause of cancer related death and the second most frequent cause, after colorectal cancer, when considering digestive tract cancer alone. [1] More than 85% of pancreatic cancers are ductal adenocarcinoma and arise most commonly in the head of the gland. About 15 to 20% of the patients have resectable disease at the time of presentation, because of its silent course, late clinical symptoms and rapid growth patterns, it has been named the “silent killer”. The overall 5 years survival rate of pancreatic cancer range from 0.4 to 4%, the lowest for any cancer. [2] Most pancreatic cancers arise from the exocrine pancreas, while endocrine subtypes, such as Islet-cell tumors, sarcomas, and lymphomas, are very uncommon. Approximately 90% of pancreatic neoplasms are adenocarcinomas, two-thirds of which occur in the head of the organ with the remainder in the body or tail. [3]

Pancreatic cancer is commonly diagnosed through imaging techniques, including, transcutaneous ultrasound, computed tomography (CT), magnetic resonance imaging, and more recently endoscopic ultrasound (EUS). [4] Biopsies in patients with resectable tumors can be taken during surgery, while for patients who are not suitable candidates for radical surgery, the most common approaches to obtain a tissue are by CT-guided biopsy, endoscopic retrograde cholangiopancreatography, or EUS with fine needle aspiration. Because the organ is inconveniently located and because of the morbidity associated with biopsy, pancreatic cancer continues to have among the lowest

proportion of histologically verified cases among major cancers. [3]

Pancreatic adenocarcinoma is a devastating disease. Unfortunately, determining which patients have localized disease is not straightforward and often occult metastases are discovered during laparotomy. Hence, the curative resection of pancreatic adenocarcinoma can be carried out in only 10% of patients and resection margin-positive pancreatic tumors are associated with a poor prognosis. [5] The only way to cure pancreatic adenocarcinoma is to remove the entire tumor with no residual disease. A preoperative assessment for the possibility of complete resection for patients with pancreatic adenocarcinoma is very important because precise estimation results in fewer unnecessary operations that do not afford survival benefit to the patients. [6] Currently, the study of choice to stage pancreatic adenocarcinoma is computed tomography (CT).

The two most studied tumor markers that have been evaluated in the diagnosis and prognosis of patients with pancreatic adenocarcinoma are carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9). Little is known, however, about the association between the levels of these tumor markers and the existence of metastasis or locally advanced disease in patients with pancreatic adenocarcinoma. [7] The purpose of the present study was to determine the utility of serum tumor markers CA 19-9, CEA in determining resectability of pancreatic cancer.

METHODOLOGY

This Prospective Observational study was carried out in the Department of surgery, Dhaka Medical College & Hospital (DMCH),

during July 2016 to June 2017. A total of 54 patients were participated in the study. Patient of pancreatic cancer those who are admitted in the general surgery ward in DMCH. Patients aged between 35-75 years both male and female, clinically diagnosed with pancreatic cancer were included in the study. History/evidence of infections, recent trauma, fracture, malignancy, tuberculosis, severely ill patients and not willing to participate were excluded

from the study. After taking consent and matching eligibility criteria, data were collected from patients on variables of interest using the predesigned structured questionnaire by interview, observation. Statistical analyses of the results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences.

RESULTS

Table I: Distribution of the patient by age (n=54)

Age (Years)	n=54	%	Mean±SD
<40	3	5.56	59.24±8.94
40-50	5	9.26	
50-60	14	25.93	
>60	32	59.26	
Total	54	100	

Table I shows distribution of patient according to age. Maximum (59.26%) patient were in age group >60 years followed by 25.93%, 9.26% and 5.56% were in group 50-60 years, 40-50 years and <40 years respectively. Mean age was 59.24 years within the range of 38-70.

Table II: Distribution of the patients by gender (n=54)

Gender	n=54	%	Male female ratio
Male	34	62.96	1.70:1
Female	20	37.04	
Total	54	100	

Table II shows distribution of patient according to gender. Among the patient 62.96% were male and 37.04% were female and male: female ratio was 1.70:1.

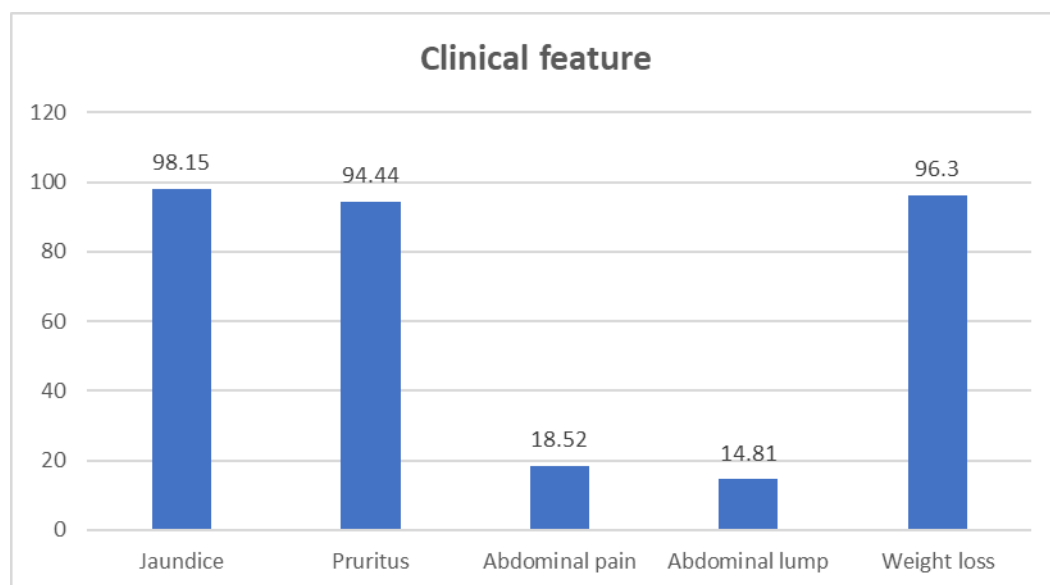


Fig. I: Distribution of patient according to clinical feature

Figure I shows most of patient have jaundice (98.15%) followed by weight loss (96.30%). Pruritus (94.44%), abdominal pain (18.52%) and abdominal lump (14.81%).

Table III: Characteristics of tumour according to CT findings (n=54)

Character of tumour	n=54	%
Location of tumour		
Pancreatic head & neck	53	98.15
Body	1	1.85
Size in cm		
≤2 cm	31	57.41
>2 cm	23	42.59
Local LN involvement		
Present	2	3.70
Absent	52	96.30
Vascular involvement		
Present	1	1.85
Absent	53	98.15
Local spread		
Present	3	5.56
Absent	51	94.44

Table III shows most of the tumour was located at pancreatic head & neck region (98.15%) followed by body (1.85%). Most of the tumour was ≤2 cm size (57.41%) followed by >2 cm size (42.59%). Local LN involvement was absent in most of the tumour

(96.30%) and present in 3.70%. Most of the tumour do not have vascular involvement 98.15%, present in 1.85%, local spread was absent in most of tumour 94.44% and present in 5.56%.

Table IV: Distribution of patient according to preoperative CA19-9 level (n=54)

CA 19-9 level (U/ml)	n=54	%
≤150 U/ml	44	81.48
>150	10	18.52
Total	54	100

Table IV shows distribution of patients according to preoperative level of CA19-9 which is ≤150 U/ml. Most of the patient (81.48%) had ≤150 u/ml.

Table V: Distribution of patient according to preoperative CEA level (n=54)

CEA level (ng/ml)	n=54	%
≤5.8	39	72.22
>5.8	15	27.78
Total	54	100

Table V shows distribution of patient according to preoperative level of CEA which is ≤5.8 ng/ml. Most of the patients (72.22%) had ≤5.8 ng/ml.

Table VI: Distribution of patient according to operative findings (n=54)

Group	n=54	%
Resectable	45	83.33
Unresectable	9	16.67

Locally advanced	4	7.41
Distant metastasis	5	9.26
Total	54	100

Table VI shows most of tumour was resectable (83.33%), unresectable 16.67% of which 7.41% due to locally advanced tumour and 9.26% due to distant metastasis.

Table VII: Association of CA 19-9 and age, sex, clinical feature

Age (Years)	CA 19-9				P value
	≤150 (n=44)		>150 (n=10)		
	No	%	No	%	
<40	2	4.55	1	10.0	0.126
40-50	3	6.82	2	20.0	
50-60	12	27.27	2	20.0	
>60	27	61.36	5	50.0	
Sex					
Male	28	63.64	6	60.0	0.829
Female	16	36.36	4	40.0	
Clinical feature					
Jaundice	43	97.7	10	100.0	0.487
Pruritus	44	100	7	70.0	0.061
Abdominal pain	9	20.45	1	10.0	0.126
Abdominal lump	7	15.9	1	10.0	0.542
Weight loss	43	97.7	9	90.0	0.563

Table VII shows the association of CA19-9 with patients characteristics like age, sex, clinical features. There is no significant association.

Table VIII: Association of CEA and age, sex, clinical feature

Age (Years)	CEA				P value
	≤5.8 (n=39)		>5.8 (n=15)		
	No	%	No	%	
<40	1	2.56	2	13.3	0.119
40-50	4	10.26	1	6.67	
50-60	10	25.64	4	26.7	
>60	24	61.54	8	53.3	
Sex					
Male	27	69.2	7	46.7	0.124
Female	12	30.8	8	53.3	
Clinical feature					
Jaundice	38	97.44	15	100	0.687
Pruritus	39	100.00	12	80	0.079
Abdominal pain	8	20.51	2	13.3	0.451
Abdominal lump	6	15.38	2	13.3	0.586

Weight loss	37	94.87	15	100	0.675
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Table VIII shows the association of CEA with patients characteristics like age, sex, clinical features. There is no significant association.

Table-IX: Association between CA 19-9 and resectability

CA 19-9	Resectability				P value
	Resectable (n=45)		Unresectable (n=9)		
	No	%	No	%	
≤150	40	88.9	4	44.4	0.002
>150	5	11.1	5	55.6	

Table IX shows there is significant association (p value- 0.002) between CA 19-9 and resectability.

Table-X: Association between CEA and resectability

CEA	Resectability				P value
	Resectable (n=45)		Unresectable (n=9)		
	No	%	No	%	
≤5.8	35	77.78	4	44.44	0.042
>5.8	10	22.22	5	55.56	

Table X shows there is significant association (p value -0.042) between CEA and resectability.

Table XI: Validity test for CA 19-9

Validity test	%	95% CI
Sensitivity	88.9	75.95% to 96.29%
Specificity	55.6	21-20% to 86.30%
PPV (Positive predictive value)	90.91	82.71% to 95.44%
NPV (Negative predictive value)	50	26.66 to 73.34%
Accuracy (Confidence interval)	83.33	70.71% to 92.08%

Table XI shows sensitivity was 88.9% and specificity was 55.6%.

Table XII: Validity test for CEA

Validity test	%	95% CI
Sensitivity	77.78	62.91% to 88.80%
Specificity	55.56	21.20% to 86.30%
PPV	89.74	80.57% to 94.86%
NPV	33.33	18.34% to 52.67%
Accuracy	74.07	60.35% to 85.04%

Table XI shows sensitivity was 77.78% and specificity was 55.56%.

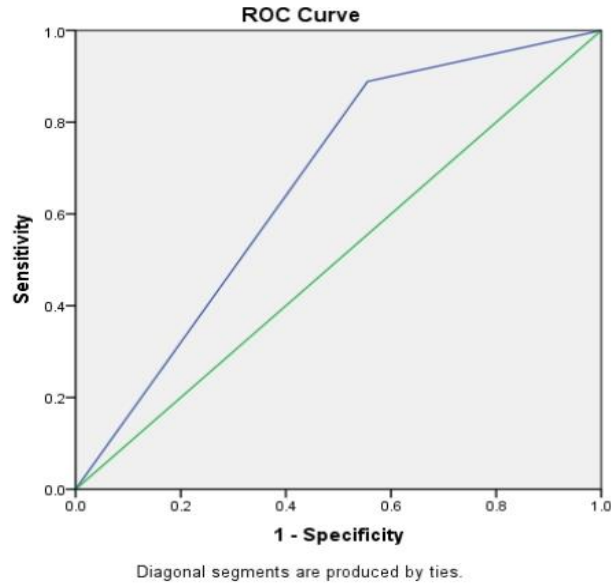


Figure II: Receiver-operator characteristic curve of serum CA 19-9

The area under the receiver-operator characteristic (ROC) curve for prediction of CA 19-9 area under curve (AUC) 0.667, which gave a cut off value of ≤ 150 with 88.9% sensitivity and 55.6% specificity for prediction of not significant ($p=0.117$).

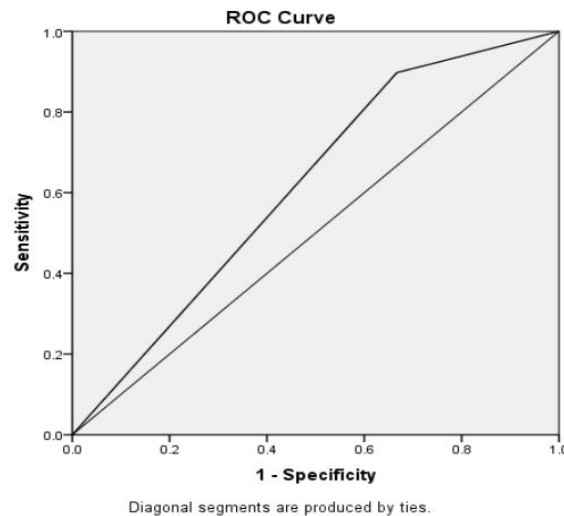


Figure III: Receiver-operator characteristic curve of serum CEA

The area under the receiver-operator characteristic (ROC) curve for prediction of CEA area under curve (AUC) 0.403, which gave a cut off value of ≤ 5.8 with 77.78% sensitivity and 55.56% specificity for prediction of not significant ($p=0.231$).

DISCUSSION

Majority of the patients of pancreatic cancer present at a late stage when there is no curative therapy is possible. This cancer can

be cured by surgery but it depends on the preoperative assessing its resectability. The accurate determination of resectability in patients with pancreatic cancer is the most important contribution of pre-operative staging; the goal being to reduce needless surgery to a minimum by Olivie D et al. [8]

In this study, age of 59.26% patients was more than 60 years and the mean age of the patients was 59.24 years. Mean age of the

patients was almost similar with the study by Appukuttan. [9] In a previous study among 61 pancreatic carcinoma patients with histologically proven adenocarcinoma the mean age was 61.2 ± 1.51 years which is near about similar to this study. [10] Male predominance (62.96%) was observed in the current study which is consistent with the studies by Aziz *et al.* as well as by Manak *et al.* But the study by Olivie D *et al.* observed equal distribution of males and females. [8, 11]

The most common clinical features were jaundice (98.15%), loss of weight (96.30%), pruritus (94.44%), abdominal pain (18.52%), and abdominal lump (14.81%) in this study. Similar signs, symptoms were also reported with the study done by Schlieman *et al.* [7] In this study majority (98.15%) of the tumours were located in the pancreatic head and neck followed by body of the pancreas (1.85%). A previous study demonstrated that approximately 75% of all pancreatic carcinomas occur within the head or neck of the pancreas, 15-20% occur in the body of the pancreas, and 5-10% occur in the tail Artinyan A *et al.* [12]

In this study 54 patients underwent surgery, 44(81.48%) had preoperative CA 19-9 level ≤ 150 U/ml. Out of these 44 patients, 40 patients had resectable surgery. On the other hand, 10 (18.52%) had CA19-9 level >150 U/ml. Out these 10 patients, 5 had resectable surgery. CA19-9 level were low in majority of patient who had resectable surgery. Similar CA 19-9 levels were also reported with the study done by Schlieman *et al.* [7] They found 89 patients, 40 (45%) had localized disease and underwent resection, 25 (28%) had locally advanced (unresectable) disease, and 24 (27%) had metastatic disease. The mean adjusted CA19-9 level was significantly lower in those with localized disease than those with locally advanced (63 vs 592; $P = .003$) or metastatic (63 vs 1387; $P < .001$) disease. When a threshold adjusted CA19-9 level of 150 was

used, the positive predictive value for determination of unresectable disease was 88%.

Kiliç *et al.* study serum CA 19-9 levels were reviewed for 51 patients with pancreatic cancer. [13] There were 18 (36%) resectable and 33 (64%) unresectable pancreatic cancers. The mean CA 19-9 level was 68.8 U/mL in the resectable group and 622 U/mL in unresectable group. When a CA 19-9 level of 256.4 U/mL was used as a cut-off point, the specificity and sensitivity was 92.3% and 82.4% respectively. Preoperative CA 19-9 levels may be a useful marker for determining preoperatively which patients have unresectable disease despite the demonstration on CT of resectable disease.

In this study 39(72.22%) patient had CEA level ≤ 5.8 ng/ml. Out these 39 patients, 35 had resectable surgery. On the other hand, 15 (27.78%) patients had CEA level >5.8 ng/ml. Out of these 15 patients, 10 had resectable surgery. CEA level was low in majority of the patient who had resectable surgery. Therefore, the findings of the study are in well agreement with the findings of the other research works. [7]

CEA and CA19-9 are the most studied serum tumor markers that have been evaluated for diagnosis and prognosis in patients with pancreatic carcinoma. However, little is known about the association between the levels of these markers and the existence of metastasis or locally advanced disease in patients with pancreatic carcinoma. Recently, several researchers have shown the relationship between these markers and resectability in pancreatic adenocarcinoma. [14] As for patients with an established diagnosis of pancreatic carcinoma, markedly elevated levels of these tumor markers may reflect unresectability in those patients who were thought to have resectable disease on preoperative imaging. Fujioka *et al.* (2007) reported that combined preoperative CEA and CA19-9 levels are suitable for assessing

expected curability and resectability in patients with pancreatic cancer. [14]

In this study sensitivity was 88.9%, specificity was 55.6%, PPV was 90.9% and NPV was 50% for CA 19-9 level. Sensitivity of CA 19-9 for the resectable pancreatic cancer ranges in various studies from 67 to 92% with specificities ranging from 68 to 92%. [7] In a report Zhang et al. reported that the preoperative serum CA19-9 level is a useful marker for evaluating the resectability of pancreatic carcinoma. [15] They obtained higher cutoff levels of CA19-9 (>353.15 U/mL) and reported 93.1% and 78.5% sensitivity and specificity, respectively. They also reported positive and negative predictive values as 84.38% and 90%, respectively. They showed much higher sensitivity, specificity, and positive predictive values and comparable negative predictive value. On the other hand, the report by Fujioka et al. have obtained the best cut-off level of CA19-9 for resectability in patients with pancreatic carcinoma as 157 U/mL and shown that the sensitivity, specificity, and positive and negative predictive values of preoperative CA19-9 to predict the resectability for these patients were 76%, 46%, 57% and 71%, respectively. [14] In this study sensitivity was 77.78%, specificity was 55.56%, PPV was 89.74% and NPV was 33.33% for CEA level. Therefore, the findings of the study are in well agreement with the findings of the other research works. [16] The main problem of both markers, and especially for CEA, is a low and wide-ranging sensitivity (30-90%) for detection of a PDAC. Specificity of CEA is between 25% to 56%. [16]

The area under the ROC curve for CA19-9 was 0.667. This result suggested that changes in the CA 19-9 levels may have a direct relation to resectability. When the cut-off value of CA 19-9 was accepted as ≤ 150 U/mL, the sensitivity and specificity were 88.9% and 55.6% respectively. On the other hand, in CEA, when a value of ≤ 5.8 ng/mL was used as the cut-off point, the sensitivity

and specificity were 77.78% and 55.56%, respectively, the area under ROC curve was 0.403. Kilic et al. reported the area under the ROC curve was 0.892. [13] This result suggested that changes in the CA 19-9 levels may have a direct relation to resectability. When the cut-off value of CA 19-9 was accepted as 189.5 U/mL, the specificity and sensitivity were 84.6% and 82.4% respectively. The ROC curve can help to assess the usefulness of the test and to determine the most appropriate cut-off point.

Limitations of the study

The present study was conducted in a very short period due to time constraints and funding limitations. The small sample size was also a limitation of the present study.

CONCLUSION

In this study CA 19-9, CEA both can be used as a tool to establish resectability in pancreatic cancer in respect to statistical significance which was proved in both validity test and in ROC curve.

RECOMMENDATION

This study can serve as a pilot to much larger research involving multiple centers that can provide a nationwide picture, validate regression models proposed in this study for future use and emphasize points to ensure better management and adherence.

ACKNOWLEDGEMENTS

The wide range of disciplines involved the utility of serum CA 19-9, CEA in determining resectability of pancreatic cancer research means that editors need much assistance from references in the evaluation of papers submitted for publication. I would also like to be grateful to my colleagues and family who supported me and offered deep insight into the study.

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