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Preoperative Prediction of Resectibility of Pancreatic Cancer by a Combined Utilization of CA19-9 and CEA

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Abstract:
Background: *Pancreatic cancer, sometimes referred to as a "silent killer," is usually detected when it is already advanced. Therefore, accurate resectability assessment is the most important component in reducing unnecessary surgery.* ***Objectives:*** *This study was done for assessment of the preoperative prediction of resectibility of pancreatic cancer by a combined utilization of CA19-9 and CEA.* ***Methods:*** *The cross-sectional Observational study was conducted in the Department of Surgery, BSMMU, Dhaka from Jan 2014 to Jan 2016 over a period of 24 months. A total of 108 patients with diagnosed cases of pancreatic cancer admitted in the hospital for treatment were included in this study. Data were collected over a period of 24 months and analyzed by appropriate computer based programmed software Statistical Package for the Social Sciences (SPSS).* ***Results:*** *In this study, this study shows 59.26% (64) patients were in >60 years age group. 62.96% (68) patients were male out of total 108 patients. 98.15% (106) of patients had jaundice, 96.30% (104) had weight loss. There was no significant association between CA 19-9, CEA with age, sex and clinical features. Out of the 108 patients, 90 patients were resectable pancreatic carcinoma, and 18 patients were 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 was 77.78%, specificity was 55.56%, PPV was 89.74% and NPV was 33.33%.* ***Conclusion:*** *According to the study, patients with pancreatic cancer can have their resectiability assessed using lower levels of CA 19-9 and CEA, which have a good positive predictive value.*
Keywords: *Preoperative Prediction, Resectability, Pancreatic Cancer, CA19-9, CEA*

I. Introduction

One of the deadliest cancers in humans is pancreatic cancer. When examining digestive tract cancer alone, it ranks as the second most common cause of cancer-related deaths, behind colorectal cancer [1]. It is also the fourth most common cause of cancer-related deaths. The most common location for ductal adenocarcinomas, which account for almost 85% of pancreatic malignancies, is the gland's head. It has been dubbed the "silent killer" due to its silent course, delayed clinical signs, and rapid growth patterns; approximately 15 to 20% of patients had resectable disease at the time of presentation. Pancreatic cancer has the lowest overall 5-year survival rate of any malignancy, ranging from 0.4 to 4% [1, 2]. While endocrine subtypes including lymphomas, sarcomas, and islet-cell tumors are extremely rare, the majority of pancreatic cancers originate from the exocrine pancreas [3]. Adenocarcinomas make up about 90% of pancreatic neoplasms; two-thirds of them develop in the organ's head, while the remaining portion occur in the body or tail [3].

Smoking, a family history of chronic pancreatitis, aging, male sex, diabetes mellitus, obesity, non-O blood group, occupational exposures, African American ethnic origin, a high-fat diet (high in meat and low in vegetables and folate), periodontal disease, and possibly Helicobacter pylori infection are risk factors for this cancerous condition. Lynch syndrome and germline mutations in the BRCA2, PALB2, CDKN2A, STK11, and

PRSS1 genes are linked to a significantly higher risk of pancreatic cancer. Genetic and epigenetic alterations are the primary cause of pancreatic cancer formation and progression [3].

Imaging methods such as transcutaneous ultrasound, computed tomography (CT), magnetic resonance imaging, and more recently endoscopic ultrasonography (EUS) are frequently used to diagnose pancreatic cancer [4, 5]. Patients who have resectable tumors may have biopsies collected during surgery; for patients who are not good candidates for radical surgery, the most popular methods for obtaining tissue are EUS with fine needle aspiration, CT-guided biopsy, and endoscopic retrograde cholangiopancreatography. Pancreatic cancer continues to have one of the lowest percentages of histologically confirmed cases among major tumors due to the organ's inconvenient location and the morbidity associated with biopsy [3]. The condition known as pancreatic adenocarcinoma is devastating. Occult metastases are frequently found after laparotomy, and it is regrettably difficult to identify which individuals have localized illness. Accordingly, only 10% of patients can have curative resection of pancreatic adenocarcinoma, and resection margin-positive pancreatic tumors are linked to a poor prognosis [3, 6].

Pancreatic adenocarcinoma can only be cured by removing the entire tumor and leaving no disease behind [7]. For patients with pancreatic adenocarcinoma, a preoperative evaluation of the likelihood of total resection is crucial because accurate estimation leads to fewer needless procedures that do not improve the patients' chances of survival. Currently, computed tomography (CT) is the preferred examination for staging pancreatic cancer. Thin-cut, bolus-contrast, triple phase helical CT shows an accuracy of about 100% in predicting inoperability, but only 75% to 80% un determining resectability [8-10]. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) are the two most researched tumor markers that have been assessed in the diagnosis and prognosis of patients with pancreatic adenocarcinoma [11-15]. However, little is known regarding the relationship between these tumor markers' levels and whether individuals with pancreatic adenocarcinoma have metastases or locally progressed disease [15]. Finding the usefulness of serum tumor markers CA 19-9 and CEA in assessing the resectability of pancreatic cancer was the aim of the current investigation.

II. Methodology

The cross-sectional Observational study was conducted in the Department of Surgery, BSMMU, Dhaka from Jan 2014 to Jan 2016 over a period of 24 months. A total of 108 patients with diagnosed cases of pancreatic cancer admitted in the hospital for treatment were included in this study. Purposive sampling was done according to the availability of the patients who fulfilled the selection criteria. **Data Collection and Processing:** After taking consent and matching eligibility criteria, data were collected from patients on variables of interest using the predesigned structured questionnaire by interview, observation. To collect data, face to face interview has been carried out with a standardized semi-structured questionnaire. Alongside, the medical records of the patients have been reviewed. Data regarding sociodemographic background, diabetic and smoking status has been collected and recorded. Collected data were edited and Statistical analyses of the results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Science. Frequency and percentages have been depicted for qualitative data and mean and standard deviation has been calculated for quantitative data.

III. Result

This observational cross-sectional study was conducted in the Department of Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. This study was conducted a total 108 patients were enrolled in this study. Patients diagnosed both sexes were selected as study population.

Table I: Distribution of the patients according to age (n = 108)

Age group	Frequency	%
<40	6	5.56
40-50	10	9.26
50-60	28	25.93
>60	64	59.26
Total	108	100.0
Mean±SD	59.24 ± 8.94 years	
Sex Distribution		
Male	68	62.96
Female	40	37.04

Table I shows that, 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 ± SD age was 59.24 years within

the range of 38-70. Among the patient 62.96% were male and 37.04% were female and male: female ratio was 1.70:1.

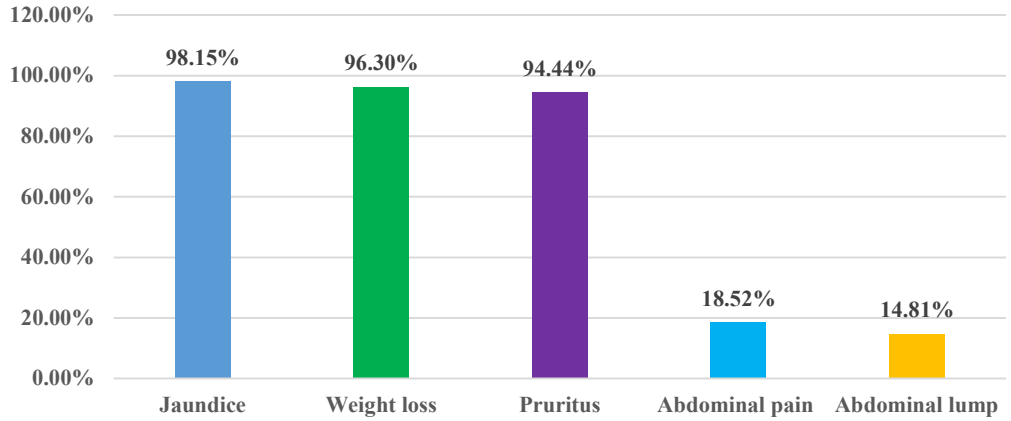

Figure II: Distribution of the patients according to sex (n=108)

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

Table II: Distribution of the patients according to character of tumour (n = 108)

Character of tumour	Variables	Frequency	Percent
Location of tumour	Pancreeatic head & neck	106	98.15
	Body	2	1.85
Size in cm	≤2 cm	62	57.41
	>2 cm	46	42.59
Local LN involvement	Present	4	3.70
	Absent	104	96.30
Vascular involvement	Present	2	1.85
	Absent	106	98.15
Local spread	Present	6	5.56
	Absent	102	94.44

Table II shows that, 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 III: Distribution of the patients according to preoperative CA19-9 and CEA level (n=108)

CA 19-9 level (U/ml)	Frequency	%
≤150 U/ml	88	81.48
>150	20	18.52
CEA level (ng/ml)		
≤5.8	78	72.22
>5.8	30	27.78
Total	108	100.0

Table III Shows that, preoperative CA19-9 level of most of the patients (81.48%) had ≤150 u/ml and preoperative level of CEA of most of the patients (72.22%) had ≤5.8 ng/ml.

Table IV: Distribution of the patients according to operative findings (n = 108)

Group	Frequency	Percent
Resectable	90	83.33
Unresectable	18	16.67
Locally advanced	8	7.41
Distant metastasis	10	9.26

Table IV shows that, 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 V: Association of CA 19-9 and age, sex, clinical feature (n = 108)

Age (Years)	CA 19-9				P value	CEA				P value
	≤150 (n=88)		>150 (n=20)			≤5.8 (n=78)		>5.8 (n=30)		
	No	%	No	No		No	%	No	%	
<40	4	4.55	2	10.0	0.126	2	2.56	4	13.3	0.119
40-50	6	6.82	4	20.0		8	10.26	2	6.67	
50-60	24	27.27	4	20.0		20	25.64	8	26.7	
>60	54	61.36	10	50.0		48	61.108	16	53.3	
Sex										
Male	56	63.64	12	60.0	0.829	54	69.2	14	46.7	0.124
Female	32	36.36	8	40.0		24	30.8	16	53.3	
Clinical feature										
Jaundice	86	97.7	20	100.0	0.487	76	97.44	30	100	0.687
Pruritus	88	100	14	70.0	0.061	78	100.00	24	80	0.079
Abdominal pain	18	20.45	2	10.0	0.126	16	20.51	4	13.3	0.451
Abdominal lump	14	15.9	2	10.0	0.1082	12	15.38	4	13.3	0.586
Weight loss	86	97.7	18	90.0	0.563	64	94.87	30	100	0.675

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

Table VI: Association between CA 19-9 and resectability (n = 108)

	Resectability				P value
	Resectable (n=90)		Unresectable (n=18)		
CA 19-9	No	%	No	%	0.002
≤150	80	88.9	8	44.4	
>150	10	11.1	10	55.6	
CEA					
≤5.8	70	77.78	8	44.44	0.042
>5.8	20	22.22	10	55.56	

Table VII shows that, there is significant association (p value- 0.002) between CA 19-9 and resectability. Table also shows that, there is significant association (p value -0.042) between CEA and resectability.

Table VII: Validity test for CA 19-9 and CEA

Validity test	Percentage	95% CI
CA19		
Sensitivity	88.9	75.95% to 96.29%
Specificity	55.6	21-20% to 86.30%
PPV	90.91	82.71% to 95.44%
NPV	50	26.66 to 73.34%
Accuracy	83.33	70.71% to 92.08%
CEA		
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%

PPV= Positive predictive value, NPV= Negative predictive value, CI= Confidence interval

Table VII shows that, sensitivity was 88.9% and specificity was 55.6%. Table also shows that, sensitivity was 77.78% and specificity was 55.56%.

IV. Discussion

The study states that pancreatic head and neck accounted for the majority of the malignancies (98.15%), with the body following in second place (1.85%). According to a previous investigation, the head or neck accounts for 75% of pancreatic carcinomas, the torso for 15-20%, and the tail for 5-10%. [16] There was no significant association found between CA 19-9, CEA, age, sex, or clinical characteristics, supporting Aziz et al. and Olivie D et al. [17,18]

During the course of the research, the usefulness of tumor markers CA 19-9 and CEA in predicting the resectability of tumors was investigated. The majority of patients who had tumors that could be removed had CA 19-9 levels that were equal to or greater than 150 U/mL (81.48%) and CEA levels that were equal to or greater than 5.8 ng/mL (72.22%). This is in line with the findings that were reported by prior study that patients who had pancreatic cancer that was localized had much lower levels of CA 19-9 when compared to those who had locally progressed or metastatic illness. [16] Similar tendencies were noted by another study that the mean CA 19-9 levels in resectable cases were 68.8 U/mL, whereas the mean levels in unresectable cases were 622 U/mL. [19]

The characteristics of CA 19-9 and CEA, including their sensitivity, specificity, and predictive values, were investigated in this study. The sensitivity for CA 19-9 was 88.9%, the specificity was 55.6%, the PPV was 90.9%, and the NPV was 50%. On the other hand, the sensitivity for CEA was 77.78%, the specificity was 55.56%, the PPV was 89.74%, and the NPV would be 33.33%. These results are consistent with the findings of the prior research, which indicates that the sensitivity of CA 19-9 can range from 67% to 92% and the specificity can range from 68% to 92%. [20] Another study found that a cutoff value of >353.15 U/mL for CA 19-9 resulted in better sensitivity (93.1%) and specificity (78.5%). [21] On the other hand, Fujioka et al. found that a cutoff value of 157 U/mL resulted in sensitivity and specificity of 76% and 46%, respectively12. For CEA level, this study had 77.78% sensitivity, 55.56% specificity, 89.74% PPV, and 33.33% NPV. Thus, the study agrees with prior research13. Both markers, but especially CEA, have low and wide-ranging sensitivity (30-90%) for PDAC identification. CEA specificity is 25%–56%. [22-23]

With a cutoff of ≤150 U/mL, the area under the ROC curve (AUC) for CA 19-9 was 0.667, indicating a modest predictive value for resectability. Additionally, the sensitivity and specificity of the test reached their highest point at this threshold. At 0.403, the area under the curve (AUC) for CEA was smaller than that of CA 19-9, indicating that it has a limited predictive value. Research conducted in the past, has demonstrated that CA 19-9 has higher AUC values (0.892), which further substantiates its usefulness as a marker for assessing resectability. [17]

Limitations of the study

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

V. 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.

VI. 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.

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