Original article

Predictive value of CA 19-9 in patients with pancreatic tumours

Faiza Abrar[1], Adnan Riaz[1], Kaukab Sultana[2], Tariq Feroz Khawaja[3]

[1]Assistant Professor Biochemistry, SIMS, Lahore, [2]Head of Department, Biochemistry Department, SIMS, Lahore, [3]Head of Department, Biochemistry Department, Sahara Medical College, Narowal

Correspondence to: Dr. Faiza Abrar, Contact No. 0322-9434939

ABSTRACT

Background: Pancreatic carcinoma is a disease with high modality and has a high incidence of recurrence after surgical resection. The prognosis depends on early diagnosis and treatment. Numerous international studies have reported use of CA 19-9 in diagnosis of pancreatic cancer. We planned this study to validate role of CA 19-9 in our local population. The objective of this study is to correlate raised serum CA 19-9 levels in patients with pancreatic tumours to distinguish between benign and malignant pancreatic disease.

Subjects and methods: The present study is a validation study. Thirty-five patients with diagnosis of pancreatic tumor on radiological imaging were included after their informed consent. Data collection forms were filled, blood samples were taken and serum CA 19-9 was estimated by ELISA in Biochemistry department, SIMS. Histopathology samples were collected at time of surgical resection, sent to pathology departments of respective hospitals and histopathological reports collected. All data was collected and analysed by using descriptive method. The study was conducted in Biochemistry department of PGMI and SIMS, Lahore from May 2015 till June 2016.

Results: Out of 35 patients, nineteen (54.3%) were female and sixteen (45.7%) were male. Thirty [85.7%] patients were between third to seventh decades of their life. The mean age range around 47.28. Thirty-four patients had malignant tumor and 1 benign on histopathology. CA 19-9 was raised (>37 U/ml) in 33 out of 34 patients with malignant pathology. The patient with benign pathology had CA 19-9 level <37U/ml (the cut off value). Head of pancreas was the commonest site in 32 patients (65%) for tumour occurrence. Total 28 (82%) patients had adenocarcinoma as the histological type of pancreatic tumour. Cholangiocarcinoma in Periampullary region of pancreas was second in frequency, 4 patients (12%). CA 19-9 shows sensitivity of 97% and specificity of 100% to diagnose carcinoma of pancreas in patients with pancreatic tumour. CA 19-9 has 100% positive predictive value to diagnose benign tumour and 50% negative predictive value to diagnose malignant tumours.

Conclusion: Raised levels of CA 19-9 has an important role in diagnosis of patients with pancreatic tumour to differentiate between benign and malignant pathology.

Keywords:

Pancreatic tumour, CA 19-9, Sensitivity, Specificity

INTRODUCTION

Pancreatic cancer has poor prognosis and shows frequent recurrence after surgical resection because of its aggressive nature.[1] Pancreatectomy is the best treatment option for cure.[2] Lack of early accurate detection methods and its clinical similarity with certain benign diseases leads to detection of pancreatic cancer only at an advanced level.[3] Validation of malignant nature of tumour is an important analytical factor that influences the management of this disease[4].

Non-invasive imaging, endoscopic ultrasound and cytology are used for an accurate diagnosis. The disadvantage of these is cost, availability and proficiency required for an accurate elucidation[5]. Various biomarkers have been studied for diagnosis of pancreatic carcinoma. These are CA 19-9, CA 125, YKL-40, IL-6 and MIC 1. CA 19-9 levels were associated with higher sensitivity as compared with levels of others in regard to diagnosis of Pancreatic cancer[5]. CA 19-9 is a biomarker widely studied for diagnosis, prognosis and predictive implication of pancreatic cancer[6]. First described in 1979, as a tumour associated antigen[6]. CA 19-9 is a Monosialosyl Lewis antigen of Le blood group[7]. Generally 7% of population are Lewis negative. This leads to a large percentage of undetectable CA 19-9 despite tumour pathology[8].

Normal upper limit for CA 19-9 is taken as 37 U/ml[9]. Preoperatively CA 19-9 studies help predict pathological stage and resectability in pancreatic carcinoma patients. In non-resectable pathology CA 19-9 at time of diagnosis is a valuable prognostic factor[9]. Among non-invasive methodologies used to complement success of surgical procedure, biochemical markers are least expensive[3]. Analysis of this tumor marker should be recommended before other therapeutic and diagnostic

Conflict of interest: The authors declared no conflict of interest exist.

Citation: Abrar F, Riaz A, Sultana K, Khawaja TF. Predictive value of CA 19-9 in patients with pancreatic tumours. J Fatima Jinnah Medical Univ. 2020; 14(1): 45-48.

DOI: https://doi.org/10.37018/ubug4188

Table 1. Pathology distribution above and below age of 40 years

Age (years)	Tumour type				Total
	Benign	%	Malignant	%	
<40	0	0	11	32.35	11
>41	1	100	23	67.64	24
Total	1	100	34	100	35

procedures are used in case of suspected pancreatic carcinoma. Hence the strong association of CA 19-9 with pancreatic cancer mandates to find correlation of raised serum CA 19-9 levels in patients with pancreatic tumours to distinguish between benign and malignant disease.[6]

PATIENTS AND METHODS

A cross sectional comparative validation study was conducted at Biochemistry Department of Post Graduate Medical Institute and Services Institute of Medical Sciences, Lahore. The study was carried out from May 2015 to June 2016.

Nonprobability convenience sampling was used. Special Data collection form was filled from patients and on its basis inclusion and exclusion of patients in study was established. Inclusion criteria was both male and female patients with diagnosis of pancreatic tumour on radiological findings and patients above the age of 12 years. Exclusion criteria was patients unfit for surgery, patients below the age of 12 years, patients with other co morbidities of pancreatitis, hepatitis and cirrhosis and patients who refuse to be part of the study. All information was collected by filling data collection form at time of sampling in the respective surgical unit of various teaching hospitals of Lahore. Research protocol was approved from ethical and review committee of Post Graduate Medical Institute, Lahore.

Study included 35 patients after taking informed consent from them. Special data collection forms were used to collect information from the patients. Information collected included clinical history and demographic characteristics. Laboratory investigations included blood complete and liver function tests. Tissue samples were prepared, preserved in formalin by respective surgical unit after the operative procedure and was taken to pathology laboratory of respective hospital for histopathology report. Reports were used to establish benign or malignant nature of tumour. Reports were collected later on.

Blood sample for detection of CA 19-9 drawn from patient was taken to biochemistry laboratory. They were immediately centrifuged and serum stored at -30 ^{o}C in freezer of biochemistry laboratory, SIMS. The 35 samples were run together on ELISA machine and levels of CA 19-9 were estimated by commercially accessible Enzyme Linked Immunosorbent Assay (ELISA) kit by DiaMetra Company. The principal involves competitive binding between unknown antigen in test samples and known enzyme labelled antigen (conjugate) for limited antibody binding sites on micro well plate. An enzyme substrate was added after its washing and decanting step. Stop solution was added to terminate reaction. Absorbance was measured using microliter plate reader. The absorbance of sample is inversely proportional to amount of CA 19-9 antigen in sample. Series of standards were used to plot a standard curve. All the data collected was analysed by using SPSS version 22.

RESULTS

A total of 35 patients with diagnosis of tumour of pancreas, on radiological imaging were included in the study after informed consent. Out of these 19 (54%) patients were female and 16 (46%) were male. Mean age of patients was 47.28 years $\pm$ 31.51 [13-90] as shown in Fig 1. Thirty (85.7%) patients were between third to seventh decades of their life. CA 19-9 levels performed in patients ranged from 14.7 - 218.5 U/ml. CA 19-9 levels in male had mean value of 102 and that of female was 114 as shown in Table 1. Twenty-two patients (65%) had tumour in head of pancreas on radiological evidence. Periampullary tumour was the second commonest site (17%) for tumour occurrence Fig 2. Frequency distribution according to histological type on histopathology report of tumor showed that twenty eight (82%) patients had adenocarcinoma, four (12%) with cholangiocarcinoma, one (3%) neuroendocrine and one (3%) included giant cell and undifferentiated types.

Total 34 patients had malignant tumours. Out of 34 patients with malignant pathology one had CA 19-9 levels less than cut off value 37 mg/dl. One patient had benign pathology insulinoma and had CA 19-9 levels less than cut off value of 37 mg/dl as shown in Table 2.

The results analysis of this study showed that CA 19-9 has sensitivity of 97% and specificity of 100% to diagnose carcinoma of pancreas in patients with pancreatic tumour. CA 19-9 has 100% positive

Table 2. CA 19-9 levels in pancreatic tumour patients above and below the age of forty years

Age	Pathology	CA 19-9 levels							
		<37 mg/dl	Mean	38-100mg/dl	Mean	>100 mg/dl	Mean	Total	Mean
<40	Malignant	0		6	65.905	5	169.940	11	113.194
	Benign	0	0	0	0	0	0	0	0
>41	Malignant	1	14.78	12	81.281	10	149.99	23	108.250
	Benign	1	15.92					1	15.92

Table 3. CA 19-9 level in relation to benign and malignant tumour of pancreas

CA 19-9 level	Malignant	Benign	Total
CA 19-9 >37mg/dl	33	Nil	33
CA 19-9 <37mg/dl	01	01	02
Total	34	01	35
Diagnostic accuracy			
Sensitivity [Tp/Tp+Fn =33/34]		97%	
Specificity [Tn/Tn+Fp= 1/1]		100%	
Negative Predictive Value [Tn/Tn+Fn=1/2]		50%	
Positive Predictive Value]Tp/Tp+Fp= 33/33]		100%	

predictive value to diagnose benign tumour and 50% negative predictive value to diagnose malignant tumours as shown in Table 3.

DISCUSSION

Carcinoma pancreas is a hostile tumour with poor outcome and is on rise as well. It was the disease of elderly as shown in different studies around the world, however, observation and statistics of our study have shown different results. It is more prevalent in younger age group, which is alarming. The treatment outcome is dismal because of its late presentation and recurrence.[1]

In this study mean patient age is 47.28 years. Studies of Karren and colleagues have shown average age of 72 years in patients who presented with carcinoma of pancreas.[10] This is in contrast to this study findings. This study has shown that 54% of patients are younger than 50 years. Eleven patients are < 40 years of age. The youngest patient was 13 years of age. Only 23 percent patients in our study are more than 60 years of age. Study of Bobby and coauthors reviewed data and found 33 cases out of 576 of early onset pancreatic cancer less than 50 years of age which is around 5.7%.[11] The higher frequency of early onset pancreatic cancer in this study is of concern and should on its own account necessitate making an inquiry to identify the reasons for such pattern of tumour in our population.

This study has shown that pancreatic tumour is more frequent among females 54%. In literature carcinoma pancreas is more common in males as compared to females. However other studies have shown that 58% male patient had tumour. In this study overall female ratio was high as compared to male.[12] This change in pattern of disease is also alarming.

Head of pancreas (65%) was the commonest site of tumour followed by Periampullary (17%) and body of pancreas (15%). Adenocarcinoma (82%) was the commonest histopathology followed by Cholangiocarcinoma (12%) in this study. Study of Smith and colleagues has shown that adenocarcinoma is histopathology in 80% of the patients.[13] This study results are in line with most of the studies found in literature. Studies have shown that more than 95% of tumours arise from exocrine portion of the gland rest are from endocrine portion of the gland.[14,15] This study results are mirror image of the literature.

In this study the range of CA 19-9 was 14.7 - 218.53 with mean CA 19-9 levels of 107.2 (± 53.47) mg/dl, which is well within figures quoted in other studies.[15,16] The mean CA 19-9 level in male patients was 102.3 mg/dl (±51.27) and that of in female patients was 114.42 mg /dl (± 55.67). There is no statistical difference in mean values of CA 19-9 in both genders.

In this study out of 35 patients, 34 patients had proven carcinoma pancreas on histopathology and one had benign pancreatic tumour. Out of these 34 patients, 33 had elevated serum CA 19-9 more than cut of value of 37 u/ml and one patient had serum CA 19-9 levels less than 37u/ml. This study has shown 97% sensitivity of CA 19-9 to diagnose malignancy in pancreatic tumour with elevated levels above 37 U/ml. However elevated levels of CA 19-9 above 37 U/ml have 100% specificity to diagnose malignant pancreatic tumour. In study of Goonetilke and coauthors CA 19-9 was also considered the best serum marker to diagnose pancreatic carcinoma with sensitivity range of 70-90% and specificity close to 90%. The higher value of sensitivity and specificity of CA 19-9 in our study is because of our stringent inclusion

(patients with pancreatic tumour) and exclusion criteria. Hence this study proves that raised levels of CA 19-9 above 37 u/ml in patients with pancreatic tumour can predict carcinoma in these patients. The studies of Kim et al and Chang et al also support our results as sensitivity in them was 100% in both and specificity 98.5% and 92.8 respectively.

The positive predictive value of CA 19-9 in this study was found to be 100% in patients with pancreatic tumour. Tessler et al studied 150 patients who had pancreatic tumour with positive predictive value of 72.3% they were subjected to surgery without preoperative tissue diagnosis. Hence we also conclude that patients can be put to surgery without predisposing to tissue diagnosis with raised CA 19-9 levels above 37 u/ml.[17]

Finding of negative predictive value of CA 19-9 in this study was 50% which is far less in contrast to literature.[15] In addition the low prevalence of the pancreatic tumour and limited number of study size put questions on the generalizability of the results. Study of Safi and coauthors have suggested that elevated CA 19-9 levels should not be the only criteria to put patient on surgery. It should be supported by diagnostic modalities like CT scan, MRI and Endoscopic ultrasound to prevent false positive and false negative surgical exploration.[16] Hence, we also recommend that patients must undergo radiological survey with raised CA 19-9 above 37 u/ml to predict outcome of surgical exploration.

CONCLUSION

Measurement of serum CA 19-9 is helpful in differentiating benign from malignant tumours of pancreas. However, surgical resection cannot be done alone on high levels of CA 19-9. It should be supported with further appropriate diagnostic and staging investigations before a decision for surgery is made.

REFRENCES

1. Sugiura T, Uesaka K, Kanemoto H, Mizuno T, Sasaki K, Furukawa H, Matsunaga K, Maeda A. "Serum CA19-9 is a significant predictor among preoperative parameters for early recurrence after resection of pancreatic adenocarcinoma". J. gastrointest Surg. 2012. **16**: 077-985.
2. Butterini G, Stocken DD, Wente NM. Influence of resection margins and treatment on survival in patients with pancreatic cancer, meta-analysis of randomized control trial. Arch Surg. 2008**. 143**: 75-83.
3. Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. J of gastrointestinal oncology. 2012. *3*(2), p.105.
4. Tingting Y, Kevin A, Brian F, Lin L, Katie P. Enhanced discrimination of malignant from benign pancreatic disease by measuring the CA19-9. Antigen on specific protein carriers. Plos One. 2011. **6**: 12.
5. Xing H, Wang J, Wang Y, Tong M, Hu H, Huang C, Li D. Diagnostic value of CA 19-9 and carcinoembryonic antigen for pancreatic cancer: A meta-analysis. Gastroenterology Research and Practice. 2018. https://doi.org/10.1155/2018/870475. **10.**1155.
6. Boeck S, Haas M, Rudiger P, Kullmann F, Klose C, Brunce CJ, Wilkowski R, Stieber P, Holdenrieder S, Buchner H, Mansmann U, Heinemann V. Application of a time varying covariate model to the analysis of CA19-9 as serum biomarker in patients with advanced pancreatic cancer. Clin Cancer Res. 2010. **13**(3)37**.**
7. Itzkowitz S, Yuan M, Fukushi Y, Lee H, Shi Z, Jr V, Hakomori S, Kim Y. Immuno histochemical comparison of Le^a, Monosialosyl Le^a (CA 19-9), and Disialyl Le^a Antigens in Human Colorectal and Pancreatic Tissue. Cancer research.1988. **48**: 3834-3842.
8. Vestergaard EM, Hein Ho, Meyer H, Grunnet N, Jorgensen J, Wolf H, Orntoft TF. Reference values and biological variation for tumor marker CA19-9 in serum for different Lewis and genotyping in a Caucasian population. 1999. Clin Chem. **45:1**, 54-61.
9. Humphris J.L, Chang D.K, Johns A.L, Scarlett C.J, Pajic M, Jones M.D, Colvin EK, Naqrial A. The prognostic and predictive value of serum CA19. 9 in pancreatic cancer. Ann Oncol. 2012. **23**(7), pp.1713-1722.
10. Dickinson K, Gomez D, Lowe A, Gokhale J, Ausobsky J, Gulilliou P, Rahman S. Carcinoma of the body of pancreas in evolution: An aggressive disease affecting younger patient. JOP. 2007. 8(3):312-319.
11. Tingstedt B, Weitkamper C, Andersson R. A. Early onset pancreatic carcinoma: A controlled Trial. Ann Gastroenterol. 2011. 24, 206-212.
12. Chandrasegaram M, Chiam S, Chen J, Khalid A, Mittinty M, Neo E, Tan C, Dolan P, Brooke-Smith M, Kanhere H, Dolan P. Distribution and pathological features of pancreatic ampullary, biliary and duodenal cancers resected with pancreatico duodenectomy. World J surg Oncol. 2015. 13:85.
13. Kondo N, Murakami Y, Uemura K, Hayashidani Y, Sudo T, Hashimoto Y, Nakashima A, Sakahe R, Shigemoto N, Kato Y, Ohge H, Sueda T. Prognostic impact of perioperative serum CA 19-9 levels in patients with resectable pancreatic cancer. Ann surg oncol. 2010. 17 (9),2321-2329.
14. Bond SG, Banga N, Hammond TM, Imber CJ, Pancreatic Adenocarcinoma. BMJ. 2012. 344: 2476.
15. Ferrone CR, Finkelstein DM, Thayer SP. Perioperative CA 19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. J Clin Oncol, 2006; 24: 2897-902.
16. Safi F, Roscher R, Bittner R, Schenkluhn A, Dopfer HP, Beger HG. High sensitivity and specificity of CA 19-9 for pancreatic carcinoma in comparison to chronic pancreatitis, serological and immunohistochemical findings. Pancreas. 1987; 2:398-403.
17. You L, Ma L, Zhao WJ, Zhao YP, Dai MH. Emerging role of tumor markers and biochemistry in the preoperative invasive assessment of Intraductal papillary mucinous neoplasm of the pancreas. Clin Chim Acta. 2016. 15, 454: 89-93.