DISSERTATION ON PREDICTORS OF MALIGNANCY IN CHRONIC PANCREATITIS

This Dissertation is submitted to

The Tamilnadu Dr.M.G.R. Medical University, Chennai for partial fulfillment of requirement for the award of M.Ch.degree – branch VI in surgical Gastroenterology,

Govt.Stanley Medical College&Hospital,Chennai

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DECLARATION

I, **Dr.E.Selvakumar,** solemnly declare that dissertation titled,

" Predictors of malignancy in chronic pancreatitis " is the bonafide work done by me at Govt. Stanley Medical College and Hospital during the period August 2004 to February 2007 under the expert guidance and supervision of **Prof. R. Surendran,M.S.,M.N.A.M.S.,M.Ch. Head of the Department,** Department of Surgical Gastroenterology.

The dissertation is submitted to the **Tamil Nadu Dr. MGR Medical University** towards partial fulfillment of requirement for the award of M.Ch Degree (Branch VI) in Surgical Gastroenterology**.**

Place : Chennai

Date : 21.05.07 **Dr. E.Selvakumar**

CERTIFICATE

This is to certify that this dissertation entitled **"Predictors of malignancy in chronic pancreatitis"** is a bonafide original work of **Dr. E.Selvakumar** in partial fulfillment of the requirement for **M.Ch (Branch VI) Surgical Gastroenterology** examination of the Tamil Nadu Dr.MGR Medical University to be held in August 2007

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PREDICTORS OF MALIGNANCY IN CHRONIC PANCREATITIS

CONTENTS

INTRODUCTION:

Chronic pancreatitis is a condition characterised by irreversible destruction and fibrosis of the exocrine parenchyma, leading to exocrine pancreatic insufficiency and progressive endocrine failure leading to diabetes. Alcoholic chronic pancreatitis is the commonest type of chronic pancreatitis seen in the western world, while in the tropics there is a distinct non-alcoholic type of chronic pancreatitis of uncertain aetiology, which is far more common. Several names have been proposed for this type of chronic pancreatitis including tropical chronic pancreatitis (TCP), tropical calcific pancreatitis, juvenile pancreatitis syndrome, Afro-Asian pancreatitis, and fibrocalculous pancreatic diabetes.

TCP can be defined as a juvenile form of chronic calcific non-alcoholic pancreatitis prevalent almost exclusively in the developing countries of the tropical world. Some of its distinctive features are younger age at onset, presence of large intraductal calculi, an accelerated course of the disease leading the end points of diabetes and/or steatorrhoea, and a high susceptibility to pancreatic cancer.

Kini reported the first case of pancreatic calculi from India in 1937 and this was followed by reports of pancreatic calculi observed at postmortem from Vellore in southern India. However, it was after Geevarghese, one of the pioneers in the field, documented one of the largest series in the world from Kerala state in Southern India that TCP attracted international attention.

SPINK 1(Serine protease inhibitor, Kazal type 1) is a potent protease inhibitor and is considered to be a major protective mechanism in preventing inappropriate activation of pancreatic enzyme cascade by inhibiting up to 20% of trypsin activity.[1] Since the inhibitory molecule provides the first line of defence against premature activation of trypsinogen inside the pancreas, it has recently attracted a lot of attention as a possible cause of chronic pancreatitis. Recently an association of hereditary pancreatitis has been shown with the SPINK 1 gene.[1] The association between SPINK gene and TCP has now been reported by a number of groups [2-6].Since all the above studies on TCP and others on other forms of chronic pancreatitis have shown a strong association with this gene,[7] it is likely that this could be at least one of the genes predisposing to chronic pancreatitis in general and TCP in particular.

Surgeons frequently find pancreatic head mass when operating. The obvious difficulty is to make the correct preoperative differential diagnosis between chronic pancreatitis and pancreatic tumor. The first step is to reach a diagnosis, with some certainty, prior to the operation. The second step in the case of a tumor is the accurate staging and deciding whether or not it is resectable. On the one hand, time and cost must be considered; on the other hand, the therapy must be decided. Obtaining information about the characteristics of the pancreatic disease (nature, size, exact location) and establishing the tissue diagnosis preoperatively may simplify the decision to operate and the operation itself.

In the case of chronic pancreatitis, the aim of the operation is to eliminate pain and other symptoms, while in the case of cancer; the purpose is to remove the malignant tissue. In most patients, it is possible to identify the disease on the basis of previous examinations together with preoperative diagnostic techniques such as exploration, palpation and fine-needle aspiration biopsy.

Chronic pancreatic head mass should be operated upon with Beger's or Frey's procedure while pancreatic head tumors should be treated by means of head resection with the aim of preserving the pylorus or the Whipple procedure may be used. When the diagnosis is in doubt, a radical approach is thought to be best.

Differential Diagnosis

Frequently both chronic pancreatitis and pancreatic carcinoma may present with the same symptoms. In either condition, most patients are thin, and even emaciated, and may appear to have malignant disease, which should always be considered in the differential diagnosis. A variety of non-invasive and invasive diagnostic methods are available to differentiate pancreatic cancer from chronic pancreatitis, and, used in combination, they can accomplish these goals with considerable accuracy. Despite remarkable technical advances in diagnostic procedures within the last decade, there is more potential for misclassification of adenocarcinoma of the pancreas, than for any other type of cancer because of the difficulty of an accurate diagnosis. Major differential diagnoses are proximal duct dilation or pancreatic carcinoma that has developed from pre-existing chronic pancreatitis. The definitive diagnosis can be difficult or impossible, even when the pancreas is exposed at surgery. Direct biopsies are about 60% sensitive for malignancy. This difficulty is compounded by the facts that patients with chronic pancreatitis are at increased risk of developing pancreatic ductal adenocarcinoma and patients with pancreatic ductal adenocarcinoma often have focal areas of chronic pancreatitis.[1] Hence, the two key issues in the evaluation of focal pancreatic masses in the setting of chronic pancreatitis are the ability to differentiate between carcinoma and chronic pancreatitis mimicking carcinoma and the impact of this differentiation on subsequent surgical triage and management. So many patients with carcinoma of the

pancreas die because their disease is not detected until late in its course. Methods that can detect pancreatic neoplasms earlier, while still resectable, improve patient outcome.

Pancreatic Head Mass

There is a subgroup of these patients with pancreatic head mass, in whom the complexity of differential diagnosis is enhanced. The majority of pancreatic tumors (70%) are localized to the pancreatic head and chronic pancreatitis seems to prefer the head region as well thus causing pancreatic head mass. The largest portion of resectable pancreatic tumors is present in the pancreatic head. This expression is widespread in clinical practice but not so extensively present in the literature. It reflects a disparity involving two different diseases, chronic pancreatitis and carcinoma of the pancreas, with specific diagnostic and therapeutical aspects.

Chronic pancreatitis has been suggested as a risk factor for pancreatic carcinoma, and can mimic pancreatic carcinoma as well. In a larger series of patients who underwent resection for chronic pancreatitis, cancers were found in 4/64 cases[8] and 4/250 cases, [9] but the number of patients who underwent pancreatic head resection due to false positive tumor diagnosis is not known.

The management and prognosis in the case of chronic pancreatitis or carcinoma of mass in the pancreatic head region is different. The diagnosis is still problematic.

The aim of diagnostic efforts in the case of "head mass" is:

- To choose conservative therapeutic measures
- To determine interventional and surgical treatment
- To avoid the misdiagnosis either chronic pancreatitis or pancreatic cancer.

REVIEW OF LITERATURE

Evidence that chronic pancreatitis increases the risk of pancreatic cancer

The association between chronic pancreatitis and cancer has been confirmed in a number of epidemiological studies. During the 1980s, two small case-control studies noted an increased yet insignificant number of pancreatic cancers among patients with chronic pancreatitis .[10, 11] Between 1990 and 1993, three studies noted a small but significant increased risk of pancreatic cancer in patients with chronic pancreatitis .[12, 13, 14] In 1993, Lowenfels et al [15] published the results of the International Pancreatitis Study Group's multicenter historical cohort study of 2015 subjects with chronic pancreatitis. These subjects were recruited from clinical centers in six countries. A total of 56 cancers were identified among these patients during a mean follow-up of 7.4±6.2 years. For subjects with a minimum of 5 years of follow-up, the standardized incidence ratio was 14.4. The cumulative risk of pancreatic cancer in subjects with chronic pancreatitis for 10 and 20 years was 1.8% and 4.0%, respectively. Furthermore, the risk of pancreatic cancer was independent of the underlying cause of chronic pancreatitis. Thus, the risk of pancreatic cancer in patients with chronic pancreatitis appeared to far exceed any other known risk factor, including cigarette smoking (relative risk from 8 studies varied from 1.2 to 3.1 .[16] Subsequently, five additional studies demonstrated a significant risk of pancreatic cancer in patients with chronic pancreatitis.[17-21]

Evidence that tropical pancreatitis increases the risk of pancreatic cancer

The link between TP and pancreatic cancer is strong. The incidence of pancreatic cancer among adult patients with TP is striking, however. For example, in 1992 Augustine and Ramesh [22] reported 22 pancreatic cancers among 266 patients with TP over an 8-year period (8.3%). In this cohort, the risk was highest after age 40, and patients with TP often had features of dysplasia as well as cancer in resected pancreatic specimens. In 1994 Chari et al [17] reported that over a 4.5-year period 24 of 185 patients with TP died, and that 6 (25%) died of pancreatic cancer. The average age of onset was 45±7 years, and the relative risk compared with those without TP was 100. Other reports confirm these observations.[23] Thus, current evidence suggests that the risk of pancreatic cancer is very high in patients with long-standing TP.

Pathways to carcinogenesis

Development of pancreatic cancer in any individual requires a progressive series of genetic events typically occurring within pancreatic duct cells.[24, 25] The genetic events must alter a critical group of genes that have been broadly categorized as oncogenes, those that promote cell growth, and tumor suppressor genes that normally suppress cell growth and division. Mutations in the oncogene K-*ras* and in the tumor suppressor genes p53, p16, DPC4 have been detected in a majority of pancreatic tumors [24]. As the number of mutations accumulates in the cells progressing toward adenocarcinoma, the morphology acquires the characteristics of more aggressive tumors. However the exact sequence of mutation development, if necessary and the complete repertoire of critical mutations have yet to be discovered.[24-29]

Specific genes that are known to be mutated in ductal pancreatic adenocarcinoma can be divided into four groups based on the frequency with which they can be detected. The k-ras codon 12 and the p16 gene alterations are found in more than 90% of pancreatic cancers [30-33]. These mutations appear to occur early as they are often detected in preneoplastic lesions and may be found in patients with chronic pancreatitis [34-37]. The frequency of k-ras mutation is approximately 90% in all ductal pancreatic adenocarcinomas, and nearly 100% in typical ductal adenocarcinoma cancer [31, 32]. The p16 gene product is also frequently altered or lost through nucleotide deletions, mutations, and epigenetic alterations including methylation that alters gene expression[38]. The fact that the p16 and k-ras mutations occur early, and that they are in the overwhelming majority of tumors, suggests that these mutations are necessary but not sufficient for pancreatic cancer development.

A second group of genes in which mutations that occur in approximately 50% of those tumors examined include the p53 (50–75%) and DPC4 (55%) [39, 40]. The third group includes germline mutations, including those in the BRCA2 gene. Mutations in the BRCA2 gene occur in 7–10% of pancreatic cancer tumors [41]. A fourth group that includes a group of genes mutated in 5% or less of pancreatic tumors include the LKB1/STK11 and MKK4, the transforming growth factor-beta receptors I or II, and the retinoblastoma (RB1) genes. [42-45]

Carcinogenesis in chronic pancreatitis

As the pathway from normal ductal epithelium to pancreatic cancer becomes clear, we can begin to investigate the accelerated pathway from chronic pancreatitis to pancreatic cancer. The first question is whether cationic trypsinogen mutations or Cystic fibrosis transmembrane conductance regulator (CFTR) mutations represent key steps in the carcinogenesis pathway. The second question is whether chronic pancreatic inflammation per se promotes mutations and chromosomal deletions in known oncogenes.

At least two studies investigated chronic pancreatitis-associated mutations in the trypsinogen gene or CFTR gene in patients with apparently sporadic pancreatic cancer. Hengsler et al[46] analyzed genomic DNA for R122H mutations in the trypsinogen gene in pancreatic cancer samples from 34 patients and corresponding normal tissue from 28 of these individuals. No mutations were found. These data suggest that underlying trypsinogen gene mutations are uncommon in sporadic pancreatic cancers, and that trypsinogen R122H mutations are unlikely to be an important step in carcinogenesis. Malats et al [47] investigated the possibility that common CFTR mutations were a risk factor for sporadic pancreatic cancers. The incidence of deltaF508 mutation and the 5T allele variant was similar to controls, however. Again, the presence of these pancreatic disease-associated mutations is unlikely to

be an important step in pancreatic cancer development. Although these two studies have limitations in size and scope, they suggest that pancreatitis-associated genes are in themselves not important in sporadic carcinogenesis. The increased risk of pancreatic cancer is likely through a different mechanism.

Does chronic pancreatic inflammation per se facilitate development of key mutations or loss of chromosomal material? Substantial experimental data is becoming available, especially with respect to K-*ras* mutations. These mutations are generally not seen in normal pancreatic tissue and were thought to be specific for pancreatic cancer. Numerous reports suggest, however, that K-*ras* mutations are also common in chronic pancreatitis. [48, 49] Indeed, the K-*ras* in patients with chronic pancreatitis may be localized to areas of the duct with hyperplasia [50], suggesting focal progression toward carcinogenesis. Ductal dysplasia also appears to be increased in TP. Augustine and Ramesh[22] observed dysplasia in two of five resected specimens in patients with TP and cancer, whereas no dysplasia was seen in sporadic pancreatic cancers. Thus, focal areas of dysplasia, possibly harboring K-*ras* mutations, frequently arise within the context of chronic pancreatitis. The mechanism remains to be determined, however.

Future risk reduction and preventative strategies will likely include chemoprevention [51] or vaccination [52]. Researches in these areas are in their infancy, however, and no recommendations can yet be given.

DIABETES MELLITUS:

In the diagnosis of pancreatic head tumors, diabetes mellitus has received particular attention. This metabolic alteration is, in fact, associated with pancreatic cancer in more than 80% of cases, and in some it is characterized by reduced glucose tolerance and reduced insulin secretion[53-56]. There is a body of clinical and experimental data demonstrating that pancreatic-cancer-associated diabetes mellitus is due to the cancer itself. It has been suggested that soluble mediators released by pancreatic cancer cells play a role in interfering with the metabolism of glucose. Pancreatic-cancer-associated diabetes mellitus or glucose intolerance are improved, or cured, following surgical removal of the pancreatic mass[57]. This indicates that diabetes mellitus is not correlated with islet cell destruction, but to the presence of the tumor itself. Furthermore, in pancreatic cancer patients, the release of insulin after glucagon stimulation indicates a reduced beta cell function[58]. In agreement with this clinical data, the treatment of isolated islets of Langerhans with pancreatic cancer conditioned media dissociates insulin from amylin secretion[59]. Moreover, it has been demonstrated in clinical series that besides the presence of an altered function of Langerhans islets, there is also a peripheral insulin resistance[56, 57]. In this respect it has been demonstrated that pancreatic tumor extracts determine an altered glycogen synthesis in isolated rat muscles[60]. Furthermore, pancreatic cancer conditioned media can also induce fasting hyperglycaemia in SCID mice[61] as well as inhibiting hepatic glycolysis, thus possibly favouring the synthesis of tryglycerides [62,63]. It has been suggested that, one of the possible pancreatic cancer-associated diabetogenic products, soluble low molecular weight peptides play a role[63]. A further valuable laboratory tool in the diagnosis of pancreatic head mass might be the identification of this/these substances and their determination in serum or urine.

Evidence For the primary alteration of islet cells in pancreatic carcinogenesis:

The incidence of 72% of cases with islet cell alteration in the study by saruc et al correlates with the frequency of abnormal glucose metabolism in the pancreatic cancer patients[131]. Remarkably, most altered islet cells were in the vicinity of the cancer.Another noteworthy finding was the sign of altered islet cell differentiation, including the formation of intrainsular ductular structures and the expression of tumor- associated antigens CA 19-9, TAG-72, and/or DU-PAN-2 in islet cells and in intrainsular ductular cells.This finding indicates that islet cells have the ability to form abnormal cell populations in these patients.

Differences in the clinical expression of pancreatic cancer:

It is presently unclear why mosy pancreatic cancer patients (70-80%) develop Impaired glucose tolerance (IGT) or diabetes and the minority (20-30%) do not.Although IGT improves after surgery in many patients, in some it either does not or it gets worse.It is highly possible that either the altered cells producing the diabetogenic substances exist in the teletumoral area not removed by surgery or some hidden (metastatic) tumors are left behind, for example in the liver[131].

Differences in diabetes induced by chronic pancreatitis and pancreatic cancer:

Unlike the islets in pancreatic cancer patients, which are of normal size or enlarged, about 95% of the islets in primary chronic pancreatitis measure less than 100 micro meter in diameter.Diabetes improves after a 70% pancreatectomy in pancreatic cancer but not after resectional surgery in chronic pancreatitis.

Thus the occurrence of diabetes in pancreatic cancer cannot be explained by a single mechanism.The increase in peripheral insulin resistance, suppression of insulin secretion, impaired proinsulin conversion, altered fat and carbohydrate metabolism, presence of acute and chronic pancreatitis, medications for underlying disease, altered nutritional habits and many other factors seem to play important roles in the development and course of pancreatic cancer.

JAUNDICE:

The distal bile duct traverses the posterior aspect of the head of the pancreas before entering the duodenum in 60% to 80% of individuals. In the remainder, the duct lies in a groove between the pancreatic parenchyma and the duodenum. Therefore, several types of changes involving the pancreas may affect the distal CBD, including reversible edema, pseudocyst formation, and progressive, irreversible pancreatic fibrosis and calcification.[64]

Chronic pancreatitis accounts for 10% of all common bile duct (CBD) strictures. Such stenoses occur in up to 30% of all patients with chronic pancreatitis and up to 40% of patients undergoing ERCP with moderate to severe disease[65] .The highest incidence of biliary obstruction occurred in chronic pancreatitis patients who had an inflammatory mass in the head of pancreas. Izbicki et al and Beger et al reported a 60% and 56% incidence, respectively, in patients with chronic pancreatitis that predominantly involved the head of the gland and who underwent duodenum-preserving pancreas head resection. The majority of these strictures do not cause symptoms and are found incidentally at ERCP.[66, 67] However, they also may cause persistent obstructive jaundice, chronic abdominal pain, abnormalities in biochemical tests of liver function, recurrent cholangitis, secondary biliary cirrhosis, and choledocholithiasis.[68] Of the patients who present with symptoms, 70% will have changes

because of obstructive biliary disease as seen in a liver biopsy specimen.

Petrozza et al have reported different shapes of stricture segments including the smooth tapering variety, funnel shape, rat-tail, bent-knee, hourglass and complete obstruction. However, it has been reported that a particular radiologic configuration of CBD stricture is not helpful in predicting the nature of underlying process. Therefore it is very difficult to discount pancreatic cancer on the basis of radiologic findings, particularly in patients with tumor- forming pancreatitis.

Determining whether biliary obstruction is due to chronic pancreatitis or malignancy can be a very challenging clinical problem. This differentiation is of utmost importance since malignancy will require resection whereas a biliary drainage procedure would suffice for benign disease.

CT ABDOMEN:

Transabdominal ultrasonography of the pancreas is limited by different patient dependent restrictions (obesity, meteorism, etc.). Nowadays, CT is the most important, and sometimes, the initial imaging modality of the pancreas.

We can elevate the tumor detection rate and reliable assessment of resectability with the use special examination techniques such as spiral hydro-CT. The latter is a combination of pharmacological intestinal paralysis and water distension of the stomach and duodenum with specific reference to the tumor detection rate, differentiation of malignant versus benign tumors and assessment of tumor resectability.

Pancreatic tumours

The main question in cases with pancreatic head mass is the verification or the exclusion of malignancy which is often difficult.

A circumscribed mass is the primary, but not necessarily an early sign of ductal pancreatic adenocarcinoma. An increase in diameter and roughness of the contour of the pancreas are unreliable signs of malignancy. The masses contained a central zone of diminished attenuation in about 80% of the cases[69]. On unenhanced CT most tumors have the same density as normal pancreatic tissue and can easily be missed if the tumor is small and the contour of the gland is not deformed. With spiral CT and bolus contrast administration, the tumor-pancreas contrast is best seen during the early phase of pancreatic perfusion. The tumor as a hypodense lesion can be distinguished from the opacified pancreatic parenchyma. A cystic central portion can demonstrate necrosis or the hemorrhage in the tumor. The border between the pancreas and the retroperitoneal space and the surrounding organs is often indistinct[70].

The pancreatic duct and/or common bile dilatation is critically indicative of malignancy. After intravenous contrast enhancement, dilatation of the biliary tract becomes clearly visible and the contour of the pancreatic duct can be better evaluated [71, 72].

Reaction surrounding the tumor occasionally creates a fuzzy appearance of the tumor region mimicking pancreatitis. The high contrast of peripancreatic vessels on contrast-enhanced CT allows assessment of vascular encasement.

The secondary signs, such as enlarged lymph nodes, regional metastases, hepatic metastases, ascites confirm the diagnosis of malignancy.

In contrast to adenocarcinoma, the mass of *anaplastic carcinoma* show marked enhancement after contrast administration

Acinar cell carcinomas usually present as well demarcated tumors of low attenuation and minor or no enhancement after contrast administration.

MRCP:

The most sensitive diagnostic modality in suspected biliopancreatic diseases is endoscopic retrograde cholangiopancreatography (ERCP). However, the success rate of the examination mainly depends on the experience of the endoscopist, and does not exceed 95-98% even in the largest specialized centers. Previous operations (Billroth II, Roux-en-Y or biliary-enteric anatomy), duodenal stenosis, or duodenal diverticulum make cannulation of the ducts difficult or even impossible, and increase the risk of complications. If ERCP fails, intravenous (i.v) or percutaneous transhepatic cholangiography (PTC) is the alternative method. Since the diagnostic accuracy of i.v cholangiography is very low, it is no longer used. PTC is invasive, may be associated with severe complications, and can successfully be applied if the intrahepatic biliary tree is dilated. PTC and i.v cholangiography are both unable to visualize the pancreatic duct. There is clearly a need for a noninvasive, sensitive and specific diagnostic modality for patients with suspected biliopancreatic disease if ERCP fails. Magnetic resonance cholangiopancreatography (MRCP) is a new noninvasive diagnostic modality capable of producing high-quality images of the pancreatobiliary tree. It has been

emphasized that its sensitivity (81-100%), specificity (94-98%), positive (86-93%) and negative (94-98%) predictive values and diagnostic accuracy (94-97%) are as high as those of ERCP, which makes MRCP a promising alternative to diagnostic ERCP[73-77]. Moreover, MRCP has the following advantages over ERCP. It is noninvasive; there are no complication, no radiation, and no need for any contrast agent. It causes less discomfort for the patients, and can provide useful information on the parenchymatous organs in this region in combination with conventional cross-sectional MR sequences.

Patients who undergo ERCP need sedation. Another disadvantage is that it affords no information on extraductal lesions, and does not opacify the obstructed segment in the event of total duct obstruction. It was unsuccessful in 3-10% of the cases, even in the largest endoscopic centers.

When findings of chronic pancreatitis are identified in a patient without a prior history of chronic pancreatitis or of ethanol abuse, an obstructing lesion should be suspected. Pancreatic ductal adenocarcinoma is the usual cause of chronic obstructive pancreatitis and comprises 75% to 90% of all pancreatic carcinomas [78]. Differentiating adenocarcinoma from mass-forming chronic pancreatitis with MR imaging is sometimes difficult. Typically, the chronically inflamed pancreas will enhance more than will pancreatic tumors on immediate post-gadolinium images, particularly those tumors arising in the head. Unfortunately, the degree of enhancement cannot be used to reliably distinguish these entities because abundant fibrosis is seen in both chronic pancreatitis and carcinoma, accounting for their similar appearances [79].

MRCP may be helpful to aid in this differentiation, because chronic alcoholic pancreatitis, compared with chronic obstructive pancreatitis due to adenocarcinoma, is more frequently associated with an irregularly dilated duct with intraductal calcification [80]. The ratio of duct caliber to pancreatic gland width is higher in patients with carcinoma[81]. Also, the “duct-penetrating sign,” seen in 85% of chronic pancreatitis and in only 4% of patients with cancer, helps to distinguish an inflammatory pancreatic mass from pancreatic carcinoma. The “duct-penetrating sign” refers to a nonobstructed main pancreatic duct penetrating an inflammatory pancreatic mass, unlike its usual obstruction by pancreatic carcinoma.[82] Furthermore, MRCP can depict the classic “double duct sign” of pancreatic carcinoma (enlargement and noncommunication of the pancreatic and common bile ducts) and the imaging counterpart of Courvoisier's sign (an enlarged, nontender gallbladder caused by an obstructing tumor) [83]. A normal-sized pancreatic duct is present in up to 20% of patients with adenocarcinoma, however, and should not dissuade its diagnosis in the setting of common bile duct dilation.

These latter signs are useful when present, but MRCP (like ERCP) is thought to be a poor way to differentiate benign from malignant strictures. Because morphologic features of benign and malignant strictures overlap, ERCP may be the imaging modality of choice because of its ability to obtain a diagnostic sample with brush cytologic biopsy [84]; however, MRCP, including MR imaging pulse sequences, has a sensitivity of 84% for diagnosing pancreatic carcinoma, whereas the corresponding sensitivity for ERCP with brush cytology varies between 33% and 85% [79] . Adding MRCP to conventional T1-weighted and T2-weighted sequences improves specificity by depicting extraductal structures not seen with ERCP [85].

MRCP has certain drawbacks. Most importantly, it does not allow simultaneous therapeutic intervention. While ERCP offers a therapeutic option in the same session after the diagnosis is made (papillotomy, removal of choledocholithiasis, stenting of a biliary stricture, etc.), MRCP yields only the diagnosis. Clips, stents, pneumobilia, hemobilia and ascites might result in artifacts and impede interpretation of the MRCP image. Despite the new technological advances in MR imaging, its resolution has remained behind that of ERCP[86].

The combination of conventional MR imaging with MRCP and MR angiography could increase the accuracy in the diagnosis, the staging of pancreatic malignancies and the assessment of resectability[87-90]. With this combined MR imaging technique, the biliary tree and pancreatic duct with the surrounding vessels and parenchymatous organs could be depicted in one examination, which makes it cost-effective.

CA 19-9:

Several families of molecules have been studied as possible tumor markers, including oncofetal antigens (CEA and POA), pancreatic enzymes, blood group-related antigens and, more recently, oncogenes and tumor suppressor genes. Several studies indicate the value of circulating tumour marker evaluation as a simple, sensitive, and reliable test facilitating the differential diagnosis between chronic pancreatitis and cancer.[91-97] Blood group related antigens, CA 19-9 in particular, have the highest diagnostic efficacy in distinguishing between pancreatic cancer and chronic pancreatitis.

The sensitivity and the specificity of CA 19-9 in diagnosing pancreatic cancer range from 70 to 95% and 72 to 90% respectively. Although most pancreatic cancers cause an increase in serum CA 19-9 levels, this tumor marker does not approach 100%. This results from two main pathophysiological aspects: 1) since individuals with Lewis a-/b- status (7-10% of the general population) cannot synthesize sialyl Lewis a antigenic determinant, even if they have a large tumor they will have low circulating CA 19-9 levels; 2) the release of CA 19-9 antigen in cell culture media is correlated with the number of neoplastic cells in culture, and this phenomenon is reflected "in vivo" by the association between CA 19-9 levels and the tumor stage. The clinical effect of this is that CA 19-9 has a low sensitivity in the diagnosis of circumscribed tumors and when used for screening programs. Regarding specificity, the lack of absolute results is due to several factors: 1) tumors of non-pancreatic origin may cause an increase in CA 19-9 serum levels (biliary: sensitivity 55-79%; hepatocellular and cholangiocellular: sensitivity 22-51%; gastric; colorectal; ovarian; lung; breast and uterine); 2) benign diseases of the pancreo-biliary tree (chronic pancreatitis and obstructive jaundice) may also cause significant increases in serum CA 19-9. An altered hepatic function, whether caused by cancer or a benign disease, may give rise to increased serum CA 19-9 levels, due to its reduced molecular clearance, which occurs mainly through the hepatic metabolism[98].

CA 19-9 may also be useful in monitoring pancreatic cancer since it correlates closely with the clinical course of the disease after surgery and chemotherapy and/or radiotherapy. It reaches normal levels within 2 to 4 weeks after radical surgery: there is a transient decrease after successful palliative therapy and an increase before clinical relapse[99, 100].

To improve the effectiveness of serological diagnosis of patients with pancreatic carcinoma, different tumour markers have been assessed, including CEA, CA 242, CA 50, and CA 72-4.[91-94] However, the sensitivity and specificity of these markers appeared to be insufficient for differentiation of pancreatic carcinoma from chronic pancreatitis. In 1996, CAM 17-1[95] was described as a new useful diagnostic marker in pancreatic carcinoma. It showed sensitivity similar to that of CA 19-9 but higher specificity, giving only 10% false positive results in patients with chronic pancreatitis.

Tissue polypeptide specific antigen (TPS) is a different type of antigen that does not correlate with tumour mass but reflects tumour proliferative activity.[101] One study[96] revealed that elevated levels of TPS detected preoperatively 100% of patients with pancreatic carcinoma. The introduction of 200 U/l as a decision criterion for TPS level allowed an increase in the specificity of this marker to 98% and eliminated all but 2% of the false positive results in patients with chronic pancreatitis. Moreover, TPS is useful for detection of the early stages of clinical advancement of pancreatic carcinoma.

It seems that measurement of TPS, using 200 U/l as the cut off value, should facilitate more precise discrimination between the early stages of pancreatic carcinoma and chronic pancreatitis.

DOUBLE DUCT SIGN:

The double duct sign was more specifically defined as nodular, excentric, or rat-tailed encasement of the 2 ducts.[102, 103] Ralls et al.[102] examined the ERCP images from 49 patients with a stenosis of the common bile or main pancreatic duct without reference to clinical information. The double duct sign appeared in 4 of 8 cases of pancreatic carcinoma and in 15 of 41 patients with chronic pancreatitis. The investigators concluded that ERCP criteria alone are unreliable in differentiating pancreatitis from pancreatic cancer.

Shemesh et al.[104] compared 45 patients with chronic pancreatitis alone with 10 others who had coexisting pancreatic carcinoma. Histologic confirmation of malignant disease was obtained in all cases and of benign disease in 19 cases (42%) by laparotomy. All of the patients with cancer and 19 (42%) of those with pancreatitis were found to have a double duct sign. The length of the pancreatic duct stricture discriminated between benign and malignant disease in that all of the patients with cancer had strictures longer than 10 mm, whereas the length of strictures in the patients without cancer did not exceed 5 mm. The investigators concluded that ERCP is highly accurate in the diagnosis of pancreatic cancer even when there is coexisting pancreatitis. The results of this study, however, differ from those of Plumley et al.,[105] who found in the average even longer segments of the pancreatic duct in patients with benign disease.

When comparing these studies, one explanation for the different results is the lack of a uniform definition for the term *double duct sign*. If the criterion is only an abnormality of the ducts, there will be loss of specificity, because a number of benign diseases will be included, for instance, chronic inflammatory changes. Restricting the definition to adjacent stenoses or strictures of the ducts increases the specificity

In patients with a pancreatic mass or obstructive jaundice the strictly defined double duct sign on ERCP yields a specificity of around 85% in predicting the presence of pancreatic carcinoma. Even the combination of a pancreatic mass by CT or MRI and a double duct sign on ERCP is no proof of pancreatic cancer.

CYTOLOGY:

In general, the ductal cells seen in chronic pancreatitis are not easily confused with those of pancreatic ductal adenocarcinoma. The diagnosis of primary pancreatic carcinoma is made by the identification of typical cytomorphologic features, including eccentric nuclei and vacuoles in the cytoplasm.

However, a problem arises when rare groups of cells suspicious for pancreatic carcinoma are found. The lack of sufficient atypical cell groups makes an unequivocal diagnosis of pancreatic cancer difficult (low sensitivity). The quantity of atypical cells generally determines whether or not a diagnosis of pancreatic cancer is superimposed on chronic pancreatitis. This typically results from obtaining an inadequate specimen without glandular tissue. Further difficulties in cytologic interpretation result from the presence of pancreatic intraepithelial neoplasia (PanIN) and chronic inflammatory cells. PanIN represents a pancreatic cancer precursor lesion commonly found in chronic pancreatitis as well as in “normal” tissue associated with pancreatic cancer. Cytologic sampling of PanIN in the setting of chronic pancreatitis can result in a false-positive diagnosis because of the presence of ductal atypia.

Most cytopathologists have high diagnostic thresholds for the diagnosis of pancreatic ductal adenocarcinoma. This explains the high specificity for pancreatic cancer diagnosis in the absence of chronic pancreatitis. The sensitivity, however, is never 100%, and a review of false-negative diagnoses shows most to be caused by sampling error and rarely

because of interpretive results.[106] In one study of false-positive EUS-FNAs (rate of 5%), both patients had a final diagnosis of chronic pancreatitis, and the reasons given for the false-positive results were inadequate hypocellular specimen and misinterpretation of enlarged acinar cells as malignant.[107]

EUS:

Linear EUS coupled with color Doppler provides real-time US imaging during FNA.The impact of EUS-FNA in the management of pancreatic cancer continues to expand. The procedure is safe, with reported complication rates being less than 1%. [108]

EUS-FNA of the pancreas can be technically challenging in patients with Chronic Pancreatitis for two reasons: First, EUS images alone cannot reliably detect and differentiate malignant from inflammatory lesions, because adenocarcinoma and focal pancreatitis have a similar EUS appearance.[109, 110,111] Second, even when FNA is used in conjunction with EUS, cytologic evaluation of pancreatic tissue in the setting of chronic inflammation is very difficult, because the inflammatory infiltrate may obscure or simulate a pancreatic malignancy.[112,113] Recently, two European studies have attempted to address this issue.[114,115] In the first study, from Germany, by Brand et al,[114] the specificity of EUS to diagnose malignancy based on morphologic criteria was found to be as low as 53% in the setting of Chronic Pancreatitis. In the second study, also from Germany, by Fritsher-Ravens et al, [115] the sensitivity of EUS-FNA to diagnose malignancy in the setting of Chronic Pancreatitis was much lower when compared with patients with focal pancreatic lesions and a normal pancreas, 54% vs. 89%, respectively.

However, the sensitivity is much lower when compared with evaluations of other lesions by EUS-FNA, such as mediastinal masses (89%-96%). This decrease in sensitivity may be from the presence of underlying Chronic Pancreatitis that limits imaging and thereby interpretation of pancreatic masses.[110, 112, 113,] Even in patients with less advanced disease, difficulties in diagnosis may be caused by multiple hypoechoic foci in the pancreatic parenchyma that makes it difficult to decide on which area to puncture. In consequence, the needle may miss small-sized lesions. On the other hand, in advanced Chronic Pancreatitis, calcifications create an acoustic shadowing that may conceal a malignant mass.[112]. Several investigators have reported cases of false-negative biopsy results with EUS-FNA of pancreatic masses, mostly in patients with underlying Chronic Pancreatitis. [112,116, 117,]

Needle-track seeding has been a concern ever since a few cases were reported from use of the percutaneous route.[118, 119] Lesions in the head and the uncinate process of the pancreas are sampled transduodenally, the duodenum usually being included in the resection specimen in operable patients. A potential risk is only encountered while aspirating lesions in the body or tail of the pancreas via the transgastric approach.

The following limitations of EUS for the detection of pancreatic tumors have been found:

Despite the high accuracy of EUS for detection of pancreatic masses, careful review of published studies shows that EUS is not foolproof for detection of a pancreatic mass. Pancreatic tumors that were not visualized by EUS have been reported in the literature.[120, 121]

A pancreatic tumor may not appear as a pancreatic mass on EUS if there is underlying chronic pancreatitis or if the tumor has similar echogenicity as the rest of the pancreatic parenchyma.[120]

Technical factors, such as prior sphincterotomy or a stent in the biliary or pancreatic duct system, may create air artifacts limiting a EUS examination of the pancreatic head.

EUS by imaging alone is also unable to differentiate between a pancreatic neoplasm and focal pancreatitis. EUS-guided fine-needle aspiration (FNA) helps in some of these cases and is discussed later.

It has long been appreciated that not only is it more difficult to identify focal masses, let alone malignant ones, in the setting of chronic pancreatitis, but that the specificity and the sensitivity of EUS-FNA in this setting is inferior.[112, 122]

Table 1. Sensitivity for diagnosing pancreatic cancer in the setting of focal chronic pancreatitis

	Sensitivity (%)
CT/MRI	77
PET	88
EUS	63-76
EUS-guided FNA	54-74

Table 2. Reasons for false EUS diagnosis of pancreatic malignancy

The presence of a focal hypoechoic mass in the absence of diffuse evidence of chronic pancreatitis
Apparent signs of vascular involvement
Apparent extension of the mass into adjacent structures

Table 3. Tips for improving the yield of pancreatic mass EUS-guided FNA in the setting of chronic pancreatitis

More FNA passes; repeating the procedure
On-site cytology interpretation
Sampling of suspicious nonpancreatic lesions: lymph nodes, liver lesions
Use of EUS-core biopsy needles
Experienced pancreatic cytologist

PET:

Positron emission tomography (PET) with ^{18} fluoro-deoxyglucose (FDG) exploits increased glucose metabolism by malignant tumors. Increased glucose utilization can be demonstrated for most solid tumors, including pancreatic adenocarcinoma.[123] Cell membrane glucose transport proteins and intracellular hexokinase levels are high in tumors, leading to increased uptake and phosphorylation of glucose and FDG.[124, 125] The ^{18}FDG emits positrons that collide with electrons, creating two gamma rays at 180-degree angles. A ring detector reconstructs the point of origin to generate images. The ^{18} FDG has proven useful in imaging a variety of solid tumors, for both primary tumors and metastatic disease. Primary pancreatic tumors also can be diagnosed with FDG-PET scanning with high sensitivity.[126]PET scanning has sensitivity similar to that of EUS for the diagnosis of local pancreatic disease. The main additional value of PET scanning relates to the evaluation of suspected metastatic disease. PET scanning clarifies CT abnormalities seen in the liver.

Imdahl et al studied 48 patients with a histologic diagnosis of pancreatic cancer, chronic or acute pancreatitis, and normal controls with FDG-PET. The evaluators of the PET scans were blinded to the patient diagnosis. An SUV cutoff of 4.0 at 1.5 hours resulted in a 96% sensitivity and 100% specificity for pancreatic cancer, and a 100% sensitivity and 97% specificity for chronic pancreatitis. PET was not helpful in distinguishing acute pancreatitis

from cancer[127]. The markedly different values for the reported SUV cut-off points highlight some of the problems that need to be resolved before this becomes a routine clinical procedure. In essence, the SUVs chosen in these studies were descriptive rather than diagnostic.

In summary, helical CT, EUS, and PET are complementary techniques in the evaluation of pancreatic carcinoma. CT is a standard technique that yields important data about local and metastatic disease. EUS is more sensitive than CT for local disease and local vascular invasion, which determines resectability. FNA is possible at the time of staging. PET scanning offers the most additional information when CT findings raise a suspicion of or are ambiguous for metastatic disease.

AIM OF THE STUDY:

The aim of the study was to

A] Prospectively analyse the mass lesion arising in the background of chronic pancreatitis clinically, biochemically &radiologically.

B] To identify the predictors of malignancy in patients with chronic pancreatitis without a tissue diagnosis.

PATIENTS AND METHODS:

Between August 2004 to February 2007, 32 patients who presented with chronic pancreatitis and mass lesion to the Department of Surgical Gastroenterology, Government Stanley Hospital, Chennai were included for the study. Among these 10 were due to Alcoholic pancreatitis and 22 were due to Tropical calcific pancreatitis (TCP). Alcoholic chronic pancreatitis was defined as chronic pancreatitis associated with the consumption of greater than 50 units of alcohol per week for atleast 5 years. TCP was defined as non-alcoholic pancreatitis with features of younger age at onset, presence of large intraductal calculi, an accelerated course of the disease leading to the end points of diabetes and/or steatorrhoea.Detailed history was obtained from all patients.

The variables analysed from history included

-Abdominal pain (duration/sudden increase)

-Jaundice

-Significant weight loss (Loss of >10% body weight in 6 months)

-Persistent vomiting (due to Gastric outlet obstruction)

-Diabetes (recent onset/ sudden worsening)

-Steatorrhoea

-Family history.

The diagnostic work up included Serum Bilirubin, CA 19-9.All patients underwent Ultrasonogram (USG) Abdomen and Contrast enhanced computed tomography (CECT) Abdomen.

In CECT the parameters that were analysed:

A] Main pancreatic duct (MPD) size

B] Calcification – Distribution& Type (Chunky, Stippled)

C] Intrapancreatic cystic areas-Single/multiple

D] Common bile duct (CBD) size

MRCP was done in selected cases. All the cases of chronic pancreatitis were confirmed by either histological examination or by CT features of chronic pancreatitis (eg. Calcification). All the mass was subjected to either intra operative biopsy or preoperative USG guided FNAC to rule out malignancy.

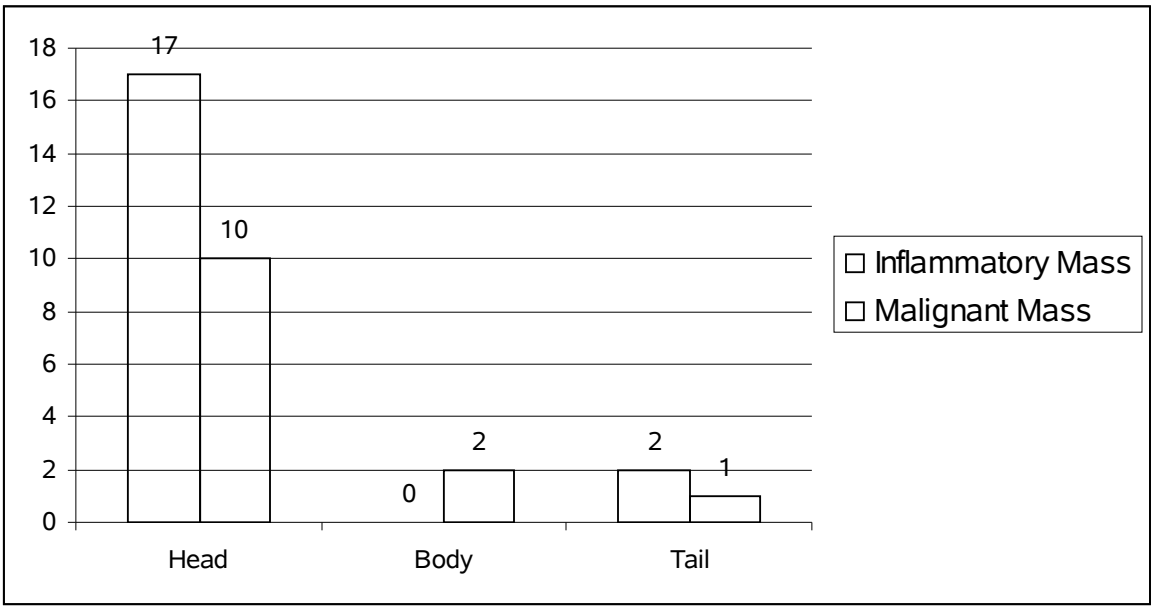
Follow up data were collected by periodic visits, telephonic interviews.

Statistical analysis:

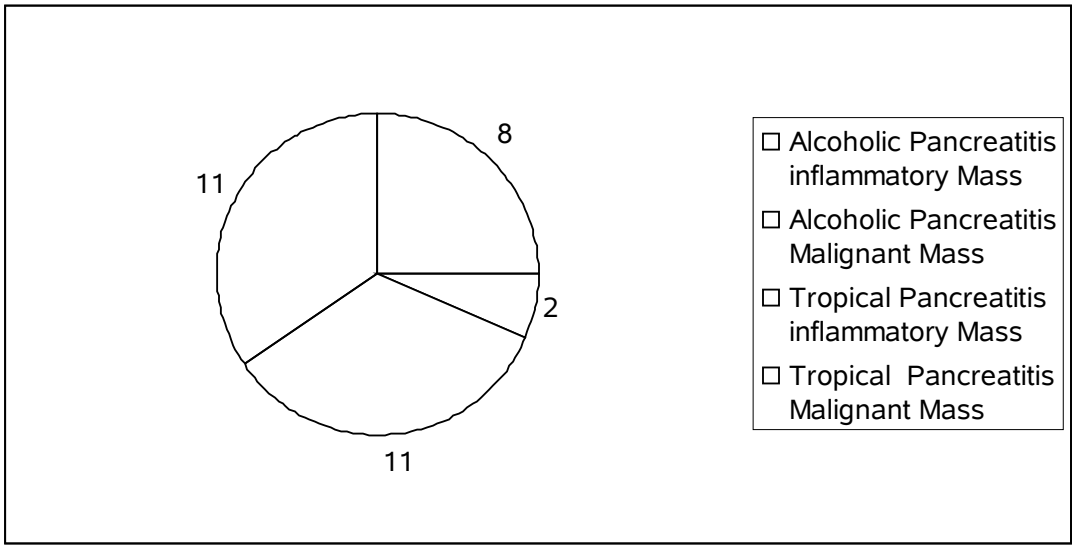
Simple descriptive statistics were used. Means and frequencies were calculated based on the numerous data points. The *P* values were provided to indicate statistical significance. Chi-square tests were used to compare categoric variables such as sex, and student t test was used to compare mean age, MPD size, CBD size, S.Bilirubin, CA 19-9 between the groups. Weight loss, Bilirubin, MPD size, CBD size, CA 19-9, Presence of intra parenchymal cystic areas in CECT were also evaluated for predictive purposes of final cancer diagnosis. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) were calculated using combination of variables with cut-offs of 6.5 g/dl for bilirubin, 114 U/ml for
CA 19-9, 13.5 mm for MPD size, 16 mm for CBD size. All statistical analyses were performed using SAS software.

RESULTS:

A total of 32 patients presented with pancreatic mass in the setting of chronic pancreatitis. The age of the patients ranged from 19-65 years. The mean age of patients with malignant mass was 48.77 years whereas in inflammatory mass it was 39.47 years.



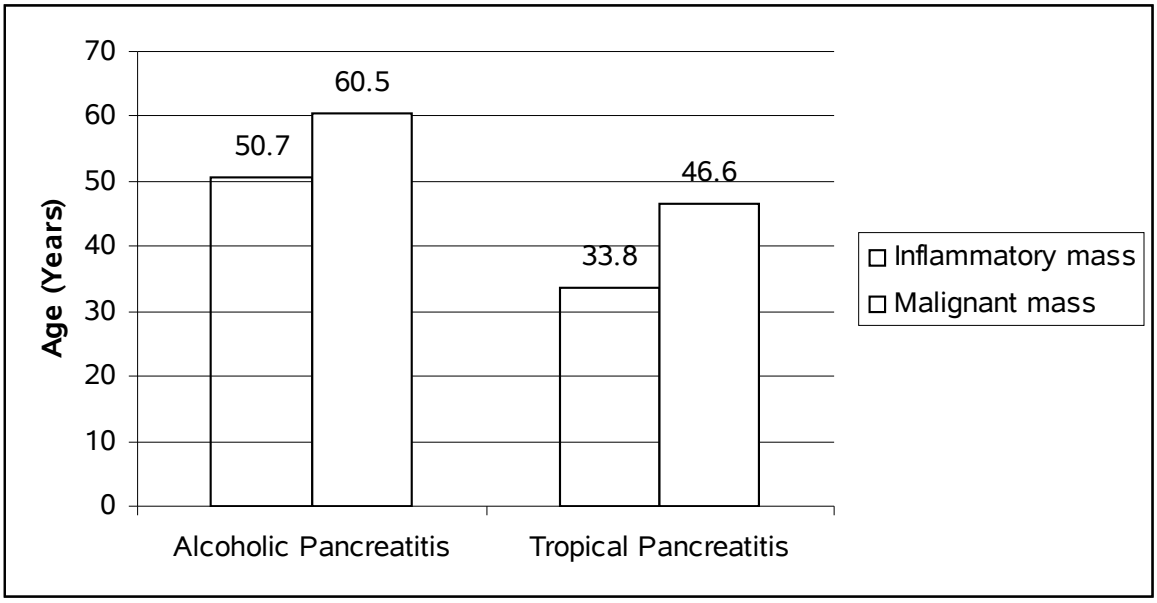
Bar Chart showing distribution of Mass



Pie Chart showing Etiological Classification of Mass

Comparison of age in chronic pancreatitis with inflammatory and malignant mass

Pancreatic mass	N	Mean age (yrs)	Std. Deviation	Student independent t-test
Malignant	13	48.77	10.473	**t= 1.95 p=0.06**
Inflammatory	19	39.47	14.785	Not significant



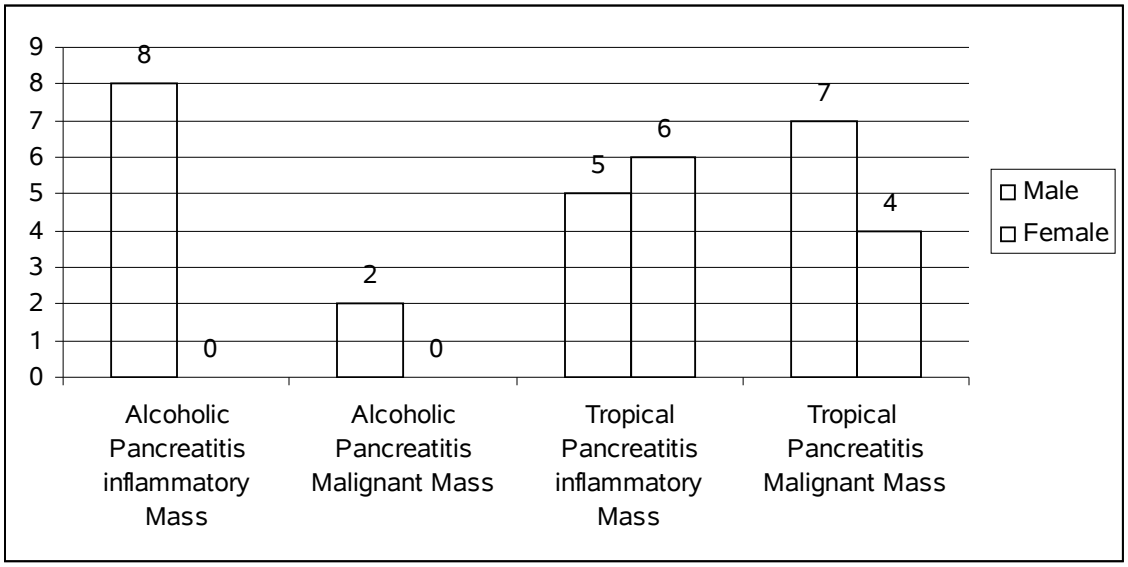
Bar chart showing age distribution

22 men and 10 women presented with pancreatic mass

Comparison of sex in chronic pancreatitis with inflammatory and malignant mass

		Pancreatic mass		
		Benign	Malignant	Total
Sex	Male	13	9	22
	Female	6	4	10
Total		19	13	32

$\chi 2=0.002$ P=0.96 not significant



Bar Chart showing sex distribution

All patients presented with abdominal pain. 3 patients with inflammatory mass and 9 patients with malignant mass had sudden worsening of pain, which was statistically significant. None of the patients with inflammatory mass had gastric outlet obstruction whereas 2 patients with malignant mass had gastric outlet obstruction.10 of 19 patients with inflammatory mass and 12 of 13 patients with malignant mass had Diabetes mellitus (DM). Among these sudden worsening of DM was noted in 2 patients with inflammatory mass and 4 patients with malignant mass. Significant weight loss was noted in 10 of 19 patients with inflammatory mass and 11 of 13 patients with malignant mass. Features of Gastric outlet obstruction, recent onset/sudden worsening of Diabetes mellitus and significant weight loss were not statistically significant between the two groups.

Comparison of clinical/radiological features in chronic pancreatitis with inflammatory and malignant mass

Variables		Pancreatic mass				Significance
		Benign		Malignant		
		N	%	N	%	
Jaundice	No	14	82.4%	1	10.0%	$\chi 2=11.23$
	Yes	3	17.6%	9	90.0%	P=0.001 Significant
Abd pain (Sudden worsening)	No	16	84.2%	4	30.8%	$\chi 2=9.41$ P=0.002
	Yes	3	15.8%	9	69.2%	Significant
Vomiting	No	19	100.0%	11	84.6%	$\chi 2=3.12$ P=0.08
	Yes			2	15.4%	Not significant
Wt loss	No	9	47.4%	2	15.4%	$\chi 2=3.50$ P=0.06
	Yes	10	52.6%	11	84.6%	Not significant
Diabetes.	No	9	47.4%	2	15.4%	$\chi 2=3.50$ P=0.06
	Yes	10	52.6%	11	84.6%	Not significant
Smoking	No	11	57.9%	6	46.2%	$\chi 2=0.43$ P=0.51
	Yes	8	42.1%	7	53.8%	Not significant
Intra pancreatic Cystic areas (CECT)	No	19	100.0%	6	46.2%	$\chi 2=13.09$ P=0.001 Significant
	Yes			7	53.8%	
Diabetes (Sudden worsening)	No	8	80.0%	6	54.5%	$\chi 2=1.53$ P=0.22
	Yes	2	20.0%	5	45.5%	Not significant

Serum bilirubin:

It was analysed only in patients with head mass (i.e., 27 pts). Of 17 patients with inflammatory head mass serum bilirubin was elevated only in 3 patients. It ranged from 2.1 mg% to 5.6 mg% with a mean of 3.26 mg%.In 2 of 3 patients with inflammatory head mass, jaundice subsided in 3 weeks whereas in none of the patients with malignant head mass jaundice subsided. Of 10 patients with malignant head mass serum bilirubin was elevated in 9 patients. It ranged from 3.2 to 24.2 mg% with a mean of 10.85 mg%. From the ROC

(Receiver operating characteristic) curve it can be noted that for an S.bilirubin value of 6.5 mg % the sensitivity was 63.6% and the specificity was 100% in predicting malignancy. When an S.Bilirubin value less than 6.5 mg% was chosen the sensitivity increased but specificity decreased. When a bilirubin value more than 6.5 mg% was chosen the sensitivity decreased. Hence 6.5 mg% was used in combination with other variables to predict malignancy.

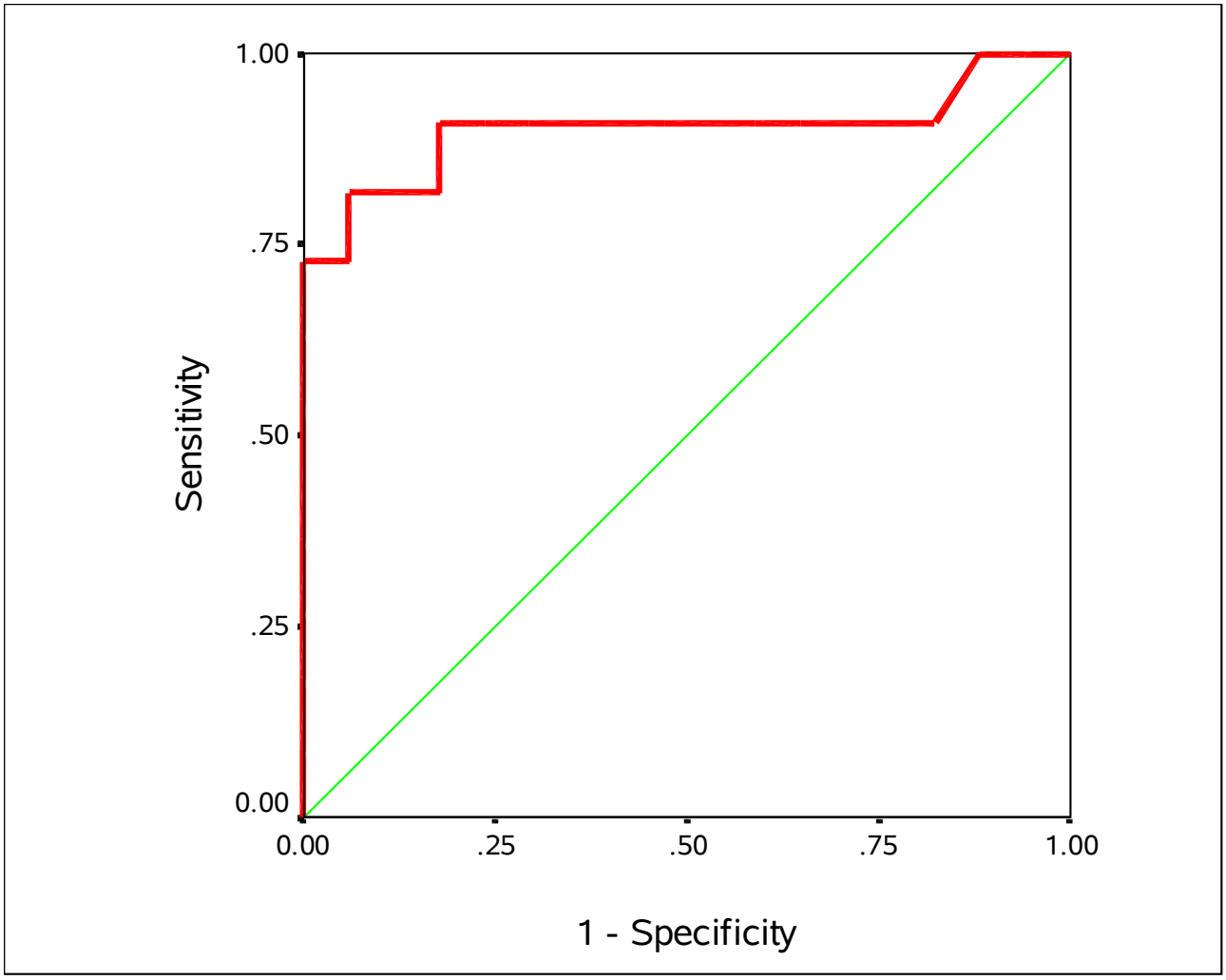


Figure: ROC (Receiver operating characteristic) curve for predicting malignancy by serum bilirubin

Test Result Variable(s): S.Bilirubin (mg%)

Positive if Greater Than or Equal To	Sensitivity	Specificity
.40	1.000	1.000
.65	1.000	.941
.75	1.000	.882
.85	.909	.824
.95	.909	.647
1.05	.909	.588
1.15	.909	.471
1.35	.909	.294
1.55	.909	.235
1.70	.909	.176
1.95	.818	.176
2.65	.818	.059
4.40	.727	.059
5.90	.727	.000
6.50	.636	.000
8.20	.545	.000
9.85	.364	.000
11.85	.273	.000
14.00	.182	.000
19.30	.091	.000
25.20	.000	.000

CA 19-9:

Since obstructive jaundice per se can elevate CA 19-9, subgroup analyses were done in patients with inflammatory mass.

Inflammatory mass	N	CA 19-9 U/ml (mean)
Without jaundice	16	24.98
With jaundice	3	75.43

In 3 patients with equivocal findings, serial changes in CA 19-9 level were monitored .It identified malignancy in 2 patients in whom there was more than 3 fold rise in CA19-9 value . Subgroup analyses were done in patients with malignant head mass

Malignant mass	N	CA 19-9 U/ml (mean)
Resectable	1	245
Locally advanced	3	97.26
Distant metastases	9	1170.74

CA 19-9 value of 114 U/ml was found to have a sensitivity of 61.5% and a specificity of 100% in predicting malignancy. Any value less than 114 U/ml had a lower specificity with a higher sensitivity and any value more than 114 U/ml had a lower sensitivity. Hence CA 19-9 value of 114 U/ml was used for predicting malignancy.

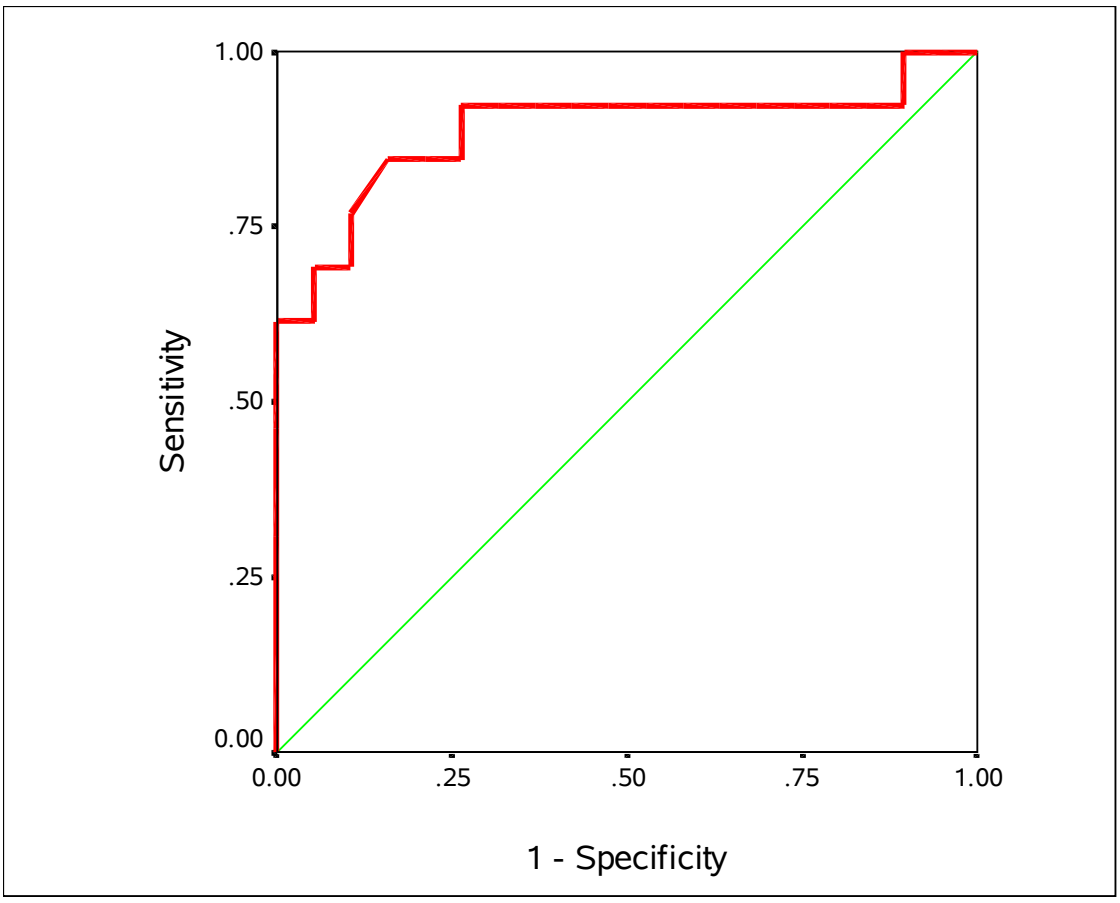


Figure: ROC curve for predicting malignancy by serum CA 19-9

Test Result Variable(s): CA 19-9 (U/ml)

Positive if Greater Than or Equal To	Sensitivity	Specificity
1.330	1.000	1.000
2.665	1.000	.947
3.400	1.000	.895
3.950	.923	.895
6.100	.923	.842
8.950	.923	.789
9.900	.923	.737
10.100	.923	.684
11.100	.923	.632
13.200	.923	.579
15.200	.923	.526
18.000	.923	.474
21.850	.923	.421
25.850	.923	.368
33.000	.923	.316
40.850	.923	.263
56.000	.846	.263
73.150	.846	.211
79.000	.846	.158
83.850	.769	.105
89.985	.692	.105
98.135	.692	.053
106.000	.615	.053
114.000	.615	.000
164.000	.538	.000
354.000	.462	.000
1184.500	.308	.000
1870.000	.000	.000

MPD size:

It was analysed by CECT and size ranged from 3 mm to 30 mm. MPD size was calculated proximal to the level of obstruction (mass) .The mean value was 7.89 mm in patients with inflammatory mass and 14.92 mm in patients with malignant mass. MPD size of 13.5 mm had a sensitivity if 53.8% and specificity of 100% in predicting malignancy.MPD size <13.5 mm had a low specificity and MPD size >13.5 mm had a low sensitivity.Hence MPD

size of 13.5 mm was chosen to predict malignancy.

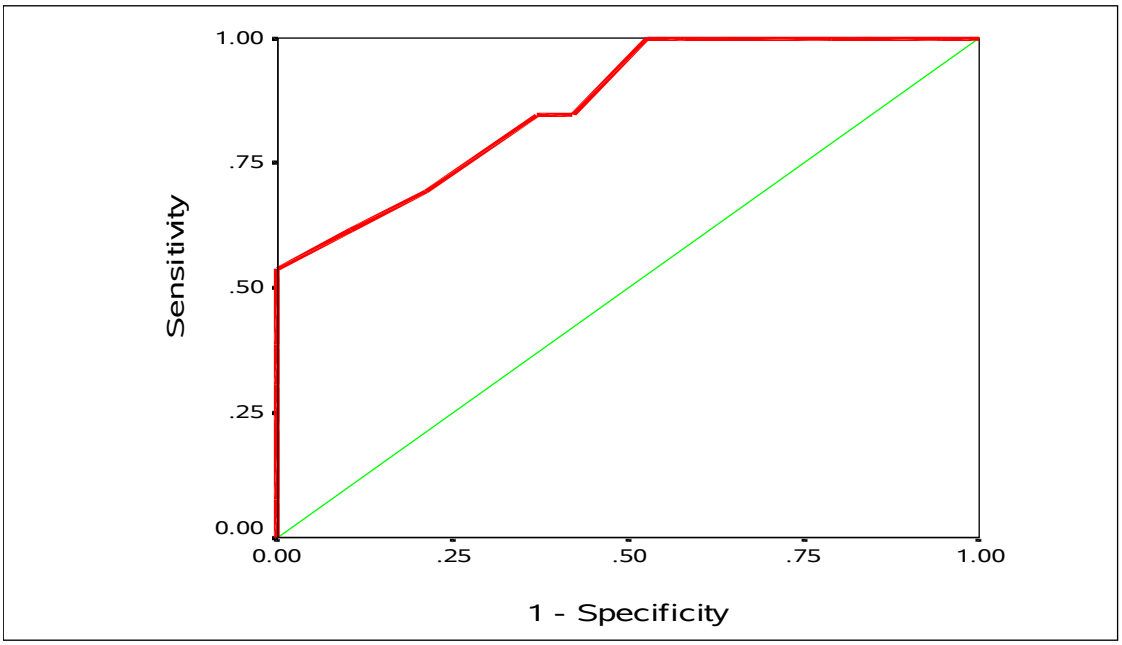


Figure: ROC curve for predicting malignancy by MPD size

Test Result Variable(s): MPD size (mm)

Positive if Greater Than or Equal To	Sensitivity	Specificity
2.00	1.000	1.000
4.00	1.000	.947
5.50	1.000	.789
6.50	1.000	.579
7.50	1.000	.526
8.50	.846	.421
9.50	.846	.368
10.50	.692	.211
11.50	.615	.105
13.50	.538	.000
15.50	.385	.000
17.50	.308	.000
19.50	.231	.000
25.00	.077	.000
31.00	.000	.000

CBD size:

It was analysed only in patients with head mass. In inflammatory head mass it ranged from 3 to 15 mm with a mean of 9.85 mm. In malignant head mass it ranged from 15 to 30 mm with a mean of 20.1 mm. CBD size of 16 mm had a sensitivity of 80% and a specificity of 100% in predicting malignancy. CBD size >16mm had a lower sensitivity and a value < 16 mm had a lower specificity. Hence CBD value of 16 mm was chosen to predict malignancy.

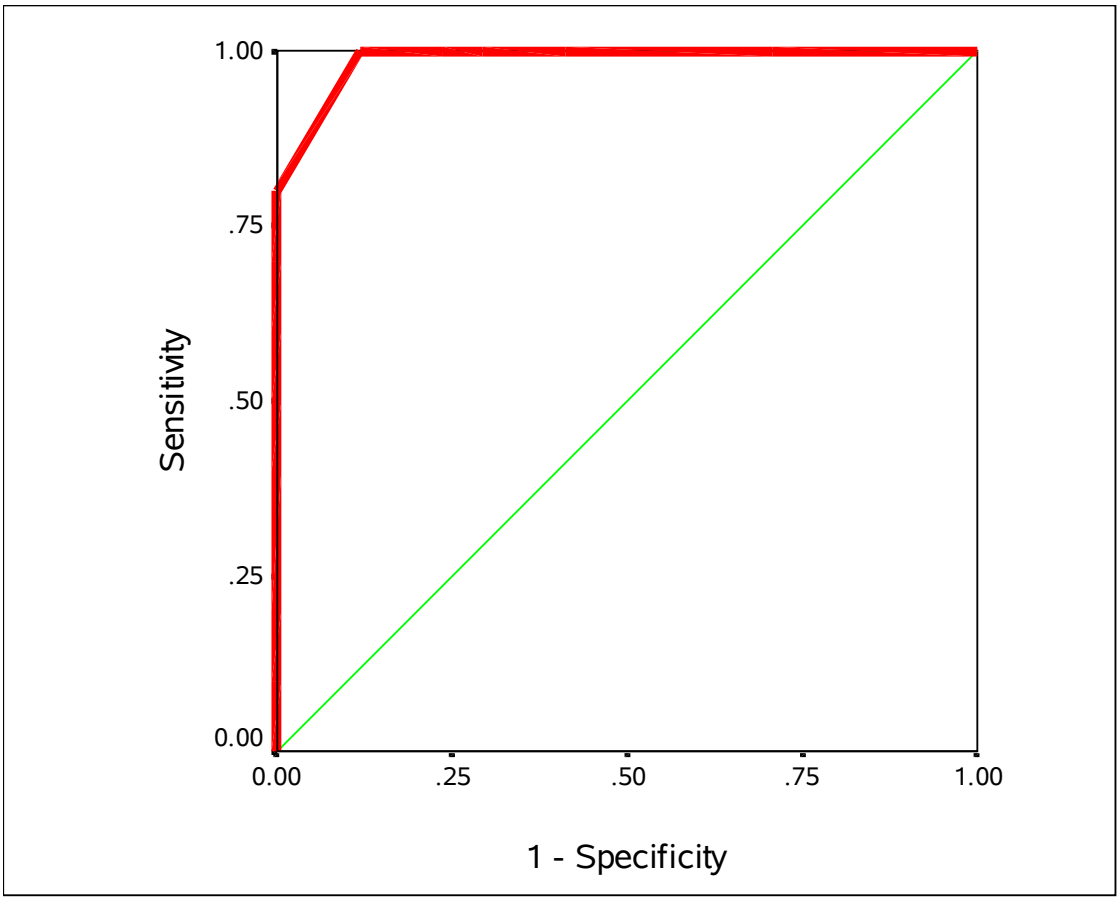


Figure: ROC curve for predicting malignancy by CBD Size

Test Result Variable(s): CBD Size (mm)

Positive if Greater Than or Equal To	Sensitivity	Specificity
3.00	1.000	1.000
4.50	1.000	.706
5.50	1.000	.412
9.50	1.000	.294
13.50	1.000	.235
14.50	1.000	.118
16.00	.800	.000
17.50	.700	.000
18.50	.600	.000
19.50	.500	.000
20.50	.400	.000
23.00	.200	.000
27.50	.100	.000
31.00	.000	.000

Comparison of radiological features/Lab values in chronic pancreatitis with inflammatory and malignant mass

	Pancreatic mass	N	Mean	Std. Deviation	Student independent t-test
S.Bilirubin (mg %)	Malignant	10	9.95	6.44	t= 4.14 p=0.002
	Benign	17	1.44	1.155	
CA 19-9 (U/ml)	Malignant	13	701.785	824.3491	t= 2.92 p=0.01
	Benign	19	32.958	34.0607	
MPD size (mm)	Malignant	13	14.92	6.224	t= 3.83 p=0.002
	Benign	19	7.89	2.706	
CBD Size (mm)	Malignant	10	20.10	4.60	t= 6.95 p=0.001
	Benign	17	7.53	4.50	

Predicting malignancy by combination of variables:

Head mass:

Variables	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**
Bil >6.5 g%, CA 19-9>114 U/ml MPD>13.5mm	92	100	100	94
Bil >6.5 g%, CA 19-9>114 U/ml MPD>13.5mm Multiple cystic areas (CECT)	92	100	100	94
Bil >6.5 g%, CA 19-9>114 U/ml MPD>13.5mm CBD>16mm	100	100	100	100

Body and Tail mass:

Variables	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**
CA 19-9>114 U/ml MPD>13.5mm Multiple cystic areas (CECT)	85	100	100	85

DISCUSSION:

The differential diagnosis of chronic pancreatitis and pancreatic carcinoma is difficult- clinically, surgically and even histologically. The specificity of pre operative imaging methods is relatively low.

The majority of pancreatic tumors (70%) are localized to the pancreatic head and chronic pancreatitis seems to prefer the head region as well thus causing pancreatic mass[128.] The reason being the expression of growth factor receptor c-erb B2, which belongs to the EGF receptor family, is positively correlated to the size of pancreatic head. In our study 89.4% of inflammatory mass and 76.9% of malignant mass were located in the pancreatic head. In patients with TCP, 81.8% of malignant mass was located in the head region. This is in contrast to the study by H.Ramesh et al in which only 22.2 % of malignant mass was located in the pancreatic head.[129]

The major etiology for malignant mass in our study was TCP (84.6%) and only 15.4% of malignant mass were due to Alcoholic pancreatitis.

Frequently both chronic pancreatitis and pancreatic carcinoma present with the same symptoms. In either condition, most patients are thin, and even emaciated, and may appear to have malignant disease.[130] Augustine et al stated that weight loss and sudden worsening of abdominal pain to be more common with malignancy[22]. In our study sudden worsening of abdominal pain was significantly associated with malignancy whereas there was no difference in weight loss between the two groups.

80% of pancreatic cancer patients have impaired glucose metabolism[131] .It has been proposed that amylin, a peptide with a molecular weight of 2030, or other yet unknown substances released from cancer cells are responsible for the impaired glucose tolerance. In our study there was no significant difference in recent onset/sudden worsening

of diabetes between the two groups.

Wapnick and associates have shown that total serum bilirubin was much higher with pancreatic malignancy being 18.5 mg% compared with 5.6 mg% in chronic pancreatitis. Perhaps more important than the absolute rise of bilirubin was the pattern of elevation. In patients with malignancy, bilirubin rose progressively until the biliary tree was decompressed, while with chronic pancreatitis, bilirubin rose to an apex and then fell as the attack subsided. They concluded that the course of the bilirubin during the first 7-10 days of hospitalization was the single most accurate test distinguishing carcinoma from pancreatitis[132]. Frey and coworkers found that serum bilirubin was seldom higher than 10 mg% in chronic pancreatitis and usually diminished within 7-10 days as the inflammatory exacerbation subsides[133].
In our study only 3 of 17 patients with inflammatory head mass (17.6%) presented with jaundice. Among the 3 patients jaundice subsided in 2 patients in 3 weeks.90% of patients with malignant head mass presented with jaundice. The mean S.bilirubin value was 3.26 g% in inflammatory head mass and 10.85 mg% in malignant head mass.

The usefulness of serial changes in serum CA19-9 levels in the diagnosis of pancreatic cancer has been emphasized by Tanaka et al[134].They concluded that close follow-up with various diagnostic modalities may be required for patients whose serum CA 19-9 levels increase to more than two fold the initial level,because such patients are highly suspected of having pancreatic cancer.In our study,3 patients with equivocal findings had serial changes in CA 19-9 levels monitored.There was more than 3 fold rise in 2 patients which helped in identifying malignancy.

The “duct-penetrating sign,” seen in 85% of chronic pancreatitis and in only 4% of patients with cancer, helps to distinguish an inflammatory pancreatic mass from pancreatic carcinoma. It refers to a nonobstructed MPD penetrating an inflammatory pancreatic mass, unlike its usual obstruction by pancreatic carcinoma.[82] Hence, gross dilatation of MPD occurs

proximal to obstruction in malignancy. In our study gross dilatation of MPD (>13.5 mm) was more common with malignancy and predicted malignancy with a sensitivity of 53.8% and a specificity of 100%.

Different variables were used in combination to predict malignancy without a tissue diagnosis.S.Bilirubin> 6.5 mg%, CA 19-9>114 U/ml, MPD>13.5 mm, CBD>16 mm was found to have a sensitivity, specificity, PPV&NPV of 100% in chronic pancreatitis with head mass. In patients with body or tail mass multiple intrapancreatic cystic lesions in CECT was included whereas S.Bilirubin and CBD size was excluded. CA 19-9>114 U/ml, MPD>13.5 mm& multiple cystic lesions predicted malignancy with a specificity&PPV of 100%, sensitivity &NPV of 85%.

Though pancreaticoduodenectomy has been described as the procedure of choice in patients with chronic pancreatitis with suspected malignancy most of the evidence comes from the western literature where alcohol is the common etiology. In the Indian scenario, Where TCP is very common pancreaticoduodenectomy is associated with considerable postoperative morbidity because TCP patients do nutrionally very poor with frequent hospitalization following pancreaticoduodenectomy. Hence preoperative diagnosis of malignancy has to be made with certainity. In this setting our model for predicting malignancy may be of considerable value.

Strength of the study:

a) Ability to suggest predictive factors to aid in the differentiation of benign and malignant disease without a tissue diagnosis.

b) The variables like S.Bilirubin, MPD size, CBD size, multiple intrapancreatic cystic lesions are unlikely to be influenced by the presence of metastases. Hence it is applicable to patients with operable tumors.

c) No study has been reported in the international literature of predicting malignancy in chronic pancreatitis with mass lesion using a combination of variables.

The limitation of the study is the small sample size.

FUTURE DEVELOPMENTS:

The genes most frequently found to be altered in patients with pancreatic adenocarcinoma are K-*ras*, p53, p16 and they are deleted in pancreatic carcinoma-locus 4 (DPC4).

More than 90% of pancreatic tumors bear codon 12 K-*ras* point mutations. This is the highest frequency to be reported for any tumor type. Such mutations have been observed in the early phases of pancreatic carcinogenesis, determining the synthesis of an altered p21 protein. Normal p21 shifts from an active (bound to GTP) to an inactive (bound to GDP) state via its intrinsic GTPase activity and via its sensitivity to the activity of GTPase activating protein (GAP). The transformed p21 becomes insensitive to GAP, thus leading this protein to a constitutive and permanent activation stimulating cell growth. Another gene frequently altered in pancreatic cancer is p16 (homozygously deleted in about 40% of pancreatic carcinomas), an inhibitor of cyclin-dependent kinase 4 (CDK4) that promotes the progression of the cell division cycle through the late G1 phase to G1/S [135]. The genetic alterations involving p16 may be the methylation of the promoter region (15% of cases), homozygous deletion (40%) or deletion accompanied by intragenic mutations in the other allele (40%). The tumor suppressor gene p53, which controls the cell cycle and induces apoptosis, is altered in 50 to 70% of different types of pancreatic cancer, and is usually inactivated by the loss of one allele accompanied by a intragenic mutation of the other allele [135, 136]. The gene DPC4 is altered in about 50% of pancreatic tumors, and encodes a protein belonging to the SMAD family, which is involved in the nuclear translocation of the inhibitory signal for cell growth starting from the interaction between transforming growth factor (TGF)

beta1 and its membrane receptor, TGF-beta1R [135, 137, 138].

The above-mentioned genes have been studied in tissue samples and some, K-*ras* in particular, have also been evaluated in biological samples (not only pancreatic tissue) in order to enable the identification, in easily obtained samples, of gene alterations indicating the presence of a pancreatic tumor. K-*ras* point mutations have been studied in duodenal juice, in stools and in serum samples [139, 140, 141]. Overall, its sensitivity in the detection of pancreatic tumors decreases when a search is made for K-*ras* in samples other than from the tumor tissue.

The detection of pancreatic cancer: sensitivity and overall specificity of K-*ras* point mutation identification in different samples.

	Sensitivity	Specificity
Tumor tissue	71-100%	
Duodenal juice	25-100%	
Stool	55%	
Serum	0-60%	
Overall		66-100%

In laboratory medicine, serum and/or stools should be satisfactory for use as samples for diagnostic purposes, since they are easily obtained, thus favouring patient compliance. However, the sensitivity of K-*ras* point mutation identification is unsatisfactory in diagnosing pancreatic cancer using these samples, perhaps partly due to methodological problems (presence of Taq polymerase inhibitors in faecal samples and low amounts of mutated K-*ras* in a wide background of normal serum K-*ras*). It cannot therefore as yet be used in clinical practice, although it may be routinely used in the future, in line with improvements in molecular biology techniques.

CONCLUSION:

In the appropriate clinical setting, a patient with sudden worsening of abdominal pain with S.Bilirubin > 6.5 mg%, CA 19-9>114 U/ml, MPD>13.5 mm, CBD>16 mm& multiple Intrapancreatic cystic lesions should be strongly considered to have malignancy.

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Abbreviations :-

1.	TCP	:	Tropical Calcific Pancreatitis
2.	USG	:	Ultrasound
3.	CECT	:	Contrast Enhanced Computed Tomography
4.	MRCP	:	Magnetic Resonance Cholangio Pancreatography
5.	ERCP	:	Endoscopic Retrograde Cholangio Pancreatography
6.	EUS	:	Endo Ultrasound
7.	EUS - FNA	:	Endo Ultrasound guided Fine Needle Aspiration
8.	PET	:	Positron Emission Tomography
9.	MPD	:	Main Pancreatic duct
10.	CBD	:	Common Bile Duct
11.	PPV	:	Positive Predictive Value
12.	NPV	:	Negative Predictive Value
13.	ROC	:	Receiver Operating Charecteristic
14.	SPINK	:	Serine Protease Inhibitor,Kazal type 1
15.	PTC	:	Percutaneous Transhepatic Cholangiography
16.	FDG	:	Fluoro – deoxy glucose.