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Original Article

Unresectable Carcinoma Pancreas: A Study on Clinical Presentations, Laboratory Investigations and Imagings

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Abstract

Background: At the time of diagnosis most of pancreatic cancer is in the advanced stage and curative resection becomes impossible. These inoperable diseases are labeled as "uresectable carcinonma pancreas." Accurate and early assessment is essential for such patients to gain a better outcome. **Objective:** This study was carried out to evaluate clinical presentations, laboratory investigations, histopathology and imaging modalities used to diagnose and label pancreatic carcinoma as unresectable. **Methods:** This retrospective study was carried out from July 2004 to June 2006 in BIRDEM Hospital, Dhaka. After careful scrutiny of clinical presentation, laboratory imaging studies, tissue diagnosis, tumor markers and operative findings it was seen that 50 patients (sample size $n = 50$) were labeled as unresectable carcinoma pancreas. Male patients were 28 ($n_1 = 28$) and female patients were 22 ($n_2 = 22$). Chi-square (χ^2) test was applied and P value <0.01 was considered as significant. **Result:** Most (72%) of the unresectable carcinoma pancreas patients presented with weight loss and obstructive jaundice. Laboratory study and ultrasonography (USG) were carried out in all patients ($n = 50$). Computerized tomography (CT) scan was done in 45 patients, magnetic resonance imaging (MRI) in 8 patients, endoscopic retrograde cholangiopancreatography (ERCP) in 20 patients and upper gastrointestinal (UGI) contrast was carried out in 10 patients. Preoperative biopsy was taken from 25 patients. Most of the patients presented with abnormal liver functions and raised tumor markers. Three patients had mild renal impairment. USG was able to diagnose 84% patients with pancreatic carcinoma and could delineate features of unresectibility in 69% patients. CT scan diagnosed 90% patients with pancreatic carcinoma and outlined the features of unresectibility in 84.44% patients. ERCP was able to diagnose 13 (65%) patients as carcinoma pancreas but failed to delineate the features of unresectibility in any of the patients. UGI contrast was able to diagnose only 10% unresectable pancreatic carcinoma. MRI was 100% accurate in delineating unresectable carcinoma pancreas. Preoperative tissue diagnosis was 88% sensitive in diagnosing pancreatic carcinoma. **Conclusion:** Presentation of unresectable carcinoma pancreas was obvious in most cases. Laboratory studies were of great help. Multimodal preoperative imagings were 87.5% accurate in diagnosing unresectable carcinoma pancreas. Tissue diagnosis was important as all the lesions were not pancreatic cancer.

Key words: Carcinoma pancreas; Unresectable; Presentation; Investigation.

INTRODUCTION

Cancer pancreas is the 4th leading cause of all cancer deaths. The peak incidence is in the 5th and 6th decades of life.[1] In clinical practice, pancreatic cancer is synonymous with pancreatic ductal adenocarcinoma which constitutes 90% of all the malignant tumor of the gland.[2] It arises most frequently from the pancreatic ducts and most commonly in the head of the pancreas. The incidence is 70% in the head and 30% in the body and tail of the pancreas.[3]

It is mandatory to have a cytological proof/confirmation before the lesion is labeled as pancreatic cancer because many benign conditions or treatable malignant condition (e.g., lymphoma) simulate the features of cancer. Cytological diagnosis is also essential for planning postoperative chemotherapy as newer chemotherapeutic agents are producing satisfactory response in some pancreatic cancers.[4]

Pancreatic cancer is diagnosed on the basis of clinical presentation, laboratory investigations including tumor markers, imaging studies and some endoscopic procedures. Initial symptoms and signs depend on site and extent of the lesion.[1]

Laboratory studies like elevated serum total bilirubin (S. bilirubin), alkaline phosphatase (AlkP) and alanine transaminase (ALT) helps in diagnosis. Coagulation profile like prothrombin time (PT) may be abnormal in patients with deep jaundice.[4]

Tumor markers are now available. Carbohydrate antigen 19-9 (CA 19-9), using upper limit (37 U/ml) is 80% accurate. Carcinoembryonic antigen (CEA) is another tumor marker.[5]

Imaging studies that are helpful in pancreatic carcinoma are ultrasonography (USG), endoscopic ultrasound (EUS),[6] surgeon performed USG,[7] computerized tomography (CT) scan,[1] contrast CT scan,[6] magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP).[4] Upper gastrointestinal (UGI) series provides information about the patency of the duodenum.[1] Minimally invasive procedures like endoscopic retrograde cholangiopancreatography (ERCP)[1] and laparoscopy[6] are of great help for both diagnosis and assessment of unresectability. A sequential approach consisting of CT scan as an initial test and EUS as a confirmatory technique seems to be the most reliable and cost minimizing strategy for pancreatic cancer imaging.[8]

Biopsy is the only way to make a definitive diagnosis of pancreatic cancer. Biopsies of the pancreas and bile duct can be performed in several ways as image guided fine needle aspiration cytology (FNAC), ERCP and biopsy, brush cytology and by laparoscopic or open surgical procedures.[6]

Findings that contraindicate curative resection are liver metastasis, celiac lymph node involvement, peritoneal implant, invasion of transverse colon and hepatic hilar lymph node involvement.[9] These are labeled as unresectable carcinoma pancreas (UCP).

In our country we still depend mostly on clinical findings, laboratory investigations and USG as only in few centers; CT scan, ERCP, MRI and MRCP are available. Due to the scarcity of specialized centers and investigations facilities, quite a considerable number of patients remain undiagnosed and untreated or diagnosed at the advanced stage of the disease or may be maltreated. Benign conditions like chronic pancreatitis may be treated as malignant condition of pancreas may even simulate with inoperable pancreatic cancer!

Present study was carried out in Bangladesh Institute for Research and Rehabilitation in Diabetic Endocrine and Metabolic Disorders (BIRDEM) hospital to evaluate current practice regarding diagnostic tools that have been used to diagnose pancreatic cancer and label them as unresectable.

METHODS

This retrospective study was carried out from July 2004 to June 2006 (study period 2 years) in the Department of Hepato Biliary Pancreatic Surgery in BIRDEM Hospital, Dhaka, Bangladesh. Hospital records were evaluated. Initially, 58 patients were recorded to have UCP. Among them, it had been decided not to carry out any surgical intervention in 10 cytologically proved pancreatic cancer patients as there was distant metastasis in four patients, locally advance disease in three patients and three patients had very poor general condition to withstand surgery. Laparotomy was carried out in the rest 48 patients with the plan to take open biopsy along with surgical palliation. Unresectable lesion was 43 (89.59%) and resectable lesion, 5 (10.41%). Among 43 unresectable lesions, histopathology reports showed carcinoma pancreas in 40 patients. The rest three patients were suffering from other lesions than pancreatic carcinoma. So, total 50 (10 + 40) patients had UCP (sample size $n = 50$). Male patients were 28 ($n_1 = 28$) and female patients were 22 ($n_2 = 22$). Record files of these patients were scrutinized further for clinical presentations, laboratory imaging studies, tissue diagnosis and tumor markers. Data were processed and analyzed. Chi-square (χ^2) test was applied to show significant difference between observed and expected value (qualitative), P value < 0.01 was considered as significant.

RESULT

Sex distribution: Among 50 patients, 28 (n_1) were male were and 22 (n_2) were female. Male–female ratio was 1.27:1.

Age distribution: As shown in Table 1, patients most commonly presented were between the ages of 56–60 years (16 patients, 32%). Least common age of presentation was between 45–50 years (2 patients, 4%). Nine patients (18%) presented between 51–55 years of age, 8 patients (16%) presented between 61–65 years of age, 7 patients (14%) presented between 66–70 years of age, 5 patients (10%) presented between 71–75 years of age and only 3 patients (6%) presented after 75 years of age. Overall common age of presentation was in between 51 to 70 years of age (80%). No patient was under 45 years of age.

Personal history: Male patients were mostly (71%) from rich family but female patients were mostly (68%) from poor socio-economic status. All the male patients (100%) were either smoker or used to take tobacco orally. Out of 22 female patients, 20 (91%) were habituated with tobacco ingestion. Only 2 male patients (7%) took alcohol whereas female patients never took alcohol. None of the cancer sufferer had positive family history (Table 2).

Presentation of the patients (Table 3): Patients were commonly presented with obstructive jaundice and weight loss (36 patients 72%). Next common modes of presentations were abdominal pain (27 patients 54%), palpable mass (21 patients 42%), fever (11 patients 22%), palpable gall bladder (7 patients 14%) and hepatomegaly (2 patients 04%). No patients were presented with bone pain, thrombophlebitis or cough.

Laboratory investigation (Table 4): It shows that most of the patients were presented with abnormal liver functions. S. bilirubin were raised in 36 patients (76%), AlkP in 30 patients (60%), ALT in 23 patients (46%) and PT were raised in 17 patients (34%). Tumor markers were also found to be raised. CA 19-9 was raised in 29 (58%) patients and CEA were raised in 32 (64%) patients. Three (6%) patients had mild renal impairment.

Imaging studies: According to Table 5: USG was used in all suspected cases (n =50). USG was able to diagnose 42 patients (84%) with pancreatic carcinoma. Out of 42 cancer patients, USG could delineate features of unresectibility in 29 patients (69%). It had missed 8 (16%) patients with pancreatic cancer and could not say about unresectibility in 7 (17%) patients.

Table 1: Age at first presentation

Age of presentation (Year)	Number (%)
<45	00 (00%)
45–50	02 (04%)
51–55	09 (18%)
56–60	16 (32%)
61–65	08 (16%)
66–70	07 (14%)
71–75	05 (10%)
>75	03 (06%)

Table 2: Personal history of the patients

Personal history	Male (%) n_1= 28	Female (%) n_2 = 22
Socioeconomic condition	Poor-08 (29%) Rich-20 (71%)	Poor-15 Rich-07
Tobacco >10 sticks/day or ingestion of tobacco >10 times/day. Duration of these habit >10 years	28 (100%)	20 (91%)
Alcohol	02 (7%)	00
Family history	00	00

Table 3: Clinical presentation of the patients

Clinical features	Number of patients with percentage (%)
Obstructive jaundice & weight loss	36 (72%)
Abdominal pain	27 (54%)
Palpable abdominal mass	21 (42%)
Fever	11 (22%)
Palpable gall bladder	07 (14%)
Hepatomegaly	02 (04%)

Table 4: Laboratory findings of the patients

Parameters	Number of patients (n = 50)	Raised (%)
S. bilirubin	50	38 (76%)
Alk.P	50	30 (60%)
ALT	50	23 (46%)
PT	50	17 (34%)
CA 19-9	50	29 (58%)
CEA	50	32 (64%)
S. creatinine	50	03 (06%)

CT scan was able to diagnose 45 patients (90%) with carcinoma pancreas. Out of 45 cancer patients, CT could delineate features of unresectibility in 38 (84.4%). It had missed 5 (10%) patients with pancreatic cancer and could not say about unresectibility in 7 (15.5%) patients.

MRI was used only in 8 patients suspected clinically as UCP where USG /CT scan had failed to give any clue about the diagnosis. MRI was 100% accurate to diagnose the entire patient as cancer pancreas. Out of 8 cancer patients MRI delineated the features of unresectibility in all patients (100%). It had not missed any patients who had pancreatic cancer.

ERCP were used in 20 patients of pancreatic cancer for diagnosis (in 20 patients), biopsy (in 12 patients) or therapeutic purpose (endoprosthesis in 9 patients). ERCP were able to diagnose 13 (65%) patients as cancer pancreas. Out of 13 cancer patients it failed to delineated the features of unresectibility in any of the patients (00%). ERCP had missed 7 (35%) patients suffering from pancreatic cancer.

UGI contrast had been carried out in 10 pancreatic cancer patients having UGI obstructive symptoms. It was able to diagnose only 1 (10%) pancreatic cancer having invasion of duodenal wall and labeled as UCP.

Preoperative biopsy: Preoperative biopsy was taken in 25 patients (50% of the total patients). ERCP and biopsy was the commonest (12 patients, 48%). Image assisted fine needle aspiration biopsy (FNAB) was taken from the lesion (10 biopsy 40%) and hepatic metastasis (3 biopsy 12%). Histopathological report showed pancreatic duct cell carcinoma in 19 (76%) patients, 1 (4%) patient had chronic pancreatitis. Biopsy report was inconclusive in 2 (8%) patients. All 3 (12%) biopsies from liver focus were metastatic pancreatic cancer.

DISCUSSION

The incidence of pancreatic cancer has back tripled over the last 40 years throughout the West.[2] The incidence was 10 per 100,000 per year. Unfortunately at the time of presentation 90%–95% patients were unsuitable for curative resection because of local spread, involvement of the mesenteric lymph nodes, hepatic or distant metastasis.[3]

According to Russel, pancreatic cancer affects male and female to the same degree.[3] Male to female ratio has been decreased in the recent years suggesting that more women are now being diagnosed with this cancer.[2] Present study showed that male (28 patients) are affected more than the female (22 patients) and male–female ratio was found to be 1.27:1. Yeo and Cameron[4] also noted male sex was more vulnerable to pancreatic cancer.[4]

Pancreatic cancer is a disease of aging.[3] The peak incidence is 5th and 6th decades.[1] Present study also supports it. Out of 50 studied patients (n = 50), 40 patients (80%) presented between 51–70 years age. Two patients (4%) were diagnosed between 45–50 years of age and it is the least common age of presentation. No patient was diagnosed before 45 years of age.

Male patients were mostly (71%) rich but 68% of the female patients were from poor socio-economic status (as per Statistical Pocket Book of Bangladesh 1997[10]). All the 28 male patients (100%) were either smoker or used to take tobacco. Out of 22 female patients, 20 (91%) were habituated with tobacco ingestion only. Smoking more than 10 sticks and tobacco ingestion more than 10 times in a day with duration more than 10 years were taken into consideration. Only 2 male patients (7%) took alcohol whereas female patients never took alcohol. No male or female patient had a family history of pancreatic cancer. Tobacco, in the form of either smoking or ingestion, is a strong risk factor for pancreatic cancer. Yeo and Cameron also pointed smoking as an etiological factor for pancreatic cancer.[4] Cancer research group, UK also found that cigarettes, cigars, pipes and chewing tobacco will increase pancreatic cancer risk. They noticed that although long-term drinking alcohol causes chronic pancreatitis, these type of chronic pancreatitis are less likely to increase pancreatic cancer risk than other type of pancreatitis. Sometimes pancreatic cancer is found to run in families. There may have some genetic link in up to 1 in 10 cases.[11]

Table 5: Findings of imaging studies

Investigation	Patients assessed	Diagnosed as pancreatic cancer with their percentage (%)	Unresectable tumor with their percentage (%)
USG	50	42 (84%)	29 (69%)
CT scan	50	45 (90%)	38 (84.44%)
MRI	08	08 (100%)	08 (100%)
ERCP	20	13 (65%)	00 (0%)
UGI contrast	10	01 (10%)	01 (10%)

From the present study it is revealed that the disease occurs more commonly in high socio-economic group in male and lower class in female. But Pukkala (1995) found no variation in the incidence of pancreatic cancers by social classes.[12]

Seventy-five percent (75%) of pancreatic cancer patient presented with weight loss, obstructive jaundice and upper abdominal pain.[1] In another study it was shown that jaundice was the commonest presentation (82% patients). Upper abdominal pain (53%) and weight loss (40%), were also common first symptoms.[13] In the present study, patients were most commonly presented with obstructive jaundice and weight loss (36 patients, 72%). Next common modes of presentations were abdominal pain (27 patients 54%), palpable abdominal mass (21 patients 42%), fever (11 patients 22%), palpable gall bladder (7 patients 54%) and hepatomegaly (2 patients 4%). No patient was presented with bone pain, cough or thrombophlebitis.

Laboratory findings

Most of the patients were presented with abnormal liver functions. S. bilirubin were raised in 38 patients (76%), AlkP in 30 patients (60%), ALT in 23 patients (46%) and PT were elevated in 17 patients (34%). In a prior study, it was noted that S. bilirubin was elevated in 95% paients and AlkP was raised in 97% patients which were much higher than our study.[13] In UCP patients with jaundice, PT can be elevated indicating biliary obstruction. Transaminases (ALT/AST) was also elevated.[14]

Tumor markers were also found to be raised. CA 19-9 was raised in 29 patients (58%) with a mean level 198 U/ml (normal level <37 U/ml). CEA were elevated in 32 (64%) patients with a mean level 9.8 ug/L (normal level <2.5 ug /L). Kilic et al.[15] showed that serum CA 19-9 is a useful marker for UCP. They found raised CA 19-9 level in 64% of UCP patients with a mean level 622 U/ml. According to them when cut-off point is set as 256.4 U/ml, specifity and sensitivity is 92.3% and 82.4%, respectively. They also commented CA 19-9 is superior in diagnosing pancreatic cancer.[15] High CEA were slightly but not significantly more frequent in patients with UCP.[16] Only 3 patients (06%) had mild renal impairment.

USG is safe, non-invasive and relatively brief. High frequency USG can outline the pancreas. It can also detect dilated bile duct, hepatic metastasis, ascites or coexistent gallstones.[6] Surgeon-performed USG provide rapid and accurate diagnosis of hepatobiliary pathology and may constitute to the management of hepatobiliary disease.[7] USG is 83% sensitive and 99% specific in diagnosing advanced pancreatic cancer.[17] In this study it is noted that USG is used in all suspected cases (n = 50) of pancreatic cancer. USG was able to diagnose 42 patients (84%) with pancreatic cancer. Out of 42 cancer patients USG could delineate features of unresectibility in 29 patients (69%). It had missed 8 (16%) patients with pancreatic cancer and could not say about resectibility in 13 (31%) patients.

CT scan was able to diagnose 45 patients (90%) with pancreatic cancer. Out of 45cancer patients CT could delineate features of unresectibility in 38 patients (84.44%). It had missed 5 (10%) patients with pancreatic cancer and could not say about unresectibility in 7 (15.56%) patients. CT scan has highest accuracy in assessing primary tumor (75%), locoregional extension (74%), vascular invasion (88%) and distant metastasis (88%).[8] CT scan shows pancreatic lesion in 95% cases and pancreatic and bile duct can be noted. Features that suggest unresectability are local extension of the tumor (behind the pancreas, into the liver hilum, contiguous organ involvement like stomach, duodenum), involvement of superior mesenteric or portal vessels, ascites, distant gross nodal metastasis and distant metastasis.[1] Contrast medium can be used before the study to distinguish tumor from normal tissue.[6] Present study showed better delineation of pancreatic cancer than that of Soriano et al.[8] probably due to delay in referral which made it easily detectable! In this study, efficacy of CT scan (90%) in diagnosing pancreatic cancer is lower than that shown by Doherty and Way (95%).[1]

MRI were used only in 8 patients suspected clinically as pancreatic cancer where USG/CT scan had failed to give any clue about the diagnosis. MRI was 100% accurate to diagnose all the patients as cancer pancreas. Out of 8 cancer patients, MRI delineated the features of unresectibility in all patients (100%). It had not missed any patients with pancreatic cancer. It is difficult to make an inference from this as small number of patients were evaluated. MRI clearly displays pancreas and its duct system. MRCP can replace endoscopic pancreatography and cholangiography only in diagnostic purpose.[3] MRI can detect vascular invasion in 96% patients.[8]

ERCP were used in 20 patients of pancreatic cancer for diagnosis (in 20 patients), biopsy (in 12 patients) or therapeutic purpose (endoprosthesis in 9 patients). ERCP were able to diagnose 13 (65%) patients as cancer pancreas. Out of 13 cancer patients it failed to delineate the features of unresectibility in any of the patients (00%). ERCP had missed 7 (35%) patients suffering from pancreatic cancer. In the absence of pancreatic mass ERCP is indicated. It is the most

sensitive test (95%) for detecting pancreatic cancer. A finding consistent with stenosis or obstruction of pancreatic duct, adjacent lesion of the bile and pancreatic duct (double duct sign) is highly suggestive of pancreatic cancer. Present study was able to diagnose 65% pancreatic cancer by ERCP which is much lower than had been reported.[1]

UGI series provides information about the patency of the duodenum and indicated in patients having vomiting due to duodenal obstruction.[1] UGI contrast had been carried out in 10 pancreatic cancer patients having UGI symptoms. It showed 6 patients (60%) having narrow duodenal lumen with regular mucosa probably pressured by pancreatic growth. It was able to diagnose only 1 (10%) pancreatic cancer having gross invasion of the duodenal wall and labeled as unresectable.

Preoperative biopsies of the pancreas and bile duct can be performed in several ways as image guided FNAC, ERCP and biopsy, brush cytology and by laparoscopic or open surgical procedures.[6] ERCP is helpful in taking biopsy specimen.[1] ERCP safely and precisely locate the biopsy site for cytological diagnosis of unresectable pancreatic cancer in 93% cases.[18] CT guided fine needle aspiration biopsy (FNAB) is a safe procedure with 83% sensitivity and low rate (10%) of minor complications.[19]U S-guided FNA is 62% sensitive in detecting pancreatic cancer.[20] In the present study, preoperative biopsies were taken only in 50% of the patients (done 25 patients out of 50 patients). Biopsy taken by ERCP was the commonest (12 patients, 48%). Image-assisted core needle biopsy was taken from the lesion (10 biopsy 40%) and hepatic metastasis (3 biopsy 12%). USG was used to obtain biopsy in 6 patients (24%) with pancreatic lesion and CT guided biopsy were taken from 04 (16%) pancreatic lesions and from all 03 (12%) liver metastasis.

After evaluating all the clinical, laboratory, radiological and histopathological data 50 patients were labeled as UCP.

Multimodal preoperative imagings were carried out in 50 patients. Among them 40 patients underwent laparotomy and biopsy. In 35 patients biopsy reports were pancreatic carcinoma. Multimodal preoperative imagings were 87.5% accurate in diagnosing unresectable carcinoma pancreas.

CONCLUSION

Unresectable carcinoma pancreas (UCP) can be diagnosed by history, clinical examination laboratory investigations, tumor markers and imaging. Multimodal preoperative imagings are 87.5% accurate in diagnosing UCP. Moreover, tissue or cytological proof is essential to confirm the diagnosis of clinically labeled UCP. Suggestive clinical features along with USG are good enough to diagnose UCP where CT or MRI is not available.

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