Adenocarcinoma of the Pancreas : The Clinical Experience of 45 Histopathologically Proven Patients, a 6 Year Study

PINIT KULLAVANIJAYA, M.B., Ch.B. (Leeds), M.R.C.P. (UK)*, SOMBAT TREEPRASERTSUK, M.D., M.Sc., F.R.C.P. (T)**, DUANGPORN THONG-NGAM, M.D., M.Sc., F.R.C.P. (T)***, NUSONT KLADCHAROEN, M.D., M.R.C.P. (UK)*, VAROCHA MAHACHAI, M.D.*, PONGSEPEERA SUWANAGOOL, M.D.****

Abstract

A retrospective study of 45 cases of adenocarcinoma of the pancreas at Chulalongkorn University Hospital from 1993 to 1998 was reviewed by clinical and histopathological criteria. Male and female ratio was 25:20. The mean age of the patients was 59.5 ± 10.0 years. The common presenting symptoms and signs were epigastric discomfort (80.0%), weight loss (60.0%) and jaundice (51.1%). Twenty four patients (53.3%) were screened for a tumor marker (CA 19-9) and 87.5 per cent of these had high level of CA 19-9 (> 37 IU/ml). Thirty five patients (77.8%) had tumors located in the head of the pancreas. Most of the cases were investigated by using radiological imaging (ultrasonography or computerized tomography of the abdomen). Thirty five histopathological data (77.8%) were made by the operation, and the rest (22.2%) were performed by a fine needle aspiration from the pancreatic mass or liver metastasis. Whipple operation and the bypass procedure were the most common surgical procedures in our studies. Twenty five patients (55.6%) had post treatment complications from all modalities consisting of gastrointestinal bleeding, respiratory failure and infection. However, the mortality rate within 30 days postoperatively was 8.11 per cent which was due to blood loss during the operation and infections. The post treatment mortality rate from all modalities was 33.3 per cent. The average duration from the diagnosis until death was 82.3 days.

Key word : Adenocarcinoma, Pancreas, Clinical, Histopathological

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* Gastroenterology Unit, Department of Medicine, Faculty of Medicine, Chulalongkorn University,
** Gastroenterology Unit, Department of Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400,
*** Department of Physiology,
**** Department of Pathology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

Adenocarcinoma of the pancreas is the second most common gastrointestinal malignancy and the fourth most common cause of cancer death in Western countries. The prevalence of this disease is approximately 9 to 10 per 100,000 persons[1,2]. The five year survival rate is poor, only 3 per cent. In Thailand, it is somewhat uncommon and is not included in the top ten malignancies [3,4]. However, this malignancy is a rapidly growing tumour and most cases are fatal.

The clinical data, diagnostic methods and results of treatment in Thailand are not well documented. There was only one previous report from Songklanagarind Hospital, a university hospital in the southern part of Thailand. There were only 30 cases of carcinoma of the pancreas from 1982 to 1985[5] but this report lacked diagnostic methodology and the results of surgical management. Therefore, the purpose of this study was to categorize clinical presentation, results of radiological imaging, tumor markers, procedures and results of surgical treatment in patients with pancreatic adenocarcinoma.

MATERIAL AND METHOD

The records of all patients with pancreatic adenocarcinoma (pathological and ICD.9) in the Department of Pathology and the Department of Medicine, Chulalongkorn Hospital between January 1993 and December 1998 were reviewed. Forty five cases of pancreatic adenocarcinoma which were histopathologically proven from surgical specimens and fine needle aspiration in the 6 year period were included. The outpatient and admission records were completely reviewed.

The general demographic data and clinical manifestations of patients were collected and analyzed. Histopathology was proven by the pathologists (Fig. 1, 2). The invasiveness of the tumor at the operation was evaluated and classified by clinical staging. First: the resectable group, without encasement of the celiac axis or superior mesenteric artery (SMA), the tumor did not extend directly to any of the following : duodenum, bile duct or peripancreatic tissue. Second: the locally advanced group, the tumor invaded into the surrounding arterial or venous system {SMA, SMV and portal vein (PV) }, or the tumor extended directly to any of the following : stomach, spleen, colon. Third: the advanced group, which presented with distant metastases which were usually to liver, peritoneum and occasionally to the lung.

The diameter of the tumor size was assessed by either the operation or imaging study. All data were recorded and analyzed by using the SPSS 7.5 for Windows.

RESULTS

Forty-five patients with pancreatic adenocarcinoma were included into this study between 1993 and 1998. The clinical and demographic data are shown in Table 1. The ages at the time of the

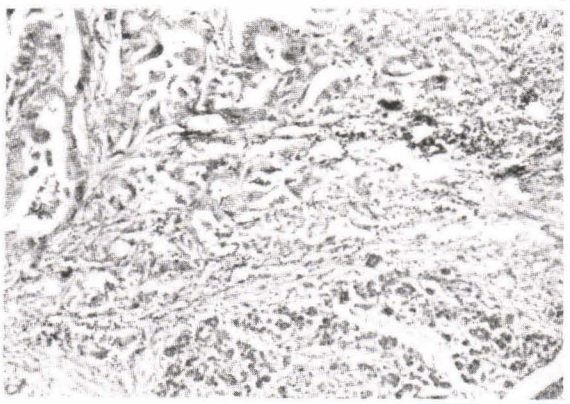

Fig. 1. Showing moderate differentiated adenocarcinoma of the pancreas (H-E * 200: surgical section).

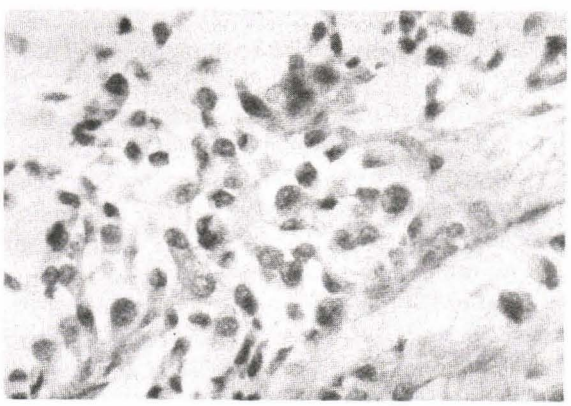

Fig. 2. Showing undifferentiated carcinoma of tail of pancreas (H-E * 400 : surgical section).

Table 1. The demographic and clinical data of 45 cases of pancreatic adenocarcinoma in King Chulalongkorn Memorial Hospital, during 1993-1998.

Demographic-Clinical data	Number of patients	
Sex : male / female	25:20	
Age at presentation (years)		
- < 60 / > 60	25:20	
- mean ± SD	59.5 ± 10.0	
Address		%
- Bangkok and central area		66.7
- Northeastern area		13.3
- Northern area		11.1
- Southern area		6.7
- Western area		2.2
Possible risk factors		
- diabetes mellitus	14	31.1
- smoking	13	28.3
- gallstones	3	6.7
- history of pancreatitis	3	6.7
Symptoms and signs		
- abdominal discomfort	36	80.0
- weight loss	27	60.0
- jaundice	23	51.1
- pale colored stool	11	24.4
- nausea and vomiting	10	22.2
- pruritus	7	15.6
- abdominal mass	6	13.3
- fever	2	4.4

Table 2. Laboratory parameters of 45 cases of pancreatic adenocarcinoma in King Chulalongkorn Memorial Hospital, during 1993-1995.

Laboratory parameters (normal value)	Mean ± SD
Hematocrit (%)	35.7 ± 6.79
White blood cell (/mm^3)	11,005.2 ± 4,795.9
Platelet (/mm^3)	310,571.4 ± 135,459.4
Total bilirubin (0-1 mg/dl)	8.8 ± 8.9
Direct bilirubin (0-0.25 mg/dl)	6.2 ± 6.3
Alkaline phosphatase (98-279 U/L)	768.2 ± 744.8
SGOT (0-38 U/L)	92.7 ± 91.3
SGPT (0-38 U/L)	103.4 ± 119.3
Albumin (3.4-5.5 g/dl)	3.9 ± 0.8
Globulin (2.0-4.0 g/dl)	3.3 ± 0.7
Amylase (0-220 U/L)	173.8 ± 230.6
Lipase (< 50 U/L)	409.7 ± 431.4
Fasting blood sugar (< 110 mg/dl)	137.7 ± 55.7
CA 19-9 (< 37 IU/ml)	721.3 ± 2,195.8
CEA (< 5 ng/ml)	15.5 ± 17.7

first presentation varied from 33 to 81 years (mean 59.5 ± 10.0 year). Male to female ratio was 25:20. Most of the patients (66.7%) lived in Bangkok or the suburbs. The number of patients who had risk factors of pancreatic adenocarcinoma compared to those who had no risk factors was 2:1. The most common clinical presentations were abdominal discomfort (80.0%), weight loss, averaging 6.6 ± 4.7 kg/person (60.0%) and jaundice (51.1%).

The blood chemistry findings and the tumor markers are shown in Table 2. The serum amylase and lipase in most cases were normal. The carbohydrate antigen (CA 19-9), the most common tumor marker, used in our study was elevated in 87.5 per cent while the two patients who had normal level of CA 19-9 were in the locally advanced group. Four of 45 patients (8.8%) were in the resectable group, 18 of 45 patients (40.0%) were in the locally advanced group and 23 of 45 patients (51.2%) had metastases. The clinical and laboratory results in each group of staging are shown in Table 3. Most common sites of metastatic lesions were liver, vascular invasion including SMV, SMA, PV and duodenum but the stomach, supraclavicular lymph nodes, gall bladder, extrahepatic bile duct, colon, adrenal glands and lungs also had metastatic lesions.

The average diameter of the tumors was 4.5 x 4.1 cm. The most common site of tumors was the head of the pancreas (77.8%), while the rest of the tumors were in the body and tail in about 26.7 per cent and 28.9 per cent respectively. Radiology was done in 42 patients (93.3%) and most of the patients were diagnosed for pancreatic tumors. Twelve patients (26.7%) were investigated by ultrasonography (US) or CT scan alone and 40 per cent of the 45 patients had both radiological investigations (US and CT). Two patients were undiagnosed by ultrasonography. Fine needle aspiration (FNA) under ultrasound guidance was used for the diagnosis in 11 patients (24.4%) and most of them were in the advanced stage and had liver metastases (90.9%). In the advanced stage group of pancreatic adenocarcinoma, 47.36 per cent was diagnosed by operation procedure and 52.63 per cent was diagnosed by FNA.

The mode of treatment in our series was surgery (71.1%), chemotherapy (2.2%), radiotherapy (2.2%), combined therapy (11.1%) and conservative treatment (13.3%). Whipple operation (pancreaticoduodenectomy) was the most common

Table 3. Clinical and laboratory findings of pancreatic adenocarcinoma classified by staging in King Chulalongkorn Memorial Hospital, during 1993-1998.

Variables	Resectable group n = 4	Locally advanced group n = 18	Advanced group n = 23
Mean age (years)	60.0 ± 0.8	58.3 ± 11.6	60.3 ± 9.7
Mean weight loss/month (kgs)	4.7 ± 4.8	3.2 ± 3.2	2.7 ± 2.7
Hematocrit (%)	36.3 ± 7.1	35.2 ± 5.1	36.0 ± 8.0
Total bilirubin (mg/dl)	18.3 ± 3.8	11.3 ± 10.0	5.1 ± 6.7
Alkaline phosphatase (< 279 u/l)	882.7 ± 535.0	882.4 ± 871.6	659.1 ± 681.4
Albumin (3.4-5.5 g/dl)	4.0 ± 0.6	3.9 ± 0.7	3.8 ± 0.8
Globulin (2.0-4.0 g/dl)	3.1 ± 0.5	3.0 ± 0.7	3.4 ± 0.7
CA 19-9 (< 37 iu/ml)	401.0 ± 99.0	284.2 ± 179.2	1082.2 ± 2984.6
Diameter of tumors (cm)	3.6 ± 0.2	3.6 ± 1.5	5.6 ± 3.1
Number of Loss follow-up	4	10	12
Number of Death	0	5	10
Number of Alive	0	3	1

Table 4. Post – treatment complications of 45 cases of pancreatic adenocarcinoma in all modalities of treatments in King Chulalongkorn Memorial Hospital, during 1993-1995.

Post – treatment complications	Number of cases	%
Gastrointestinal bleeding	19	42.2
Sepsis	9	20.0
Respiratory failure	6	13.0
Hypo or hyperglycemia	2	4.0
Severe blood loss in operation	1	2.0

surgical procedure. All patients who received chemotherapy alone, radiotherapy alone or conservative treatment were in the advanced group. Post treatment complications in all modalities developed in 25 patients (55.6%) and the most common complications were gastrointestinal bleeding (19 patients). Most of the patients were lost to follow-up (57.8%). The fatal cases were in the locally advanced group (8 cases) and advanced group (7 cases). The average duration from the diagnosis until death was 82.3 days.

The causes of death were sepsis (10 patients), respiratory failure (4 patients), metabolic disturbance (3 patients), liver failure (1 patient) and blood loss (1 patient). The 30 days postoperative mortality was 8.1 per cent. The causes of perioperative death were sepsis in 2 patients and blood loss in 1 patient. There were 4 patients who were still alive with an average duration of follow-up about 293.7 days up till December 1999. Most of them (75%) were in the locally advanced group and had received surgical treatment. All of the patients in the resectable group (4 patients) were lost to follow-up and the average duration of follow-up was 141.6 days. Of the thirteen patients who did not receive surgical treatments, 4 died, 5 were lost to follow-up and 2 are still alive.

DISCUSSION

Adenocarcinoma of the pancreas is still uncommon in King Chulalongkorn Memorial Hospital. There are only about 7.5 cases per year. At present, there is no effective method of screening for early detection of pancreatic adenocarcinoma and effective therapy for the advanced diseases. From our studies, most of the patients were in the locally advanced and advanced groups, therefore, the disease was advanced at the time of diagnosis. Because there is no specific laboratory test for early detection, clinicians should be aware of this disease when there are warning symptoms and signs such as epigastric discomfort, weight loss and jaundice. As previously reported, the risk factors include smoking, chronic pancreatitis, long standing diabetes mellitus, hereditary pancreatitis, multiple endocrine neoplasia, history of partial gastrectomy and a high fatty diet[6-8]. However, some risk factors such as coffee, alcohol and diabetes mellitus are controversial[9-11]. The tumor markers, especially the CA19-9, the most widely used as the gold standard for pancreatic cancers,

had the sensitivity and specificity of 76-85 per cent and 81-90 per cent at the cut-off level of 37 IU/ml[12-15]. However, most of the previous studies regarding the sensitivity and specificity of CA 19-9 used advanced cases of pancreatic cancers. Therefore, it is difficult to consider CA 19-9 determination useful for early detection of this cancer[16]. However, it is judged to be useful for the diagnosis when combined with clinical presentation, especially if the CA 19-9 is of a very high level (more than 100 IU/ml)[12,14,17]. From our study, if we used the cut-off level of CA 19-9 at 82 IU/ml, the sensitivity and specificity of classification between the resectable group and advanced group were 84.6 per cent and 27.3 per cent, respectively (analysis by using ROC curve, SPSS programme). Recently, the knowledge of molecular alteration in the pathogenesis of pancreatic adenocarcinoma was studied and it was found that the K-ras oncogene mutation was the most frequent genetic alteration in pancreatic carcinogenesis [18-20]. K-ras gene mutations at codon 12 was detected in both pancreatic adenocarcinoma and in metastatic lesions, while other tumors such as lymphoma, ampullary cancers did not exhibit a K-ras mutation[21]. This knowledge may be useful for the early detection and differentiation of adenocarcinoma of the pancreas from other pancreatic cancers in the future.

The first radiological investigation for pancreatic cancers is still ultrasonography. If satisfactory imaging is not obtained, then computed tomography (CT) should be considered. In our study, we used US or CT in 50 per cent of cases and both US and CT were used in the rest. The results were very good. There were only 2 patients from 42 patients who were undiagnosed due to small size of the tumor in one case (2 cm.), and the other case was diagnosed as pseudocyst of the pancreas. Both cases were investigated with CT. scan and received surgical or FNA diagnosis later. The previous report of ultrasonographic findings of pancreatic carcinoma from Chulalongkorn University Hospital showed that masses and biliary tract dilation greater than 8 mm were present in 76.7 per cent[22]. Lymphadenopathy was identified in 32.6 per cent and the smallest pancreatic tumor detected in this study was 2 cm in diameter. So ultrasonography is cost effective for the detection of pancreatic cancer but it is also operator dependent. The spiral CT is currently considered to be better than ultrasonography in detecting small pancreatic lesions of less than 2 cm and to stage the pancreatic cancer[23,24]. The new radiological developments for early diagnosis of pancreatic cancer such as MRI, endoscopic ultrasound (EUS), laparoscopic ultrasound (LUS), positron emission tomography (PET) in combination with the use of the glucose analog (2-^{18} F-fluoro-2-deoxy-D-glucose : FDG) are very promising but they require further evaluation and have high costs[23-26].

Ultrasound guided fine needle aspiration (FNA) was commonly used in the advanced stage in our report. This technique is very useful in elderly patients or in those who were thought to have high morbidity and mortality if laparotomy was performed. The accuracy of the diagnosis by FNA from a previous study was 91 per cent and the sensitivity and specificity were 77-100 per cent and 100 per cent respectively[27-31]. Some reports considered the efficacy of FNA cytology and histology was the same[31].

The 30 days postoperative mortality rate in the surgically resected and bypass operation was 8.1 per cent. The mortality rate was slightly higher than the previous reports which were about 0-5 per cent in pancreatic specialist centers[32-36]. Many factors have played a part in the mortality rate such as comorbid disease, intensive care postoperatively, and nutritional status of the patients. Advanced age is also associated with a higher mortality rate. Recent data showed that surgery can be performed in elderly patients with acceptable mortality[34,36]. The role of bypass or palliative resection is worth considering for improving the quality of life in cases of obstructive jaundice, duodenal obstruction or pain from cancer compression [2]. However, it should be considered along with acceptable morbidity and mortalities and compared to other modalities of supportive treatment such as chemotherapy. In our report, 6 patients received bypass operation. Two patients died an average of 103.5 days after the operation, while the other 3 patients were lost to follow-up after operation, an average of 401.6 days.

To improve the survival, adjuvant treatment after tumor resection should be considered. They include chemotherapy, radiation and hormo-

nal therapy such as tamoxifen but more research is needed. However, it seems that the median survival time of the combination treatment of surgery, radiation and chemotherapy was significantly longer than that observed from the surgical treatment alone(26,38-39).

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มะเร็งตับอ่อนชนิดอะดีโนคาร์ซิโนมา : ประสบการณ์จากผู้ป่วย 45 ราย ในช่วงเวลา 6 ปี ของโรงพยาบาลจุฬาลงกรณ์

พินิจ กุลละวณิชย์, พ.บ., สมบัติ ตรีประเสริฐสุข, พ.บ., ว.ว. (อายุรศาสตร์)**,*
*ดวงพร ทองงาม, พ.บ., ว.ว. (อายุรศาสตร์)***, นุสนธิ์ กลัดเจริญ, พ.บ.*,*
วโรชา มหาชัย, พ.บ., พงษ์พีระ สุวรรณกูล, พ.บ.*****

การศึกษาย้อนหลังในผู้ป่วยที่มารับการรักษาและวินิจฉัยว่าเป็นมะเร็งตับอ่อนชนิดอะดีโนคาร์ซิโนมา จากผลตรวจทางพยาธิวิทยา จำนวน 45 ราย ตั้งแต่ มกราคม พ.ศ. 2536 ถึง ธันวาคม พ.ศ. 2541 พบว่าเป็นเพศชาย ต่อ เพศหญิง เท่ากับ 25 : 20 ส่วนใหญ่มีอายุอยู่ระหว่าง 59.5 ปี ± 10.0 (33-81 ปี) อาการและอาการแสดงที่พบได้บ่อยที่สุด 3 ลำดับ คือ อาการอืดแน่นไม่สบายในท้อง (ร้อยละ 80.0) อาการน้ำหนักลด (ร้อยละ 60.0) เฉลี่ย 2.7 กิโลกรัม/เดือน หรือน้ำหนักลดเฉลี่ย 6.6 ± 4.7 กิโลกรัม/คน อาการตัว ตาเหลือง (ร้อยละ 51.1) มะเร็งตับอ่อนที่พบส่วนใหญ่มักมาในระยะที่เริ่มมีการกระจายไปอวัยวะใกล้เคียงแล้ว ร้อยละ 91.2 และมีผู้ป่วย 4 ราย (ร้อยละ 8.8) ที่พบว่าอยู่ในระยะแรก ซึ่งสามารถผ่าตัดมะเร็งออกได้ทั้งหมด การตรวจเลือดหา CA 19-9 พบความผิดปกติถึงร้อยละ 87.5 มะเร็งส่วนใหญ่อยู่ในตำแหน่งส่วนหัวของตับอ่อน (ร้อยละ 77.8) การรักษาส่วนใหญ่ คือ การผ่าตัด โดยวิธี Whipple และการต่อทางเดินน้ำดี ให้หายจากการอุดตันได้ (ร้อยละ 28.9 และ 13.3 ตามลำดับ) ภาวะแทรกซ้อนที่พบหลังการรักษาทั้งหมดพบถึงร้อยละ 55.6 โดยส่วนใหญ่เป็นภาวะแทรกซ้อนที่เกี่ยวกับภาวะเลือดออกในทางเดินอาหารส่วนต้น, ภาวะหายใจล้มเหลวและการติดเชื้อ อัตราตายที่เกิดหลังการผ่าตัดภายใน 30 วันแรก พบได้ ร้อยละ 8.1 และอัตราการตายหลังการวินิจฉัยแล้วมีร้อยละ 33.3 (15 ราย) โดยสาเหตุส่วนใหญ่เป็นจากภาวะติดเชื้อในกระแสเลือด, ภาวะหายใจล้มเหลว และความผิดปกติ ของระดับน้ำตาลและเกลือแร่ในร่างกาย ระยะเวลาที่นับจากการวินิจฉัยจนถึงเสียชีวิตเฉลี่ย 82.3 วัน

คำสำคัญ : มะเร็งตับอ่อน, อะดีโนคาร์ซิโนมา, พยาธิวิทยา, อาการทางคลินิก

พินิจ กุลละวณิชย์, สมบัติ ตรีประเสริฐสุข, ดวงพร ทองงาม,
นุสนธิ์ กลัดเจริญ, วโรชา มหาชัย, พงษ์พีระ สุวรรณกูล
จดหมายเหตุทางแพทย์ ฯ 2544; 84: 640-647

* สาขาวิชาโรคทางเดินอาหาร, ภาควิชาอายุรศาสตร์, คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย,
** สาขาวิชาโรคทางเดินอาหาร, ภาควิชาอายุรศาสตร์เขตร้อน, คณะเวชศาสตร์เขตร้อน มหาวิทยาลัยมหิดล, กรุงเทพ ฯ 10400
*** ภาควิชาพยาธิวิทยา,
**** ภาควิชาสรีรวิทยา, คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย, กรุงเทพฯ 10330