Pancreatic Cancer : From Clinical to Molecular Aspects

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Abstract : **Pancreatic ductal adenocarcinoma usually has a very poor outcome. The majority of patients present late with locally advanced or metastatic disease, and only 10-20% are candidates for resection. The tumor marker CA19-9 may be elevated but is not specific for pancreatic cancer. Dual-phase spiral computed tomography is the most important imaging modality for the diagnosis of pancreatic cancer. Despite the continuing development of body imaging methods and serum determination of tumor markers, the diagnosis of pancreatic carcinoma often remains problematic. Endoscopic retrograde cholangiopancreatography is considered to be one of the most reliable diagnostic procedures for pancreaticobiliary diseases. Endoscopic ultrasonography has been developed as an intracorporeal imaging method that now provides precise ultrasonic images of the pancreas. Pancreaticoduodenectomy is the mainstay of surgical treatment which offers the only hope of cure for this disease. Biliary-enteric and gastrojejunal bypass used to be the standard operation for inoperable pancreatic cancer. Endoscopic stenting can produce good palliation of biliary obstruction. The median survival after resection is only 18-20 months and up to 50% of those who survive 5 years may die of recurrent cancer. The factors that predict recurrence and survival are the resection margin, the size of the tumor, lymph node involvement and histological appearance of the degree of differentiation of the cancer tissue.**

Pancreatic cancer is a consequence of stepwise accumulated genetic alterations which disturb the equilibrium of a cell by altering the relative balance between the roles of the cell cycle, differentiation and dedifferentiation, and programmed cell death (apoptosis). Multiple genetic alterations involving the activation of oncogenes (*K-ras*) and inactivation of tumor suppressor genes (*p53*, *p16* and *DPC4*) and telomerase. The detection of early tumor, ie., the establishment of a screening strategy, the development of adjuvant therapy and molecular approaches might provide more options and a better clinical outcome for pancreatic cancer.

เรื่องย่อ : มะเร็งตับอ่อน : จากคลินิกสู่โมเลกุล

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มะเร็งตับอ่อนเป็นสาเหตุที่พบบ่อยของการเสียชีวิตจากโรคมะเร็ง มีการพยากรณ์โรคไม่ดี ผู้ป่วยมักได้รับการวินิจฉัยเมื่ออาการอยู่ในระยะท้าย ๆ จึงมีผู้ป่วยเพียงประมาณร้อยละ10-20 เท่านั้นที่สามารถรับการรักษา

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โดยการผ่าตัดได้ ผู้ป่วยอาจมี tumor marker CA 19-9 ขึ้นสูงแต่ไม่จำเพาะ ปัจจุบันการใช้ dual-phase spiral computed tomography มีบทบาทสำคัญในการวินิจฉัยมะเร็งตับอ่อน อย่างไรก็ตามถึงแม้จะมีการพัฒนาการตรวจภาพรังสีและการตรวจหา tumor marker มาอย่างต่อเนื่อง ก็ยังเป็นการยากในการวินิจฉัยโรคนี้ การตรวจ endoscopic retrograde cholangiopancreatography และ endoscopic ultrasonography เป็นการตรวจที่สามารถแสดงให้เห็นลักษณะกายวิภาคและพยาธิสภาพของตับอ่อนได้อย่างดี การผ่าตัด pancreaticoduodenectomy เป็นวิธีรักษาในปัจจุบัน ส่วน biliary-enteric, gastrojejunal bypass และ endoscopic stenting ใช้สำหรับผู้ป่วยที่ไม่เหมาะต่อการผ่าตัด ระยะเวลาการอยู่รอดหลังผ่าตัดประมาณ 18-20 เดือน และ 50% ของผู้ป่วยที่อยู่รอดถึง 5 ปี จะเสียชีวิตจากการเกิดโรคซ้ำ ปัจจัยที่มีผลต่อการเกิดโรคซ้ำ และการอยู่รอด คือ ขอบเขตของการผ่าตัด, ขนาดของก้อน, ต่อมน้ำเหลืองที่เกี่ยวข้อง และผลทางจุลพยาธิวิทยา

มะเร็งตับอ่อนเป็นผลของการสะสมการเปลี่ยนแปลงทางพันธุกรรมต่างๆ จนกระทั่งสมดุลระหว่างวงจรของเซลล์ (cell cycle), การแบ่งเซลล์ และ apoptosis เสียไป การเปลี่ยนแปลงในทางอณูชีววิทยาต่างๆ ได้แก่ activation ของ oncogenes เช่น *K-ras* และ mutation ของ tumor suppressor genes เช่น *p53, p16, DPC4* และ activation ของ telomerase เป็นต้น การตรวจกรองหามะเร็งนี้ในระยะเริ่มแรก, การพัฒนาการแบบผสมผสาน รวมถึงความก้าวหน้าทางด้านอณูชีววิทยา จะเป็นความหวังที่สามารถนำไปสู่การรักษา และการป้องกันโรคมะเร็งตับอ่อนที่ได้ผลอย่างสมบูรณ์ต่อไปในอนาคต

INTRODUCTION

Pancreatic ductal adenocarcinoma usually has a very poor outcome and is aggravated by the fact that the majority of patients present late with locally advanced or metastatic disease, and only 10-20% are candidates for resection. It has the lowest 5-year survival rate of any cancers. Ninety percent of patients die within the first year of diagnosis. The detection of early tumor is important to improve survival. High risk conditions for pancreatic cancer are idiopathic and alcoholic chronic pancreatitis, new onset of diabetes mellitus (less than 2 years, no family history, age over 50 years), hereditary pancreatitis (over 45 years), cystic disease of the pancreas and intraductal papillary mucinous tumor. However, a screening strategy for this disease has not been established.

CASE REPORT

A 61-year-old man was admitted to Siriraj Hospital with discomfort and pain in the right subcostal region for 1 month. He had lost 2 kilograms during this period but had no other abnormal symptoms including jaundice. He had no underlying disease and stopped smoking 30 years ago. Physical examination showed T 37°C, PR 80/min regular, RR 18/min, BP 110/80 mmHg, not pale, mild jaundice, no signs of chronic liver disease, neither liver, gallbladder nor spleen were palpable, and there was no superficial lymphadenopathy. Investigations showed no anemia. Liver function tests showed aspartate aminotransferase 116 units/l, alanine aminotransferase 304 units/l, alkaline phosphatase 743 units/l, gamma-glutamyltranspeptidase 987 units/l, direct bilirubin 1.7 mg/dl, total bilirubin 3.0 mg/dl and a normal coagulogram. Moreover, the serum CA19-9 was elevated to 93.6 IU/ml (0-35.6) whereas the CEA was normal. Abdominal ultrasonography showed dilatation of the gallbladder, common bile duct and intrahepatic bile ducts with two large common bile duct stones about 1.8 cm in diameter. The pancreas, spleen and both kidneys were normal. Computed tomography (CT) (Figure 1) demonstrated a heterogeneous mass, 3.5 x 3.5 x 4.0 cm, at the pancreatic head and uncinate process obstructing the biliary tract, possibly invading the duodenal loop, with evidence suggestive of superior mesenteric vein

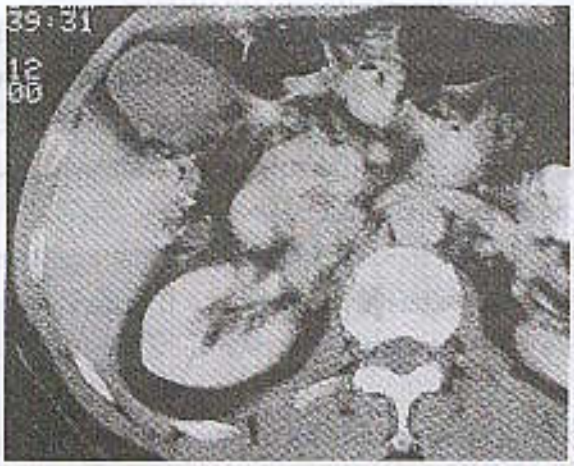

Figure 1. The computed tomography (CT) demonstrated a heterogeneous mass, 3.5x3.5x4.0 cm, at the pancreatic head and uncinate process obstructing the biliary tract, possibly invading the duodenal loop, with suggestive evidence of superior mesenteric vein and inferior vena cava invasion. No isolated peripancreatic, periportal or paraaortic lymphadenopathy was demonstrated.

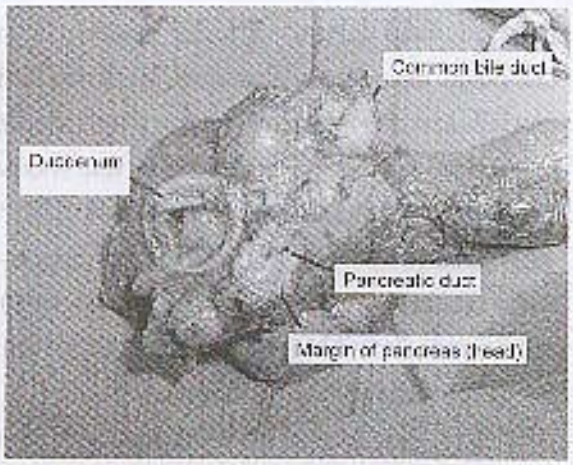

Figure 2. The surgical specimen taken from pyloric-preserving pancreatoduodenectomy procedure including the head of pancreas, duodenum, distal common bile duct and adjacent tissues.

Figure 3. The surgical specimen demonstrated a grayish mucinous ulcerative mass, 3x2 cm in size, extending from the ampulla of Vater and invading the duodenal wall with focal invasion into pancreatic tissue around the pancreatic duct.

and inferior vena cava invasion. No isolated peripancreatic, periportal or paraaortic lymphadenopathy was demonstrated. Subsequently, the endoscopic retrograde cholangiopancreatography (ERCP) found an ulcerative mass, 2.5 cm in diameter, involving the whole papilla with partial obstruction. The common bile duct was dilated but no stone was found in the common bile duct.

He underwent surgical excision of the tumor. At laparotomy, no ascites, distant lymph node metastases, peritoneal seedings or liver metastases were found. A firm mass was palpated at the head of pancreas. Pylorus-preserving pancreatoduodenal resection was performed. The postoperative course was uneventful. Pathology reported a grayish mucinous ulcerative mass, 3 x 2 cm in size, extending from the ampulla of Vater and invading the duodenal wall with focal invasion into pancreatic tissue around the pancreatic duct (Figure 2, 3). Histopathology demonstrated mucinous adenocarci-noma, poorly to moderately differentiated with angiolymphatic,

perineural and neural invasion and the tumor had metastasized to two out of ten parapancreatic lymph nodes. However, all margins were free of tumor.

DISCUSSION

Diagnosis and staging of pancreatic cancer

About 70% of pancreatic cancers are found in the head of the pancreas, and most patients present with jaundice, weight loss and abdominal pain. Early symptoms such as epigastric bloating and dyspepsia are nonspecific, and hence early diagnosis requires a high index of suspicion. Obstructive jaundice is a more specific sign associated with pancreatic head cancer but is often a late manifestation. The presence of back pain is often suggests tumor infiltration of the celiac plexus and thus unresectability.

Tumor markers

The specificity and sensitivity of CA19-9 in detecting pancreatic cancer is 78% and 87%, respectively. It is elevated in more than 75% of pancreatic cancer cases and the level depends on the size and the differentiation of the tumor. A CA19-9 level of more than 120 IU/ml suggests a metastatic tumor. However, the CA19-9 is also elevated in some benign conditions such as chronic pancreatitis and biliary tract obstruction with cholangitis.

Radiological imaging

Ultrasonography is the initial diagnostic modality, but it is suboptimal in visualizing pancreatic lesions. A high quality computed tomography (CT) is the most important imaging modality for the diagnosis of pancreatic cancer. The sensitivity of dual-phase spiral CT in detecting a tumor of less than 1.5 cm is 67% and up to 100% in a tumor larger than 1.5 cm. In contrast, conventional CT which is routinely used can detect a tumor less than 3 cm in size in 53% of cases. The criteria for a resectable tumor are 1) absence of extrapancreatic disease; 2) no direct tumor extension to the celiac axis or superior mesenteric artery and 3) patent superior mesenteric vein-portal vein confluence. The low resectability rate of pancreatic cancer is partly attributable to the close proximity of this organ to the major visceral vasculature in the abdomen, and the frequency of early metastasis to regional lymph nodes and liver. Vascular grading by CT findings is associated with a surgical resection rate (in percentage) as follows; grade A: fat plane visible between tumor and vessel (100); grade B: normal pancreatic tissue between tumor and vessel (75); grade C: tumor adjacent to vessel with a convex contour towards vessel (67); grade D: tumor adjacent to vessel with a concave contour towards vessel (31); grade E: circumferential involvement of vessel (0); and grade F: vascular occlusion (0).

Magnetic resonance cholangiopancreatography (MRCP) is a new noninvasive imaging technique to examine the biliary and pancreatic ducts and is highly sensitive (93-100%) in detecting biliary and pancreatic duct strictures. It is possible that MRCP may replace ERCP as the initial investigation for obstructive jaundice.

Endoscopic aspect

Despite the continuing development of body imaging methods and serum determinations of tumor markers, the diagnosis of pancreatic carcinoma often remains problematic. The pancreas is one of the most difficult intraabdominal organs to evaluate, and by the time symptoms indicate the presence of carcinoma, the disease is well advanced in the majority of cases. Usually the tumor is unresectable and the prognosis for the patient is poor.[1] Endoscopic retrograde cholangiopancreatography (ERCP), now widely employed throughout the world,[2-5] is considered to be one of the most reliable diagnostic procedures for pancreaticobiliary diseases, especially cancer of the pancreas and biliary tract.[6-12] Moreover, advanced endoscopic instruments coupled with retrograde cannulation of the main duodenal papilla have brought about direct visualization of the biliary and pancreatic ductal systems. Endoscopic ultrasonography (EUS) has been developed as an intracorporeal imaging method that now provides precise ultrasonic images of the pancreas.

ERCP is usually performed for precise diagnosis of biliary and pancreatic disease, demonstrating the pancreaticobiliary ductal system, for which purposes it has a number of advantages. By combining endoscopic and radiologic examinations, it provides radiographic information

about the biliary and pancreatic ducts as well as endoscopic information concerning the main duodenal papilla. Evidence of pancreatic carcinoma can often be detected as secondary alterations in the stomach, duodenum, and bile duct produced by the tumor. Biopsies can be obtained directly from the main duodenal papilla and bile and pancreatic juice can be aspirated for cytologic study.[12-15] A histologic diagnosis of pancreatic carcinoma can sometimes be established by obtaining a biopsy when there is malignant invasion of the duodenal wall including the periampullary area. However, the diagnosis of cancer of the pancreas by ERCP depends mainly on the interpretation of x-ray films of the pancreatic ductal system obtained by injection of contrast media.

Pancreatic ductal changes in cancer of the pancreas are of two kinds.[5] Either there are significant changes in the main pancreatic duct or an abnormality occurs in only the branch ducts or the acinar field of the pancreas. From this standpoint, pancreatograms in cancer of the pancreas can be classified into the following types: (I) obstructive, (II) stenotic, (III) diffuse narrowing, (IV) abnormal branching, and (V) cyst formation.[16-17] In the obstructive type (I), there is complete obstruction of the main pancreatic duct, and characteristically, the terminal end of the obstructed portion is irregular or tapered or shows cystic dilation. The stenotic type (II), in which there is a localized stricture of the main duct, is often accompanied by dilation of the duct proximal (upstream) from the stenosis, this being correctly termed prestenotic dilation. Pancreatograms of the diffuse narrowing type (III) reveal generalized or segmental narrowing of the main pancreatic duct, which also has an irregular contour in the region of the tumor. The abnormal branching type (IV), in which there is no marked change in the main duct, demonstrates only abnormally shaped main duct branches. Findings such as filling defects, obstruction, stenosis, or cystic dilation are included in cyst formation type (V), in which there is cystic dilation of the main duct or one or more of its branches, and is characteristic of cystadenocarcinoma.

Diseases involving the pancreas may produce secondary changes in the bile duct because of the anatomic relation of these structures. Cholangiographic abnormalities include displacement, effacement, stenosis, and obstruction. Freeny et al[18] has termed the cholangiographic findings of secondary biliary involvement in pancreatic carcinoma, the double-duct sign. In a blind review of 40 pancreatograms, these investigators correctly diagnosed 11 cases of pancreatic cancer. They found that diagnostic accuracy increased in pancreatic cancer when the bile duct also showed evidence of encasement with an irregular margin. They also found secondary biliary involvement in other pancreatic diseases, but disorders other than cancer tended to produce smooth and symmetric stenoses of the bile duct. Plumley et al[19] encountered the double-duct sign in 52 out of 1,180 pancreatograms. This was caused by pancreatic cancer in 30 and by benign pancreatic diseases in 22 patients. Although they did not regard this radiographic sign as disease-specific, they found that certain characteristics favored a malignant or benign process. Ductal obstruction, especially of the common bile duct, close proximity radiographically of the abnormalities in both ducts, and an abrupt and irregular transition from a normal to an obstructed or a stenotic bile duct favored the diagnosis of carcinoma. All cases of complete obstruction of the common bile duct were due to carcinoma. Long, smooth stenotic bile duct segments were more characteristic of benign pancreatic disease such as chronic pancreatitis.

There are reports of cases in which the main pancreatic duct appeared to be normal in the presence of proved pancreatic cancer.[5,7,8,19,20] Special care is required for the diagnosis of cancer in the uncinate portion of the pancreas because this location is relatively blind in terms of pancreatographic visualization.[21]

Metastatic malignancy may occasionally involve the pancreas and the main pancreatic duct. The main pancreatographic findings, stenosis and obstruction of the main duct, are indistinguishable from those of pancreatic carcinoma.[22]

Nix et al[23] reported the results of a 10-year study of 123 patients with carcinoma of the head of the pancreas who underwent ERCP. Many patients had "early" nonspecific complaints such as the sudden onset of diabetes mellitus (33.3%), weight loss (80.5%), tiredness and malaise (42.3%), change

in bowel habits (41.5%), and upper abdominal discomfort (22.0%). Jaundice (88.6%) and pain typical of pancreatic cancer (70.7%) were considered late symptoms. The diagnostic accuracy of ERCP was 92.7% and was considerably higher than that of CT (58.5%) or US (54.5%). The patients were divided into three groups according to tumor diameter: group 1, diameter 2.5 to 4 cm (44 patients); group 2, diameter 4.5 to 6 cm (45 patients); and group 3, diameter 7 to 15 cm (34 patients). Resection for cure was possible in 22% of the patients, and in these the 4-year survival was 44%. Four-year survival for the entire group of patients was 7.9%. Over the decade-long study period, there was a tendency toward diagnosis of smaller tumors with a higher chance of resectability. The authors suggested that aggressive use of ERCP in patients with nonspecific, "early" symptoms might improve the results of treatment of pancreatic cancer. In a subsequent study of 220 patients with carcinoma of the pancreas, Nix et al[24] found that patients with small tumors (<4.4 cm in diameter) in the absence of distant metastases had the best survival as well as the best chance for operative resection. Similarly, other investigators have noted a relationship between tumor size and survival, although the diagnosis of small lesions having a good prognosis is unusual.[24]

Based on experience at a single tertiary referral center, Gloor et al[26] suggested a rational strategy for the diagnosis of pancreatic carcinoma. They recommended helical CT as the best imaging test for periampullary malignancy. When this demonstrates a mass in the head of the pancreas that appears to be resectable, they advise surgical exploration. If there is a suspicion of pancreatic malignancy on the basis of clinical and laboratory findings but the helical CT is negative, Gloor et al[27] propose that ERCP be performed. In a retrospective cost-benefit analysis of 126 cases of pancreatic cancer, Alvarez et al[27] found that ERCP seldom resulted in a change in management when CT demonstrated a mass. ERCP was most useful when CT findings were either negative or equivocal. Cytologic diagnosis is recommended by Gloor et al[26] to obviate the need for surgery when the malignancy appears to be unresectable based on CT findings. If a cytologic diagnosis cannot be obtained, these authors recommend laparoscopy. Laparoscopic US may prove to be of additional assistance at this point in the management of patients. In a study of 73 patients with apparently early-stage cancer arising in the head of the pancreas, Bemelman et al[28] found that laparoscopic US changed the stage of the lesion in 41% of cases; laparotomy was avoided in 19%. The highly aggressive, CT-based approach advocated by Gloor et al[26] is predicated on the idea that a certain fraction of pancreatic cancers can be resected, in some cases with curative intent.

Endoscopic ultrasonography (EUS)

Transcutaneous abdominal US is a widely used imaging method. Because it is noninvasive, US has special value in the visualization of tumors of the liver, bile duct, and pancreas. However, ultrasonographic detection of small cancers of the pancreas remains difficult because of technical restrictions presented by intraabdominal gas, subcutaneous fatty tissue, bone, and the anatomically deeper position of the pancreas. Intraluminal EUS circumvents some of these problems. We have found EUS to be especially valuable in the evaluation of patients with pancreatic diseases, particularly the diagnosis and staging of pancreatic cancer.[29-31]

The unique aspect of EUS as a method of ultrasonographic imaging in relation to the pancreas is the close proximity of the transducer to the target organ. This reduces the depth of penetration of the ultrasound, thereby making possible the use of ultrasound frequencies (7.5 MHz or 12 MHz) that are higher than those that can be employed with US. These higher frequencies provide better resolution. Thus, lesions less than 5 mm in diameter can be identified by EUS.

Another unique attribute of EUS, in addition to the ability to identify small tumors, is the ability to accurately demonstrate the relation of pancreatic tumors to adjacent organs and structures. Thus, EUS can be especially helpful in determining the degree of invasiveness (stage) of a tumor and therefore the prospect for surgical resection. The criteria for vascular invasion are direct visualization of tumor growth within the vessel or vascular obstruction and loss of the hyperechoic interface between the tumor and the vessel.

Table 1. Visualization rate of pancreatic carcinoma on EUS compared with US, CT, and ERCP. Data compiled after Rosch Rösch and Classen,[26] Rosch Rösch,[6] and Rosch Rösch.[11] All four imaging methods were not compared in all of the included studies. (EUS-endoscopic ultrasonography; US-ultrasonography; CT-computed tomography; ERCP-endoscopic retrograde cholangiopancreatography).

	EUS	US	CT	ERCP
All tumors (n = 237)	n = 237	n = 210	n = 180	n = 126
	97%	3%	76%	92%
Small tumors (<3 cm)	n = 63	n = 50	n = 53	n = 41
	100%	59%	53%	85%

In clinical practice, most pancreatic cancers that produce clinical signs and symptoms are relatively large. They are therefore readily detectable by US, CT, and ERCP, or at least by some combination of these imaging methods.[32] Valuable additional information can be obtained by EUS in cases of smaller tumors that cause indirect ductal changes on ERCP and no positive findings by US and CT (Table 1). Early pancreatic carcinoma (staged according to the tumor-node-metastasis [TNM] classification as T1, N0, M0) has a considerably better prognosis after radical resection than more advanced cancers.[33] Although EUS recognizes even small pancreatic tumors with a high degree of accuracy, its use in screening asymptomatic individuals is at present not feasible. It has been shown that ERCP in patients with nonulcer dyspepsia detects pancreatic carcinoma in 9% of cases.[34] Whether EUS, rather than ERCP, in such patients will ultimately lead to an improvement in the early diagnosis and prognosis of pancreatic carcinoma remains to be shown.

Brush cytology

Direct cytologic sampling of pancreatic and bile duct strictures can be performed at ERCP using cytology brushes. Most of the available studies of the usefulness of brush cytology have focused on cytologic sampling of biliary strictures, and there is limited information specifically on specimen procurement from the pancreatic duct.

One of the largest studies is that of Ryan,[35] in which brushing was attempted in 69 patients with biliary or pancreatic duct strictures noted at ERCP. Satisfactory specimens were obtained in 62 patients (90%), with an overall sensitivity of 44% and a specificity of 100%. The sensitivity of brushing cytology for the bile duct (48.8%) was higher than that for the pancreatic duct (30%). The result was positive in 6 out of 20 patients with pancreatic carcinoma. There were no false-positive results, but brushing was falsely negative in 25 cases. During follow-up of 9 patients in whom the specimen was interpreted as showing atypical or reactive cells, a diagnosis of malignancy was made in all cases.

In the study by Osnes et al,[36] in which samples were obtained solely from the pancreatic duct, there were 11 technical failures, but these investigators found a much higher sensitivity (72%), a positive diagnosis having been achieved in 21 out of 29 patients.

One factor that may account for the lower sensitivity of pancreatic duct cytology in pancreatic carcinoma compared with biliary cytology in biliary malignancies may be the desmoplastic reaction seen in pancreatic cancer with eccentric displacement of the tumor. This may produce a situation wherein very few tumor cells are in contact with the brush, thereby reducing the yield. Although it might be assumed that sampling the pancreatic duct would have better sensitivity than sampling the bile duct in patients with pancreatic adenocarcinoma, diagnostic material may be obtained from both. In one series, the sensitivity of sampling from the common bile duct (CBD) versus the MPD was identical in 6 of the 20

patients with pancreatic cancer and positive brushings. Positive specimens were obtained from the CBD in 3 cases and from the MPD in 3 cases as well.[39] This suggests that sampling of both ducts is beneficial when pancreatic cancer results in strictures in both ducts ("double-duct" sign).

EUS-guided fine-needle aspiration biopsy (FNAB)

The accuracy of EUS-guided FNAB in diagnosing pancreatic malignancy in several series in which the presence or absence of a pancreatic mass was considered indeterminate on the basis of other imaging studies is shown in Table 2. The sensitivity is 80 to 85% in those cases in which FNAB provides sufficient cytologic material. In the various series, an adequate sample was obtained in 80 to 90% of cases. The results reported from more recent trials are, however, less encouraging, especially in difficult cases. Usually, two to four needle passes are adequate to obtain sufficient material for diagnosis. It has also been shown that assessment of the adequacy of the specimens by a cytopathologist at the time of the procedure increases diagnostic accuracy. As in other studies of cytologic methods for the diagnosis of pancreaticobiliary disorders, at ERCP for example, specimens that are classified as "suspicious" for malignancy, such as cellular atypia, are often considered as a positive diagnosis and these data are then combined with the unequivocal positive results to achieve high accuracy rates.

Table 2. Results of EUS-guided FNAB for pancreatic tumors. (EUS-endoscopic ultrasonography; FNAB-fine-needle aspiration biopsy)

Study	No. of Patients	Sensitivity (%)	Specificity (%)
Giovannini, 1995[40]	43	75	-
Chang et al., 1996[41]	164	83	90
Gress et al., 1996[42]	102	90	100
Nguyen & Chang, 1996[43]	45	85	85
Ciaccia et al., 1997[44]	28	67	100

The clinical necessity of EUS-guided FNAB of pancreatic tumors is controversial. Favorable opinion holds that it is essential to the decision process when the presence or absence of a pancreatic mass is indeterminate. The counteropinion, however, argues that because surgery is currently the only definitive treatment option for pancreatic cancer, patients fit for surgery who appear to have resectable tumors based on the results of imaging studies should undergo operation irrespective of the FNAB results, as there is a 15 to 20% chance of missing a carcinoma with this technique. For unresectable tumors, tissue should be acquired to rule out rare forms of pancreatic tumors (e.g., endocrine, lymphoma) that are treated differently. The relative role of EUS-guided versus US- or CT-guided percutaneous FNAB is not clear. Based mostly on retrospective and nonrandomized comparison studies, some investigators claim that the EUS approach is superior and they argue that lesions can be visualized and punctured under EUS control that are not visible by CT.[45] Data from a prospective and randomized comparison study of both techniques would be extremely helpful but are lacking. Such a study may be difficult to perform, at least in patients with resectable masses, because of the concern that percutaneous puncture may give rise to intraabdominal spread of the malignancy. This risk is theoretically lower with the endosonographic approach. In summary, therefore, FNAB should be recommended whenever the results of the procedure are likely to have definite implications for clinical management of the patient. A more general statement of the clinical role of EUS-guided FNAB in pancreatobiliary malignancy is not possible at present.

Laparoscopy

Laparoscopy immediately before laparotomy is an investigation that is worthwhile for pancreatic cancer. The conditions that should consider for laparoscopy are 1) larger primary tumor, 2) lesions in the neck, body and tail of pancreas, 3) equivocal radiographic findings such as low-volume ascites, CT findings indicating possible carcinomatosis and small hypodense lesions in liver, and 4) subtle clinical and laboratory findings suggesting more advanced disease such as marked hypoalbuminemia and/or weight loss, significant increases in CA19-9 level and relatively severe pain.

Surgical management

Surgical resection offers the only hope of cure for patients with pancreatic cancer. The Whipple operation, or pancreaticoduodenectomy, is the mainstay of surgical treatment for pancreatic cancers, most of which occur in the pancreatic head. The Whipple operation has been a classical operation for decades and the mortality has dropped dramatically as a result of improved perioperative care and increased experience in tertiary referral centers. In the 1990s, an operative mortality rate of less than 5% has become the standard in many experienced centers.

Pancreaticojejunostomy leakage remains one of the commonest and most dreadful complications after pancreaticoduodenectomy, with leakage rate of 14-18% reported in recent studies.[45-48] The techniques of pancreaticojejunal anastomosis, whether end-to-side or end-to-end, and whether duct-to-mucosa or dunking, have not been found to have a significant influence on the anastomotic leakage rate.

Apart from the immediate postoperative complications, long-term morbidities such as gastric dumping, marginal ulceration and bile-reflux gastritis are also major concerns after pancreaticoduodenectomy. The pylorus-preserving pancreaticoduodenectomy (PPPD) is a modification that aims at reducing such morbidities and preserving digestive function. However, there is no definite difference in postoperative nutrition between Whipple and PPPD.

Adherence or encasement of the portal vein or superior mesenteric vein by pancreatic head cancer has been regarded as locally advanced disease with poor outcome and thus a contraindication to resection. A recent study found that tumors adherent to the portal vein or superior mesenteric vein were not associated with more aggressive tumor characteristics, suggesting that venous adherence was a function of tumor location rather than an indicator of aggressive tumor biology.[49] Some Japanese reports have shown improved survival but other studies have reported no significant difference in operative mortality rate or long-term survival between patients who underwent portal vein or superior mesenteric vein resection for isolated tumor involvement and those without venous resection.[50,51] These studies suggested that isolated portal vein involvement should not be a contraindication for pancreatic resection in patients with pancreatic adenocarcinoma. Hence, resection of the portal vein should be performed if all diseases can be encompassed within the resection. Reconstruction of the portal vein and superior mesenteric vein can be accomplished by end-to-end anastomosis in most cases if the segment of portal vein or superior mesenteric vein resected is less than 2 cm.

Palliative surgery

Obstructive jaundice and duodenal obstruction are the two main symptoms that can be palliated by surgical means. Biliary-enteric and gastrojejunal bypass (double bypass) used to be the standard operation for inoperable pancreatic cancer. However, the role of surgeons in palliation of pancreatic cancer has diminished as endoscopic stenting can afford good palliation for biliary obstruction. Pain is one of the commonest problem that most patients suffer at the terminal stage of disease. Proper analgesic drugs and/or celiac plexus block can relieve the patient's pain. More than one-third of patients also suffer with depression, weight loss and malabsorption (exocrine insufficiency).

Prognosis

Though surgery is the treatment of choice in pancreatic cancer, the median survival after resection is only 18-20 months. The overall 5-year survival is 10% (7-25%) and up to 50% of those who survive 5 years may die of recurrent cancer. The factors that predict the recurrence rate and survival of the disease are resection margin, size of tumor (5-

year survival in tumor less than 2 cm is 20% whereas those larger than 3 cm is only 1%), lymph nodes involvement (median survival in negative and positive lymph nodes involvement are 4.5 years and 11 months, respectively) and the differentiation (5-year survival in poorly and well differentiated are 10% and 50%, respectively).

Molecular aspects

Pancreatic cancer is a consequence of stepwise accumulated genetic alterations which, for that reason, disturb the equilibrium of a cell by altering the relative balance between roles of the cell cycle, differentiation and dedifferentiation, and programmed cell death (apoptosis). Multiple genetic alterations involving activation of oncogenes and inactivation of tumor suppressor genes characterise the development of cancer in pancreas, notably *K-ras* oncogene, *p53*, *p16* and *DPC4* tumor suppressor genes and telomerase (Table 3, Figure 4). Moreover, abnormal expression of growth factors and growth factor receptors are also found to be associated with pancreatic cancer.

Table 3. Genetic profile of pancreatic cancer

Gene	Locus	Frequency (%)
K-ras	12p12.1 - pter	80-95
p53	17p13	50-70
p16	9p21	85
DPC4	18q21.1	~55
BRCA2	13q12	7-10
Telomerase	-	90

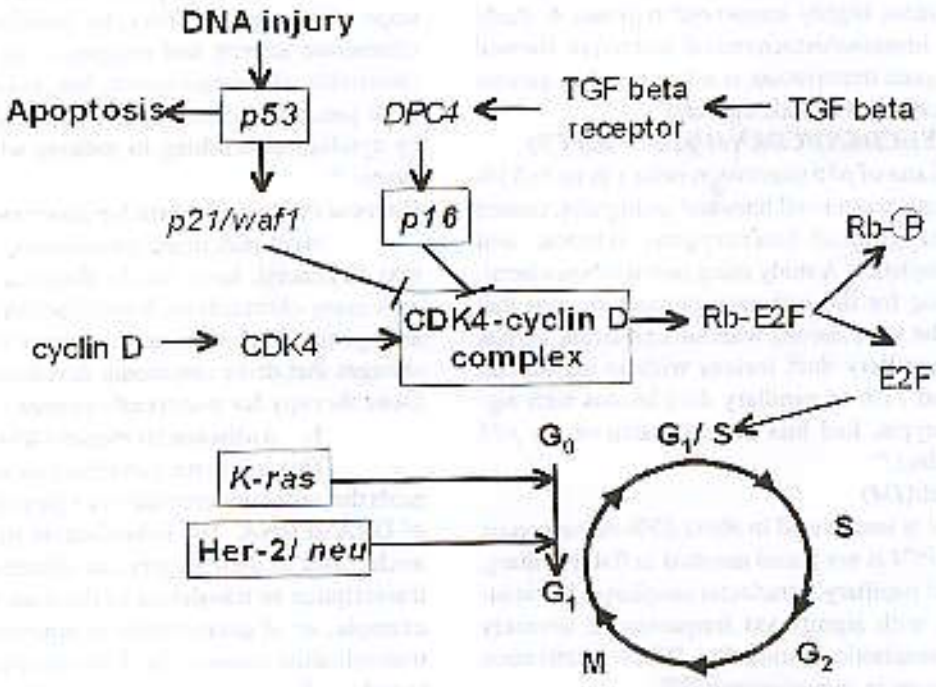

Figure 4. Genes and molecules involved in pancreatic tumorigenesis

Oncogene

Activation of *K-ras*

The most common genetic alterations to date in pancreatic cancer are activating point mutations in codon 12 of the *K-ras* oncogene. These mutations occur early in the neoplastic progression and can be found in 80 to 95% of pancreatic cancers. Single nucleotide substitutions of *K-ras* codon 12 are predominantly GAT, GTT and CGT. *K-ras* mutations have been detected in the pancreatic duct aspirates and stools of most patients with adenocarcinoma of the pancreas. The presence or the type of *K-ras* mutation in pancreatic tumors has not been shown to be associated with patient survival.[52]

Tumor suppressor genes

Most tumor suppressor genes have pivotal roles in cell cycle control and apoptosis. Loss of function can be associated with uncontrolled cell growth and proliferation, decreased apoptosis, and malignant transformation.

p53

It is inactivated in 50-70% of pancreatic cancer by a missense point mutation. The majority of the mutations are found in exons 5-8, which contain the most highly conserved regions. A study using an immunohistochemical technique showed that *p53* gene inactivation is a late event in genetic progression of pancreatic cancer.[53]

p16 (MTS1/CDKN2/CDKN4I/p16^{INK4a}/DPC3)

Loss of *p16* expression occurs in up to 85% of pancreatic cancer cell lines and xenografts, caused by homozygous or heterozygous deletion, and hypermethylation. A study using immunohistochemical labeling for the *p16* gene product showed that 30% of flat duct lesions without significant atypia, 55% of papillary duct lesions without significant atypia, and 71% of papillary duct lesions with significant atypia, had loss of expression of the *p16* gene product.[54]

DPC4 (SMAD4)

It is inactivated in about 55% of pancreatic cancer. *DPC4* is not found mutated in flat, papillary, or atypical papillary intraductal neoplasias but is inactivated with significant frequency in severely atypical neoplastic lesions. So, *DPC4* inactivation is a late event in tumorigenesis.[55,56]

BRCA2

It is inactivated in 7-10% of pancreatic cancer. The BRCA2 protein is believed to function as a genome-maintenance gene by preventing DNA strand breaks that occur during normal cell cycle division. The inactivation of the *BRCA2* gene, like *DPC4* and *p53* inactivation, occurs relatively late in neoplastic progression in the pancreas.[57]

Telomerase

Telomerase is an enzyme that is believed to be involved in the *de novo* synthesis of telomeric DNA onto chromosomal ends. Almost all normal somatic cells have no detectable telomerase activity except for proliferative cells of self-renewal tissues.[58] Activation and stabilization of telomerase are considered to be necessary for immortalization of human tumor cells. Telomerase activity was found in 90% of pancreatic ductal carcinomas while no adenoma tissue showed any telomerase activity. Thus, reactivation of telomerase may occur at a late stage of pancreatic ductal carcinogenesis and may be a specific marker for distinguishing pancreatic cancer from pancreatitis and adenoma. By detecting telomerase activity in pancreatic juice at an early stage of pancreatic cancer, no correlation between telomerase activity and prognosis has been found. Detectable telomerase activity has also been reported from pancreatic ductal cells obtained during ERCP by cytological brushing in patients with pancreatic cancer.[59]

Current cytogenetic data for pancreatic cancer

Most pancreatic carcinomas, like carcinomas in general, have highly abnormal karyotypes, with many chromosome translocations and other rearrangements. These must contribute to the genetic changes that drive carcinoma development.[60]

Gene therapy for pancreatic cancer

1. **Antisense strategies (AS)**

This technique comprises the use of nucleic acids that are complementary to a particular sequence of DNA or RNA. The hybridisation of these oligonucleotides to their targets can effectively obstruct transcription or translation of the gene product. For example, an oligonucleotide complementary to the transinitiation codon of the *K-ras* gene has been used to reduce *K-ras* expression which thereby inhibited the growth of pancreatic cancer cells in culture.[61]

2. Gene-directed prodrug activation therapy (GPAT)

This technique utilises enzymes that are nonmammalian in origin or in small quantities within human cells. For example, the herpes simplex virus thymidine kinase (*HSV-tk*) gene is delivered preferentially to pancreatic cancer cells by a vector and then prodrug, ganciclovir (GCV), is added so that cancer cell which now harbor the activating enzyme thymidine kinase will die. This is because *HSV-tk* phosphorylates GCV to GCV monophosphate, which is then further phosphorylated by the host cell to the toxic form, GCV triphosphate. GCV triphosphate inhibits DNA polymerase and is toxic to cells in the S phase of the cell cycle. The regression of hepatic metastases and peritoneal dissemination of pancreatic cancer caused by *HSV-tk* has been reported.[42,43]

3. Promoter gene strategies (PS)

This technique utilizes mammalian tumor-associated promoters to drive the expression of certain genes, e.g., tk. The delivered gene will not be expressed in normal cells because these promoters are theoretically not active in normal tissues and so they will be unable to generate toxic metabolites from prodrugs such as GCV. Promoters that are commonly used are CEA, MUC1, and CA19-9 promoters.

4. Oncolytic viral therapy (OVT)

This technique characterises the targeting of replication-competent adenoviruses and herpes viruses to tumor cells and their destruction by viral replication and resultant cell lysis. The benefit is that not every cell needs to be infected because there is inherent amplification as the virus replicates and destroys adjacent tumor cells. Moreover, these viruses can carry transgenes like thymidine kinase in order to augment tumor cell killing by combining prodrug activation with oncolysis.

CONCLUSION

We demonstrate a case with ductal adenocarcinoma at the head of pancreas that was diagnosed by dual-phase helical computed tomography. Subsequently, he underwent pyloric-preserving pancreaticoduodenectomy. Though surgery is the treatment of choice in this disease, the median survival after resection is only 18-20 months. It has the lowest 5-year survival rate of any cancer and up to 50% of those who survive 5 years may die of recurrent cancer. Detection of the cancer at an early stage by the establishment of the screening strategy and the development of adjuvant therapy and molecular approaches might provide more options and better clinical outcome for pancreatic cancer patient.

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