MINI-REVIEW

Pancreatic Cancer: Pathogenesis and Diagnosis

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Abstract

   Pancreatic cancer is a fatal malignancies which is predominantly seen in men and at advanced age (40-85 years) and has an aggressive course. Its frequency is gradually increasing over the past years. It accounts for 2% of all cancers and 5% of cancer-related deaths. Pancreatic cancer takes the first place among asymptomatic cancers. Ninety percent of cases are adenocarcinomas. Ten percent of the patients have a familial disposition. The disease is very difficult to detect as it has no early signs and spreads rapidly to surrounding organs is one of the most deadly types of cancer. Pancreatic cancer may result from hereditary germline or somatic acquired mutations in cancer-related genes and mutations also cause cancer progression and metastasis.

Keywords: Pancreas cancer - pathogenesis - diagnosis

Introduction

Pancreas is an important retroperitoneal organ with exocrine and endocrine functions. Tumors of pancreas are divided into two groups (Wolfgang et al., 2013). 1) Non-endocrine pancreas tumors 2) Endocrine pancreas tumors. Non-endocrine pancreas tumors are categorized as benignant and malignant. Benignant non-endocrine tumors of the pancreases: adenoma, cystadenoma, lipoma, fibroma, hemangioma, lymphangioma and neuroma. Malignant tumors of the pancreases have different histological features i.e. 1) Ductal adenocarcinoma 2) Cystadenocarcinoma and 3) Other (sarcomas, metastatic etc) malignant tumors. Diabetes Mellitus (DM) with an onset after 45 years of age may sometimes foresee pancreatic cancer. Pancreatic cancer may sometimes manifest as acute pancreatitis. Today, there are opinions that pancreatic cancer originates from a genetic disposition (stem cell disease) (Hezelet al., 2006; Jamiesen et al., 2012; Avila et al., 2013; Fang et al., 2013; Gnoni et al., 2013; Wood et al., 2013). Presence of some colonic polyp types or cancer in the family or personal history increases the likelihood of pancreas cancer.

Risk Factors

Age, being overweight, smoking, long-term alcohol use, pre-existing chronic pancreatitis, family history, prior abdominal radiotherapy are important risk factors (Table 1) (Wolfgang et al., 2013). Smoking is a very important risk factors with smokers being at a 2.2-fold higher risk of pancreatic cancer compared to non-smokers. The 'fingerprint' method demonstrated more mutations in

pancreatic cancers in smokers compared to pancreatic cancers in non-smokers. Long-term DM is associated with increased pancreatic cancer. In addition, new-onset DM may be the initial sign of pancreatic cancer. Increased body mass index (BMI) is associated with increased pancreatic cancer. Higher alcohol consumption is associated with increased pancreatic cancer compared to lower alcohol intake. Low to moderate alcohol consumption does not increase the risk. Chronic pancreatitis increases the risk of pancreatic cancer by 2.71 fold compared to people without chronic pancreatitis.

Hereditary Risk Factors

Individuals with familial history of pancreatic cancer are at an increased risk of cancer. Several germline genetic mutations are involved in pancreatic cancer development (Table 2). In the BRCA2 mutation, pancreatic cancer, breast, ovarian, prostate cancer risk is increased.

Table 1. Risk Factors in Pancreatic Cancer (BMI: Body mass index)

Risk Factor	Risk Estimate (595 Ci)
Currently smoker	OR= 2.20 (1.71-2.83)
Ex-smoker	
1-10 years	OR=1.64 (1.36-197)
15-20 years	OR=1.12 (0.86-1.44)
D. MELLITUS	
< 3 years	RR=7.94- (4.70-12.55)
>10 years	OR= 1.51 (1.16-1.96)
BMI > 35 and 18.9-24.9	OR= 1.55 (1.16-2.07)
Excessive alcohol consumption	OR= 1.46 (1.16-1.83)
Pancreatitis (> 2 years)	2.71 fold (1.96-3.74)

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Hereditary pancreatitis, Lynch syndrome and Peutz-Jeghers syndrome is associated with increased pancreatic cancer risk (Wolfgang et al., 2013).

Screening groups

Patient groups with conditions including hereditary pancreatitis, familial pancreatic cancer, Peutz-Jeghers disease, familial atypical mole melanoma, cystic fibrosis of pancreas, familial cancer syndromes [(Lynch syndrome, familial adenomatous polyposis (FAP), hereditary breast and ovarian cancer-BRCA1 and BRCA2 mutations)] are at an increased risk of pancreatic cancer and should therefore be screened for pancreatic cancer using specific methods (Lee et al., 2009).

Causes of Pancreatic Cancer

Pancreatic cancer results from hereditary germline or somatic acquired mutations in cancer-related genes (oncogenes, tumor suppressor genes, cell cycle genes,

apoptosis and genome maintenance genes), and mutations also case cancer progression and metastasis (Hezelet al., 2006; Jamiesen et al., 2012; Avila et al., 2013; Fang et al., 2013; Gnoni et al., 2013; Wood et al., 2013). In addition, cell turnover, shortened telomerase and genomic instability have significant roles in progression of pancreatic epithelial cells to pancreatic cancer (Figure 1).

Precursor conditions

There are some precursor diseases to pancreatic cancer. These include 1) Pancreatic intraepithelial neoplasm (PanIN) 2) Intraductal papillary neoplasm (IPMN) 3) Mucinous cystic neoplasms (MCN). These 3 precursors are believed to originate from pancreatic cancer stem cells (CSC) (2). Figure 1 demonstrates the progression of normal pancreatic duct epithelium to pancreatic adenocarcinoma by the events in early (telomerase shortened, KRAS mutation, p16 loss) and late stage (p53 loss, SMAD4/DPC loss).

1) PanIN: PanINs are non-invasive microscopic

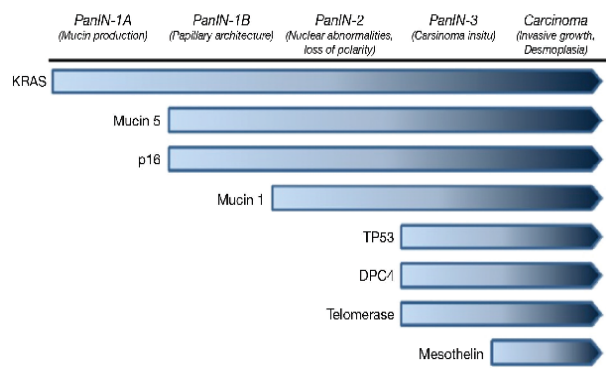**Table 2. Predisposing Genes in Pancreatic Cancer**

Gene/Risk Groups	Risk Estimate (95% CI)	Risk Estimate Life Expectancy In Pancreatic Cancer
General population		0.96 (80 years)
Familial pancreatic cancer		
Mean	RR=6.79 (4.54-9.75)	
≥3 first degree relatives with pancreas cancer	RR= 17.2 (7.34-33.5)	
High penetrance		
BRCA2	RR=3.51 (1.87-6.58)	3.36% (80 years)
PALB2	Increased	Increased
BRCA1	OR=2.26 (1 .26-4.06)	2.16% (years 80)
Mismatch Repair (HNPCC)	RR=8.6 (4.7-15.7)	3.68% (1.45-5.88%) (years 70)
Hereditary Pancreatitis (PRSS1)	RR=8.6 (4.7-15.7)	30-40% (years 70)
Petuz-Jeghers (STK11)	RR=58 (23-105)	11-32%
Familial Melanoma (CDKN2A)	RR= 132 (44-261)	17% (years 75)
ATM	RR=38 (10-97)	Increased
Low penetrance		
AB0 blood type	OR= 1.20 (1.12-1.28)	1.15% (years 80)
1 q32.1 (rs3790844 T/C)	OR=0.77 (0.71 -0.84)	0.73% (years 80)
13q22.1 (rs9543325 T/C)	OR=1.26 (1.18-1.35)	1.2% (years 80)
5p 15.3 (es401681 C/T)	OR=1.19 (1.11-1.27)	1.10% (years 80)
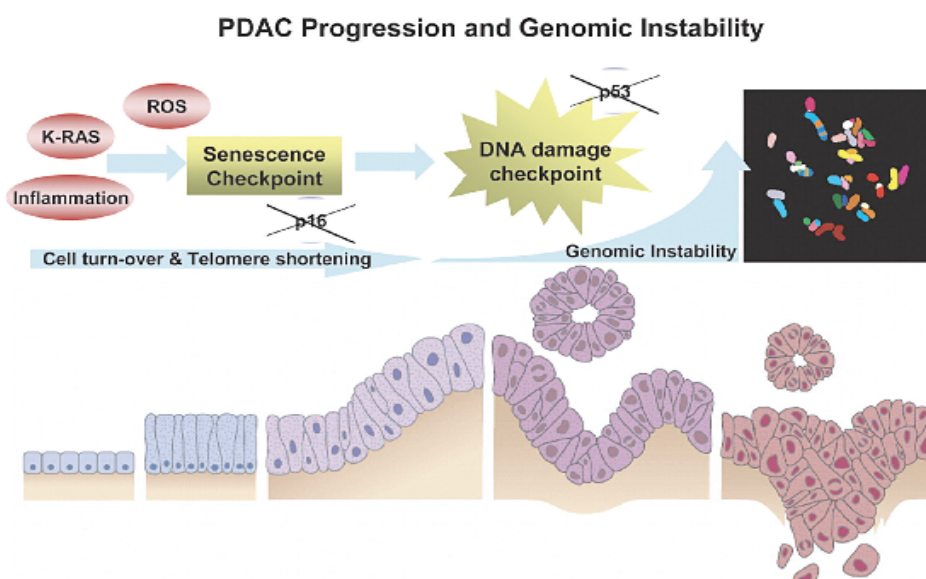
Figure 1. Progression to Pancreatic Cancer and Genomic Instability

Pancreatic Cancer: Pathogenesis and Diagnosis
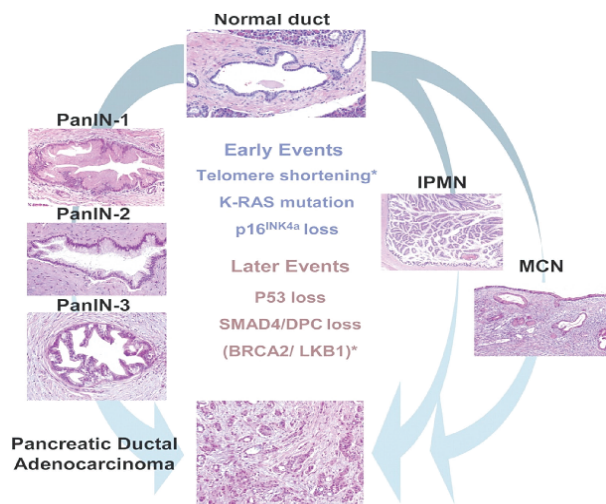
Figure 2. Events During Progression from Normal Pancreatic Duct Structure to Pancreatic Adenocarcinoma

Figure 3. Genetic Mutations Detected in the PanIN Group

epithelial neoplasms (Gnoni et al., 2013). They are usually located at the small pancreatic duct. There are divided into 3 subgroups by epithelial atypia. 1) PanIN-1 (minimal atypia), which also has 2 subgroups, i.e. A) PanIN-1A (flat type) B) PanIN-1B (papillary type); 2) PanIN-2 and 3) PanIN-3 (limited atypia). PanIN is associated with mutations, its prevalence increases with age and is usually located at the head of the pancreas. It is associated with invasive carcinoma and chronic pancreatitis, and endoscopic ultrasonography (EUS) is useful in diagnosis. KRAS mutations occur at codon 12, 13 and 61. HER-2/neu expression is 82% in PanIN 1A, 86% in PanIN 1B and 92% in PanIN-2. Figure 2 demonstrates the steps in PanIN cancer development and Figure 3 demonstrates mutations detected in PanINs.

2) IPMN: It is usually small and asymptomatic. It progresses slowly and is more common among smokers (Gnoni et al., 2013). It may be together with Peutz-Jeghers syndrome, FAP, familial pancreatic carcinoma (FPC). It has 2 subtypes: 1) IPMN-MD (main duct type) and 2) IPMN-BD (branch duct type). It accounts for 1-2% of all pancreatic exocrine tumors and 20-50% of all cystic tumors. Its actual incidence is not known as it is small and asymptomatic. It develops from the main pancreatic duct or branch ducts and releases mucin. In 2010, WHO classified IPMNs by malignant transformation properties as low, intermediate, high grade dysplasia and by invasive cancer characteristics. They can be differentiated by mucin antibody staining properties using immunohistochemical dyes in 4 subgroups as gastric, intestinal, pancreatobiliary and oncocytic. The intestinal type is the most common one. It is usually seen at the head of the pancreas, around the ampulla of Vater, at the inlet of the pancreatic duct.

Table 3. Genetic Alternations in Common Pancreatic Cancers

Tumor Type	Genes	Prevalence
Invasive Ductal Carcinoma	APC	
	CTNNBI (beta catenin)	5%
	KRAS	95%
	p16/CDKN2A	95%
	TP53	75%
	SMAD4	55%
	MLL3, TGFBR2, FBXW7, ARIDIA, AIRD2, ATM	<5%
IPMN	KRAS	80%
	RNF43	75%
	GNAS	60%
	P16/CDKN2A	Variable by histological degree
	TP53	Variable by histological degree
	SMAD4	Variable by histological degree
	PIK3CA	10%
MCN	KRAS	75%
	RNF43	40%
	P16/CDKN2A	Variable by histological degree
	TP53	Variable by histological degree
	SMAD4	Variable by histological degree
Pancreatoblastoma	Chromosome II	85%
	CTNNBI (beta catenin)	55%
	APC	10%
PanNET	MENI	45%
	DAXX or ATRX	45%
	TSC2, PTEN, PIK3CA	15%
	SCN VHL	50%
SPN	CTNNBI	95%

Genes involved in IPMN are listed in Table 3. Main duct type IPMN is treated surgically. For IPMN from branch ducts, yearly or 6-12-monthly checks are performed if the tumor is <10 or 10-20 mm respectively, while mm whereas >20 mm tumors are resected surgically.

3) MCN: It is generally solitary and may vary between 5 and 35 cm in size. It has thick/fibrotic wall and may contain mucin, hemorrhagic fluid pr necrotic material. It is rare, has a female to male ratio of 20:1 and the median age of onset is around 40-50 years. Its diagnosis is usually incidental and it is asymptomatic. Nausea, weight loss and back pain can be seen. It is usually located at the head and tail. Microscopically, it is divided into 3 groups by dysplasia severity as a) mild MCN b) moderate MCN and c) severe MCN. Macroscopically, it is divided into 3 groups as solitary, multilocular and unilocular. Genes responsible in MCN are listed in Table 3. They usually grow slowly, may cause epigastric discomfort and distension and are incidentally detected during abdominal mass screening. Nausea, vomiting and back pain may occur. If malignant changes occur, lack of appetite and weight loss may be seen. Five-year survival is about 20-60% in invasive MCN (Gnoni et al., 2013).

Oncogenes

Oncogenes are involved in cancer development when they are mutated and activated. They are activated by different mechanisms (point mutation, amplification). Increasing numbers of oncogenes responsible for pancreatic cancer have been identified recently (Hezel et al., 2006; Avila et al., 2013; Fang et al., 2013; Gnoni et al., 2013; Wood et al., 2013). Genetic alternations, germline and somatic mutations were held responsible in pancreatic cancer. Sixteen mutated oncogenes have been identified in this disease, including KRAS, TP53, CDKNA2A, SMAD4, MLL3, TGFBR2, ARID1A, SF3B1, EPC1, ARID2, ATM, ZIM2, MAP2K4, NALCN, SLC16A4, MAGEA6. Mutation in oncogene KRAS is most frequently at codon 12 and was found in 90% of pancreatic cancer cells and 20% of whole body cancer cells. KRAS oncogene adversely affects cell life and cellular functions

such as cell differentiation and cell proliferation.

KRAS mutation occurs in codon 12 but sometimes in codon 61 or 13. KRAS mutation induces formation of ductal precancerous formations and causes multifocal hyperplastic focus at the pancreatic duct. These are precancerous formations. KRAS also activates many signaling pathways. P13K-AKT pathway is activated (affects cell life and cell circulation). It activates MEK and ERK1/2 pathway (affects angiogenesis, cell proliferation, cell apoptosis, cancerous cell migration and cell cycle regulation). It also activates NOTCH pathway (affects cell proliferation, cell differentiation and cell apoptosis). It affects Hedgehog pathway (causes metastases). STAT3 activation is also observed in patients with pancreatic cancer (STAT3 inhibitors are used in cancer treatment).

MiRNA

micRNAs are small uncoded RNA molecules and regulate gene expressions. miRNAs are about 1000 and are involved in pancreatic tumor development and have oncogenic functions. miRNA-196a, miRNA-190, miRNA-186, miRNA-200b, miRNA-15b, miRNA-95, miRNA-21, miRNA-155, miRNA-221, miRNA-222 have important roles in the development of pancreatic cancer (Jamiesen et al., 2012).

Tumor suppressor genes

Tumor suppressor genes (TSG) protect cell cycle or cell apoptosis from tumorogenesis. p53 mutation is seen in 75% of pancreatic cancer cases. DPC4 (deleted in pancreatic cancer, locus 4), LKB1 (liver kinase B1) mutation, deletion and mutation in INK4a are found in 95% of the cases. MKK4 (mitogene activated protein kinase 4) deletion are seen in patients with pancreas cancer. DPC4 causes distant metastases in pancreatic cancer. LKB1 gene mutation causes Peutz-Jeghers syndrome and therefore pancreas cancer.

Symptoms

Approximately 70-80% of the patients with pancreatic cancer has pain in the epigastrium. The pain is in the stomach area and may sometimes radiate to sides and back. Sitting still or bending forward alleviates the pain. Jaundice, findings of cholestasis, lack of appetite, unexplained weight loss, depression and sometimes diarrhea/steatorrhea are seen. In cancers at the head of the pancreas, a progressive and dark jaundice is seen due to the obstruction of the bile duct. The physician should consider the possibility of pancreas cancer especially in the presence of permanent-persistent pain around the abdomen, navel and stomach, indigestion, swelling, weight loss and lack of appetite. Gallbladder will be palpable as vesicle hydrops (Courvoisier-Terrier findings) if the bile ducts are constricted by the tumor.

Diagnostic Methods in Pancreas Cancer

Many methods are used in the diagnosis of pancreatic cancer (Ozkan et al., 1995 ; Lee et al., 2009; Kaur et al., 2012; Bardou et al., 2013; Cote et al., 2013; Hackert.,

Table 4. Methods used in Diagnosing Pancreatic Cancer

Test	Specifity	Sensitivity	Staging Benefit
Ultrasonography	80%	90%	NO
EUS	90%	90%	YES
CT	90%	95%	YES
ERCP	90%	90%	NO
MR	90%	90%	NO
Thin Needle Aspiration	90%	98%	NO

Table 5. Role of Tumor Markers by Pancreatic Cancer Stage in Diagnosis

CSTAGE	CA-50	CA 72-4	CA 19-9
I	15.21±1.12	3.72±0.67	26.31±6.56
II	32.42±19.07	1 7.1 3±1.97	875.45±329.31
III	98.97±30.18	49.55± 10.91	1223.43±479.73
IV	179.46±24.91	76.15+17.64	2018.19±731.36

*Serum CA-50, CA 72-4, CA 19-9 and CA 242 levels

2013; Munroe et al., 2013). The features of these methods are provided in Table 4.

Tumor Markers

Tumor markers including carcinoembryonic antigen (CA) 19-9, CA 72-4, CA 50, CA 242 are used in the diagnosis of pancreatic cancer. The associations of these markers with the disease are shown in Table 5. A number of new tumor markers have been suggested recently. Novel markers will probably be introduced in the near future by genomic, epigenetic and proteomic techniques. These diverse markers include CEACAM1: Carcinoembryonic antigen-related cell adhesion molecule 1 (biliary glycoprotein), MIC-1: Macrophage inhibitory

cytokine-1 (MIC-1), Fibrinogen gamma, Sialylated plasma protease C1, N83 glycolsylation of antitripsyn, N83 glycolysylation of 1-antitripsin, Apolipoprotein A1, transithretin, apolipoprotein E, gelsolin, lumican, metalloproteinase 1 tissue inhibitor, HSP27, HSP70, PGK1, HMGB1, DJ-1 etc. There are also other diagnostic markers such as cytokine and chemokine levels (C3, C5, CD40, CD40 ligand factor B, GLP-1IFN-gama, IgM, IL-10,-11,-12,-13,-16,-18, integrin-alpha-11, procathepsin W, TGF-β1, TGF-α, VEGF etc.), different miRNA levels, autoantibodies (anti-MUC1 IgG antibody, anti-ENOA1/2, anti-CTDSP1; anti-MAPK9 and anti-NR2E3 etc.).

Figure 4. Tumor at the Pancreas Head Infiltrating the Lower end of the Choledoch (ERCP)

Figure 5. Intraductal Ultrasonography

Imaging methods

Several methods including EUS, magnetic resonance cholangiopancreatography (MRCP), magnetic resonance (MR), computed tomography (BT), positron emission tomography (8) (PET), biopsy (percutaneous or endoscopic), endoscopic approaches (Pancreatoscopy, endoscopic retrograde cholangiopancreatography (Ozkan et al., 1995) (ERCP), optical endomicroscopy, intraductal ultrasonography (Cote et al., 2013; Munroe et al., 2013) (USG), enhanced USG, and elastography are used for early detection of pancreatic cancer, to locate the tumor, to determine invasion, for screening and staging. Because percutaneous biopsy may result in micrometastases (seeding) in younger patients for whom surgery is feasible, it is appropriate in elderly, inoperable patients.
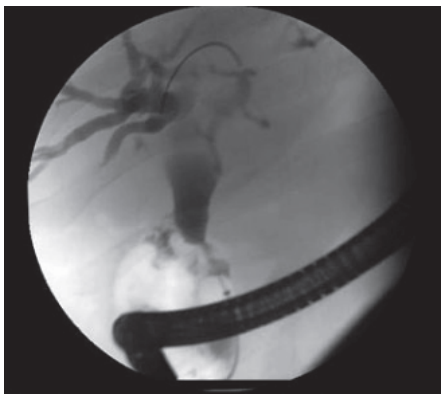
ERCP

It is performed to diagnose cancer in the head of the pancreas, for biopsy and stent insertion (Figure 4). It allows biopsy from ampulla of Vater tumors. If cholestasis has developed at the pancreas head, plastic or metallic stent needs to be inserted into the choledoch (Lee et al., 2009; Kaur et al., 2012; Ozkan et al., 2012). During ERCP, pancreatic fluid can be taken and CEA, IGFBP2 (Insülin–like growth factor binding protein-2), MMP-9, DJ-1, AIBG etc. can be investigated.

MRCP

It should be performed before ERCP, and information about bile ducts and pancreatic ducts should have been collected (Lee et al., 2009).
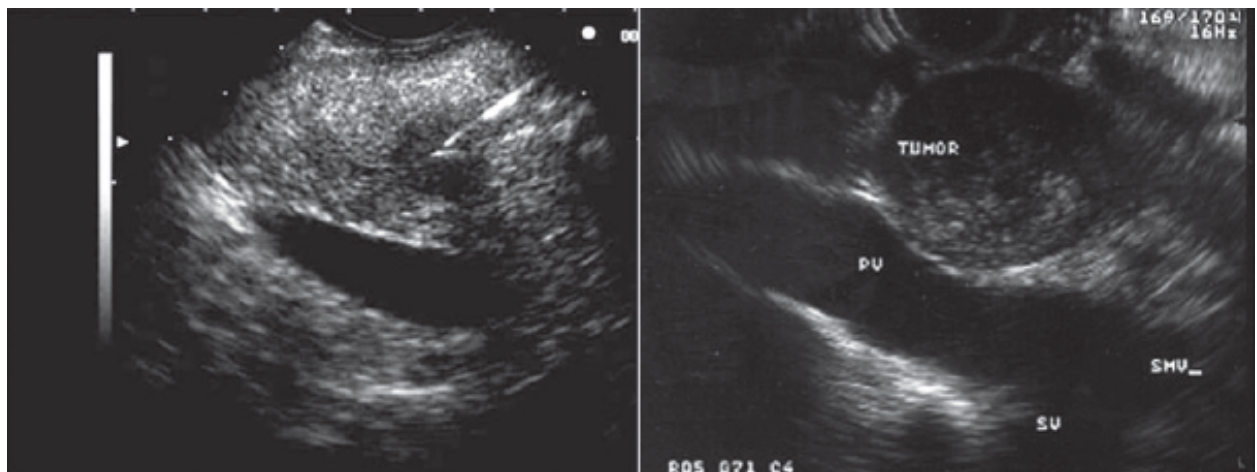

Figure 6. This Image Shows the Mass in the EUS-assisted Pancreas and Biopsy Procedure

Abdominal MR and Abdominal CT

They are helpful in detecting pancreatic cancer, determining its location and metastases.

PET

It provides information regarding the diagnosis, differential diagnosis of pancreatic cancer and extrapancreatic involvement (Lee et al., 2009). By performing pancreaticoscopy, endoscopic investigation of the interior pancreatic duct is performed (Ozkan et al., 1995).With intraductal ultrasonography (Figure 5) and EUS (Figure 6), information are obtained on the location of the tumor and peripancreatic invasion (Cote et al., 2013; Munroe et al., 2013).

Conclusions

In conclusion, pancreatic cancer is a fatal malignant disease. Pancreatic cancer results from hereditary germline or somatic acquired mutations in cancer-related genes and mutations also case cancer progression and metastasis. In addition, cell turnover, shortened telomerase and genomic instability have significant roles in progression of pancreatic epithelial cells to pancreatic cancer. We need much more studies and research about this disease.

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