



Sofía Cáceres. *El Reptil y la Fruta (The Reptile and the Fruit)*. Mixed media on canvas, 30" × 46".

Risk factors, genetic syndromes, screening modalities, and screening studies of pancreatic cancer are reviewed.

Early Detection of Pancreatic Cancer: Why, Who, and How to Screen

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Background: Pancreatic cancer represents the fourth-leading cause of cancer death in the United States, with a dismal 5-year survival rate of less than 5%. Despite advancements in screening and early detection of other cancers such as breast and colon cancer, no reliable screening test exists for pancreatic cancer. Subsequently, the majority of patients present with advanced-stage disease leading to a poor prognosis. Because of the relatively low incidence, current efforts are focused on early detection and screening only in patients at high risk for the development of the disease.

Methods: We discuss the practical considerations encountered when determining if an individual should be screened for pancreatic cancer. The current literature was reviewed regarding risk factors, genetic syndromes, screening modalities, and screening studies of pancreatic cancer. The current high-risk pancreatic screening program at our institute is also summarized.

Results: Current efforts to detect pancreatic cancer at a curative phase are focused on screening individuals at high risk for the development of this disease. They include kindreds with two or more first-degree relatives affected with this disease and those with known hereditary pancreatic cancer syndromes. Hereditary pancreatic cancer syndromes include Peutz-Jeghers syndrome, familial breast cancer syndrome, and familial atypical multiple mole melanoma syndrome. Of all the screening modalities available, endoscopic ultrasound is the most sensitive and specific screening tool to evaluate the pancreas and has been proven to detect early precancerous and cancerous changes in clinical studies.

Conclusions: Early detection and screening for pancreatic cancer in the current state should be limited to high-risk patients, although hereditary/familial factors account for only 10% of patients with pancreatic cancer. Continued efforts are needed to discover effective test to identify patients with nonhereditary risk factors who will benefit from screening and also to develop less invasive and more cost-effective screening modalities aimed at controlling pancreatic cancer.

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Submitted January 17, 2008; accepted March 26, 2008.

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Abbreviations used in this paper: EUS = endoscopic ultrasound, FNA = fine-needle aspiration.

Introduction

The American Cancer Society estimates that 37,680 Americans will be diagnosed with cancer of the pancreas during 2008.¹ An estimated 34,290 Americans will die of pancreatic cancer in 2008, making this type of cancer the fourth-leading cause of cancer death overall.¹ Approximately 75% of patients will die within 1 year of diagnosis, and only about 4% will survive 5 years after diagnosis.¹ Even for patients diagnosed early who undergo a curative resection, the 5-year relative survival rate is < 20%.¹ A critical factor in the poor outcome is due to the silent nature of pancreatic cancer until late in the disease process. Patients present for a medical evaluation only when the cancer is advanced and they experience signs and symptoms of obstructive jaundice, abdominal pain, and weight loss. Clearly, early detection is an important strategy to improve outcomes. The most practical issues regarding early detection that need to be considered include identifying who should be screened and selecting the most appropriate modality to use for screening. Screening programs for pancreatic cancer need to be conducted in the context of carefully designed studies to determine if screening for early pancreatic neoplasia and timely interventions results in decreased pancreatic cancer incidence and mortality. Furthermore, molecular analysis of tissue specimens and carefully collected epidemiologic data may shed light and lead to the discovery of less invasive and more widely applicable methods to detect this highly lethal disease early. Table 1 summarizes the principles of a successful screening program and also outlines how the pancreatic cancer screening program at our institute satisfies these principles.

Screening: Targeting Individuals at High Risk

The ideal goal of screening for pancreatic cancer is to detect the disease at an early phase (preinvasive or early invasive) when it is curable. It is well established that pancreatic adenocarcinoma arises from pancreatic ductal cells and progresses through precursor lesions. The three known precursor lesions are pancreatic intraductal neoplasia, intraductal pancreatic mucinous

neoplasm, and mucinous cystic neoplasm (Fig 1). The grading scheme reflects increasing atypia until eventually it leads to carcinoma. Since patients seldom exhibit disease-specific symptoms at the early phase of the disease, screening needs to be done in asymptomatic individuals. However, given the low incidence and prevalence of pancreatic cancer, it would not be cost effective or worthwhile to screen the general population since the yield of screening would be extremely low. For screening to be cost effective, a recent study estimated that the probability of detecting preinvasive or invasive disease needs to be 16% or greater.² Therefore, screening should be targeted to individuals at high risk for developing pancreatic cancer in order to enrich the screening population.

Risk Factors

Several risk factors have been identified that increase an individual's risk of developing pancreatic cancer. Table 2 summarizes these factors and the relative risk for developing pancreatic cancer if present in the patient's medical history.

Familial Pancreatic Cancer

Familial pancreatic cancer is defined as a clinical setting in which a family has at least 2 first-degree relatives affected with pancreatic cancer without accumulation of other cancers or familial diseases. It is estimated that up to 10% of pancreatic cancers may have a familial component.^{3,4} Population-based studies have shown that almost 8% of patients with pancreatic cancer have a family history of pancreatic cancer.⁵ Based on data from the National Familial Pancreatic Tumor Registry (NFPT), the risk of developing pancreatic cancer in relatives of families with at least 2 affected first-degree relatives was 18-fold higher than that of sporadic cases. Kindreds with 3 affected first-degree relatives had a 57-fold risk increase of developing pancreatic cancer.⁶

Hereditary Pancreatic Cancer Syndromes

Certain germline mutations are known to give rise to hereditary pancreatic cancer syndromes including BRCA2,⁷⁻¹⁰ p16,^{11,12} *STK11/LKB1*,^{13,14} and *PRSS1*.¹⁵

Table 1. — Principles of a Successful Screening Program

Principles	Moffitt's Pancreas Screening Program
Reasonable yield is expected	Estimated yield is 10%
The most sensitive/specific screening tool is used	EUS is the most sensitive specific screening tool to evaluate the pancreas
Screening is voluntary	Participation is voluntary
Results are appropriately interpreted	Screening procedure is performed by an expert endoscopist
Supportive care is offered	Psychosocial support and genetic counseling are offered to participants
Screening improves survival	Early detection and treatment of pancreatic neoplasia improves survival
Benefits of screening outweigh risks	Potential early detection of pancreatic neoplasia in an asymptomatic high-risk individual outweighs the minimal risk of the procedure to the patient

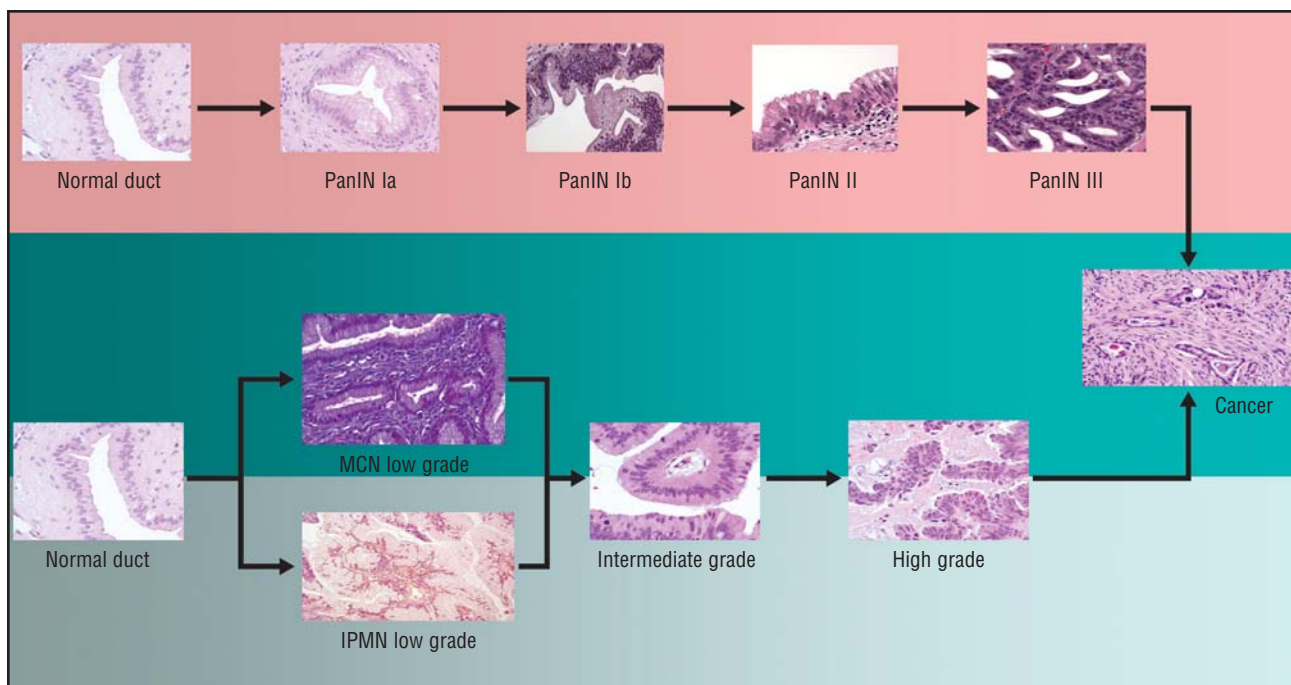


Fig 1. — Pathways of pancreatic adenocarcinoma progression. The three known precursor lesions are pancreatic intraductal neoplasia (PanIN), mucinous cystic neoplasm (MCN), and intraductal pancreatic mucinous neoplasm (IPMN).

BRCA2: BRCA2 is a key regulator of gene transcription. Mutation in this gene results in hereditary breast and ovarian cancer syndromes. Over the last 10 years it has been noted that some families with BRCA2 mutations have a high incidence of pancreatic cancer. Recent studies have shown that BRCA2 is present in 17% to 19% of families where at least 2 first-degree relatives have pancreatic cancer.^{7,9} People of Ashkenazi Jewish descent who carry a BRCA2 mutation are also at increased risk of developing pancreatic cancer. In this patient group, cancer is attributable to the BRCA2 6174delT mutation in 1 of 10 patients who develop pancreatic cancer.¹⁶

Familial Atypical Multiple Mole Melanoma Syndrome: Familial atypical multiple mole melanoma (FAMMM) is an autosomal dominant inherited syndrome characterized by multiple nevi, atypical nevi,

and multiple melanomas. Recent reports note that the p16 mutation associated with FAMMM is responsible for the increased risk of pancreatic cancer among affected individuals with a lifetime risk of 16%.^{11,12}

Peutz-Jeghers Syndrome: Peutz-Jeghers syndrome is an autosomal dominant syndrome characterized by hamartomatous gastrointestinal polyps and mucocutaneous pigmentation. The germline mutation that accounts for this syndrome is the *STK11/LKB1* gene. Patients with known Peutz-Jeghers syndrome have a relative risk of 132 and a cumulative lifetime risk of 36% for ages 15 to 64 for the development of pancreatic cancer.^{13,14}

Hereditary Pancreatitis: Hereditary pancreatitis is inherited as an autosomal dominant trait, with 60% of cases attributed to the *PRSS1* mutation. There is a high incidence of pancreatic cancer 30 to 40 years after the age of onset of recurrent attacks of pancreatitis.¹⁷ Pancreatic cancer risk is 50 times higher in patients with hereditary pancreatitis, with an estimated lifetime risk of pancreatic cancer of 40% by 70 years of age.¹⁵ The risk is double in patients with hereditary pancreatitis who smoke, and it is diagnosed 20 years earlier than in patients who do not smoke. Patients with non-hereditary chronic pancreatitis also have an increased risk of developing pancreatic cancer regardless of the cause of pancreatitis, and the total risk increases with a longer history of chronic pancreatitis.¹⁸

Table 2. — Risk Factors and Relative Risk for Developing Pancreatic Cancer

Risk Factor	Relative Risk
Familial pancreatic cancer:	
2 first-degree relatives affected	18
3 first-degree relatives affected	57
Hereditary pancreatic cancer syndromes:	
BRCA2 mutation	5.9
Familial atypical multiple mole melanoma	16
Peutz-Jeghers Syndrome	36
Hereditary pancreatitis	50
Cigarette smoking:	
Positive family history of pancreatic cancer	3.7
Diabetes > 20 years	2

Cigarette Smoking

Cigarette smoking is associated with 25% of pancreatic cancers.^{19,20} Patients who are long-time smokers (ie,

more than 20 years) have double the risk of developing pancreatic cancer than patients who never smoked.^{19,20} In those with a family history of pancreatic cancer, smoking has even a greater effect; they have up to a 3.7-fold increase of developing pancreatic cancer and may present with the disease one to two decades earlier.²¹⁻²³ Smoking also increases the risk for pancreatic cancer in individuals with hereditary pancreatitis by 2-fold,²³ as noted above.

Long-Standing Diabetes

Patients who have been diagnosed with adult-onset diabetes have a 2-fold increase in the risk of pancreatic cancer.²⁴ Whether this is a consequence of the disease or an independent risk factor is unclear. Given the high prevalence of long-standing diabetes in the general population and the low incidence of pancreatic cancer, screening patients with diabetes is likely to produce a low yield and will not be cost effective.

Common Imaging Modalities for Suspicion of Pancreatic Cancer

Despite advancements in technology and better capability in screening for many cancers, no ideal single screening test exists for pancreatic cancer. Although a variety of tumor markers have been proposed for the diagnosis and surveillance of pancreatic cancer, including CEA and CA19-9, none has been proven to be highly sensitive or specific to pancreatic cancer and therefore is not ideally suited for screening. Imaging studies are useful to diagnose pancreatic cancer once the tumor is large enough to cause symptoms, but at this point the disease is more likely to be at an advanced and unresectable stage. When pancreatic cancer is suspected, the most common imaging modalities include transcutaneous ultrasound (TCUS), computed tomography (CT) scan, magnetic resonance imaging (MRI), and most recently endoscopic ultrasound (EUS).

EUS vs Other Imaging Modalities

Of all the imaging studies, EUS and helical CT scans are the most sensitive imaging modalities for detecting pancreatic tumors and should be considered as the first imaging studies when there is a clinical suspicion of pancreatic cancer.²⁵ When comparing all the modalities available to screen patients for pancreatic cancer, EUS should be the modality of choice due to its ability to perform fine-needle aspiration (FNA). When evaluating patients with suspected pancreatic cancer, EUS has been shown to be superior as a diagnostic modality in sensitivity, specificity, and accuracy compared with other staging modalities including CT scan, TCUS, angiography, and MRI.²⁶⁻³⁰ This is especially true when evaluating and aspirating tumors less than 2 cm in diameter.³¹

Once a pancreatic mass is detected, the most common approaches to obtain a tissue diagnosis are by CT-



Fig 2. — High-frequency ultrasound waves are transmitted from the transducer at the tip of the echoendoscope to the target tissue. For optimal imaging, a balloon surrounding the transducer is inflated with water to improve ultrasound transmission.

guided biopsy, by endoscopic retrograde cholangiopancreatography (ERCP) with brushings of an obstructed bile duct/pancreatic duct if the mass is in the head of the pancreas, or by EUS with FNA. When evaluating pancreatic masses, EUS-guided FNA is the most accurate diagnostic modality. Harewood and Wiersema³² demonstrated this in 185 patients with pancreatic masses and negative tissue sampling by ERCP or negative CT-guided FNA. EUS-guided FNA had a sensitivity of 94% and accuracy of 92% for detecting malignant disease in patients with negative ERCP tissue sampling and 90% sensitivity and 84% accuracy in patients with negative CT-guided biopsy. The established superiority of EUS in evaluating pancreatic masses led to exploring its merit as a screening tool for patients at high-risk for the development of pancreatic cancer.

EUS as a Screening Tool for Pancreatic Cancer

EUS was originally developed in the early 1980s as an alternative diagnostic imaging modality to address the inherent limitations of TCUS such as limited depth of penetration and image interference from intra-abdominal gas and bony structures.³³ Initial ultrasound scopes provided a 360° image but were unable to perform biopsies. Over the last 20 years, technological advances have broadened the field of endosonography. With the development of linear array echoendoscopes and incorporation of FNA and color flow/Doppler data, the utilization of EUS has evolved from a diagnostic tool to an interventional procedure. EUS combines real-time endoscopy with high-frequency ultrasound to detect pancreatic abnormalities through the stomach and duodenum. The principles of EUS are based on the development and interpretation of ultrasound waves. High-frequency ultrasound waves are transmitted from the transducer at the tip of the echoendoscope to the target tissue. For optimal imaging, a balloon surrounding the transducer is inflated with water to improve ultrasound transmission (Fig 2). This process is known as acoustic coupling. Images are constructed from the reflective properties of the tissue components and utilize real-time imaging techniques similar to a B-mode

(brightness modulation) display format. The brightness is dependent on the amount reflected. Intensely reflected areas appear white (hyperechoic), while areas of low reflection appear dark (hypoechoic). This allows for high-resolution imaging of the five histologic layers of the gastrointestinal wall and the surrounding structures, including the pancreas. Given the minimal invasiveness

and low complication rate of the procedure, which are similar to those of standard endoscopy for patients who do not undergo FNA,³⁴ as well as an overall complication rate of 1.6% to 2%^{35,36} when FNA is performed, EUS and EUS-guided FNA have become attractive, highly accurate, and safe procedures in the diagnosis and treatment of many gastrointestinal diseases.

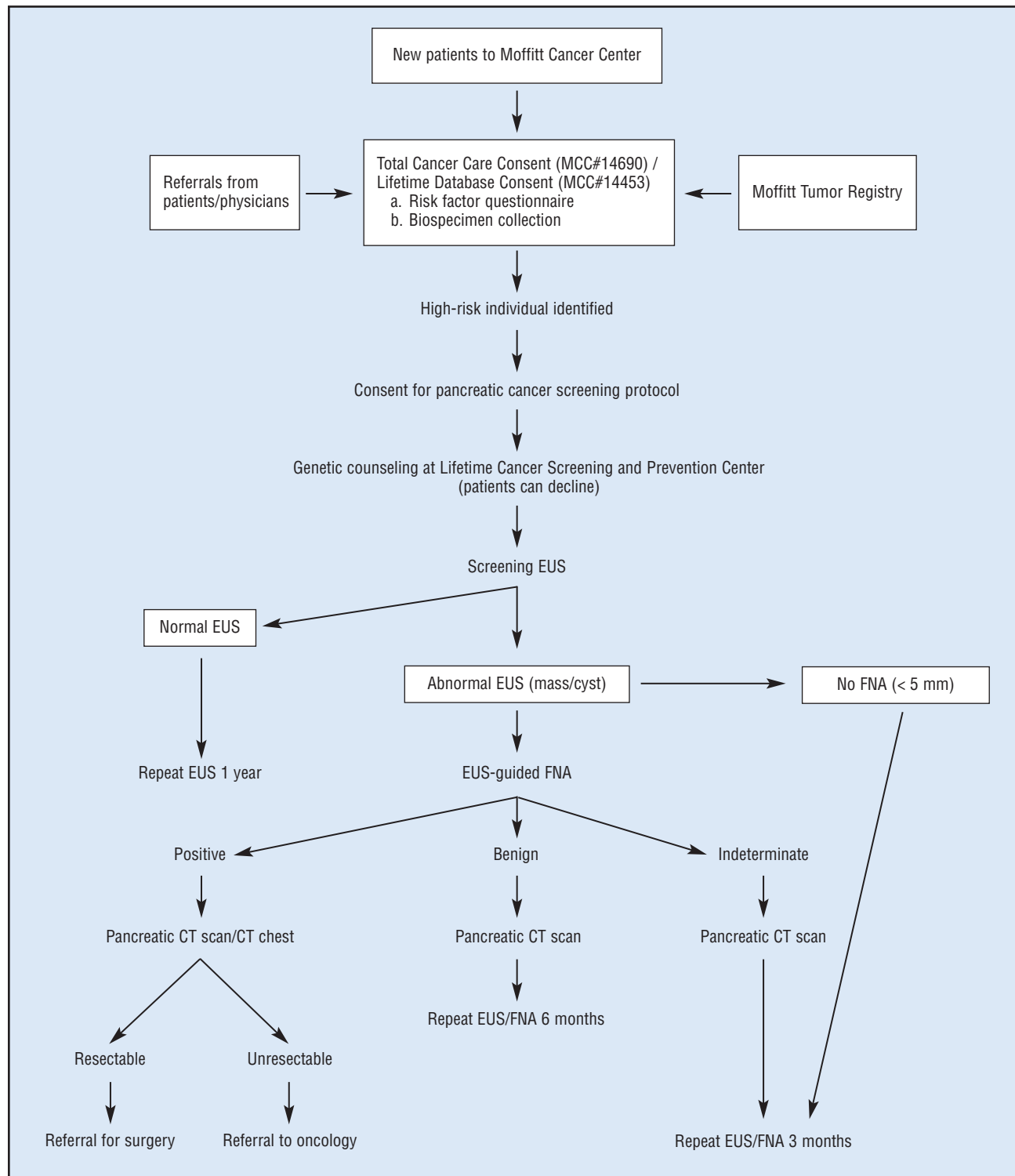


Fig 3. — Protocol for high-risk assessment, screening, and early detection of pancreatic cancer at Moffitt Cancer Center.

Experience With Screening Using EUS

In a pilot study by Canto et al,³⁷ screening was performed on individuals determined to be at high-risk for developing pancreatic cancer using an EUS-based approach. Thirty-eight asymptomatic patients with at least 2 first-degree relatives affected with pancreatic cancer were studied over a 3-year period. Six pancreatic masses were found, one was an invasive adenocarcinoma and one was an intraductal papillary mucinous tumor. The study concluded that screening an asymptomatic high-risk patient population could detect prevalent pancreatic neoplasia. A follow-up study by Canto et al³⁸ evaluated screening for early pancreatic neoplasia in high-risk individuals in a prospective, controlled study. The study screened 78 patients determined to be high-risk for pancreatic cancer and found

8 patients with pancreatic neoplasia (10% yield of screening). Four of the patients were diagnosed at the initial screening examination, and 4 were diagnosed within the first year of follow-up. Based on this study, the authors concluded that screening of high-risk individuals is warranted due to the number of significant asymptomatic pancreatic neoplastic lesions found in this cohort of individuals.

Moffitt Cancer Center Screening Program for Pancreatic Cancer

Based on these preliminary studies, some centers are involved in clinical trials that are screening patients deemed to be at high-risk for the development of pancreatic cancer based on family history of pancreatic cancer or rare genetic syndromes that increase the risk of pancreatic cancer. A program for screening patients at high-risk for the development of pancreatic cancer was recently established at our institute. This program, which is based on using EUS as the screening procedure, is conducted under an Institutional Review Board (IRB) protocol (Fig 3).

Patient Recruitment

Eligible subjects for the program, as described in Table 3, may be identified and recruited either from our institute or from the Lifetime Cancer Screening and Prevention Center located in Tampa, Florida, by completing the self-reported risk factor questionnaire. Patients may also be referred from physicians at our institute or from physicians in the community or by patients themselves. Also, eligible subjects who are enrolled in the Family Cancer Genetics Network may be contacted regarding interest in this study. Lastly, first-degree relatives of patients with pancreatic cancer from our institute's tumor registry may also be contacted to determine eligibility. These potential high-risk individuals are then referred to determine eligibility.

Total Cancer Care Protocol/Lifetime Cancer Screening Database for Cancer Risk Assessment and Early Detection

Patients are asked to participate and consent to the IRB-approved Moffitt Total Cancer Care protocol. The purpose of the Total Cancer Care initiative is to improve our ability to predict diagnosis, prognosis, and response to therapy in the management of the cancer patient. This study requires patient permission to store (for long-term use) their blood and tissues and also clinical data collected during their regular medical care and during specific therapeutic trials. The goal of the study is to establish a unique collection of blood, tissues (normal and tumor), and associated clinical data (survey data, medical record data, and cancer registry data) from thousands of cancer patients. The blood, tissue, and clinical data will be used for a number of different

Table 3. — Eligibility and Exclusion Criteria for Screening Patients at High Risk for Pancreatic Cancer

Eligibility Criteria
Correlation with one of the following high-risk groups:
<ul style="list-style-type: none">• Patient has 2 or more relatives with pancreatic cancer and has a first-degree relationship with at least one of the relatives with pancreatic cancer.• If only 2 family members are affected, then both must have had pancreatic cancer and a first-degree relationship with the individual screened.• If there are more than 2 affected individuals on the same side of the family, at least 1 of the individuals must have a first-degree relationship with the member being screened.• Patient is at least 40 years of age or 10 years younger than the youngest affected individual.
Peutz-Jeghers syndrome patients age > 30 years
Hereditary pancreatitis patients
Patients with familial atypical multiple mole melanoma (FAMMM) syndrome
Patients with BRCA2 mutation and at least 1 first- or second-degree relative with documented pancreatic cancer
Willingness to undergo EUS with possible FNA
Willingness to undergo surgical evaluation for abnormal EUS/FNA finding
Willingness to undergo radiographic evaluation if screening findings are abnormal
Exclusion Criteria
Medical contraindications to undergoing endoscopy or obstruction of the gastrointestinal tract that precludes passage of the endoscope
Personal history of pancreatic adenocarcinoma
Previous partial or complete resection of the pancreas for adenocarcinoma
Prior partial or total gastrectomy with Billroth II or Roux-en-Y anastomosis
Coexisting cancer in other organs or AIDS/HIV
Life expectancy < 5 years
Pregnancy
Previous CT scan or ultrasound of the abdomen within the last 3 years

types of cancer research studies defined by future IRB-approved studies.

Patients seen at the Lifetime Cancer Screening and Prevention Center are asked to consent to the Lifetime Database for Cancer Risk Assessment and Early Detection protocol. The purpose of this protocol is to establish a cohort of individuals with self-reported risk factor information and biospecimens (serum, urine, and DNA) using the patient population at the Lifetime Cancer Screening and Prevention Center. The goal of the protocol is to obtain permission to use the data, biospecimens, medical records, and questionnaires obtained from this patient population for investigator-initiated studies on etiology and/or early detection of cancer. In addition, patients may be followed actively or passively for subsequent cancer events, and they may be contacted for participation in future clinical trials to reduce their risk of cancer.

Genetic Counseling

Patients consented for the pancreatic cancer screening study are offered genetic counseling through the Lifetime Cancer Screening and Prevention Center. A team of professionals at the Center, including board-certified clinical geneticists, genetic counselors, physicians and nurse-practitioners, help formulate and develop a screening and surveillance plan for those patients at increased risk for cancer. Genetic counseling includes a detailed review of the patient's family history to determine if a cancer does indeed run in the family. Counseling of the patient is conducted and a cancer-screening plan formulated. Genetic testing will be offered to individuals when appropriate.

EUS Results

Once patients are consented for the screening protocol, EUS is performed in the usual fashion. Patients are evaluated for changes in the pancreatic duct and pancreatic parenchyma, and these abnormalities are documented in the endoscopy report. If a mass or cyst is found during the EUS examination, FNA is performed in the usual fashion



Fig 4. — EUS examination of a normal pancreas.

with the aid of a cytopathology technician in the endoscopy suite to ensure adequacy of the specimen.

Patients with a normal EUS examination of the pancreas are placed in the surveillance arm of the protocol and undergo yearly EUS examinations. A normal examination consists of complete evaluation of the pancreas that reveals either a completely normal-appearing pancreas (Fig 4) or parenchymal changes defined by strict EUS criteria but without the development of a mass or cyst. If at any future EUS assessment a mass/cyst is detected, FNA is performed and the patient follows that arm of the protocol.

An abnormal EUS examination is defined as the finding of a mass or cyst during evaluation that requires FNA (Fig 5). If the lesion is too small to aspirate (< 5 mm), patients are entered into surveillance with a repeat EUS in 3 months. If during EUS examination a mass or cyst is found that is large enough to undergo an FNA, an FNA is performed. If the FNA results are consistent with cancer, patients undergo standard-of-care workup and staging of the cancer with radiology studies to determine resectability. If the tumor appears resectable, surgical evaluation is performed with an expert pancreatic surgeon who determines and weighs the patient's risks, benefits, and alternatives to pancreatic surgery that, at our institute, has an operative mortality of less than 1%.

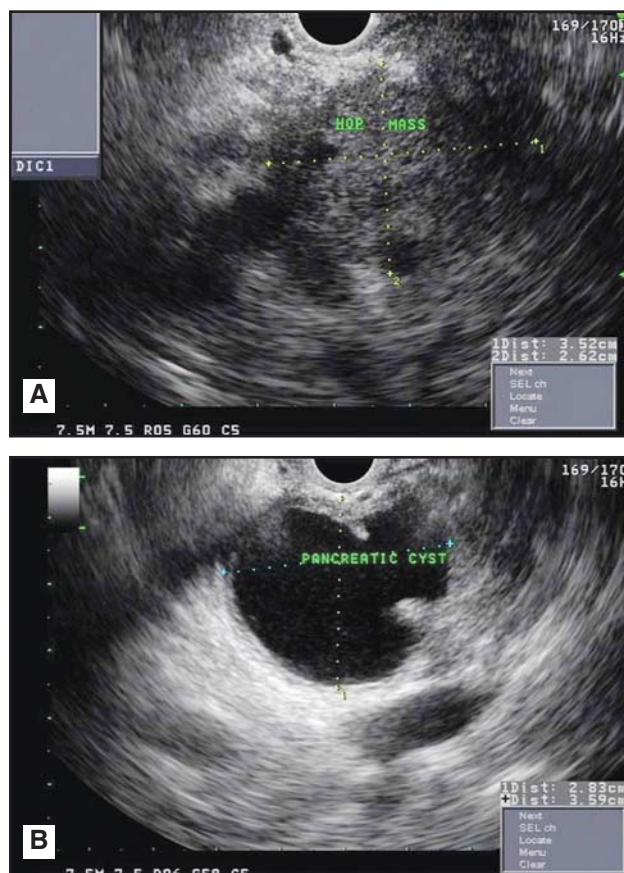


Fig 5A-B. — An abnormal EUS examination defined as the finding of a mass (A) or cyst (B) during evaluation that requires FNA.

If the cancer is unresectable, patients are referred for oncologic evaluation. If the FNA results are benign or indeterminate, patients undergo a CT scan of the pancreas. If the CT scan is unrevealing in both cases, patients who had a benign FNA will undergo a repeat EUS with FNA in 6 months, while patients who had an indeterminate FNA will undergo a repeat EUS with FNA in 3 months. Depending on the results of the repeat FNA, patients enter either the treatment arm or the surveillance arm of the protocol. Patients with severe dysplasia or cancer who decline surgery or are unable to undergo surgery are offered surveillance follow-up with either CT scan or EUS in 3 to 6 months to assess stability of the abnormality.

Conclusions

Screening high-risk individuals for pancreatic cancer is the only practical approach to detect precancerous or cancerous changes in the pancreas at the phase in which surgical intervention will have a high chance of cure. The limitations of the current screening strategy include the fact that we can screen only about 10% of individuals who will develop pancreatic cancer and that an invasive procedure (EUS) is the best screening modality. Screening protocols that are poised to exploit molecular advances in oncology will likely yield insights that will help identify a larger subset of patients who will be at risk to develop pancreatic cancer and will lead to the development of less invasive and effective screening modalities.

Disclosures

No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.

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