Screening and Surveillance of Pancreas Neoplasia. Can we and should we?

Luis F. Lara, M.D.
Assistant Professor of Internal Medicine
Division of Digestive and Liver Diseases

[July 11, 2008]

Dr. Lara is on the speaker's bureau of Boston Scientific Corporation and receives financial support from them for clinical studies. No off label use of medication or equipment will be discussed.

Introduction

Pancreas cancer has a terrible survival rate and is being diagnosed more frequently according to published national data. The incidence is similar to the death rate, underscoring the aggressiveness of this disease. While survival rates depend on the stage of the disease at time of diagnosis, the overall survival at five years is dismal, and has not changed significantly over the years. This probably reflects that the disease when it becomes symptomatic is usually beyond a curative window.

Being a relatively rare cancer it would be ineffective to launch a massive screening effort. There is no proven screening or surveillance technique. Focused efforts to diagnose the disease at an early malignant, or even better, at a pre-malignant state in a population at increased risk for the disease would be a more effective way of channeling resources. The hope would be that this would translate in to a broader program that could include a more generalizable test, or tests, applicable to the general population.

Consensus meetings [Brand, Gut 2007] have been established to create practice recommendations to bring some degree of homogeneity to efforts in the United States and abroad to establish practical ways to perform surveillance in patients considered to be at high-risk for developing pancreas malignancy.

The focus of this review is on pancreas ductal adenocarcinoma (PanCA) recognizing that there are other histological forms of pancreas malignancy (lymphoma, pseudo-papillary tumor, medullary pancreas cancer, etc) but that comprise only about 5% of neoplasia that affect the pancreas. Risk factors, precursor lesions and selected gene mutations that could be used to diagnose the disease at an early or even pre-malignant state are reviewed. Surveillance strategies, including the one being used at the University of Texas Southwestern are discussed, and future directions are proposed.

Epidemiology

PanCA is the 4th leading cause of cancer related death in the United States, and affects males more than females (13/100,000 vs 10.3/100,000). The overall life time risk of an average individual is 1.3% or about 1 in 75 adults. African-Americans and those older that 60 years are also at increased risk. About 34,000 new cases occur each year, and that number continues to rise. About 32,000 die from the disease each year. Overall, about 20% survive over 12 months, and the five year relative survival rate is <5%. Only 20% are resectable at time of diagnosis, and another 30% believed to be resectable are actually not at time of surgery. This is because only 7% of the disease is limited to the pancreas, 26% have lymph node involvement and over 52% have metastatic disease at time of diagnosis [Yeo, Curr Probl Surg 1999; Ariyama Pancreas 1998; www.seer.cnacer.gov].

Risk Factors for Pancreas Cancer

There are epidemiological risk factors that clearly increase the risk of developing PanCA. Knowledge and identification of these could trigger an aggressive behaviour modification program, especially in high-risk individuals. (Table 1).

Tobacco smoking is very much linked to PanCA. Twenty-five percent of PanCA patients have a history of tobacco smoking. The risk is up to four-fold, and smoking "less" does not reduce the risk; actually, the risk is similar even at half a pack a day. PanCA also

develops at least a decade earlier in smokers who have chronic pancreatitis, and the risk remains elevated even in after quitting [Warshaw, New Engl J Med 1992; Doll, Br Med J 1976; Rulyak, Gastroenterology 2003].
Chronic pancreatitis increases the risk of PanCA at a rate of 2% per year [Lowenfels, N Engl J Med 1993]. Interestingly, while alcohol abuse is a risk factor for chronic pancreatitis it is does not increase the risk of PanCA.
Certain workers (metallurgic, combustibles) have an up to five fold increased risk of developing PanCA [Alguacil, Occup Environ Med 2003], and an association between cadmium exposure has been reported.
A high fat and low fiber diet also is associated with an increased risk of PanCA, and it is now evident that obesity is also a risk factor [Banke, Med Clin North Am 2000].
The association between diabetes mellitus (DM) and pancreas cancer is interesting [Banke, Med Clin North Am 2000; Everhart, JAMA 1995; Gapstur, JAMA 2000]. Up to 80% of patients with PanCA develop glucose intolerance. Compared to a control population, a higher incidence of PanCA has been reported within the first two years of the diagnosis of DM [Gupta, Clin Gastroenterol Hepatol 2006]. This association becomes less relevant by year five [Chari, Gastroenterology 2001]. At the same time, "PanCA induced DM" occurs two to 3 years before the diagnosis of PanCA is established. The mechanism is unknown, but a paracrine signaling mechanism is supposed as the glucose intolerance can develop even in the presence of a small tumor, where the rest of the gland is unaffected.

Table 1. Risk Factors

Tobacco smoking
Chronic Pancreatitis
Work related
Diet
Obesity
Diabetes Mellitus

<u>High Risk Pancreas Cancer Groups</u>
Cohorts at an increased risk for developing PanCA compared to the general population have been identified. They can be grouped as being part of a syndrome (*Syndromic PanCA*) or can occur independently.

Family History of Pancreas Cancer
The risk of developing PanCA increases with the number of family members that are affected, and the closeness of the relationship to the index case. The risk is 2.3 fold if a first degree relative is affected, and increases to 32 fold if more than two first degree relatives have suffered the disease [Canto, Clin Gastroenterol Hepatol 2006; Maitra, Annu Rev Pathol Mech Dis 2008]. Other malignancies (breast, ovarian, prostate, etc) are also more frequently reported in family members of patients affected with PanCA, and

the primary malignancy in first degree relatives of PanCA cohorts is PanCA [Lucas, DDW 2008]. This knowledge should increase the awareness of potential neoplastic associations that increase the risk of pancreas malignancy, and a referral to genetic counseling should be considered.

Hereditary or Familial Pancreas Cancer

This should be considered if more than two immediate family members have suffered PanCA, and especially so if one was less than 50 years old. A familial form of PanCA accounts for 10% of all PanCA cases, but genes are mostly unknown. It displays an autosomal dominant pattern, with widely variable penetrance [Silverman, Br J Cancer 1999; Lynch, Semin Oncol 1996]. It is associated with other malignancies, so vigilance of associations may help identify yet another syndromic type of PanCA. A young onset of PanCA has been traced to FANC mutations [Hruban, Ann Oncol 1999; Brentnall, Ann Intern Med 1999].

Tropical Pancreatitis

It is a form of idiopathic chronic pancreatitis that occurs in southern India and sub-Saharan Africa. Symptoms and morphological abnormalities start in childhood. Impressive pancreas calcifications, and endocrine and exocrine insufficiency are usually evident by the second decade of life. Mutations in the SPINK gene may a risk factor. The risk of PanCA is up to 100 fold [Chari, Pancreas 1994].

Hereditary Pancreatitis

It is a familial form of chronic pancreatitis that increases the risk of PanCA. It is due to a mutation (usually R122H or N29I) in the cationic trypsinogen gene (PRSS1) on chromosome 7, and is inherited as an autosomal dominant trait. As in tropical pancreatitis, the disease manifests itself clinically in childhood, and evidence of pancreas insufficiency and calcifications become evident in the second or third decade of life [Lowenfels, Med Clin North Am 2000; Witt, Gastroenterology 1999; Howes, Digestion 2000]. Later onset of disease may be due to variable gene penetrance, or as yet to be identified gene mutations in PRSS1 or other genes. A family history of recurrent and/or chronic pancreatitis is almost invariably present. Actually, discovering a PRSS1 mutation in patients with idiopathic chronic pancreatitis and no family history of chronic pancreatitis is very rare. This suggests that *de novo* PRSS1 mutations are very infrequent, and should give pause when ordering the test when the prior probability it will be positive is very low. The cumulative risk of developing PanCA at age 70 is 40%, and smoking increases the risk 150 fold, and it is diagnosed in younger patients [Lowenfels, JAMA 2001].

Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)

It occurs due to a deletion in *p16/CDKN2A*. The overall risk of PanCA is similar to melanoma, and is 13 to 22 fold compared to the general population.

Others

Peutz-Jeghers, and the associated *STK 11/LKB1* mutation has a 36% lifetime risk of PanCA.

Cystic fibrosis almost invariably causes pancreas exocrine insufficiency by the early teens, and an 32 fold increased risk of PanCA has been reported.
BRCA2 mutations have been reported in up to 25% of PanCA, and more recent data suggests an association with BRCA1 gene mutations. It is not clear if HNPCC and mismatch repair gene mutations increase the risk of PanCA. (Table 2)

A genetic mutation is more likely to be found in syndrome associated PAnCA, but, as with other diseases, the absence of a family history of the disease does not rule out a possible germ-line mutation. Confirmation of a genetic mutation, on the other hand, may help identify high risk individuals and could single out candidates for surveillance of PanCA or pre-cancerous lesions.

Table 2. Hereditary Pancreas Cancer

	Chromosome	Gene	Organs	Risk
FAMMM	9p	*p16*	skin	34x
HNPCC	2p,q	mismatch		
	3p,7p	repair gene	GI/GU	?
Breast CA	17q	*BRCA1*	ovarian,	2x
	13	*BRCA2*	prostate	10x
Peutz-Jeghers	19p	*STK11/LKB1*	GI	4x
FAP	5q	*APC*	GI, liver, brain	5x
CF	7q	*CFTR*	GI	32x
HP	7q	*PRSS1*		50x
Familial PanCA	?	?	?	32x
Young onset PanCA	numerous	*FANC-C* *FANC-G*	blood	?

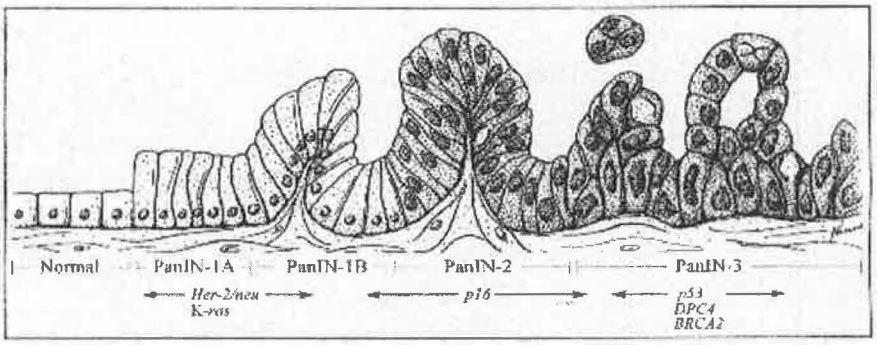
Precursor Lesions

Beyond genetic mutations and syndrome associated PanCA there are three lesions within the pancreas that portend a higher risk of developing PanCA. These include pancreatic intra-epithelial neoplasia, called PanIN lesions, intrapapillary mucinous neoplasia, or IPMN, and mucinous cystic neoplasia, or MCN.

PanIN lesions are microscopic epithelial abnormalities described as PanIN1, 2 or 3 depending on the degree of cellular atypia. This progression follows a sequence of dysplasia similar to what has been described for colorectal carcinoma, and progression from a more benign PanIN 1 lesion, to a severely dysplastic PanIN3 lesion (or carcinoma in-situ) to PanCA has been described [Brat, Am J Surg Pathol 1998; Wilentz, Cancer Res 1999; Biankin, Cancer Res 2001]. More interestingly, this progression is accompanied by a progressive sequence of gene mutations, some of which are almost

exclusively associated with a higher degree of dysplasia, whereas others may indicate an earlier PanIN lesion. IPMN's and MCN's follow PanIN progression. These are potential targets for early pancreas cancer detection, and are discussed further below. (see Figure 1)

Precursor Lesions



DPC4		>90%			33%
p53		0		20%	57%
p21	9%	16%	32%	56%	80%
Cyclin D1		0		15%	41%

Figure 1. Progression of PanIN lesions as the pancreas duct epithelial cells become more dysplastic. Some of the genetic abnormalities (activation or deletions) as PanIN lesions progress are indicated (modified from Hruban, Am J Surg Pathol 2001.

IPMN's are mucin producing epithelial neoplasms that affect the main pancreas duct, side branches or both. They are usually multifocal, so different degrees of PanIN lesions can be found in the same specimen. Moreover, gene mutations may be present even in histologically appearing normal pancreas tissue. They are considered a pre-malignant lesion, and the progression to PanCA is about 30% at 7 years. Non-invasive IPMN's and side-branch type IPMN's usually have a more benign prognosis. A consensus conference has made recommendations on IPMN management [Tanaka, Pancreatology 2006].
A CT scan and EUS of a patient with IPMN is illustrated below. (see Figure 2).

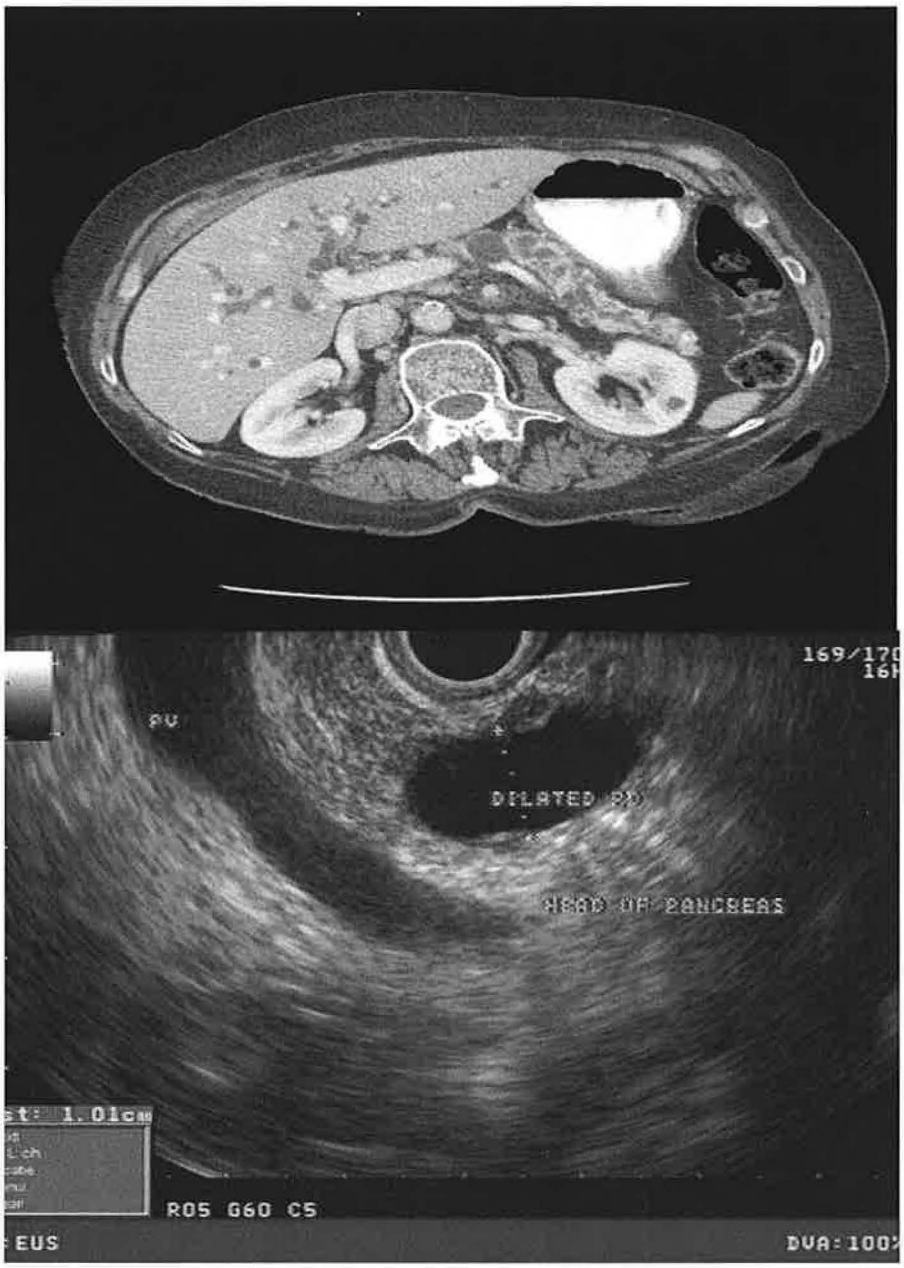


Figure 2. Massively dilated main pancreas duct, with side-branch dilatation on the CT scan image on top. Representative image of a dilated main pancreas duct by EUS below. Note that the pancreas duct is as wide as the portal vein (PV). Courtesy J. Sreenarasimhaiah.

MCN's have ovarian type stroma in the epithelial lining, and are thus mostly present in women. The cyst is solitary, but septations may give the appearance of a multicystic lesion. They usually are present in the body and tail of the pancreas. MCN's are more benign in behavior than IPMN's, and lesions less than 5 cm rarely harbor malignancy. A CT scan and EUS of an MCN is shown below. (see Figure 3)

control cell life cycles. Precursor and germ cells cannot be destroyed, so an enzyme called telomerase adds telomere repeats to the ends of the telomeres using an RNA template, always producing the sequence TTAGGG. Telomerase is activated in neoplastic cells also, and explains, in part, the ability of malignant cells to immortalize [Artandi, et al N Engl J Med 2006]. (see Figure 4).

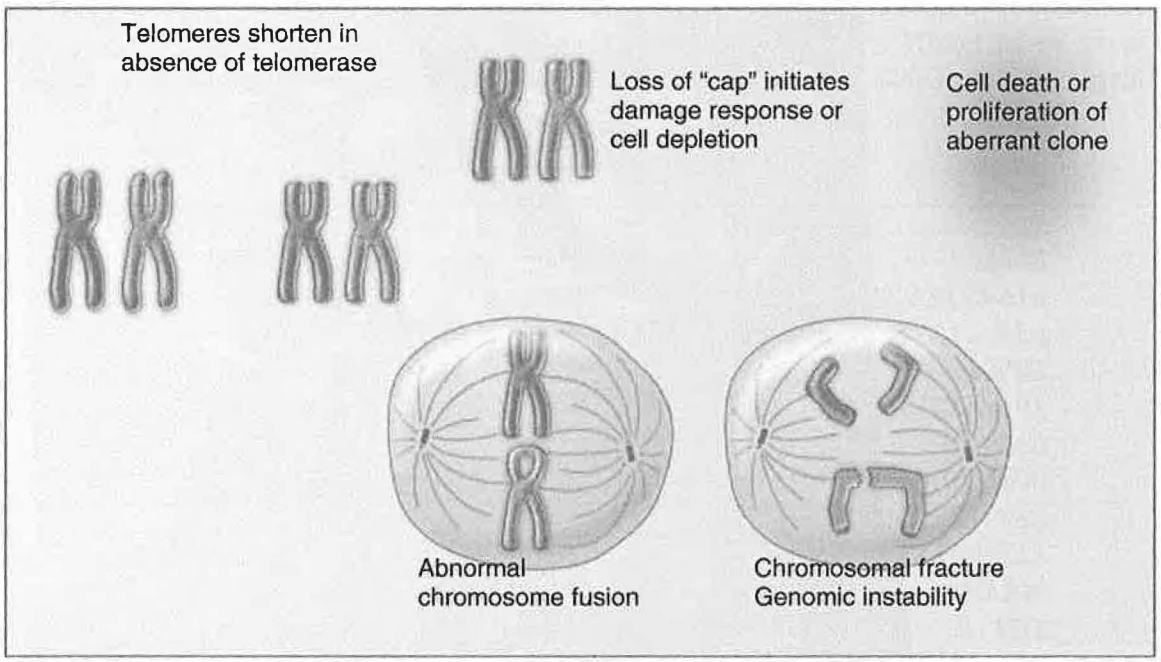


Figure 4. Illustration of telomere shortening [Adapted from Artandi, N Engl J Med 2006].

The pancreas duct epithelium does not express telomerase normally, so its presence is interpreted as representing malignancy [Hiyama, Cancer Res 1997]. The degree of tissue dysplasia where telomerase activation occurs in pancreas duct cells is not known, but published data shows a comparable sensitivity to cytology for solid lesions, and more importantly, it complements cytology. A study on the ability of telomerase to diagnose PanCA showed that telomerase was positive in the presence of a false negative cytology for PanCA, and vice-versa, cytology complemented telomerase when the telomerase test was false negative [Mishra, Gastrointest Endosc 2006]. Human telomerase reverse transciptase, a component of telomerase, has also been identified in malignant pancreas specimens and in cells obtained from pancreas juice, and may indicate malignant transformation in IPMN's [Hashimoto, Surgery 2008]. Telomerase is another attractive target for PanCA diagnosis.

The presence or absence of genetic mutations in PanCA has been established comparing known malignant tumors to benign tissue. The true ability of these mutations to help establish a diagnosis of early PanCA or identify patients at risk of developing PanCA is not known.

Imaging studies have variable sensitivities and specificities for diagnosing PanCA. ERCP and EUS have the better yield for diagnosing PanCA [Martin, Med Clin North Am 2000], but as with genetic alterations, their ability to establish a diagnosis of PanCA was established comparing known malignancies to normal controls. Their ability to diagnose early PanCA is also unknown.

CA 19-9 has the highest sensitivity of serum tumor markers for PanCA, especially when used in combination with an imaging study such as CT scan, but specificity is low. CA 19-9 and others, such as CEA, may also be elevated in patients with chronic pancreatitis and benign diseases such as choledocolithiasis. It is also falsely negative in patients with a negative Lewis antibody, which can happen in 5 to 15% of the population [Ritts, Pancreas 1994, Homma, Int J Pancreatol 1991].

Screening vs Surveillance

We screen in order to find disease in people with no symptoms who are not known to have the disease being screened for. Any screening program should meet these criteria:

1. Importance
2. Prevalence
3. Accuracy of testing
4. Cost-effectiveness of testing.

The US Preventive Services Task Force advises against screening for PanCA due to the lack of evidence that this would work. Population based screening for this more rare form of neoplasia is unrealistic due to the prevalence of the disease. This would lead to potentially more false positive rather than true positive results.

Surveillance is the close observation of a person or group at risk, and is a better description of any attempts at early diagnosis in a select high risk group for PanCA, as focusing efforts to this group could lead to either a cure or prevention of the disease.

The definition of high risk group varies by Institution.

The University of Washington considers high risk individuals when two or more first degree relatives, a single first degree relative at age < 50, or two or more second degree relatives, one < 50 years old have had PanCA [Brentnall, Ann Intern Med 1999]. The European consortium EUROPAC [http://www.liv.ac.uk/www/surgery/europac.html] identifies high risk individuals as anyone over 40 years with two first degree relatives with PanCA, or three relatives (any degree) with PanCA, or the known presence of a gene mutation (like BRCA2) in a relative who's also had PanCA. John Hopkins University focuses on patients with Peutz-Jeghers, and high risk individuals defined as two or more first degree relatives with PanCA or PanCA associated with a known genetic syndrome that increases PanCA risk [Canto, Clin Gastroenterol Hepatol 2006].

The Seattle protocol is detailed below. (see Figure 5) Basically, high risk individuals undergo an EUS, with specific criteria previously specified. If normal its repeated in 12 months. An abnormal EUS triggers an ERCP, which also has set criteria. When abnormal the patient is offered an open biopsy, and if abnormal, a pancreatectomy [Brentnall, Med Clin North Am 2000].

6. Patients with other mutations, such as BRCA2, BRCA1, MMR are considered only if there is an established family history of PanCA in at least one family member, preferably less than 50 years old.

CA 19-9 and CEA are obtained every 6 months, and a glucose tolerance test every year. An EUS is performed every year, and alternates every 6 months with a CT or MRCP if a contrast allergy is reported. The weight is also monitored with each clinic visit.
An imaging abnormality must be followed by attempts to obtain tissue via biopsy or brushings. An ERCP may be performed but will unlikely be done in all cases. A positive result will prompt a surgery consultation, and will probably result in a total pancreatectomy. Pancreas juice and other tissue will also be stored in the tissue bank. (see Figure 7)

Future directions:
Incorporating gene mutation analysis: K-*ras* and telomerase activity from pancreas juice aspirates, FNA biopsies and duct brushings.
Establish the utility of higher resolution CT or MRI.
Consider pancreas transplantation at time of total pancreatectomy to reduce the risk of hypoglycemia.

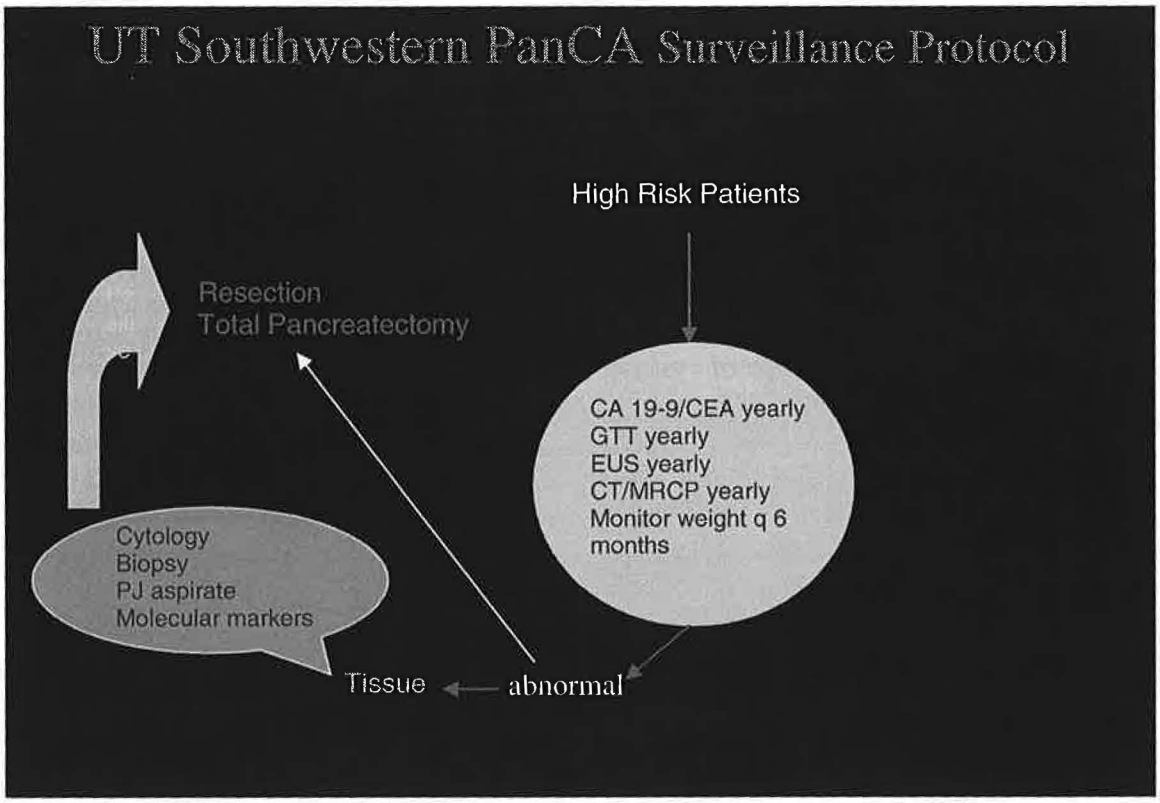


Figure 7

Conclusions

PanCA is a terrible disease with a dismal prognosis. There is data showing that the aggressive pursuit of PanCA using family history, gene mutation analysis and morphological changes on imaging identifies high risk lesions and even early cancers. This may alter the natural history of PanCA. Gene mutations occur at a predictable rate in PanCA, and probably reflect the degree of dysplasia. It is time to incorporate this knowledge into clinical practice. Local expertise suggests that we should be able to perform K-*ras* and telomerase assays in this group of patients. Pancreas duct visualization using optical aides such as narrow band imaging or image amplification need to be investigated. A pancreas transplant protocol after total pancreatectomy to avoid potentially lethal complications of pancreas resection needs to be discussed.