HIGHLIGHT ARTICLE

Screening for Early Pancreatic Ductal Adenocarcinoma: An Urgent Call!

Highlights from the "2009 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 15-17, 2009

Michael Xiang Lee, Muhammad Wasif Saif

Yale Cancer Center, Yale University School of Medicine. New Haven, CT, USA

Summary

Cancer of the pancreas is the fourth leading cause of cancer mortality in the United States. The annual death rate from the disease almost equals the annual incidence due to the aggressive nature of the cancer as well as to the lack of effective means of screening for it during its early curable stage. Molecular markers and imaging have not proven to be accurate modalities for screening for pancreatic cancer. The diagnosis and management of pancreatic cancer continues to be an overwhelming challenge. The authors discuss the current status of screening for pancreatic cancer and summarize relevant studies presented in the 2009 GI Cancers Symposium: utility of endoscopic ultrasound in screening high risk patients (Abstract #112), diagnostic performance of a highly specific antibody for MUC1 (Abstract #113), use of metabonomics for the early detection of pancreatic adenocarcinoma (Abstract #126), and a report on the potential impact of delay in diagnosis and treatment on pancreatic cancer outcomes at a tertiary care center (Abstract #137).

Introduction

Cancer of the exocrine pancreas is the fourth leading cause of cancer mortality in the United States. It is estimate that over 37,000 patients will be diagnosed with and 34,000 patients will die of pancreatic cancer annually [1]. The high mortality rate is largely due to the late detection of pancreatic cancer, since most cases are not symptomatic until the disease is in the advanced stages. At the time of diagnosis, surgical cure is no longer a feasible option for most patients. Only 10-25% of pancreas cancer cases are candidates for surgical cure [2]. The overall 5-year survival rate is about 5%, based on the Surveillance, Epidemiology and End Results (SEER; http://seer.cancer.gov/) data from 1996 to 2004 [1]. In order to improve survival, efforts to establish effective screening tests, such as we have for breast and colon cancers, are imperative.

Keywords Adenocarcinoma; CA-19-9 Antigen; Carcinoma, Pancreatic Ductal; Early Detection of Cancer; Endoscopes; Mucins; Ultrasonography

Abbreviations BRCA1: breast cancer 1, early onset; BRCA2: breast cancer 2, early onset; CEACAM1: carcinoembryonic antigen-related cell adhesion molecule 1; CK: cystine knot; CK-19: cytokeratin-19; Cys: cysteine-rich domains; FAMMM: familial atypical multiple mole melanoma

Correspondence Muhammad Wasif Saif
Yale Cancer Center, Yale University School of Medicine, 333 Cedar Street, FMP 116, New Haven, CT, USA
Phone: +1-203.737.1569; Fax: +1-203.785.3788
E-mail: wasif.saif@yale.edu

Document URL http://www.joplink.net/prev/200903/20.html

For a screening test to be useful, it should have high sensitivity and specificity. It must also be cost-effective, widely available, safe, and offers effective treatment when the disease is detected in early stage. Currently there is no approved modality for screening pancreatic cancer in the general population. The deep anatomic location of the pancreas makes routine physical examination ineffective (Figure 1).

Magnetic resonance imaging and computed tomography (CT), endoscopic retrograde cholangio-pancreatography and endoscopic ultrasound are not cost-effective in the general population.

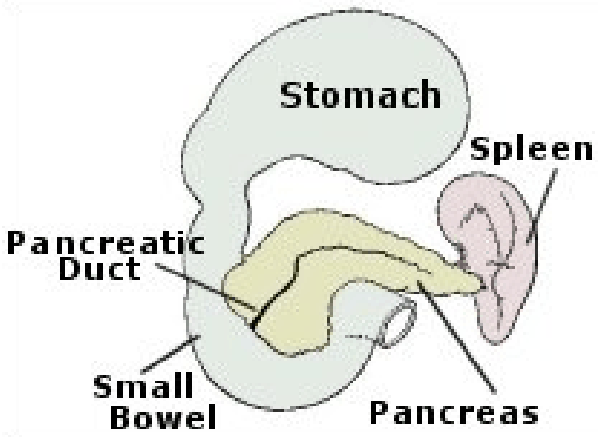

Figure 1. Deep anatomic location of pancreas.

Molecular Markers for Pancreatic Cancer

Many serologic markers have been examined as potential screening tools, such as CA 19-9, carcino-embryonic antigen-related cell adhesion molecule 1 (CEACAM1), MIC1, carcinoembryonic antigen, alpha-fetoprotein, DU-PAN-2, alpha4GnT, cytokeratin-19 (CK-19) mRNA, and tissue polypeptide antigen (Table 1) [3, 4, 5, 6, 7, 8, 9]. Unfortunately, none of these markers have achieved the levels of sensitivity and specificity to be recommended as screening asymptomatic patients in the general population. CA 19-9 is the best studied of these tumor markers. CA 19-9 has poor specificity for pancreatic cancer, being elevated in many cancers of the upper gastrointestinal tract, in ovarian cancer, hepatocellular cancer, and in benign conditions of the hepatobiliary system [10]. CA 19-9 is the best available tumor marker for following the progression of the disease but has low positive predictive value for identifying patients with pancreatic cancer, with sensitivity of 80% and specificity of 90% [11]. Due to the inability of CA 19-9 to identify early potentially curable disease, several other markers have been studied including pancreatic associated antigen (SPan-1), CA-50 antigen, DU-PAN-2, elastase-1, tissue polypeptide antigen and tissue polypeptide-specific antigen. These markers have not performed nearly as well as the CA 19-9. CA 19-9 is considered the standard for monitoring response to chemotherapy and recurrence following surgical resection in patients with pancreatic cancer but not for the initial diagnosis of the disease. Table 1 summarizes the new molecular markers for pancreatic cancer.

Updates from 2009 GI Cancers Symposium

Development of Mab PAM4, a Monoclonal Antibody Specific for a MUC1 (Abstract #113) [12].

Currently all biomarkers of pancreatic cancer have limited accuracy as screening tools. Mucin-associated markers such as CA 19-9 are non-specific. Mucins are heavily glycosylated high molecular weight glycoproteins with an aberrant expression profile in some malignancies. At present there are a total of 21 genes named MUC. The 14 classical mucins are classified into two subfamilies: secreted and membrane bound.

Secreted mucins are expressed exclusively by specialized epithelial cells, are secreted in the mucus, and display a restricted expression pattern within the human body. Among these, MUC2, MUC5AC, MUC5B, and MUC6 are expressed in the pancreas either under normal physiologic or tumoral conditions. These four mucins, referred to as the gel-forming mucins, have a common architecture with a high level of similarity to the pro-von Willebrand factor. The secreted mucins whose genomic sequences have been fully characterized are known to harbor five D domains, thus called because of their homology to the D domains of the von Willebrand factor. The D1, D2, D', and D3 domains are located in the N-terminal region and the D4 and CK (cystine knot) domains in the C-terminal region. Moreover, cysteine-rich domains (called Cys) alternate with the tandem repeat sequences in a variable number depending on the mucin [13]. The gel-forming mucins form intermolecular disulphide-linked multimers. Mucin subunits initially form homodimers through the disulphide bonds from their CK domains and subsequently hetero-oligomerize through the D domains from their N-terminal extremities [14]. The Cys domains are believed to bring another level of complexity to the oligomerization process via intermolecular disulphide bond formation.

Membrane-bound mucins, composed of MUC1, MUC3A, MUC3B, MUC4, MUC11, MUC12, MUC16, and MUC17 share a common property of being expressed by distinct cellular types, epithelial or other. Implanted at the apical surface of epithelial cells, they are also secreted and, therefore, take part in mucus formation. As compared to the secreted mucins, they present a wider and more complex expression pattern. Indeed, they can be expressed in four distinct forms:

- membrane-anchored;
- soluble;
- secreted;
- lacking the tandem repeat array [13, 14].

The ratio of one form to another appears to be tissue-specific and associated to the physiologic conditions (normal or tumoral). In addition to the proteolytic cleavage that releases the secreted forms from the cell surface, mucin precursors from this group, MUC1 and MUC4, possess a second proteolytic cleavage site that processes the precursor into a mature heterodimer. This second cleavage is thought to confer upon mucins their functional conformation. Among the membrane-bound mucins, MUC1 and MUC4 are the two main mucins associated with pancreatic cancer (Figure 2).

Table 1. Summary of new molecular markers for pancreatic cancer.

Source	Marker	Sensitivity	Specificity	Author
Serum	MUC1	71%	96%	Gold [3]
Serum	CEACAM1	85%	98%	Simeone [4]
Serum	MIC1	90%	62%	Koopmann [5]
Serum	Alpha4GnT	76%	83%	Ishizone [6]
Serum	CK-19 mRNA	64%	100%	Hoffmann [7]
Serum	K-*ras*	0	0	Marchese [8]
Pancreatic juice	Methylation pattern	82%	100%	Matsubayashi [9]

CEACAM1: carcinoembryonic antigen-related cell adhesion molecule 1; CK-19: cytokeratin-19

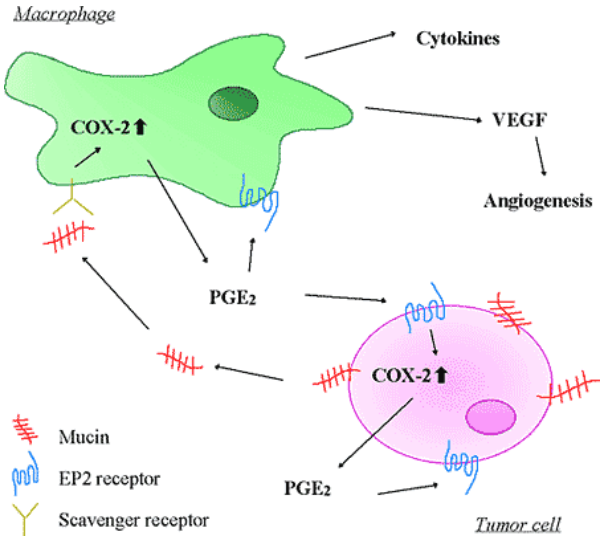

Figure 2. Cascade originated from mucin in the tumor microenvironment (adapted from Inaba T, *et al*. [20].)

MUC1 is the most studied of the group. Previous studies have found that MUC1 might be a valuable tumor marker for early diagnosis of pancreatic cancer. Gold *et al*. developed a monoclonal antibody (Mab PAM4) which is highly specific for a MUC1 produced by pancreatic carcinoma [3]. This antigen is identified in over 90% of pancreatic carcinoma and its precursor lesions but is not detected in normal pancreas. The authors demonstrated that the sensitivity and specificity of the immunoassay for pancreatic cancer were 77% and 95%, respectively, with a positive likelihood ratio of 16.8. In their current study, both immuno-histochemical and enzyme immunoassay were used to detect and/or quantify PAM4-mucin in tissue and sera, respectively, of normal and cancer patients in whom staging of cancer is known. The overall sensitivity and specificity were 82% and 85%, respectively, which is consistent with previous results. An exciting finding in their study is that 92% of stage I cancer cases were above cutoff value for positive response. A positive correlation was observed for mean antigen concentration in the serum with stage of disease. The data suggest that PAM4 has potential utility as biomarker in the early detection of pancreatic cancer.

Serum Metabonomics as a New Diagnostic Test for Pancreatic Cancer (Abstract #126) [15].

Metabonomics has been defined as the metabolic response of living systems to drug toxicity or disease via multivariate statistical analysis. Recent advances in analytical chemistry technology have made it possible to quickly and accurately measure alterations in metabolite concentrations found in urine, serum, and tissues. Metabonomics investigates the relationship between endogenous metabolite levels and potential toxicities during chronic drug administration with out the scientific bias associated with predetermined clinical chemistry measurements. Metabonomics research is primarily aimed at tracking temporal patterns of metabolites found in biofluids, but can also be directed at developing novel non-invasive biomarkers of disease and toxicity where none are evident. Metabonomics research will have important implications for medical, pharmaceutical, and regulatory agencies (Figure 3).

Metabonomics is being developed in other areas of oncology such as breast cancer. The comparison of metabolic profiles between cancer and normal patients has the potential to allow clinicians to detect pancreatic cancer at its early stage.

In a study by Bathe *et al*., serum samples from patients with pancreatic cancer and from those with benign hepatobiliary disease were analyzed by spectroscopy to identify and quantify metabolites. Metabolic profiling was performed using special computer software that also enables comparison of the whole sample spectrum between groups. The metabolic profile of patients with pancreatic cancer was significantly different from that of patients with benign disease. The authors conclude that more studies are needed to develop metabonomics as a valuable modality for the early diagnosis of pancreatic cancer.

Use of Endoscopic Ultrasonography (EUS) in Screening Patients at High Risk for Pancreatic Cancer (Abstract #112) [16].

Although pancreatic cancer is the fourth most deadly cancer in the United States, its incidence and prevalence are relatively low (about 37,000 cases diagnosed in 2008). Given the low prevalence of pancreatic cancer, it is not cost-effective to perform population wide screening. The current testing modalities with their low positive predictive value would produce too many false positives. An unacceptably high number of patients would undergo unnecessary invasive diagnostic testing. Therefore, many experts propose that screening should be targeting individuals at high risk of developing pancreatic cancer. Populations at higher risk include patients with at least two first degree relatives affected

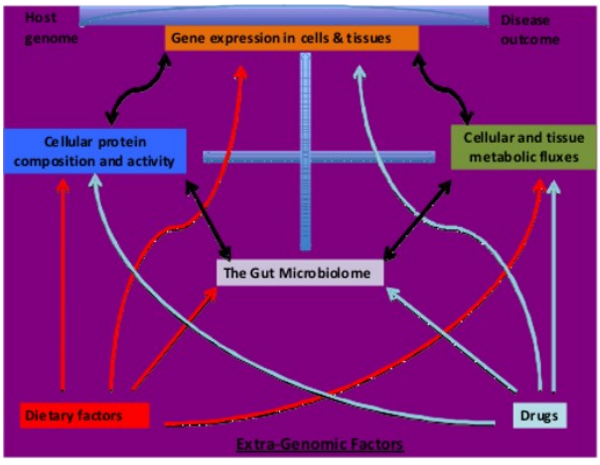

Figure 3. Rationale for metabonomics. Shown above are some of the key factors that affect the likelihood of disease outcomes. Disease results from a complex interaction of host and environmental factors.

with pancreatic cancer without increased presence of other cancers, patients with known family history of hereditary pancreatic cancer syndromes such as breast cancer 2, early onset (BRCA2) and p16, and patients with the following conditions: Peutz-Jeghers syndrome, familial atypical multiple mole melanoma (FAMMM) syndrome, hereditary pancreatitis. Longstanding cigarette smoking and diabetes mellitus are also known to be associated with increased risk of pancreatic cancer.

Canto *et al*. performed a prospective study examining the feasibility of using endoscopic ultrasound (EUS) to screen for pancreatic neoplasia in high risk individuals [17]. Two of the 38 patients (5.3%) undergoing the screening procedure were found to have clinically significant pancreatic neoplasms. Four out of 38 had benign pancreatic masses. The authors concluded that EUS-based screening of asymptomatic high-risk individuals can detect early stage pancreatic neoplasia but also yields false positive diagnosis. A subsequent prospective controlled study by the same authors using both EUS and CT scan also concluded that screening using EUS and CT is feasible for diagnosing asymptomatic early stage pancreatic cancer in high risk patients [18].

The current study is consistent with the findings of the Canto papers [17, 18]. Forty-three asymptomatic patients at high risk of developing pancreatic cancer were screened using EUS. Backgrounds of the patient population include 13 from families with FAMMM, 21 with familial pancreatic cancer, 2 with Peutz-Jeghers disease, 3 had hereditary pancreatitis, 5 with BRCA1 or BRCA2 mutations, 1 patient with p53 mutation. Pancreatic cancer was found in 3 out of 43 patients (7%). Branch type intraductal papillary mucinous neoplasia, considered to be a premalignant lesion, was found in 7 patients (16%).

The authors conclude that screening patients at high risk for pancreatic cancer is safe and feasible. Despite these encouraging results, we have no data to indicate that screening high risk individuals have benefits on mortality (Table 2).

Delay in Diagnosis and Treatment of Pancreas cancer (Abstract #137) [19].

The diagnosis of pancreatic cancer at its early stage when it is curable remains a challenge. Delays in diagnosis often occur due to non-specific symptoms of the disease. Given the aggressive biology of the disease, delay in treatment can also contribute to its high mortality. The authors presented their experience in a tertiary referral hospital examining the delays that occurred from onset of symptom to initiation of treatment. The authors reviewed case records of 134 patients from 2004 to 2005 at their institution. They considered the time from first symptom to initial diagnosis (Sx-MD), from first provider contact to initial diagnosis (MD-Dx), from initial diagnosis to initial treatment (Dx-Tx), and from first symptom to initial treatment (Sx-Tx). Results of their study are displayed in Table 3.

Table 2. Summary of high risk conditions for developing pancreatic cancer.

Genetic predisposition	Number of patients
Familial atypical multiple mole melanoma (FAMMM)	13
Familial pancreatic cancer	21
Peutz-Jeghers	2
Hereditary pancreatitis	3
Breast cancer 1/2, early onset (BRCA1, BRCA2)	5
p53	1

Table 3. Delay periods from first symptom to treatment.

Time intervals	Median days (range)
From first symptom to initial diagnosis (Sx-MD)	30 (0-120)
From first provider contact to initial diagnosis (MD-Dx)	35 (1-365)
From initial diagnosis to initial treatment (Dx-Tx)	21 (0-120)
From first symptom to initial treatment (Sx-Tx)	112 (20-1610)

The authors noted day-delay was significantly shorter in patients with resectable pancreatic cancer and longer among patients with non-head pancreatic cancer. Ages at diagnosis, presenting symptoms, prior history of diabetes mellitus, pancreatitis, or prior GI condition, patient insurance type, and dwelling distance from referral center were not associated with delay. Authors concluded that delay in time to diagnosis and/or treatment may be a substantial fraction of overall survival and thus may negatively impact treatment outcome. Their observations underlie urgency to develop improved strategies for earlier detection and treatment of pancreatic cancer.

Discussion

The late detection and poor prognosis of pancreatic cancer patients highlight the importance of an effective early detection strategy, especially for those at high risk of developing pancreatic cancer. At the present, the use of biomarkers and imaging techniques are not recommended as routine screening tools for screening asymptomatic patients in the general population. Screening of high-risk patients with endoscopic ultrasound is gaining wider acceptance but evidence of efficacy and cost-effectiveness is still needed. The Pancreatic Cancer Progress Review Group (http://www.cancermap.org/pancreatic/prg.jsp) of the U.S. National Cancer Institute (NCI) has drawn specific attention to the “urgent need for better screening and diagnostic techniques”, with a recommendation to “delineate and validate effective molecular biomarkers for pancreatic cancer”. Early detection and diagnosis of pancreatic cancer would lead to appropriate and timely therapy that lowers mortality and morbidity caused by pancreatic cancer.

Conflict of interest The authors have no potential conflicts of interest

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer Statistics, 2008. CA Cancer J Clin 2008; 58:71-96. [PMID 18287387]

2. Sener SF, Fremgen A, Menck HR, Winchester DP. Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985-1995, using the National Cancer Database. J Am Coll Surg 1999; 189:1-7. [PMID 10401733]

3. Gold DV, Modrak DE, Ying Z, Cardillo TM, Sharkey RM, Goldenberg DM. New MUC1 serum immunoassay differentiates pancreatic cancer from pancreatitis. J Clin Oncol 2006; 24:252-8. [PMID 16344318]

4. Simeone DM, Ji B, Banerjee M, Arumugam T, Li D, Anderson MA, et al. CEACAM1, a novel serum biomarker for pancreatic cancer. Pancreas 2007; 34:436-43. [PMID 17446843]

5. Koopmann J, Rosenzweig CN, Zhang Z, Canto MI, Brown DA, Hunter M, et al. Serum markers in patients with resectable pancreatic adenocarcinoma: macrophage inhibitory cytokine 1 versus CA19-9. Clin Cancer Res 2006; 12:442-6. [PMID 16428484]

6. Ishizone S, Yamauchi K, Kawa S, Suzuki T, Shimizu F, Harada O, et al. Clinical utility of quantitative RT-PCR targeted to alpha1,4-N-acetylglucosaminyltransferase mRNA for detection of pancreatic cancer. Cancer Sci 2006; 97:119-26. [PMID 16441422]

7. Hoffmann K, Kerner C, Wilfert W, Mueller M, Thiery J, Hauss J, Witzigmann H. Detection of disseminated pancreatic cells by amplification of cytokeratin-19 with quantitative RT-PCR in blood, bone marrow and peritoneal lavage of pancreatic carcinoma patients. World J Gastroenterol 2007; 13:257-63. [PMID 17226905]

8. Marchese R, Muleti A, Pasqualetti P, Bucci B, Stigliano A, Brunetti E, et al. Low correspondence between K-ras mutations in pancreatic cancer tissue and detection of K-ras mutations in circulating DNA. Pancreas 2006; 32:171-7. [PMID 16552337]

9. Matsubayashi H, Canto M, Sato N, Klein A, Abe T, Yamashita K, et al. DNA methylation alterations in the pancreatic juice of patients with suspected pancreatic disease. Cancer Res 2006; 66:1208-17. [PMID 16424060]

10. Frebourg T, Bercoff E, Manchon N, Senant J, Basuyau JP, Breton P, et al. The evaluation of CA 19-9 antigen level in the early detection of pancreatic cancer. A prospective study of 866 patients. Cancer 1988; 62:2287-90. [PMID 3179943]

11. Steinberg W. The clinical utility of the CA 19-9 tumor-associated antigen. Am J Gastroenterol 1990; 85:350-5. [PMID 2183589]

12. Gold DV, Modrak DE, Newsome G, Karanjawala Z, Hruban RH, Goggins M, Goldenberg DM. Early detection of pancreatic carcinoma. 2009 ASCO Gastrointestinal Cancers Symposium (Abstract #113).

13. Moniaux N, Escande F, Porchet N, Aubert JP, Batra SK. Structural organization and classification of the human mucin genes. Front Biosci 2001; 6:D1192-206. [PMID 11578969]

14. Van Klinken BJ, Einerhand AW, Büller HA, Dekker J. Strategic biochemical analysis of mucins. Anal Biochem 1998; 265:103-16. [PMID 9866714]

15. Bathe OF, Shaykhutdinov R, Weljie A, McKay A, Sutherland F, Dixon E, Vogel H. A new diagnostic test for pancreatic cancer based on serum metabonomics. 2009 ASCO Gastrointestinal Cancers Symposium (Abstract #126).

16. Poley J, Kluijt I, Gouma DJ, Wagner A, Aalfs C, van Eijck CH, et al. Use of endoscopic ultrasonography in screening patients at high-risk for pancreatic cancer. 2009 ASCO Gastrointestinal Cancers Symposium (Abstract #112).

17. Canto MI, Goggins M, Yeo CJ, Griffin C, Axilbund JE, Brune K, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. Clin Gastroenterol Hepatol 2004; 2:606-21. [PMID 15224285]

18. Canto MI, Goggins M, Hruban RH, Petersen GM, Giardiello FM, Yeo C, et al. Screening for pancreatic neoplasia in high-risk individuals: a prospective controlled study. Clin Gastroenterol Hepatol 2006; 4:766-81. [PMID 16682259]

19. Picozzi VJ, Delgado EC, Neil NJ, Malpass TW. Delay in diagnosis and treatment of pancreas cancer: The experience of a tertiary referral center. 2009 ASCO Gastrointestinal Cancers Symposium (Abstract #137).

20. Inaba T, Sano H, Kawahito Y, Hla T, Akita K, Toda M, et al. Induction of cyclooxygenase-2 in monocyte/macrophage by mucins secreted from colon cancer cells. Proc Natl Acad Sci U S A 2003; 100:2736-41. [PMID 12598658]