

Early diagnosis of pancreatic cancer

Moderators:

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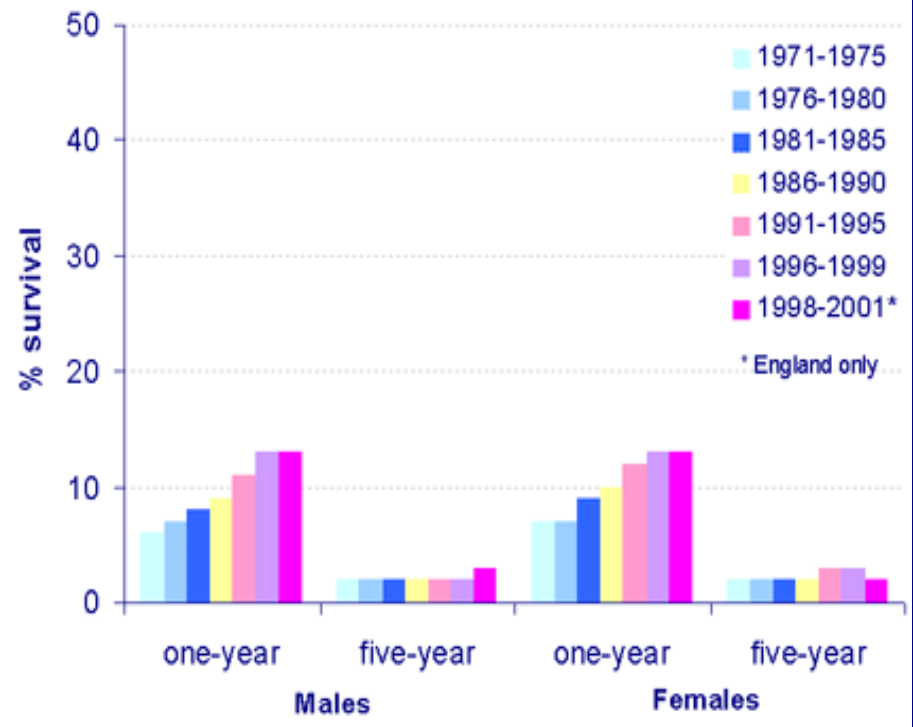
Maurits Weirsema, MD

Why is early diagnosis so desirable?

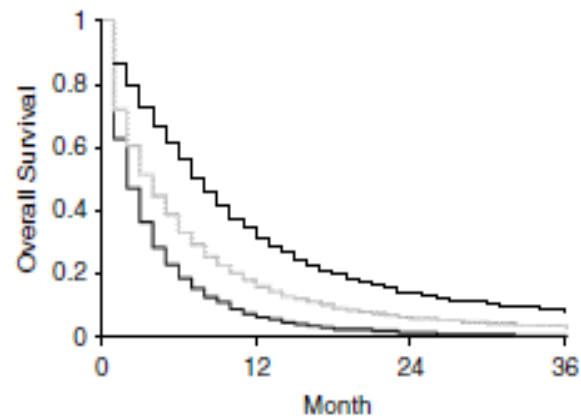
Despite considerable investment in improving therapy,

- the outcomes in pancreatic cancer have not changed much in past several decades

Figure 3.1: One- and five-year relative survival by sex, adults diagnosed with pancreatic cancer, England and Wales, 1971-2001 and followed up to the end of 2003



- Approximately 85% of patients have Stage IV disease at the time of initial presentation and
- that proportion has not changed significantly in last 20 years



Metastatic	18,370	1,348	337	143
Unstaged	6,175	1,096	396	210
Nonmetastatic	12,008	3,764	1,409	741

FIG. 5. Overall survival after pancreatic cancer diagnosis, by disease stage. Upper solid line = patients with nonmetastatic disease Gray line = patients with unstaged disease Lower solid line = patients with metastatic disease.

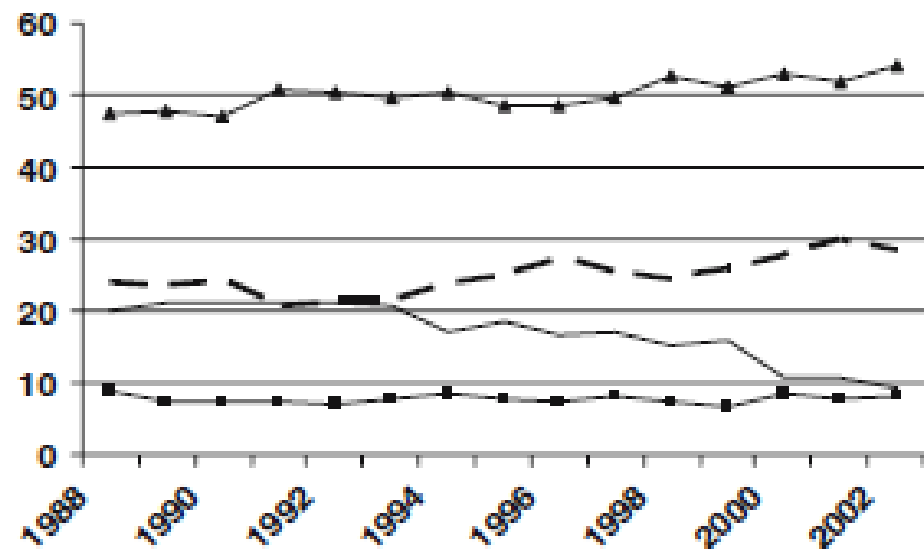
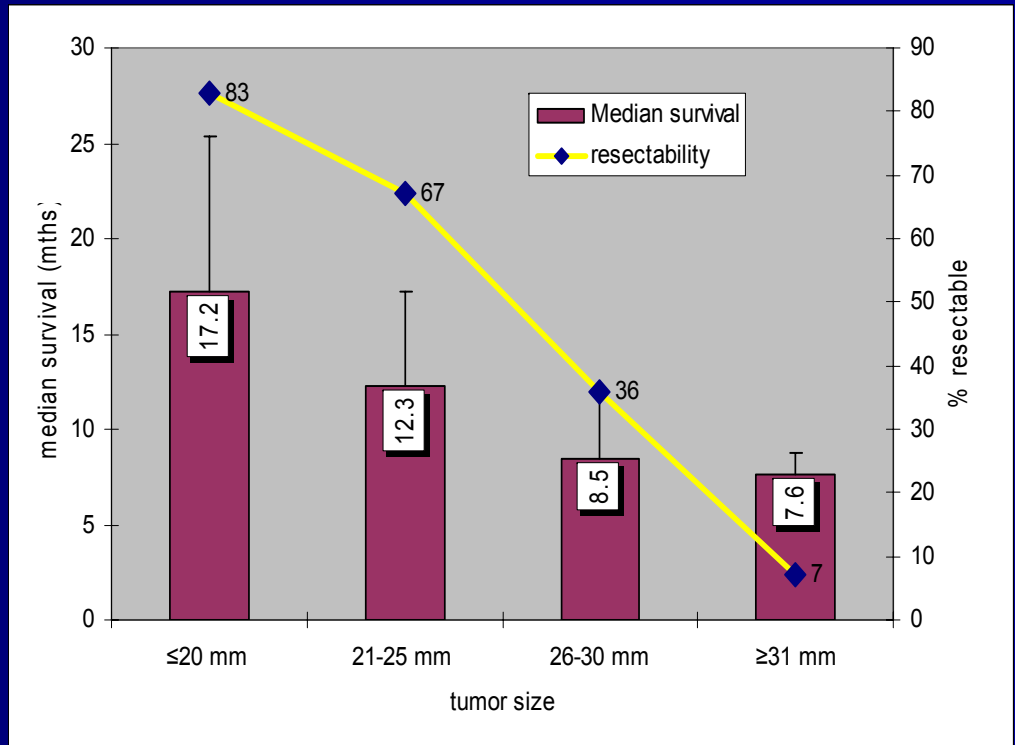
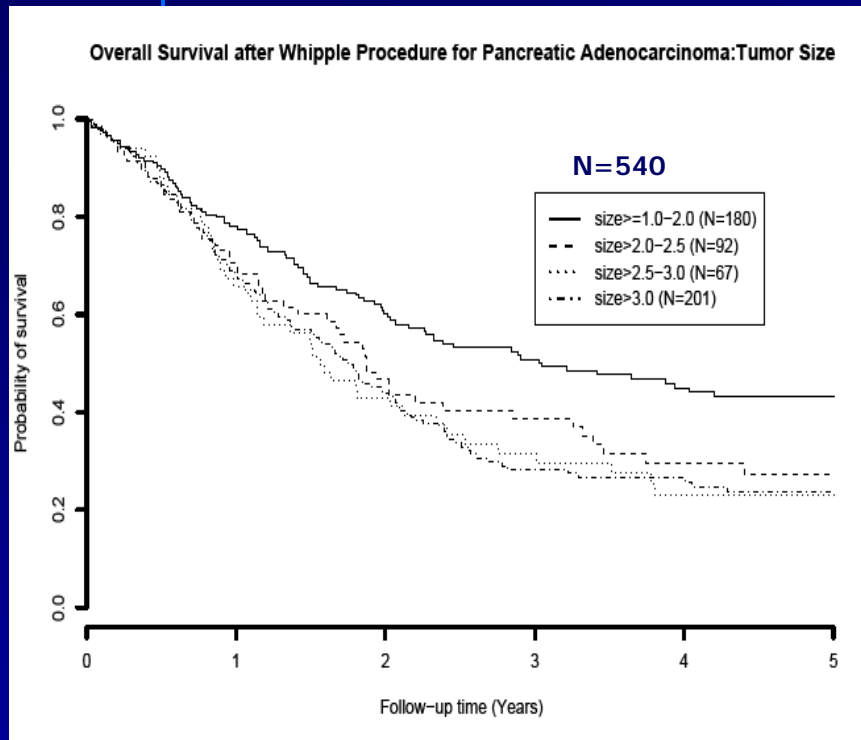


FIG. 2. Yearly proportion (%) of patients diagnosed, disease stage. Triangles = metastatic disease, Dashed line = regional disease, Solid line = unstaged disease, Squares = localized disease.

- The outcomes in patients with smaller tumors are consistently better than those with larger tumors in several published studies

Survival and resectability in patients with pancreatic cancer based on tumor size



Washington University Pancreas Cancer Database
2000-2007
(unpublished)

Agarwal et al Pancreas 2008

Early detection of small asymptomatic neoplasms may result in cure

Ariyama et al. Nippon Geka Gakkai Zasshi. 1997;98:592-6

Best outcome:

- 79 patients with pancreatic cancers \leq 1 cm
- 5-year survival 100% after surgery
 - if PC limited to duct epithelium (? Carcinoma in situ)

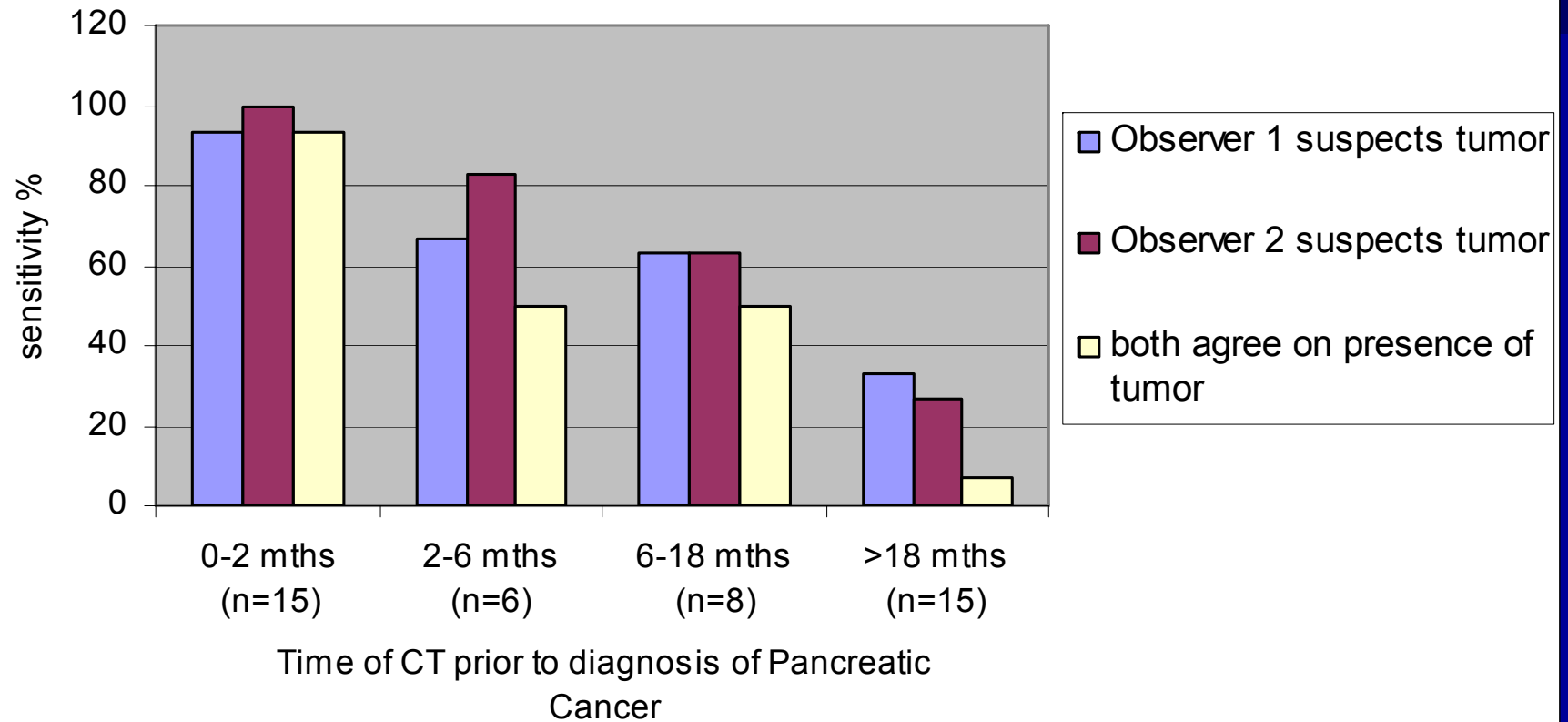
Size of pancreatic tumor at diagnosis over past few decades

First author	Year of publication	Patient accrual	Institution	Mean tumor size
Yeo	1995	1970-1994	JHMI	3.0 cm
Nitecki	1995	1981-1991	Mayo	3.1 cm
Fortner	1996	1979-1991	MSKCC	3.9 cm
Sohn	2001	1984-1999	JHMI	3.2 cm
Schmidt	2004	1980-2002	IUPUI	3.2 cm
Agarwal	2004	2000-2002	MDACC	3.0 cm

Why are we not diagnosing early cancers despite improvements in imaging?

- Patients with early cancers are usually asymptomatic and do not present for medical attention
 - or are not suspected of having pancreatic cancer
- Early cancers noted in asymptomatic patients are often overlooked by radiologists

Findings suggestive of pancreatic cancer in CT scans performed prior to diagnosis of Pancreatic Cancer



AQ 1. Why is renewed emphasis on early diagnosis now?

1. Improved resolution with CT/MRI
2. Advent of EUS-FNA
 1. to provide cytologic diagnosis in patients with early stage pancreatic cancers
3. Advances in molecular testing
4. Better understanding of pathogenesis and natural history of pancreatic cancer
5. Less nihilism?
6. All of the above

Attempts at early
diagnosis of
pancreatic cancer

???

=

pancreatic cancer
screening

Is there an identifiable prodrome?

Can we identify an at-risk population?

AQ 2

1. Yes
2. No
3. Maybe

Characteristics of diseases amenable to screening:

How it applies to pancreatic cancer

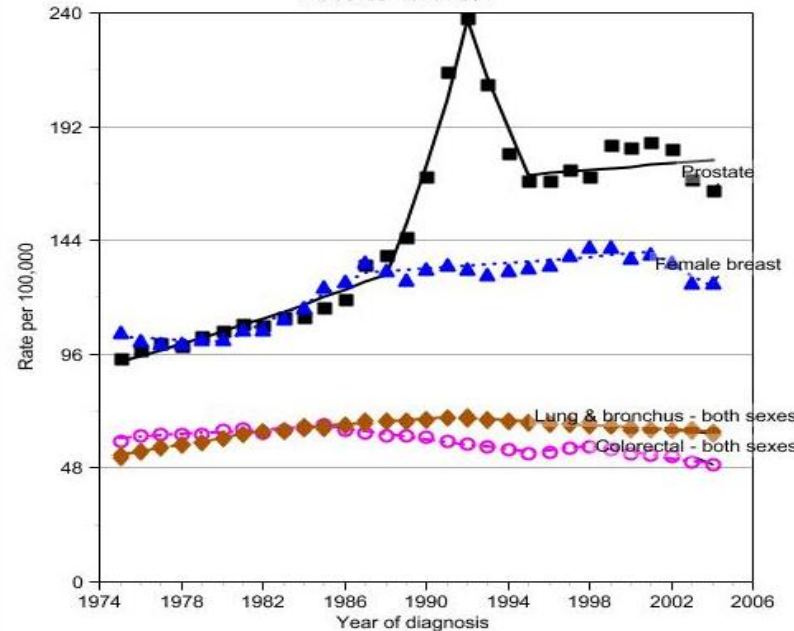
- Substantial morbidity or mortality if untreated
 - Yes
- Existence of critical point and appropriate therapy
 - Still needs to be established
- Low incidence of pseudo-disease
 - Yes
- High clinical prevalence
 - 10 in 100,000 in general population
 - ? High risk populations

Prevalence of cancers that are currently screened

Diagnosis

Cancer Trends Progress Report – 2007 Update

Figure D2. Rates of new cases of the four most common cancers, delay-adjusted cancer incidence: 1975-2004



Source: SEER Program, National Cancer Institute. Incidence data are from the SEER 9 areas (<http://seer.cancer.gov/registries/terms.html>). Data are age-adjusted to the 2000 standard using age groups: <1, 1-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85+. Analysis uses the 2000 Standard Population (Census P25-1130) as defined by NCI (<http://seer.cancer.gov/stdpopulations/>).

<http://progressreport.cancer.gov/>

What speaks against screening of pancreatic cancer?

- Harm due to screening
 - Complications
 - Related to screening test
 - Related to further evaluation of false positive diagnosis
 - Over-treatment
 - Related to treatment of very early lesions of indeterminate significance
- Low yield/cost
 - The existing data is based on old technology
- No proof that stage migration results in improved outcome
 - Although data is emerging that early diagnosis is associated significantly better outcomes

Characteristics of screening test

- accuracy
- reproducibility
- safety, availability and cost effectiveness

AQ3. Which test is the best potential candidates for pancreatic cancer screening

1. Serum markers
2. Cross sectional imaging with spiral CT or MRI
3. EUS/FNA
4. ERCP
5. Abdominal US
6. None of the above

Potential strategies for diagnosing pancreatic cancer in early stages

- Screening/surveillance of patients with familial or environmental predisposition
- Identification of high risk groups for screening
- Development of molecular biomarkers for screening or identifying high risk population

Familial pancreatic cancers

David Whitcomb 10 mins

- What proportion of pancreatic cancers are familial?
- What is the risk of pancreatic cancer in various familial conditions?
- What are the familial conditions where surveillance for pancreatic cancer would seem justified?
- What are the currently available means for evaluating these patients for pancreatic cancer and how effective are they?
- Will lessons learned in familial cancers apply to sporadic ones?

New-onset diabetes as a marker of early pancreatic cancer

Suresh Chari- 10 mins

- What is the prevalence of DM in PaC?
- What proportion of new-onset DM will have PaC?
- Does DM occur early enough in the course of PaC to be clinically useful?
- Are we ready to screen new-onset diabetes for PaC?

Other enriched populations for pancreatic cancer

Banke Agarwal

Acute and Chronic pancreatitis
and
pancreatic cancer

AQ4. Pancreatic Imaging to rule out an underlying pancreatic cancer is indicated in following patients

1. Idiopathic acute pancreatic after > 50 years age
2. recurrent acute pancreatitis
3. new diagnosis of chronic pancreatitis
4. 1 and 2 only
5. All of the above
6. None of the above

Risk of developing pancreatic cancer and in patients with acute pancreatitis, recurrent pancreatitis and chronic pancreatitis

	Number of patients	Pancreatic cancer in <1 yr		Pancreatic cancer in 1-4 years		Pancreatic cancer in 4-24 years	
		n	%	n	%	n	%
Single episode of Acute pancreatitis	24573	61	0.25%	35	0.14%	56	0.22%
Recurrent acute pancreatitis	7328	42	0.57%	20	0.27%	39	0.53%
New diagnosis of Chronic Pancreatitis	4546	110	2.42%	46	1.01%	24	0.52%

Britt Marie Karlson et al. Gastroenterology 1997

Risk of pancreatic cancer after new diagnosis of chronic pancreatitis

Lowenfels et al. New England Journal of Medicine 1993

- 462 patients with new diagnosis of chronic pancreatitis
- 27 (5.8%) were diagnosed to have pancreatic cancer within 2 years

Chronic pancreatitis and pancreatic cancer

- ? Pancreatic cancer may be misdiagnosed as chronic pancreatitis
- ? Development of pancreatic cancer may exacerbate the symptoms of chronic pancreatitis and bring the patient to medical attention

Idiopathic Acute pancreatitis and Recurrent acute pancreatitis and risk of pancreatic cancer

- Youseff et al GI Endoscopy 2004
 - 0.8% patients with pancreatic cancer

Prior to making a diagnosis of chronic pancreatitis for the first time.

- Should we always rule out pancreatic cancer?
- What is the appropriate test to rule out cancer in this setting ??

Pancreatic Cancer
and
Depression

AQ. Which of the following statements is correct about pancreatic cancer and depression

1. There is no association between pancreatic cancer and depression
2. Patients with pancreatic cancer develop severe depression because of grim prognosis
3. Signs of depression can precede a diagnosis of pancreatic cancer by several months

Depression as early presentaion of
pancreatic cancer ??

Fras et al, Gastroenterology 1968

- Detailed and prospective psychiatric evaluation of all patients (n=139)
 - with suspected pancreatic or colon cancer that presented to Mayo Clinic in 1 year
- Psychiatric evaluation done using well validated questionnaires
 - Psychiatric evaluation as soon as these cancers were suspected
 - Psychiatrists were unaware of the type of cancer suspected
- Patients were finally diagnosed to have
 - Pancreatic cancer (n=46)
 - Colon cancer (n=64) – 1st control group
 - Others (including other cancers or benign conditions) (n=29) – 2nd control group

Findings:

- 76% of pancreatic cancer (PaCa) patients had preceding mental symptoms
 - vs 17% in colon cancer group and 20% in mixed group
- 48% of PaCa patients reported only mental symptom as first indication of present disease
- In 26% of PaCa patients, the symptoms were severe enough to be regarded a psychiatric disorder per se
- These mental symptoms preceded the first physical symptom by median of 6 months (range 1-43mths)

Mental symptoms

1. Depression was most frequent first symptom
 - “Loss of ambition” or “loss of push” or “loss of go”
 - Not related to fatigue
 - Usually mild or moderate in intensity
 2. Anxiety- generally increased tension without significant agitation.
 - Frequently accompanied by depression or feeling of premonition
 3. Feeling of premonition of serious illness
-
- Differential Diagnosis
 1. Manic Depressive Psychosis
 2. Involutional Melancholia

Biomarkers for Screening and Diagnosis of Pancreatic Cancer

Value of potential biomarkers in screening for pancreatic cancer

In population with a prevalence of 1/10,000 (100 cancers in 1,000,000 population)

- eg. General US population

N=1,000,000	sensitivity	specificity	Estimated PPV %	False Positives	Estimated NPV %	False negatives
Miracle biomarker	99%	99%	0.9%	9,999	99.9%	1
Fantastic biomarker	95%	95%	0.1%	49,995	99.9%	5
Good biomarker	90%	90%	0.08%	99,990	99.9%	10
Currently available marker	70%	80%	0.03%	199,980	99.9%	30

In population with a prevalence of 0.5% (100 cancers in 20,000 population)

- eg. Enriched populations such as new onset diabetes, familial pancreatic cancer families

N=20,000	sensitivity	specificity	Estimated PPV %	False Positives	Estimated NPV %	False negatives
Miracle biomarker	99%	99%	33.2%	199	99.9%	1
Fantastic biomarker	95%	95%	8.7%	995	99.9%	5
Good biomarker	90%	90%	4.3%	1990	99.9%	10
currently available marker	70%	80%	1.7%	3980	99.8%	30

Biomarkers for use in diagnosis of pancreatic cancer

in population with a prevalence of 10% (100 cancers in 1000 patients)

- eg. patient with enlarged head of pancreas on CT or dilated PD on CT with weight loss ± abdominal pain

N=1,000	sensitivity	specificity	Estimated PPV %	False Positives	Estimated NPV %	False negatives
Miracle biomarker 1	99%	99%	91.7%	9	99.8%	1
Fantastic biomarker 2	95%	95%	67.8%	45	99.4%	5
Great biomarker 3.	90%	90%	50%	90	98.7%	10
Currently available markers	70%	80%	28%	180	96%	30

•in population with a prevalence of 50% (100 cancers in 200 patients)

- eg. pancreatic mass on CT/MRI in an asymptomatic patient.

N=200	sensitivity	specificity	Estimated PPV %	False Positives	Estimated NPV %	False negatives
Miracle biomarker 1	99%	99%	99%	1	99%	1
Fantastic biomarker 2	95%	95%	95%	5	95%	5
Great biomarker 3.	90%	90%	90%	10	90%	10
CA19-9	70%	80%	77.7%	20	72.2%	30

Molecular markers to aid in early diagnosis of pancreatic cancer

Michael Goggins 10 mins

- Are there any molecular markers in the horizon that can potentially be used for above purposes?
- What is the current state of the art in development of biomarkers for pancreatic cancer?
- Is there a precursor in pancreatic cancer carcinogenesis (analogous to HGD e.g., PanIN3) that can be reliably diagnosed pre-operatively.

How can EUS/FNA help in early diagnosis of pancreatic cancer

Maurits Wiersema 10 mins

- What are the performance characteristics of EUS-FNA for identifying and diagnosing early tumors?
- How does EUS/FNA compare with CT or MRI for diagnosis of early cancers?
- What is the risk of complications with EUS and EUS-FNA?
- Can EUS potentially be used for detecting and diagnosing pancreatic cancer in enriched population subsets?
- Role of EUS in diagnosing cancer in patients with subtle/non-specific findings suggestive of cancer on CT scan/MRI?
- Are there workforce issues if screening became generally accepted?
- Is there a realistic mechanism for quality control for EUS?

Questions to panel

- What is the current status of pancreas cancer screening or early diagnosis today?
 - Who should be screened?
 - How much should the population be enriched before testing for pancreatic cancer becomes justifiable?
 - How often? What age should we start/stop?
 - What modality?

Questions to panel

- What is the future of pancreas cancer screening or early diagnosis?
 - EUS
 - Biomarkers
 - Where should we look (serum, plasma, pancreatic fluid, urine)?
 - Functional or molecular imaging
 - Can we “see” PanIns?

Questions to panel

- Will stage migration/early detection lead to better outcomes?
- What are the impediments to screening and how do we overcome them?
- Is there a role for prophylactic pancreatectomy?