

Gastrointestinal Cancers Symposium

Scott C. Wadler Keynote Lecture

Title: What will it take to Diagnose Pancreatic Cancer Early?

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- ✚ The five-year survival rate for patients diagnosed with pancreatic cancer (PC) is 5%. The survival rate has not changed because patients still present with unresectable disease; most present with metastases.
- ✚ Metastases are particularly hard to treat because each of the metastases is genetically different. Research by Dr. C. Iacobuzio-Donahue compared liver and lung metastases from the same patient via the rapid medical donation program. She showed that the lung and liver metastases from the same patient were genetically and distinctly different. Metastases are not only numerous but also genetically heterogeneous.
- ✚ The message Dr. Hruban hoped to leave with the audience is that, “*Precursors to invasive pancreatic cancer can be detected and lives can be saved!*” He felt there are four steps to go about detecting these early neoplasms:

Step 1- Identify and characterize the curable precursor lesions that give rise to incurable invasive PC.

Step 2- Identify populations at risk for PC who will benefit from screening.

Step 3- Establish a method to detect these lesions.

Step 4- Develop an evidence-base that screening at risk individuals is beneficial.

Step 1: Identify and characterize the curable precursor lesions that give rise to invasive PC.

- There are two particularly common precursors that give rise to invasive PC: pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN).
- PanINs and IPMNs are curable neoplasms. However, if left untreated some will progress to invasive carcinoma.
- Understanding the histology of these lesions has revealed the genetic alternations. The cure for pancreatic neoplasia rests on understanding that small microscopic lesions are curable.

Step 2: Identify populations at risk for developing PC who will benefit from screening.

- If the aim is to utilize an early detection test, it should be applied to a population that is at increased risk for developing PC. The Iceland Cancer Registry is a powerful tool for studying the role inheritance plays in cancer phenotype. This registry contains all the diagnosed cancer cases in Iceland after January 1955; approximately 95% of the cancers were histologically confirmed. It is a genealogic database containing 687,500 individuals.
- The registry data shows that if one has a first degree relative with PC, their risk of developing PC is 2.33 fold elevated. In comparison, breast cancer which has a strong familial component has only 2.02 fold increase risk; for colon cancer it is 1.92. PC has a stronger genetic component than breast and colon cancer.
- In order to study the genetics of PC, JHU established the National Familial Pancreas Tumor Registry (NFPTR). As of 1/7/08 there are 2661 families enrolled. Of that, 934 are familial kindreds (at least a pair of first degree relatives with PC).

- Currently, the registry has 32 families who have five or more members of the family who died from PC. Seventy-three families have four family members who have died from PC. Registries like NFPTA provide a unique tool to study the familial aggregation of PC.
- Registry families are followed up annually; a postcard is included requesting an update. Sixty one families reported that since joining the registry a new family member has been diagnosed with PC. 55 of these incidents were in a blood relative of the index case. Six in spouses. Only 9 of the 61 were resectable. Dr. Hruban pointed out that these are families that are well aware of the risk, and yet only 9 were caught early enough to have surgery.
- The overall risk of PC and risk based on first degree relatives who have PC can now be quantified.
 - The risk in the general population is 9 per 100,000.
 - The risk with one first degree relative is 2-4 fold elevated.
 - The risk with two family members with PC is six fold elevated.
 - The risk with three family members is 14-32 fold elevated.
- Some of the genes responsible for the aggregation of PC in families are known!
- Familial syndromes include: BRCA2, Familial Atypical Multiple Mole Melanoma Syndrome, Familial pancreatitis, and Peutz-Jeghers syndrome.
- By understanding which genes are responsible for the aggregation of cancer in a family we can now quantify the risk.

Risk Quantification of PC

Individual's History	Risk	Age 50	Age 70
No history	1	0.05%	0.5%
BRCA2	3.5-10	0.5%	5%
P16 (FAMMM)	20-34	1.0%	10-17%
Familial	14-32	0.8-1.6%	8-16%
PRSS1 (Pancreatitis)	50-80	2.5%	25-40%
STK11/LKB1 (Peutz-Jeghers)	132	6.6%	30-60%

- Dr. Hruban clarified that he is not stating that PC is all because of genetics. Clearly environmental exposures play a significant role. It is estimated that 1 in 4 or 1 in 5 cases of PC is caused by cigarette smoking.

Step 3: Establish a method to detect the precursor lesions early.

- We can identify who is at risk for developing PC, but simply telling someone their risk does not help them unless the medical community can offer some sort of early detection.
- For patients who we know are at risk of developing PC, the endoscopic ultrasound (EUS) offers the best imaging modality of the periampullary area.

- Dr. Hruban states that as a pathologist, the resected pancreata from patients with a family risk provide a unique opportunity to study unadulterated early pancreatic neoplasia before the pancreas is taken over by invasive cancer. He showed that although the precursor lesions (PanINS) themselves are small (the size of a head of a pin) they produce a lot of scarring (fibrosis).
- Patients with few precursor lesions have relatively homogenous glands, while patients with many lesions have heterogeneous glands. The other dramatic thing from these pancreata in patients with a strong family history of PC, is they tend not to have just one precursor lesion but they have dozens and dozens of precursor lesions.
- From studies we can conclude that:
 - PanINS produce larger lesions that can be detected with currently available imaging modality.
 - PanINs can be multifocal.
 - Precursor lesions are detectable and curable!

Step 4: Establish an evidence base that screening at risk individuals is beneficial.

- Dr. Hruban stated that this is by far the most challenging task, because we know precursors exist, and we can detect them. But should we detect them?
- The math is disheartening because you need to consider sensitivity and specificity of screening modalities, and the prevalence of the disease.
- Example: The prevalence of PC is 9 per 100,000.
 - Screen 100,000 unselected individuals (general population) with a test that has a screening sensitivity of 100% and specificity of 98%. We would then detect all the cases of PC (in this example nine would be detected). But with a specificity of 98% we are going to end up with 2,040 people who will be false positives (falsely alarmed). For every nine PC cases detected, over 2,000 people will be falsely alarmed. Also, need to consider the astronomical costs of screening large groups. It is not conducive to screen the general population which is disheartening.
 - But, Dr. Hruban sincerely believes it is going to take working together as a team to identify families, understand genetics, and identify individuals who are genetically predisposed to PC and have a risk that is high enough that makes it worthwhile to screen them.
 - Need better imaging to detect these small precursor lesions, better understanding via pathology whether familial PC differs from sporadic PC, and need great surgeons who can resect these lesions with minimal morbidity and mortality.
 - Almost half of the reduction in mortality from breast cancer in the last 25 years is attributable to early detection (mammography). The challenge is that we are not going to be able to treat carcinomas of the pancreas that are clinically evident because they are too complex genetically in all the different forms and all the different metastases.
 - Dr. Hruban stated that if the medical community can push down the limit of detection that this is where we are going to win the war against PC.
 - If we wait until these curable precursors have progressed to invasive cancer we are not going to win the war. The lesson here is don't let them grow too big!!