

Gastrointestinal Cancers Symposium

General Session IV: Cancers of the Pancreas – Prevention, Screening and Diagnosis

Title: Controversies in the Diagnosis and Management of Cystic Neoplasms of the Pancreas

Speaker: Pascal Hammel, MD

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Overview of Cystic Neoplasms of the Pancreas

- The diagnosis of cystic neoplasms is an emerging problem. Improved detection methods are identifying smaller and smaller lesions which can be benign, pre-malignant or malignant. Essential to determine the type, because the type determines the course of disease management.
- The main types of cystic lesions are:
 1. Pseudocysts
 - Account for 90% of cystic lesions. They are abnormal collections of fluid, necrotic tissue, pancreatic enzymes, and blood that can produce a painful mass in the pancreas.
 - Usually develop after an episode of acute pancreatitis. Alcoholism and biliary disease are also contributing factors.
 2. Serous cystadenomas
 - Usually unifocal in >90% of cases. Honey comb like feature.
 - 10% are prominently macrocystic.
 - Complications are rare (jaundice can occur due to compression of bile duct).
 - Malignancy is rare.
 3. Mucinous cystadenomas
 - Malignancy estimated to be about 10%.
 - Mucinous cystadenomas can mutate into mucinous cystadenocarcinomas.
 - The 5-year survival rate of mucinous cystadenocarcinomas depends on the possibility of complete resection and pathology results.
 - Prognosis is very good if it is focal carcinoma and complete resection is achieved. Survival is near 100% at five years. When there is malignant invasion and metastatic lymph nodes or distant metastases, the prognosis is less than 20%.
 4. Intraductal Papillary Mucinous Neoplasms (IPMN)
 - IPMN are mucinous epithelial neoplasms which involve the main pancreatic duct (MPD) or the branch ducts.
 - Risk of malignancy is much high in patients with MPD. In addition, MPD diameter ≥ 10 mm is predictive of malignancy.
 5. Other

IPMN and Pancreatic Intraepithelial Neoplasia (PanIN)

- PanINs are a new concept that has emerged recently in pancreatic disease.
- PanINs and IPMNs are similar in that both progress from low-grade dysplasia to moderate and high grade dysplasia (invasive cancer) via accumulation of genetic mutations.

- IPMNs and PanINs differ in the following ways:

| IPMN | PanIN |
|--------------------------------|--|
| ▪ Macroscopically visible >1cm | ▪ Microscopic, ducts <5mm <i>(difficult to diagnosis via imaging)</i> |
| ▪ Mainly papillary | ▪ Flat or micro papillary |
| ▪ Branch duct and MPD | ▪ Branch ducts |
| ▪ Mucin production high | ▪ Mucin production lower than IPMNs |

- Both PanINs and IPMNs can progress to ductal adenocarcinoma, possibly through different carcinogenesis pathways.

The Natural Progression of Small Cystic Lesions

- Dr. Hammel discussed the natural history of small incidental cystic lesions. Five large studies showed that a small cyst (<2cm) is rarely found to be malignant (3.5%). With time, most cystic lesions remain stable and do not undergo malignant transformation.
- Two studies observed the progression of branch duct IPMN. With a median follow-up of 61 months, both studies found that surgery was required about 10% of the time because of increased size or mural nodules. It was rare to find invasive cancer in the first five years.

Management of Cystic Neoplasms – To Operate or Observe?

- Serous Cystadenoma:
 - *Observe*- The risk of surgery is greater than the risk of malignant transformation. Would consider surgery if the diagnosis is unsure or the patient is symptomatic.
- Mucinous Cystadenoma:
 - *Operate* - Would elect surgery because there is a malignant potential. Would not consider surgery when it is located on/in the head of the pancreas and small in size <2cm, or when the patient is older with co-morbidities.
- Branch Duct IPMN:
 - *Observe* – The risk of surgery is probably greater than the risk of malignant transformation. Would elect surgery when the lesion is >3cm with nodules and the patient is symptomatic and in good condition.
- Main Pancreatic Duct IPMN:
 - *Operate* - Would elect surgery because the risk of malignancy is high.

Dr. Hammel's Take Home Message:

- Use all available tools to assess a correct diagnosis. Evaluate the benefit/risk ratio of surgery. Consider the risk of malignancy, location of lesion, and general condition of the patient.
- Small benign lesions can be observed and most of them remain unchanged with time.
- Studies are investigating the role of non-surgical treatments including the use of ethanol injection and radiofrequency ablation.

Title: Controversies in the Diagnosis and Management of Cystic Neoplasms of the Pancreas

Speaker: Keith Lillemoe, MD

Indiana University, Melvin and Bren Simon Cancer Center

- Dr. Lillemoe concurred with Dr. Hammel's points that cystic neoplasms of the pancreas are increasingly diagnosed in part because they are being picked up on routine CT scans. Dr. Lillemoe's talk focused on the surgical aspects of cystic neoplasms of the pancreas.

Surgical Management of Cystic Neoplasms of the Pancreas

- There are a number of objectives in surgically managing cystic neoplasms of the pancreas:
 - Treat the symptoms.
 - Cure/prevent pancreatic malignancy.
 - Provide surgical management with the best short and long-term outcomes including perioperative morbidity, mortality, and pancreatic endocrine and exocrine function.
 - Cystic neoplasms usually occur in younger patients, predominantly female, so it is important to consider quality of life, disability and cosmesis (the preservation of physical appearance).
- The surgical options for the management of cystic neoplasms of the pancreas include:
 - Pancreaticoduodenectomy (Whipple procedure)
 - Distal pancreatectomy
 - Total pancreatectomy
 - Central pancreatectomy (for tumors in the neck of the pancreas)
 - The body and tail of the pancreas is preserved. This is a procedure designed for removing benign neoplasms of the pancreas.
 - Pancreatic Cyst Enucleation
 - An operation reserved for patients with benign tumors because this surgery does not allow for adequate surgical margins or lymph node clearance. Small islet cell tumors or mucinous cystic neoplasms are perfect cases for this surgical approach.
 - Generally, enucleation involves a shorter operative time, less blood loss and usually no increase in total complications or pancreatic resection specific complication.
 - Over the last five years laproscopic pancreatic surgery has been introduced for distal pancreatectomy, central pancreatectomy, and enucleation.
 - Advantages of laparoscopic surgery in treating benign pancreatic neoplasms include:
 - Decreased post-operative pain.
 - Shorter hospital stay.
 - Rapid return to pre-op activity.
 - Decreased post-operative ileus.
 - Preserved immune function.
 - Superior cosmesis.

Surgical Management of Various Pancreatic Neoplasms

- Serous cystadenoma
 - Essentially always benign with rare reported cases of malignancy.
 - May grow to substantial size and even become unresectable.
 - Usually only operate for symptoms, size or diagnostic dilemma.
 - The incidence of this tumor is increased in patients with von Hippel-Lindau disease.
- Mucinous Cystic Neoplasms
 - By far the most common cystic neoplasms (40-50%), although IPMNs are increasing in frequency. Mucinous cystic neoplasms are distinct from IPMN in their clinical behavior and diagnostic features.
 - Have a defined malignant potential. Dr. Lillemoe referenced 33-50% as having a malignant potential. (Dr. Hammel referenced 10-15%). Regardless of the percent, Dr. Lillemoe said they can be very difficult to distinguish preoperatively if they are malignant or benign.
 - Surgical survival for non-invasive mucinous cystadenomas is 100%. For invasive cases survival falls to 30-40% at five years; this is comparable to the range found in ductal pancreatic adenocarcinoma.
- Intraductal Papillary Mucinous Neoplasms (IPMN)
 - The diagnosis of IPMN is a relatively new classification that came into play in the 1990's.
 - IPMNs are classified into two types: Main duct and branch duct
 - The course of treatment differs according to the type of IPMN. A working group of the International Association of Pancreatology proposed guidelines for treating different IPMNs:
 - Surgical resection is recommended for main duct IPMN because it has a high risk of malignant transformation.
 - For branch duct IPMNs, surgical resection is recommended if the patient is symptomatic (the risk of malignancy is higher when symptomatic), if the diameter >10mm, or there is the presence of intramural nodules, or suspicious cyst cytology.
- Dr. Lillemoe explained that no level I and very little level II evidence has gone into the consensus, and added the data is flawed, including bias in operative and observational studies. He discussed three recent studies published in 2007 in *Gut* and *American Journal of Gastroenterology*. The overall consensus from these studies is that only a small percentage require surgery; the majority (~80%) with small tumors can be followed safely without the need for surgery.
- How do you follow these patients after resection?
 - Periodic imaging even with benign disease is needed (CT, ERCP, EUS). Reoperation as needed.

Dr. Lillemoe's Closing Remarks:

- Surgical options for IPMNs are dictated by tumor size and location. Optimal perioperative morbidity and mortality are essential. Minimally invasive techniques appear appropriate.
- With serous cystadenoma operate for symptoms and size. For mucinous cystadenoma, operate for symptoms, size and cancer risk.
- For IPMNs, operate for symptoms, tumor type (main duct, branch duct), size and risk factors. Long term post-operative surveillance is very important.