

ADVANCES IN ENDOSCOPY

Current Developments in Diagnostic and Therapeutic Endoscopy

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Advances in the Diagnosis and Management of Pancreatic Cysts



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G&H Why should physicians be vigilant for pancreatic cysts?

AML Ninety percent of patients in whom pancreatic cancer is diagnosed will die within 5 years. Studies show that patients with stage 1a pancreatic cancer have an 80% chance of survival; thus, the key to improving survival for patients with pancreatic cancer is identifying it earlier. One way to do this is to identify the precursors to pancreatic cancer.

There are 3 precursors: pancreatic intraepithelial neoplasias (PanINs), mucinous cystic neoplasms (MCNs), and intraductal papillary mucinous neoplasms (IPMNs). PanINs are tiny lesions—less than 5 mm—that can only be seen under a microscope after they are resected. Currently, there is no way to detect PanINs on imaging. MCNs and IPMNs, however, are easily identified on computed tomography and magnetic resonance imaging (MRI). Proactive identification of pancreatic cysts raises the potential to detect pancreatic cancer earlier.

G&H How can IPMNs and MCNs be distinguished from benign cysts?

AML One of the difficulties is that not all pancreatic cysts are IPMNs and MCNs. Many of them are cysts that have no risk of developing into cancer. These include pseudocysts and serous cystadenomas.

When a clinician identifies a patient with a pancreatic cyst, the challenge is to differentiate IPMNs and MCNs, which can develop into pancreatic cancer, from all of the other cysts that do not need surveillance. This

can be done in a number of ways. One is a review of the clinical history. For example, MCNs occur almost exclusively in women. If a man has a pancreatic cyst, it is very unlikely to be an MCN. If there is a clinical history of acute pancreatitis, a pseudocyst is more likely. If the

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patient has a strong family history of pancreatic or related cancers or a documented germline genetic mutation, such as a *BRCA1* or *BRCA2* mutation, the risk is higher for development of an IPMN.

The next step is to review the imaging. Forty percent of IPMNs will present as multiple cysts. Pseudocysts also can occasionally be multiple. Almost all of the other cysts are typically single. The location of the cyst can be helpful for identification. For example, almost all MCNs are located in the body or tail of the pancreas. Awareness of these characteristics helps narrow down what type of cyst is being dealt with.

Endoscopic ultrasound (EUS) and cyst fluid analysis are other important modalities that differentiate benign cysts from IPMNs and MCNs. Among the different types of tests used, the classic one is cyst fluid carcinoembryonic antigen. A measurement higher than 192 ng/mL is strongly suggestive of an IPMN or MCN. Recent studies have suggested that analysis of cyst fluid glucose may be helpful as well. Cyst fluid also can be sent to cytology to look for mucin and to detect cancer or high-grade dysplasia.

G&H When should physicians be concerned about an IPMN or MCN because of the potential for progression to cancer?

AML Pancreatic cancer will not develop in the majority of patients with IPMNs and MCNs. Indeed, patients are more likely to die with their pancreatic cyst than because of it. One of the biggest challenges facing physicians is how to identify which patients will have IPMNs and MCNs that progress to pancreatic cancer. The presence of symptoms or signs such as jaundice, acute pancreatitis secondary to the cyst, or an elevated carbohydrate antigen 19-9 is concerning, as is the presence of a mural nodule or enhancing mass, an enlarged pancreatic duct of 5 mm or greater, a large cyst (>3 cm) on imaging, or the presence of high-grade dysplasia or adenocarcinoma on cytology. Patients with any of these features should be referred for further evaluation and consideration of surgical resection if appropriate. New-onset diabetes is also a risk factor for pancreatic cancer. Patients with new-onset diabetes or a rapid increase in the size of a cyst should undergo short-interval surveillance with MRI or EUS.

G&H How can physicians best identify patients who would benefit from surveillance, considering that most pancreatic cysts are identified incidentally?

AML Only patients with an IPMN or MCN should undergo surveillance. Patients with benign cysts, such as a serous cyst, do not require surveillance.

In patients with an IPMN or MCN, the initial question that needs to be asked is whether the patient is suitable for surveillance. The number one consideration is whether the patient is fit for surgery and would be willing to undergo surgery for removal of a precancerous pancreatic cyst. If the patient is not fit or not willing to undergo surgery, surveillance should not be undertaken.

The second question is whether there is an age or stage at which surveillance should be stopped. The American College of Gastroenterology (ACG) guidelines recommend reviewing whether surveillance is appropriate in patients who are 75 years or older. An alternative

approach is to look at comorbidities and their impact in relation to survival prospects. A study by a group led by Dr Carlos Fernandez-del Castillo showed that patients

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with multiple comorbidities were far more likely to die of them than of an IPMN. Surveillance for patients who have multiple comorbidities and have a life expectancy of less than 5 years may not be appropriate.

G&H Is it possible to treat pancreatic cysts with endoscopic techniques?

AML Lesions can now be ablated endoscopically, and groups have looked at whether it is possible to ablate pancreatic cysts. What these groups have shown is that paclitaxel can be injected into a cyst to decrease its size or even cause it to resolve. One question is whether ablation of the cyst will stop progression to malignancy. For example, IPMNs, which are the most common precancerous cysts, affect the entire pancreas. Cancer can develop not only within the cyst but also in a completely separate area of the pancreas. Guidelines currently do not recommend use of ablation of pancreatic cysts outside of a clinical trial.

G&H How can physicians effectively navigate and synthesize information from the different management guidelines that are currently available?

AML There are 5 different guidelines currently available, which are known as the International Consensus Guidelines (also referred to as the Fukuoka Guidelines), the American Gastroenterological Association Guidelines, the ACG Guidelines, the Radiology Guidelines, and the European Guidelines. One of the most important things for physicians to remember is that the quality of the evidence on which these guidelines are based is low or very low. Because of this, the recommendations in all of the guidelines are based on expert opinions.

Many similar ideas are shared through all of the guidelines. Among these are that pancreatic cysts determined to be IPMNs and MCNs should undergo

surveillance. Most of the guidelines also concur regarding when patients should be referred for consideration of surgical intervention as previously discussed.

In addition, most of the guidelines agree that very small cysts (<1 cm) should be followed every 2 years, small cysts (<2 cm) should be followed every year, and cysts that are 2 cm or larger should be followed every 6 months. The guidelines also agree that if the cyst is stable over a period of time, the time between follow-up can be lengthened. Conversely, if features that are concerning or worrisome are apparent, then the interval between follow-up should be shortened and EUS should be considered.

The major area in which the guidelines diverge is whether to stop surveillance after a fixed amount of time. This is controversial, and there are no high-quality data to either support or refute this approach.

G&H What new technologies are available or under investigation for the evaluation of pancreatic cysts?

AML Multiple tools are currently available to help determine whether a pancreatic cyst is benign or is an IPMN or MCN. The emerging area of investigation is how to identify the small number of patients whose IPMNs and MCNs will ultimately go on to develop high-grade dysplasia and invasive cancer and, therefore, benefit from surveillance. Many different groups are working on this challenge, and the field is rapidly advancing.

Assessment of cyst fluid for characteristic gene mutations is one method of identifying different types of pancreatic cysts. For example, IPMNs and MCNs can have a mutation in *KRAS*, IPMNs may have a mutation in *GNAS*, and the presence of a mutation in *VHL* with

no other mutation was found to have 100% specificity for a serous cystadenoma in a recent study of over 860 patients with pancreatic cysts.

Another new technique is through-the-needle confocal endomicroscopy (nCLE). In nCLE, a tiny probe with a microscope on the tip is placed through the EUS device and the biopsy needle and into the cyst, providing live imaging of the lining of the cyst. Studies have shown high specificity and sensitivity for identifying IPMNs from other types of pancreatic cysts.

Also new are microbiopsy forceps, which allow for a higher yield of tissue to help identify IPMNs and MCNs from other types of cysts. A systematic review and meta-analysis of over 400 patients found a diagnostic yield of 73% compared with 38% for cytology. Of note, the adverse event rate was 7%, which is higher than that typically seen for EUS fine-needle aspiration.

Disclosures

Dr Lennon has no relevant conflicts of interest to disclose.

Suggested Reading

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