Introduction

Pancreatic cysts are frequently identified incidentally on ultrasonography during health check-ups and investigations of unrelated diseases. With the improved sensitivity of imaging studies, small neoplastic cysts, especially branch duct-type intraductal papillary mucinous neoplasms (BD-IPMNs) are frequently being detected. Most pancreatic cysts do not require surgery. However, the differential diagnosis is not always easy by imaging tests only. Therefore, the appropriate treatment and follow-up strategy of such cysts remain controversial.

Basic treatment strategy for neoplastic pancreatic cysts

Serous cystic neoplasms (SCNs) are almost always benign serous cystadenomas. Hence, if their diagnosis is confirmed, they need only be observed periodically. Mucinous cystic neoplasms (MCNs) show low prevalence of invasive carcinoma (<15%). However, the natural history of MCNs remains unknown and non-operative management requires years of follow-up with high-resolution imaging, which is associated with high costs. Therefore, surgical resection is recommended for all surgically fit patients. In patients with BD-IPMNs, the mean frequency of malignancy is 25.5% (range, 6.3-46.5%) and the mean frequency of invasive cancer is 17.7% (range, 1.4-36.7%) in the surgically resected specimens. Thus, resection of BD-IPMNs warrants consideration. However, these lesions mostly occur in elderly patients, and the annual malignancy rate is only 2-3%. [1]

International Consensus Guidelines

The international consensus guidelines for the management of cystic mucinous neoplasms were formulated in Sendai in 2006 and updated in Fukuoka in 2012 [1]. “High-risk stigmata” includes obstructive jaundice in patients with cystic lesions of the head of the pancreas, an enhancing solid component within the cyst, and a main pancreatic duct (MPD) ≥ 10 mm in size. “Worrisome features” on imaging include cysts ≥3 cm, thickened enhanced cyst walls, MPD size of 5-9 mm, non-enhanced mural nodules, abrupt changes in the MPD caliber with distal pancreatic atrophy, and lymphadenopathy. All cysts classified as “high-risk stigmata” should be resected. If no “worrisome features” are present, further initial work-up is not recommended, although surveil-
lance is still required. All cysts with “ worrisome features” should be evaluated using endoscopic ultrasonography (EUS) to further stratify the risk of the lesion. EUS can detect small mural nodules and minimal invasion, and is considered the most effective method for delineating malignant characteristics. If the patient has definite mural nodules and main duct features suspicious for involvement, surgical resection should be considered. If not, periodical surveillance by imaging tests is recommended. However, the most appropriate follow-up strategy has not been established yet, and there is always the risk that malignant cysts might be missed. EUS-fine needle aspiration (FNA) and cyst fluid analysis performed prior to prescribing conservative treatment with periodical follow-up might be helpful for choosing the optimal treatment strategy.

**EUS-FNA and cyst fluid analysis**

1. **Cytology**

   Whereas the specificity for EUS-FNA cytology is close to 100%, it has a very poor sensitivity. The sensitivity is 22-50% for detecting mucinous cysts and 20-40% for the diagnosis of malignant mucinous cysts. This low sensitivity results from factors such as the low yield of lesion cells from the aspirate, insufficient sample volume, and contamination of samples with gastrointestinal wall cells. [2]

2. **CEA and amylase**

   A very low level of carcinoembryonic antigen (CEA; < 5 ng/mL) carries a positive predictive value of 94% and an accuracy of 70% for diagnosing a serous cystadenoma or pseudocyst over a mucinous cyst. A very high level of CEA (> 800 ng/mL) carries a positive predictive value of 94% and an accuracy of 79% for diagnosing a mucinous cyst over a serous cystadenoma or a pseudocyst. [3] Distinction of BD-IPMN from a small oligocystic SCN is sometimes challenging on imaging studies, but may be possible by assessing the cystic fluid CEA and amylase levels. SCNs typically have low levels of both CEA and amylase. However, the cyst fluid amylase level is not uniformly elevated in IPMNs, and MCNs may also exhibit elevated amylase levels. Therefore, it is difficult to distinguish between MCNs and IPMNs. Instead, elevated CEA levels can be considered a marker that distinguishes mucinous from non-mucinous cysts. However, the CEA level of pancreatic cyst fluid does not correlate with the risk of malignancy.

3. **Molecular analyses**

   Recently, many studies have attempted to differentiate between mucinous and non-mucinous cysts, or between benign and malignant cysts by molecular analysis. Khalid et al. [4] evaluated the utility of a detailed DNA analysis of pancreatic cyst fluid, including analyses of the K-ras mutation status, allelic imbalance, and the quantity/quality of DNA to diagnose mucinous and malignant cysts (the PANDA study). However, they failed to accurately differentiate between mucinous and non-mucinous, as well as between benign or malignant cysts; DNA analysis had poor operating characteristics values and detected cancer with low sensitivity and specificity. On the other hand, some recent studies have shown that panels of molecular markers and clinical features classified cyst types with high sensitivity and specificity. In addition, composite molecular markers correctly identified patients requiring surgery (high-grade dysplasia or invasive carcinoma) with a relatively high sensitivity and specificity. However, these molecular analyses are complicated and expensive. Further investigation is re-
quired for their use to be considered reasonable in routine clinical practice.

4. Complications

Even if these analyses were sufficiently helpful for the differential diagnosis and evaluation of the malignant grade, the safety must be guaranteed before they can be routinely performed. The overall complication rate of EUS-FNA for pancreatic cysts has been reported to be between 1% and 6%. The reported complications include hemorrhage (0.2-6%), infectious complications (0.2-5%), acute pancreatitis (0.6-2.6%), and others. A recent systematic review of the morbidity associated with EUS-FNA showed that the complication rate was higher in cases of pancreatic cysts than for pancreatic masses. [5] Further, there have been concerns about peritoneal dissemination after EUS-FNA of cystic mucinous neoplasms. Recently, Yoon et al. [6] compared the frequency of postoperative peritoneal seeding in patients with IPMN who had undergone preoperative EUS-FNA with that in patients with IPMN who had undergone surgery without preoperative tissue sampling (the PIPE study). As a result, the frequency of postoperative peritoneal seeding was found to be similar in the EUS-FNA and no sampling groups. However, most Japanese investigators still hesitate to perform EUS-FNA and cyst fluid analysis for the diagnosis of mucinous cystic lesions, and believe that a cyst of any size with “worrisome features” should not be aspirated to avoid leakage of the cyst content, as this is associated with a risk of peritoneal dissemination.

In summary, although cyst fluid analysis may avoid misdiagnosis of mucinous versus non-mucinous cysts and benign versus malignant cysts, the insufficient diagnostic yield and the potential risk for cyst fluid leakage leading to peritoneal dissemination of the tumor detract against its widespread use, especially in Japan.

EUS-guided pancreatic cyst ablation

EUS-guided ablation with either ethanol or ethanol followed by paclitaxel has been proposed for pancreatic cysts. [7] The indications are unilocular cysts without obvious ductal communication or high-risk pancreatic cysts where the patient refuses surgery or is considered at too high risk. Complete cyst epithelial ablation is obtained in 33-62% of cases. Procedure-related complications include pancreatitis (2%), abdominal pain (7.9%), and splenic vein obliteration (0.7%). Of note, in the above study, information about the degree of cyst ablation was available in only a smaller number of patients who underwent surgical resection. Due to concerns about incomplete destruction of premalignant tissue, uncertainty about the impact of the natural histories of BD-IPMN and MCN, and lack of long-term outcome data, this approach is still considered experimental and should be performed under a research protocol.

References


