To fine needle aspiration or not? An endosonographer's approach to pancreatic cystic lesions

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ABSTRACT

Endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) is an established diagnostic tool in the management of pancreatic cystic lesions (PCLs). Due to the proximity to the target lesion, the fine diagnostic needle travels through only minimal normal tissues. The risks of bleeding, pancreatitis and infection are small. Valuable diagnostic morphological information can be obtained by EUS before the use of FNA. The additional cytopathologic and cyst fluid analysis for the conventional markers such as amylase, carcinoembryonic antigen (CEA) and CA19.9 improves the diagnostic capability. Pancreatic cyst fluid CEA concentration of 192 ng/mL is generally the most agreed cutoff to differentiate mucinous from non-mucinous lesion. A fluid amylase level of <250 IU/L excludes the diagnosis of pseudocyst. Technical tips of EUS-FNA and the limitations of the procedure are discussed. Promising technique and FNA needle modifications have been described to improve the diagnostic yield at the cytopathologic analysis. The use of novel cyst fluid proteomics and deoxyribonucleic acid-based biomarkers of the PCLs are reviewed. Although it is considered a safe procedure, EUS-FNA is not a routine in every patient. Recommendations of the role of EUS-FNA at various common clinical scenarios are discussed.

Key words: Cytopathology, endoscopic ultrasound, fine needle aspiration, pancreatic cystic lesion

INTRODUCTION

With the widespread and increasing use of high-resolution abdominal cross-sectional imaging, more and more pancreatic cystic lesions (PCLs) are detected. Patients with a PCL may or may not have symptoms arising from the lesion, which may be completely benign without any malignant potential, may be benign but could become malignant, or already may be malignant.

Depending on the type of imaging technique and the inclusion and exclusion criteria of individual studies, the prevalence of incidental pancreatic cysts has been reported to a range from 2.6-13.6% respectively.[1,2] In one autopsy study, the prevalence of pancreatic cysts was even 24.3%. In the same study, atypical hyperplasia and carcinoma *in-situ* was found in total 19.8% of these PCLs.[3] Not all PCLs are resected, therefore the true incidence of neoplastic PCL remains largely unknown. Among those resected, cystic neoplasms were estimated to account for 60%.[4]

Management options of PCLs are diverse. Some patients with PCL can be discharged without any need for follow-up, whereas others require close observation with noninvasive imaging tests that may or may not detect malignancy before it is too

late to treat effectively. Whereas other patients may require invasive tests such as endoscopic retrograde cholangiopancreatography and endoscopic ultrasound (EUS) or even go directly for surgical resection. Due to this wide range of treatment and surveillance options, the need for an accurate differential diagnosis of PCLs is of the utmost importance.

The potential ability of EUS-guide fine needle aspiration (FNA) to make a preoperative diagnosis based on cytology and biochemical markers of cyst fluid together with the development of new needles and accessories is very attractive. Thus, the endosonographer can be tempted to perform EUS-FNA of every encountered PCLs. Sometimes however, based on symptoms and the morphologic features on cross-sectional and ultrasound images, a diagnosis and the management plan can be made regardless of the additional information provided by the needle puncture. In this review paper, we hope to offer some insights regarding to when EUS-FNA should be performed based on balancing risks (complication) and benefits (diagnostic yield) and what information it could provide for the final decision-making in the management of PCLs.

MORPHOLOGY ALONE

Most of the patients with PCLs already underwent one or more cross-sectional imaging methods, such as magnetic resonance imaging (MRI) and more commonly computed tomography (CT) due to its widespread availability. CT generally is able to provide a good image of PCLs and the rest of the pancreas. In a recent systematic review,[5] it offered good specificity with regards to the detection of malignancy when associated with PCLs, ranging from 63.9-100% respectively. Sensitivity of CT however was well below 70% and accuracy for a specific diagnosis was poor, ranging from 39-44%. With the use of higher resolution multi-detector CT and pancreas specific protocols, the accuracy has been shown to improve.[6]

Compared with CT, MRI and specifically the T2-weighted imaging, has inherently superior soft tissue contrast and effectiveness in highlighting fluid-containing structures.[2] It has a better ability to demonstrate communication between the cystic lesion and the main pancreatic duct (PD) compared to CT and the added benefit of not using ionizing radiation. In the same recent systematic review,[5] the sensitivity for the

detection of malignant lesions ranged from 65.4-94.3% with specificity ranging from 58.3-88.9%. However, similar to CT, MRI only had a moderate accuracy for specific diagnoses ranging from 39.5-44.7%. Therefore, further investigations than only cross-sectional imaging alone are usually required.

EUS has the unique advantage of having the transducer very close to the PCLs in question. Therefore, it can offer superb definition of the structural component of the target lesions. Lesion size, location, locularity, internal structural features, mural nodules, contours, cystic wall thickness, aspect of the PD, the presence of calcifications and ductal communication can all be assessed by EUS. Various more or less specific endosonographic characteristics of the different kinds of the pancreatic cysts have been described.

Serous cystadenomas (SCA) are typically microcystic with a honeycomb aspect in classical cases.[7,8] A central stellate scar is pathognomonic. The cystic wall is poorly developed. The thin internal septa are hypervascular on Doppler. Communication with the PD is not seen. However, in about 10% of the case, SCA can be unilocular without a clear microcystic component although often in seemingly unilocular SCA a microcystic area can be identified.

The morphology of mucinous cystadenoma (MCA) is variable. It is usually multiloculated with a visible cystic wall.[8] Because of the thick mucoid cystic content; it may appear granulated on EUS. It may have a peripheral wall with curvilinear calcifications (egg shell calcification) that is more or less pathognomonic.[9] Features suggestive of invasive malignancy for MCA include intramural nodules, solid component, focal thickening of cystic wall or septa.[10]

Branch-duct type intraductal papillary mucinous neoplasia (BD-IPMN) may appear as either a cyst or a cluster of cysts usually in the uncinate process.[11] IPMNs are defined as intraductal grossly visible epithelial neoplasms of mucin producing cells, arising in either the main PD or its branches. Tumors arising in the main PD, cause segmental or diffuse dilatation of the main PD >5 mm. The adjacent pancreas is usually normal. Produced by dilatation of secondary order branches of the PD due to mucin and/or polypoid tissue, a BD-IPMN is a mutiloculated cyst with a "bunch of grapes" appearance.[12,13] As oppose to the "cyst in cyst" internal structure in mucinous

cystic neoplasm (MCN), BD-IPMN has "cyst by cyst" internal cystic structure.[13] Sometimes, these lesions are formed by only one ecstatic pancreatic secondary duct and can appear round and unilocular. The most important diagnostic feature for these lesions is the communication with the PD. It has been shown that EUS and MRI are equally capable in determining this.[5] Multifocality is one of the differentiating features from MCN. In addition, during EUS, the papilla can be examined for the occasionally seen but classical "fish mouth papilla" which is diagnostic of main-duct type (MD-) or mixed type-IPMN.[14]

Pseudocysts are often round and unilocular without internal septations or mural nodules. Mobile hyperechoic material inside the cyst can be seen when changing the position of the patient or during aspiration of the intracystic fluid. Communication with the PD is often not identifiable on cross-sectional imaging or EUS despite the general belief.[15] Care should be taken to examine the rest of the pancreatic parenchyma for the features of chronic pancreatitis without which the diagnosis of pseudocyst should be given with caution.

Although EUS is capable to offer detailed morphologic description of various PCLs, the diagnostic accuracy of EUS morphology alone is rather disappointing and reported to be between 51% and 90% respectively.[16] Its performance is slightly better in terms of detecting overtly malignant lesions. However, it is less reliable in differentiating among non-malignant lesions, which include premalignant and benign lesions. Definitive diagnosis in these situation guides the subsequent management plan. In addition, because some of the cystic lesions share morphologic characteristics, the interobserver agreement is also suboptimal.[17] However, with the addition of FNA, cystic fluid could be sampled for cytologic and biochemical analysis. This further improves the diagnostic capability of EUS. In a recent study looking at the incremental diagnostic yield and accuracy of EUS with or without FNA over CT and MRI for the prediction of neoplastic pancreatic cyst, in 154 patients with final surgical pathologic diagnosis, the diagnostic yield after EUS ± FNA improved by 36% and 54% over CT and MRI, respectively.[18]

RISKS OF EUS FNA

EUS guided pancreatic cyst fluid sampling by traversing the gut lumen with a fine needle via the working channel of echoendoscope offers additional information such as fluid viscosity, cyto-pathology, pancreatic enzymes and tumor markers to aid in the differential diagnosis of PCLs. It is generally considered to be a safe procedure. In a large systematic analysis of EUS-FNA-related complications that included 909 patients with EUS-FNA of PCLs, the overall complication rate was 2.75%.[19] The most common complication was pancreatitis (1.1%), followed by chest or abdominal pain (0.77%). Only a few patients developed fever (0.33%), bleeding (0.33%) or infection (0.22%). In a large prospective multicenter study specifically examining the complication rate of EUS FNA of PCLs, 18/298 (6%) developed complications, all of which resolved on medical therapy.[20] The most frequently encountered complications were bleeding: 7 (2.35%), followed by fever and pain in 4 each (1.34%). Only 2 patients (0.67%) developed pancreatitis. Acute pancreatitis after EUS-FNA of pancreatic cysts seems to occur most frequently after FNA of cysts in the pancreatic head and uncinate process. Most likely this is related to the distance that the needle needs to travel through normal pancreatic tissue. Most cases are mild to moderate pancreatitis that responds to conservative measures within 2-3 days. In order to avoid infection, an effort should be made to completely empty the cyst being sampled. Prophylactic antibiotic fluroquinolone given during and 3-5 days after EUS FNA is recommended in most guidelines.[21,22] Hemorrhage into the cyst is evident with expanding hyperechoic areas within the cystic lesion after puncture. Before the fine needle puncture, Doppler signal should be used to screen for intervening blood vessels in the potential needle path. Contrary to EUS FNA for solid lesions, discontinuation of all antiplatelet agents including aspirin, thienopyridines and anticoagulation therapy is recommended for all EUS FNA of PCLs.[23] Depending on the thrombotic risk of individual patients, bridging therapy with heparin should be considered during the period of anticoagulation withdrawal. For patient with high thrombotic risk, the withdrawal of clopidogrel, rivaroxaban or dabigatran should be individualized. Tumor cell seeding along the FNA needle tract is theoretically possible. However, this complication is rarely reported. At the time of writing, only six case reports of tumor seeding after EUS FNA have been published.[24] Within these, only one case was related to pancreatic cyst puncture.[25]

TECHNICAL ASPECTS OF THE PROCEDURE

In general, EUS-FNA of PCLs is considered to be relatively easy. For FNA, a 22-G or 19-G needle is

preferred because of the potentially high viscosity of cyst fluid content in case of mucin rich lesions. Other addition factors to consider are the location of the cyst and the distance of the needle passage. In case of a cystic lesion in the head of the pancreas, needle access can be possible from both the duodenum and the stomach. The echoendoscope is in a relatively straight position in the stomach compared with in the duodenum making the passage of a larger caliber needle easy. However, the needle from the stomach may need to traverse a larger amount of normal pancreatic tissue thereby increasing the risk of pancreatitis. Sometimes, after the passage of a large bore needle into the working channel, the original image angle may be lost especially when approaching the lesion from the duodenal bulb. With Doppler interposing blood vessels are identified and avoided.

The needle is introduced to the center of the cystic lesion. The stylet is then removed and vacuum is applied. Whereas keeping the needle at the center of the lesion, cyst fluid is aspirated until the lesion completely emptied. For larger volume cysts a large syringe connected to an inflation device normally used for the inflation of dilation balloons can be a timesaving option. Solid components such as septations or nodules and also the wall of the cyst should be avoided initially since this may lead to incomplete emptying of the cyst due to needle blockage. Multiple passes should be avoided because of the potentially increasing chance of gastric or duodenal contamination from repeated punctures. After emptying the cyst and aspiration of all fluid, the cyst wall and solid components are sampled and individually processed for cytopathological analysis.

While cytopathologic analysis is the most reliable diagnostic test, offering high specificity for identification of malignancy and PCL subtypes, it has a low sensitivity.[26,27] This is because of the small number of cells present in the fluid aspirate. Various techniques and modifications of the FNA needles were explored in order to obtain a better cytopathologic sample.

In a small study with 10 patients with PCLs located in the pancreatic body and tail, a tru-cut biopsy device containing a 19-G needle with a tissue tray and sliding sheath was used to obtain tissue cores specimen of the cystic wall.[28] After a mean of 2.4 EUS guided tru-cut biopsies (range, 1-6), useful histology was obtained 7 out of the 10 patients. No complication

was identified. After its publication in 2005, no further report of the use of this tru-cut needle on PCLs is available. Due to the rigidity of the device, it is not possible to use this for lesions in the head of the pancreas. In addition, larger studies are needed to provide more reassuring safety data of the device. With the recent development of the ProCore needle (Cook Endoscopy), obtaining histological samples has become easier and more predictable although experience with its use in PCLs is very limited.[29]

Targeted FNA of the cyst wall can be attempted after aspiration of cyst fluid. The cyst wall is identified as a hypoechoic remnant in the region of the needle tip. Before the removal of the needle from the pancreas, targeted FNA of the cyst wall was reported to improve the diagnostic yield for premalignant and malignant PCLs in one study. Cellular material adequate for cytologic assessment was obtained in 56/69 cysts (81%).[30] The additional incremental diagnostic yield by this cystic wall puncture (CWP) over combined fluid carcinoembryonic antigen (CEA) and cytology was 29% (20 of 69 cysts). The technique appeared safe with only one patient developing mild pancreatitis post CWP. No bleeding complications were reported. However, since only 6 of 66 patients underwent surgical resection in this cohort, definitive pathologic correlation is limited. Nevertheless, without the need for further investment of time and equipment and in the light of the favorable safety profile, this technique seems promising.

A disposable through-the-needle cytology brush, the EchoBrush (Cook Endoscopy) was introduced in 2007.[31] Promising superiority over FNA in providing adequate cytologic assessment was noted in several studies.[31-35] Various techniques using this device were reported. In general, though, after the introduction of a 19-G needle into the cystic lesion, the EchoBrush is introduced through the needle and moved repeatedly against the cystic wall to scrape off cells. Some of the authors advocate back-and-fro movement while only rotating movement was used in one particular study.[31,34] The use of the device has been described both before and after complete cystic aspiration. Due to the small sample size of individual studies and the lack of comparative studies, the optimal technique using this device remains to be determined. The prerequisite for a 19-G needle potentially limits its use for lesions located in the pancreatic head and uncinate process. The overall pooled complication rate (14/142, 10%) is

more than would be expected from EUS-FNA without cytobrush.[32-36] Especially worrisome is delayed major bleeding in patients on anticoagulation (even though the INR at the time of procedure was according to protocol).[33] Cautions need to be taken for this special patient sub-group.

Furthermore, in a recent study, a 22-G needle with reverse bevel and a 2 mm side fenestration (Procore, Cook Endoscopy) was used in 58 patients with PCLs.[37] Punctures from the stomach and the duodenum were technically feasible in all cases. After aspiration of the cyst fluid and the cyst walls had collapsed on the needle, sampling with aspiration was continued to allow cystic wall tissue to enter the side fenestration of the needle which was then moved back and forth 3-4 times about 5-10 mm. Due to the needle architecture, small pieces of tissue core sample or microbiopsies could be obtained for full histological evaluation. The overall sample adequacy for cyto-histological diagnosis was 39/60 (65%). Adequacy for histological evaluation was 46.1% and in these cases a more precise diagnosis with immunohistochemical or further special staining was possible. There were 2 complications (3.3%) reported: One intracystic bleeding and one fever, both were settled with medical treatment.

CYST FLUID BIOCHEMISTRY AND TUMOR MARKERS

As we have shown in the previous section, the results of cytological analysis of cyst material in general are disappointing mainly due to its low cellularity.[26] However, cyst fluid does not only contain cells shed from the lining epithelium. Molecular components such as nucleic acids and proteins released from the cells of interest can be found and analyzed in cyst fluid as well. The quantification of various tumor marker concentrations in pancreatic cyst fluid has been shown to differentiate mucinous from non-mucinous cyst. CEA is considered the most accurate for this purpose compared with others such as CA19-9, CA72-4 and CA-125.[38,39] It is secreted by the neoplastic mucinous epithelium and is the most extensively studied protein for the important distinction between mucinous and serous pancreatic cysts. Various cut-off values would produce different degrees of sensitivities and specificities. The most agreed upon cut-off of 192 ng/mL was derived from a large prospective study by Brugge et al.[39] on 112 patients. In that particular study, using this cut-off level a diagnostic sensitivity

of 75%, a specificity of 84% and an accuracy of 79% in differentiating mucinous from non-mucinous cystic lesions could be reached. The extreme ends of the CEA value can be quite helpful as well. A very low CEA value (<5 ng/mL) is highly diagnostic for non-mucinous lesion such as serous cystoadenomas or pseudocysts.[40] On the contrary, a value of >800 ng/mL is highly specific for mucinous lesions.[40] It is important however to realize that value of CEA itself is not indicative for the presence (or absence) of malignancy even for very high values (>1000 ng/mL).[40,41]

Amylase levels in PCLs can be used to identify communication with the PD. The median values of amylase in pseudocysts, SCA, MCA and mucinous cystadenocarcinoma were 11,000, 250, 8000 and 150 IU/L, respectively in a large pooled data report of cyst fluid analysis.[40] However, the amylase values of MCA were found to distribute evenly in a wide range. The median amylase level for IPMN was noted to be 5000 IU/L in another study.[42] Cysts with amylase <250 IU/L were SCA, MCA or MCAC (sensitivity 44%, specificity 98%, accuracy 65%) and thus virtually excluded pseudocysts.[40]

The research for novel cyst fluid protein biomarkers continues. It was hypothesized that dysplasia in the epithelial lining of IPMN causes an immunogenic and proinflammatory microenvironment. One study could indeed demonstrate that among other cytokine expressions, interleukin-1 beta levels could differentiate between high-risk (IPMN with high-grade dysplasia) and low-risk (IPMN with low- or intermediate-grade dysplasia) IPMN in a pilot study analyzing 40 pancreatic cyst fluid aspirants collected at resection[43] Specific protein glycan variants from pancreatic cyst fluid were also noted to be useful in the distinction of mucinous and non-mucinous lesions.[44]

Plectin-1, a marker related to pancreatic ductal adenocarcinoma, was found to be a potentially promising biomarker for the detection of malignancy in IPMNs.[45] Plectin-1 expression was assayed using immunohistochemistry in cyst fluid and tissue sample from benign and malignant IPMN, as well as lymph node metastasis from carcinoma arising from IPMN. The sensitivity and specificity were 84% and 83%, respectively. In another study, protein expression profiles were examined in mucus samples from resected IPMNs. Among all the protein peaks analyzed using a special mass spectrometry for proteomic assessment,

5 candidate proteins were selected by their high diagnostic accuracy and ability to distinguish between malignant and benign IPMNs.[46]

From dysplastic changes to cancer, it is essentially a disease of the genes. Because of their remarkable stability, deoxyribonucleic acid (DNA)-based biomarkers have been investigated in pancreatic cyst fluid analysis. In a large multicenter trial, 113 patients who underwent resection for a PCL, cyst fluid samples were harvested through EUS preoperatively.[47] KRAS mutational status and the mean allelic loss amplitude (MALA) were assessed in the purified DNA. It was found that both a MALA of >65% and the presence of KRAS mutations were indicative of a mucinous cyst on multivariate testing. Similarly, the differential expressions of microRNAs (miRNAs) were observed in cancer including pancreatic cancer. The miRNA are 19-24 nucleotide-long non-coding single-stranded RNA molecules with high biostability. In a recent study, together with IPMN surgical specimens, 65 cyst fluid samples were examined for differential selective miRNA candidate expression.[48] A subset of 18 miRNAs separated high-grade from low-grade lesions. A logistic regression model using nine miRNAs allowed prediction of high-grade IPMNs, pancreatic neuroendocrine tumors and solid pseudopapillary neoplasms (SPNs) versus low-grade IPMNs and SCA with a sensitivity of 89%, a specificity of 100% and area under ROC curve of one.

INTERPRETATIONS OF ALL FEATURES

Pancreatic cystic neoplasms are reported to account for up to 60% of all PCLs, followed by inflammation-related and injury-related cysts (30%).[4] PCNs include intraductal papillary mucinous neoplasm, MCN, serous cystic neoplasm (SCN), solid-pseudopapillary neoplasm, cystic neuroendocrine neoplasm, ductal adenocarcinoma with cystic degeneration and acinar-cell cystic neoplasm. The first four entities account for the majority of cases and will be discussed in more detail below.

IPMNs

Patients with PCLs suspicious for IPMNs can be asymptomatic when incidentally found on cross-sectional imaging performed for other purposes. When symptomatic, they may present with acute or recurrent acute pancreatitis, abdominal pain, jaundice, weight loss or exocrine pancreatic insufficiency.[11] On reviewing the cross-sectional imaging for the features discussed in the previous section, MD-IPMN is usually

identified without difficulty. MD-IPMNs may show diffuse or focal involvement of the main PD of more than 5 mm.[49] Differential diagnoses to consider are pseudocysts and chronic pancreatitis complicating with focal dilatation of main PD. In an otherwise surgically fit the patient without the overtly high risk features mentioned in the revised Sendai Criteria such as obstructive jaundice, main PD dilation of more than 10 mm or the presence of solid component, the purpose of EUS-FNA is to confirm the diagnosis of MD-IPMN and thus surgical resection could be recommended.[38] Cystic fluid cytology is rarely sufficient to distinguish IPMN from MCN; the result is usually a generic cytology report of "mucinous cyst." Additional cyst fluid features compatible with IPMN include all the common mucinous lesion characteristics: The high viscosity of the aspirated cyst fluid, the presence of mucin on cytologic staining and a high cyst fluid CEA value. Unless clearly indicated by cyst fluid cytology, which is rarely the case, differentiation between malignant from benign IPMNs can be difficult.[40,41] However, this is usually not needed in the formulation of management plan because surgical resection recommendation is strongly supported by the revised Sendai Criteria once the diagnosis of MD-IPMN is made due to its relatively high reported incidence of malignancy or invasive foci at the time of diagnosis.[38]

The diagnosis of BD-IPMN should often be considered in the differential diagnosis of PCLs unless a typical morphology indicative of a certain type of cyst is seen with cross-sectional images or under EUS assessment. The communication with the main PD and "cyst-by-cyst" or bunch of grapes appearing cystic lesion located in the uncinate are remarkably helpful in this case. Because of its premalignant nature, an accurate diagnosis is sometimes required before subjecting patients into regular surveillance programs that may not be necessary in other non-mucinous lesions. Similar to the main duct counterpart, the cyst fluid has usually a high viscosity. Cyst fluid cytology yield is usually disappointing. Features to be sought are all the mucinous cyst fluid characteristics discussed previously. In addition, when high risk features are detected such as a definite solid component and possible main duct involvement, surgical resection is recommended by the revised Sendai Criteria.[38] In contrast to the previous Sendai criteria,[13] cyst size >3 cm and PD dilation more than 6 mm are no longer features that should automatically lead to resection. Asymptomatic cystic lesions >3 cm without the presence of a definite

mural nodule or thickened main duct walls should not warrant immediate resection. On the other hand, in case of rapidly increasing cyst size in the subsequent surveillance or when high-grade atypia is noted in cyst fluid, patients should be referred for surgery.

MCA

The 2010 WHO classification of tumors defines MCA as a cyst-forming epithelial neoplasm that is usually without communication with the PD and consisting of columnar, mucin-producing epithelium with an underlying ovarian-type stroma.[49] Although it is sometimes difficult to distinguish from IPMN, there are some classical features which, when present, may make differentiation between MCA and IPMN easier. For reasons yet to be known, these single thin walled septated cystic lesions are rarely located in the head of the pancreas, they rarely communicate with the PD and are extremely rare in males.[11] MCA smaller than 4 cm and those without solid component carry no malignancy. Therefore, in elderly frail patients, these lesions could be monitored without the immediate need for surgery. Thus, EUS-FNA is not advised in this situation.[38]

Otherwise, as all MCAs are potentially malignant with undefined natural history, younger patients should be referred for resection when the MCA is larger than 4 cm or there is a mural nodule. Similarly, EUS-FNA is not advised in this situation when clear indications for surgery are present. In addition, one should not rely on EUS-FNA based cytology to look for evidence of invasive carcinoma because the invasive component of the lesion may be focal and the epithelium of MCA shows a typical mixture of different grades of dysplasia although abrupt transition between low and high-grade epithelium has been reported.[11] Even though the presence of p53 protein by immunohistochemical staining is correlated with poor disease outcome, its expression was seen in only half of malignant MCNs.[50] CEA levels have no role in the prediction of malignancy. Until then, the true invasiveness cannot be accurately assessed pre-operatively. For all non-invasive MCA, post resection prognosis is excellent. Depending on the extent of the invasive component, tumor stage and resectability, the 2- and 5-year survival rate of patients with resected invasive MCA are about 67% and 50%, respectively.[49]

SPN

SPNs are uncommon low-grade malignant neoplasms occurring predominantly in young women (>80%) in their 20-30 s. They are usually large mixed cystic and solid lesions with a thick capsule on CT. On EUS, they are usually identified as well-defined, hypoechoic masses. Internal calcifications can be seen in some cases. The reported diagnostic accuracy of EUS-FNA for SPN based on cytology and immunohistochemistry is 65%.[51] Microscopically, they are a combination of solid pseudopapillary components and hemorrhagic-necrotic pseudocystic components. Mucin is absent and glycogen is not conspicuous. Even SPNs without histologic criteria of malignant behavior such as perineural invasion, angioinvasion, or infiltration of the surrounding parenchyma, may metastasize. The mainstay of treatment is surgery and after complete surgical resection, 85-95% of patients are cured.[49]

SCN

SCNs account for about 16% of resected cystic tumors of the pancreas.[52] They are benign, slow-growing tumors that predominantly affect women in their 60 s. Because of the presence of the typical microcystic component of the lesion on imaging morphology, a presumptive diagnosis of SCN can often be made. In order to reassure both the patient and the doctor that the PCL can be discharged without the need for follow-up, EUS-FNA is sometimes performed. As mentioned previously, the typical cyst fluid characteristics are the low viscosity and the exceedingly low CEA levels (<5 ng/mL). In addition, because of the vascular nature of the SCN, cyst fluid sample by EUS FNA may be bloody or contain hemosiderin-laden macrophages.

CONCLUSION

EUS FNA carries a small but non-negligible risk. It has a complementary role in the diagnostic work-up of PCLs. Depending on patient's demographic data and surgical fitness, wise selective application of this technique can offer valuable information in patient management. Cyst fluid analysis utilizing proteomics and miRNA are promising novel tools. Further large studies with EUS FNA of PCLs are awaited.

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