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Review:

Pancreatic cystic neoplasms: a review of preoperative diagnosis and management*

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Abstract: Pancreatic cystic neoplasms (PCNs) are a diverse group of neoplasms in the pancreas, and are more increasingly encountered with widespread abdominal screening and improved imaging techniques. The most common types of PCNs are serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs), and intraductal papillary mucinous neoplasms (IPMNs). Clinicians frequently feel bewildered in the differential diagnosis and subsequent management among the various types of lesions in the pancreas, which may lead to overtreatment or delayed treatment. The current review provides recent developments in the understanding of the three most common types of PCNs, the latest modalities used in preoperative diagnosis and differential diagnosis, as well as the most up to date management. Suggestions for diagnosis and differential diagnosis of SCNs, MCNs, and IPMNs are also provided for young surgeons. Better understanding of these neoplasms is essential for clinicians to make accurate diagnosis and to provide the best management for patients.

Key words: Pancreatic cystic neoplasms, Serous cystic neoplasms, Intraductal papillary mucinous neoplasms, Mucinous cystic neoplasms, Diagnosis

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1 Introduction

With the widespread use of advanced radiological and endoscopic techniques, an increasing number of patients are being diagnosed with pancreatic cystic lesions. The incidence of pancreatic cystic lesions is about 1 in 100 hospitalized patients (Khalid and Brugge, 2007). These lesions can be caused by injury, infection, or congenital anomalies. Pancreatic cystic neoplasms (PCNs) account for 10% to 15% of all pancreatic cystic lesions (Garcea *et al.*, 2008). PCNs are a diverse group of neoplasms, including serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs), intraductal papillary mucinous neoplasms (IPMNs), mucin solid pseudopapillary neoplasms, cystic endocrine neoplasms, and acinar cell cystadenocarcinomas. For clinicians, a reliable diagnosis and the subsequent management of PCNs are critical. When the cystic lesion is large or when the mass-related symptoms exist, surgical resection is recommended even when the diagnosis is uncertain. However, a majority of PCNs are asymptomatic and are found incidentally. These are challenging to preoperatively distinguish among the various types of lesions and to identify whether these lesions are benign, malignant, or potentially malignant. Therefore, an exact diagnosis is very important to avoid overtreatment or missing the opportunity to cure.

Approximately 90% of PCNs are SCNs and

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mucin-producing neoplasms (MCNs and IPMNs) (Brugge *et al.*, 2004a). In this review we focus on clinical features, preoperative differential diagnostic strategies, and management of these three types of PCNs. We aim to provide updated knowledge about these three most common types of PCNs and to provide helpful recommendations on the appropriate treatment.

2 Clinical features

2.1 Serous cystic neoplasms (SCNs)

SCNs mainly occur in women (70% to 75%), with the highest incidence in women in their 60s (Solcia *et al.*, 1997; Tseng *et al.*, 2005). SCNs can occur anywhere in the pancreas. A multicenter study of SCNs in Japan showed that the tumors were located in pancreatic head (39%), body (35%), tail (22%), and uncinate process (3%) (Kimura *et al.*, 2012). Although a majority of the patients with SCNs are asymptomatic, the most common presenting symptom is abdominal pain (25%), followed by palpable mass, jaundice, fatigue, and malaise (Tseng *et al.*, 2005).

SCNs are broadly classified into microcystic adenomas and macrocystic (oligocystic) adenomas and are usually less than 2 cm (Buck and Hayes, 1990). Serous microcystic adenomas (SMAs) are most common and they are mostly benign. These glycogen-rich cystadenomas are surrounded by fibrous capsules which separate them from the normal tissue (Buck and Hayes, 1990). In the interior they form a honeycomb appearance, or a sponge-like structure with numerous small closely packed cysts arranged around a central stellate calcified scar (Buck and Hayes, 1990). There are very few cases of microcystic adenocarcinomas reported (Abe *et al.*, 1998; Eriguchi *et al.*, 1998; Wu *et al.*, 1999). Histologically both microcystic adenomas and microcystic adenocarcinomas are identical and the presence of metastasis in liver or lymph nodes is the only way to differentiate them.

Serous macrocystic adenomas are rare and have fewer and larger cysts. The cysts are often more than 1 cm (Kimura *et al.*, 2012). They mostly occur in the pancreatic head and, since they have a large size, they cause obstructive symptoms, including jaundice.

von Hippel-Lindau disease, an autosomal dominant genetic disease that has a germline mutation in von Hippel-Lindau gene on chromosome 3p25 (Yoon and Brugge, 2012), is also associated with serous macrocystic adenomas of the pancreas (Mohr *et al.*, 2000). The patients often have their entire pancreas involved and can have lesions on the central nervous system, kidneys, adrenal glands, and reproductive adnexal organs (Lonser *et al.*, 2003).

2.2 Mucinous cystic neoplasms (MCNs)

MCNs are far more common in women (female: male, 20:1) and usually occur in the perimenopausal women (Goh *et al.*, 2005; 2006). The incidence peaks in the 5th decade of their life (Yoon and Brugge, 2012). In a study on 56 patients with MCNs, all were found to be women (Zamboni *et al.*, 1999). They are usually found in the tail or body of the pancreas, with only 5% to 10% in the head (Zamboni *et al.*, 1999). The clinical symptoms are non-specific, including abdominal pain and weight loss; however, most of the patients are asymptomatic and are found incidentally. Macroscopically MCNs are single spherical mass which may be unilocular or multilocular. They are frequently lined by mucinous epithelium and are supported by cellular, ovarian-like stroma. The identification of the feature is necessary to make the diagnosis of MCNs. Unlike IPMNs, MCNs do not have a connection with the pancreatic duct, unless there is fistula formation (Zamboni *et al.*, 2010).

The World Health Organization (WHO) has classified MCNs into three different pathologies: adenomas, borderline tumors, and carcinomas (Zamboni *et al.*, 2010; Yoon and Brugge, 2012). The columnar epithelial cells of the adenomatous tumors have abundant cytoplasm, basally located nuclei, have mild dysplasia, and are not mitotic. Borderline tumors show a moderate dysplasia, increased nuclei atypia, increased papillary projections and mitosis. MCNs of carcinoma type have multilayered epithelium forming papillary projections with high grade dysplasia, severe nuclear atypia, and increased mitosis. This type is further divided into non-invasive and invasive subtypes, with the presence or absence of malignant cells outside the cyst lining (Zamboni *et al.*, 2010). Most adenomatous type is unilocular and carcinomas are multilocular with papillary projections and mural nodules (Zamboni *et al.*, 2010).

2.3 Intraductal papillary mucinous neoplasms (IPMNs)

IPMNs are neoplasms of mucinous producing epithelial cells and communicate with the pancreatic ducts (Fig. 1). They can arise in the main pancreatic duct and/or its branches (Adsay *et al*., 2010). In Ohhashi *et al.* (1982)'s study, the first four cases of IPMNs were reported and they had a triad of mucus secretion, main pancreatic duct dilation, and a swollen duodenal papilla. IPMN was previously known as mucinous producing carcinoma, mucinous hypersecreting carcinoma, and intraductal mucinous producing tumor among others (Longnecker and Adler, 2000). Currently the preferred name is intraductal papillary mucinous neoplasm (Xiao, 2012), and is classified as IPMN with low or intermediate dysplasia, IPMN with high grade dysplasia, and IPMN with an associated invasive carcinoma (Adsay *et al*., 2010).

IPMNs are most frequently seen in patients in their late 60s and 70s and are more prevalent in men (Sohn *et al.*, 2004). They are usually found in the head of the pancreas as a solitary cystic mass, but in 20% to 30% of the cases they may be multifocal. In 5% to 10% cases they may involve the pancreas diffusely (Campbell and Azadeh, 2008). Most of the patients are found incidentally and are asymptomatic. In symptomatic patients the typical symptoms include abdominal pain, weight loss, jaundice, new onset diabetes, and pale stools; non-typical symptoms can include acute necrotizing pancreatitis and sepsis due to acute cholangitis (Tibayan *et al.*, 2000). IPMNs may lead to chronic pancreatitis in the surrounding tissues, so serum amylase and lipase levels might also be elevated. IPMNs have also been associated with other syndromes such as Peutz-Jeghers syndrome and familial adenomatous polyposis (Sato *et al.*, 2001; Maire *et al.*, 2002). Some authors suggested that 30% of IPMN patients have a history of extra pancreatic neoplasms particularly in the stomach, colon, or rectum (Sugiyama and Atomi, 1999; Adsay *et al.*, 2000; Adsay, 2002).

IPMNs are divided according to their location, including the main duct (MD) IPMN, branch duct (BD) IPMN, and combined IPMN which involves both MD and its branches. MD IPMNs are thought to be more aggressive (Fig. 2) and have a higher malignant potential, while BD IPMNs are less aggressive (Sohn *et al.*, 2004). The presence of a solid or gelatinous nodule suggests an invasive carcinoma which might not be seen grossly, so an extensive sampling is mandatory in all patients.

Histologically, intraductal proliferation of columnar mucin-producing epithelial cells can be seen and the epithelial cells may be of four different types, including intestinal, gastric, pancreatobiliary, and oncocytic types (Furukawa *et al.*, 2005). These types are associated with different survival rates. Patients with gastric type have the best prognosis whereas patients with pancreatobiliary type have the worst (Furukawa *et al.*, 2011).

3 Preoperative diagnosis

3.1 Computed tomography (CT) and magnetic resonance imaging (MRI)

An appropriate differential diagnostic modality is critical for patients with PCNs to avoid unnecessary surgery. The two noninvasive imaging modalities which have been most frequently used to evaluate pancreatic cysts are CT and MRI.

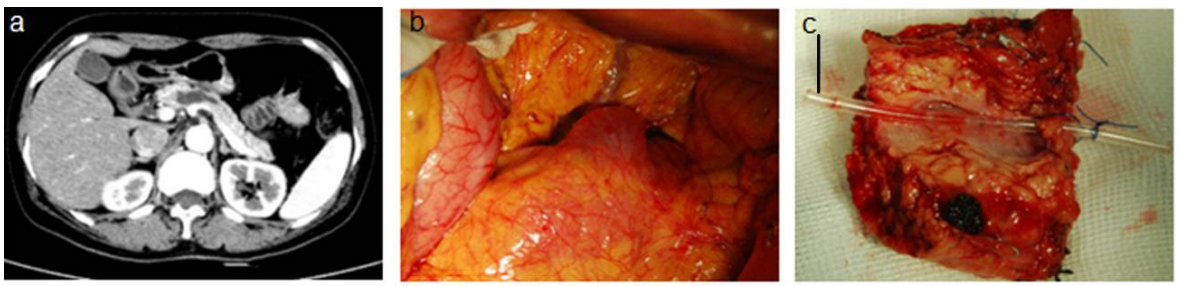

Fig. 1 A 72-year-old asymptomatic woman with a pancreatic neck cyst incidentally found by routine examination
(a) Computed tomography (CT) scan shows a 2-cm size of cyst at the neck of pancreas with the dilation of main pancreatic duct. (b) During operation, cystic lesion was seen in the neck of pancreas. (c) Regional pancreatic resection was done, and from specimen, cystic lesion was shown to communicate with the main pancreatic duct. Intraductal papillary mucinous neoplasm (IPMN) was confirmed by pathology

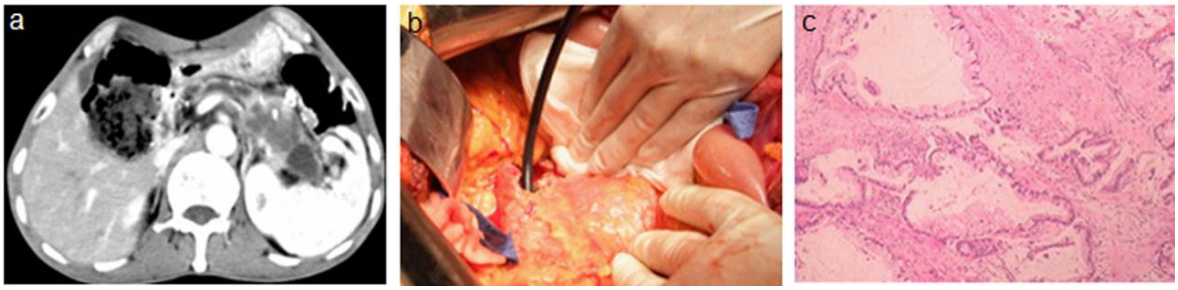

Fig. 2 Intraductal papillary mucinous neoplasm (IPMN) with an associated invasive carcinoma
(a) Computed tomography (CT) findings of main branch type IPMN in the body of pancreas. The margin of the mass was unclear and the splenic vein was involved. Note mucus can enlarge main duct dramatically. (b) Cholangioscopy can go through the proximal part of main duct smoothly during operation. (c) Pathology demonstrated a combined IPMN with an associated invasive carcinoma

On CT scans and MRI, SCNs can have two kinds of appearances. SMAs have a distinct honey comb-like appearance (Fig. 3). The typical lesion is numerous (usually more than 6) microcysts (less than 2 cm), which are closely packed and thin-walled (Khurana *et al.*, 2003). In the Japanese study mentioned before, the honeycomb appearance was noted in 75.0% by CT, 89.2% by ultrasound (US), 100% by endoscopic ultrasound (EUS), and 86.2% by MRI in the microcystic type lesions (Kimura *et al.*, 2012). They are sometimes arranged around a central calcified scar presenting in around 20% of the cases (Yoon and Brugge, 2012). This so-called sunburst appearance is pathognomonic for SMA. Macrocystic or oligocystic adenomas are more difficult to differentiate from MCNs on CT. In the CT scans, macrocystic adenomas are presented as unilocular cystic lesions with lobulated contour without wall enhancement (Cohen-Scali *et al.*, 2003). They lack a central scar, as is seen in SMAs, and were proven not to be sensitive to imaging (Kimura *et al*., 2012). von Hippel-Lindau disease multiple pancreatic cysts are found on CT and MRI (Iwamuro *et al*., 2012). According to one study done in Japan on von Hippel-Lindau disease, 82% of the cases had multiple cysts in the pancreas (Iwamuro *et al.*, 2012). Magnetic resonant cholangiopancreatography (MRCP) can show the ductal relationship with the lesions, but is not so important in the diagnosis of SCNs.

MCNs on CT scan appear as large cysts usually greater than 2 cm and are less than 6 in number as compared to SCNs (Megibow, 2008; Yoon and Brugge, 2012). Thin septae can be seen on CT, especially after administration of intravenous contrast (Fig. 4). Egg-shell like calcifications, presenting at the periphery of the lesions, are suggestive of malignancy (Yoon and Brugge, 2012).

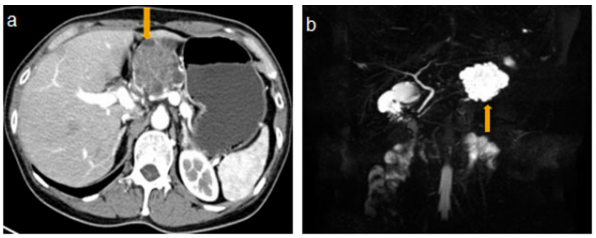

Fig. 3 Serous cystic neoplasm (SCN) in the neck of pancreas
(a) A distinct honeycomb-like appearance on computed tomography (CT) scan (see arrow). (b) The lesion has numerous microcysts and does not communicate with main duct on magnetic resonant cholangiopancreatography

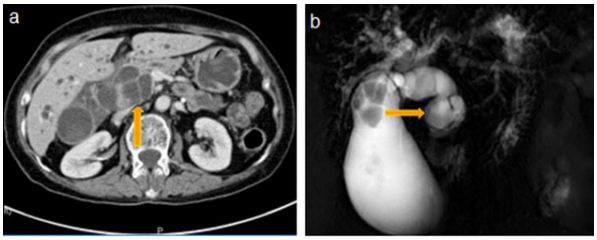

Fig. 4 Typical imaging findings of mucinous cystic neoplasms (MCNs)
(a) Computed tomography (CT) findings. Note the cystic lesion at the pancreatic head with the dilation of biliary tract caused by the oppression of the cystic lesion. The late enhancement of septa can be seen (see arrow). (b) Magnetic resonant cholangiopancreatography shows that the cystic lesion does not communicate with main pancreatic duct (see arrow). The dilation of biliary tract is clearly found. For patients with suspected malignant pancreatic cystic neoplasms, in order to identify the relationship with adjacent vessels, CT angiography is strongly recommended. CT angiography is very helpful to evaluate the resectability preoperatively

In IPMNs, CT and MRI are used to see the exact anatomic location of the lesions and to check for metastasis. BD IPMN shows multiple small cysts (usually 1 to 2 cm) and MD IPMN shows a dilated main duct (Grogan *et al.*, 2001). MRCP is better than CT in the diagnosis of IPMNs as it can show the cystic lesion communicating with the ducts more clearly.

3.2 Endoscopic retrograde cholangiopancreatography (ERCP)

ERCP can show whether the cyst is communicating with the ductal system or not. It is not so important in the diagnosis of SCNs or MCNs but is often used for the diagnosis of IPMNs as it can clearly show the anatomy of the pancreatic ducts. It is also useful to detect any mucin that is being extruded from the ampulla which is pathognomonic for IPMNs (Mohr *et al.*, 2000; Yoon and Brugge, 2012). In MD IPMNs, ERCP shows dilated ducts and a filling defect caused by mucin or the cysts themselves, while in BD IPMNs the involved branches show dilation and communicate with the main duct (Lim *et al.*, 2001). It has been reported that ERCP showed the communication of the cystic lesion with the pancreatic duct in 80.8% of the cases while MRCP showed 55.7%, CT showed 53.8%, and MRI showed 42.3% (Kawamoto *et al.*, 2005). Another advantage of ERCP is that cytological sampling can be required, though it is an invasive procedure.

3.3 Endoscopic ultrasound (EUS) and fine needle aspiration (FNA)

EUS is widely used to perform FNA in order to provide fluid for cytological analysis and tumor markers or amylase testing, which plays an important role in diagnosis of PCNs (Penman and Lennon, 2011). It can also be used to analyze morphological features of PCNs. In EUS, multiple small anechoic cysts with thin septations can be seen in SMAs. SCNs normally do not express carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, CA 125, etc. (Lewandrowski *et al.*, 1993). Amylase is also not easy to find because SCNs almost never communicate with the ductal system of the pancreas.

In EUS, MCNs have thin-walled, fluid-filled large cysts, and very large cysts with irregular walls are highly suggestive of malignancy (Levy, 2009). CEA in MCNs is high because of the production by mucinous epithelium. Other tumor markers like CA 15-3 and CA 72-4 are also high (Brugge *et al.*, 2004b). These features can be used to differentiate MCNs from SCNs, but not from IPMNs since they have the same markers elevated. Amylase is not present because MCNs do not communicate with the ducts.

The main EUS finding which may suggest malignancy for MD IPMNs is dilatation of main duct greater than 10 mm, and for BD IPMNs malignancy is suggested by large tumors (greater than 4 cm) with irregular septa (Kubo *et al.*, 2001). Large mural nodules (greater than 10 mm) are also associated with malignancy in both types (Kubo *et al.*, 2001). CEA and other tumor markers are usually high but this makes it difficult to distinguish from MCNs alone. Amylase in the fluid is also high because of the lesions' communication with the ducts.

3.4 Contrast enhanced ultrasound (CEUS)

CEUS is a relatively new technique, currently used for diagnosis of hepatobiliary and pancreatic tumors. It has led to major improvements in the diagnostic capabilities of conventional US (D′Onofrio *et al.*, 2010). For PCNs, CEUS gives a good view of the septa and mural nodules. SCNs appear as a well delineated mass with small cysts inside. Following contrast administration, septa are enhanced, with the tumor showing a mulberry-like or honeycomb pattern. MCNs are characterized by cystic areas separated by septa, with parietal nodules and papillary wall protrusions. The parietal nodules might not be detected by conventional US due to the rich mucinous content. IPMNs are rarely detected by US. They appear as a non-homogeneous mass just below a dilated duct when they are large. Contrast agents might show the intraductal growth (Badea *et al.*, 2009). However, in most PCN cases, CEUS does not add significant diagnostic information; therefore CT scans and other diagnostic modalities are always necessary for their proper characterization (Recaldini *et al.*, 2008).

3.5 Fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT)

FDG-PET is a sensitive and specific imaging protocol for the diagnosis and staging of several

types of malignancies including pancreatic cancers (Nakamoto *et al.*, 2000; Pakzad *et al.*, 2006). It has been recognized that FDG-PET/CT is more sensitive than conventional imaging in the diagnosis of both primary pancreatic adenocarcinoma and associated distant metastases (Kauhanen *et al.*, 2009). FDG-PET/CT has also been used in distinguishing benign from malignant cystic lesions of the pancreas, and found to be more accurate than CT (Sperti *et al.*, 2007). It has been demonstrated that using FDG-PET/CT in combination with CT and tumor markers testing could improve the preoperative diagnostic sensitivity and accuracy in the patients with pancreatic cystic lesions. Thus FDG-PET/CT is instructive to manage PCNs. A positive result on FDG-PET strongly suggests malignancy and, therefore, a need for resection. A negative result shows a benign tumor that may be treated with limited resection or, in selected high-risk patients, with biopsy, follow-up, or both (Sperti *et al.*, 2001; 2005; Mansour *et al.*, 2006).

4 Management

4.1 Surgery

Until today, surgery is considered the best management option for PCNs. It has a number of benefits, including long term survival of patients, relief of symptoms, and diagnostic certainty (Roggin *et al.*, 2010). A study showed that out of 73 patients with PCN who underwent surgery, 70 patients survived and had a low rate of surgical complications (Sheehan *et al.*, 2003). Management of patients with PCNs depends on whether the lesions are mucinous or non-mucinous.

Since SCNs are mostly benign, the prognosis is excellent. The incidence of serous cystadenocarcinoma is very low (Abe *et al.*, 1998; Eriguchi *et al.*, 1998; Wu *et al.*, 1999). The multicenter study of SCNs in Japan showed that out of 172 patients with SCNs only 2 had liver metastasis (Kimura *et al.*, 2012). Therefore the management is mostly to monitor and observe the patient. There are some exceptions to this rule and surgery should be considered for patients with symptoms (e.g., abdominal pain, mass effect, jaundice, and nausea), tumor size greater than 4 cm, or if the diagnosis is uncertain (Sakorafas *et al.*, 2011). Observation is also recommended for SCNs in elderly patients with typical signs on CT scan and smaller size of the lesion (Kimura *et al.*, 2012).

The type of surgery depends on where the cystic lesion lies as SCNs can occur in any part of the pancreas. If it is in the proximal part of the pancreas Whipple's procedure or pylorus-preserving pancreaticoduodenectomy is recommended (Warshaw *et al.*, 1998; Roggin *et al.*, 2010). A duodenum preserving resection of the pancreatic head is also suitable for lesions in the proximal part (Schwarz and Beger, 1996). This procedure has a better outcome compared to Whipple's procedure. If the tumor is in the distal part of the pancreas a distal pancreatectomy is performed (Warshaw *et al*., 1998), and if it is not invasive, the spleen is often preserved. The tumor lying in the middle of the pancreas is removed by performing middle pancreatectomy (Warshaw *et al.*, 1998). Total pancreatectomy is seldom performed for SCNs as its mortality is very high.

For mucinous neoplasms including IPMNs and MCNs, a more aggressive approach is required. MCNs are always surgically removed, because around 30% cases of MCNs are malignant (Reddy *et al.*, 2004) (Fig. 5). In a study done by Loyola University, 5 out of 20 MCN patients had mucinous cystadenocarcinoma (Sheehan *et al.*, 2003). Distal pancreatectomy was performed in four patients and one pancreatoduodenectomy was done, without any mortality (Sheehan *et al.*, 2003). In mucinous cystic adenoma, most patients had a distal pancreatectomy performed and the mortality was 0% in this study (Sheehan *et al.*, 2003).

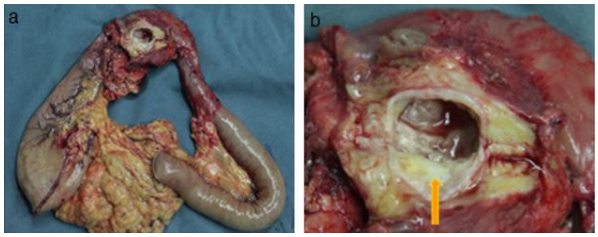

Fig. 5 Malignant mucinous cystic neoplasms (MCNs) were found at the head of pancreas in a 77-year-old woman with obstructive jaundice and high carcinoembryonic antigen 19-9 level

Whipple's procedure was done. (a) Whipple's specimen; (b) Pancreatic head cystic lesion being malignant (see arrow)

IPMNs have an even greater chance of being malignant (around 60% for MD IPMNs and 30% for BD IPMNs) (Tanaka *et al.*, 2006). Most IPMNs are located in the head of the pancreas, and therefore a pancreatoduodenectomy is needed. IPMNs grow longitudinally in the ducts, so a negative margin needs to be established by a frozen section to confirm clearance of the tumor. If a clear negative margin cannot be established, a total pancreatectomy is performed (Brugge *et al.*, 2004a). In the study mentioned above, of the 18 patients who were surgically treated for IPMN, 11 patients had pancreatoduodenectomy, 5 patients had distal pancreatectomy and 2 patients had total pancreatectomy performed (Sheehan *et al.*, 2003). However, the mortality was higher for IPMN cases and 2 patients who underwent total pancreatectomy died (Sheehan *et al.*, 2003). In another study, the 5-year survival rate of IPMNs with invasive cancer was over 50% after resection (Chari *et al.*, 2002).

For the mucinous neoplasms, Sendai Consensus Guidelines suggests surgical resection when there are symptoms associated with the cyst, the main pancreatic duct is dilated more than 10 mm, cyst size is more than 30 mm, intramural nodules are present, or cyst fluid cytology is positive or suggestive of malignancy (Tanaka *et al.*, 2006).

The most common complication after surgery for PCN is pancreatic fistula. Other complications include abscess formation, wound infection, hemorrhage and other various complications like stroke, deep venous thrombosis, urinary tract infections, and delayed gastric emptying (Sheehan *et al.*, 2003). In the study mentioned before, 10% patients had fistula formation, all of which closed spontaneously (Sheehan *et al.*, 2003).

4.2 Cyst ablation

Cyst ablation is a relatively new and less invasive method than surgery. This is particularly useful in patients who have high risks for surgery. It is an EUS-guided injection of ethanol or other ablative agents into the cavity of the cyst. Histological evidence of epithelial ablation in resected cysts has been showed and there was very few complications reported post procedure (Gan *et al.*, 2005). Recently, paclitaxel has been added to increase the ablative capacity of this procedure and was called EUS-guided ethanol lavage with paclitaxel injection (EUS-ELPI) (Yoon and Brugge, 2012). In one study 52 patients underwent EUS-ELPI, 43 patients were followed up and a complete response was seen in 29 patients (Oh *et al.*, 2011). Cyst ablation is still in the experimental stage but seems a promising method in the future.

5 Summary

Owing to the increased knowledge of clinical, endoscopic, and radiographic characteristics of PCNs, we can now better diagnose the most common types of PCNs preoperatively. This provides great information for further management of patients, including surgeries, follow-ups, or other procedures like cyst ablation. Since surgery itself increases a patient's mortality and morbidity, a balance is required as when to perform surgery or observe the patient. Therefore careful diagnosis as to whether a lesion is benign, malignant or has a malignant potential is required, and clinicians need to assess whether a patient is at high risk or low risk for surgery. Keeping in mind all these factors, we should manage the patient accordingly.

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