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REVIEW ARTICLE

Management of cystic and solid pancreatic incidentalomas: A review analysis

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Summary

Incidentally discovered pancreatic lesions that are asymptomatic have become much more common in recent years. It is important to characterize these lesions and to determine which patients can be safely observed and which should undergo an operation, as a substantial proportion of them might be malignant or premalignant. This review focus on the diagnostic approach and management of the different types of cystic and solid incidental pancreatic lesions based on appropriate clinical input, imaging screening and histological criteria. The task of developing guidelines to deal with an incidentally found pancreatic lesion, however, is much more complex and controversial than with other organs incidentalomas. In most series, pancreatic incidentalomas (PIs) <2 cm and of cystic appearance are likely to be benign, whereas those >2 cm are usually premalignant or malignant. Serous cystadenomas can reach very large size and are usually benign lesions. The presence of a solid mass or a mural nodule in a cystic lesion along with main pancreatic duct dilatation, thick septations and biliary obstruction are considered features suspicious of malignancy. Mucinous cystic neoplasms and intraductal papillary mucinous neoplasms are malignant or lesions of malignant potential and need surgical exploration. Solid lesions are much more likely to be premalignant or malignant and most of patients will undergo resection. The decision to operate rather than follow a solid lesion is a matter of tumor size and of clinical judgment based on the age and patient comorbidities. The present study should serve as a general guide and not applied as strict principles.

Key words: cystic pancreatic incidentalomas, diagnostic approach, management, solid pancreatic incidentalomas

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Introduction

Asymptomatic lesions of the pancreas described as PIs have been defined as lesions that are incidentally discovered during imaging or other diagnostic tests and follow-up screening, for clinical manifestations unrelated to the incidental lesion [1]. The first report of a PI was published in the Russian literature in 2001 by Kostiuk [2].

An incidental lesion of the pancreas can be solid or cystic. Asymptomatic pancreatic lesions are now known to comprise between 6-23% of all pancreatic surgical resections [3,4]. They are mostly discovered during imaging for genitourinary complaints, chest pain or malignancy follow-up screening [3]. Up to half of such asymptomatic lesions of the pancreas are solid, with the vast majority of the latter being malignant or at least premalignant and therefore mandate surgical resection as for their symptomatic counterparts [1,3]. There is a general idea that early treatment of incidental malignant lesions may achieve a higher cure rate and prolonged survival [5]. The incidence of benign disease in solid pancreatic tumors suspicious of cancer ranges from 6-21%. Chronic pancreatitis accounts for almost 70% of the benign lesions, alcoholic pancreatitis being the most common cause, summing up to 60% [5,6].

Diagnostic approach

Pancreatic incidental lesions can be detected with a variety of diagnostic methods by using imaging modalities, biochemical tests and endoscopic evaluation. Specific characteristics on imaging studies can help to differentiate malignant from benign lesions. The likelihood of identifying a PI on imaging studies depends basically on the features of lesion such as size, density, echogenicity etc., on the quality of study and the experience of the person interpreting the study [5].

Ultrasonography (US) and CT scan are usually effective in the diagnosis of pseudocysts which account for approximately 75% of pancreatic cystic lesions. Multislice contrast-enhanced CT scan is an excellent examination for the initial detection of pancreatic lesions and for characterization of calcifications, septa, nodules and findings suggestive of pancreatitis [7,8]. MR imaging (MRI/with combination of rapid T2-weighed sequences and unenhanced and contrast-enhanced T1-weighed sequences) has the additional advantage of providing better tissue characterization, allows optimal evaluation of the internal architecture of a cyst and optimal demonstration of enhancing soft tissue elements [9,10]. Both CT and MRI studies permit better distinction between cystic and solid lesions and in the presence of a cystic lesion give a precise estimation of the thickness of the wall, mural irregularities, septa, duct communication and also help to identify worrisome features such as the presence of mural nodules, dilation of the common bile duct, involvement of the main pancreatic duct, peripancreatic or vascular invasion and lymphadenopathy. Endoscopic US (EUS) may add more detailed information about the lesion but cannot differentiate between benign and malignant tumors [9,11,12]. Fluid analysis for biochemical tests and tumor markers and cytological examination can help differentiate mucinous from nonmucinous tumors, and prevent unnecessary pancreatic resection of benign lesions. In the future newer techniques including F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) may help distinguish benign and malignant pancreatic incidentalomas.

Cystic lesions

Incidental cystic lesions of the pancreas can be classified mainly from a clinical perspective into several types: congenital (true serous cysts and syndromes associated with multiple cysts), inflammatory (pseudocysts, hydatid cysts) and neoplastic (serous cystadenomas/SCNs, mucinous cystic neoplasms/MCNs) and intraductal papillary mucinous neoplasms (IPMNs). Incidentally discovered pancreatic cysts <10mm characterized as microcystic lesions are formed by numerous tiny cysts and their presence is more prevalent in MRI [7]. Larger lesions (>2cm), lesions with mural nodules on endoscopic US and cystic lesions with solid component need to be characterized. Almost all serous cysts are benign but will require further investigation or investigation depending on their size, characteristics and content. It is important, however, to characterize cystic lesions and to distinguish true cystic lesions from pancreatic pseudocysts which are the most common type of pancreatic cysts.

The presence of a solid mass or a mural nodule in a cystic lesion is suspicious of malignancy. This character-

istic could be present in serous cystadenomas, mucinous cystic neoplasms and intraductal papillary mucinous neoplasms and along with main pancreatic duct dilatation, thick septations and biliary obstruction are considered the other suspicious features of malignancy [13].

SCNs, previously referred to as "microcystic" adenomas, form a well-demarcated, multicystic cluster of individual small cysts often forming a honeycomb-like appearance. Each cyst is almost always <2 cm and filled with clear, watery fluid without mucin. The lesions are normally single. The overall size of SCNs varies from a few centimeters to as large as 25 cm and are invariably located in the pancreatic parenchyma [14]. Large SCNs are well-demarcated masses, composed of numerous small (<2 mm) thin-walled cysts and have a sponge-like appearance on cross-section with a stellate scar in the center of the neoplasm which is often calcified [15].

The cystic neoplasms of the pancreas SCNs, MCNs and IPMNs account for more than 90% of primary cystic pancreatic neoplasms [16]. IPMNs are further classified into main duct, branched duct and mix variant subtypes. Their discrimination is of paramount importance, as there is a significant difference in the malignant potential of these subtypes of IPMN (main duct 65%, branched duct 15%) [3,7]. IPMN and MCN malignant potential is likened to the adenoma-carcinoma sequence [7]. Whilst pure cystic asymptomatic lesions are benign and can be safely followed, mucin-producing lesions are potentially malignant and require surgical resection [16,17].

Solid lesions

In most series of PIs, solid lesions are more common than cystic ones. The precise number of patients with completely benign conditions is not clearly defined. Among the benign diagnoses for solid PIs that have been published are focal pancreatitis, lipomatosis, solid pseudopapillary tumors and benign neuroendocrine tumors. Results from large series report that about 10-15% of solid incidentalomas could be benign, 30-40% premalignant and 50-60% malignant [1,4].

Solid tumors can be classified according to the cell of origin. Tumors arising from the ductal epithelium represent the great majority of pancreatic cancers, islet cell tumors account for 5% and the remaining are other rare malignancies and metastases. Sachs et al. in a series of 110 patients who had incidentaloma and were subjected to surgery for confirmation of pathologic diagnosis, 53 lesions (48%) were solid. Among them, 38% were malignant, 49% premalignant and 13% completely benign lesions [18]. In their patients, Bruzoni et al. found that 61% of PIs were solid and about 54% were malignant and almost 20% were premalignant (neuroendocrine tumors, borderline intraductal papillary mucinous neoplasms, pseudopapillary tumors and mucinous cystadenomas) [19]. Asymptomatic nonfunctioning pancreatic neuroendocrine tumors (pNETs) are low-incidence pancreatic tumors. In recent years the incidence of pNETs has increased 2-3 fold. In nonfunctional pNETs, histology is always necessary to establish the diagnosis. Endoscopic US-guided fine needle aspiration (FNA) has a diagnostic accuracy of 80% for pancreatic adenocarcinoma and 46% for NETs. Immunohistochemistry for chromogranin A will provide also good characterization of a pNET [8,20].

Management of pancreatic incidentalomas

While solid pancreatic masses, even without any clinical manifestation, prompt for surgical management, there is considerable debate regarding the management of cystic asymptomatic lesions incidentally found in the pancreas (Figure 1).

Management of cystic lesions

Since the first report of PIs, considerable effort has been devoted to construct a relative consensus regarding the management of pancreatic cystic lesions. Incidental cystic lesions pose a crucial dilemma to the surgeon as a significant proportion of them are benign [3]. Type, size and features of the lesion on imaging studies are very important in deciding appropriate management. Simple cysts ≤ 2 cm in size are generally stable and benign. Some studies reported that 59% remained unchanged or became smaller in a 9-year period [8,17]. The frequency of cancer in surgically resected simple cysts <3 cm in size is 3.5%. Considering the benign nature of most cystic lesions, annual follow-up has been recommended for simple cysts <1 cm in size. For cysts

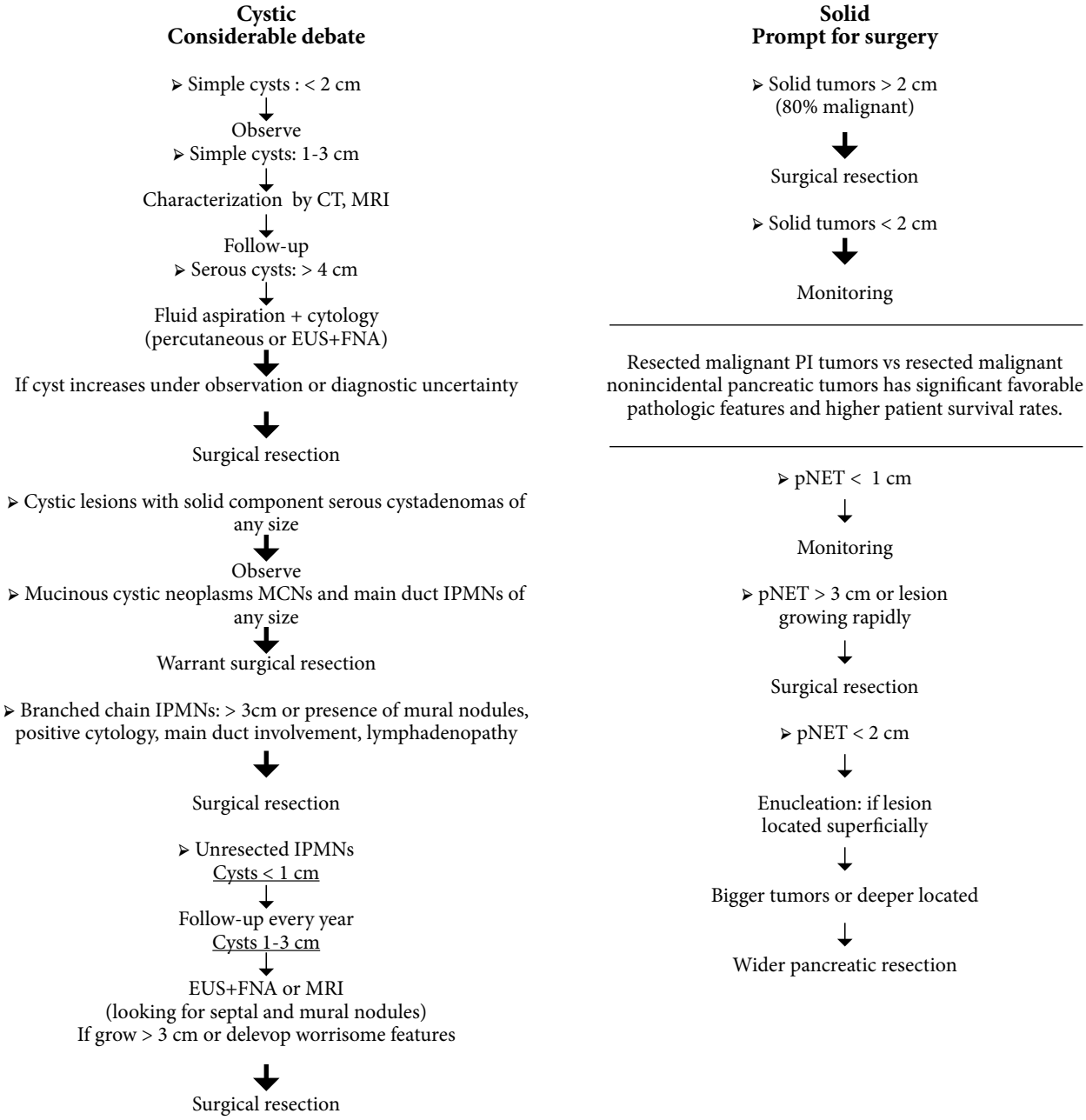

Figure 1. Algorithm of management of cystic and solid pancreatic incidentalomas. For abbreviations see text.

between 1 and 3 cm, further imaging tests in addition to CT should be performed for better characterization [8,17].

The generally benign course of SCNs has led to an 'observational' trend for many years; however this policy has been recently debated. The decrease in perioperative mortality after major pancreatectomy during the last two decades probably accounts in part for the change of view toward a more aggressive approach with resection [21,22]. Currently, surgery is warranted for serous cystic lesions with a size >4cm, any presence of symptomatology or diagnostic uncertainty [21]. In the last decade some authors recommended cyst FNA for cytological examination and

fluid content analysis for biochemical tests and tumor markers estimation, hoping to differentiate mucinous from nonmucinous tumors and preventing unnecessary pancreatic resection of benign lesions [23]. More recently, EUS with FNA has been suggested as a method to differentiate among benign, premalignant, and malignant lesions. However, fluid aspiration either percutaneously or endoscopically - via EUS - has a significant spillage potential and therefore is not routinely recommended [14,24]. Spinelli et al. mandate surgical excision for pancreatic cysts that increase under observation, manifest with symptoms or are discovered in healthy older patients. He also found that older patients over 70 years are more likely ($p<0.02$) to have premalignant or malignant cystic pancreatic neoplasms [24].

According to the Sendai guidelines, published in 2006, surgical resection is warranted for all mucinous lesions of any size for main duct IPMNs and MCNs in reasonable surgical candidates [22]. Regarding branched chain IPMNs, surgical resection is reserved for lesions >3cm or the presence of worrisome features – mural nodules, positive cytology aspirate, main pancreatic duct involvement and/or lymphadenopathy [3,24]. Any unresected IPMN is observed using CT, MRI and EUS/FNA in intervals according to size as follows: cysts <1 cm are followed yearly, cysts between 1-3 cm are sent for further imaging (EUS or MRI) looking for septae and mural nodules, and simple cysts are followed at 6-month intervals for 2 years and then yearly. If they grow above 3 cm or develop any of the aforementioned worrisome features, patients are considered candidates for resection. Any presence of nodules, symptomatology, size increase >3cm or main duct dilatation >6mm prompts surgical management [3,24,25].

Fernandez del Castillo et al. reported that incidental cysts had a diameter of 3.3±1.9 cm, and cysts < 2 cm rarely were malignant (3.5%) [17]. Similarly, Handrich et al. reported that no patients developed symptomatic pancreatic disease or death due to a pancreatic cause after detection of an asymptomatic, incidental pancreatic cyst ≤ 2 cm or smaller, assumed to be a cystic neoplasm, and followed-up for a mean of 8–10 years [26].

Management of solid lesions

Most series agree that 80% of patients who had solid tumors > 2cm had a malignancy, indicating that these patients are more likely to need resection, whereas those with smaller tumors may simply be monitored. The presence of a potentially resectable solid pancreatic tumor should prompt us to offer surgical treatment. As solid lesions are much more likely to be malignant or premalignant, most of patients will undergo resection assuming they are reasonable surgical candidates. Some retrospective studies reported that solid PI lesions had a rate up to 20% of low or no malignant potential following pancreatectomy [1,4]. The extent of surgery in solid PIs should be dictated by tumor size, location, number of lesions and feasibility of establishing the diagnosis. If malignancy is confirmed or cannot be ruled out, a standard resection depending on the location of the tumor should be performed (pancreatoduodenectomy or distal pancreatectomy). In most series that compared retrospectively patients who had pancreatectomy for malignant or malignant potential PI lesions with symptomatic malignant tumor patients, it was proved that resected malignant PIs had favorable pathologic features and improved survival, compared with patients resected for malignant nonincidental pancreatic tumors [4,19].

Lahat and colleagues reviewed a series of 475 pancreatectomies performed from 1995 to 2007. Sixty-four patients out of 475 (13.5%) of all pancreatectomies performed in the series underwent a surgical resection for a PI [1]. Fifty-six percent of all PIs in the cohort were located in the body and tail of the pancreas, while 44% were located in the head. The vast majority of incidental tumors were malignant (94%) and almost half of malignant PIs had metastasized to lymph nodes. According to the authors, the higher incidence of PIs in the distal pancreas could be expected, as in this area tumors can grow large without any clinical manifestations. PI tumors had significantly favorable features, such as smaller tumor diameter, lower rates of vascular and perineural invasion and higher grade of differentiation compared with nonincidental pancreatic tumors, that could explain the less aggressive local behavior and the higher survival rates of PIs for the patients who had pancreatectomy [1].

Winter and colleagues reviewed 1944 consecutive Whipple procedures during an 8-year period [4]. Six percent of these periampullary or cephalic pancreatic tumors were discovered incidentally. Thirty-one percent of the PI patients had malignant disease, 47% had premalignant disease amenable to curative resection. The remaining 22% had little or no risk for malignant progression. The most common diagnosis for PIs in the Winter cohort was IPMN (30% of cases), while in the Lahat study the most common diagnosis was ductal adenocarcinoma [1,4]. The authors confirmed that the resected malignant PIs had favorable pathologic features as compared with resected malignant nonincidental pancreatic tumors and resection of these early PI lesions is associated with improved survival compared with patients with symptomatic disease. Furthermore, improved survival was observed in the PI group when the data were confined to pancreatic ductal adenocarcinoma [1,4].

The management of non-functional endocrine tumors varies according to size and nature of the tumor. For small lesions < 10 mm it has been proposed to monitor growth by serial EUS and to determine when surgical resection is indicated. Surgical resection is indicated when a lesion is increasing rapidly, or when the tumor is ≥ 3 cm [27]. Some authors have reported a malignancy rate as high as 92 % and claim that patients with early-stage pNETs may benefit from surgical resection [28]. pNETs< 2 cm may be enucleated as long as they are located superficially and are clear of the pancreatic duct. Enucleation of deeper lesions should be avoided as they are associated with high rates of pancreatic leak postoperatively. Considering the high frequency of benign tumors in patients with pNET, lesions even > 2 cm may be safely enucleated. Bigger tumors require a wider pancreatic resection. For well-differentiated malignant pNET curative surgery is recommended [28,29].

Table 1. Essential clinical and treatment points of pancreatic incidentalomas

Pancreatic incidentalomas may be malignant and hence further diagnostic work up is required:

CT angiography of the pancreas is preferred for solid lesions.

MRI is the primary modality used for follow-up of cystic lesions to best delineate the cyst.

EUS with fluid aspirate analysis is frequently used in the evaluation of both cystic and solid lesions.

- High amylase and CEA levels in cyst fluid aspirates confirm the diagnosis of pseudocyst and mucinous neoplasms, respectively.
- Simple cysts up to 3 cm in size with no worrisome features can be safely monitored with regular imaging.
- Solid lesions are clinically approached according to size, location, number of lesions and feasibility of establishing the diagnosis.
  - Small lesions (<2 cm) may simply be monitored.
  - Solid lesions up to 2 cm in size are more likely to be premalignant or malignant and will require surgical resection.
- pNETs warrant serum hormonal biochemical workup and the possibility of a hereditary cancer syndrome should be considered.
  - Small pNET (< 1 cm) are simply monitored.
  - Bigger pNETs lesions are treated by enucleation or resection depending on size, location and relationship of the tumor to the pancreatic duct.
- In summary, pancreatic incidentalomas have a better prognosis than symptomatic lesions.

CT: computerized tomography, MRI: magnetic resonance imaging, EUS: endoscopic ultrasound, pNETs: pancreatic neuroendocrine tumors

Conclusions

PIs have become a more frequent problem and require prompt surgical evaluation. A diagnosis should be reached, if not always with certainty, but at least with a high degree of probability (Table 1). Observation with follow-up imaging studies should be considered as part of the evaluation process for selected patients in whom the lesions are small simple cystic and do not show any sign of malignancy. Cysts > 4cm call for surgery. SCNs have a characteristic gross and microscopic appearance, so diagnosis is usually relatively easy. The benign nature of these lesions allows follow-up in asymptomatic patients. Cystic lesions which present worrisome features such as mural nodules, main pancreatic duct involvement, positive cytology aspirate, require surgical resection. Surgery is warranted for all mucinous cystic neoplasms of any size main-duct IPMNs and MCNs in reasonably surgical can-

didates. For branched chain IPMNs, surgical resection is reserved for lesions >3cm or with evidence of malignancy. Any unresected IPMN is observed using imaging studies according to the size of the lesion.

Solid lesions are much more likely to be premalignant or malignant and most of the patients will undergo resection. The decision to operate rather than follow a solid lesion is a matter of size of the tumor and of clinical judgment based on the age of the patient and comorbidities. Small lesions (< 2 cm) may simply be monitored. The indolent nature of asymptomatic solid tumors should not mislead clinicians to favor a conservative approach. The extent of surgery should be dictated by tumor size, location, number of lesions and feasibility of establishing the diagnosis. Interestingly, resected malignant PIs had favorable pathologic features and improved patient survival compared with patients with resected symptomatic malignant pancreatic tumors. Enucleation or resection of pNET is performed depending on the location of the tumor and its relationship to the pancreatic duct. A multidisciplinary strategy is recommended for surgical evaluation and decision-making to provide the best care for the patient with an incidentally found pancreatic lesion.

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