### **Review Article**

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## Pancreatic cystic lesions: classification, diagnosis and treatment

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### **ABSTRACT**

Pancreatic cystic lesions (PCLs) are being increasingly identified in recent years. The diagnosis and discrimination of these lesions are very important because of the risk for concurrent or later development of malignancy. Pcls are usually first diagnosed in adults and characterized by conventional imaging modalities such as trans-abdominal ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI). However, their ability to differentiate the benign and malignant lesions remains limited. Endoscopic US may be more helpful for the diagnosis and differentiation of PCLs because of its high resolution and better imaging characteristics than cross-sectional imaging modalities. It also allows for fine-needle aspiration (FNA) of cystic lesions is biochemical, cytological and DNA analysis that might be further helpful for diagnosis and differentiation. Owing to improvements in imaging techniques, cystic lesions of the pancreas are being identified more often, even in patients who are asymptomatic. These range from benign to premalignant lesions to highly malignant. Due to the high morbidity related to pancreatic resections, the surgeon should balance very carefully the advantages of the radical resection with the risks of an unrequested dangerous procedure. This review offers guidance on the strategies for establishing the diagnosis, assessing risk, and making difficult decisions about when surgical resection is indicated. While many CNPs have an indolent behaviour that justifies surveillance, others should be resected because of the risk of progression to invasive cancer.

Keywords: Pancreatic Cyst, Pancreatic pseudocyst, Pancreatic neoplasms, Pancreatic surgery, Pancreas, Pancreatic ductal carcinoma

### INTRODUCTION

Although the clinical, radiological and pathological features of pancreatic cystic lesions are well established, the preoperative diagnosis is still a difficulty. Despite the radiological assessment be of paramount importance in the diagnosis of pancreatic cystic lesions, the careful clinical history of the patient is important to the diagnostic accuracy. A pseudocyst in a patient without clinical history of pancreatitis can be a problem diagnosis. Cystic pancreatic lesions are diagnosed in approximately 1% of patients undergoing abdominal

computed tomography (CT).<sup>8,9</sup> A study that conducted the autopsy of 300 patients, cystic lesions in 73 patients demonstrated, representing 24.3%, and approximately 20% of these lesions were cystic Neoplasms.<sup>10</sup> However, in clinical studies, the prevalence of cystic neoplasms (CN) in patients undergoing abdominal CT (CT) or magnetic resonance imaging (MRI) was between 1-2% of cases.<sup>11</sup> Comparing surgical of the last 2 decades series it is clear that most of these CN are asymptomatic, being identified so incidental image methods for non-pancreatic diseases.<sup>9</sup>

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The definitive diagnosis is often possible when the lesion has a typical radiological feature, but in many cases the radiological diagnosis is inconclusive. The cystic lesions comprise a spectrum of injuries that are classified as benign, premalignant/borderline and malignant. The cystic neoplasm serosa (32-39%), Mucinous cystic neoplasm (10-45%) and intraductal papillary mucinous neoplasms (21-33%) represent the majority of tumors. 1.6

The pseudopapilar solid neoplasm, cystic endocrine neoplasia, ductal adenocarcinoma with cystic degeneration and the cystadenocarcinoma of acinar cells represent less than 10% of in Lions. Some authors have advocated surgical approach for all patients with cystic lesions suspected. The difficulty in diagnosing and treating the Cystic Neoplasms would be based on the following points: the method that give a definitive diagnosis of cystic neoplasm type; the deficiency in distinguishing malignant from benign lesions; the lack of understanding of the natural history of cystic Neoplasms of the pancreas. 11,12

### Goal

The objective of this research is to identify, through a review of the literature, the best way to make the preoperative diagnosis of the cystic lesions premalignant and malignant, selecting the most suitable patients the surgical approach, reducing the number of asymptomatic patients with benign lesions, which are subjected to high morbidity and mortality of pancreatic surgery.

### **METHODS**

The present study is a review of the literature in PubMed, Lilacs databases, Web of Science, Scopus and Scielo, using the key words "pancreatic cyst", "pancreatic pseudocyst", "pancreatic neoplasms", "pancreatic surgery", "pancreas", "pancreatic ductal carcinoma". We have included articles in english, spanish and portuguese, published in the last 30 years, covering the diagnosis and treatment of pancreatic cystic lesions.

### Clinical Presentation

Most of the lesions show no sign or symptom in diagnosis, only one found on an ultrasound or CT scan. When the lesions involve some sign or symptom, usually the patients have recurrent pancreatitis, chronic abdominal pain or jaundice. 1,13

A multicenter study which surveyed 166 patients with cystic lesions under 3 cm, showed that 121 patients (72.8%) presented with abdominal pain, jaundice, weight loss, nausea, vomiting and diarrhea. The other 45 patients (27%) were asymptomatic at diagnosis. This same study showed that most patients with malignant disease symptomatic (28/31 was-90%), with a large association with malignancy and symptoms of jaundice, weight loss and anorexia. <sup>14</sup>

The pseudocysts may arise after an episode of acute or chronic pancreatitis. <sup>1,15</sup> Pseudocysts may have abdominal pain, nausea, vomiting, early satiety, jaundice, cholangitis and when the head of the pancreas, as well as thrombosis of the splenic vein, superior mesenteric or door, resulting in venous congestion and gastrointestinal bleeding. <sup>16-18</sup>

# Classification and differential diagnosis of cystic pancreatic lesions

The nomenclature, classification and characterization of cisticas lesions of the pancreas were set in the last two decades. The intraductal papillary mucinous neoplasm (IPMN) became an entity distinct pathological <sup>12</sup>. The cystic neoplasms may be classified by several systems, through the pathophysiology of the cyst, the morphological characteristics and the composition of the cyst fluid.<sup>2</sup>

### Pancreatic pseudocyst

The inflammatory pancreatic cyst (pseudocyst) is the most common pancreatic lesion, covering 75% of cystic lesions<sup>12</sup>. The pancreatic pseudocyst is a collection of pancreatic juice enclosed by a wall of fibrous tissue or granulation tissue that arises after an acute pancreatitis, chronic pancreatitis or trauma. <sup>16-20</sup> In acute pancreatitis, the pseudocyst is formed by gallstones or sporadic intake of alcohol, the pancreas has no signs of injury, and the architecture of the pancreatic duct is normal. In chronic pancreatitis to repeated intake of alcohol promotes the loss of the acinar cells, activation of pancreatic stellate cells and collagen deposition. The pancreatic duct becomes narrow, dilated or stenotic. The pseudocyst can be distinguished from other cystic pancreatic lesions, in about 15% of cases. <sup>16</sup>

The diagnosis of pseudocyst include a well-circumscribed, unilocular lesion, tumor markers normal serum and cystic fluid of low viscosity with high level of amylase. In the ultrasound image, the pseudocysts are usually well defined, with thin walls, anechoic content. In CT, not a pseudocyst complicated features a wall or well defined capsule, with a low central area attenuation. The distinction between pure mixed lesions of cystic lesions is a problem, and the magnetic nuclear resonance with T2-weighted image can show the cyst and the differences in fluid components in case of bleeding from the lesion. The MRI has the advantage of carrying out the campaign that evaluates the pancreatic duct with the cyst, which can occur in both the pseudocyst and pancreatic Mucinous neoplasm intraductal (Figure 1).

### Simple cyst

The simple cyst of the pancreas is an abnormal cleavage of the ducts of the pancreas and primitives have inner surface coated with a true epithelium. The real isolated cysts are rare, most common in newborns. Are unilateral or multilocular lesions of variable size, between

microcysts and dimensions up to 5 cm. On CT scan is a low mass attenuation coefficient, which does not capture intravenous contrast. Most congenital cysts are multiple and associated with genetic diseases that involve other organs, such as polycystic kidney disease, Von Hippel-Lindau disease and cystic fibrosis. True pancreas cysts are seen in 10% of patients have polycystic kidney disease. The cysts are usually small and may involve diffusely the pancreas or a specific region. The finding on CT and ultrasound of injuries involving liver, kidney and pancreas also facilitates in the differential diagnosis. 1,22 (Figure 2).

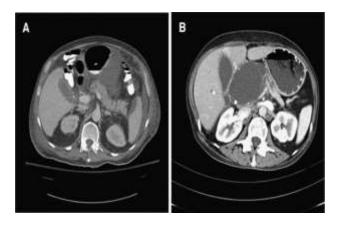


Figure 1: CT scan showing fluid collection in the acute phase and the formation of pancreatic pseudocyst.

Note the well-defined edge of pseudocyst in contrast with the faintly fluid.



Figure 2: CT in axial view showing multiple cystic lesions throughout the pancreas, in a patient with von Hippel-Lindau.

Cystic neoplasm serosa (NCS)

Known as cystadenoma, microcytic adenoma and serous adenoma rich in glycogen, this disease corresponds to 32-39% of pancreatic cystic neoplasms.<sup>23</sup> Is a benign neoplasm composed of cuboid glycogen rich epithelial cells.<sup>1,4-10</sup>

The serous cystadenomas occur frequently in women (86%), with an age average of 59.9 years. Asymptomatic are a third to half of the cases.<sup>22</sup> Abdominal pain is the most frequent symptom. Half of all cases occur in the head of the pancreas, but rarely the patients have jaundice due to bile duct obstruction.<sup>23</sup> In a series of 106 patients, Tseng et al. observed that the symptoms were present in approximately one quarter of patients with lesions smaller than 4cm, and in three-quarters of patients with lesions greater than 4 cm.<sup>2,23,24</sup> (Figure 3).



Figure 3: Serous adenoma microcytic. Lobulated appearance with peripheral cysts surrounding a fibrous area focuses on.

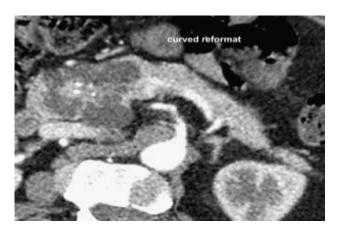
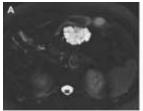


Figure 4: Cystic neoplasm serosa. CT with contrast, in axial view, showing image hypodense in head polylobulated, pancreas, composed of multiple cysts, scar starring with areas de calcification.

The sonogram shows a les will be well circumscribed. The fibrous portion of the lesion is hyperechoic, while the cystic portion is hypoechoic.<sup>32</sup> Seen on computed tomography; the NCS has the polylobulated form. After administration of iodized contrast, the fibrous portions of the lesion enhance the contrast. The NCS are the only pancreatic cystic neoplasms hypervascular, which allows distinguishing it from otherpancreatic cystic lesions.<sup>32</sup> (Figure 4, 5, 6).



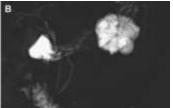




Figure 5: Cystic Neoplasm serosa. a-weighted Image in T2; b- cholangiopancreatography for MRI showing damage in cystic pancreatic body polylobulated predominantly hypertensive in relation to parenchyma, with fibrous SEPTA to show hypointense. C-after administration of gadolinium during the arterial phase there is an enhancement of the fibrous SEPTA.

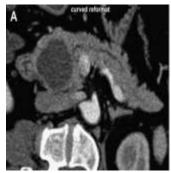




Figure 6: Cystic neoplasm serosa. The-CT image showing a polylobulated, unilocular lesion, greater than 2cm, without calcifications, mural nodules or highlight-free capsule. Endoscopic Retrograde Cholangiopancreatography b-showing external compression of the pancreatic duct by mass. Result of pathology revealed a deepening of serous macrocistico.

The accuracy of ultrasound, CT and MRI for the diagnosis of cystic neoplasm serosa is around 53%, 54% and 74%, respectively. 32-35

Biochemical analysis of fluid of cystic lesion obtained by endoscopic USG and fine needle puncture consists of a low level of amylase (< 250IU/L), low carcinoembryonic antigen (CEA) (< 5ng/ml) and low carbohydrate Antigen 19-9 (CA 19-9) (< 37U/L). <sup>29,36</sup> (Figure 7).

The definitive diagnosis of cystadenocarcinoma is only established when there are metastases.<sup>2</sup> Bassi, et al evaluated 50 NCS patients that have not been operated, and there was no growth of lesions after an average follow-up 69 months.<sup>2,28</sup> Tseng et al. in their series of 24

patients, accompanied with serial CT, showed a growth rate of 0, 12 cm per year for < 04cm tumors, and a growth rate of 1, 98 cm per year for tumors > 04cm.  $^{2,24,29}$ 

Surgical treatment is indicated for lesions larger than 4cm, since these lesions have 3 times more likely to develop symptoms.<sup>23</sup>

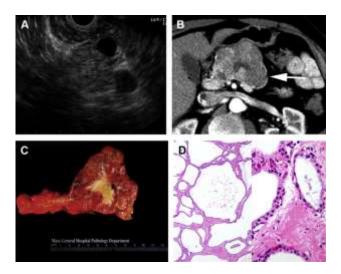


Figure 7: Radiological and histological Characteristic NCS. the-endoscopic multiple small cysts showing USG creating the appearance in sponge; b-TC with same features plus the central scar; c-macroscopic appearance; d-histological aspect epithelium grins cuboid stained by hematoxylin and teaches.

Malleo, et al observed a series with 145 asymptomatic patients for operative management, with realization of RNM annually by an average of 7 years. In contrast to the study of Tseng, the authors have not shown any association between the size of the tumor and the subsequent growth rate. During follow-up, 23 patients underwent surgical resection after 4 years of diagnosis-19 because of increase in the size of the tumor and 4 due to the choice of patients. The authors concluded that this study does not need to be offered to asymptomatic patients and tumors larger than 4cm, provided that there is no change in the growth pattern of.<sup>36</sup> Seems to be reasonable for a second examination of 3-6 months after diagnosis, and depending on the characteristics of the lesion, growth pattern, size of the lesion and low potential for malignancy, this range could be extended for 1-2 years.<sup>35</sup> The survival rate after surgical resection has been approximately 100% over a period of 4 years average follow-up, with isolated reports of recurrence in less than 1% of the cases.<sup>29</sup>

### Mucinous cystic neoplasm

A mucinous cystic neoplasm (MCN) represents 10-45% of pancreatic cystic Neoplasms. Has producing cells formed epithelial mucin with a stroma of ovarian type. These lesions may be unilateral or multiloculares with debris extending into the lumen of the cyst. The

mucinous cystic neoplasm varies from a spectrum of benign disease, mucinous cystadenoma, until the mucinous cystadenocarcinoma, very aggressive and invasive. 12 Non-invasive disease occurs in more than 70% of patients.<sup>2,25</sup> Patients with MCN are almost exclusively middle-aged women. The lesions are localized in the body and tail of the pancreas in more than 90% of the cases.  $^{36}$  Morphologically the MCN are typically round, thick-walled, with septa, forming a cystic mass in pancreatic parenchyma without communication with the pancreatic duct.<sup>2</sup> Although the image of TC cannot reliably distinguish between an invasive or not, injury findings of NCM include invasive calcification in "eggshell", presence of solid components or mural nodule and tumor diameter greater than 3 cm.<sup>2,25</sup> On endoscopic Ultrasound (EUS) associated with fine needle puncture of the cyst fluid, antigen carcinoembryonic values above 200ng/mL, 192-favor the diagnosis of MCN; as well as DNA sequence analysis with mutation in the KRAS without mutation of GNAS, favors the diagnosis of MCN at the expense of other cystic lesions. <sup>29</sup> (Figure 8, 9).

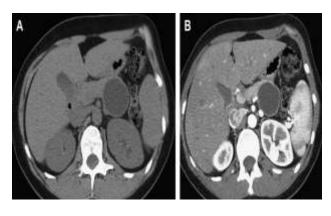


Figure 8: Mucinous cystic neoplasm. CT in axial view (A) without contrast and contrast (B) showing unilocular image well circumscribed and encapsulated in the tail of the pancreas.

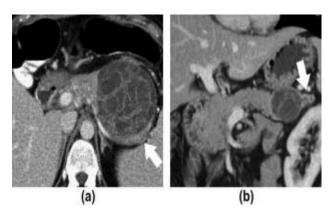


Figure 9: Mucinous cystic neoplasm. The TC showing image macrocystic in syrup of the pancreas (cysts within cysts). Notice the wall thickening (arrow). b-cystic mucinous neoplasia in the tail of the pancreas, causing pancreatic duct dilation by compression.

According to the guideline of Fukuoka 2012 resection is recommended for all surgical lesions of suggestive of MCN. The rationale for this is 17-18% of the risk of malignancy; progression malignant disease even with benign characteristics; inability to predict which lesions contain or will progress to malignancy; and the characteristic of the lesion be distal, in younger patients and healthy, leading to a lower morbidity in operation. <sup>29,32</sup> (Figure 10).

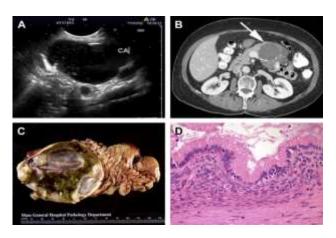


Figure 10: Mucinous cystic neoplasm in body and tail of the pancreas. Female patient, 55 years of age, with nonspecific abdominal pain. The-EUS showing complex cyst; fluid aspirated showed thick mucus. B-TC showed injury multi loculated with calcifications. Undergone distal with preservation of Bacchus figure. C-macroscopic aspect. D-microscopic aspect, with producer epithelium equips ovarian type.

Intraductal papillary mucinous neoplasm (IPMN)

The IPMN cystic pancreatic neoplasms are diagnosed and more dry (30-40%). The histological point of view the IPMN are cystic tumors, intraductal, producers of mucin, whose arrest cells range from benign adenoma invasive carcinoma. There are two variants, IPMN-MD and IPMN-BD, which are distinguished based on the involvement of the main pancreatic duct or accessory respectively, being seen by the image as ductal dilatation. The variant that affects the main duct presents a high risk of malignancy and requires immediate surgical resection, so it is important to discern the IPMN variants at the time of the diagnosis, in order to guide your management and determine the prognosis.<sup>29</sup> Most patients with IPMN show symptoms when the diagnosis, and abdominal pain the most frequent symptom associated with weight loss, jaundice or obstructive pancreatitis.<sup>29</sup> The are best diagnosed by CT IPMNs (TC) with Protocol for pancreas, venous and arterial phases venous contrast: magnetic resonance cholangiopancreatography (MRCP) with contrast with option of 3D reconstruction. The accuracy of the MRCP is greater than CT for detecting ductal communication, involvement of the main duct, extent of disease and the high risk features present in cysts.<sup>29</sup>

Endoscopic Ultrasound (EUS) and fine needle aspiration guided by EUS of fluid from the cyst may assist in the diagnosis and treatment decisions. A chemical analysis of the fluid demonstrating a high carcinoembryonic antigen (CEA) to levels above 192-200ng/mL has an accuracy of 80% in mucinous not mucous cysts distinguish.<sup>29</sup>

After the MD management-IPMN shelter most often malignancy than the BD-IPMN, with about of IPMN 43% of MD-containing invasive carcinoma in resection and an additional 19% containing high-grade dysplasia.<sup>26</sup>

The current consensus of 2012, the International Association of Pancreatology in Fukuoka, makes the following recommendations:

- 1. Resection of all MD-IPMN, determined by x-ray main duct dilation with 10 mm or more seen on CT or MRI; or borderline of 5-9mm dilatation with subsequent EUS evaluation demonstrating the involvement of the main duct.
- 2. Surgical resection of only the BD-high-risk IPMN, determined by the following:-obstructive jaundice; TC/MRCP with solid components enhancing contrast or main duct greater than or equal to 10mm; b-pancreatitis; main duct between 5-9mm); without contrast enhancement mural nodule; thickening of the wall of cyst; change the caliber of the duct with distal atrophy; Lymphadenopathy; greater than or equal to 3cm cyst associated with EUS confirming the involvement of the main duct, mural nodule or cyst fluid cytology suspicious or positive for malignancy.
- 3. Surveillance for all BD-IPMN without high risk or worrying features. The frequency and type of monitoring is stratified by the size of the cyst: a-2-3 cm size: EUS 3-6 months each, and can be extended if range is stable (consider surgery in young patients); b-1-2cm size: CT or MRCP annually (up to 2 years if stable); c-less than 1cm: CT or MRCP every 2 or 3 years.<sup>30</sup>

Endocrine pancreatic cystic neoplasm (CPEN)

The cystic pancreatic endocrine neoplasms are a variant of cystic pancreatic neuroendocrine tumors (PNET). The CPEN comprise 5-7% of all pancreatic cystic neoplasms dry and 10-17% of PNET are operated<sup>29</sup>. The CPEN has equal gender distribution and affect people of 50-60 years of age. Most (80%), CPEN present no clinical manifestations of hormone production.<sup>29-32</sup>

Compared the les s solid, the CPEN has high association with the genetic syndrome multiple endocrine neoplasia type 1 (MEN 1), involving mutation tumor suppressor gene MEN 1 and predisposes to endocrine tumors of the pituitary, pancreas and hen.<sup>29</sup>

Around 45% of the CPEN feature wall enhancement of the cyst by contrast in arterial phase in pancreatic

protocol by TC. Solid components and septa are also present in approximately 25% of cases. <sup>29-33</sup> EUS/FNA can be effected to characterize the cyst. Suspicious or positive cytology with cromogranina coloring and synaptophysin can establish the diagnosis of 73% to 78 in CPEN% of cases. Diagnosis established, the recommendation of treatment is surgical resection, once the CPEN 11 presents% to 14% risk of malignancy and 8% to 14% risk of metastasis. Patients treated surgically have overall survival at 5 years from 87% to 100%, and disease-free survival rate of 94% to 96%. <sup>29,30</sup>

Solid pseudopapilar neoplasia (SPN) - tumor of frantz

The SPN, also known as papillary epithelial neoplasm and solid and cystic papillary neoplasia, or solid-cystic neoplasm, is characterized by its low potential for malignancy and prognosis. Typically affects young patients and women, with a predilection for Asians and black patients.<sup>4</sup> Comprises some 3% of pancreatic cystic neoplasms dry. The age range varies from 30 to 38 years. Most patients (84-87%) with SPN have symptoms, abdominal pain and lower proportion pancreatitis, jaundice or palpable mass.<sup>31</sup> Seen by NMR the SPN appear as a well-defined mass of heterogeneous appearance in both signals T1 and T2. Areas of hemorrhage appear hyperintense relating to the pancreas in T1 and T2-hipointensa. After the infusion of gadolinium, a contrast uptake in peripheral portion is noted in the arterial phase.<sup>32</sup>

The definitive management with surgical resection is currently recommended for all injuries, since 10% to 20% of cases demonstrated features of malignancy.<sup>29</sup> (Figure 11).

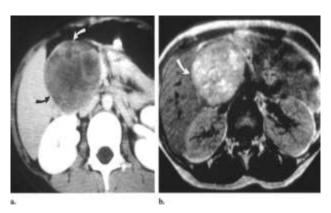


Figure 11: SPN in a 32-year-old woman with pain epigastric: a-TC with contrast showing a mixed solid and cystic mass in head of pancreas (arrow); b-RNM axial image in T1, showing high signal corresponding to areas of bleeding in the mass (arrow); c-part surgery photo showing solid mass with spinocerebellar cystic and surrounded by a fibrous capsule hemorrhage.

### Cystic metastatic disease

The metastasis to pancreas is most common in renal cell carcinoma, lung cancer, sarcomas, melanomas or ovarian carcinoma. Metastatic disease to the pancreas occurs through hematogenous. Because of this, the outbreak of the disease in multiple organs is expected in patients with pancreatic lesions metastatic. 32-35 (Figure 12).



Figure 12: Axial view of CT with contrast of the pancreas showing a cystic lesion in the tail of the pancreas, with central necrosis area without capture contrast. Result of pathology was consistent with metastasis of sarcoma of soft parts.

The resections are indicated for isolated metastases resectable in patients unable to tolerate a figure, pancreaticoduodenectomy and figure total. High rate of recurrence after these atypical resections are observed.<sup>34</sup> The benefit of metastasectomy in terms of patient survival has been observed for metastases of renal cell carcinoma, while for other primary tumors the role of surgery is generally palliative.<sup>35-37</sup>

### Cystic lymphangioma

The lymphangiomas are benign tumors found in loose tissues of the neck and axillae in the paediatric population. Less than 1% of these lesions occur in the The abdomen. lymphangiomas are congenital malformations of the lymphatic system and are classified as capillaries, or cystic cavernous. 36,37 Patients are often asymptomatic, the diagnosis is incidental; When symptomatic, epigastric pain is the most common symptom. A palpable mass in the hypochondrium or left upper quadrant can also occur.<sup>34</sup> The ultrasonography shows a cystic lesion typically hypoechoic or multicystic injury or anechoic in region of the pancreas. On the image of TC, cystic masses multiple well circumscribed are observed, juxtaposed or pediculate to the pancreas.<sup>37</sup> On MRI image is well circumscribed in all you do, being increased signal on T2 and T1-hypointense signal. 32,35

Surgical resection is usually indicated for establishing the accurate diagnosis of the resected specimen. The

Lumpectomy is usually curative, however the recurrence can be observed after incomplete resection.<sup>37</sup> (Figure 13).



Figure 13: TC showing a great lymphangioma in its most common form (cystic) is affecting the pancreas.

Cystic pancreatic neoplasms of solid variants

Are changes mutations necrotic, degenerative, with formation of cystic cavities described in virtually every pancreas neoplasms with solid previous characteristics. In most patients, cystic area involves the neoplastic component of ductal adenocarcinoma. The invasive pancreatic cancer may cause obstruction of the ductal system, leading to cystic dilation of the duct or the formation of a small retention cyst. Endoscopic ultrasound fine needle aspiration of contents of injury may help, but the definitive diagnosis is made only after histological analysis after surgical resection. (Figure 14).

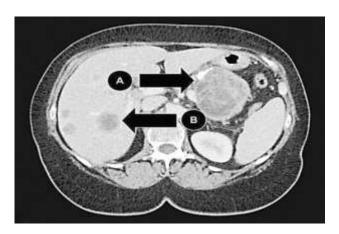


Figure 14: TC showing cystic degeneration of pancreatic adenocarcinoma (arrow) with liver metastases (arrow B).

### Final Considerations

Cystic pancreatic lesions are increasingly common, affecting up to 10% to 15% of patients undergoing Imaging tests in cross section. Although some cystic Neoplasms of the pancreas head invasive malignancy or potential of evolution over time for the malignancy, most

are benign and can be observed. The accurate diagnosis is critical to the proper approach, whether conservative or surgical. This requires a multidisciplinary team and high surgeons know scientific about it, as far as the final result of the treatment.

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