Diagnostic Approach and Management of Solid Pancreatic Mass

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ABSTRACT

The pancreas is a complex organ in which a suspicious lesion can appear which can be benign or malignant. Clinical manifestation can guide the clinician to choose the appropriate tests such as autoimmune tests, tumor markers, imaging with ultrasonography (USG), computerized tomography (CT), magnetic resonance imaging (MRI), or magnetic resonance cholangiopancreatography (MRCP), and endoscopic or surgical tissue biopsy. Pancreatic nodule therapy is tailored to the nature of the nodule, etiology-appropriate therapy for benign nodules or surgery, chemotherapy, and radiotherapy for cancerous nodules. Knowledge of the diagnostic approach of pancreatic solid mass is important for clinician to make prompt and accurate treatment for patients and to prevent unnecessary examination or intervention.

Keywords: *pancreatic mass, pancreatic nodule, solid pancreatic mass*

ABSTRAK

Pankreas merupakan organ kompleks yang didalamnya dapat muncul lesi tumor mencurigakan yang dapat bersifat jinak atau ganas. Anamnesis perjalanan penyakit pasien dapat membantu klinisi untuk memilih pemeriksaan penunjang yang dapat dilakukan seperti pemeriksaan laboratorium autoimun, penanda tumor, pencitraan dengan ultrasonografi (USG), computerized tomography (CT), magnetic resonance imaging (MRI), atau magnetic resonance cholangiopancreatography (MRCP), serta pengambilan sampel dengan teknik endoskopi atau pembedahan. Terapi nodul pankreas disesuaikan pemeriksaan terkait sifat nodul, terapi sesuai etiologi untuk nodul jinak dan terapi pembedahan, kemoterapi, atau radiasi untuk nodul kanker. Pengetahuan terkait berbagai metode pendekatan diagnosis pada nodul pankreas dapat membantu klinisi untuk memilih pendekatan klinis, patologi, dan radiologi yang tepat bagi pasien agar mencegah intervensi yang tidak diperlukan.

Kata kunci: *nodul pankreas, massa pankreas, massa padat pankreas*

INTRODUCTION

The pancreas is a parenchymatous and homogenous organ. There are some neoplasms and nonneoplastic lesions that can occur in the pancreas.[1] Pancreatic lesion in the pancreas is further divided into solid, cystic, and combined.[2] Solid mass in the pancreas is associated with the pathological condition and when a patient is diagnosed with pancreatic mass, the first suspicion would be pancreatic cancer.[3] Solid pancreatic lesions are mainly caused by adenocarcinoma, neuroendocrine tumor, pancreatoblastoma, pancreatic lymphoma or pancreatic metastasis with adenocarcinoma being the most frequent pancreatic solid mass between 70-95%.[4] Diagnostic approach of solid pancreatic mass is challenging because it will direct the course of treatment to avoid under or over-treatment. Since the most common pancreatic solid mass is adenocarcinoma, a swift diagnostic is needed regarding its rapid progression.

Less than 1/3 of pancreatic tumor patients are treated with curative intent and the mortality rate of pancreatic cancer is almost the same with its incidence with the ratio of 0.98.[5] Clinical history, laboratory parameters, and imaging such as computerized tomography (CT), magnetic resonance imaging (MRI), and endosonography are the backbone of diagnosis. Biopsy of a pancreatic nodule is very important to confirm the diagnosis and can be done by percutaneous ultrasound, CT-guided, or endosonography. Patients with suspicious nodules estimated resectable can be directly scheduled for surgery. Clinicians also have to be cautious to decide which patient will benefit most from surgical approach to avoid unnecessary resections given that 5% of patients resected due to suspicion of cancerous lesions finally present with benign histology.[6]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for pancreatic solid mass includes two different etiologies: neoplastic or inflammatory/autoimmune. Neoplastic masses have a wide array of histological variability and diagnosis that depends on the clinical symptoms where malignant masses are usually symptomatic. A pancreatic mass with symptoms like jaundice, weight loss, back pain suggests pancreatic cancer, with incidence of pancreatic ductal adenocarcinoma (PDAC) in up to 70-80%.[7] Some incidental findings of asymptomatic solid pancreatic mass are 23-42% to be pancreatic neuroendocrine tumor (panNET), 31-34% pancreatic ductal adenocarcinoma, 3-15% solid pseudopapillary tumour, and 0-11% focal chronic pancreatitis.[3]

Pancreatic solid masses that are inflammatory in its nature consist of chronic pancreatitis and autoimmune pancreatitis (AIP). Chronic pancreatitis (CP) has irreversible damage of exocrine pancreatic parenchyma and fibrosis. Incidence of CP around the world varies only around 1-15/100,000 per year. CP is caused by alcohol consumption, smoking, hereditary factors, and ductal obstruction or anatomical anomalies. Although CP is benign, it is a risk factor for pancreatic cancer development. Approximately 5 from 100 patients with CP will develop pancreatic cancer in 20 years mainly located in the pancreatic head. Patients with CP also tend to have inflammatory masses in pancreatic head that can be mistaken for cancer. Other very rare inflammatory condition that can present as solid mass in the pancreas is autoimmune pancreatitis with only 0.8 per 100,000 incidence in Japan which characterized by abundant infiltration of inflammatory cells and associated fibrosis that will impair the pancreas' function.[8] There are two types of AIP, lymphoplasmacytic sclerosing pancreatitis (type 1) and indiopathic duct-centric pancreatitis (type 2). The first type is the most frequent form where biopsy can show periductal infiltration with IgG4-positive plasma cells that leads to interlobular and periductal fibrosis that narrow pancreatic duct and acinar atrophy. 28-41% of cases imitate PDAC due to its local involvement.

Neoplastic diseases that present as a solid pancreatic mass can be a primary tumor that origins from pancreas or metastasis from other sites. Pancreatic ductal adenocarcinoma as mentioned before is the most common etiology of pancreatic solid mass. Pancreatic neuroendocrine neoplasms account for 5% of all pancreatic tumor. Most pancreatic neuroendocrine tumors are endocrine secreting tumor such as insulin, glucagon, vasoactive intestinal peptide, gastrin, or somatostatin but only a few patients are symptomatic. PanNET can impersonate as PDAC in computerized tomography (CT) and magnetic resonance imaging (MRI) due to its heterogeny and atypical enhancement, in these findings laboratory tests or biopsy can help diagnosis. Neuroendocrine carcinoma is rare and more aggressive with poorly differentiated and highly proliferatife features and abundant necrosis with prominent angioinvasion. Pancreatic neuroendocrine tumor usually occurs as hypervascular lesion, while neuroendocrine carcinomaa which has high proliferative index will present as a hypovascular lesion.[9] Pseudopapillary tumor is a rare pancreatic tumor with only 1-2% incidence and frequently occurs in young women. It can be of benign or low-grade malignant

lesion. Solid pseudopopillary tumor is an encapsulated tumor with large size that contains mixture of cystic, solid, and hemorrhagic components. Acinar cell carcinoma is very rare and represents 1% of all exocrine pancreatic cancer eventhough most of the pancreatic parenchyma is composed of acinar cells. Acinar cell carcinoma (ACC) should be suspected when a solid hypovascular pancreatic mass is found. Periampullary neoplasms include ampullary adenocarcinomas and adenomas, duodenal adenocarcinomas and gastrointestinal stromal tumors (GISTs), and distal cholangiocarcinoma. Metastatic lesions must be considered eventhough the incidences are low around 2%. It has various characteristics depending on its primary origin. The most common metastatic diseases of pancreas are renal cell carcinoma, non small cell lung cancer, breast cancer, sarcoma, melanoma, colon cancer, thyroid, and hepatocellular carcinoma. Some hematologic malignancies can manifest in pancreas particularly non-Hodgkin lymphoma by direct extension from surrounding lymph nodes or by hematogenous spreading. Primary pancreatic lymphoma can occur in the pancreas which accounts for less than 0,5% pancreatic malignancies and 1% extranodal lymphomas.[3]

CLINICAL PRESENTATION

Patients may have no complaint or unspecific complaints like fatigue with incidental radiologic finding of pancreatic mass. A large study shows that pancreatic cancer is associated with twelve alarms symptoms: weight loss, abdominal pain, nausea and vomiting, bloating, dyspepsia, new-onset diabetes, bowel changes, pruritus, lethargy, back pain, shoulder pain, and jaundice. Five symptoms that can occur more than six months before diagnosis are back pain, shoulder pain, dysphagia, bowel changes, and lethargy.[10] Around 80-90% of patients with mass located in the head of pancreas will lead to obstructive jaundice due to obstruction of biliary duct. It is characterized with extremely high level of conjugated bilirubin and alkaline phosphatase, absence of urobilinogen and stercobilinogen, with pale stools and dark urine. While mass in body and tail of pancreas often has no symptom, and only around 6% has obstructive jaundice. Functional tumor like neuroendocrine tumor will result in symptoms related to the hormone released. Weight loss and pancreatic solid mass are the feature of pancreatic adenocarcinoma, but it can also occur in patient with focal chronic pancreatitis due to the reduction of pancreatic enzymes needed for food absorption. Pain is usually the symptom that brings the patient to medical attention. Upper abdominal pain that radiates to the back or a vague discomfort can present even if the mass is only less than 2 cm. Almost all patient with mass in the body and tail of pancreas (90%) will experience pain whereas only 70% of patient with mass in the head of pancreas experience pain.[3] Pain in pancreatic mass is the result of pancreatic capsule stretching, ductal stenosis or obstruction, or perineural invasion. Pain is also a predictor of poor outcome in pancreatic adenocarcinoma.[11] Around 80% of pancreatic cancer patients have glucose intolerance and most patients with pancreatic cancer have newly diagnosed diabetes or during the two years prior to cancer diagnosis.[12] Pancreatic cancer patients with diabetes have insulin resistance that is shown to be improved after tumor resection. Disruption of glucose tolerance also occurs in a patient with neuroendocrine neoplasms.[13] Very huge mass can results in duodenum compression creating obstruction that will leads to early satiety, nausea, and vomiting.[14]

Table 1. Clinical finding in pancreatic mass[3,11,12,14]

Pancreatic mass clinical findings	
Alarm symptoms for malignancy	Weight loss, abdominal pain, nausea and vomiting, bloating, dyspepsia, new-onset diabetes, bowel changes, pruritus, lethargy, back pain, shoulder pain, and jaundice
Head of pancreas mass	Obstructive jaundice, pale stool, dark urine
Functional tumor	Symptoms due to hormon released

DIAGNOSTIC APPROACH

Clinical history can guide clinicians to narrow the differential diagnosis for pancreatic solid mass but further evaluation with laboratory tests, imaging, and interventional procedures are often needed for accurate diagnosis. Laboratory tests can be used to guide diagnosis and for patient's general condition to see the evidence of subclinical jaundice or inflammatory process with faecal elastases-1 or IgG4 in the suspicion of autoimmune pancreatitis.[3] Tumor markers such as CEA and CA 19-9 have sensitivity around 80-90%, and specificity of 87% and 25-56% respectively for diagnosis of pancreatic cancer.[5] Although 10% of population will have normal CA 19-9 because the lack of enzyme and unspecific elevation in patients with obstructive jaundice. Chromogranin A as a protein released by neuroendocrine cells helps for diagnosing patients with NET with sensitivity and specificity about 80%.[15]

Imaging has important role for diagnosis of pancreatic mass. Ultrasonography is the first-line diagnostic tools for patients with jaundice or abdominal pain because it is non-invasive and cost-effective however it is operator dependent and can't determine the definite diagnosis. Ultrasound has the sensitivity and specificity from 75-89% and 90-99% respectively for pancreatic cancer detection, respectively. PDAC in ultrasound shows hypoechoic mass, dilatation of pancreatic, and bile duct. Necrosis and colliquation present as hypoechoic central areas in the aggressive tumor. Pseudopapillary tumor will present as a large and well-defined mass with heterogenous appearances due to its solid and cystic composition. Chronic pancreatitis should be suspected in atrophic, calcified, or fibrotic pancreas. Mass located in pancreatic body or tail is more challenging to be seen from ultrasound due to the lack of indirect signs and abdominal meteorism. Doppler ultrasound can evaluate vascularization of the mass and peripancreatic vessels. PDAC will show limited or absent vascularization, while panNET will be presented as a highly vascularized mass. Contrast administration enhances margins, tumor measurements, and its relationship with peripancreatic vasculatures for staging.[16]

Abdominal CT with contrast and specific pancreas protocol that distinguish arterial and venous phases with the optimal exam consists of four phases (unenhanced, pancreatic/late arterial phase, portal/venous phase, and late phase) plays the key role in radiologic diagnostic of pancreatic masses as it also has the ability to predict resectability.[17] Pancreatic adenocarcinoma is typically detected as hypovascular mass in abdominal CT scan. It is best seen in pancreatic phase with poorly defined contours without necrosis and hemorrhage with a tendency for focal infiltration and vascular encasement. Early phase will detect abundant fibrous stroma and hypovascularity that will show poor enhancement of tumor compared to normal pancreatic parenchy, and lesion will be recognizable if it alters pancreas and nearby structures morphology. The tumor is best seen in arterial phase as the venous phase is better for detecting liver metastases. Dilatation or interruption of pancreatic duct, double biliary and pancreatic obstruction, sheathing of celiac trunk, or mesenteric artery, and intralesional calcification are also suggestive for pancreatic adenocarcinoma. Although multidetector computed tomography (MDCT) is great for predicting resectability with positive predictive value of 89%, sensitivity of 100%, and specificity of 72%, it has limitation in finding tumor < 1 cm, absence of biliary dilatation, vascular involvement and mass effect, and little difference with normal parenchyma. It also has limited sensitivity in evaluating nodal involvement, small hepatic, and peritoneal metastases. Pancreatic neuroendocrine tumor presents as hypervascularized lesions on CT or hypovascularized mass if there is necrosis.

Patients with suspicion of hepatic involvement may benefit from abdominal MRI, or MRCP for patients who need bile and pancreatic ducts evaluation. Patients with pancreatic NET are more challenging to diagnose because they are often less than 2 cm and may need specialized imaging such as somatostatin receptor scintigraphy or increasingly gallium positron emission tomography (PET) CT. Invasive procedure like endosonography is also very crucial in diagnostic process of pancreatic mass for its ability to discover tumor extension, lymph node involvement, vascular invasion, and tissue diagnosis by fine needle aspiration. Together with CT scan, they will give the highest accuracy to assess tumor resectability. While endoscopic retrograde cholangiopancreatography (ERCP) ability to evaluate pancreatic mass is replaced by MRCP, it still has therapeutic role to release and drain obstruction in patients with cholangitis or extensive jaundice.[18]

Biopsy is not routinely indicated for patients with pancreatic mass because although it has a good sensitivity of 87% and specificity of 100%, the accuracy of pancreatic mass biopsy is 84-88% and negative predictive value of 58-72%.[19] In patients with suspicious pancreatic masses estimated resectable by imaging are recommended to be resected. While patients that may have to undergo neoadjuvant chemotherapy or radiochemotherapy may need to unde bioaesent psy. Patients with suspected pancreatic NET are indicated for biopsy to verify diagnosis and tumor speci features like antigen Ki-67 to decide further therapy. Biopsy can be done with EUS-guided and percutaneous approach. The two methods have similar accuracy with median of 88% and 84% respectively. Although EUS FNA is less invasive and may reduce the possibility of tumor cell seeding, it will generate small size of sample due to its smaller-sized probes and may hamper cytologic and histopathologic diagnosis. This affects its wide ranges of sensitivity from 54-95% and accuracy from 65-96%. But this can be avoided by using core or trucut needle for larger specimen.[20] Surgical exploration may be considered in patients with suspicious mass with negative or inconclusive biopsy. Laparoscopy can help to avoid exploratory laparotomy in systemic disease that is not detected

during preoperative staging. However there is still no study that compares advantage of staging laparoscopic over radiologic imaging.[6]

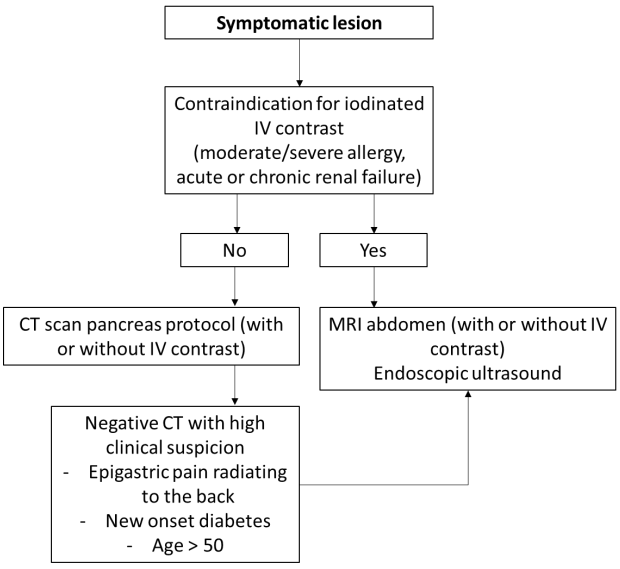

Figure 1. Imaging options for pancreatic nodules

TREATMENT

Treatment option for solid pancreatic mass depends on clinical suspicion whether it is suspected to be benign or malignant. Patients with suspicious mass that are still resectable and fit for surgery are indicated for surgical resection.[6] The goal of surgery is radical removal of tumor both microscopically and macroscopically. It is important to identify non resectable tumor which is indicative of the systematic disease that can't achieve the goal of radical tumor removal. The universally accepted criteria of non-resectability are: (1) presence of distant metastasis; (2) presence of lymph node metastasis in non-local-regional lymph node stations, which are lymph node stations that were not taken away during expected standard lymphadenectomy with the pancreatic resection in question (for example mediastinal or supraclavicular lymph nodes, mesentery lymph nodes, inter-aortal-caval or peri-aortal lymph nodes); (3) direct infiltration of contiguous visceral extra-pancreatic structures, except via the biliary tree and the duodenum.[21]

Patients with pancreatic cancer may need adjuvant chemotherapy. Gemcitabine or 5-fluorouracil prolongs median survival by 3 months, with gemcitabine being first-line adjuvant agent due to its safety profile.[21,22] Chemoradiation is one of adjuvant therapy option, although its benefit is still unclear based on the results of European Study Group for Pancreatic Cancer (ESPAC) trial that shows that median survival with chemoradiation was similar to that with observation (13.9 months, 95% CI: 12.2-17.3) and (16.9 months, 95% CI: 14.2-22.5) and survival will increase when chemoradiation is followed by chemotherapy (19.9 months, 95% CI: 14.2-22.5) and longest with adjuvant chemotherapy alone (21.6 months, 95% CI: 13.5-27.3).[21]

Patients with benign pancreatic nodule need to be treated accordingly. Treatment of chronic pancreatitis includes lifestyle modification such as smoking cessation and pain management with pain medication or surgery if patient doesn't respond with adequate pain management. AIP is treated with corticosteroid to achieve remission of acute phase. Remission is referred to as symptoms alleviation since laboratory and imaging normalization may take some time.[22]

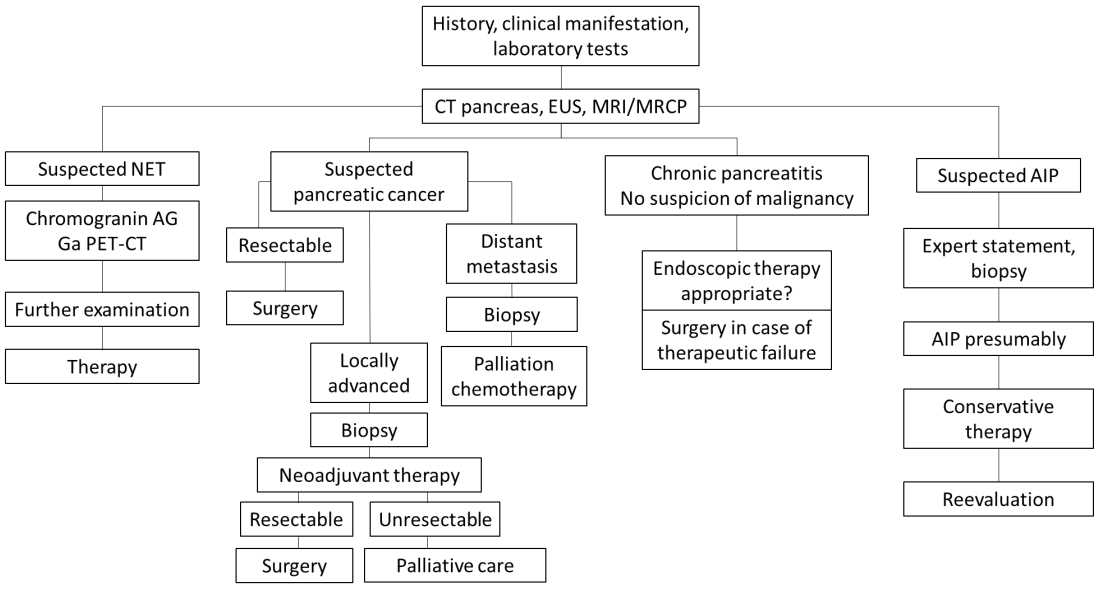

Figure 2. Clinical approach of pancreatic nodules[6]

CONCLUSION

Most of the solid pancreatic masses are malignant, so an immediate diagnostic process is needed due to its aggressive nature. However, there are a few benign conditions that cause a solid pancreatic mass in which clinicians must be careful to avoid unnecessary intervention. Clinical history, laboratory tests, imaging may help to determine clinicians to narrow down the differential diagnosis and later select the appropriate treatment.

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