Diagnosis and treatment of pancreatic incidentalomas.
An overview

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AIM: *The aim of this study is to describe the incidence, imaging characteristics and pathological features of pancreatic incidentalomas. Moreover, surgical indications are discussed according to the nature and location of the neoplasms.*
BACKGROUND: *Pancreatic incidental lesions are more commonly diagnosed, due to the widespread of high quality cross sectional imaging. These lesions can be cystic or solid, benign, pre-malignant or already malignant and they cover a wide spectrum of histological diagnosis. Cystic lesions are more commonly benign or at least pre-malignant. Surgery should be reserved in case of unexpected changes in aspect during follow-up or for large cysts (>3 cm). Among solid pancreatic incidentalomas, ductal adenocarcinoma is the most common diagnosis, followed by neuroendocrine tumors. Surgical treatment of pancreatic incidentaloma depends on the location of the tumor: a Whipple's procedure should be performed for neoplasms of the head, while distal pancreatectomy is indicated for body and tail lesions. Pancreatic surgery is still delicate and burdened by serious complications. Both procedures can be performed with minimally-invasive technique which is connected to lower complications rate but, at present, they have shown no advantages in terms of mortality and oncologic outcomes.*
CONCLUSIONS: *Pancreatic incidentalomas are becoming more and more common but when and how to operate them is still subject of debate. Precise criteria about treatment strategy are still lacking and definite guidelines are needed to clarify the best approach.*

KEY WORDS: Incidentaloma, Laparoscopy, Pancreatic tumors, Surgery

In modern medicine, the use of advanced radiological techniques and the widespread of cross-sectional diagnostic imaging, has led to an increased detection of asymptomatic masses. The term "incidentaloma" defines a non-symptomatic lesion, detected during imaging or biochemical tests for unrelated causes. Incidentalomas of the adrenal gland are largely described and their management is well characterized. In international literature, incidental findings of thyroid, parathyroid, pituitary and liver are also frequently reported [1]. Among these incidental findings, pancreatic incidentalomas (PI) are increasingly detected. PIs' first case series was reported in literature in 2001 by Kostiuk et al. [2] and, since then, many other series have been published. However, PI prevalence is not clear and changes according to different studies: two large series reported a prevalence of 2.5% of incidental pancreatic masses detected with computed tomography (CT) scan and magnetic resonance imaging (MRI) studies performed for non-pancreatic symptoms [3,4]. At the same time, other studies report PI prevalence to be around 10% (and up to 30% in the elderly) when using high-resolution MRI [5].
PIs can be either solid or cystic lesions. Their histological nature includes a wide range of neoplasms. Pancreatic ductal adenocarcinoma (PDAC), as expected,

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is the most frequently diagnosed lesion among PIs (30-35%)[1,6]. Other findings include neuroendocrine tumors (NET) (20-25%), serous cystadenoma neoplasm (SCN) (15–20%), intraductal papillary mucinous neoplasm (IPMN) (15-20%) and mucinous cystic neoplasms (8-10%) [7-9].

At present, the optimal characterization of a PI is obtained by a CT scan with dual-phase contrast-enhanced acquisition in pancreatic and portal venous phases. Also an MRI, as well as a magnetic resonance-cholangiopancreatography (MRCP) might be useful. MRI pancreatic protocol includes pre- and post-Gadolinium T1 weighted sequences and T2-weightened sequences with fat suppression[10]. These radiological studies can accurately distinct cystic from solid lesions and also define size, localization and vascularization of the mass. Moreover, they complete the characterization of the lesions by describing the presence of mural nodules, dilation of the common bile duct, involvement of the main pancreatic duct, and peripancreatic or vascular invasion.

Endoscopic ultrasound (EUS) with fine needle aspiration (FNA) is becoming progressively more employed in the study of pancreatic lesions. It provides good quality of the imaging and contributes to histological differentiation.

Once a PI is diagnosed, the next step is to understand its degree of malignancy. In fact, even if they do not present any symptom, PIs can be benign, pre-malignant, or even already malignant. In their case series, Bouquot et al. concluded that, at the time of incidental diagnosis, there is a 90% chance of malignancy for lesions >2 cm with simultaneous bile duct dilatation [11].

Cystic lesions are more commonly benign or at least pre-malignant. Pancreatic cystic masses can be classified into several types: congenital (true cysts and syndromes associated with multiple cysts), inflammatory (pseudocysts, pancreatic abscesses, hydatid cysts) and neoplastic (SCNs, MCNs, IPMNs, solid pseudopapillary neoplasms – SPPN-, cystic NETs and cystic metastatic lesions) [12]. MCN and IPMN are the most frequent pancreatic cystic tumors. MCNs are thick-walled macrocystic lesions frequently located in body and tail region of the gland and characterized by the absence of communication with pancreatic ductal system. They frequently affect middle-age women. IPMNs are intraductal tumors characterized by epithelial papillary proliferation and mucin hypersecretion causing cystic dilatation of ductal system. IPMNs often occur in the head of the pancreas [8]. IPMNs are more frequent in the seventh decade of life and they show an equal gender distribution [8,9]. IPMNs can originate from the main pancreatic duct or from secondary ducts. The communication between the cystic tumor and the pancreatic ducts is a specific feature of this neoplasm [4,9].

Management includes imaging follow-up and surgical resection. For cysts between <1 and 3 cm further imaging, besides CT, should be performed for better characterization [13]. At CT scan, the presence of a solid mass or a mural nodule is suspicious for malignancy but also main pancreatic duct dilation, thick septations and biliary obstruction can indicate a malignant tumor. While defying a cystic lesion, MRI can also give precious information like a precise estimation of the thickness of the wall, mural irregularities, septa and duct communication (especially their relationship with the main duct) [14]. Further studies can include EUS with FNA to assess cytopathologic examination and biomarkers determination (amylase concentration and carcinoembrionic antigen levels).

However, this assessment is not always accurate, since IPMNs with connection to the main pancreatic duct might be related with high lipase and amylase levels [15]. Once imaging features suggesting a benign lesion are confirmed, annual follow-up is recommended [16]. If the cyst enlarges or develops any unexpected features, surgical resection should be considered. For patients with cysts >3 cm surgery is always recommended [17].

PIs solid lesions are more common than cystic ones and they get classified according to their origin. Solid lesions represent 30-65% of all masses [18]. PDACs are by far the most frequent solid PIs diagnosed, followed by solid NETs. PDACs located in the head of the gland are more frequently symptomatic than body and tail tumors. They are responsible for jaundice and main pancreatic duct dilatation with consequential endocrine and exocrine pancreatic insufficiency [19]. TNM stage III and IV and poorly differentiated carcinomas are related to an increased risk of death and poor survival [20].

In asymptomatic patients, the body and the tail of the pancreas are more frequently involved [21]. TNM scores seem to be significantly lower in PIs than symptomatic tumors[22]. According to Winter et. al 35% of PDACs accidentally discovered were classified as stage I (vs 10% of symptomatic lesions). The same series showed that PIs were also more commonly well differentiated. Early detection may be connected to these advantageous characteristics; for this reason PIs are expected to be related to better prognosis compared to symptomatic tumors, but interestingly, there is no evidence in medical literature that early detection of pancreatic masses is related to higher survival rates, therefore this is still debated [1,23].

In the last decades NETs have been diagnosed with increasing frequency and to date are about 2% of pancreatic neoplasms [24,25].

On CT-scan images most NETs are hyperdense masses with arterial phase contrast enhancement, while adenocarcinomas show a hypodense or isodense appearance. EUS-guided FNA is essential to discriminate the two lesions and to gather further information regarding their relationship with the bile ducts [26]. The management of small non-functional endocrine tumors < 10 mm is controversial. A non-operative management has been proposed but large series demonstrated that even NET less

than 2 cm of size may develop local or distant disease progression, therefore surgical resection is recommended. Acinar cell carcinoma (ACC) is a rare malignancy that accounts for 2% of all pancreatic tumors. Its malignant cells are organized in small glandular structures and can produce low quantity of enzymes. Its clinical features and malignancy are quite unknown. ACC's aggressiveness seems intermediate between NPT and PDAC , nevertheless its overall survival is low [27].

The surgical treatment of pancreatic cancer depends on the location of the tumor: a pancreaticduodenectomy (PD) should be performed for lesions of the head, while distal pancreatectomy (DP) is indicated for body and tail benign and pre-malignant lesions. For distal malignancies, DP includes the splenectomy, to perform a radical lymphadenectomy [28]. Surgical treatment of pancreatic cancer is still delicate, and characterized by high rate of morbidity and mortality. Mortality ranges between 1-3% in large centers and up to 10% in small ones. Post-operative morbidity (especially hemorrhage, pancreatic fistula and intra-abdominal abscess) concerns 30-40% of procedures [29]. Both PD and DP can be performed laparoscopically [30]. However, while laparoscopic PD is only performed in high-specialized centers, minimally-invasive DP is considered technically less challenging and consequently it is more widely performed [28]. Recent meta-analyses have demonstrated that minimal-invasive approach shows advantages in pancreatic surgery, such as decreased blood loss, minor risk of wound infection and shorter hospital stay. At the same time, these studies showed no difference in mortality and oncologic outcomes [31,32]. It must be mentioned that no randomized trials comparing long term outcomes after the two approaches has ever been performed, and coherently definitive conclusions cannot be drawn.

In conclusion, PIs are becoming more and more common but surgical timing and technique is still subject of debate. In a case series of 881 pancreasectomies published by Bouquot et al. in 2018, the Authors suggest that a careful selection of patients undergoing surgery for PI must be done since only 50% of incidentalomas resected were malignant [11]. At present, the risks of pancreatic surgery are still relevant, and the impact of post-operative morbidity must be always taken in consideration. Generally, surgical resection for cystic lesions of the pancreatic head must be evaluated case by case, while solid lesion of the distal pancreas should always be surgically resected. However, precise criteria about treatment strategy (conservative vs aggressive) are still lacking and further studies are needed to produce definite guidelines to clarify the best approach.

Riassunto

SCOPO: Obiettivo dello studio è descrivere l'incidenza, le caratteristiche radiologiche e anatomo-patologiche degli incidentalomi pancreatici. Nell'articolo, Inoltre, sono discusse le indicazioni chirurgiche di queste lesioni in base alla loro natura e localizzazione.

PREMESSE: Le lesioni pancreatiche incidentali sono sempre più frequentemente diagnosticate grazie alla larga diffusione di tecniche radiologiche di elevate qualità. Gli incidentalomi pancreatici possono essere cistici o solidi, benigni o maligni, coprendo un ampio spettro di varietà istologiche. Le lesioni cistiche sono più frequentemente di natura benigna o pre-maligna. L'asportazione chirurgica deve essere riservata solo in caso di variazioni sospette in senso degenerativo al follow-up oppure per le masse cistiche di larghe dimensioni (>3 cm). Tra gli incidentalomi pancreatici solidi l'adenocarcinoma duttale è la neoplasia più frequentemente diagnosticata, seguita per frequenza dei tumori neuroendocrini. Il trattamento chirurgico dipende dalla localizzazione dell'incidentaloma: la duodenocefalopancreasectomia dovrebbe essere eseguita per le lesioni a carico della testa, mentre la pancreasectomia distale è indicata per quelle del corpo e della coda. La chirurgia del pancreas è delicata e tuttora gravata da serie complicazioni. Entrambi gli interventi chirurgici possono eseguiti con tecnica mini-invasiva, che è caratterizzata da un minor tasso di complicazioni, ma al momento attuale, non è stata dimostrata una miglior sopravvivenza nei pazienti oncologici

CONCLUSIONI: Gli incidentalomi pancreatici sono di riscontro sempre più frequente nella pratica clinica, ma quando e come intervenire chirurgicamente è ancora materia di dibattito. Attualmente mancano precisi criteri circa la strategia di trattamento e sono quindi necessarie linee-guida per definire il miglior approccio di queste lesioni del pancreas.

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