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Pancreatic cystic tumours: when to resect, when to observe

R. SALVIA, S. CRIPPA, S. PARTELLI, G. MALLEO, G. MARCHEGGIANI, M. BACCHION, G. BUTTURINI, C. BASSI

Department of Surgery, Chirurgia Generale B, Policlinico "GB Rossi", University of Verona, Verona (Italy)

Abstract. – *Background and Objectives:* **In recent years there has been an increase in the diagnosis of cystic tumors of the pancreas. In this setting, difficult diagnostic problems and different therapeutic management can be proposed.**

Material and Methods: **A review of the literature and authors experience were undertaken.**

Results: **Cystic tumors of the pancreas include different neoplasms with a different biological behaviour. While most serous cystadenomas (SCAs) can be managed nonoperatively, patients with mucinous cystic neoplasms (MCNs), solid pseudopapillary tumors (SPTs), main-duct intraductal papillary mucinous neoplasms (IPMNs) should undergo surgical resection. Branch-duct IPMNs can be observed with radiological and clinical follow-up when asymptomatic, < 3 cm in size and without radiologic features of malignancy (i.e. nodules).**

Conclusions: **Cystic tumors of the pancreas are common. Differential diagnosis among the different tumor-types is of paramount importance for appropriate management. Nonoperative management seems appropriate for most SCAs and for well-selected branch-duct IPMNs.**

Key Words:

Pancreatic cystic tumors, Pancreas neoplasms.

Introduction

The classification of cystic tumours of the pancreas has become clearer only in the past few years with two articles by Compagno and Oertel[1,2]. Since when first identified, by Becourt in 1830[3], the major unsolved issue has been to have a definitive pre-operative diagnosis. This clinical problem is obviously due to the fact that different cystic neoplasms require different treatment.

The first differentiation among pancreatic cystic lesions has to be done between cystic tumours and non-neoplastic cystic lesions: this is based on the presence/absence of epithelial lining inside the cystic wall and permits to rule out all simple cysts and pseudocysts. Once epithelial lining is detected, its different features define different kinds of tumours[4].

Most of the time, cystic neoplasms are slow growing clinically asymptomatic lesions, whenever symptoms are present, they are related to the mass and sometimes associated to a vague abdominal discomfort. Only the IPMNs clinical onset appear as a chronic pancreatitis like pain[5].

From the pathological point of view, the presence of the epithelium and its features enable us to classify and provide the prognostic value for the different types of cystic neoplasms[4].

Classification

The understanding of pancreatic cystic tumours is based on the WHO Classification of Tumours, edited in 1996[4]. Pancreatic cystic tumors can be classified as follows:

- Serous cystic tumours
  - Serous cystadenoma
  - Serous cystadenocarcinoma
- Mucinous cystic tumours
  - Mucinous cystadenoma
  - Mucinous cystadenoma with moderate dysplasia
  - Mucinous cystadenocarcinoma
  - Not infiltrating (carcinoma-in-situ)
  - Infiltrating
- Intraductal papillary mucinous adenoma
- Intraductal papillary mucinous tumours with moderate dysplasia
- Intraductal papillary mucinous carcinoma

Corresponding Author: Claudio Bassi, MD; e-mail: claudio.bassi@univr.it

  – Not infiltrating (carcinoma-in-situ)
  – Infiltrating
- Solid pseudopapillary tumours

Laboratory Findings

In the clinical work up a specific serum tumour marker, which can help the clinician to discriminate the different types of cystic tumours, is not available yet.

However, positive CEA serum marker status and/or the presence of more than two positive serum markers (CEA, Ca 19-9, or Ca 125) suggests the presence of a mucinous cystic neoplasm, potentially malignant, and so can prevent delayed diagnosis[6].

Serous Cystic Tumours (SCTs)

Epidemiology

Women in their fifties seem to be the population more affected by serous cystic tumours (SCT). Any portion of the pancreatic gland can be interested by SCT but they are more frequently detected in the pancreatic head[7]

Histologically, SCT appears as multiple cysts lined with cubic flat epithelium with clear cytoplasm glycogen-rich cells. The cytoplasm of these cells is usually clear or eosinophilic and the nuclei are centrally located, small and hyperchromatic; mitoses are generally absent. Based on morphological aspects these tumours can be divided in three types: microcystic, macrocystic or oligocystic (<3% of cases), and mixed forms (micro-macrocystic). The majority of serous cystadenoma are microcystic with a honeycomb-like appearance.

Clinical Findings

Most of serum cystic adenomas (SCAs) are asymptomatic and incidentally detected by radiological investigation for symptoms that may not be related to the pancreas. Whenever is present, the most common symptom is abdominal discomfort or a low grade pain. Weight loss, palpable mass, jaundice and obstruction of upper GI tract are rare and may be correlated to an extensive growth of the lesion. Label a pancreatic mass as a SCA is important because this tumour, unlike the other cystic tumours of the pancreas, is benign. Therefore, whenever possible, a conservative approach should be the treatment of choice[7].

Despite of symptoms are not helpful for diagnostic purpose, they can grossly indicate towards a benign or malignant neoplasms. A suspect of SCA should arise also in the presence of Von Hippen-Lindau (VHL) syndrome which is a genetic condition associated in 15-30% of cases with SCA[8,9].

Radiology

Ultrasound (US) is usually the first step in the diagnostic work up and, due to its widespread use in clinical practice, it has significantly increased the number of incidental SCA observations. The diagnosis is easily made when US shows a mass with multilobulated borders, no posterior acoustic enhancement and an internal "honeycomb" architecture due to the presence of multiple septa which delimit small (<2 cm diameter) cystic spaces. In 10%-30% of cases, there can be calcifications within the septa and, even less frequently a central calcified scar[10]. The microcystic appearance is also seen in SCA correlated to VHL syndrome but, in these cases the tumour is multicentric or diffusely involves the whole gland. The macrocystic type is easily detectable even when the size is small. The aspects is of a sharply marginated, hypoechoic mass; there might be sparse, thin central septa and in this case the differential diagnosis from the other cystic mass is very difficult. In the mixed SCA, together with the microcysts, larger (>2 cm) cystic spaces can be found at the periphery of the lesions resulting in a mixed pattern[10]. The macrocyst can grow up to 8-10 cm making difficult the recognition of the true nature of the tumour.

Computed tomography (CT) appearance of SCA depends on two factors: macroscopic feature and timing of data acquisition. Microcystic tumours appear as a unenhanced mass effecting or deformating the profile of the gland. When calcifications are present the location is quite always central, punctate or globular, as opposed to the lamellar calcifications seen in mucinous cystic tumours[11]. Usually a central fibrous scar is visible in the larger masses since it forms later on. The presence of central calcification in correspondence with scars or septa definitively characterizes a cystic mass as a SCA. Macrocystic patterns are indistinguishable from other macrocystic masses of the pancreas, as the mucinous cystic tumours.

Magnetic resonance imaging (MRI) is assuming a main role in the work up of these tumours due to the given accurate informations about the

structure of the lesion in particular the presence of septa. In the microcystic pattern, MRI is able to demonstrate even a small content of fluid within the dense septa of a "sponge-like" mass but has the disadvantage that it is insensitive to calcifications[12]. In the macro-microcystic cases the two components are well recognisable. The magnetic resonance colangiopancreatography (MRCP) technique gives an even better evaluation of spatial relation between the mass and the biliary or pancreatic duct by discriminating, in this case, the ship diagnosis with intraductal papillary mucinous tumours (IPMN) in particular when the tumour is located on the head or in the uncinate process of the gland. MRCP should be routinarely carried out in the staging of these tumours since it helps to distinguish microcystic SCA from intraductal tumour of the peripheral branches which septate appearance[13]. The absence of communication with the Wirsung duct will allows for a certain diagnosis on SCA.

Serous Cystic Adenocarcinoma

In literature only 10 cases of serous cystic adenocarcinoma were reported, all of them described as microcystic[14,15].

A recent review reported how patients with suspicious of cystoadenocarcinoma can be 5 years older than the statistic value of the significancy and, in most of the cases, the patients are asymptomatic.

The potential malignancy risk in case of a suspicious serous cystic tumour has been worked out around 3%[16]. In our experience no case of serous cystadenocarcinoma has never been detected.

Differential Diagnosis

The finding of a mass in the pancreatic head with the mentioned features in a female patient with no dilation of the duct, normal parenchyma and calcification, leads to a definitive diagnosis of SCT. The diagnosis can be considered definitive when the lesion shows a mixed aspect with macrocysts in the periphery of microcystic nucleus. Despite of the microcystic aspect, when the cystic mass is located in the uncinate process of a male patient and associated with a main duct dilation the diagnosis could be more difficult: in this case, in order to make a differential diagnosis with IPMN of branch ducts it is mandatory to demonstrate the relationship between mass and Wirsung. MRCP is useful for this purpose but, in those cases where the lesion is very closed to the main duct, an endoscopic retrograde colangiopancreatography (ERCP) is necessary[13].

Macrocystic SCT lack of a proper radiological characterization on US, CT and MRI findings and endoscopic US seems to be the only technique able to supply further informations.

Treatment

Resection of CASs is generally carried out for symptomatic patients, in the case of large size tumours, or due to the inability to distinguish a CAS from other cystic tumours of the pancreas (mucinous cystadenoma, IPMN). Some Authors have reccomended resection for all CASs but we believe that a more selective approach should be considered.

Recently Tseng et al.[17] have reported the experience of the Massachusetts General Hospital, Boston, USA with a total of 106 patients affected by CAS, analyzing their experience over 28 years in order to better define the natural history of the disease and the optimal management. They reported a 47% of patients beeing asymptomatic while, among those with symptoms, abdominal pain was the commonest; large tumours (>4 cm) were significantly associated with the presence of symptoms. Moreover in 24 patients serial radiography was available and analyzed; the median growth rate was only of 0.6 cm/year but in tumour larger than 4 cm it was 1.98 cm/year.

In conclusion, in absence of symptoms and for lesion less than 4 cm in diameter a yearly follow-up can be safely recommended.

Mucinous Cystic Tumours (Mcts)

Mucinous Cystadenomas and Cystadenocarcinomas

Epidemiology

Mucinous cystic tumours (MCT) occur exclusively in women. These neoplasms are preferentially located in the body and tail and are characterized by a uni-multilocular cysts that do not communicate with the ductal system. The tumor is encapsulated and lined by columnar mucin-producing cells overlying an ovarian type stroma[18], thus explaining the exclusive incidence in a female population. The patient age range is large, with an average that seems to depend on the degree of malignancy of the neoplasm: patients with malignant MCT appear to be older suggesting a timing related degeneration from benign lesions.

MCT is a pre-malignant lesion and it is important therefore to distinguish it from other cystic lesions of the pancreas. Pathologists can detect, all the different degrees of malignant transformation at the same time in the same lesion. This has a great relevance suggesting an adenoma-carcinoma sequence[19].

Clinical Findings

As well as serous cystic tumours, symptoms in MCT are non specific and are not really helpful in the differential diagnosis of the pancreatic cystic lesions. The most frequent symptoms are abdominal discomfort or pain. Uncommonly, the patient complains a upper quadrants abdominal pain irradiated to the flanks which could guide to a pancreatic localisation. However, also non-specific symptoms can suggest malignant forms, such as: weight loss, anorexia, obstructive jaundice are common in malignancies.

Radiology

Radiological investigations enhance the two patterns of MCT: the *macrocystic multilocular one* and the *macrocystic unilocular one*[20]. The former is not pathognomonic, but it is frequently located in the body-tail of the gland, appearing on US images as a sharply defined mass surrounded by a variably thickened wall. Thin septa delimit cystic spaces and calcifications are a common finding. On CT scan, the pre-contrast phase can easily detect calcifications. The density of content depends on the amount of mucin or fluid-fluid level from underlying bleeding. This pattern is clearly demonstrated by contrast medium: walls and septa display a lower enhancement if compared to the surrounding pancreatic parenchyma because of the fibrous tissue composition and minimal vascularization. The outer wall and septa have similar thickness. The *macrocystic unilocular* pattern is less specific and simulates any kind of pancreatic cystic mass both on US and CT scan images. As a consequence, the differentiation cannot be made easily in cases with unique cysts with thin wall, no calcifications and no parietal nodules[20].

From the radiological point of view thickened wall, presence of papillary proliferations arising from the wall or septa, evidence of peripheral calcifications as well as invasion of surrounding vascular structure are considered the best signs of malignancy. The diagnosis will be clearer if extracapsular extension of the lesion is detected on a CT contrast-enhanced images. When thick walls, thick septa and calcifications are simultaneously present, the probability of malignancy is 95%. When fewer than three signs are present, the probability of malignancy decreases until zero when there are no calcifications, septa and the wall is thin. Because calcifications can not be detected by MRI, CT is the primary imaging modality for these patients.

The predominant fluid content of these masses renders MCT brighter on T2-weighted MRI images. The presence, features and distribution of internal septa are better seen with these techniques. T-2 weighted images are optimal for the study of the Wirsung duct. When the mass clearly appears to be isolated from it, thereby excluding the possibility of an intraductal tumour, no further examinations with MRCP are required[21].

Differential Diagnosis

The macrocystic multilocular pattern is considerated typical but not pathognomonic. Oligocystic SCT, solid pseudopapillary tumors (cystic variant) and cystic endocrine tumors have identical appearance. In these cases, clinical history and laboratory data are essential for diagnosis. Oligocystic SCT is almost never pre-operatively differentiated from benign MCT[13].

In neuroendocrine and pseudopapillary tumors the cystic component is due to previous necrosis and intratumoral bleeding. In the former the clinical syndrome might help for diagnosis, in the latter MRI will enhance the different appearance of fluid content.

Pseudocysts make the diagnosis difficult mainly with macrocystic unilocular pattern: if the clinical history is silent CMT should be suspected.

Treatment

All MCTs should be resected, both cystadenomas and cystadenocarcinomas, when possibile[22,23]. Recently we have reported our caseload with 164 patients who underwent resection for MCNs[22]. The great majority of them had only adenoma, while only 11% had invasive carcinoma. However, patients with carcinomas were significantly older compared to those with noninvasive tumors, suggesting tumor progression from adenoma to invasive cancer. Therefore, considering this risk and the young age of these patients, surgical resection is advisable in all surgically fit patients. Predictors of malignancy are large size, the presence of nodules, septa and eggshell calcification. In these cases surgery is mandatory. In

these cases surgical "standard" pancreatic resection should be performed, avoiding middle pancreatectomies and spleen preservation in left pancreatectomies. On the other hand, in "low-risk" lesions (size <4 cm, no nodules) parenchyma-sparing resections as well as laparoscopic distal pancreatectomies with spleen preservation whenever feasible, should be performed.

Intraductal Papillary Mucinous Neoplasms (IPMNs)

Once considered as a "rare" entity, intraductal papillary mucinous neoplasm (IPMN) of the pancreas is nowadays more common recognized, even in asymptomatic patients in which they represent an incidental finding[23,24]. At our Institution IPMN has become the second most common indications for pancreatic resection, after ductal adenocarcinoma.

First descripted by Ohashi et al.[25] in 1982 with the term of "mucinous secreting cancer of the pancreas", the knowledge on the clinical, radiological and pathological characteristics of IPMN has significantly improved. A large number of confusing terms have been used in the past two decades to describe IPMN and the most common was "mucinous ductal ectasia". Subsequently, the nomenclature of these neoplasms has been clarified and the term IPMN, proposed by the World Health Organization (WHO) is nowadays widely accepted. The WHO defined IPMN as intraductal papillary mucinous neoplasm with tall, columnar, mucin-containing epithelium, with or without papillary projections, involving the main pancreatic duct and/or the branch ducts.

Epidemiology

In the last ten years the number of diagnosis of IPMN has significantly improved. This is probably due to two reasons: first, a significant increase of the incidentally discovered "cystic lesions" of the pancreas; second, the unification of this tumor under the heading of IPMN and the widely acceptance by clinicians of this new terminology. In fact it is clear that IPMN were present even before 1982 but they were misclassified as mucinous cystic neoplasms or mucinous ductal cancers.

IPMN occurs more frequently in the seventh and eighth decades of life, even if it not uncommon in the fifth and sixth decades. Once believed to be a neoplasm with a higher incidence in men, large series have showed that the male-female ratio is about 1:1.

Recently several Authors have reported an higher incidence of extrapancreatic neoplasms, and above all of colorectal cancers, among patients affected by IPMNs. Some Authors have included IPMNs within those neoplasms that may develop in patients affected by PAF.

Pathology and Molecular Biology

In 2000 the World Health Organization (WHO) classified IPMN in two different entities: main duct IPMN and branch duct IPMN. Main duct IPMNs are characterized by involvement of the main pancreatic duct with or without associated involvement of the branch ducts too (combined IPMNs)[23]. Main duct IPMN usually presents as a dilated (≥1 cm) main pancreatic duct full of mucus that may extrude through a bulging ampulla, even if it can more simply look as a "cyst" along the main pancreatic duct[26].

Branch duct IPMN involves the side branches of the pancreatic ductal system, appearing as a cystic lesion communicating with a non dilated main pancreatic duct. The communication might be macroscopically demonstrable or not and this is usually related to the amount of mucous produced.

Main duct IPMNs are usually located in the proximal portion of the gland (75%) but they can spread to the rest of the main pancreatic duct; branch duct IPMNs more commonly involve the uncinate process, but they can be seen in the head, neck and distal pancreas. Multifocal involvement of the gland with two or more branch duct IPMNs is not an uncommon finding[24]. In recent years the diagnosis of multifocal IPMNs at our Institution has dramatically increased. Metachronous IPMN may reflect either multifocality or a "field defect", predisposing the entire ductal epithelium to the development of IPMN[26-30].

Histologically IPMNs may be divided in benign (adenoma and borderline) and malignant (*in situ* carcinoma and invasive carcinoma). Only IPMNs with invasive carcinoma can metastasize.

Recentely, Tanaka et al.[23] found that main duct and branch duct IPMN were associated with malignancy in 70% and 25% of the cases, respectively while the rate of invasive carcinoma was 43% for main duct IPMN and 15% for branch duct type. Thus, these two neoplasms seem to have a significant different biological behavior and this can affect the decision-making

of the clinicians with regard to the appropriate management of these two "entities". Likewise with the Massachusetts General Hospital, of the 140 our resected patients affected by main duct IPMNs, 12% had adenoma, 28% borderline, 12% carcinoma *in situ* and 42% had invasive carcinoma. Similar data have been reported by other Authors[29].

It is not uncommon to recognize within the same surgical specimen different degree of dysplasia; the average age of our patients with malignant main duct IPMN was 6.4 years older than that of patients with adenoma or borderline tumor[29]; these observations support the theory of a "clonal progression" to malignancy in this variant[31].

Considering the molecular biology of these neoplasms, mutations in the K-ras, p16 and p53 genes are present but are less common in IPMNs than in ductal carcinoma, and DPC4 loss is usually not detected. Wada et al.[31] showed in 23 cases of resected IPMNs that 65% had K-ras mutation. Moreover they showed that the loss of heterozygosity (LOH) in 9p21 (p16) increased from 12.5% in adenomas to 75% for carcinomas while LOH in 17p13 (p53) was present only in invasive carcinomas. These results suggest that LOH in 9p21 (p16) was an "early" event while LOH in 17p13 (p53) is a later event, supporting the theory of "clonal progression"[31,32].

MUC proteins are a heterogeneous family of glycoproteins, some of which are located within the cell membrane and others excreted as secretory products. MUC expression profiles of IPMNs have not been clearly characterized yet. However, MUC1 expression has been found to be associated with pancreatobiliary type papillae and tubular carcinomas whereas MUC2 expression has been associated with intestinal type and colloid carcinoma, which has a more indolent course[32].

Clinical Presentation

There are no signs or symptoms pathognomonic for IPMNs. Patients affected by main duct IPMN are often symptomatic, and complain of abdominal pain, pancreatitis, steathorrea, and not rarely, jaundice, diabetes and weight loss[23,27-30]. Even though patients affected by branch duct IPMN can present with abdominal pain, pancreatitis or other symptoms, a large proportions of them is completely asymptomatic and neoplasms are incidentally detected during radiological work-up performed for other reasons[33-37]. This latter is a challenging situation.

It is remarkable that unlike pancreatic adenocarcinoma, jaundice is an uncommon presentation and occours only in about 15-20% of patients. Jaundice and steatorrhea at presentation should alert the physician to a much higher prevalence of malignant IPMN (8- and 5- fold, respectively). A recent onset or worsening diabetes is more common in IPMNs with invasive carcinoma (3-fold). Interestingly, patients with benign IPMNs had a higher frequency of abdominal pain and a longer duration of symptoms[29,37].

Diagnostic Work-Up

The diagnosis of IPMN was traditionally made after an ERCP, which showed the "triad" of Ohashi: a bulging ampulla of Vater, mucin secretion, and dilated main pancreatic duct[25].

Currently the great majority of IPMNs are characterized with cross-sectional imaging study such as computed tomography (CT) or magnetic resonance cholangiopancreatography (MRCP). The typical feature of IPMNs is cystic dilatation of the main pancreatic duct and/or of the branch ducts; nodules and papillary projections, which are significantly associated with the presence of a malignant neoplasms, usually appear as filling defects within the cystic lesions. CT and MRCP can localize the tumor and assess its relationship with vessels and other organs. MRCP is particularly useful in the characterization of single or multifocal branch duct IPMN, given its ability to demonstrate a communication between the main duct and the cyst[38].

In the initial workup of patients with suspected IPMN we use also contrast-enhanced ultrasounds (US), which able to identify and characterize the "cysts" as well.

In those cases in which the diagnosis is uncertain endoscopic ultrasound (EUS) may be helpul. EUS can well study the main pancreatic duct, the presence of nodules or small projections in the main duct and/or in the cyst communicating with it. Moreover, EUS guided fine needle aspirate (FNA) may be done. FNA can be obtained even through US, which is less invasive. Cytologic examination and detection of K-ras mutation in the pancreatic juice can indicate the presence of a malignant IPMN, even though this procedure has a low sensitivity (less than 20%). Others showed that the CEA level in pancreatic juice can be very useful to differentiate benign from malignant IPMNs. However, we consider EUS with or without FNA as a "second level" procedure which should be done only in selected cases[32].

Three are the goals of diagnostic workup:

1. Make a correct diagnosis of IPMN and differentiate it from other cystic neoplasms such as serous cystadenoma or mucinous cystic neoplasms or by other cystic lesions of the pancreas (pseudocyst, true pancreatic cyst).
2. Make a differential diagnosis between main duct and branch duct IPMN.
3. Identify those parameters which are associated with an high risk of malignancy.

Currently the following parameters have been proven to be associated with malignancy in IPMNs:

– presence of symptoms, particularly of jaundice, steatorrhea and new onset or worsening diabetes;
– a bigger diameter of the cystic lesion (>30 mm);
– presence of nodules, thick walls, papillary projections;
– presence of dilated main pancreatic duct (>10 mm);
– an elevated CEA levels (>120 ng/ml) in the pancreatic juice.

Nonoperative Management

As suggested by the guidelines for the management of the IPMN proposed by the International Association of Pancreatology, all suspected main duct and combined IPMNs should be resected, even in asymptomatic patients, since the risk of malignancy is high among these patients and there is no way to surely distinguish between benign and malignant IPMN preoperatively[23].

Branch duct IPMN are associated with malignancy in about 25% of cases and patients with malignant branch duct IPMN are more likely symptomatic, have a bigger lesion (>3 cm) and have mural nodules[23,33-37]. Surgery is recommended in these cases, while asymptomatic patients with small (<30 mm) branch duct IPMN without nodules can be managed with careful observation[23]. It is important that this non-operative approach is carried out in experienced centers and data from large series is needed to validate this approach[23].

We have carried out a prospective study for the non-operative management of asymptomatic patients affected by a suspected branch duct IPMN (evidence of a cystic lesion clearly communicating with a normal main pancreatic duct at MRCP) with a diameter less than 3.5 cm and without nodules, papillae, and with normal tumoral markers[36]. In this study ERCP and EUS were not routinely employed but we have used these procedures only in those cases with an unclear diagnosis. The follow-up was carried out with contrast enhanced US and with MRCP every 6 months for the first two years and yearly thereafter. Between 2000 and 2003, 109 patients were observed. Twenty patients (18.3%) underwent immediately surgery because of the presence of symptoms and/or parameters associated with malignancy; pathological diagnosis of branch duct IPMN was always confirmed and only two patients had an invasive carcinoma (10%), while on (5%) a carcinoma *in situ*. Eighty-nine patients (81.7%) were followed up for a median of 32 months; of these, 57 (64%) had multifocal disease. After a mean follow-up of 18.2 months, 5 patients (5.6%) showed an increase in size of the lesion and underwent surgery. The pathological diagnosis was branch-duct adenoma in three patients and borderline in two.

This study suggests that in very well selected cases, a non-operative approach is safe and feasible and that the biological behavior of branch duct IPMNs is different if compared to main duct ones.

Surgical Management

Main Duct IPMNs

The surgical management of main duct IPMNs represents a challenge for the surgeon. While in other pancreatic tumors the preoperative studies can accurately locate the tumor and accordingly plan a pancreatic resection, this is not always the case in main duct IPMN. In fact preoperative studies can show only a segmental dilatation of the main pancreatic duct with or without cysts. Dilatation may occur both proximally and distal to the tumor because of overproduction of mucus, making more problematic the localization of the neoplasia. Finally, main duct IPMN can spread long the duct involving the whole duct[32].

A typical resection (pancreaticoduodenectomy, left pancreatectomy, total pancreatectomy, according to the site and estension of the disease) with lymph node dissection must be performed. Limited resections, such as middle pancreatectomy, have been proposed for main duct IPMN, but we had a high rate of positive resection margins and recurrences when this procedure was performed for main duct IPMN. Similar results have

been reported by other Authors[23,39,40]. For these reasons we believe that standard resections should be performed in this setting.

The intraoperative examination of the transaction margin is of paramount importance in the management of patients affected by main duct IPMN[23,28-30,41-43]. Since IPMN may extend along the main pancreatic duct, it is important to assess the presence of tumor at the margin. Different results can be obtained by analyzing the surgical margin: "negative" with normal epithelium in the main duct, "de-epithelialized" with denuded epithelium or "positive" for adenoma, or borderline or carcinoma. De-epithelialization should not be considered as a negative margin since local recurrence can occur[27]. The presence of high-grade dysplasia or carcinoma requires an extension of the surgical resection up to total pancreatectomy. In case of de-epithelialization, adenoma or borderline tumor at surgical margin the optimal surgical strategy remains controversial[23]: we usually extend the resection a few centimeters to obtain a new margin, trying to obtain a negative resection margin. In our caseload of 140 patients affected by main duct IPMN who underwent surgical resection, the rate of negative margins in the surgical specimen was 58.5%, and the results of the intraoperative frozen section analysis modified the surgical plan, leading to an extension of the resection or to total pancreatectomy in 29 patients (20.7%)[29].

Recurrence in the pancreatic remnant may develop even if the transection margin is negative and even in patients with noninvasive disease[28,30]. Recurrence in the pancreatic remnant after resecting a main duct IPMN can be related to three different reasons:

1. The presence of a "positive" resection margin;
2. Main duct IPMN can be multicentric with synchronous "skip" lesions along the main duct, still present at the time of surgery;
3. Given that IPMN may be a marker of a "field defect" associated with a propensity for tumor development, metachronous lesions may occur years later in the remnant.

For all these reasons the role of total pancreatectomy in IPMN shall be carefully evaluated and individualized. Some Authors have reported that for malignant IPMN the frequency of recurrence (local recurrence or distant metastases) is similar whether or not total pancreatectomy was performed[23,32]; Chari et al.[30] reported a recurrence rate of 62% after total pancreatectomy and of 67% after partial pancreatectomy. The risks and long-term complications of total pancreatectomy must be considered and discussed with patients. Finally, in patients with main duct IPMN undergoing pylorus-preserving pancreaticoduodenectomy, pancreaticogastrostomy can be preferred instead of pancreaticojejunostomy. Pancreaticogastrostomy permits direct access by endoscopy to the pancreatic stump during follow-up, by allowing direct opacification of the main pancreatic duct and sampling of pancreatic juice for cytological examination[41,44].

Branch Duct IPMNs

A typical resection should be performed for branch duct IPMNs. For asymptomatic patients with small single lesion (<3 cm) of the neck of the pancreas, without any suspicion for malignancy, a middle pancreatectomy can be considered[23,36,37].

In the case of multifocal disease, a total pancreatectomy or an extended standard resection would be necessary to assure a radical treatment. However a more selective approach can be considered, with resection of the segment of the gland with the biggest lesion (or with the lesion "suspected" for malignancy) and non-operatively management with strict follow-up of the remnant.

Even in multifocal branch duct IPMNs surgery must be performed in symptomatic patients and in those cases with radiological findings related to the presence of a malignant tumor. We usually do not perform an intraoperative frozen section for branch duct IPMN. This might be done in the case of a malignant tumor, when an incomplete resection or an involvement of the main pancreatic duct are suspected. At final histopathological examination it is always important to rule out an extension of the IPMN from the branch duct system to the main pancreatic duct, since the biological behaviour of "combined" main duct-branch duct IPMN seems to be the same of main duct IPMN[37].

Follow-Up and Re-Resection

After resection, strict follow-up should be done. Patients affected by malignant IPMN are certainly at higher risk of recurrence, but neoplastic recurrence can develop even in the presence of a benign tumor with negative resection margins, particularly for main duct IPMN. It is important to detect a "recurrence" or the development of a new disease in the remnant since an-

other resection shall be considered[23,27,28]. In our experience with 140 resected patients affected by main duct IPMN, eight (7%) developed a recurrence in the remnant[29]. Of these, seven had invasive carcinoma at initial histology while the remaining had an adenoma with negative resection margin; this patient underwent a completion pancreatectomy for a carcinoma in situ.

We perform a clinical-laboratory-radiological evaluation every 6 months in cases with malignant tumors and yearly for benign IPMNs. Radiological follow-up can include US, CT or MRCP.

With regard to multifocal branch duct IPMN who underwent partial pancreatectomy, strict follow-up should be performed to evaluate the remaining lesion or lesions in the remnant and possible development of new ones. MRCP is particularly useful in this setting[38].

Prognosis

The survival of patients with IPMN, even when malignant and invasive can be quite good. In our recent caseload with follow-up of 137 resected patients, 5- and 10-year disease specific survival for 80 patients with adenoma, borderline and in situ carcinoma was 100% while for 57 patients with invasive carcinoma they were 60% and 50%, respectively[29]. In other large series the 5-year disease-specific survival for IPMN with invasive carcinoma ranged from 36% to 43%[28,30,45,46].

The rate of lymph node metastases in patients affected by manignant IPMN ranges from 16% to 46%[27-30,45,47]. In 41% of 58 patients with invasive main duct IPMN had nodal metastases and had a 5-year survival rate of 45%, which was not significantly different compared to that of patients with invasive carcinoma and negative nodes[29]. These observations suggest that adenocarcinoma arising in a IPMN is probably a different disease than ductal adenocarcinoma, in which long-term survival in patients with positive nodes is a rare event.

Overall, the long-term survival for IPMN is very good in non-invasive tumors; however, even the prognosis of IPMN with invasive cancer is much better thn that reported for ductal adenocarcinoma.

Solid Pseudopapillary Tumours (SPTs)

Epidemiology

The SPTs of the pancreas are the less common lesions among the cystic tumours.

They were reported the first time in 1959 by Frantz[48].Then this tumour has been described with different names: solid tumor, cystic-solid, papillary-epithelial and cystic papillary.

Only in recent years, this tumour has been considered in the World Health Organization classification as a lesion of indefinite origin.

Although, in the last few years, the number of patients is increased the histopathology and biological behaviour of these tumours is still unknown. However, some cases of malignancy among SPTs have been reported. From the epidemiological point of view, most of the patients are young female between 30 to 40 years old.

Clinical Findings

Abdominal pain is the predominant and, sometimes, the only symptom present.

Sometimes the pain could be associated to palpable abdominal mass, anorexia and weight loss or these signs could appear as only one.

The appearance of abdominal mass is not a symptom. Patients complained weight sensation and abdominal discomfort and only on the examination a mass could be appreciate, especially, in the left upper quadrant.

The aspecific clinical features and the young mean age at the time of presentation could be the reason of the tendency to underestimate this tumour by patients and physicians.

It could be useful divide the patients from the anatomical location of the lesion.

Laboratory Findings

The laboratory data are not significant in these tumours because they do not have a specific tumour marker.

Cromogranine A, which has higher sensibility for endocrine tumours (68%), could be useful in the differential diagnosis between non functioning endocrine tumours and the SPTs[49] even if in the literature was reported a positive result without an endocrine tumour in 19% of cases[50].

In our practice the Cromogranine A test was always negative in SPTs.

Radiological Findings

The tumor appears as a well vascularised and encapsulated mass with definite margins[51].

Calcifications and septa inside the mass could be identified, but they are not pathognomonic.

The distinctive finding of these tumors is the alternation of solid and cystic areas, in which could be present a necrotic haemorrhagic component.

These findings could be see in the same lesion although the relationship between the two component could be changeable. The lesions were reported as a cystic lesions even though the finding of rich vascularization could lead to a misdiagnosis of neuroendocrine tumor.

Treatment

Surgical treatment must be considered in all the patients affected by SPTs, in consideration of their still unknown biological behaviour and their potential malignancy.

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