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آموزش مهارت‌های کاربردی
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Focus on the intraductal papillary mucinous neoplasm of the pancreas

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ABSTRACT
Intraductal papillary mucinous neoplasms (IPMNs) are rare pancreatic tumours, accounting for less of 1-2% of all neoplasms of the gland. Main characteristics of IPMNs are their favourable prognosis as these pre-malignant or frankly malignant lesions are usually slow-growing tumours and radical surgery is frequently possible. According with the localization of the lesions, three different entities are identified: the main-duct IPMN (type I), the branch-duct IPMN (type II) and the mixed type (type III, involving both the main pancreatic duct and side branches). IMPNs do not present pathognomonic signs or symptoms. Obstruction of the main pancreatic duct system may cause abdominal pain and acute pancreatitis (single or recurrent episodes). The tumour may be incidentally discovered in asymptomatic patients, particularly in those with branch-duct IPMNs. In clinical practice, any non-inflammatory cystic lesion of the pancreas should be considered as possible IPMN. Computed tomography, magnetic resonance imaging with cholangiopancreatography and endoscopic ultrasonography can localize IPMN and assess its morphology and size. The choice between non-operative and surgical management strictly depends from the risk of malignancy and of the definitively distinction between benign and malignant IPMNs. Main-duct IPMNs are at higher risk of malignant degeneration, especially in older patients; as a consequence no doubt does not exist as concerns the need of surgery for IPMN type I and III. A less aggressive surgical approach as well as the possibility of conservative management have been suggested for asymptomatic, small size (< 3-3.5 cm), branch-duct IPMN.

Keywords: Pancreatic neoplasm, Mucinous pancreatic tumour, Pancreatic cyst, Diagnosis, Treatment.

Introduction
The World Health Organization first classified in 1996 (1) cystic mucin-producing pancreatic lesions into intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms. Among the uncommon exocrine tumours of the pancreas (1-2% of all neoplasms of the gland), IPMNs have received increasing attention in recent years because of their favourable prognosis, obscure nature and their relationship with pancreatic adenocarcinoma (2). In addition, over the last ten years the number of diagnosed IPMNs has significantly improved and this entity is more commonly recognized even in asymptomatic patients as an incidental finding. Nowadays IMPN represents the 10-30% of all resectable pancreatic tumours in high-volume referral surgical Centres (3). Physicians should familiarize with IPMNs as it is possible that affected patients are admitted because of not-
specific general complaints and of an incidentally discovered “cystic lesion” of the pancreas.

This article presents an overview on the pathologic/clinical features and diagnostic/therapeutic problems of IMPNs together with a personal series of eight patients.

Pathology

IPMNs of the pancreas are characterized by intraductal proliferation of neoplastic mucinous cells, which usually form papillae, and cystic dilation of the pancreatic ducts, thus forming a clinically and macroscopically detectable mass (4). IPMN is a grossly visible (≥1 cm), mucin-producing neoplasm that arises in the main pancreatic duct and/or its branches. Two different entities were initially identified: the “main-duct” IPMN and the “branch-duct” IPMN (1, 2). Main-duct IPMNs may be associated with contemporary involvement of the side branch ducts; as a consequence, a third anatomo-clinical subtype of IMPN, named “mixed” type, has been identified (5). Macroscopically, the main-duct IPMN usually presents a dilated, full of mucin main pancreatic duct or as a cystic-like lesion along the main pancreatic duct (6). The usual location is in the proximal portion of the pancreas even if the tumour can spread to the entire main pancreatic duct. Sometimes the mucus may extrude through a bulging ampulla and it is clearly identified at duodenoscopy (Figure 1). Branch-duct IPMN more frequently involves the side branches of the uncinate process, but it can also be observed into the remaining portions of the gland with a possibility of multifocal involvement of two or more distant side branches. Branch-duct IMPNs appear as a cystic lesion communicating with a non-dilated main pancreatic duct.

According with the “Morphology Code of the International Classification of Diseases for Oncology (ICD-O) and the Systematic Nomenclature of Medicine” (http://snomed.org) there are different pathologic forms:

a) Intraductal papillary-mucinous adenoma (845/0)
b) Intraductal papillary-mucinous neoplasm with moderate dysplasia (845/1)
c) Intraductal papillary-mucinous carcinoma (845/3) with two subtypes: non-invasive (845/2) and - invasive (845/3)

Figure 1. Duodenoscopy: characteristic mucin extrusion through the ampulla of Vater

Behaviour is coded as follows: 0 for benign tumours; 1 for unspecified, borderline or uncertain behaviour; 2 for in situ carcinoma; 3 for malignant tumours. To simplify, IPMNs may be divided into benign (adenoma and borderline) and malignant (in-situ carcinoma and invasive carcinoma) (7, 8). The latter type (invasive carcinoma) accounts for more than 40% of the resected specimens and its rate was 43% for main-duct IPMN and 15% for branch-duct type (6). Recently, an International Consensus Guidelines on IPMNs (5) stated that main-duct type and branch-duct type are associated with malignancy in 70% and 25% of the cases, respectively. So, side branches IPMNs have a low risk for malignant transformation. Histologic sub-classification based upon the morphology of proliferative nodules and papillae identifies five types of IPMNs: gastric foveolar
type, intestinal type, pancreatobiliary type, intraductal oncocytic papillary neoplasm, and intraductal tubulopapillary neoplasm (9, 10). On the other hand, it is not uncommon to discover different histologic types with different grades of dysplasia within the same surgical specimen (7).

**Molecular Biology**

Over the last ten years many studies showed several genetic alterations in ductal pancreatic adenocarcinoma (11). Less frequently, some of these alterations have been described in IPMNs also. Mutational activation of the oncogene K-ras was observed in 15 out of 23 (65%) of resected IPMNs while the loss of heterozygosity in p16 oncosuppressor gene was found in 12.5% of adenoma and 75% of carcinoma IPMNs respectively (12). Similar results were observed by Yang and co-workers (13) as concerns K-ras mutations studied in 41 patients (resected specimens) and detected in 20.8% of benign IPMNs, and in 61.5% of malignant IPMNs. Another study (14) showed K-ras and p53 mutations present in 71% and 6% of 52 operated IPMNs, respectively. In vivo studies show a little bit different results. Mizuno and co-workers (15) evaluated K-ras mutations in pure pancreatic juice in a group of 53 IPMNs and observed mutations in 80% of the carcinoma group and 71% of the adenoma group.

IPMN-cells secrete a thick mucin that causes dilatation of the pancreatic ducts. Recent studies pointed out different expression of various mucins in IPMNs with different degree of malignancy. Mucin-1, mucin-4 and mucin-5AC were more frequently associated with invasive carcinoma and mucin-2 was found only in the intestinal type and more frequently in adenomas or borderline IPMNs (16-19). Recently, it has been reported that molecular biology analysis of mucin products may be investigated not only in surgical specimens but also in vivo by means of endoscopic ultrasonound-guided fine-needle aspiration (20). This appears of utmost importance as it renders now feasible a “molecular” prognosis before to plan the timing and strategy of surgical treatment (limited pancreatectomy, extended resection, lymphoadenectomy and so on).

**Clinical features**

IPMNs do not present pathognomonic signs or symptoms. Obstruction of the main pancreatic duct system may cause abdominal pain, pancreatitis, steathorrea, jaundice, diabetes and weight loss (2, 3, 5, 7). The last three symptoms have been described more frequently in patients with malignant IPMNs (3, 21). In this setting (invasive main-duct IPMNs), asymptomatic patients account for the 13.5% (22). Patients affected by branch-duct IPMN are often completely asymptomatic and the lesion is incidentally discovered at ultrasound or at other radiologic examinations performed for various reasons (23, 24). A recent report on a large series of branch-duct IPMNs (24) showed that the neoplasm is incidentally discovered in 40% of the patients and that jaundice is more frequent in patients with invasive tumours (12.5% vs 1.8% in benign lesions) whereas abdominal pain is predominant in patients with benign tumours (45% vs 25% in malignancy).

In clinical practice, it is not uncommon to observe patients with a “cystic lesion” of the pancreas with not specific symptoms. First of all, it is necessary to exclude pseudocysts (lesions not presenting lining of their wall) such as those related with acute and chronic pancreatitis, paraduodenal wall cyst and infection-related pseudocysts. Afterwards, differential diagnosis of “true” cysts of the pancreas (lined by epithelium, acinar cells and other cells) includes several pathologic entities (Table 1).

**Imaging**

Diagnostic procedures of IPMN include endoscopic retrograde cholangiopancreatography
Intraductal mucinous pancreatic tumor

**Table 1.** Types of “true” (non-inflammatory) cystic lesions of the pancreas; these cysts may be lined by epithelium, acinar cells or other cells

**a) Cysts with mucinous epithelium**
- Intraductal papillary mucinous neoplasms with its variants
- Mucinous cystic neoplasms
- Mucinous non-neoplastic cysts (mucoceles and retention cysts)
- Serous (clear-cell) cystic tumors
- Serous cystadenoma and cystadenocarcinomas
- Von Hippel Lindau-associated pancreatic cysts
- Squamous-lined cysts
- Lymphoepithelial cysts
- Epidermoid and dermoid cysts
- Squamous cyst of pancreatic ducts

**b) Cysts lined by acinar cells**
- Acinar cell cystadenoma and cystadenocarcinomas
- Endothelial-lined cysts
- Lymphangiomas
- Degenerative or necrotic changes in solid tumours
- Solid-pseudopapillary tumor
- Cystic change in ordinary ductal adenocarcinoma
- Cystic pancreatic endocrine neoplasia (islet cell tumours)
- Cystic change in other invasive carcinomas and cystic mesenchymal tumours

**c) Other rare cystic lesions**
- Cystic hamartomas
- Enterogenous (congenital; duplication) cysts and duodenal diverticula
- Endometriotic cyst
- Secondary tumours
- Congenital or developmental cysts
- Unclassified cysts

**Table 2.** Main clinical characteristics of patients; AP: acute pancreatitis

| Patients | age | gender | IPMN type | related symptoms | comorbidity | treatment | Follow up |
|----------|-----|--------|-----------|-----------------|-------------|-----------|----------|
| 1        | 79  | M      | main-duct | AP (single episode) | pulmonary disease | conservative | died 6 yrs later |
| 2        | 63  | F      | main-duct | AP (single episode) | diabetes | surgery | alive at 2,4 yrs |
| 3        | 72  | F      | mixed     | recurrent AP      | coronary disease | surgery | alive at 3,1 yrs |
| 4        | 59  | F      | main-duct | abdominal pain    | diabetes | surgery | alive at 3,7 yrs |
| 5        | 63  | F      | main-duct | recurrent AP      | no | surgery | alive at 2,7 yrs |
| 6        | 62  | F      | branch-duct| AP (single episode) | liver cirrhosis (transplanted) | conservative | died 2,6 yrs later |
| 7        | 60  | M      | main-duct | no symptoms       | peptic ulcer | surgery | alive at 3,5 yrs |
| 8        | 54  | M      | branch-duct| no symptoms       | no | conservative | alive at 2,4 yrs |

(ERCP), computed tomography (CT), magnetic resonance imaging (MRI) with cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS). In the recent past, ERCP represented the gold standard at least for the main-duct neoplasms. Detection of bulging ampulla of Vater, mucin secretion, and dilated main pancreatic duct allowed physicians to a direct diagnosis. Relative invasiveness and a poor visualization of the entire main pancreatic duct
and side branches relegated nowadays this procedure as optional examination. Currently, in fact, the vast majority of IPMNs are characterized by means of cross-sectional imaging studies (9, 23, 25, 26). CT and MRI/MRCP can localize the tumour and assess its morphology and size (Figures 2, 3, 4, 5).

Figure 2. Contrast-enhanced CT scan; main-duct IPMN: presence of multiple cystic lesions at the head of the pancreas (main-duct IPMN)

Figure 3. Magnetic Resonance Cholangio-Pancreatography; IPMN of the distal main pancreatic duct (tail of the pancreas)

The characteristic feature of IPMNs is cystic dilation of the main pancreatic duct and/or of the side branch ducts. Filling defects representing nodules and papillary projections may be demonstrated within the cystic lesions (Figure 6). In addition, CT and MRI with contrast enhancement usually well assess the relationship of IPMN with local vessels and adjacent organs. MRCP is particularly useful in the characterization of single or multifocal branch-duct neoplasms. This procedure is able to check a communication between the main pancreatic duct and the cystic lesions. Quality of MRCP images is improved by the use of secretin stimulation. EUS may be very useful in patients who remain without definite diagnosis after CT/MRCP.

Figure 4. Magnetic Resonance: axial and cholangio-pancreatographic sequences in main-duct IPMN of the pancreatic head

EUS can assess the main pancreatic duct and the presence of nodules and papillae in the main duct with possible limits only in patients with previous gastrointestinal surgery (Figure 7). In addition, EUS may be completed with fine-needle aspiration and possible cytologic and molecular/biochemical exams on the mucin/solid tissue samples (5, 20).

Figure 5. Magnetic Resonance: axial and cholangio-pancreatographic sequences in mixed-type IPMN of the
pancreatic head (multiple side branches lesions and involvement of the main pancreatic duct at the tail level)

International consensus guidelines (5) suggested that EUS should be considered a second-level procedure, which should be performed only in selected cases. On the other hand, there is no doubt that over the last few years EUS with fine-needle aspiration is more and more often utilized as valuable complementary pre-operative procedure also in patients with already established diagnosis. In recent years, contrast-enhanced abdominal ultrasound, intraductal pancreatic endoscopy and intraductal endosonography have been introduced for diagnostic purpose but the experience with these procedures is still limited and further studies are needed (27).

Figure 6. Magnetic Resonance Cholangiopancreatography with secretin stimulation (1 IU/Kg/body weight); branch-duct IPMN (uncinate process): presence of filling defects within the cystic lesion representing nodules and papillary projections

Treatment

The choice between non-operative and surgical management strictly depends from the risk of malignancy and of the definitively distinction between benign and malignant IPMNs. Despite the fact that our understanding of their natural history is still incomplete, recent data indicate that main-duct and branch-duct IPMNs show significant differences in terms of biological behaviour with main-duct IPMNs at higher risk of malignant degeneration. The frequency of malignancy (in situ and invasive) in main-duct IPMNs ranges between 60 and 92%, with a mean of 70%, and approximately two-thirds of these malignant neoplasms have been invasive (5).

Figure 7. Endoscopic ultrasonography; IPMN of the main pancreatic duct at the head of the gland presenting as multiple anechoic lesions

Malignancy is more common in older patients, in symptomatic patients (mainly those presenting with jaundice and/or worsening of diabetes), in neoplasms with higher dilation of the main pancreatic duct, presence of mural nodules and eggshell calcifications (7, 19, 21). Evidence of clonal progression’ in these neoplasms (12) and the age difference between patients with malignant and benign lesions (10) are indicative that most if not all benign main-duct IPMNs may progress into invasive cancer. Furthermore, the long-term follow-up of resected patients shows excellent survival for benign and non-invasive neoplasms and 5-year survival between 36 and 60% for invasive carcinomas (7, 28, 29). Based upon these considerations, no doubt does exist as concerns the management of main-duct neoplasms while branch-duct tumours still present areas of
uncertainty. International guidelines stated that all suspected type-1 (main-duct) and type-3 (mixed-type) IPMNs should be resected, even in asymptomatic patients (5). Various surgical procedures such as pancreaticoduodenectomy, left pancreatectomy or total pancreatectomy (according to the site and extent of the neoplasm) with lymph node dissection must be performed (3, 6, 7, 22, 30). Intraoperative frozen section assessment of the pancreatic resection margin can guide the extent of resection, keeping in mind that IPMNs are often multifocal. For these reasons, oncological radicality is of paramount importance and limited resections and/or laparoscopic approach are few indicated in this setting (22, 29, 30). Branch-duct IPMNs have a less harmful biological behaviour with a frequency of malignancy ranging from 6% to 46%, (mean 25%) and of invasive cancer from 0% to 31% (mean 15%) (5,19). This suggested a less aggressive surgical approach as well as the possibility of conservative management associated with a careful follow up (24). On this concern, some malignancy-related parameters have been proposed: presence of symptoms (in particular recent-onset or worsened diabetes), size of the lesion >3.5 cm, presence of nodules or thick walls, carbohydrate antigen 19.9 serum level > 25 U/l. In a recent prospective study (31) in which these parameters were utilized, surgery was indicated in 18.3% of 109 patients with branch-duct IPMNs; in the remaining group of patients (89 cases, 81.7%), only 5 patients (5.6%), after a mean follow up of 18.2 months, showed an increase in lesion size and underwent surgery. Similar results were observed in another recent study involving 194 patients from South Korea (32): 34 patients (17.5%) were immediately operated on and 18 (11.8%) underwent surgical resection after a median follow up of 12.7 months. After surgery of non-invasive IPMNs (branch- and main-duct varieties), recurrence is rare (< 6%) while recurrence occurs in 50-65% of patients resected for invasive IPMNs (21, 23). The International Association of Pancreatology guidelines (5) for the management of pancreatic IPMNs suggested for branch-duct neoplasms a yearly follow-up if lesion is <10 mm in size, 6–12 monthly follow-up for lesions between 10 and 20 mm, and 3–6 monthly follow-up for lesions >20 mm. Suggested diagnostic procedures for lesions up to 10 mm in size are CT/MRCP while for lesions > 10 mm EUS with fine-needle aspiration cytology is added into the protocol. Another point to be considered is that branch-duct IPMNs are frequently multifocal and, as a consequence, when surgery is planned, total pancreatectomy or subtotal extensive pancreatectomy is required to perform radical surgery. Therefore, it remains questionable whether these high-risk surgical procedures with secondary definite exocrine and endocrine insufficiency are appropriate in elderly and asymptomatic patients suffering by pancreatic tumour with, at least, uncertain biological behaviour (33).

Personal series

Our series include eight patients observed over the last ten years. Main clinical characteristics are showed in Table 2. Mean age is 64 years (range 54-79). Clinical presentation was related to acute pancreatitis in five patients: three with single episode and two with recurrent attacks; one additional patient was observed because of not-specific abdominal dull pain. Only two patients (one with main-duct and one with branch-duct IPMN) were asymptomatic. Complete laboratory work up including serum tumour markers was performed in all cases. The first two patients of this series underwent ERCP. All patients were studied by means of abdominal ultrasonography, contrast-enhanced CT scan and MRCP (five of them with secretin stimulation). Three patients were also studied with EUS and fine-needle aspiration. Five-years and global mortality are 12.5% and 25%, respectively. Both patients who
died during the follow up refused surgery. For another asymptomatic patient with an incidentally discovered branch-duct IPMN (2 cm at the tail of the gland) surgical resection was not indicated; the size of this lesion remains stable during the follow up (last MRCP performed after two years from the diagnosis). So, surgical resection was performed in 5 out of 8 patients (62.5%). Post-operative course was complicated by pleural effusion and pneumonitis in one patient, by pancreatic fistula in two patients (recovery in two and three months, respectively). No recurrence is still registered in the six patients actually followed up.

Conclusions

IPMN should be considered in any non-inflammatory cystic lesion of the pancreas and in patients suffering from a single or recurrent episode of acute pancreatitis without a definite etiological factor. Physicians should familiarize with IPMNs as these pre-malignant or frankly malignant lesions are usually slow-growing tumours. As a consequence, curative resection is possible in the majority of cases, both in the more aggressive type (main-duct IPMN) and in the more favourable tumours (branch-duct type). Because of malignancy is more common in older patients, chances of complete resection often depend on the comorbidity and on anesthesiological class-risk more than local invasiveness.

References

1. Kloppel G, Solcia E, Longnecker DS, Capella C, Sobin LH. Histological typing of tumours of the exocrine pancreas. In: World Health Organization. International Histological Classification of Tumors, 2nd ed. Berlin: Springer, 1996: 11-20
2. Hruban RH, Takaori K, Klimstra DS, Adsay NV, Albores-Saavedra J, Biankin AV, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. Am J Surg Pathol 2004; 28: 977-87
3. Crippa S, Salvia R, Partelli S, Armatura G, Bassi C. Intraductal papillary mucinous neoplasms of the pancreas.

In “Surgery of Pancreatic Tumors”, Shrikhande SV, Friess H and Buchler MW (Eds), New Delhi: BI Publications, 2008, 289-98
4. Yamaguchi H, Inoue T, Eguchi T, Miyasaka Y, Ohuchida K, Mizumoto K, et al. Fascin overexpression in intraductal papillary mucinous neoplasms (adenomas, borderline neoplasms, and carcinomas) of the pancreas, correlated with increased histological grade. Modern Pathology 2007; 20: 552–561
5. Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Panreatology 2006; 6: 17-32
6. Shi C, Hruban RH. Intraductal papillary mucinous neoplasm. Hum Pathol 2012; 43: 1-16
7. Salvia R, Fernandez-del Castillo C, Bassi C, Thayer SP, Falconi M, Mantovani W, et al. Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. Ann Surg 2004; 239: 678-85
8. Weitz J, Buchler MW. Branch intraductal papillary mucinous neoplasms: just the tip of the iceberg. Gut 2008; 57: 1490-91
9. Katabi N, Klinstra DS. Intraductal papillary mucinous neoplasms of the pancreas: clinical, pathological features and diagnostic approach. J Clin Pathol 2008; 61: 1303-13
10. Adsay NV. Cystic lesions of the pancreas. Mod Pathol 2007; 20: S71–S93
11. Vitone UJ, Greahelf W, McFaul CD, Ghanie P, Neoptolemos JP. The inherited genetics of pancreatic cancer and prospects for secondary screening. Best Pract Res Clin Gastroenterol 2006; 20: 253-83
12. Wada K, Takada T, Yasuda H, Amano H, Yoshida M, Sugimoto M, et al. Does “clonal progression” relate to the development of intraductal papillary mucinous tumours of the pancreas? J Gastrointest Surg 2004; 8: 289-96
13. Jang JY, Park YC, Song YS, Lee SE, Hwang DW, Lim CS, et al. Increased K-ras mutation and expression of S100A4 and MUC2 protein in the malignant intraductal papillary mucinous tumor of the pancreas. Hepatobiliary Pancreat Surg 2009; 16: 668-74
14. Chadwick B, Willmore-Payne C, Tripp S, Layfield LJ, Hirschowitz S, Holden J. Histologic, immunohistochemical, and molecular classification of 52 IPMNs of the pancreas. Appl Immunohistochem Mol Morphol 2009; 17: 31-39
15. Mizuno O, Kawamoto H, Yamamoto N, Horiguchi S, Tsutsumi K, Fujii M, et al. Single-pattern convergence of K-ras mutation correlates with surgical indication of intraductal papillary mucinous neoplasms. Pancreas 2010; 39:617-21

16. Kanno A, Satoh K, Kimura H, Hirota M, Umino J, Masamune A, et al. The expression of MUC4 and MUC5AC is related to the biologic malignancy of intraductal papillary mucinous neoplasms of the pancreas. Pancreas 2006; 33: 391-96

17. Kobayashi N, Inamori M, Fujita K, Fujisawa T, Fujisawa N, Takahashi H, et al. Characterization of K-ras gene mutations in association with mucinous hypersecretion in intraductal papillary-mucinous neoplasms. J Hepatobiliary Pancreat Surg 2008; 15: 169-77

18. Jang JY, Park YC, Song YS, Lee SE, Hwang DW, Lim CS, et al. Increased K-ras mutation and expression of S100A4 and MUC2 protein in the malignant intraductal papillary mucinous tumor of the pancreas Hepatobiliary. Pancreat Surg 2009;16: 668-74

19. Lee JH, Lee KT, Park J, Bae SY, Lee KH, Lee JK, et al. Predictive factors associated with malignancy of intraductal papillary mucinous pancreatic neoplasms. World J Gastroenterol 2010; 16: 5353-58

20. Carrara S, Cangi MG, Arcidiacono PG, Perri F, Petrone MC, Mezzi G, et al. Mucin expression pattern in pancreatic diseases: findings from EUS-guided fine-needle aspiration biopsies. Am J Gastroenterol 2011; 106: 1359-63

21. Bassi C, Sarr MG, Lillemoe KD, Reber HA. Natural history of intraductal papillary mucinous neoplasms (IPMN): current evidence and implications for management. J Gastrointest Surg 2008;12: 645-50

22. Partelli S, Fernandez-del Castillo C, Bassi C, Mantovani W, Thayer SP, Crippa S, Ferrone CR, et al. Invasive Intraductal papillary mucinous carcinomas of the pancreas: predictors of survival and the role of lymph node ratio. Ann Surg 2010; 251: 477–482

23. Salvia R, Crippa S, Partelli S, Armatura G, Malleo G, Paini M, et al. Differences between main-duct and branch-duct intraductal papillary mucinous neoplasms of the pancreas. World J Gastrointest Surg 2010 ; 2: 342-46

24. Rodriguez JR, Salvia R, Crippa S, Warshaw AL, Bassi C, Falconi M, et al. Brach-duct intraductal papillary mucinous neoplasms: observations in 145 patients who underwent resection. Gastroenterology 2007; 133: 72-79

25. Manfredi R, Grazioli R, Motton M, Mantovani W, Baltieri S, Tognolini A, et al. Main pancreatic duct intraductal papillary mucinous neoplasms: accuracy of MR imaging in differentiation between benign and malignant tumours compared with histopathologic analysis. Radiology 2009; 253: 106-15

26. Tirkes T, Aksif K, Tann M, Balci NC. Imaging of the pancreas with secretin-enhancement. Top Magn Reson Imaging 2009; 20: 19-24

27. Yamao K, Ohashi K, Nakamura T, Suzuki T, Sawaki A, Hara K, et al. Efficacy of peroral pan-creatoscopy in the diagnosis of pancreatic diseases. Gastrointest Endosc 2003; 57: 205–209

28. Chari S, Yadav D, Smyrk TC, DiMagno EP, Miller LJ, Massimo M, et al. Study of recurrence after surgical resection of intraductal papillary mucinous neoplasm of the pancreas. Gastroenterology 2002; 123: 1500–507

29. Sohn TA, Yeo CJ, Cameron JL, Hruban RH, Fukushima N, Campbell KA, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. Ann Surg 2004; 239: 788–99

30. Crippa S, Partelli S, Falconi M. Extent of surgical resections for intraductal papillary mucinous neoplasms. World J Gastrointest Surg 2010; 2:347-51

31. Salvia R, Crippa S, Falconi M, Bassi C, Guarise A, Scarpa A, et al. Branch-duct intraductal papillary mucinous neoplasm of the pancreas: to operate or not to operate? Gut 2007; 56: 1086-90

32. Bae SY, Lee KT, Lee JH, Lee JK, Lee KH, Rhee JC. Proper management and follow-up strategy of branch duct intraductal papillary mucinous neoplasms of the pancreas. Dig Liver Dis 2012;44:257-60

33. Garcea G, Dennison AR. Branch-type intraductal papillary mucinous neoplasms: an update. Pancreatology 2011; 11: 336-42.
کارگاه‌های آموزشی مرکز اطلاعات علمی

مقاله نویسی علوم انسانی

اصول تنظیم قراردادها

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