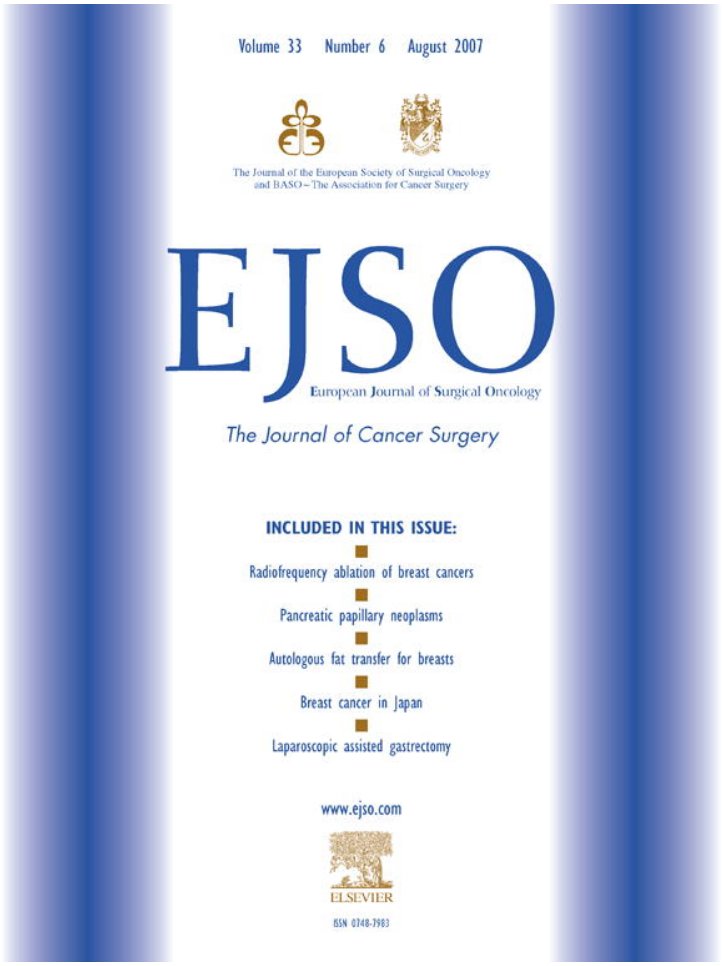
Provided for non-commercial research and educational use only.
Not for reproduction or distribution or commercial use.



This article was originally published in a journal published by Elsevier, and the attached copy is provided by Elsevier for the author's benefit and for the benefit of the author's institution, for non-commercial research and educational use including without limitation use in instruction at your institution, sending it to specific colleagues that you know, and providing a copy to your institution's administrator.

All other uses, reproduction and distribution, including without limitation commercial reprints, selling or licensing copies or access, or posting on open internet sites, your personal or institution's website or repository, are prohibited. For exceptions, permission may be sought for such use through Elsevier's permissions site at:

http://www.elsevier.com/locate/permissionusematerial

Available online at www.sciencedirect.com
ScienceDirect
EJSO
the Journal of Cancer Surgery
ELSEVIER
EJSO 33 (2007) 678–684
www.ejso.com

Review

Intraductal papillary mucinous neoplasms of the pancreas

S. Gourgiotis [a,*], M.P. Ridolfini [b], S. Germanos [c]

[a] Hepatobiliary and Pancreatic Surgery Department, Royal London Hospital, Whitechapel, London E1 1BB, UK
[b] Department of Surgical Sciences, Gemelli University Hospital, Catholic University of the Sacred Heart School of Medicine, Rome, Italy
[c] Upper GI and General Surgery, Leighton Hospital, Mid Cheshire NHS Trust, UK

Accepted 28 November 2006
Available online 4 January 2007

Abstract

Background/aims: Intraductal papillary mucinous neoplasms (IPMNs) are neoplasms of the pancreatic duct epithelium characterized by intraductal papillary growth and thick mucin secretion. Quantities of mucin fill the main and/or branches of pancreatic ducts and cause ductal dilatation. This review encompasses IPMNs, including symptoms, diagnosis, management, and prognosis.
Methods: A Pubmed database search was performed. All abstracts were reviewed and all articles in which cases of IPMNs could be identified were further scrutinized. Further references were extracted by cross-referencing.
Results: Only one-third of all patients are symptomatic. According to the site of involvement, IPMNs are classified into three types: main duct type, branch duct type, and combined type. Most branch type IPMNs are benign, while the other two types are frequently malignant. The presence of large mural nodules increases the possibility of malignancy in all types. Presence of a large branch type IPMN and marked dilatation of the main duct indicate the existence of adenoma at least. Synchronous or metachronous malignancies may be developed in various organs. Endoscopic retrograde cholangiopancreatography, endoscopic ultrasonography, and intraductal ultrasonography clearly demonstrate ductal dilatation and mural nodules, while magnetic resonance pancreatography best visualizes the entire outline of IPMNs.
Conclusions: Prognosis is excellent after complete resection of benign and non-invasive malignant IPMNs. The extent of pancreatic resection and the intraoperative management of resection margins remain controversial. Total pancreatectomy should be reserved for patients with resectable but extensive IPMNs involving the whole pancreas; its benefits, however, must be balanced against operative and postoperative risks. Regular monitoring for disease recurrence is important after surgery.
© 2006 Elsevier Ltd. All rights reserved.

Keywords: Intraductal papillary mucinous neoplasm; Pancreatic tumour

Author's personal copy

Introduction

The first cases of intraductal papillary mucinous neoplasms (IPMNs) were reported in the 1970s and 1980s.[1,2] In the 1990s, the term IPMN was coined, and the tumour was established as a special entity among the pancreatic neoplasms.[3] In 2000, the World Health Organization (WHO)[4] and the Armed Forces Institute of Pathology[5] classified cystic mucin-producing pancreatic neoplasms into two distinct entities: IPMNs and mucinous cystic neoplasms (MCNs).

The IPMN is characterized by cystic dilatation of the main and/or branches of the pancreatic duct. The disease originates from the epithelium of the pancreatic ducts and can evolve all the biological stages, from slight dysplasia to carcinoma that could be simultaneously present with the same lesion.[2,6–13] It mainly occurs in the sixth to seventh decades of life, affecting males slightly more frequently than females.[14–22] IPMNs account for 0.5% of all pancreatic neoplasms found at autopsy, 7.5% of clinically diagnosed pancreatic neoplasms, and 16.3% of surgically resected pancreatic neoplasms.[23] The majority of IPMNs occur in the head of the pancreas.

Recent advances in diagnostic imaging have led to an increased frequency of diagnosis of IPMNs,[14–17] but the clinical features of them can range broadly from benign, borderline, and malignant non-invasive to invasive lesions, and their management has not yet been clearly defined.[18,24–28]

* Corresponding author. Tel.: +44 207 377 700; fax: +44 207 377 7439.
E-mail address: drsgourgiotis@tiscali.co.uk (S. Gourgiotis).

0748-7983/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejso.2006.11.031

Because IPMNs are slow-growing neoplasms with a good prognosis, their clinical treatment varies from observation to surgical resection. However, it is very difficult to distinguish between benign IPMNs and malignant IPMNs using preoperative diagnostic imaging. Because the prognosis of IPMNs that have infiltrated into the parenchyma of the pancreas is poor, surgical resection of a malignant IPMN is essential.[15,16,19,29,30]

This study reviews the clinical symptoms, diagnosis, management, and prognosis of IPMNs. A Pubmed database search was performed. All abstracts were reviewed and all articles in which cases of IPMNs could be identified were further scrutinized. Further references were extracted by cross-referencing.

Pathology

IPMNs are separated into various categories depending on the degree of atypia: IPMN adenoma, IPMN borderline, IPMN with carcinoma in situ, and IPMN with invasive carcinoma. IPMN adenoma, IPMN borderline and IPMN with carcinoma in situ are considered as non-invasive IPMNs. IPMN with invasive carcinoma is considered as invasive IPMN. Twenty-five to 48% of IPMNs contain invasive carcinoma.[14–17,19–22,31,32] Invasive carcinoma consists of mucinous (colloid) type and conventional tubular type.[18,32]

IPMN has been reported to have a variety of different features in a single tumour.[15,32] Similar to colorectal carcinoma (adenoma–carcinoma sequence) and pancreatic ductal adenocarcinoma (transformation from pancreatic intraepithelial neoplasia to invasive ductal carcinoma), there is increasing evidence to support a progression model for IPMN.[16,32] The molecular steps of such progression have not been well established. There is still no answer to the timeline of this tumour progression and whether all non-invasive IPMNs have malignant potential. Currently, most authors agree that their evolution towards the carcinoma stage is slow, but probably inexorable.[33–35] Based on the mean age of occurrence of the different subtypes of IPMNs, the lag time between IPMN adenoma and IPMN with invasive cancer is estimated to be 3 to 6.4 years.[15–17,19] Malignant IPMN is associated with a lower incidence (22%) of lymph node metastasis than ductal adenocarcinoma,[13] and a more favourable prognosis.[2,6–13]

Clinical symptoms

Patient with IPMN often presents with acute pancreatitis of mild to moderate severity and IPMN can be mistaken for idiopathic pancreatitis when patient has a large, dilated pancreatic duct. It has been reported that approximately one-third of patients with IPMN experience symptoms including epigastric discomfort and/or pain, backache, weight loss, diabetes, and jaundice.[15,17,36,37] These episodes are generally referred to as continuous pain, related to meals, localized to the upper quadrants of the abdomen, irradiating to the back. Another frequent symptom is weight loss which might have two different physio-pathological mechanisms related to the stage of the disease. In the early phases, the hyperproduction of mucin obstructs normal pancreatic secretion, causing pain related to meals. Thus the patients stop eating in order to avoid pain. In more advanced stage, weight loss is more probably due to the production of neoplastic factors responsible for cachexia. Jaundice plays an important role, being a typical symptom of pancreatic head diseases. Jaundice may ensue when viscid mucin obliterates the ampulla, when the IPMN is large enough to cause compression of the common bile duct, or when benign or malignant mural nodules involve the common bile duct and/or ampulla. Persistent occlusion of the main pancreatic duct with viscid mucin may result in pancreatic insufficiency, presenting with diabetes and/or steatorrhea. In addition, hyperamylasemia is often present for many years.[37,38]

However, two-thirds to three-fourths of patients with IPMN do not display any symptoms due to relatively inactive production of mucin and/or the location of the tumour in the body or tail portion of the pancreas.

Classification

IPMNs are usually classified into three types: main duct, branch duct, and combined, according to the site and extent of involvement.[39] Main duct and branch duct IPMN have significant differences in prevalence of cancer ranging from 57% to 92%[15,16,29,39–44] and 6% to 46%,[16,29,39–44] respectively, and therefore the classification has prognostic implications. This classification of IPMNs is based on imaging studies. Histological examinations of surgical specimens of branch duct IPMN, however, may prove some degree of main duct involvement, thus putting many branch duct IPMNs into the mixed category.

Main duct type

A main duct type IPMN is characterized by a diffusely or partially dilated main pancreatic duct filled with excessive mucin. This type occurs predominantly in the head of the pancreas and only occasionally in the tail. The inner surface of the dilated duct frequently contains mural nodules. Patients with marked dilatation of the main pancreatic duct >1 cm and mural nodules >1 cm face probable diagnosis of malignant IPMN.[36,45] Several years of main duct obstruction with viscid mucin or mural nodules may result in chronic pancreatitis, in which case the entire pancreas is markedly fibrotic. When main duct type IPMN is associated with invasive carcinoma, the gross appearance may not demonstrate the presence of the IPMN.

Branch type

The branch type IPMN affects one or more branches of the pancreatic duct, which consequently show cystic

Author's personal copy

dilatation. The dilated branch duct may contain solitary or multiple tumours and/or viscid mucin. The presence of large and high mural nodules indicates an increased likelihood of malignancy. When the IPMN is large enough to cause compression of the main pancreatic duct, obstructive pancreatitis may result, and jaundice may develop when the compression affects the common bile duct. Branch duct type IPMN is less often associated with invasive carcinoma than main duct type IPMN.[15,17,39,40,42] However, the difference in the prognosis of the main duct type and the branch duct type is still a controversial issue.[15,17]

Combined type

Any combination of the above two types of IPMN is designated as combined type IPMN. This type is an advanced form of the branch type, in which the IPMN has spread to the main pancreatic duct, or an ultimate form of the main duct type, in which the IPMN has involved the branch ducts as well. In combined type, the main pancreatic duct contains papillary growth of columnar epithelia of various degrees of dysplasia that produce excessive mucin. Mere dilatation of the main pancreatic duct due to excessive mucin production by the branch type IPMN should not be designated as a combined type IPMN.

Diagnosis

Computed tomography (CT) may reveal one or more cystic dilatations in the pancreas (branch type) or diffuse or segmental dilatation of the main pancreatic duct (main duct type) with or without polypoid lesions.[46–50] The typical feature is a lobulated multilocular cystic lesion located in the uncinate process and in contiguity with the dilated main pancreatic duct. CT is also useful for monitoring for recurrence.[15,16,50]

Endoscopic retrograde cholangiopancreatography (ERCP) is considered as a standard for the diagnosis of IPMNs.[46,47] It reveals any dilatation of the main pancreatic duct or branches with filling defects due to the presence of either mural nodules or mucin. Communication between a branch type IPMN and the main pancreatic duct is usually evident.[51] On ERCP, these lesions are often suggested by findings such as a dilated pancreatic duct, a gaping ampulla, extrusion of mucin, mucous plugging or obstruction, and a cystic lesion in communication with the main pancreatic duct or a side branch. Currently, localized stenosis and marked dilatation of the main pancreatic duct can be demonstrated clearly by an improved method of endoscopic retrograde pancreatography (ERP), namely balloon-catheter ERP–compression study (ERP–CS).[52] The use of a long balloon-catheter makes it possible to obtain better quality pancreatograms by spot film compression. Maeshiro et al.[53] reported that in two groups of patients with main duct type and branch duct type neoplasms, the diagnostic ability of balloon ERP–CS was calculated as sensitivity 100% and 73%, specificity 40% and 86%, and accuracy 84% and 82%, respectively.

Recent reports show that magnetic resonance cholangiopancreatography (MRCP) is more sensitive than ERCP.[54–58] Furthermore, MRCP is also non-invasive and not operator dependent. MRCP shows the high signal intensity of the dilated duct and demonstrates the complex cystic mass associated with side branch IPMN. ERCP occasionally fails in demonstrating the whole pancreatic ductal system because of mucin plug obstruction, while MRCP visualizes the entire outline of either main duct type or branch type IPMN and plays an important role in the postoperative follow-up.

Endoscopic ultrasonography (EUS) improves the accuracy of assessment of the pancreatic parenchyma.[13,59,60] The classical features of IPMNs in EUS include dilatation of the main pancreatic duct, hypoechoic thickening of the duct wall, mural nodules or papillary projections, and pancreatic atrophy. However, EUS is highly operator dependent. Recently, intraductal ultrasonography and peroral pancreatoscopy have been used to locate the tumour and the mural nodules, and to perform biopsies. In a main duct IPMN, peroral pancreatoscopy may demonstrate the fish-egg appearance of a papillary neoplasm, granular or polypoid mucosa, or rough mucosa, while in a branch type IPMN, peroral pancreatoscopy may reveal mucin in the main pancreatic duct.[61,62] It is also impossible for peroral pancreatoscopy to assess the tumour located at a side branch. Further studies are needed to define the true role of these new tools.

Preoperative predictors of malignancy

Several researchers have described preoperative variables common in patients with IPMNs, and some have attempted to correlate them with subsequent histologic findings or survival outcomes. These variables have included tumour size, sex, diabetes mellitus, pancreatitis, steatorrhea, abdominal mass, weight loss, serum CA 19-9 level, and serum carcinoembryonic antigen (CEA) level.

Kawai et al.[63] estimated tumour size (>30 mm) and mural nodule size (>5 mm) from preoperative imaging and showed a correlation of increasing size with malignancy. The same study correlated cytologic findings in pure pancreatic juice (CEA level > 110 ng/ml) with malignancy. Salvia et al.[15] and Wiesenauer et al.[27] suggested jaundice and worsening or new onset of diabetes mellitus as preoperative predictors for IPMN malignancy. Kubo et al.[60] suggested some EUS findings as predicted factors for IPMN malignancy: main duct type tumour with dilated main pancreatic duct $\geq$ 10 mm, branch duct type tumour > 40 mm with irregular septa, and large mural nodules > 10 mm. Finally, based on other authors' reports,[17,41,64,65] three features suggest malignant IPMN: tumour size > 30 mm, main duct type tumour and mural nodules.

Authors personal copy

Differential diagnosis

Distinction of IPMNs from chronic pancreatitis is of clinical significance, especially in patients with main duct type IPMN. Demographic data (sex, age) and life habits (alcohol, smoking) may contribute to the differential diagnosis between IPMN and chronic pancreatitis, while the presence of jaundice and diabetes are suggestive of malignancy.

Differentiation between the IPMNs and the MCNs still presents some complications. Tumour cells of MCNs have the same cytologic features as those of the IPMNs. MCNs occur almost exclusively in women of around 25 years of age. The average age is higher when the neoplasm takes on malignant behavior. The topography of the neoplasm can be useful for differential diagnosis since IPMN is electively located in the uncinate process, while 93% of MCNs involves the body and the tail. Moreover, it is necessary to point out that IPMNs are almost always symptomatic, mimicking chronic pancreatitis, while the MCNs are almost always asymptomatic. It has also been proposed that ovarian-type stroma is a characteristic histologic feature of MCNs.[36,66]

Association with other malignancies

Another characteristic of IPMNs is their association with malignancy in other organs. Not infrequently, patients with an IPMN have synchronous or metachronous malignancy in various organs. The rate of association of IPMNs with malignant neoplasms in extrapancreatic organs has been reported to range from 23.6% to 32%.[51,67] Yamaguchi et al.[51] described non-pancreatic malignancies in 18 of 56 patients (32%) with resected IPMNs. Sugiyama and Atomi[67] reported that 15 of 42 patients (32%) with benign and malignant IPMNs had also non-pancreatic neoplasms including colorectal, gastric, and bile duct cancer before, at, or after surgery for an IPMN.

These results may suggest that patients with IPMN may be genetically predisposed to the development of malignant tumours in a variety of organs. This may be biased, however, in part by the fact that some IPMNs are detected during follow-up of other, previously treated malignant tumours. Nonetheless, we should be well aware of the possibility that an IPMN may be an indicator of pancreatic cancer.[68] Increased knowledge of an IPMN and its relationship with pancreatic cancer may lead to an earlier diagnosis of pancreatic cancer and improved patient prognosis.

Management

IPMNs are the most common lesions among cystic tumours with many difficulties for the physician not only in their detection but also in choosing the best therapy and intraoperative management. Surgical resection is the treatment of choice for IPMNs for the following reasons: (1) surgical resection remains the option that gives the best chance of a cure; (2) there are no reliable criteria and investigatory tools to differentiate non-invasive from invasive IPMNs; (3) the treatment outcome is worse for other treatments than for surgical resection, especially for non-invasive IPMNs; (5) the operative mortality and morbidity is acceptably low.[11,14–17,19–22,69]

For IPMN which involves the whole pancreas, total pancreatectomy should be performed. For localized IPMN shown on preoperative imaging, whether the extent of resection should be partial or total pancreatectomy remains controversial. Even after partial pancreatectomy with negative surgical margin for non-invasive IPMN, the tumour can recur as disseminated disease or as locally invasive or non-invasive disease in the pancreatic remnant.[14–17,19–22] Theoretically, prophylactic total pancreatectomy for IPMN solves this problem. In clinical practice, only 8%–23% of surgical resections for IPMNs were total pancreatectomies because total pancreatectomy causes a complete loss of pancreatic endocrine and exocrine function which is very difficult to manage, and total pancreatectomy cannot entirely solve the problem of tumour recurrence.[14–17,19,21,22,31]

For non-invasive IPMN, the reported overall disease recurrence rate is low (1.3%–9.3%), which includes pancreatic remnant recurrence rate (1.3%–6.3%) and disseminated disease recurrence rate (0%–4.7%).[15–17,19,22] Furthermore, some of the isolated pancreatic remnant recurrence can be cured by a repeat pancreatectomy. Thus, total pancreatectomy is not necessary for the majority of patients. For invasive IPMN, the overall disease recurrence rate is 12%–68%.[15–17,19,22] However, the recurrence in the form of disseminated disease (3.4%–44%) is higher than isolated pancreatic remnant recurrence (0%–15%).[15–17,19,22] Thus, prophylactic total pancreatectomy may not solve the problem of the high incidence of disseminated disease recurrence. Based on the available studies, patients with IPMN should receive segmental pancreatectomy, which preserves exocrine and endocrine pancreatic functions, as far as negative ductal margins can be obtained, while total pancreatectomy should be reserved for patients with resectable but extensive IPMN involving the whole pancreas.[15–17,19,22,70]

It is difficult to assess the extent of pancreatic ductal involvement of IPMN before surgical resection. Intraoperative ultrasonography[71] and pancreatoscopy may be helpful in determining the site of resection. Diffuse dilatation of the main pancreatic duct can be due to mucus plugs, tumour obstruction of the pancreatic duct, or diffuse tumour involvement of the pancreatic duct. Tumours involved ductal margins after resections, including both benign and malignant pathology, were reported from 23% to 52%.[15–17,19,22,72] Intraoperative, frozen-section diagnosis should be adequately used, although diagnosis by frozen histology is not always accurate and definite.[30,72] The resection should be extended if the ductal margin shows malignant invasive disease. However, the management of the ductal resection margin with benign non-invasive disease, such as the various degrees of atypia or dysplasia, is a controversial issue. Some patients may

Author's personal copy

necessitate total pancreatectomy to achieve complete resection, but the benefits of such an aggressive treatment must be balanced against perioperative risks.

Prognosis, recurrence, and surveillance

The overall 5-year survival for IPMNs is 36%–77%.[14–17,19,22,31,73,74] The 5-year survival of surgical resection for non-invasive IPMNs was reported from 77% to 100%,[15–17,19,22,31,75] while the 5-year survival of surgical resection for IPMNs with invasive carcinoma has been reported from 27% to 60%.[15–17,19,22,75] The presence of invasive carcinoma, the type of the invasive component (tubular is worse than colloid), lymph node involvement, the presence of vascular invasion, surgical margin involvement and the presence of jaundice are poor prognostic factors for patients with IPMNs after resection.[15–17,19,22] It has been reported that the malignant IPMN acquires aggressive behavior similar to that of common-type pancreatic carcinoma once it has invaded the pancreatic parenchyma.[76]

Patients with resected benign IPMNs have a risk of recurrence in the remaining pancreas, and if it occurs can benefit for further resection. The overall recurrence rate for IPMNs varies from 7% to 43%.[15–17,19,22] There is a risk of recurrence in both the non-invasive and the invasive IPMNs, so follow-up and monitoring is important. Repeat resection for isolated recurrence in the pancreatic remnant gives good results.[15–17,19,22] Sohn et al.[16] reported five patients with isolated recurrent IPMN in the pancreatic remnant, treated with repeat pancreatectomy. Two patients had non-invasive IPMN recurrence and three patients had invasive IPMN recurrence; only one patient died of disseminated disease. Salvia et al.[15] reported six patients with isolated recurrent IPMN in the pancreatic remnant, treated with repeat pancreatectomy. One patient had non-invasive IPMN recurrence and five patients had invasive IPMN recurrence; only three patients had died of disseminated disease.

There is no evidence in the literature to define the frequency and type of surveillance that is required to detect these recurrences. One study suggests only clinical follow-up and imaging if symptoms appear.[19] A regimen consisting of an yearly CT or MRCP is most widely used for surveillance.[15–17,19] It has also been suggested that pancreaticogastric anastomosis should be used after pancreaticoduodenectomy to allow disease surveillance with endoscopy and sampling of pancreatic juice for cytology.[30]

References

1. Klöppel G. Clinicopathologic view of intraductal papillary–mucinous tumor of the pancreas. *Hepatogastroenterology* 1998;**45**:1981–5.
2. Itai Y, Ohhashi K, Nagai H, et al. 'Ductectatic' mucinous cystadenoma and cystadenocarcinoma of the pancreas. *Radiology* 1986; **161**:697–700.
3. Sessa F, Solcia E, Capella C, et al. Intraductal papillary–mucinous tumours represent a distinct group of pancreatic neoplasms: an investigation of tumour cell differentiation and K-ras, p53 and c-erbB-2 abnormalities in 26 patients. *Virchows Arch* 1994;**425**: 357–67.
4. Longnecker DS, Adler G, Hruban RH, Klöppel G. Intraductal papillary–mucinous neoplasms of the pancreas. In: Hamilton SR, Aaltonen LA, editors. *World Health Organization classification of tumors. Pathology and genetics of tumors of the digestive system*. Lyon: IARC Press; 2000, p. 237–41.
5. Solcia E, Capella C, Kloeppel G. Tumors of the pancreas. In: Rosai J, editor. *Atlas of tumor pathology*. Washington D.C.: Armed Forces Institute of Pathology; 1997. Fascicle 20, 3rd series.
6. Klöppel G, Solcia E, Longnecker DS, Capella C, Sobin LH, Solcia E. *Histological typing of tumours of the exocrine pancreas*. 2nd ed. New York: Springer; 1996.
7. Ohashi K, Murakami Y, Maruyama M, Takekoshi T, Ohta H, Ohashi I. Four cases of 'mucin-producing' cancer of the pancreas on specific findings of the papilla Vater. *Prog Dig Endosc* 1982;**20**:348–51.
8. Morohoshi T, Kanda M, Asanuma K, Klöppel G. Intraductal papillary neoplasms of the pancreas. A clinicopathologic study of six patients. *Cancer* 1989;**64**:1329–35.
9. Rickaert F, Cremer M, Devière J, et al. Intraductal mucin-hypersecreting neoplasms of the pancreas. A clinicopathologic study of eight patients. *Gastroenterol* 1991;**101**:512–9.
10. Milchgrub S, Campuzano M, Casillas J, Albores-Saavedra J. Intraductal carcinoma of the pancreas. *Cancer* 1992;**69**:651–6.
11. Loftus Jr EV, Olivares-Pakzad BA, Batts KP, et al. Intraductal papillary–mucinous tumors of the pancreas: clinicopathologic features, outcome, and nomenclature. Members of the Pancreas Clinic, and Pancreatic Surgeons of Mayo Clinic. *Gastroenterol* 1996;**110**: 1909–18.
12. Sugiyama M, Atomi Y, Kuroda A. Two types of mucin-producing cystic tumors of the pancreas: diagnosis and treatment. *Surgery* 1997;**122**:617–25.
13. Sugiyama M, Atomi Y. Intraductal papillary mucinous tumors of the pancreas: imaging studies and treatment strategies. *Ann Surg* 1998; **228**:685–91.
14. Sohn TA, Yeo CJ, Cameron JL, Iacobuzio-Donahue CA, Hruban RH, Lillemoe KD. Intraductal papillary mucinous neoplasms of the pancreas: an increasingly recognized clinicopathologic entity. *Ann Surg* 2001;**234**:313–21.
15. Salvia R, Fernandez-del Castillo C, Bassi C, 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**:678–87.
16. Sohn TA, Yeo CJ, Cameron JL, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. *Ann Surg* 2004; **239**:788–97.
17. D'Angelica M, Brennan MF, Suriawinata AA, Klimstra D, Conlon KC. Intraductal papillary mucinous neoplasms of the pancreas: an analysis of clinicopathologic features and outcome. *Ann Surg* 2004;**239**:400–8.
18. Adsay NV, Conlon KC, Zee SY, Brennan MF, Klimstra DS. Intraductal papillary–mucinous neoplasms of the pancreas: an analysis of in situ and invasive carcinomas in 28 patients. *Cancer* 2002;**94**: 62–77.
19. Chari ST, Yadav D, Smyrk TC, et al. Study of recurrence after surgical resection of intraductal papillary mucinous neoplasm of the pancreas. *Gastroenterol* 2002;**123**:1500–7.
20. Cuillerier E, Cellier C, Palazzo L, et al. Outcome after surgical resection of intraductal papillary and mucinous tumors of the pancreas. *Am J Gastroenterol* 2000;**95**:441–5.
21. Falconi M, Salvia R, Bassi C, Zamboni G, Talamini G, Pederzoli P. Clinicopathological features and treatment of intraductal papillary mucinous tumour of the pancreas. *Br J Surg* 2001;**88**:376–81.
22. Wada K, Kozarek RA, William Traverso L. Outcomes following resection of invasive and non-invasive intraductal papillary mucinous neoplasms of the pancreas. *Am J Surg* 2005;**189**:632–6.

Authors personal copy

23. Furuta K, Watanabe H, Ikeda S. Differences between solid and duct-ectatic types of pancreatic ductal carcinomas. *Cancer* 1992;**69**: 1327–33.
24. Zapiach M, Yadav D, Smyrk TC, et al. Calcifying obstructive pancreatitis: a study of intraductal papillary mucinous neoplasm associated with pancreatic calcification. *Clin Gastroenterol Hepatol* 2004; **2**:57–63.
25. Adsay NV, Pierson C, Sarkar F, et al. Colloid (mucinous noncystic) carcinoma of the pancreas. *Am J Surg Pathol* 2001;**25**:26–42.
26. Stelow EB, Stanley MW, Bardales RH, et al. Intraductal papillary–mucinous neoplasm of the pancreas. The findings and limitations of cytologic samples obtained by endoscopic ultrasound-guided fine-needle aspiration. *Am J Clin Pathol* 2003;**120**:398–404.
27. Wiesenauer CA, Schmidt CM, Cummings OW, et al. Preoperative predictors of malignancy in pancreatic intraductal papillary mucinous neoplasms. *Arch Surg* 2003;**138**:610–7.
28. Paal E, Thompson LD, Przygodzki RM, Bratthauer GL, Heffess CS. A clinicopathologic and immunohistochemical study of 22 intraductal papillary mucinous neoplasms of the pancreas, with a review of the literature. *Mod Pathol* 1999;**12**:518–28.
29. Kitagawa Y, Unger TA, Taylor S, Kozarek RA, Traverso LW. Mucus is a predictor of better prognosis and survival in patients with intraductal papillary mucinous tumor of the pancreas. *J Gastrointest Surg* 2003;**7**: 12–8.
30. Gigot JF, Deprez P, Sempoux C, et al. Surgical management of intraductal papillary mucinous tumors of the pancreas: the role of routine frozen section of the surgical margin, intra-operative endoscopic staged biopsies of the Wirsung duct, and pancreaticogastric anastomosis. *Arch Surg* 2001;**136**:1256–62.
31. Maire F, Hammel P, Terris B, et al. Prognosis of malignant intraductal papillary mucinous tumours of the pancreas after surgical resection. Comparison with pancreatic ductal adenocarcinoma. *Gut* 2002;**51**: 717–22.
32. Hruban RH, Takaori K, Klimstra DS, 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.
33. Brat DJ, Lillemoe KD, Yeo CJ, Warfield PB, Hruban RH. Progression of pancreatic intraductal neoplasias to infiltrating adenocarcinoma of the pancreas. *Am J Surg Pathol* 1998;**22**:163–9.
34. Longnecker DS. Observations on the etiology and pathogenesis of intraductal papillary–mucinous neoplasms of the pancreas. *Hepatogastroenterology* 1998;**45**:1973–80.
35. Rivera JA, Fernandez-del Castillo C, Pins M, et al. Pancreatic mucinous ductal ectasia and intraductal papillary neoplasms. A single malignant clinicopathologic entity. *Ann Surg* 1997;**225**:637–44.
36. Yamaguchi K, Ogawa Y, Chijiiwa K, Tanaka M. Mucin-hypersecreting tumors of the pancreas: assessing the grade of malignancy preoperatively. *Am J Surg* 1996;**171**:427–31.
37. Obara T, Matuchi H, Saitoh Y, et al. Mucin-producing tumor of the pancreas: a unique clinical entity. *Am J Gastroenterol* 1991;**86**: 1619–25.
38. Rogers PN, Seywright MM, Murray WR. Diffuse villous adenoma of the pancreatic duct. *Pancreas* 1987;**2**:727–30.
39. Kobari M, Egawa S, Shibuya K, et al. Intraductal papillary mucinous tumors of the pancreas comprise 2 clinical subtypes: differences in clinical characteristics and surgical management. *Arch Surg* 1999; **134**:1131–6.
40. Terris B, Ponsot P, Paye F, et al. Intraductal papillary mucinous tumors of the pancreas confined to secondary ducts show less aggressive pathologic features as compared with those involving the main pancreatic duct. *Am J Surg Pathol* 2000;**24**:1372–7.
41. Sugiyama M, Izumisato Y, Abe N, Masaki T, Mori T, Atomi Y. Predictive factors for malignancy in intraductal papillary–mucinous tumours of the pancreas. *Br J Surg* 2003;**90**:1244–9.
42. Matsumoto T, Aramaki M, Yada K, et al. Optimal management of the branch duct type intraductal papillary mucinous neoplasms of the pancreas. *J Clin Gastroenterol* 2003;**36**:261–5.
43. Doi R, Fujimoto K, Wada M, Imamura M. Surgical management of intraductal papillary mucinous tumor of the pancreas. *Surgery* 2002; **132**:80–5.
44. Choi BS, Kim TK, Kim AY, et al. Differential diagnosis of benign and malignant intraductal papillary mucinous tumors of the pancreas: MR cholangio-pancreatography and MR angiography. *Korean J Radiol* 2003;**4**:157–62.
45. Yamaguchi K, Tanaka M. Mucin-hypersecreting tumor of the pancreas with mucin extrusion through enlarged papilla. *Am J Gastroenterol* 1991;**86**:835–9.
46. Visser BC, Muthusamay R, Mulvihill SJ, Coakley F. Diagnostic imaging of cystic pancreatic neoplasms. *Surg Oncol* 2004;**13**:27–39.
47. Yamaguchi K, Tanaka M. Radiologic imagings of cystic neoplasms of the pancreas. *Pancreatology* 2001;**1**:633–6.
48. Fukukura Y, Fujiyoshi F, Sasaki M, Inoue H, Yonezawa S, Nakajo M. Intraductal papillary mucinous tumors of the pancreas: thin-section helical CT findings. *AJR Am J Roentgenol* 2000;**174**:441–7.
49. Taouli B, Vilgrain V, Vullierme MP, et al. Intraductal papillary mucinous tumors of the pancreas: helical CT with histopathologic correlation. *Radiology* 2000;**217**:757–64.
50. Christensen JA, Fletcher JG, Fidler JL, et al. Intraductal papillary mucinous neoplasms of the pancreas: CT patterns of recurrence and multiobserver performance in detecting recurrent neoplasm after surgical resection. *AJR Am J Roentgenol* 2004;**183**:1367–74.
51. Yamaguchi K, Tanaka M. *Atlas of cystic neoplasms of the pancreas*. Fukuoka: Kyushu University Press/Kager; 2000.
52. Inoue K, Ohuchida J, Ohtsuka T, et al. Severe localized stenosis and marked dilatation of the main pancreatic duct are indicators of pancreatic cancer instead of chronic pancreatitis on endoscopic retrograde balloon pancreatography. *Gastrointest Endosc* 2003;**58**:510–5.
53. Maeshiro K, Nakayama Y, Yasunami Y, Furuta K, Ikeda S. Diagnosis of mucin-producting tumor of the pancreas by balloon-catheter endoscopic pancreatography–compression study. *Hepatogastroenterology* 1998;**45**:1986–95.
54. Koito K, Namieno T, Ichimura T, et al. Mucin-producing pancreatic tumors: comparison of MR cholangiopancreatography with endoscopic retrograde cholangiopancreatography. *Radiology* 1998;**208**: 231–7.
55. Fukukura Y, Fujiyoshi F, Sasaki M, Ichinari N, Kajiya Y, Nakajo M. HASTE MR cholangiopancreatography in the evaluation of intraductal papillary–mucinous tumors of the pancreas. *J Comput Assist Tomogr* 1999;**23**:301–5.
56. Albert J, Schilling D, Breer H, Jungius KP, Riemann JF, Adamek HE. Mucinous cystadenomas and intraductal papillary mucinous tumors of the pancreas in magnetic resonance cholangiopancreatography. *Endoscopy* 2000;**32**:472–6.
57. Irie H, Honda H, Aibe H, et al. MR cholangiopancreatographic differentiation of benign and malignant intraductal mucin-producing tumors of the pancreas. *AJR Am J Roentgenol* 2000;**174**:1403–8.
58. Sugiyama M, Abe N, Tokuhara M, et al. Magnetic resonance cholangiopancreatography for postoperative follow up of intraductal papillary–mucinous tumors of the pancreas. *Am J Surg* 2003;**185**: 251–5.
59. Cellier C, Cuillerier E, Palazzo L, et al. Intraductal papillary and mucinous tumors of the pancreas: accuracy of preoperative computed tomography, endoscopic retrograde pancreatography and endoscopic ultrasonography, and long-term outcome in a large surgical series. *Gastrointest Endosc* 1998;**47**:42–9.
60. Kubo H, Chijiwa Y, Kazuya A, et al. Intraductal papillary–mucinous tumors of the pancreas: differential diagnosis between benign and malignant tumors by endoscopic ultrasonography. *Am J Gastroenterol* 2001;**96**:1429–34.
61. Jung M, Zipf A, Shoonbroodt D, Hermann G, Caspary WF. Is pancreatoscopy of any benefit in clarifying the diagnosis of pancreatic duct lesions? *Endoscopy* 1998;**30**:274–80.
62. Hara T, Yamaguchi T, Ishihara T, et al. Diagnosis and patient management of intraductal papillary–mucinous tumor of the pancreas by

Author's personal copy

using peroral pancreatoscopy and intraductal ultrasonography. *Gastroenterol* 2002;**122**:34–43.
63. Kawai M, Uchiyama K, Tani M, et al. Clinicopathological features of malignant intraductal papillary mucinous tumors of the pancreas: the differential diagnosis from benign entities. *Arch Surg* 2004;**139**:188–92.
64. Wakabayashi T, Kawaura Y, Morimoto H, et al. Clinical management of intraductal papillary mucinous tumors of the pancreas based on imaging findings. *Pancreas* 2001;**22**:370–7.
65. Bernard P, Scoazec JY, Joubert M, et al. Intraductal papillary–mucinous tumors of the pancreas: predictive criteria of malignancy according to pathological examination of 53 cases. *Arch Surg* 2002;**137**:1274–8.
66. Izumo A, Yamaguchi K, Eguchi T, et al. Mucinous cystic tumor of the pancreas: immunohistochemical assessment of 'ovarian-type stroma'. *Oncol Rep* 2003;**10**:515–25.
67. Sugiyama M, Atomi Y. Extrapancreatic neoplasms occur with unusual frequency in patients with intraductal papillary mucinous tumors of the pancreas. *Am J Gastroenterol* 1999;**94**:470–3.
68. Yamaguchi K, Nakamura K, Yokohata K, Shimizu S, Chijiiwa K, Tanaka M. Pancreatic cyst as a sentinel of in situ carcinoma of the pancreas: report of two cases. *Int J Pancreatol* 1997;**22**:227–31.
69. Yeo CJ. Intraductal papillary mucinous neoplasms of the pancreas. *Adv Surg* 2002;**36**:15–38.
70. Zamora C, Sahel J, Cantu DG, et al. Intraductal papillary or mucinous tumors (IPMT) of the pancreas: report of a case series and review of the literature. *Am J Gastroenterol* 2001;**96**:1441–7.
71. Kaneko T, Nakao A, Inoue S, et al. Intraoperative ultrasonography by high-resolution annular array transducer for intraductal papillary mucinous tumors of the pancreas. *Surgery* 2001;**129**:55–65.
72. Paye F, Sauvanet A, Terris B, et al. Intraductal papillary mucinous tumors of the pancreas: pancreatic resections guided by preoperative morphological assessment and intra-operative frozen section examination. *Surgery* 2000;**127**:536–44.
73. Yamaguchi K, Chijiiwa K, Shimizu S, et al. Intraductal papillary neoplasm of the pancreas: a clinical review of 13 benign and four malignant tumours. *Eur J Surg* 1999;**165**:223–9.
74. Suzuki Y, Atomi Y, Sugiyama M, et al. Cystic neoplasm of the pancreas: a Japanese multiinstitutional study of intraductal papillary mucinous tumor and mucinous cystic tumor. *Pancreas* 2004;**28**:241–6.
75. Tenner S, Carr-Locke DL, Banks PA, et al. Intraductal mucin-hypersecreting neoplasm 'mucinous ductal ectasia': endoscopic recognition and management. *Am J Gastroenterol* 1996;**91**:2548–54.
76. Seki M, Yanagisawa A, Ohta H, et al. Surgical treatment of intraductal papillary–mucinous tumor (IPMT) of the pancreas: operative indications based on surgico-pathologic study focusing on invasive carcinoma derived from IPMT. *J Hepatobiliary Pancreat Surg* 2003;**10**:147–55.

Author's personal copy