

Clinical Presentation Can Predict Disease Course in Patients with Intraductal Papillary Mucinous Neoplasm of the Pancreas

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Abstract

Background Preoperative diagnosis of malignancy within intraductal papillary mucinous neoplasm of the pancreas (IPMN) solely by clinical or radiological findings is not always possible. We sought a correlation between preoperative clinico-radiological findings and outcome.

Methods A prospective database of pancreatic resections for IPMN (2002–2008) and a retrospective pathological revision of all pancreatic cancer specimens (1995–2001) were analyzed. The patients were grouped into asymptomatic with preoperative diagnosis of IPMN (group 1), symptomatic with a preoperative diagnosis of IPMN (group 2), and those with a preoperative diagnosis of pancreatic cancer whose specimen revealed a background of IPMN (group 3). The groups were compared for demographics, clinical presentation, pathological findings, and outcome.

Results Of the 62 patients with IPMN, 19 were in group 1, 23 in group 2, and 20 in group 3. Their median age (range) was 65.6 (46–80), 67 (50–84), and 73.4 (57–86)

years, respectively. The clinical presentation for groups 2 and 3 included abdominal pain (56% vs. 32%), weight loss (8% vs. 52%), obstructive jaundice (4% vs. 57%), pancreatitis (22% and 5%), and new onset of diabetes (14% and 44%). Invasive cancer was found in one patient in group 1 (5.2%), two patients in group 2 (8.7%), and all patients in group 3. IPMN was present in 23 of 217 (10.6%) of all resected pancreatic cancer specimens. Five year survival for patients with invasive disease was 47% and 92% for patients with noninvasive disease (mean follow-up 37.6 months).

Conclusions Benign IPMN can usually be differentiated from adenocarcinoma preoperatively. The clinical presentation is highly indicative of disease course.

Introduction

Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a relatively new clinicopathological entity, first reported in 1982 by Ohhashi et al. [1]. Much information has been gathered about IPMN during the past decade, but its natural course and optimal treatment have still not been clearly defined. Several retrospective series have demonstrated that 40–60% of patients with IPMN have a component of invasive cancer [2–4]. These studies stressed the importance of radical surgical treatment for these patients. It has been suggested that the natural course of IPMN begins with a long-standing benign disease, which may be symptomatic or asymptomatic, until a certain cancerous change occurs, similar to the adenoma-carcinoma sequence of colon cancer. It has not been established whether it is possible to preoperatively differentiate between benign IPMN from IPMN with invasive cancer [2]. The optimal treatment for patients with IPMN has not been established.

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Recommendations have ranged from observation, partial pancreatectomy (with or without intraoperative modalities to assess the surgical margins) to total pancreatectomy.

The purpose of the current study was to seek a correlation between preoperative clinical presentation, preoperative diagnosis (benign IPMN vs. invasive pancreatic cancer), and ultimate patient outcome.

Materials and methods

Patients

We used a prospective database of all patients treated surgically for IPMN in our institution since February 2002. Patients managed at our institution for IPMN who were not treated surgically were excluded from the study. The reasons for the nonoperative approach in these patients were their not being candidates for a major surgical procedure due to comorbid conditions, refusal to undergo surgery, or asymptomatic patients with branch-type IPMNs and very low suspicion of cancer on CT and EUS studies that were treated at our institution during the preceding 3 years. These latter patients are followed regularly with EUS and aspiration of cystic fluid at 1-year intervals. The diagnosis of IPMN in patients who were included in this study was based on computerized tomography (CT) and endoscopic ultrasound (EUS), and confirmed of final pathological examination of the resected specimen. We reviewed all pathological results of pancreatic resections performed in our department since 1995 (350 specimens). In all cases suspected of being IPMN according to the pathological report, a single pathologist experienced in pancreatic pathology (EB) revised the histological slides. The ones that were confirmed as IPMN were included in the study and underwent a retrospective review of the relevant clinical and pathological factors. Specifically, information on demographics, preoperative workup, operative procedures, postoperative course, and long-term outcome was recorded. Patients were categorized into three groups according to their preoperative diagnosis: group 1 was comprised of asymptomatic patients with an incidental finding of IPMN, group 2 included symptomatic patients with a preoperative diagnosis of IPMN, and group 3 included symptomatic patients with a preoperative diagnosis of pancreatic cancer. Most of the patients in group 3 were diagnosed as having IPMN according to the presence of typical cystic lesions on CT and EUS. However, these patients had a well-demonstrated pancreatic mass or a EUS-guided biopsy demonstrating adenocarcinoma and were operated with a working diagnosis of pancreatic cancer. Only patients with a histological specimen that demonstrated adenocarcinoma and a background of IPMN of the pancreas were included. The

three groups were compared with regard to demographics, clinical presentation, pathological findings, and outcome.

Materials

Preoperative imaging consisted of abdominal computerized tomographic (CT) scan in all patients and endoscopic ultrasound (EUS) in most patients (i.e., all patients treated since September 2000). We generally do not perform endoscopic retrograde cholangiopancreatography in these patients unless biliary drainage with transpapillary stent is required. The criteria for suspecting pancreatic cancer within IPMN on EUS included main pancreatic duct diameter ≥ 10 mm, the presence of two or more intramural nodules, size of cyst > 3 cm, or the presence of malignant cells on EUS-guided fine needle aspiration (FNA).

The criteria for suspecting pancreatic cancer within IPMN on CT were the presence of a solid mass, main pancreatic ductal dilatation > 10 mm, diffuse or multifocal involvement, and attenuating intraluminal content. Other signs suggestive of malignancy include heterogeneous cyst content and thick walls and septae [5, 6]. Malignant tumors also may be identified by invasion of the duodenum, lymphadenopathy, peritoneal deposits, and liver metastases.

The extent of pancreatic resection was determined preoperatively in most patients using preoperative imaging (CT and EUS). Patients with IPMN in the head, neck, or uncinate process of the pancreas underwent pancreaticoduodenectomy, whereas those with tumors in the body or tail underwent distal pancreatectomy (including splenectomy in most patients). Total pancreatectomy was performed for tumors diffusely involving the pancreatic duct. Intraoperative methods to assist in determining the extent of resections included intraoperative ultrasound (IOUS), intraoperative pancreatoscopy (IOP), and frozen section analysis of the resected margins. The decision to use these modalities was made according to the preference of the attending surgeon.

All microscopic slides were reviewed by a single pathologist to confirm the diagnosis of IPMN. Histological typing of the tumors was performed according to the classification recommended in the revised WHO classification in 2000 as having tall, columnar, mucin-containing epithelium with or without papillary proliferations and involving the pancreatic ducts [7]. Tumors were graded as low-, moderate-, and high-grade dysplasia or as invasive carcinomas. High-grade dysplasia was differentiated from invasive carcinoma according to the presence of stromal invasion. The margins of the pancreatic resection were reevaluated to determine presence and degree of atypia. Peripancreatic lymph node involvement also was assessed.

Perioperative mortality was defined as in-hospital death or death within 30 days of surgery. The overall incidence

of postoperative complications was evaluated. Overall survival information was available in 96% of the patients. Follow-up information was obtained by direct patient contact and outpatient clinic charts.

Statistical analysis

Survival analysis was performed by the methods of Kaplan and Meier. Comparison between patient groups with regard to demographics and clinical factors was by the Mann-Whitney and Fisher's exact test as appropriate. Univariate Cox regressions were used to calculate hazard ratios. A multivariate Cox regression model was applied to the data to study independent relationships between each risk factor and survival. Significance was set at <0.05 , and the SPSS for windows software version 12.0 was used for the analysis.

Results

We obtained the data for this study (February 2002 to May 2008) from the prospective database maintained by our department of all patients with IPMN of the pancreas. During the study period, 47 patients with IPMN of the pancreas underwent surgical resection. Revision of all the pathological results of pancreatic resections performed in our department since 1995 (a total of 350) identified 18 cases of suspected IPMN. After revision of the histological slides of these patients by a single pathologist, 15 cases were confirmed as being IPMN. Their surgical margin status was reevaluated as well.

Clinical presentation

We categorized the study patients into three groups. Group 1 included 19 asymptomatic patients who were diagnosed as having IPMN. Group 2 included 23 patients diagnosed as having IPMN (the working diagnosis of the five patients who were treated before 2000 was mucinous neoplasm of the pancreas), which presented with symptoms related to their pancreatic pathology. Group 3 included 20 patients with a working diagnosis of pancreatic adenocarcinoma, most with a preoperative diagnosis of IPMN, in which the histological slides demonstrated a background of IPMN. The relevant clinical characteristics of the various subgroups are shown in Table 1. There was a gradual increase in median age between the groups. The difference was not statistically significant. The difference in age between patients with benign IPMN and patients with invasive IPMN was significant (66.7 years vs. 73.8 years, $P = 0.018$). Group 3 patients had a higher incidence of weight loss, jaundice, and new onset of diabetes mellitus.

Table 1 Clinical characteristics of the study patients

	Group 1 (<i>n</i> = 19)	Group 2 (<i>n</i> = 23)	Group 3 (<i>N</i> = 20)
Male/female ratio	8/11	7/16	9/11
Median age, yr (range)	65.6 (46–80)	67 (50–84)	73.4 (57–86)
Chief complaint			
Abdominal pain		13 (56%)	6 (32%)
Weight loss		2 (8%)	10 (52%)
Obstructive jaundice		1 (4%)	12 (60%)
Pancreatitis		5 (22%)	1 (5%)
Diabetes mellitus		3 (14%)	8 (44%)

Surgical procedures

Table 2 lists the operative procedures performed in this cohort. Pancreaticoduodenectomy was the most common operation and it was performed in 32 patients (52%). Sixteen patients (25%) underwent distal pancreatectomy, including one laparoscopically. Thirteen patients (22%) underwent total pancreatectomy, and one patient had a locally unresectable tumor. Intraoperative methods to assist in determining the extent of pancreatic resections were not routinely used; they included frozen section analysis (FSA) ($n = 6$), IOP ($n = 2$), both FSA and IOP ($n = 1$), and IOUS ($n = 4$). The decision to use these modalities was taken by the attending surgeon performing the operation, according to personal preference. Three of the six patients who had normal FS margins were found to have IPMN adenoma in the resection margins on final paraffin blocks. Intraoperative pancreatoscopy was performed with an ultrathin ureteroscope. After amputation of the pancreas, the scope was inserted into the main pancreatic duct from the cut surface of the pancreas. Use of IOP did not result in extension of pancreatic resection. The surgical margins were histologically normal in two cases. Both FSA and IOP demonstrated negative margins during the operation in the one patient who underwent the two modalities, but the final pathological result demonstrated IPMN adenoma in the resection margin. All cases in which IOUS was used resulted in negative surgical margins.

There were three perioperative deaths (4.8%) secondary to septic complications ($n = 1$), sudden death ($n = 1$), and postoperative bleeding ($n = 1$). The postoperative complications are listed in Table 3.

Table 2 Pancreatic resections

Pancreaticoduodenectomy	32
Subtotal distal pancreatectomy	16
Total pancreatectomy	13
Palliative bypass	1

Table 3 Postoperative complications

Major bleeding requiring reoperation	1
Pancreatic fistula	6
Delayed gastric emptying	6
Intra-abdominal collection	6
Pseudomembranous colitis	4
Pulmonary embolus	5
Wound dehiscence or infection	4
Pneumonia	3

Pathology

The pathological findings are detailed in Table 4. After revision of all specimens of ductal adenocarcinoma, IPMN was found in the background of 23 of 217 (10.6%) of the cases. Only one patient in group 1 (5.2%) and two patients in group 2 (8.6%) had invasive cancer in their pathology. The surgical margins were negative in 33 patients (70% of the patients who underwent partial pancreatectomy), had moderate dysplasia in 1 patient, and displayed low-grade dysplasia in 10 patients. Invasive carcinoma was present in four patients in the resection margins (18% of patients with adenocarcinoma). The margin was positive at the transection margin in three patients and at the retroperitoneal

Table 4 Pathological results

	Group 1 (n = 19)	Group 2 (n = 23)	Group 3 (n = 20)
Tumor type			
Main duct type	13	10	12
Branch type	3	6	3
Mixed	2	4	3
Type unknown	1	3	2
Tumor grade			
Low-grade dysplasia	3	6	0
Moderate dysplasia	15	15	0
Invasive carcinoma	1	2	20
Metastatic lymph node	0	0	8
Resection margin			
Normal mucosa	10	12	11
Low-grade dysplasia (Transection margin)	3	5	2
Moderate dysplasia (Transection margin)	0	0	1
Invasive carcinoma			
Transection margin	0	0	3
Retroperitoneal margin	0	0	1
Irrelevant	6	6	2

Irrelevant, patients who underwent total pancreatectomy (n = 13) or palliative bypass with no resection (n = 1)

margin in one patient. Eight patients with noninvasive IPMN had surgical margins with IPMN. Seven patients with IPMN and invasive cancer had positive surgical margins: four with invasive cancer and three with noninvasive IPMN.

Outcome

Complete follow-up information was available for 60 patients (96.6%). The mean follow-up was 37.6 (range, 3–117) months. The overall survival curves and disease-free survival curves of patients with noninvasive IPMN and IPMN with invasive cancer are displayed in Figs. 1 and 2. Five-year disease-free survival and overall survival for the patients with noninvasive IPMN were both 92% compared with 47% and 41%, respectively, for the patients with invasive IPMN.

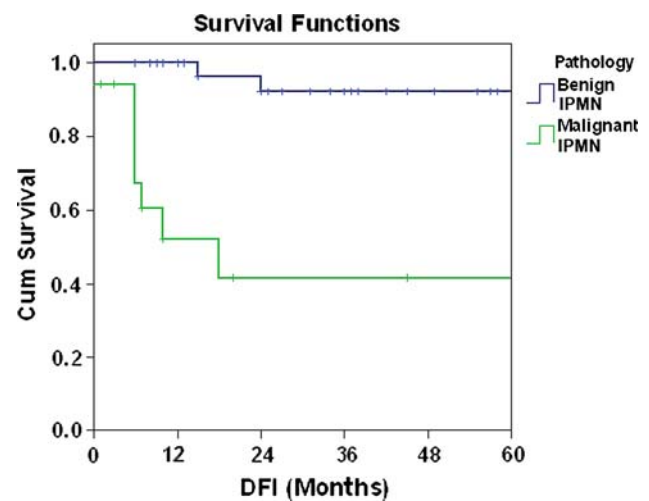


Fig. 1 Disease-free survival of patients with benign or malignant IPMN

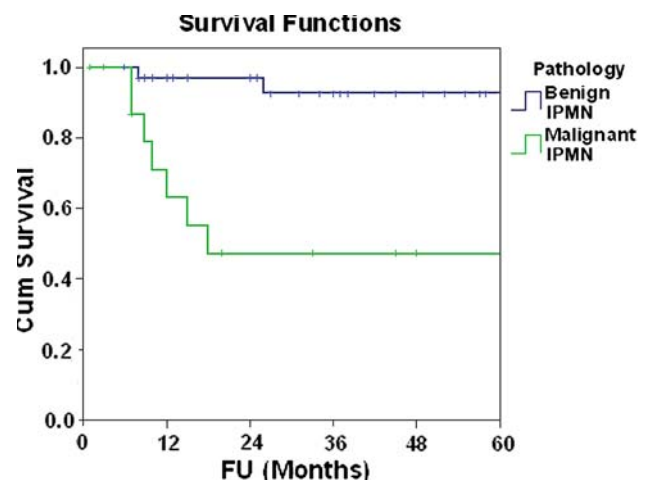


Fig. 2 Overall survival of patients with benign or malignant IPMN

Three patients (8%) with noninvasive IPMN had recurrence in the remnant pancreas. Two of these patients had negative surgical margins and the third had surgical margins involved with IPMN with low-grade dysplasia. Two of these patients developed additional cystic tumors, which were detected on follow-up EUS and underwent completion to near-total pancreatectomy 15 and 36 months after the initial operation. These patients are currently without evidence of disease at 52 and 39 months after the original operation. The third patient had IPMN with low-grade dysplasia with negative margins and recurred with diffuse peritoneal spread of pancreatic adenocarcinoma 24 months postoperatively. This patient died from disease 2 months later. He is the only patient with noninvasive IPMN who died of pancreatic disease in our series.

Eight of the patients who underwent resection for noninvasive IPMN had surgical margins involved with noninvasive IPMN. One patient who had a strong family history of pancreatic cancer underwent completion to total pancreatectomy. Another patient who developed new pancreatic cysts in the pancreatic remnant underwent completion to total pancreatectomy and is currently free of disease. All other patients are currently without evidence of disease after a mean follow-up of 50 (range, 12–102) months. Seven of the patients treated for invasive IPMN had positive surgical margins: four of them had invasive cancer, one had moderate dysplasia, and two had low-grade dysplasia. One of these six patients died during the perioperative period, four patients had disease recurrence after an average of 9 months postoperatively, and two patients are alive without evidence of disease 20 months postoperatively.

Discussion

Intraductal papillary mucinous neoplasm of the pancreas represents a distinct clinicopathological entity that is being recognized with increasing frequency. Several institutions have reported an increase in the annual number of pancreatic resections due to IPMN during the last decade [8, 9]. This is probably the result of the improved accuracy of the imaging modalities, increasing awareness of this clinical entity, previous misclassification, and possibly a true increase in the prevalence of the disease. We treated surgically a total of 62 patients diagnosed with IPMN of the pancreas—47 (75%) between 2002 and 2007. IPMN is the precursor lesion of a significant portion of pancreatic adenocarcinoma cases [10]. Our estimate is that 10.6% of resected pancreatic adenocarcinomas may have originated from IPMN lesions. This is probably an underestimation of the actual figure for two reasons: our study was performed retrospectively (1995–2001), and some tumors may outgrow and distort the adenomatous parts of the tumor.

Only patients with histologically proved IPMN were included in this study. Although the exclusion of the nonoperated patients may have caused a selection bias, their inclusion may have led to an equivalent bias as well. In our series, almost 10% of the patients who underwent surgery with a clinical diagnosis of IPMN (based on CT, EUS, and aspiration of cyst fluid) were found to have a different lesion on final pathology (two neuroendocrine tumors, one inclusion cysts, and two mucinous cystadenomas). The rate of false diagnosis of IPMN may be even higher in patients who were chosen for follow-up only. Also, the inclusion of patients without definite and detailed pathological examination makes it impossible to correlate clinical parameters with pathological ones.

The natural history of IPMN apparently begins with long-standing benign asymptomatic disease, continues to a symptomatic phase during which the most prominent symptom is nonspecific abdominal pain, and ends with the development of invasive cancer within IPMN. The difference in median age between patients with benign and invasive IPMN suggests that a 5- to 10-year interval is required for the development of invasive cancer within IPMN. Several previous reports also have demonstrated that a 5- to 10-year difference exists between patients with benign and malignant IPMN [2–4, 11]. Another possibility is that these are different entities: one is a benign, slow-growing tumor, and the other is an invasive, aggressive disease. Differentiating between the two is essential when planning treatment for these patients. Notably, there is no single imaging modality that can differentiate benign IPMN from malignant IPMN with absolute accuracy.

The diagnostic tools used for patients with suspected IPMN of the pancreas include high-quality triphasic CT and EUS, preferably with aspiration of cystic fluid and biopsy of suspected masses. Using these modalities in a center experienced in treating IPMN, and following a multidisciplinary approach (including HPB surgeons, gastrointestinal pathologists, gastroenterologists, and radiologists), we believe that a diagnosis of IPMN and differentiation from adenocarcinoma of the pancreas can usually be made preoperatively. Previous studies have reported that 40–60% of resected IPMNs contain invasive carcinoma [2–4]. In our series, 37% of the patients had invasive cancer within IPMN. However, patients with asymptomatic incidentally diagnosed lesions and IPMN without a lesion suspected as invasive cancer on CT and EUS (with FNA or biopsy when feasible) are at very low risk (5%) of harboring invasive cancer within this lesion. Patients who have symptomatic disease have a higher risk for cancer (almost 50% in groups 2 + 3). When these patients complete a thorough investigation by a multidisciplinary team, cancer can be usually be diagnosed with high sensitivity and specificity. In our series, symptomatic patients with a preoperative diagnosis of nonmalignant IPMN had a

9% risk of harboring invasive cancer within the lesion, and all patients who were diagnosed with cancer preoperatively proved to have invasive cancer on pathology. Also, 91% of patients with IPMN and invasive cancer were diagnosed as having cancer preoperatively. Our data support that clinical presentation of IPMN correlates with its biological behavior. The data provided demonstrate that symptomatic patients have a high chance (almost 50%) of invasive cancer. Therefore, in such patients surgery should be seriously considered. The rate of malignancy is significantly lower for asymptomatic patients (5%), and therefore, a nonoperative approach can be considered. A key consideration in decision making is good radiological assessment, allowing identification of radiological features suggestive of invasive malignancy arising on a background of IPMN, such as a mass lesion, or EUS-guided cytology. Nevertheless, the entire clinical information should be interpreted cautiously. The lack of symptoms and radiological stigmata of malignancy does not exclude the presence of invasive cancer, nor the possibility for future malignant transformation. Surgery still remains a valid option for patients with low risk for malignancy, especially young patients with good surgical risk.

Another controversy regarding treatment of patients with IPMN is the extent of pancreatic resection. Preoperative planning of the appropriate extent of pancreatic resection for patients with IPMN is difficult. It is not always possible to accurately locate the tumor and plan a segmental pancreatic resection accordingly. Preoperative studies may show a dilated pancreatic duct, which may occur both proximally and distally to the tumor because of overproduction of mucus or duct obstruction by a proximal tumor. This problem is compounded by the propensity of the tumor to spread microscopically along the pancreatic duct, and the uncommon possibility of multicentric tumors separated by normal pancreatic tissue. Interestingly, there was only one patient in our series with a positive retroperitoneal margin compared with 14 patients with positive ductal margin, 3 of them with invasive cancer. This may reflect the more indolent biological behavior of IPMN compared with ductal adenocarcinoma of the pancreas and also correlates with the better overall survival of these patients. There are several intraoperative modalities available for assessing surgical margins and the remaining pancreas, among them IOP, FSA, and IOUS [12–15]. Even after achieving clear surgical margins, however, there is a possibility of recurrence [11, 16]. In our series, two patients with low-grade IPMN who had undergone pancreatic resection with clear surgical margins experienced recurrence. One of them developed diffuse peritoneal and liver metastases 24 months postoperatively and died 2 months later. Therefore, patients with noninvasive IPMN have a small, but real, risk of developing invasive or noninvasive IPMN in the remaining pancreas after complete resection

with negative surgical margins. Another interesting observation that even further complicates decision-making is that only one of eight patients with benign IPMN and positive surgical margins had recurrence. The remaining seven patients are still disease-free without evidence of recurrence after a mean follow-up of 50 months. One of these patients is 102 months postoperatively without disease recurrence. Therefore, disease recurrence may not be dependent on surgical margins and remaining tumor cells alone, but perhaps also on the propensity of the remaining pancreas to develop a new lesion. Finally, the importance of attaining clear surgical margins, or even complete removal of the diseased pancreas in patients with benign disease, especially in young healthy patients, is still being debated. Given the slow-growing nature of IPMN tumors, it is unclear whether the long-term morbidities of total pancreatectomy endanger the patient more than the risk of subsequent malignant transformation of IPMN in the remaining pancreas.

Conclusions

Clinical presentation of IPMN correlates with its biological behavior. Symptomatic patients have a high chance (almost 50%) of invasive cancer. The rate of malignancy is significantly lower in asymptomatic patients (5%). The radiological features of malignancy, and EUS-based cytology, enable preoperative diagnosis of malignancy in IPMN in most patients, and these findings should mandate surgery in fit patients. However, the lack of symptoms and radiological stigmata of malignancy does not exclude the presence of invasive cancer, nor the possibility for future malignant transformation. In these patients, surgery remains a valid option to be considered.

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References

- Ohhashi K, Murakami Y, Maruyama M et al (1982) Four cases of “mucin producing” cancer of the pancreas on specific findings of the papilla of Vater. *Prog Dig Endosc* 20:348–351
- Salvia R, Fernandez-del Castillo F, Bassi C et al (2004) Main-duct intraductal papillary mucinous neoplasm of the pancreas. *Ann Surg* 239:678–687
- Sohn TA, Yeo CJ, Cameron JL et al (2004) Intraductal papillary mucinous neoplasm of the pancreas. *Ann Surg* 239:788–799
- D’Angelica M, Brennan M, Suriawinata A et al (2004) Intraductal papillary mucinous neoplasm of the pancreas. *Ann Surg* 239:400–408
- Taouli B, Vilgrain V, Vullierme MP et al (2000) Intra ductal papillary mucinous tumors of the pancreas: helical CT with histopathologic correlation. *Radiology* 217:757–764

6. Prasad SR, Sahani D, Nasser S et al (2003) Intraductal papillary mucinous tumors of the pancreas. *Abdom Imaging* 28:357–365
7. Longnecker DS, Adler G, Hruban RH (2000) Intraductal papillary mucinous neoplasms of the pancreas. In: Hamilton SR, Aaltonen LA et al (eds) *World Health Organization Classification of tumors. Pathology and genetics of tumors of the digestive system*. IARC Press, Lyon, pp 237–241
8. Sohn C, Yeo C, Cameron J, Donahue C, Hruban R et al (2001) Intraductal papillary mucinous neoplasms of the pancreas: an increasingly recognized clinicopathologic entity. *Ann Surg* 234:313–322
9. Siech M, Kertin T, Schmidt-Rohlfing B, Mattfeldt T et al (1999) Intraductal papillary mucinous tumor of the pancreas. *Am J Surg* 177:117–120
10. Rial TS, Strager VM, Nealon WH et al (2007) Incidence of additional primary cancers in patients with invasive intraductal papillary mucinous neoplasms and sporadic pancreatic adenocarcinomas. *J Am Coll Surg* 204:803–814
11. Chari ST, Yadav D, Smyrk T et al (2002) Study of recurrence after surgical resection of intraductal papillary mucinous tumor of the pancreas. *Gastroenterology* 123:1500–1507
12. Pare F, Sauvanet A, Terris B et al (2000) Intraductal papillary mucinous tumors of the pancreas: pancreatic resections guided by preoperative morphological assessment and intraoperative frozen section examination. *Surgery* 127:536–544
13. Kaneko T, Nakao A, Nomoto S et al (1998) Intraoperative pancreatoscopy with ultrathin pancreatoscope for mucin producing tumors of the pancreas. *Arch Surg* 133:263–267
14. Hara T, Yamaguchi T, Ishihara T et al (2002) Diagnosis and patient management of intraductal papillary mucinous tumor of the pancreas by using peroral pancreatoscopy and intraductal ultrasonography. *Gastroenterology* 122:34–43
15. Kaneko T, Nakao A, Inoue S et al (2001) Intraoperative ultrasonography by high resolution annular array transducer for intraductal papillary mucinous tumors of the pancreas. *Surgery* 129:55–65
16. White R, D'Angelica M, Katabi N et al (2007) Fate of the remnant pancreas after resection of noninvasive intraductal papillary mucinous neoplasm. *J Am Coll Surg* 204:987–995