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Outcome of Invasive and Noninvasive Intraductal Papillary-Mucinous Neoplasms of the Pancreas (IPMN): A 10-year Experience

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Abstract
Background Intraductal papillary-mucinous neoplasms (IPMN) were officially introduced into the TNM classification in 1996. Based on a two-center database, we reevaluated histopathological findings, clinicopathological pattern, predictive markers for malignancy, and outcome.
Methods Between 1996 and 2006, a total of 1424 pancreatic resections were performed in the University Hospitals Dresden and Mannheim. Pathologists of both institutions reviewed the IPMN diagnoses and other with cystic or solid tumor diagnoses. All possible markers, such as diabetes, jaundice, etc., were analyzed for prediction of malignancy. We performed a survival analysis based on the morphologic classification to determine the prognosis of IPMN.
Results There were 43 patients of primarily diagnosed IPMN along with 1174 patients with diagnoses, such as ductal adenocarcinoma. In 207 patients, the diagnoses revealed other cystic or small solid tumors. A histopathological review of the latter patients revealed 54 IPMNs, resulting in a total of 97 IPMN patients (29 noninvasive, 68 invasive). All IPMN patients had a median survival of 36 months. Recurrence occurred more frequently in invasive IPMN. Predictive markers of malignancy were pain, preoperative weight loss, jaundice, and elevated CA 19.9. The strongest independent prognostic factor was invasive growth. The survival analysis revealed excellent prognosis for noninvasive IPMN.
Conclusions Since the introduction of IPMN in 1996, even specialized centers have had to deal with a learning curve. By reevaluating all cystic or small solid tumors, centers can improve and their patients' treatment can be optimized. Because the preoperative diagnostic methods are not sensitive enough to differentiate between benign and malignant lesions, surgery is advocated for all main duct IPMN, because they have a high malignant potential. For branch duct IPMN, surgery is advocated if the lesion is symptomatic, >3 cm, or has enlarged nodules.

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Introduction

Until the early 1980s, intraductal papillary-mucinous neoplasms (IPMN) were regarded as one of the rare tumors of the pancreas. Haban [1] was probably the first author who described a papillomatosis in 1936. Since then, many attempts have been made to categorize papillary, mucin-secreting tumors [2]. In 1982, Ohhashi and Takekoshi [3] reported on four mucin-producing tumors and referred to them as IPMN. The World Health Organization classified the cystic mucin-producing neoplasms into two distinct entities:

intraductal papillary mucinous tumor, and mucinous cystic tumor [4–6]. In the reviewed classification of 2000, the two groups were renamed as intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) [5, 7]. Since then, much has been learnt about the clinical, radiological, and histopathological characteristics of IPMNs [8]. As their name implies, these are lesions of the pancreatic duct system. There are two distinct forms being diagnosed: main duct IPMNs and branch duct IPMNs. The mixed category is no longer being proposed [5]. Microscopically, these lesions are characterized by a columnar, mucin-containing epithelium, with or without papillary projections [5]. IPMNs always have a communication to the duct but no ovarian type stroma in contrast to MCNs [5]. IPMNs grow typically for a long time within the ducts before half of them become invasive [5, 8]. As a consequence, IPMNs comprise a large spectrum ranging from adenomas to invasive cancer with various degrees of aggressiveness [5, 8]. It is important to differentiate between invasive and noninvasive IPMNs, because they are associated with completely different long-term survival rates [5, 8–11]. However, according to the standard preoperative diagnostic methods it often is impossible to differentiate between invasive and noninvasive IPMN before the final histopathological findings. Furthermore, little is known about the natural behavior of the two tumor types after surgery: the time course of the progression of noninvasive type to the invasive type is unknown, as is the frequency of recurrence in the pancreatic remnant or the rate of metastases. Based on a two-center database, histopathological findings, clinicopathological patterns, predictive markers for malignancy, and the survival and recurrence of invasive and noninvasive IPMNs were evaluated. Guidelines for the management of IPMNs were established in 2004 by the International Association of Pancreatology (IAP) [5]. The development of appropriate treatment guidelines dealing with IPMN is a critical issue, because the understanding of this tumor type is still in progress. Therefore, the second objective was to elaborate recommendations for the operative management of IPMN based on the presented results.

Materials and methods

There are two prospective databases with patients with pancreatic tumors in the Department of Surgery of University-Hospital Mannheim (MA), and the Department of Surgery of University-Hospital Dresden (DD), Germany. Throughout the 10 years between the introduction of IPMN into the WHO classification in 1996 and 2006, a total of 1424 pancreatic resections were performed in the above-mentioned institutions. Primarily, in 43 (3%) patients IPMN were diagnosed. A reevaluation was conducted for 207 other cystic and small solid tumor diagnoses as follows: mucinous cystic neoplasms, serous cystic neoplasms, solid pseudopapillary neoplasms, cystadenomas, cystadenocarcinomas, pseudocysts, cystic neuroendocrine neoplasms, cystic degerated sold carcinomas, and all "adenomas," "borderline" diagnoses, in situ carcinomas, all pT1 ductal, papillary, and distal bile duct tumors. Pathologists of both departments (RH, DD) reviewed all the IPMN subjects and all those with other cystic and small solid tumor diagnoses. The tumors were classified according to the WHO criteria for IPMN [6, 7]. The patients' characteristics, such as recent onset of diabetes, weight loss, pain, jaundice, tumor markers CA 19.9 (carcinoma antigen), and CEA (carcinoembryonal antigen) previous to surgery, were analyzed for prediction of malignancy. Frozen sections (radial) were routinely being obtained from the resection margin. In malignant diseases, a positive resection margin (tumor cells in the resection line or in a distance of <1 mm) resulted in further resection until one negative resection margin has been obtained. Furthermore, the surgical procedures, morbidity, mortality, length of postoperative stay, the pathology report, including the nodal involvement, were analyzed. Follow-up was performed through a personal contact with the patients or with the patients' primary physician and was terminated on May 1, 2007 or at patients' death. The follow-up for invasive IPMN consisted of clinical and laboratory workup, as well as CT or MRI every 6 months. Noninvasive IPMN were followed up with yearly CT or MRI. This interval was spaced if no changes have occurred during several years. Recurrence was diagnosed by ultrasound, CT, MRI, or through palliative surgery with biopsy. All deaths occurring within 30 days after surgery or during the hospital stay were classified as surgical mortality. Finally, a survival analysis was performed to determine the prognosis of IPMN.

Statistical analysis

The survival analyses were calculated by the Kaplan-Meier method (SPSS, Release 15.0, SPSS Inc., Chicago, IL), and differences in survival among subjects were compared by the log-rank test [12]. Prognostic factors were examined by multivariate and univariate analyses using Cox's proportional hazards model [13]. Comparisons of parametric data were examined by the *t* test, those with nonparametric data with Spearman's correlation. Significance was accepted at the probability level of 0.05.

Results

Histological reevaluation

Of a total of 1424 pancreatic resections between 1996 and 2006, there were 43 patients with primarily diagnosed IPMN.

In addition to 1174 "typical diagnoses," such as ductal adenocarcinoma, chronic pancreatitis, or others, there were 207 patients with other cystic and small solid tumor diagnoses, which were then qualified for reevaluation. The histological review of the latter patients resulted in 54 newly diagnosed patients with IPMN. In all primarily diagnosed IPMN patients, the diagnosis was reconfirmed. The first diagnosis for IPMN was in 2001. Both institutions counted to a total of 97 (43 primarily diagnosed plus 54 diagnosed in the reevaluation) IPMN patients (6.8% of 1424 resections), of which 29 were noninvasive and 68 were invasive IPMN according to the WHO classification (Fig. 1) [6]. Of the 68 latter patients, 28 (41.2%) had lymph node metastases, 20 (29.4%) had perineural, 21 (30.9%) lymphangio invasion, and 8 (11.8%) positive resection margins in the final histopathology (not in the frozen section). None of the noninvasive IPMNs had nodal, perineural or lymphangio invasion, or positive margins. During the first 5-year period until 2001, 1 of 22 patients was primarily correctly interpreted as IPMN, whereas during the second 5-year period (2002–2006), 67% (51/76) were correctly diagnosed. In 78 patients (80.4%), the tumor originated from the head, in 9 (9.3%) from the corpus, and in 8 (8.2%) from the tail. Two patients (2/97) presented a multifocal tumor. The median tumor diameter was 30 (range, 4–150) mm in invasive and 27.5 (range, 7–88) mm in noninvasive IPMN ($p = 0.295$). In both institutions, all resections were performed with negative intraoperative resection margins to pancreatic remnant in the frozen section. This was confirmed in the reevaluation. In ten patients (10/97), invasive IPMN was found in combination with ductal adenocarcinoma. Furthermore, in three patients with noninvasive IPMN, we found a carcinoma in situ as well as the histological features of an IPMN. All three patients are alive. One of these patients had a recurrent IPMN and was resected 1 year after primary diagnosis. Again a noninvasive IPMN and a carcinoma in situ were found.

Preoperative characteristics

Of the 97 patients with IPMN, 31 (32%) complained about weight loss, 42 (43.3%) suffered from abdominal and back pain, and 37 (38%) had a preexisting diabetes. Twenty-nine (29.9%) patients presented with jaundice, 18 of which (62.1%) were preoperatively treated endoscopically with a stent. Levels of the serum tumour markers CA 19.9 were increased (>37 kU/l) in 40 patients (41.2%). In 27 (27.8%) patients, CEA levels were elevated (>3 ng/l). Univariate analysis revealed significant correlation between malignancy and abdominal and back pain, weight loss, age (>70 years), jaundice, and elevated CA 19.9 ($p < 0.05$; Table 1). There was no correlation observed between malignancy and sex, preexisting diabetes, ASA stage, tumor location and size, and elevated CEA (Table 1).

Perioperative course

The surgical procedures and the results are summarized in Table 2. For a complete resection of IPMN, a classic Whipple procedure was performed in 29 (29.9%) patients, in 49 (50.5%) patients a pylorus-preserving pancreaticoduodenectomy, in 5 (5.2%) patients a total pancreatectomy, and in 14 (14.4%) patients a distal pancreatectomy. In 13 (13.4%) patients, an extended resection was performed: 10 (10.3%) extended venous resection (portal vein or superior mesenteric vein), 1 left hemicolectomy (together with distal resection), 1 atypical gastric resection (together with distal resection), and 1 hiatoplasty (together with pylorus-preserving pancreaticoduodenectomy). Extended resections

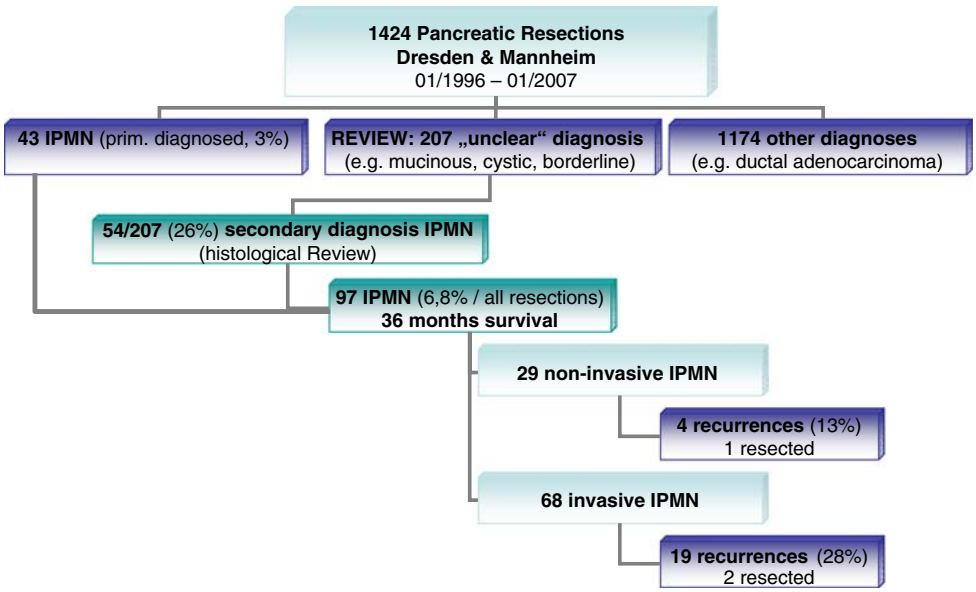

Fig. 1 Histological review process and follow-up of 1424 pancreatic resections from 1996 to 2006 in Dresden and Mannheim

Table 1 Prediction of malignancy in IPMN: Univariate statistical analysis for the correlation between clinico-pathological patterns and malignancy

Parameter	*p* value
Age ≥ 70 yr	**0.013**
Weight loss	**0.039**
Abdominal pain	**0.023**
Jaundice	**0.048**
ASA stage III + IV	0.183
Preoperative diabetes	0.091
Tumor diameter ≥ 2 cm	0.354
CEA ≥ 3 ng/l	0.176
CA 19.9 ≥ 37 kU/l	**0.001***

* Possible interaction with patients with obstructive jaundice and elevated CA 19.9 levels

Table 2 Results of surgical procedures for the resection of IPMN

	PPPD/ Whipple [*n* = 78] (%)	Distal pancreatectomy [*n* = 14] (%)	Total pancreatectomy [*n* = 5] (%)
Mortality (*n*)	0	1	0
Overall morbidity* (*n*)	47 (60.3)	4 (28.6)	4 (80)
Leakage PJ (*n*)	4 (5.1)	–	–
Leakage HJ (*n*)	2 (2.6)	–	0
Bleeding (*n*)	5 (6.4)	2 (14.3)	1 (20)
Intra-abdominal abscess (*n*)	1 (1.3)	2 (14.3)	1 (20)
Postoperative pancreatitis (*n*)	7 (8.9)	0	–
Delayed gastric emptying (*n*)	10 (12.8)	–	1 (20)
Relaparotomy (*n*)	4 (5.1)	2 (14.3)	1 (20)
Operating time (mean, min)	387	301	464
Extended resection** (*n*)	10 (12.8)	2 (14.3)	1 (20)
Blood loss (mean, ml)	890	1100	1325
No blood transfusion (*n*)	40 (51.3)	7 (50)	1 (20)
Postoperative stay (median, range 8–130 days)	17	12	23

PPPD: pylorus-preserving partial pancreaticoduodenectomy, * including cardiovascular, pulmonary, etc. Complications, ** including 10 extended venous resections, one left hemicolectomy, one atypical gastric resection, and one hiatoplasty. PJ: pancreatico-jejunostomy, HJ: hepatico-jejunostomy. No blood transfusion means no transfusion during the hospital stay at all and numbers of patients (percentage) are given

were necessary for suspected malignancies which were proven in 11 of 13 patients. The overall morbidity (surgical and general) was 56.7% (55/97 patients). One patient died postoperatively due to multiorgan failure after distal pancreatectomy for invasive IPMN. There were no differences in the morbidity rates between the two institutions with the exception of a higher relaparotomy rate in Dresden (1 vs. 6; 3% vs. 9.4%, $p < 0.05$). The morbidity and mortality rates were comparable to that of pancreatic resections due to diagnosis other than IPMN in our institutions, as previously reported [14–18]. The median postoperative stay was 17 (range, 8–130) days in both institutions.

Long-term outcome

The median follow-up was 36 (range, 1–124) months. Follow-up data could be achieved for all patients. The median survival for all IPMN patients was 36 (range, 0–124) months. The median survival for patients with invasive IPMN was 28 (range, 2–121) months, and for those with noninvasive IPMN was 65 (range, 0–124) months. The disease-specific survival for patients with invasive IPMN is 29 months. Until now, no patient died as a result of noninvasive IPMN. The disease-specific survival for these patients is 68 months. Recurrence was diagnosed in a total 23 of 97 (23.7%) patients during the observation period. Four patients (13%) with noninvasive IPMN suffered recurrence during the course of their disease. One female patient underwent distal pancreatectomy for noninvasive IPMN combined with a carcinoma in situ. One year later, recurrence was observed in the pancreatic remnant. She received a pylorus-preserving pancreatoduodenectomy, which confirmed a noninvasive IPMN combined with a carcinoma in situ again. All patients with noninvasive IPMN remained alive until the end of the follow-up period. All other recurrences occurred in patients with invasive IPMN (19/68 patients, 28%). In two patients the pancreatic remnant was resected and an invasive IPMN was confirmed. All re-resected patients are still alive. Due to distant metastases or a reduced general condition, no surgery was performed in the other patients. For the comparison of invasive versus noninvasive IPMN, the survival analysis was stratified and is shown in Fig. 2. The 10-year survival for 29 subjects with noninvasive IPMN was excellent at 90%, whereas the survival for patients with invasive IPMN was significantly lower (10-year survival rate of 25%). The median survival of invasive IPMN with nodal involvement was even worse: 26 (range, 2–121) months. These patients had a 30% 5-year survival rate, whereas those without nodal involvement revealed a 5-year survival rate of 75% (Fig. 3). In an attempt to clarify predictors for survival, a multivariate analysis was performed. As demonstrated in Table 3, the multivariate analysis indicated the invasiveness of the tumor to be the only significant marker for survival. None of the other parameters were significant.

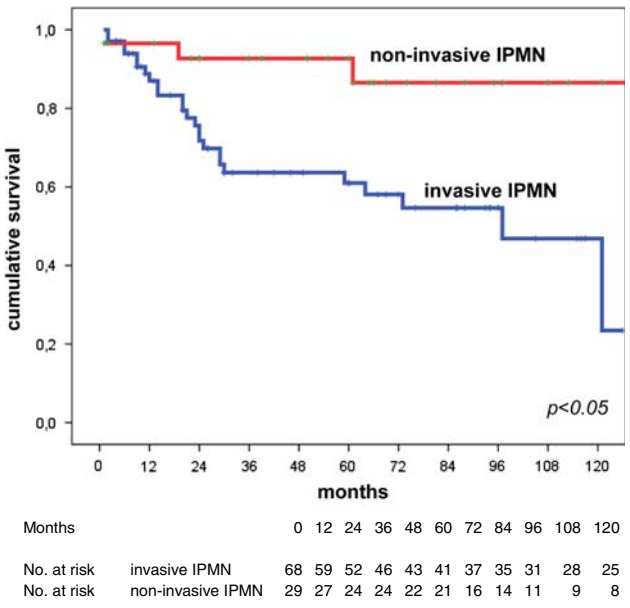

Fig. 2 Cumulative survival of 68 patients with invasive vs. 29 patients with noninvasive IPMN. The difference in survival was significant ($p < 0.05$)

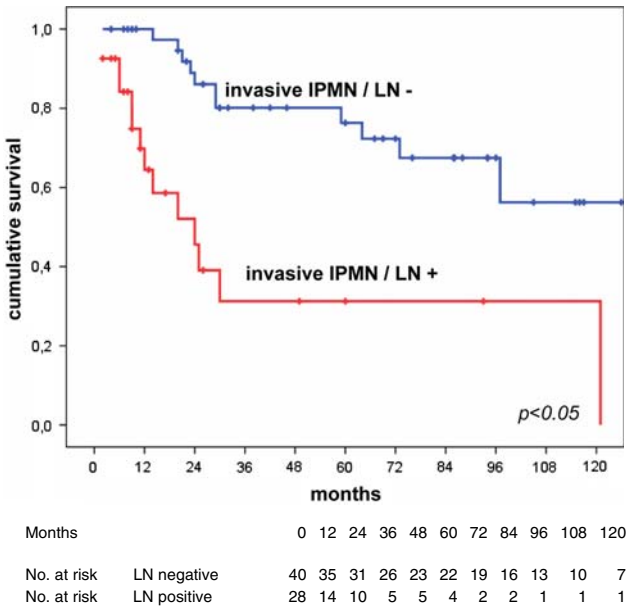

Fig. 3 Cumulative survival of 28 patients with invasive IPMN and positive lymph nodes (LN+) vs. 40 patients with invasive IPMN without lymph node involvement (LN−). The difference in survival was significant ($p < 0.05$)

Discussion

Since the introduction of the nomenclature of IPMN by the WHO in 1996 [5, 6], an increased awareness of IPMN in diagnostic imaging and histopathology has contributed to a general increase in recognition of this disease. Similar to any other "new" pathological classification, the importance of an accurate histological diagnosis cannot be overemphasized. However, the improved classification and, therefore, the increase in the identification alone cannot sufficiently explain the enormous increase in the frequency of IPMN diagnosis [8].

Even specialized centers have had to deal with a "learning curve" concerning diagnosis of IPMN. The combined experience of two large centers in Germany demonstrates a learning curve during the initial years after introduction of IPMN to the WHO nomenclature, as the first IPMN was primarily diagnosed in 2001. Reevaluation of all other cystic and small solid tumor diagnoses, which might have been falsely diagnosed in the past, is worthwhile to improve patient care. Focussing on the excellent long-term outcome of IPMN, it is worthwhile to begin such reevaluation, because patients' diagnoses can be corrected and the future therapeutic regimens can be adjusted (such as resection of recurrence). From our point of view, communication between radiologists, gastroenterologist, pathologists, and surgeons on this "new" topic is essential to improve treatment of this disease and the "learning curve," which both institutions obviously had during the period between 1996 and 2001.

The experience with IPMN was reviewed to determine predictive markers for malignancy and prognostic factors to elaborate advices for the operative management of IPMN. There have been many attempts to identify preoperative markers differentiating benign and malignant IPMN [5, 19–27]. Similar to other institutions [10, 24–26, 28–31], we could show in a multivariate approach that "symptomatic" IPMN often is associated with malignancy: abdominal and back pain, weight loss, jaundice, and elevated CA19.9 ($p < 0.05$). However, CA 19.9, a biliary epithelial marker, is elevated in patients with high bilirubin levels, which might lead to a false-positive statement, as 29 of 97 patients had jaundice before surgery. As opposed to other centers, we could not observe a positive correlation between the tumor size, location in the head [24], diabetes, elevated liver enzymes and CEA levels, and a malignant

Table 3 Multivariate Cox regression analysis for prognostic factors in IPMN

Parameter	p value
Invasive tumor growth	**0.01**
Age (yr)	0.34
Abdominal/back pain	0.11
Weight loss	0.09
Jaundice	0.12
Elevated CA 19.9	0.19

PPPD: pylorus-preserving partial pancreaticoduodenectomy, DP: distal pancreatecomy, TP: total pancreatecomy

behavior [25]. This observation also has been reported in other larger series with more than 70 patients [9, 26]. In general, the prognosis of IPMN is much more favorable compared with that of the ductal adenocarcinoma of the pancreas [5, 8, 11, 32]. Corresponding to other reports, multivariate analysis shows invasive tumor growth to be an independent prognostic marker (Table 3) [9, 10, 26, 33]. The 5-year survival rate of noninvasive IPMN has been reported to be 85–100% [9–11, 23, 26, 27, 33, 34]. In comparison, survival is poor for invasive IPMN: 5-year survival rate is 25–65% [9–11, 26, 27, 33, 34]. In the presented series, the 10-year survival for noninvasive IPMN was excellent at 90% (5-year survival 95%), whereas the survival for patients with invasive IPMN was significantly worse with a 10-year survival rate of 25% (5 years, 60%; Fig. 2). Invasive IPMN with nodal involvement shows the lowest median survival of 26 months, and a 5-year rate of 30% (Fig. 3). Regarding the actuarial survival IPMNs appear to form two different tumor entities, revealing a favorable survival for noninvasive IPMN, which is comparable to the survival rates in papillary thyroid cancer [35]. Because a poor prognosis correlates with an invasive growth, we believe that a cure can be predicted for all noninvasive IPMNs. This should even be possible for invasive IPMNs. Recurrence also occurred more frequently with invasive IPMN (28%) than with noninvasive IPMN (13%). This determines further the survival in case of an invasive tumor growth (Fig. 1). All of the 19 patients suffering from invasive IPMN with recurrence, even those with resection of the pancreatic remnant (2 patients), died from this disease during the observation period. Their median survival is reduced to 30 months compared with 36 months survival of all IPMNs and varied from 6 to 97 months. Two patients lived longer than 5 years (72 and 97 months), but died at a later period due to recurrent disease. This observation suggests that similar to ductal adenocarcinoma of the pancreas an occurrence of invasion correlates with early extrapancreatic disease or micrometastases beyond surgical margins. In comparison, 4 of 29 patients with noninvasive IPMN had recurrence, not limiting their further survival, because no patient died as a result of this disease.

A total pancreatectomy has been recommended for invasive IPMN in the past [36]. Based on the presented results, total pancreatectomy is not recommended for localized invasive IPMN [5, 9, 33, 37], because it is unlikely to prevent recurrence in this subgroup of patients, and the recurrence rates are low (28%) compared with other pancreatic malignancies [15]. Furthermore, total pancreatectomy should not be recommended for noninvasive, localized IPMN because of the severe metabolic consequences as a result of the operation and the fact that recurrence does not limit the survival in these patients.

The following strategy for (intra-) operative management is proposed: in case of positive resection margins for invasive IPMN, we suggest further resection until negative margins intraoperatively are obtained. This might result in total pancreatectomy, such as in a multifocal disease, as in our two patients with multifocal IPMN. In case of a positive margin in noninvasive IPMN, the decision on further resection should be made individually based on the patient's general condition. In healthy patients achieving a negative margin is recommended; in patients with high comorbidity we suggest limited resection (for instance resection of only the leading lesion).

Furthermore, surgery of recurrence is the only therapeutic option, even in noninvasive IPMN. This also is advocated by other reports [10, 33]. Chari and coworkers [33] describe invasive cancer as recurrence after initially noninvasive IPMN. This implies that recurrence in noninvasive IPMN might occur due to dysplastic tissue being present at the resection margin, or an undetected multifocal disease, or metachronous lesions developing in the remnant pancreas. Recurrence may become evident late because IPMN is a slow-growing tumor [5]. As a consequence, we suggest a lifetime surveillance program, because otherwise the recurrence rate might be underestimated. As previously recommended, patients with resected noninvasive IPMN should be followed with yearly CT or MRI, and then space this interval if no changes have occurred during several years [5]. In our series, no patient with noninvasive IPMN died from this disease, but 4 of 29 patients had recurrence. Patients with resected invasive IPMN should be evaluated every 6 months (CT or MRI) [5] because they do have a significant risk of recurrence; we found a 28% recurrence rate in the follow-up period. As stated in a previous report, regular follow-up CT scans can detect recurrences at an early stage, as opposed to symptoms, which are late events [33]. In patients with a good general condition, resection of recurrent disease is strongly recommended.

Like other institutions, surgery in every patient with main-duct IPMN is advocated [4, 5]. According to the IAP guidelines, in patients with branch duct IPMNs with a tumor size <3 cm, no enlarged nodules, and no symptoms observation is justified [5]. A critical issue is patients in whom no accurate radiological diagnosis of a branch duct type lesion and no potential signs of benign growth can be obtained. The ability of CT and MRI to determine whether malignant disease is present remains uncertain [38]. From our perspective, resection is recommended in these patients based on reported malignancy rates between 6 and 46 percent in branch-type IPMNs [5, 34, 39]. The surgical morbidity and mortality rates for IPMN (Table 2) are reasonable and comparable to surgery for ductal adenocarcinoma as previously reported by our group [14–18, 39, 40]. Regarding the moderate morbidity and mortality, as in

our and most large series [9, 10, 26, 27, 30, 31, 33], surgery for the above-mentioned IPMN lesions seems to be justified. This implies a definite long-term cure for noninvasive IPMN and even the chance for a long-term survival with invasive IPMN.

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