

Liver, Pancreas and Biliary Tract

Outcomes of intraductal papillary mucinous neoplasm with “Sendai-positive” criteria for resection undergoing non-operative management

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ARTICLE INFO

Article history:

Received 24 September 2012

Accepted 7 January 2013

Available online 27 February 2013

Keywords:

Conservative approach

Intraductal papillary mucinous neoplasms

Outcome

Sendai criteria

ABSTRACT

Background: There are few data on the outcome of patients with intraductal papillary mucinous neoplasms of the pancreas meeting criteria for resection (Sendai-positive), and not operated.

Aim: To evaluate outcome of patients with a resectable, Sendai-positive intraductal papillary mucinous neoplasm, and not operated.

Methods: Multicentre, retrospective analysis of prospectively enrolled patients, with resectable Sendai-positive, not-operated intraductal papillary mucinous neoplasm. Overall-survival and disease-specific survival were the primary end-point, and progression-free survival secondary.

Results: Thirty-five patients (60% male, median age 77) enrolled: 40% main-duct, 60% branch-duct intraductal papillary mucinous neoplasms. In 19 patients surgery was ruled out due to comorbidities, in 7 because aged > 80, 9 refused surgery. Twelve (34.3%) patients died after a mean of 32.5 months, 8 due to disease progression, 4 due to comorbidities. The median overall, disease-specific and progression-free survival were 52, 55, and 44 months respectively. Main duct involvement and age at diagnosis were associated with worse overall and progression-free survival, only main duct involvement with worse disease-specific survival (52 months main duct vs. 64 branch duct; $P=0.04$).

Conclusion: These results suggest that in elderly and comorbid patients with Sendai-positive intraductal papillary mucinous neoplasms, especially of the branch duct, a conservative approach could be reasonable, as associated with a relatively good outcome, and should be carefully discussed with the patients.

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1. Introduction

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are a distinct form of exocrine pancreatic neoplasm characterized by dilated ducts that are lined by a proliferation of papillary mucinous epithelium [1]. Depending on the site of the disease, IPMNs are classified as either main-duct (IPMN-MD) or branch-duct (IPMN-BD) type [2]. Mixed IPMNs, defined by a simultaneous involvement of both main pancreatic duct and its secondary branches, show close similarities with IPMN-MD in regard to clinico-pathologic and epidemiologic characteristics [3].

At the time of the diagnosis, IPMN-MD, including mixed type, have an elevated risk of malignancy, ranging from 36% to 100% in different series [4], thus requiring surgical resection [5]. On the other hand, IPMN-BD have a lower risk of malignancy, allowing the adoption of a follow-up strategy, with the aim of limiting resection to those with specific signs of malignancies [6].

On this basis, in 2006 specific criteria have been developed throughout a Consensus Conference, to define the indication for surgery in patients with IPMN. The Sendai guidelines suggest surgical resection for all patients with an IPMN involving the main pancreatic duct, and more selectively for patients with an IPMN-BD. In these latter surgery is recommended when the diameter exceeds 3 cm, in the presence of mural nodes, of specific symptoms or of positive cytology for malignant cells, or in patients who develop changes of the diameter over time [7]. These guidelines proved to have a very high sensibility in recognizing malignant IPMNs, but a lower specificity, with a high rate of patients undergoing surgery without malignancy at final pathology [8–10]. In 2012 these

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guidelines have been updated, but a similar policy in terms of indication for surgery has been maintained [4].

The Sendai guidelines suggest to limit surgery to “good surgical candidates” with a reasonable life expectancy, and to take into account patient preferences for IPMN management. However, there are few data on the outcome of patients with IPMN who meet criteria for surgical resection (Sendai positive), and are not operated upon [11].

The present study was therefore aimed at evaluating the outcome and natural history of patients with an IPMN meeting Sendai criteria for surgical resection, who, although deemed technically resectable, did not undergo surgery.

2. Patients and methods

2.1. Study design

Multicentre, retrospective analysis using institutional prospective databases.

2.2. Patients

The study included all consecutive patients seen at the participating centres (Digestive and Liver Disease Unit, University Sapienza Rome, Surgical Department Negrar, Department of Digestive Diseases and Internal Medicine, University of Bologna), who were diagnosed with an IPMN meeting Sendai criteria for surgical resection, and did not undergo surgery. All tumours were technically resectable without radiologic evidence of local infiltration or distant metastases. Patients with cystic lesions other than IPMN were excluded from the study.

Inclusion criteria were: (i) a certain or highly probable diagnosis of IPMN. The diagnosis of IPMN was considered as certain in the presence of one of the following criteria: (1) histological diagnosis obtained by endoscopic ultrasound (EUS) fine-needle aspiration (EUS FNA) or biopsy (EUS FNAB); (2) cytological diagnosis obtained by EUS FNA. A highly probable diagnosis of IPMN was based on the presence of one or several of the following accepted criteria: presence of one or several main pancreatic duct and/or branch duct dilatation(s) and/or pancreatic cystic lesions communicating with pancreatic ducts at CT, magnetic resonance cholangiopancreatography with secretin stimulation (S-MRCP), endoscopic retrograde cholangiopancreatography (ERCP) or EUS. (ii) The patients had at least one Sendai criteria for surgical resection (size > 30 mm, mural nodes, involvement of main duct, symptoms) and were deemed resectable. (iii) The patients did not undergo surgery and underwent observation without other treatments. Due to the study design, clinical approaches were not standardized, and thus patients underwent follow-up examinations at different intervals (at least every 6 months, or at shorter intervals if necessary) by means of different imaging procedures.

The research protocol has been approved by the ethics committee of each participating centres, and informed consent has been obtained from patients.

2.3. Data analysis

All data were prospectively collected at the centre where the patient had been initially observed. A unique computerized datasheet was created, and data regarding the main demographic, clinic, and pathological features were retrospectively analyzed.

Data on clinical history, tumour localization and ductal involvement were recorded at enrolment.

Data on disease progression (DP) and patients' outcome were prospectively collected at control visits.

Table 1

General features of the 35 patients with intraductal papillary mucinous tumour with positive Sendai criteria for surgical resection.

	Total (n = 35)	MD-IPMN (n = 14)	BD-IPMN (n = 21)
Age (years)	77 (43–87)	80 (63–87)	77 (43–86)
Male sex	21 (60%)	10 (71.4%)	11 (52.3%)
<i>Indication for surgery^a</i>			
Symptoms	12 (34.3%)	9 (64.2%)	3 (14.2%)
MD involvement	14 (40%)	14 (100%)	–
BD-IPMN ≥ 30 mm	20 (57.1%)	–	20 (95.2%)
Mural nodules	13 (37.1%)	7 (50%)	6 (28.6%)
<i>Potential curative surgical intervention</i>			
PD	18 (51.4%)	10 (71.4%)	8 (38.1%)
DP	4 (11.4%)	4 (28.5%)	0 (0%)
TP	13 (37.1%)	5 (35.7%)	8 (38.1%)

Data are expressed as median (range). MD, main duct; BD, branch duct; IPMN, intraductal papillary mucinous neoplasm; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy.

^a Some patients had more than one indication.

The main end points considered were overall survival (OS), and disease-specific survival (DSS), whereas progression-free survival (PFS) was considered as secondary end points. OS was defined as the time between diagnosis of IPMN with criteria for a surgical resection and the decision not to undergo surgery (which coincided with time of presentation at the centres) and date of death due to any cause. DSS was defined as the time between diagnosis and death due to IPMN. PFS was defined as the interval between the diagnosis of IPMN and the time of DP, or patient death, if it occurred before documented radiological progression. DP was defined as the appearance of new lesions or an increase in size associated with the appearance of a solid component or with signs of local or vascular invasion.

For survival analysis, data were censored if the patient was alive, or lost at follow-up (censoring date was the date of the last adequate tumour assessment). PFS, as well as OS analysis, were performed using the Kaplan–Meier method, and the results were compared by using a log-rank test. Risk factors were expressed as hazard ratio (95% confidence interval, CI). The analysis of risk factors for prediction of progression during follow-up was performed by univariate and multivariate analysis using a Cox proportional hazards model. The multivariate model was constructed by ‘enter’ method, after including all variables which had resulted significant at the univariate analysis.

3. Results

3.1. Patients' characteristics

Thirty-five patients meeting the inclusion criteria were enrolled at the participating centres. Demographics and general features of these subjects are detailed in Table 1. These patients were selected analyzing a database of 387 IPMN patients seen at the participating Units, with a certain (histological) diagnosis in 77 cases (20%) and a highly probable diagnosis in 310 (80%). The included 35 patients therefore accounted for 9% of all the initial IPMN population.

Most of these neoplasms (23/35, 65.7%) were asymptomatic at diagnosis, incidentally diagnosed in the course of radiological examinations performed for reasons unrelated to the pancreas. The remaining 12 patients had either recurrent abdominal pain (5/12, 41.7%), acute pancreatitis (3/12, 25%), jaundice (2/12, 16.7%), weight loss and steatorrhea (2/12 16.7%). The indication for surgery according to Sendai criteria are resumed in Table 1. Fourteen (40%) patients had a main duct involvement and 21 (60%) a branch duct IPMN, with a median size of 40 mm (range 27–80 mm).

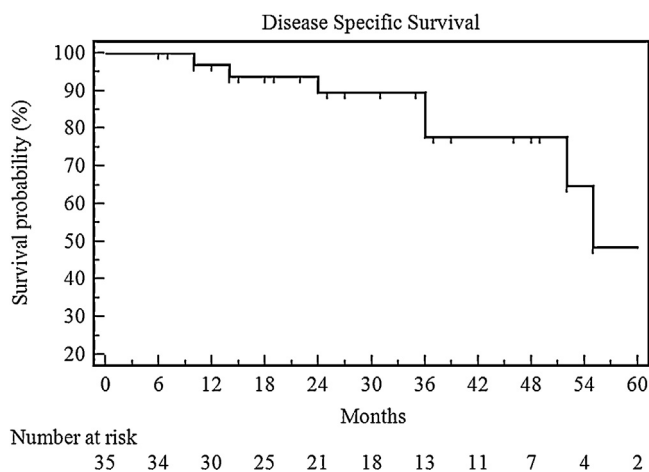


Fig. 1. Disease-specific survival probability estimated on Kaplan–Meier method.

In relation with the site and distribution of the lesions, the potential curative surgical approach would have been a pancreaticoduodenectomy (PD) in 18 (51.4%), a distal pancreatectomy (DP) in 4 (11.4%) and a total pancreatectomy (TP) in 13 (37.1%) patients.

3.2. Reasons for not undergoing surgery

In 19 of 35 subjects (54.3%) surgery was ruled out due to the presence of one or multiple relevant comorbidities determining an American Association of Anaesthetists (ASA) score ≥ 3 , and/or of synchronous neoplasms as detailed in Table 2. Seven other patients had an ASA score < 3 , but they were older than 80 years (median age 84, range 81–86), and surgery was deferred, opting for a close follow-up, as the risk of surgery, which would have been a total pancreatectomy or a pancreaticoduodenectomy, was considered to outbalance that of rapid tumour progression. The remaining 9 patients (median age 72, range 43–78), with an ASA score < 3 , refused surgery after being informed regarding their disease (BD lesions in all cases), and about the indication for surgical resection (total pancreatectomy or pancreaticoduodenectomy in all but one case) and risks.

3.3. Outcome of patients and survival analysis

A total of 12 out of 35 patients (34.3%) died after a mean follow-up of 32.5 months (95%CI 25.9–39.1). Eight of these patients died due to progression of the disease at a mean time of 36.3 months (95%CI: 19.9–52.8) from diagnosis (Table 3), while four died due to other significant comorbidities (other cancer, heart failure, pneumonia with sepsis and stroke) at a mean of 30.7 months from diagnosis (95%CI: 1.7–63.2). Accordingly, the median OS estimate at the Kaplan–Meier curve was of 52 months with a 5-year OS rate of 35.2%. The median DSS was 55 months (Fig. 1), with a disease-specific 5-year survival rate of 48.5%. The median PFS was of 44 months (Fig. 2), and the median 5-year PFS was not reached.

The variables considered as risk factors for survival were analyzed using univariate and multivariable analysis as summarized in Table 4. The only factors associated with worse OS were age at diagnosis (HR 1.26; 95%CI: 1.03–1.5 per year; $P=0.006$) and involvement of the main pancreatic duct (HR 3.29; 95%CI: 0.96–11.3; $P=0.053$). Only age was confirmed as a significant factor associated with worse OS at the multivariate analysis (HR 1.23; 95%CI: 1–1.5; $P=0.009$).

The only factor associated with worse DSS was the involvement of the main pancreatic duct (HR 4.7; 95%CI: 0.91–24.4; $P=0.048$). Accordingly, the median DSS, estimated at Kaplan–Meier analysis,

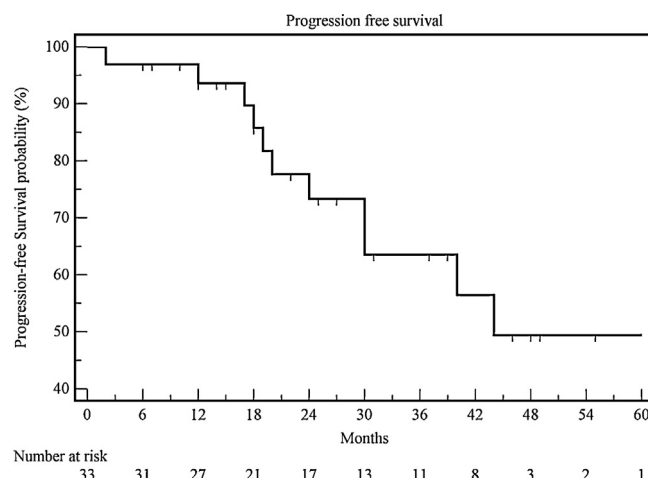


Fig. 2. Progression free survival probability estimated on Kaplan–Meier method.

resulted significantly lower in patients with IPMN-MD including mixed-type compared to those with BD-IPMN (52 vs. 64 months; $P=0.04$). The presence of mural nodules at initial presentation was not associated with the risk of disease-related death or progression. Overall of the 13 patients with mural nodules at initial presentation, only 3 had DP during the follow-up and two of them died of disease; the three patients with BD IPMN who died of invasive cancer, did not have mural nodules at diagnosis (see Table 3).

At univariate analysis, the only significant factors associated with PFS were age (HR 1.2; 95%CI: 1–1.41; $P=0.008$) and the involvement of the main pancreatic duct (HR 4.71; 95%CI: 1.1–18.5; $P=0.01$). Multivariable analysis did not identify any independent factor associated either with DSS or PFS.

4. Discussion

This is the first study analyzing the outcome of patients affected by IPMN, with clinico-radiological criteria suggesting a surgical indication according to the Sendai guidelines, that were not operated upon because of associated co-morbidities, advanced age or patients' decision.

In this cohort of 35 patients, 34% died after a mean follow-up of 32.5 months from initial diagnosis. Of note, one third of them died because of associated co-morbidities. The median OS of the entire series was 52 months with a 5-year OS of 35.2%, and a 5-year DSS of 48.5%. Factors associated with a worse prognosis were advanced age at diagnosis and the involvement of the main pancreatic duct.

These data partly provide an answer to the increasing medical problem represented by the incidental diagnosis of IPMNs during radiological examinations performed for other indications in elderly or sick subjects who are poor candidates for surgical resection. In these subjects the detection of an IPMN with "high risk stigmata", but without a clear histologic/cytologic diagnosis of malignancy, leaves the physician with difficult therapeutic decision, between an interventional attitude and a conservative management.

Indeed, although age alone should not be considered a contraindication to pancreatic surgery, elderly patients are at increased risk of morbidity after pancreaticoduodenectomy especially in the setting of cardiopulmonary co-morbidities, with higher mortality rates when complications requiring reoperation occur [12–14].

The observed OS of 52 months, with a 5-year OS rate of 35.2%, does not seem much lower than those reported in series of patients undergoing pancreatectomy for invasive IPMNs. In those series, 5-year survival after complete resection ranged in fact from 20 to 70%, based on histological subtypes [15,16].

Table 2

Reasons for not undergoing surgery in the 35 patients with patients with intraductal papillary mucinous neoplasm with positive Sendai criteria for surgical resection.

	Total (n = 35)	MD-IPMN (n = 14)	BD (n = 21)
ASA score $\geq 3^a$	19 (54.2%)	12 (63.2%)	7 (36.8%)
Cardiovascular disease	16 (45.7%)	11 (68.7%)	5 (31.3%)
Chronic respiratory failure	6 (17.1%)	1 (16.6%)	5 (83.4%)
Cerebrovascular disease	5 (14.2%)	4 (80%)	1 (20%)
Synchronous neoplasm	2 (5.7%)	1 (50%)	1 (50%)
Chronic kidney failure	1 (2.8%)	1 (100%)	0
Chronic liver failure	1 (2.8%)	0 (0%)	1 (100%)
Age > 80 years and ASA score < 3	7 (20%)	2 (28.6%)	5 (71.4%)
Patients' refusal	9 (25.7%)	0	9 (100%)

MD, main duct; BD, branch duct; IPMN, intraductal papillary mucinous neoplasm; ASA, American Association of Anaesthetists.

^a Some patients had more than one comorbidity.**Table 3**

Features at diagnosis of the 8 patients who died due to IPMN during the follow-up.

Sex	Age	MD involvement	MD size	Mural nodules	BD size	Disease progression definition
Male	80	Yes	15 mm	No	–	Metastasis appearance
Male	80	Yes	12 mm	Yes	–	Metastasis appearance
Female	85	Yes (combined type)	11 mm	No	18 mm	Increase in size and vascular invasion
Male	82	Yes (combined type)	8 mm	No	25 mm	Metastasis appearance
Female	77	Yes (combined type)	12 mm	Yes	22 mm	Increase in size and vascular invasion
Male	82	No	–	No	30 mm	Increase in size and vascular invasion
Female	80	No	–	No	80 mm	Metastasis appearance
Female	77	No	–	No	45 mm	Increase in size and vascular invasion

MD, main duct; BD, branch duct; IPMN, intraductal papillary mucinous neoplasm.

In our cohort the only factors associated in a multivariate logistic regression analysis with a worse OS was age. This may suggest that in this specific subset of elderly patients with comorbidities and reduced life expectancy, IPMN is not the main factor affecting survival, as a third of them would die for other causes. Therefore, in such elderly patients DSS is a better end point, as a quote of patients would die from other causes.

Interestingly, the main pancreatic duct involvement resulted at the univariate analysis only as a significant risk factor both for OS and DSS and PFS. Therefore surgical resection should be strongly considered in all MD-IPMN. Only in patients with major co-morbidities resulting in a significant perioperative mortality risk surgery should be avoided. On the other hand, the number of BD lesions, their size, and the presence of mural nodules, were not associated with prognosis.

These findings confirm that BD-IPMNs, even if presenting with features suspect for malignancy, have a less aggressive clinical course than MD-IPMN, and that the size of the BD lesions per se does not represent a sufficient criteria for surgery, as now detailed in the 2012 consensus [4]. Indeed, in a series of BD-IPMNs resected according to Sendai criteria suggesting malignancy (i.e. size > 3 cm and nodules), the histological rate of malignancy was as low as 15%

[9]. Recently, Genevay et al. showed that cytology added significant value to radiological examination for identifying malignancy especially in BD-IPMNs [17]. Based on these observations, EUS with fine needle aspiration (FNA) should be recommended for BD-IPMN with worrisome features or high-risk radiological stigmata for a better stratification of the malignancy risk.

The present study has a number of limitations. First, the number of enrolled patients is relatively low, and their follow-up brief. However, this is the first reported series of patients for which an outcome analysis possibly indicating the natural history of this specific population is provided, and the results may set the ground for further studies. Second, the retrospective nature of the study, although most patients received a similar follow-up protocol in the different centres, limits the significance of the data regarding tumour progression.

In this view, the present data provide a preliminary basis for the investigation of an area of IPMN management for which the current guidelines only offer marginal indications, and no previous data are available.

In conclusion, the present results suggest that in elderly subjects with IPMN, or in patients affected by relevant co-morbidities, a complete evaluation of the general medical status and life

Table 4

Risk factors for overall mortality in the 35 patients with intraductal papillary mucinous neoplasm with positive Sendai criteria for surgical resection.

	Univariate		Multivariate	
	HR (95%CI)	P value	HR (95%CI)	P value
Age at diagnosis (years)	1.26 (1.03–1.5)	0.006	1.23 (1–1.5)	0.009
MD involvement	3.29 (0.96–11.3)	0.053	2.3 (0.64–8.1)	–
Presence of comorbidities	2.04 (0.61–6.76)	0.23	–	–
Diameter of BD lesion (mm)	0.96 (0.91–1.01)	0.13	–	–
MD dilation (mm)	1.01 (0.9–1.14)	0.79	–	–
Unifocal	0.94 (0.29–3.02)	0.92	–	–
Presence of mural nodes	1.53 (0.44–5.3)	0.5	–	–
Presence of symptoms	1.67 (0.53–5.24)	0.38	–	–
Male sex	0.45 (0.14–1.45)	0.18	–	–
BMI	1.02 (0.77–1.35)	0.86	–	–

MD, main duct; BD, branch duct; BMI, body mass index.

expectancy are mandatory to make a therapeutic decision balanced between risk of IPMN-related malignancy and that of perioperative morbidity/mortality associated with pancreatectomy. In this subset of patients, a conservative approach could be reasonable and should be carefully discussed.

Conflict of interest statement

None declared.

References

- [1] Lofthus EV, Olivares-Pakzad BA, Batts KP, et al. Intraductal papillary-mucinous tumor of the pancreas – clinicopathologic features, outcome, and nomenclature. *Gastroenterology* 1996;110:1909–18.
- [2] Tanaka M. Intraductal papillary mucinous neoplasm of the pancreas: diagnosis and treatment. *Pancreas* 2004;28:282–8.
- [3] Crippa S, Fernandez-del Castillo C, Salvia R, et al. Mucin-producing neoplasms of the pancreas: an analysis of distinguishing clinical and epidemiologic characteristics. *Clinical Gastroenterology and Hepatology* 2010;8:213–9.
- [4] Tanaka M, Fernández-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology* 2012;12:183–97.
- [5] LaFemina JGS, D'Angelica MI, Jarnagin WR, et al. Malignant progression in intraductal papillary mucinous neoplasms of the pancreas: results of 157 patients selected for radiographic surveillance. *Journal of Clinical Oncology* 2012;30.
- [6] Bassi C, Sarr MG, Lillemoe KD, Reber HA. Natural history of intraductal papillary mucinous neoplasms (IPMN): current evidence and implications for management. *Journal of Gastrointestinal Surgery* 2008;12:645–50.
- [7] Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology* 2006;6:17–32.
- [8] Schmidt CM, White PB, Waters JA, et al. Intraductal papillary mucinous neoplasms: predictors of malignant and invasive pathology. *Annals of Surgery* 2007;246:644–51.
- [9] Pelaez-Luna M, Chari ST, Smyrk TC, et al. Do consensus indications for resection in branch duct intraductal papillary mucinous neoplasm predict malignancy? A study of 147 patients. *American Journal of Gastroenterology* 2007;102:1759–64.
- [10] Waters JA, Schmidt CM. Intraductal papillary mucinous neoplasm – when to resect? *Advances in Surgery* 2008;42:87–108.
- [11] Wang SE, Shyr YM, Chen TH, et al. Comparison of resected and non-resected intraductal papillary mucinous neoplasms of the pancreas. *World Journal of Surgery* 2005;29:1650–7.
- [12] Sohn TA, Yeo CJ, Cameron JL, et al. Should pancreaticoduodenectomy be performed in octogenarians? *Journal of Gastrointestinal Surgery* 1998;2:207–16.
- [13] Kow AW, Sadayan NA, Ernest A, et al. Is pancreaticoduodenectomy justified in elderly patients? *Surgeon* 2012;10:128–36.
- [14] Brozzetti S, Mazzoni G, Miccini M, et al. Surgical treatment of pancreatic head carcinoma in elderly patients. *Archives of Surgery* 2006;141:137–42.
- [15] Waters JA, Schnelldorfer T, Aguilar-Saavedra JR, et al. Survival after resection for invasive intraductal papillary mucinous neoplasm and for pancreatic adenocarcinoma: a multi-institutional comparison according to American Joint Committee on Cancer Stage. *Journal of the American College of Surgeons* 2011;213:275–83.
- [16] Mino-Kenudson M, Fernández-del Castillo C, Baba Y, et al. Prognosis of invasive intraductal papillary mucinous neoplasm depends on histological and precursor epithelial subtypes. *Gut* 2011;60:1712–20.
- [17] Genevay M, Mino-Kenudson M, Yaeger K, et al. Cytology adds value to imaging studies for risk assessment of malignancy in pancreatic mucinous cysts. *Annals of Surgery* 2011;254:977–83.