Branch-duct intraductal papillary mucinous neoplasms of the pancreas: to operate or not to operate?

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Background: Branch-duct intraductal papillary mucinous neoplasms (BD-IPMNs) of the pancreas are reported to be less aggressive than the main-duct type. Hence, less aggressive treatment has been proposed for the former.

Aim: To evaluate the effectiveness of a follow-up protocol for BD-IPMNs.

Design: Prospective study.

Setting: An academic tertiary referral centre.

Patients: From 2000 to 2003, 109 patients with BD-IPMNs underwent trans-abdominal ultrasound and magnetic resonance cholangiopancreatography with secretin. Patients who presented malignancy-related parameters (size >3.5 cm, nodules, thick walls, carbohydrate antigen 19.9 level >25 U/l, recent-onset or worsened diabetes) and/or complained of symptoms were submitted to surgery (arm A). All asymptomatic patients without suspicion of malignancy were followed up according to a 6-month clinical-radiological protocol (arm B).

Main outcome measures: The effectiveness of conservative management of BD-IPMNs.

Results: 20 (18.3%) patients underwent surgery (arm A); pathological diagnosis of BD-IPMNs was always confirmed. 89 (81.7%) patients were followed up for a median of 32 months (arm B); of these, 57 (64%) patients had multifocal disease. After a mean follow-up of 18.2 months, 5 (5.6%) patients showed an increase in lesion size and underwent surgery. The pathological diagnosis was branch-duct adenoma in three patients and borderline adenoma in two.

Conclusions: Surgery is indicated in <20% of cases of BD-IPMNs, and, in the absence of malignancy-related parameters, careful non-operative management seems to be safe and effective in asymptomatic patients. Although observation for a longer time is needed to confirm these results, our findings support the guidelines recently recommended by the International Association of Pancreatology.

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During the past 15 years, intraductal papillary mucinous neoplasms (IPMNs)^{1–2} have been reported with increasing frequency, representing an estimated 0.5–10% of pancreatic exocrine neoplasms.^{3–5} Histologically, IPMNs can exhibit a spectrum of dysplasia, ranging from adenoma to invasive carcinoma, even within the same tumour.^{1–6–8} This supports the hypothesis of progression from IPMN adenoma to carcinoma through borderline neoplasms. It is unknown whether all IPMNs have potential malignancy, and also what timescale is required for neoplastic progression to invasive carcinoma.⁹

IPMNs arise from the main duct (MD-IPMNs) or its major branches.² Branch-duct IPMNs (BD-IPMNs) are characterised by cystic dilation of secondary ducts clearly communicating with a normal-sized main pancreatic duct; MD-IPMNs present a significantly dilated main pancreatic duct with or without cystic dilation of side branches.¹⁰

In the 1990s, the distinction between BD-IPMNs and MD-IPMNs was only of morphological significance. Thus, patients with both MD-IPMNs and BD-IPMNs were always surgically treated in consideration of their potential malignancy. However, in 1999, some authors^{11–12} showed that BD-IPMNs have a less harmful biological behaviour, which suggested a less aggressive surgical approach, as well as the possibility to follow up patients without surgery.¹³

Subsequently, radiological features useful for identification of malignant lesions were described. In particular, a diameter >3 cm, the presence of nodules and/or septa, and the thickness of the wall of the cyst were all related to malignancy.^{14–16} A review of seven recent series^{5–11–12–17–20} describing BD-IPMN

showed a frequency of malignancy ranging from 6% to 46%, with a mean of 25%, and a frequency of invasive cancer from 0% to 31%, with a mean of 15%. It is noteworthy that the studies with a high prevalence of malignant BD-IPMNs showed a significant proportion of patients with symptoms, whereas other authors reported no invasive cancers among asymptomatic patients.^{4–12–13–17–21–23}

Nonetheless, the most appropriate management of BD-IPMNs remains unclear, and, in particular, it is uncertain whether patients should always undergo surgery or whether a "wait and see" policy is feasible. Although some authors judge the surgical treatment of all BD-IPMNs as preventive, stressing their potential malignancy,^{19–24–25} others advocate a more conservative management in well-selected asymptomatic patients,²⁰ considering the features of this population and the surgical risk.²⁶ However, no prospective trials have clearly demonstrated the effectiveness of either approach.

Accordingly, we have carried out a prospective study, in order to evaluate the appropriate management (surgery vs follow-up) of patients affected by BD-IPMNs observed in a single, referral

Abbreviations: BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; CA, carbohydrate antigen; CEUS, contrast-enhanced abdominal ultrasonography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; IAP, International Association of Pancreatology; MD-IPMN, main-duct intraductal papillary mucinous neoplasm; MRCP, magnetic resonance cholangiopancreatography; US, ultrasound

centre, and the safety and feasibility of conservative management in well-selected asymptomatic patients.

PATIENTS AND METHODS

All patients observed in the Department of Surgery of the University of Verona, Verona, Italy, with a suspected diagnosis of BD-IPMNs from 2000 to 2005 were prospectively included in the study. All patients underwent physical examination, medical history evaluation and blood tests that included tumour markers, glycaemia, cholestatic index and amylase levels. Abdominal ultrasound (US) and magnetic resonance cholangiopancreatography (MRCP) with secretin were also carried out. Since 2001, contrast-enhanced abdominal ultrasonography (CEUS) was routinely used. The MR examinations were carried out using a 1.5 T MRI system (Magnetom Symphony or Maestro; Siemens Medical Systems, Erlangen, Germany) with a body phased-array coil.

The diagnosis of BD-IPMN was based on the presence of a cystic lesion in any part of the pancreatic gland clearly communicating with the main pancreatic duct. The absence of any dilation of the main pancreatic duct at the MRCP with secretin was considered a strict inclusion criterion. We considered a main pancreatic duct with a maximum diameter lesser than 5, 4 and 3 mm in the head, body and tail of the gland, respectively, as normal.¹⁸

When MRCP with secretin did not demonstrate communication between the cystic lesion and the main pancreatic duct, or suspected dilatation of the main pancreatic duct, endoscopic ultrasound (EUS) and/or endoscopic retrograde cholangiopancreatography (ERCP) were performed to assess the presence of a BD-IPMN.

Diameter of the lesion >3.5 cm, the presence of nodules and thick walls, carbohydrate antigen (CA) 19.9 level >25 U/l, recent-onset or worsened diabetes, jaundice, or the presence of any other symptom were considered to be related to potential malignancy. Once a definitive diagnosis was established and informed consent obtained, patients were assigned to one of two treatment arms. Patients who presented at least one of the above-mentioned parameters underwent surgery (arm A).

The remaining patients were assigned to a conservative management protocol consisting of a strict 6-month follow-up for the first 2 years. Our protocol included clinical examination, laboratory analysis (tumour markers and glycaemia levels), a CEUS, eventually associated with MRCP with secretin, at 6 and 18 months after diagnosis, and only MRCP at 12 and 24 months. After the first 24 months, examination was carried out yearly (arm B).

The study protocol was approved by the clinical research committee of our department.

Patients who further presented any symptoms or signs with suspicion of malignancy were assigned to surgery. Resected tumours were classified according to the criteria established by the World Health Organization⁷; BD-IPMNs were defined as IPMNs that did not either grossly or microscopically involve the main pancreatic duct.

Demographics, presenting symptoms, imaging and laboratory tests, and long-term follow-up were evaluated. In patients undergoing surgery, operative management, pathology and postoperative course were also considered. Information regarding survival and long-term follow-up was available for all patients through periodical clinical examinations at external clinics and direct patient contact. For the present analysis, only those patients who had at least 24 months of follow-up were considered. The last follow-up was in December 2005, whereas the last diagnosis considered was made in December 2003.

RESULTS

A total of 109 patients affected by BD-IPMNs of the pancreas with a minimum follow-up of 24 months were included in this study (45 (41%) men and 64 (59%) women; median age 64 years (mean (range) 60.2 (28–81) years)).

Arm A

In all, 20 of the 109 (18.3%) patients were immediately submitted to surgery, owing to the presence of symptoms and/or laboratory or radiological parameters associated with potential malignancy. These included 10 (50%) men and 10 (50%) women, with a median age of 64 years (mean (range) 58 (38–72) years). The majority (75%) of patients had symptoms at presentation, and the most common presenting symptom was abdominal pain (60%). Increase of CA 19.9 level (to 1774 U/l) was evident in only one patient, who had an invasive carcinoma at the final pathological examination. Table 1 summarises the most important features that led to surgery.

In this population, MRCP showed a cystic neoplasm in all patients with a median (range) lesion diameter of 3.4 (2–13) cm. In 13 cases, the communication between the neoplasm and the main pancreatic duct was clearly evident, whereas in the remaining 7 cases it was not apparent. These seven patients underwent ERCP, which, however, did demonstrate communication with the main duct. No patient underwent EUS (fig 1). In 16 (80%) patients the lesion was located in the pancreatic head or uncinate process, in 3 (15%) in the tail and in the body in only 1 (5%) patient.

Treatment

All patients underwent standard pancreatic resections, including 16 (80%) pancreaticoduodenectomies and 4 (20%) distal pancreatectomies. There was no operative mortality. The overall morbidity rate was 45%. No patient required re-operation, and all complications were conservatively managed.

Pathology

Diagnosis of BD-IPMN was confirmed in all patients. Table 2 summarises the definitive pathological diagnosis of patients in arm A, and correlations with clinical presentation. In all, 2 (10%) patients had an invasive carcinoma IPMN with positive nodes (6 out of 32 nodes and 4 out of 26 nodes, respectively). The resection margin was negative in all cases.

Among patients with symptoms, three also had suspicious radiological features, and two had a lesion size >3.5 cm; at final pathological examination, these five patients had in situ (n = 1) or invasive carcinoma (n = 4), as shown in table 2.

Outcome

The overall median (range) follow-up was 44.5 (20–70) months, and for survivors it was 52 (24–70) months. The

Table 1 Summary of symptoms at the time of diagnosis of branch-duct intraductal papillary mucinous neoplasm in 20 patients submitted to surgery (arm A)

Presentation	n (%)	Mean (range) duration (months)
Any symptom(s)	15 (75)	—
Abdominal pain	12 (60)	8 (1–14)
Diabetes	3 (15)	6 (2–9)
Weight loss	3 (15)	8 kg/3 months
Anorexia	2 (10)	1.2 (1–1.4)
Nausea/vomiting	2 (10)	2 (2)
Jaundice	1 (5)	2 weeks
Fever	1 (5)	1

Figure 1 Diagnostic examination adopted in the protocol; the number of patients and the percentage referred to the row for each subgroup are reported in parentheses. CA, carbohydrate antigen; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography. *Since 2001, contrast-enhanced abdominal ultrasonography was performed.

two patients with invasive carcinoma developed hepatic metastases, and died of disease at 20 and 40 months, respectively, after surgical resection. One patient diagnosed with IPMA developed lung carcinoma and died of myocardial infarction 30 months after surgery. The remaining patients are alive without evidence of disease.

Arm B

In all, 89 (81.7%) asymptomatic patients with a radiological diagnosis of BD-IPMN and without any suspicion of malignancy underwent conservative management according to the above-described follow-up protocol. There were 35 (39%) men and 54 (61%) women with a median age of 64 years (mean (range) 62 28–81 years). The diagnosis was incidental in all cases.

Diabetes was already present in 4 (4.5%) patients at the time of the diagnosis. The median value of CA 19.9 was 14 U/l (mean (range) 12.1 (2–25) U/l).

Table 2 Correlations between clinical, laboratory, radiological findings, and definitive diagnosis in the 20 patients submitted to surgery (arm A)

	IPMA (n = 10; 50%)	IPMB (n = 7; 35%)	IPMCIS (n = 1; 5%)	IPMC (n = 2; 10%)
Patients with symptoms*	6	6	1	2
Asymptomatic patients (n = 5)	4	1	0	0
Jaundice	0	0	0	1
Diabetes	2	0	1	0
Increase in carbohydrate antigen 19.9 level	0	0	0	1
Suspicious radiological features†	3	0	1	2
Lesion size >3.5 cm	1	1	0	2

IPMA, intraductal papillary mucinous adenoma; IPMB, intraductal papillary mucinous borderline; IPMC, intraductal papillary mucinous carcinoma; IPMCIS, intraductal papillary mucinous in situ carcinoma.
*Any symptom except jaundice and diabetes.
†Presence of septa, nodules or thick walls of the neoplasia.

Abdominal US or CEUS showed at least one pancreatic cystic lesion with a median (range) diameter of 2.1 (0.7–3.5) cm. MRCP with secretin confirmed the diagnosis of BD-IPMN in 75 (84.3%) patients. In the remaining 14 (15.7%) cases, MRCP revealed the presence of ≥1 cystic lesions, but the communication with the main pancreatic duct was unclear. Thus, ERCP and EUS showed the communication in nine and five patients, respectively (fig 1). In 57 (64%) patients, imaging showed ≥2 cystic lesions with definite communication with the MD (multifocal BD-IPMN); 32 (36%) cases presented only one lesion (monofocal BD-IPMN). Table 3 summarises the features of the patients in arm B.

Among the multifocal BD-IPMNs subgroup (n = 57), 9 (15.8%) patients had 2 lesions, whereas 48 (84.2%) patients had ≥3 lesions. Moreover, in 18 (31.6%) patients the disease

Table 3 Main features of the patients who underwent follow-up (n = 89, arm B)

Male	35 (39)
Female	54 (61)
Median (range) age	64 (28–81) years
Median (range) FU	32 (24–71) months
Location of the main lesion	
Head or uncinate process	44 (49.4)
Neck	21 (23.6)
Body	18 (20.3)
Tail	6 (6.7)
Extension of the disease	
Unifocal disease	32 (36)
Multifocal disease	57 (64)
Two lesions	9 (15.8*)
≥3 lesions	48 (84.2*)
Whole-gland involvement	18 (31.6*)
Single-area involvement	19 (33.3*)
Head and tail involvement	20 (35.1*)

FU, follow-up.
Values are given as n (%) unless otherwise specified.
*These rates refer to patients with multifocal disease (n = 57).

involved the whole gland, whereas in 19 (33.3%) cases the lesions were localised in a single area of the gland (head, uncinate-isthmus process vs body-tail); in the remaining 20 (35.1%) patients, the neoplasms were located in the head and tail of the gland, leaving the body reasonably free of disease.

Follow-up

Five (5.6%) patients with a single lesion underwent surgery because of an increase in the size of their neoplasms during follow-up. In fact, after a mean (range) follow-up of 18.2 (12–24) months, their lesions increased in size from a mean (range) diameter of 3.2 (3.0–3.5) cm to 4.1 (4.0–4.2) cm. Symptoms, nodules or septa were absent in any case. The CA 19.9 level was within normal values in all patients. The final histopathological examination of the surgical specimens revealed BD-IPMNs adenoma in three cases and borderline adenoma in two cases. Surgical margins were negative in all cases. After a mean (range) follow-up of 24.4 (17–35) months, no recurrences were observed.

After a median follow-up of 32 months (mean (range) 33.3 (24–71) months), of the remaining 84 (94.4%) patients, 2 patients died of myocardial infarction at 60 and 50 months, respectively, after the first observation. The four patients with diabetes showed no signs of worsening, and no therapeutic modifications were necessary. All patients remained asymptomatic and were followed up according to the established protocol.

DISCUSSION

Our understanding of IPMNs has increased dramatically ever since 2000, when Irie *et al* and Fukukura *et al* reported a series of radiological parameters that could indicate degeneration.^{14–16 27 28} This is of obvious interest for two reasons: the first is that the mean age of these patients is rather high, between 60 and 70 years, with a consequent risk of comorbidity, while the second is related to the necessity of extensive pancreatic surgery for a neoplasm with a slow evolution.³ Nonetheless, it is uncertain whether all IPMNs have a malignant evolution or whether the progression of these tumours is so slow that it represents a secondary problem in an elderly population. This seems particularly true for BD-IPMNs <2 cm in diameter without solid elements, in which the prevalence of diagnosis has been increasing due to what could be termed a disease of technology.²⁹ BD-IPMNs have been described as malignant in approximately 20% of cases.^{5 11 12 17–20} Nakagohri *et al*¹¹ reported that BD-IPMNs having a maximum diameter of 2.5 cm tend to be less aggressive and have a better long-term survival than MD-IPMNs. In a series of 13 patients with BD-IPMN, Terris *et al*¹³ reported no case of invasive carcinoma.

This prospective study was planned in consideration of the aforementioned reasons and the increased number of BD-IPMNs that are detected. The first significant result to be stressed is the reliability of the imaging protocol mostly based on MRCP with secretin to correctly identify BD-IPMNs. In fact, it is true that these patients have a probable diagnosis, based on radiological and not on pathological evaluation; however, in all 25 patients undergoing surgery, the clinical–radiological diagnosis was confirmed at histological examination. These data are in accordance with previous reports^{30–33} that showed a high sensitivity and specificity of MRCP in characterising IPMNs in preoperative practice.

Other authors suggested that EUS, with or without fine-needle aspiration, should be considered as the initial diagnostic modality for any pancreatic lesion, including IPMNs.^{34–37} However, EUS is more invasive than MRCP, is operator-dependent, small lesions cannot be easily biopsied, and false-positive results have been reported in EUS-based screening of

asymptomatic high-risk individuals.³⁸ For this reason, we decided to limit its use along with ERCP only for those patients in whom communication with the MD was uncertain, which occurred in 21 (19%) patients. In our experience, the last ERCP for BD-IPMN diagnosis was performed in 2002.

It is remarkable that, following the criteria of patients with symptoms and/or radiological–clinical–laboratory signs suggesting malignancy, only 20 (18.3%) patients were immediately submitted to surgery. As reported in other studies,^{5 11 12 17–20} in this group, 3 out of 20 patients were found to have a malignant neoplasm.

Our data are significantly different from those relating to MD-IPMNs. Considering the pooled data from our institution (Department of Surgery, University of Verona, Policlinico “GB Rossi”, Verona, Italy) and those from the Massachusetts General Hospital (Boston, Massachusetts, USA), 60% of MD-IPMNs were malignant at the time of diagnosis,⁴ and similar data were described in other series.^{5 20}

In our experience, BD-IPMNs are asymptomatic in 86% of cases; among symptomatic cases (14%), pain is the most frequently encountered symptom, observed in 60% of patients.

Even if restricted and well-selected criteria for surgery were applied, the low number of malignant tumours among operated patients seems to suggest, above all in asymptomatic patients, a possible overtreatment.

Another important result of this study is the evidence that most of the patients in arm B (64%) presented multifocal disease. To our knowledge, this is the first paper reporting such a high proportion. Among patients with multifocal BD-IPMNs, only in 19 (33%) cases were the lesions located in a single area of the gland, allowing standard pancreatic resections, if any; in the remaining patients, the disease involved the entire gland or the pancreatic head and tail, leaving a portion of the body free of disease. This means that, for about 67% of patients with multifocal disease, total pancreatectomy, or at least subtotal extensive pancreatectomy, is required to perform radical surgery. In conclusion, it seems reasonable to question whether a high-risk surgical procedure with definite exocrine and endocrine insufficiency is appropriate in elderly and asymptomatic patients affected by pancreatic tumour with, at least, uncertain behaviour.

The recent International Association of Pancreatology (IAP) guidelines for the management of intraductal papillary mucinous tumours of the pancreas suggested for BD-IPMNs that “until definitive studies are performed, yearly follow-up if lesion is <10 mm in size, 6–12 monthly follow-up for lesions between 10 and 20 mm, and 3–6 monthly follow-up for lesions >20 mm”.²⁰ In our protocol, planned before the publication of the above-mentioned guidelines, we chose a follow-up time of 6 months for the first 2 years and 1-year intervals thereafter for follow-up evaluations. Based on the preliminary results that we achieved, the criteria and timing of the follow-up protocol adopted in this study seems to be reasonably safe. In fact, after a median follow-up of 32 months, all the patients in arm B were alive, and none showed frank signs of malignancy or symptoms. Only five (5.6%) patients showed an increase in size of the tumour, and hence underwent surgery. In all cases, definitive histological examination showed adenoma or at least borderline BD-IPMNs. In our series, an increase in tumour size does not necessarily indicate malignancy and does not directly reflect tumour progression. However, we still believe that neoplastic growth at the moment must remain an indication for surgery in any case, in order to avoid mistreatment.

Notwithstanding the good sample size of patients enrolled in the study, the follow-up of the asymptomatic group is only for 32 months. As the natural history of these tumours is not completely known and they might take a long time to progress,

a prudent surveillance policy is still claimed, and observation for a longer time is needed. Moreover, our study also tends to confirm the safety and validity of the IAP guidelines for the management of IPMNs, which, nowadays, have to be routinely applied in clinical practice; in particular, this applies to low-volume centres which have less confidence in dealing with this disease.

In conclusion, our study suggests that: (1) surgery is not mandatory in all patients with BD-IPMNs, but only in <20% of cases; (2) in the absence of parameters associated with malignancy, a conservative management through a strict follow-up seems to be safe and effective in asymptomatic patients, as recommended also by the IAP; and (3) the presence of clinical–radiological parameters suggesting malignancy should prompt to opt immediately for surgery.

The application of a well-defined surveillance programme through a prospective, multi-institutional study involving high-volume referral centres might help to confirm these results.

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