Cancer Imaging (2008) **8,** 220–228
DOI: 10.1102/1470-7330.2008.0028

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ORIGINAL ARTICLE

Evaluation of serial changes of pancreatic branch duct intraductal papillary mucinous neoplasms by follow-up with magnetic resonance imaging

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Date accepted for publication 11 August 2008

Abstract

The purpose of this study was to clarify the biological behaviour of branch duct type intraductal papillary mucinous neoplasm (IPMN) by evaluating serial changes at magnetic resonance cholangiopancreatography (MRCP). Fifty-two patients with a diagnosis of branch duct IPMN based on either endoscopic retrograde cholangiopancreatography (ERCP) (9/52) and/or MRCP examination (43/52), were followed up over a mean period of 31.2 months (range 12–108). All imaging data were retrospectively reviewed by two radiologists in order to evaluate serial changes in the maximum diameter of the cystic lesion, in the presence of main pancreatic duct dilatation (MPD), and filling defects within the lesion. Statistical analysis was performed using the Fisher exact probability test. Serial MRCP proved growth in seven cases. In two cases the size decreased; in the remaining 43 there was no change in size. Lesions greater than 3 cm at presentation and the presence of MPD dilatation or filling defects at imaging were most likely to grow. Only 2/37 cystic lesions less than 3 cm in diameter grew in size over the period of observation. No cystic lesion showed changes in morphology and structure. Branch duct IPMNs smaller than 3 cm, without associated filling defects, tend to be stable, making 'watch and wait' management possible.

Keywords: *Pancreas; intraductal papillary mucinous neoplasm (IPMN); magnetic resonance (MR).*

Introduction

The intraductal papillary mucinous neoplasm (IPMN) of the pancreas was first described in the 1980s; its actual classification among cystic lesions of the exocrine pancreas was established in 1996[1,2]. With the improvement of techniques and modalities of cross sectional imaging studies, the detection of this lesion continues to increase and has become a topic of growing scientific interest[3–8].

IPMN arises from the epithelium of the pancreatic ductal system and can display the full spectrum of histologic dysplasia, including hyperplasia, adenoma, borderline tumour, in situ or invasive carcinoma. The hypothesis of a temporal sequence of progressive adenoma–carcinoma degeneration is generally accepted[9]. Three morphologic types of lesions are recognized based on their location within the duct system: lesions exclusively of the main duct, lesions restricted to the branch ducts, and those in both main duct and branch duct (combined). Radiological features strongly correlated with a given lesion's malignant potential include: size > 3 cm, mural irregularity or nodules, and dilation of the main pancreatic duct (MPD)[4]. When involvement is limited to the branch ducts (BD-IPMN), the lesion is more often benign, non-symptomatic and slow growing[5,10,11].

There is considerable controversy regarding the treatment of these lesions. Some centres advocate surgical resection for most lesions, whereas others favour serial follow-up[12–15], especially in cases with normal clinical laboratory analyses and minimal radiological findings, or in patients with significant comorbidities[16,17].

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As a result of the non-uniform approach to these lesions, there are few available studies analysing significant numbers of patients undergoing long term follow-up[6–8,17].

The aim of this study is to analyse retrospectively serial changes in the imaging history of branch duct type IPMN as depicted by magnetic resonance cholangiopancreatography (MRCP) in a series of patients in whom non-surgical management and 3 years follow-up were obtained.

Materials and methods

Patients

The study was approved by our institutional review board. In our hospital, according to the international guidelines for the management of BD-IPMN[6] patients were considered candidates for follow-up based on either (a) imaging criteria: largest diameter of the mass less than 35 mm; absence of papillary proliferations, calibre of MPD less than 5 mm and (b) clinical criteria: no abdominal symptoms, no evidence of diabetes, no laboratory evidence of biliary obstruction and normal tumour markers. The decision to manage BD-IPMN conservatively required patient's consent.

Fifty-two consecutive patients (22 males and 30 females, average age at initial examination 64.2 years, range 43–79 years) in whom an imaging diagnosis of BD-IPMN was made between January 1997 and December 2005 were selected from the database of our Radiology Department. The diagnosis was established by MRCP in 43/52 (82.7%) and corroborated by endoscopic retrograde cholangiopancreatography (ERCP) in 9/52 (17.3%). MRCP was considered diagnostic when a cystic pancreatic mass communicating with the main pancreatic duct (MPD) through a small channel was identified. All patients were followed every 6 months for a period of time greater than 12 months. The average time of follow-up was 31.2 months (range 12–108 months).

The number of follow-up examinations per patient varied from 1 to 6 with an average of 2.9. The total number of magnetic resonance (MR) examinations was 152. Only two patients underwent surgery during the follow-up period.

In order to avoid inclusion errors patients with previous episodes of acute pancreatitis in whom there was no ERCP corroboration of BD-IPMN were not considered; those with any dilatation of the MPD greater than 5 mm; and those followed up by methods other than MRCP, or those with less than 1 year total follow-up were also excluded. Patients unwilling to sign the consent form were also excluded.

MRCP imaging technique

The MR examinations were performed on a 1.5-T MR imaging system (Magnetom Symphony and Maestro; Siemens Medical Systems, Erlangen, Germany) using a body phased-array coil. Twenty minutes prior to the examination, the patients were given 150 ml of an oral superparamagnetic contrast medium (Lumirem®, Guerbet-France) to minimize the high signal originating in the stomach and duodenum. All the sequences, except for 3D MRCP, were carried out in breath-hold.

Two types of MRCP sequences were utilized in each patient: (a) half-Fourier single-shot turbo spin-echo (HASTE), multi-slice, and (b) RARE 60 mm 'thick slab' projection views of the bilio-pancreatic tree were obtained in each patient. The HASTE sequence (recovery time (TR) 800 ms, echo time (TE) 60 ms, field of view 350×300, matrix 240×256) was carried out on 26 slices with a thickness of 4 mm (no gap) in the axial, coronal, para-coronal oblique and sagittal planes for an acquisition time (TA) of 24 s. The 'thick slab' (TE 1100 ms) was obtained in the coronal plane with variable angulations and in the axial plane to optimise the view of the pancreatic duct system. In 10 patients we also utilized a 3D T2-weighted turbo spin echo sequence (TR 1820, TE 272 ms, field of view 350×300, matrix 240×256, partition thickness 1.5 mm) with respiratory triggering (TA 3 min). The entire pancreatic examination also included enhanced images (0.2 ml/kg of gadolinium-DOTA, Dotarem®, Guerbet, France) of the upper abdomen using initially only a fat suppressed (FS) T1-weighted 2D gradient recalled echo (GRE) sequence and since the beginning of 1999 a 3D breath-hold sequence (volumetric interpolated breath-hold examination (VIBE) with less than 2 mm voxel size, partitions thickness 1.5 mm, matrix 256×240, TA 24 s), during both pancreatic and portal phases of enhancement.

Image analysis

One hundred and fifty-two MR exams from the 52 patients were reviewed retrospectively by two expert radiologists (more than 4 years training on body MR); consensus was obtained in case of discrepancies. For the purpose of this study MRCP and post-contrast T1-weighted images were analysed. The following parameters were evaluated: multiplicity, location, size, wall thickness, presence or absence of filling defects (called also papillary proliferations or nodules), widest diameter of MPD. We considered the following features 'suspicious imaging elements', reported in the literature to indicate high risk of malignancy: size, filling defect, dilation of MPD and thick wall. The presence of a communicating duct between cystic lesions and MPD was also assessed.

The greatest diameter of the lesion in the specific plane that displayed the greatest diameter was recorded using electronic callipers. This plane of measurement was kept constant for all subsequent follow-up examinations. The eventual presence of imaging changes during serial follow-up was checked for all cystic lesions. Both absolute measurement as well as percentage change were

recorded. In an attempt to avoid errors associated with measuring small lesions, we agreed arbitrarily to consider any change greater than 20% as significant.

The wall was analysed in both HASTE and T1 post-contrast sequences considering 'thickened' when it measured >1 mm along any portion of the circumference of the lesion. Filling defects were defined as nodular or papillary projections in the wall of the cystic lesion that displayed enhancement following gadolinium injection. The widest diameter of the MPD was measured with electronic callipers. According to the literature, the following criteria indicate suspicious imaging elements: largest diameter >30 mm, papillary proliferations, thick walls, MPD size greater than 5 mm.

The initial MRCP findings and any eventual changes were analysed statistically using the Fisher exact probability test ($p < 0.001$ was considered statistically significant). The following changes in the imaging aspects were analysed: cystic lesion and MPD size, aspect of the wall (papillary proliferations and thickness). Any correlation between the presence of suspicious imaging elements and changes in the imaging history during follow-up were investigated.

Results

A total of 119 lesions were detected, however the largest in each patient ($n = 52$) was analysed. In 15/52 (28.8%) patients, the IPMNs were solitary; 37/52 (71.2%) patients had multiple lesions. In 20/52 (38.6%) patients the largest lesion was located in the head or in the uncinate process of the pancreas, in 15/52 (28.8%) in the isthmus (also referred to as the neck), in 15/52 (28.8%) in the body and in 2/52 (3.8%) in the tail. In 12/37 (32.4%) patients with multiple tumours, all the pancreatic segments were involved; in 25/37 (67.6%), the neoplasms were located in the head and tail of the gland, sparing the body (Fig. 1). The largest diameters of the lesions at the initial examination varied between 7 and 35 mm (average 17.0 mm; median size 15.0 mm); 6 lesions measured between 5 and 9 mm, 30 lesions measured between 10 and 19 mm, 9 measured between 20 and 30 mm, and 7 more than 30 mm. The maximum size of the main duct was between 2 and 5 mm (average 2.8 mm) at the first examination.

In 15/52 (28.8%) of the patients, excluded from surgery because of elderly age or affected by comorbidities, at least one of the previously mentioned suspicious imaging elements was present at the time of diagnosis (Table 1). The largest cystic lesion in 5/15 (33%) was >30 mm maximum diameter; 11/15 (73.3%) had papillary proliferations measuring ≤5 mm in largest dimension; in 2/15 (1.3%) of the patients the MPD was greater than or equal to 5 mm (5 mm in both cases). None of the lesions had walls >1 mm in thickness. In 37/52 (71.2%) of the patients, there were no suspicious imaging elements at diagnosis.

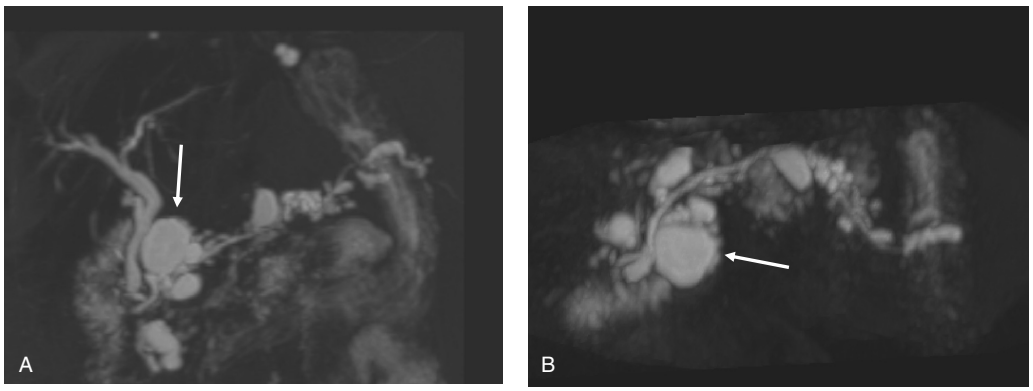

Figure 1 **A 46-year-old woman with multifocal BD-IPMN. 3D MRCP sequences in the coronal (a) and axial (b) projections show multiple cystic lesions in communication with the MPD, the greatest in the head of the pancreas (arrows). The patient did not show any change in morphology and size of the lesions after a follow-up period of 3 years.**

Table 1 ***Correlation of follow-up findings in patients with suspicious imaging findings (N = 15 patients)***

	No change	Decrease lesion size	Increase lesion size	Nodule change	Increase in MPD	Total
>3 cm	0	1	2	0	0	3
Papillary proliferations	7	0	1	0	0	8
Wide MPD	0	0	0	0	1	1
>3 cm and nodules	0	0	1	0	1	2
Wide MPD and nodules	0	0	1	0	0	1
Total	7	1	5	0	2	15

Significant changes were observed in 11/52 (21%) patients (Table 2). Seven of the patients in whom serial changes were observed were from the group of 15 patients with 'suspicious findings' at initial imaging (46.7%); 4 of the lesions increased in maximum diameter (Fig. 2); 1 lesion decreased (Fig 3), 1 showed an increase in the diameter of the MPD, one showed increasing size of the lesion and the MPD. Four of the patients in whom serial changes were observed were from the group of 37 patients with no 'suspicious findings' at the initial imaging study (10.8%). Lesions increased in size in 2 patients, decreased in size in 1 patient (Table 2). The MPD increased in size in the remaining patient.

Table 2 Comparison of follow-up observations in those patients with or without suspicious elements (lesion >3cm, papillary proliferations, wide MPD) (N = 52 patients)

	No suspicious elements	Suspicious elements
No change	33	8
Increase in lesion size	2	5
Decrease in lesion size	1	1
Enlarging papillary proliferations	0	0
Increasing size of MPD	1	1[a]
Total	37	15

[a]One patient showed increasing size of the lesion and of the MPD.

Two out of 6 patients who demonstrated more than 20% increase in size of the cystic lesion were sent to surgery. The final pathological proof diagnosis was adenoma and borderline tumour.

The MPD was normal and remained unchanged in 49/52 (94.2%) patients (Fig. 4). The widest diameter was $\geq$5 mm in 3/52 (5.8%). In 1/3 of these patients, it increased from 5 to 6 mm in the tail level over a period of 22 months; in 1 it grew from 2 to 5 mm at the pancreatic head after 42 months; in 1, there was a diffuse increase in diameter of the MPD from 4 to 5 mm after a follow-up of 46 months (Table 2).

None of the cases showed changes in the papillary proliferations or in other morphologic aspects of the masses.

Thirteen patients, whose MRCP was done at the beginning of our experience, underwent an ERCP to corroborate the diagnosis obtained with MRCP. The results were positive for IPMN in 9 (69.2%) and negative in 4 (30.8%). Four of 9 patients in which the ERCP diagnosed IPMN had lesions localized at the head or at the uncinate process, and 5/9 were multifocal. All patients in which the ERCP was not diagnostic for IPMN had cystic masses in the pancreatic tail and at the body; in these

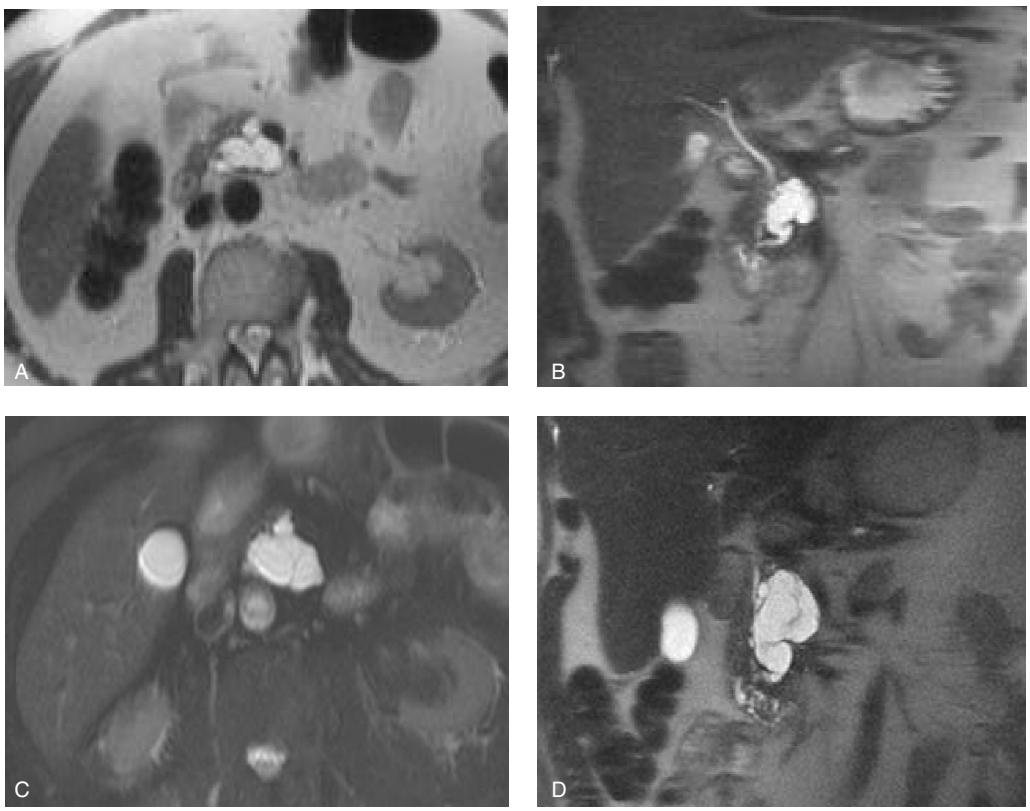

Figure 2 **A 61-year-old woman with increase in size of a BD-IPMN. Axial and coronal HASTE sequences (a,b) show a cystic lesion of the head of the pancreas larger than 30 mm communicating with the MPD. The mass had significantly increased in size over 52 months follow-up (c,d).**

cases the low pressure of the contrast medium injection failed to demonstrate the communication between the cystic lesion and MPD.

The 52 patients were then subdivided into two groups based on the duration of the follow-up (Table 3). In those with a total follow-up period of less than 36 months ($N = 38$), 25/38 (65.8%) of the patients presented only with the cystic mass; in 13/38 (34.2%), at least one additional related imaging abnormality was present: maximum diameter >30 mm (3/13 patients), papillary proliferations (8/13 patients), MPD ≥5 mm (1/13 patients), nodules and significantly dilated MPD (1/13 patients). In the group with a total follow-up period of more than 36 months ($N = 14$ patients), 12/14 (85.7%) presented only with the mass at initial imaging, and in 2/14 (14.2%), at least one element was present: maximum diameter >30 mm in 1 and papillary proliferations in the other.

Comparing those patients in whom the lesions changed size with those with stable lesions, we found a statistically significant association between those lesions >3 cm diameter and increasing size ($p = 0.0139$) (Table 4). Neither nodules nor MPD size alone have association with increase in size ($p = 0.0164$) (Table 4). The presence of nodules was not significantly associated with the lesion's size increase ($p = 0.1542$), neither was follow-up length or main duct dilation (Table 4).

Discussion

The increasing recognition of BD-IPMN in daily clinical practice is directly related to the widespread use of cross-sectional imaging and advances in technology. In attempting to establish the diagnosis, high quality MRCP is considered the gold standard study for these patients[18,19], although Sahani *et al*. showed that MDCT combined with 2D curved reformation can detect the BD-IPMN and establish communication with MPD, that are almost equivalent to those provided at MRCP[20]. The diagnosis is established by demonstrating that the cystic pancreatic mass communicates with the MPD. This communication can usually be confirmed on 2D images, but can be visualized in almost every case using current 3D T2 turbo spin echo (TSE) acquisition with respiratory trigger[3–21]. Additionally, current magnetic resonance imaging (MRI) technology can precisely depict significant morphologic and architectural features of the lesion, such as papillary proliferations, septations and nodules. MRCP is optimal for long term follow-up because of the absence of radiation and the ability to show minimal small changes[11,22]. MDCT will often be

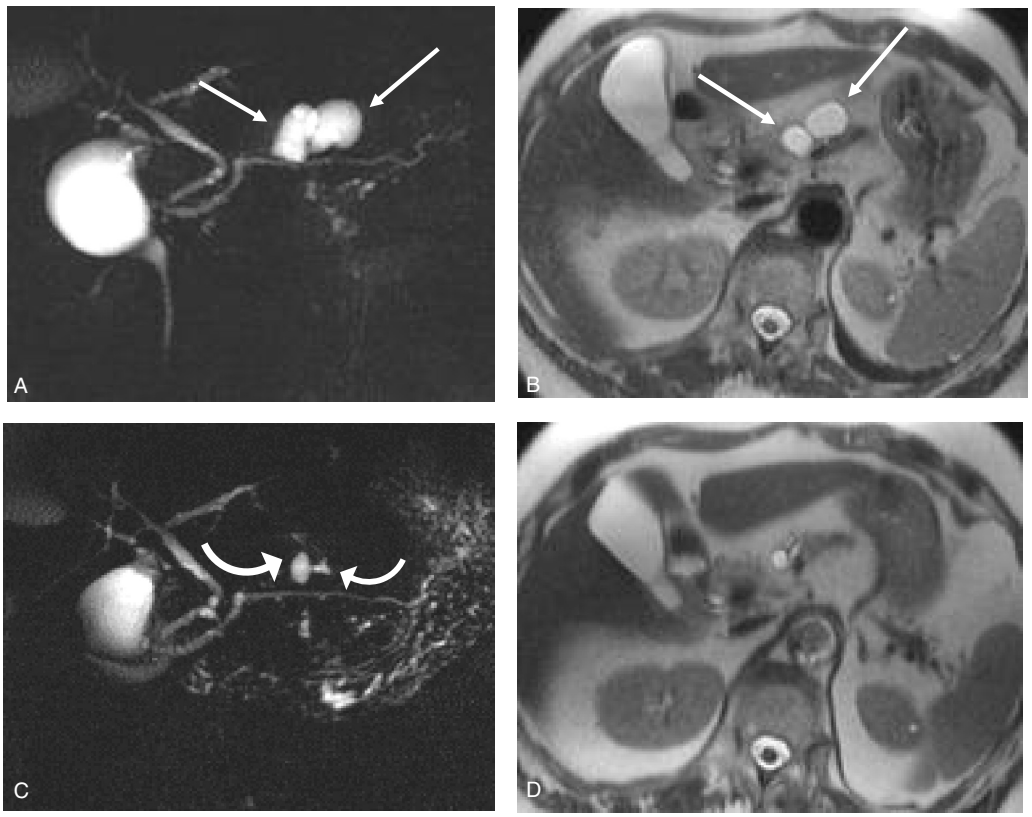

Figure 3 **A 46-year-old man with decrease in size of a BD-IPMN. Initial MR examination (MRCP and axial HASTE) (a,b) showed a bilobed cystic lesion in the body of the pancreas close to the MPD (arrows). The lesion had decreased in size 45 months later (c,d) (curved arrows).**

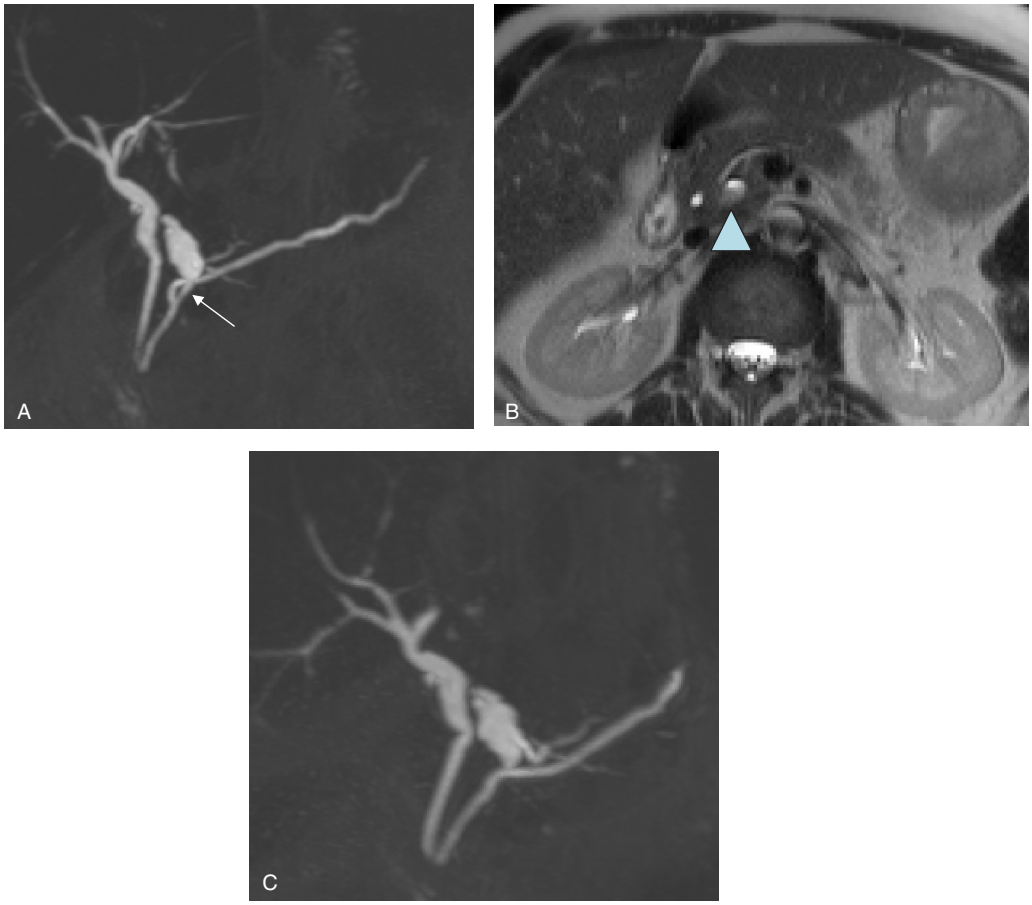

Figure 4 **A 59-year-old man with a stable BD-IPMN. Initial MR examination (MRCP and axial HASTE sequences) showed a small cystic mass in the head of the pancreas (a,b) (arrowhead in b). MRCP clearly depicted a small communicating duct (arrow). Axial HASTE showed a fluid–fluid level due to mucin within the cystic lesion (b). Subsequent MRCP examinations (c) demonstrated no change in size over a 45-month follow-up period of observation (c).**

Table 3 Correlation between duration of follow-up and increase in size of BD-IPMN

Follow-up (months)	No. of patients	Increase in size	No increase in size	Significance
>36	14	1	13	n.s.
<36	38	6	32	

the test where the lesion is initially detected and communication suggested. However, because of radiation considerations, we suggest that subsequent examinations be performed with MRI. ERCP may be useful in those cases where the presence or absence of communication is unclear. However, ERCP is limited because thick mucin may fill the side branch duct and prevent the contrast filling the mass. Sampling of pancreatic secretion at ERCP is diagnostic only in 30% of cases[23]. Some authors report the utility of endoscopic ultrasonography (EUS), with or without fine needle aspiration as the first modality of study of any pancreatic cystic lesion. However, EUS is invasive, operator-dependent, not always easily accessible; we also have to consider that small lesions cannot be easily biopsied[24], and false positive results are possible in asymptomatic high-risk patients[25]. For these reasons MRCP seems to be the new gold standard imaging modality for this kind of disease making it quite easy to differentiate BD-IPMN from, for example, serous cystadenoma, that do not communicate with MPD.

BD-IPMNs have been described as malignant in only approximately 20% of cases[6,10,26–28]. Nakagohri *et al.* reported that BD-IPMNs having a maximum diameter of 2.5 cm tend to be less aggressive and have a better long-term survival compared to main duct-IPMNs[10]. In a series of 13 patients with BD-IPMN, Terris *et al.* reported no cases of invasive carcinoma[16].

The lesions are frequently multiple (71% in our series) and of these, 23% had lesions throughout the entire gland therefore a total pancreatectomy would be necessary for complete therapy. The clinician is left with the difficult choice between surgery or follow-up. Because virtually all

Table 4 Comparison of lesions that grew against those that did not grow

Initial MRCP findings	No. of patients	Increase in size	No increase in size	Significance
Suspicious elements				
Yes	15	5	10	0.0164
No	37	2	35	
Max diameter (mm)				
>30	5	3	2	0.0139
≤30	47	4	43	
Main duct dilation				
Yes	2	1	1	n.s.
No	50	6	44	
Papillary proliferation				
Yes	11	3	8	0.1542
No	41	4	37	

There was a statistically significant independent association between lesions >3 cm at initial imaging and subsequent increase in the size of the lesion and between the general presence of suspicious imaging findings and growth. No significant correlation between the presence of nodules alone, or the MPD diameter and lesion growth could be obtained.

BD-IPMN are initially detected by imaging, those features that identify a given mass as having a higher likelihood of growth and or malignancy must be carefully investigated. The radiologist must be sure that any imaging procedure is performed with proper technique such that those features predictive of malignancy are clearly delineated[6].

In our study, 15 of the 52 patients displayed suspicious imaging features (>30 mm, papillary proliferations, MPD calibre ≥5 mm); 7 of these lesions grew, whereas only 2 lesions in the 37 patients without additional suspicious imaging features displayed serial growth.

The most significant imaging feature predicting which lesions would grow was the size of the lesion (≥3 cm in widest dimension) at the initial imaging examination. The presence of any combination of suspicious findings was predictive of growth when compared with lesions that were bland cysts (Table 4). These results have been observed by others highlighting the importance of size in the characterization of a malignant or at least suspicious IPMN[5,6].

As to the relationship between papillary proliferations and growth, as present in 11/52 patients, we never observed any change in the size or number of papillary proliferations; furthermore, all the papillary proliferations smaller than 3 mm in diameter remained stable. It is possible that since we excluded BD-IPMN with papillary proliferations larger than 5 mm in the follow-up protocol, the mural changes had poor correlation with further growth. The fact that the MPD was less than 6 mm in all cases can explain the absence of correlation with the change in the size of the lesions.

The size of MPD increased in 3/52 patients. None of these patients was operated on due to compromised clinical status but according to the literature these patients should be sent to surgery[6,17,21].

In 7/52 (13.5%) patients, an increase in size of the lesion (range 24–46.7%, mean increase 31.6%, median follow-up 27.1 months) was demonstrated. The greatest increase in our series was 46% in almost 2 years. Although increase in tumour size does not necessarily indicate malignancy, growth of a clearly diagnosed branch duct IPMN remains an absolute indication for surgical intervention. Despite this, as shown from our data, the vast majority of BD-IPMN (especially those with no suspicious imaging features) will not grow over a long period of observation. It should be remembered that growth does not necessarily indicate neoplastic transformation. Obstruction of a communicating side branch can result in a build up of mucin resulting in increasing size of the lesion.

Two of the 6 patients in whom an increase in size of the tumour was observed underwent surgery. In both cases, the final histological diagnosis was adenoma and borderline carcinoma. The remaining 4 patients did not undergo surgery because of advanced age and associated comorbidities.

Two of the IPMNs actually decreased in size. This observation has also been reported by Irie *et al.*[27] in IPMN, but is unusual in cystic neoplasms that are not IPMN. We believe that the decrease in size is explained by either changes in the blood supply, decreased mucin production, or emptying of the mucin into the MPD. For the same reason it is possible to observe minimal increase in the diameter of the MPD that may not always mean neoplastic transformation[26–28].

Our results suggest that patients with BD-IPMN > 3 cm in largest dimension, papillary proliferations and a dilated MPD, have a lesion with a greater likelihood of growth (Table 4). In patients without any suspicious feature (37/52), during a mean follow-up period of 31.2 months, we observed a significant change in only 2/37 cases (5.4%).

Total absence of suspicious features does not mean that the lesion can be ignored. A recent consensus meeting on 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 > 20–30 mm is advised'[6]. In our protocol, we chose to follow all patients at 6 month intervals for the first 2 years and 1 year intervals thereafter. The criteria and timing of the follow-up protocol adopted in our institution seems to be reasonably sensitive to detect significant growth. In fact, after a mean follow-up of 31.2 months all the patients were alive and none showed signs of malignancy or symptoms.

Because of the potential malignancy of the IPMNs long term follow-up is recommended for all patients. The interval of follow-up can be lengthened to every year after 2 years of no change[6].

The main limitations of this study are: retrospective nature; diagnosis based exclusively on imaging findings at MRCP in 82.7%; examination intervals were different in frequency and time for every patient; a mean follow-up time of 31.2 months may still be too short to judge the stability or growth rate of BD-IPMN; we checked only the biggest lesions at follow-up even in cases of multifocal IPMNs. Finally, surgical correlation is present in only 2 patients.

However, we can make the following conclusions: (i) the majority of branch IPMNs will remain stable, some will grow or less commonly shrink on MRCP follow-up; (ii) the larger branch IPMNs are more likely to grow than smaller lesions; (iii) in asymptomatic patients with BD-IPMN, a conservative management with MRCP is an effective therapeutic choice in the absence of clinical radiological parameters associated with malignancy. A large cohort of patients with longer follow-up should be considered to confirm these preliminary results and to verify the safety of a conservative management in these patients.

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