AGREEMENT AMONG MAGNETIC RESONANCE IMAGING / MAGNETIC RESONANCE CHOLANGIO-PANCREATOGRAPHY (MRI-MRCP) AND ENDOSCOPIC ULTRASOUND (EUS) IN THE EVALUATION OF MORPHOLOGICAL FEATURES OF BRANCH DUCT INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM (BD-IPMN)

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Running head: AGREEMENT MRI-MRCP AND EUS IN BD-IPMN

Key words: Agreement; BD-IPMN; EUS; Features; MRI-MRCP
Abstract

Background/Objectives: To evaluate the agreement between MRI-MRCP and EUS for study of cystic pancreatic lesions with high suspicion of BD-IPMN. Methods: Multicenter retrospective analysis of an open BD-IPMN database. Patients undergoing EUS and MRI-MRCP over a period of 5 years. Time between both less than 6 months. Location, number, size, worrisome features and high-risk stigmata were evaluated. Interobserver agreement was evaluated by Kappa score. Results: 173 patients included (97 UHSC, 76 UCLH-RFH) (mean age 65 years, range 25-87, 66 males). Size between both, was higher by MRI-MRCP than EUS, both at USCH (16.97 vs 16.04, p=0.53) and UCLH-RFH (26.43 vs 23.88, p=0.31). Interobserver agreement was good in the location of BD-IPMN. Worrisome features: Moderate agreement was obtained in main PD size of 5-9 mm and abrupt change (k=0.45 and 0.52). Fair agreement was seen in wall thickened (k=0.25). No agreement was obtained for detecting non-enhanced mural nodules and lymphadenopathy (k<0) . High-risk stigmata: Poor agreement was obtained in enhanced solid component (k=0.12). No agreement was observed in main PD size >10 mm (k<0). Conclusions: EUS and MRI-MRCP did not provide similar information about number and size. No agreement was found for detecting non-enhanced mural nodules, lymphadenopathy and main PD size >10 mm and good agreement was observed in the location of BD-IPMN.
Introduction

Pancreatic cystic lesions (PCL) are an increasingly common radiological finding, present in 1.2-2.6% \[1,2\] of patients undergoing abdominal Computed Tomography (CT) and in up to 13.5% of patients undergoing a Magnetic Resonance Imaging/ Magnetic Resonance Cholangiopancreatography (MRI-MRCP) for non-pancreatic indications \[3\]. This rising incidence is primarily attributed to the greater use of abdominal cross-sectional imaging in an ageing population.

Their management is determined by a number of guidelines, which advocate a series of imaging techniques and criteria for deciding on the handling of mucinous tumours such as “Worrisome features” and “high-risk stigmata” defined in the Fukuoka guidelines for the first time and later in the European guidelines \[4,5\].

Although pre-operative imaging allows discrimination of the different cyst types to some extent, which method is superior and when each should be employed is less clear \[6\]. Some studies have compared the utility of CT and MRI-MRCP in patients with Intraductal Papillary Mucinous Neoplasm (IPMN), with MRI-MRCP being considered to be more sensitive for high risk features and malignancy \[7–10\]. However all guidelines recognise that imaging methods that use non-ionizing techniques (e.g MRI-MRCP or EUS) are preferable, particularly for surveillance. If the techniques are equivalent is unclear and their use is often based on local expertise and availability. Although MRI-MRCP may be considered less invasive it is impossible to perform in patients with metal implants and severe claustrophobia. EUS can also be combined with fine-needle aspiration (FNA) and contrast agents to further enhance the technique.

To date, there are few studies have attempted to compare the diagnostic accuracy of these techniques \[10,11\]. Some of these studies unfortunately included some solid lesions and primarily surgically resected patients, making extrapolation to the surveillance population challenging. Two recent studies have showed different results comparing both techniques. In one of them, MRI-MRCP was considered more sensitive for differentiating malignant from benign IPMN and mucinous cystic neoplasms (MCN) \[12\]. In the other study was also included contrast-enhanced CT, but significant difference was not observed \[13\]. Larger series that compare EUS and MRI-MRCP in the surveillance population are therefore required.
The aim of our trial was to evaluate the agreement between MRI-MRCP and EUS for detecting high risk features in suspected branch duct IPMN (BD-IPMN) of the pancreas which are under active surveillance, over a 5 year period.

**Methods**

*Study design*

Multicenter retrospective analysis of a database of patients under surveillance for a suspected BD-IPMN that underwent both MRI-MRCP and EUS. All investigations were conducted at the departments of Gastroenterology & Hepatology and Radiology of University Hospital Santiago de Compostela (UHSC), Spain, University College London Hospital NHS Foundation Trust (UCLH) and the Royal Free Hospital NHS Foundation Trust (RFH), London, UK.

*Definitions*

A highly probable BD-IPMN was defined as a cystic lesion of the pancreas associated with one or more dilated branch duct/s communicating with a non-dilated main pancreatic duct on MRI-MRCP and/or EUS and/or FNA with cyst fluid carcinoembryonic antigen (CEA) >30 ng/mL [14]

*Inclusion and Exclusion criteria Patients*

Patients over the age of 18 years with a PCL, with radiological features consistent with a BD-IPMN requiring surveillance, diagnosed between January 2010 and December 2015, were included in the analysis. The MRI-MRCP and EUS needed to be performed within 6 months of each other for patients to be included in the analysis. Patients who did not undergo both investigations or where the interval between both procedures was >6 months, were excluded. Patients with a recent episode of acute pancreatitis, extensive chronic pancreatitis, a confirmed pseudocyst or suspicion of other PCL, were excluded.

*MRI-MRCP technique*

All images were evaluated on an IMPAX Workstation by one of two experienced abdominal radiologists in three hospitals (experience 15 years, reporting >10,000 MRI-MRCP). The MRI-MRCP examinations
were performed on a 1.5 Tesla MR (Avanto, Siemens, Erlangen, Germany). The following imaging sequences were acquired: axial (respiratory triggered) T2 TSE with (TR 2000/TE 104) and without fat saturation (TR 1900/TE 72) with 6 mm slices; coronal (respiratory triggered) (TR 2500/TE 682) reconstructed with 1 mm slices; axial EP 2D diffusions sequence with b-values of 50, 400, and 800 (TR 5000/TE 76) with 4 mm slices; 3D T1 (VIBE) breathhold with fat saturation before and after intravenous gadolinium dynamic (Gadovist, 1 mmol/ml, Bayer Schering Pharma, Berlin, Germany), reconstructed in 2 mm slices axial (TR 5.77/TE 2.56); arterial and portal phase post contrast after 30 and 60 s (with contrast bolus tracking).

**EUS technique**

The procedure was performed in the left lateral position under conscious sedation using midazolam and/or fentanyl or general anaesthesia. All procedures were executed by experienced endosonographers (each having performed more than 5000 procedures). In UHSC and UCLH the procedures were done using Pentax EG-3870UTK- EG-3270UK and Hitachi-Preirus echoendoscopes and at the RFH using the Olympus Medical system.

FNA was performed in some patients depending on both the decision of the endoscopist and the lesion of each patient. After aspiration, the cyst fluid was sent for cytological and biochemical analysis. In our case it was only included as biochemical analysis the CEA, as this was the common ground between the three centers. Antibiotic prophylaxis was given to all patients following FNA in line with the local hospital policy. Patients were monitored for 4 hours post procedure prior to discharge if well.

Sonovue was used for the differentiation of enhanced and non-enhanced solid component within cyst in the most recent cases due to the availability of the technique. In older cases, the diagnostic was performed as clear evidence of a solid mass in the interior of the lesion.

Different criteria for referral for EUS were used in the different hospitals in the study. At UCLH-RFH patients with a cyst >2cm, <2cm if increasing in size or with ≥1 worrisome feature on imaging were referred for an EUS. At UHSC, all patients with a cystic lesion on MRI-MRCP, regardless of size or the presence of worrisome features were evaluated by EUS.

**Data analysis and criteria**

Where available the following data were recorded for both MRI-MRCP and EUS by retrospectively
analysing the imaging reports: size, number of lesions, location, pancreatic duct wall thickening (>2mm), non-enhanced mural nodules, solid component, peripancreatic lymph nodes, dilation of the main pancreatic duct (PD) (>5mm), distal pancreatic atrophy with abrupt change in caliber of the main pancreatic duct. The location of a BD-IPMN was categorized into 6 groups: head (which included the pancreatic neck), body, tail, uncinate process, peripancreatic area and papilla. For each patient the electronic medical records were also reviewed. Although in the most of cases, the last report was reviewed, the operator was not influenced by the previous reports. There was difference between hospitals in the first technique performed, being in the most of the cases, the first technique the MRI in UCL-RFH (72 of 83), and in almost third of cases the EUS in USCH (56 of 97).

Statistical analysis
Statistical analysis of all collected data was performed using SPSS 20.0. Quantitative data were presented as mean values with standard deviations. Interobserver agreement for specific features was measured by using the Kappa statistic (score: -1.0 and 1.0). Values > 0.8 were considered excellent, values between 0.61 and 0.8 as good, values between 0.41 and 0.6 as moderate, values between 0.21 and 0.4 as fair, values between 0.01 and 0.2 as poor and values below 0.01 as not agreement. The study has been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Results
Between January 2010 and December 2015, 287 patients were under surveillance with a highly probable BD-IPMN in three centres. Of the 287 patients, 49 patients were excluded from the study because there was more than 6 months between the MRI-MRCP and EUS. Another 65 patients were excluded due to having only one technique, 36 patients performed only EUS and 29 patients performed only MRI-MRCP (Figure 1).
A total of 173 patients were included in the study (97 from UHSC, 76 UCLH-RFH). Median age was 65 (range, 25-87) years. 107 patients (62%) were female and 66 male. Overall mean time between MRI and EUS was 86 days (range, 0-178 days).
By EUS, there were 100 BD-IPMN < 20 mm, 28 were between 20-29 mm, 34 were between 30-39 mm and 9 were between 40-79 mm. By MRI-MRCP there were 85 BD-IPMN < 20 mm, 29 were between 20-29 mm, 26 were between 30-39 mm and 15 cystics between 40 and 89 mm. When we compared the reported lesion size by both techniques at each hospital, we observed a increase in the size reported by MRI-MRCP compared to EUS, at both USCH (17.0 mm vs 16.0 mm, p=0.53) and UCLH-RFH (26.4 mm vs 23.9 mm, p=0.31) (Table 1).

At EUS 62 cysts were in the head, 69 in the body, 29 in the tail and 11 in the uncinate. At MRI-MRCP and 51 in the head, 61 in the body, 33 in the tail, 8 in the uncinate, 1 in the peripancreatic area and 1 in the papilla. For the site of the lesion we found that the interobserver agreement between EUS and MRI-MRCP was good (k=0.68). Greater disagreement in the location of the lesions was seen in the proximal pancreas than in the distal pancreas (Table 2).

**Interobserver agreement between EUS and MRI-MRCP**

Almost half of patients had one or more worrisome feature or high risk stigmata by EUS or MRI-MRCP.

**Worrisome features:** A dilated main PD to 5–9 mm was observed in 25 patients at EUS and 21 by MRI-MRCP, with agreement in 12 patients, (moderate agreement, k=0.45). Distal pancreatic atrophy with abrupt change in caliber of the PD was observed in 17 BD-IPMN by EUS and 15 by MRI-MRCP with agreement in 9 patients, (moderate agreement, k=0.52). Wall thickening was observed in 10 BD-IPMN by EUS and 11 in MRI-MRCP with agreement in 3 patients, (fair agreement, k=0.25). No agreement was obtained for detecting non-enhanced mural nodules, which was observed in 12 by EUS and 1 by MRI-MRCP (k<0). No agreement was obtained in associated lymphadenopathy, observed in 17 BD-IPMN by EUS and 3 in MRI-MRCP (k<0) (Table 2).

Of the 12 patients with non-enhanced mural nodules in EUS but not MRI-MRCP, 4 underwent surgical resection, of whom 3 had a BD-IPMN with high grade dysplasia (HGD) and 1 a BD-IPMN with low to intermediate grade of dysplasia (LGD-IGD). In 3 patients contrast enhanced EUS with Sonovue was utilized, of whom 2 also had a result in CEA>30 before undergoing surgery. In the remaining 8 patients, 7 were surveyed for a median of 26 months and none developed pancreatic cancer (Sonovue used in 2 patients), and 1 was lost to follow up (Sonovue used in the patient). In none was possible to obtain sample for cytology and CEA. There was one case with non-enhanced mural nodule in MRI –MRCP but
not in EUS, after failing to be confirmed by CT or EUS and subsequent MRI-MRCP during surveillance, it was described as an error in the first diagnostic technique (Figure 2).

High-risk stigmata: Enhanced solid component was observed in 19 BD-IPMN by EUS and 7 in MRI-MRCP with agreement in just 2 patients (poor agreement, k=0.12). No agreement was observed when comparing dilation of the main PD size to >10 mm which was present in 2 BD-IPMN by EUS and 3 by MRI-MRCP (k<0) (Table 2).

Of the patients with an enhanced solid component in EUS, 6 underwent surgical resection.

In 3 patients was used contrast with Sonovue, of whom 1 had a BD-IPMN with LGD-IGD and 2 had a BD-IPMN with HGD. In the remaining 3 patients, the final pathology was microcystic serous cystadenoma (SCA). It was not possible to send the fluid for analysis in any of the 3 patients.

In the remaining patients with enhanced solid component in EUS only, 2 patients with enhanced solid component confirmed with Sonovue refused surgery and the lesion progressed to adenocarcinoma, requiring treatment with chemotherapy. The surgery was refused by multidisciplinary team meeting (MDT) in 9 patients, 6 patients for discrepancy between techniques (Sonovue was not used in any patient and neither was possible to obtain an adequate sample for cytological and biochemical analysis) and 3 patients due to comorbidities (Sonovue was used in one patient and CEA>30 was obtained in all patients but not cytology). All these patients remained stable for a median of 22 months. There were five cases where the solid component was detected on MRI-MRCP but not seen in EUS. 2 patients were to surgery and the final pathology revealed it was a BD-IPMN with HGD and BD-IPMN with LGD-IGD. In the remaining patients, 2 patients after failing to be confirmed by CT or EUS and subsequent MRI-MRCP during surveillance, they were described as an error in the first diagnostic technique. The other patient remained stable for a median of 20 months. All patients with agreement in both techniques underwent surgical procedures. They were diagnosed with EUS both with Sonovue, cytological and biochemical analysis (positive cytology for mucinous without atypia and CEA>30). The final pathology was BD-IPMN with LGD-IGD (Figure 3).

2 patients with PD>10mm in EUS but not MRI-MRCP, only one underwent surgery and the final pathology revealed it was BD-IPMN with LGD-IGD (positive cytology for mucinous without atypia and CEA<30 was obtained with EUS-FNA). The other patient was lost to follow up.

Of the 3 patients with PD>10mm on MRI-MRCP but not EUS, 2 underwent surgical resection. 1 had a
BD-IPMN with LGD-IGD and 1 patient had a microcystic SCA. The other patient died due to other causes.

**Discussion**

In this study we have directly compared the ability of MRI-MRCP and EUS to detect worrisome features and high risk stigmata in PCL with a highly probable BD-IPMN under active surveillance. We observed that although the MRI-MRCP and the EUS are the techniques of choice for the detection of worrisome features or high risk stigmata, overall the concordance between the two was poor.

To date the current guidelines have advocated different methods of imaging for surveillance e.g. the American Gastroenterology Association (AGA) guidelines only advocate MRI-MRCP whereas the international guidelines suggest EUS or MRI-MRCP. The guidelines have also not been consistent about which high risk features would prompt surgical resection and if imaging methods are sufficiently consistent to be able to be used interchangeably in surveillance programmes. We therefore compared agreement of high risk features detected by EUS and MRI-MRCP in centres with established large surveillance programmes for BD-IPMN.

With regards to high risk features in BD-IPMN, in our study we observed no-to-moderate agreement between the worrisome features and no-to-poor agreement in the high risk stigmata. The greatest agreement was observed in main PD size of 5–9 mm and abrupt change and the lowest agreement in non-enhanced mural nodules, lymphadenopathy and PD>10 mm.

A mural nodule was detected in 12 patients by EUS, which were not seen on MRI-MRCP. A third of these patients were referred for surgery of which 3 had a BD-IPMN with HGD and a further 1 with a BD-IPMN with LGD-IGD. All these lesions have the potential to progress to pancreatic cancer, and through timely detection by EUS all of these patients underwent a curative resection.

With regards to observe an enhanced solid component only with EUS, 6 patients went to surgery, of which 2 had a BD-IPMN with HGD and 1 had BD-IPMN with LGD-IGD, but 3 had a SCA. We observed that all patients had high imaging suspicious of BD-IPMN (associated with one or more dilated branch ducts and dilated PD) but in none of them a previous diagnostic could be realized with cytological and biochemical analysis. Although in this study EUS appears to be a superior technique for detecting high
risk features in BD-IPMN, it may make mistakes in some cases. However being able to differentiate SCA from other forms of PCL has improved recently due to the introduction of additional techniques such as confocal endomicroscopy and contrast enhanced EUS, as in our case in which we were able to correctly diagnose all cases. These findings have also been reported by other small studies which have compared intraobserver agreement between MRI-MRCP, EUS and EUS-FNA [11].

Minor differences in the reported site and size of the lesions by MRI-MRCP and EUS were also observed in this study. The most common site for a BD-IPMN was in the head and body of the pancreas. The greatest disagreement in the site of the lesion was seen in the proximal pancreas, which may be due to the complexities of visualizing the head of the pancreas by both MRI-MRCP and EUS. BD-IPMN were almost always reported to be larger by MRI-MRCP. Although these differences are not significant, they should be considered when using size criteria for deciding on surgical resection as measurements within the guidelines.

Results from this study highlights the importance of interpreting imaging findings in BD-IPMN under surveillance, in accordance with the imaging technique used. In addition this study underscores the important differences between the two techniques, and the need for both techniques should be incorporated at least in the initial assessment of a BD-IPMN and potentially as part of surveillance for these lesions to ensure worrisome features are detected in less time.

Our study has several strengths and limitations. On the one hand, it is a multicenter study with a significant number of patients, which is realistic and reflects daily clinical practice. On the other hand, this is a retrospective study across three centres with differing criteria for EUS during surveillance for BD-IPMN. We also accept that the efficiency of EUS and MRI-MRCP is strongly related to the physician’s experience and available local expertise, which may bias test selection. When analysing the data we noted that in some cases it was difficult to always exactly define indications for surgical resection, as it was based on a MDT where imaging may have been reanalysed. To confirm findings from this study prospective comparison studies would be necessary.

We also agree that to confirm our findings it is neccesary a gold standard like surgery. But with this study our aim was only to highlight the problems that occur on the daily practice due to discordant results obtained from the techniques which are considered of reference according to the different guidelines in 3 large centres with great experience in this type of lesions. On the other side, we have observed that with
the development in the new techniques, as in the case of contrast with EUS, every time we are closer to properly handling this type of lesions.

In conclusion, in this multicentre study of patients with BD-IPMN under active surveillance, most disagreement among MRI-MRCP and EUS was seen in the proximal pancreas compared to the distal pancreas. No-to-moderate interobserver agreement was found between MRI-MRCP and EUS for worrisome features and no-to-poor interobserver agreement was found for high risk stigmata. Surveillance guidelines for BD-PMN therefore need interpreting in light of these findings.

**Funding**

EPC-Fellowship

**Conflict of interest**

None.

**References**

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observe or operate. Ann Surg 2004; 239: 651-9


## Table 1.

Number and size of lesions identified by both imaging techniques is shown in table.

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Table 2. Concordance between EUS and MRCP findings is shown in table.