3.0-T magnetic resonance imaging in predicting subtypes of IPMN and invasive IPMN

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Purpose

Intraductal Papillary Mucinous Neoplasms (IPMNs) of the pancreas are tumors of the pancreatic duct epithelium, characterized by papillary epithelial proliferation and mucin production, leading to cystic dilatation of pancreatic involved ducts. These lesions were initially reported in the 1990s but the term IPMN was established in the 2000 classification of the WHO[1]. In recent years in pancreatic surgery referral centers, IPMNs have been increasingly diagnosed[2].

Histologically IPMNs encompasses variable grades of lesions, ranging from low-grade dysplasia to invasive carcinoma. Progression model from non invasive carcinoma via borderline lesion to invasive carcinoma have been developed [3,4].

According to their site of origin, IPMNs are subdivided into main duct (MD-IPMN) and branch duct (BD-IPMN) types. According to morphological variations, IPMNs comprise distinct subtypes, namely gastric (GT), intestinal (IT), pancreatobiliary (PBT), and oncocytic (OT). Similarly, invasive carcinoma arising in IPMN is distinguished in three histological subtypes, tubular (TCT), colloid (CCT) and oncocytic (OCT) [4,5]. Whereas intestinal, pancreatobiliary and oncocytic subtypes originate in the main duct, the gastric subtype derives from branch duct. The WHO classification of IPMNs published in 2010 has employed this concept [6].

The criteria for distinguishing the distinct subtypes of invasive IPMNs and underlying IPMNs have been established. The classification is based on the cytomorphological features of the papillae supported by the immunohistochemical features of mucin glycoproteins [5].

More recent studies have shown that these histological subtypes are closely associated with the rate of malignancy and prognosis. The gastric subtype has a relatively low malignant potential, intestinal type often progress in invasive carcinoma with colloid pattern, pancreatobiliary type mainly progress in invasive carcinoma with tubular pattern and oncocytic type usually progress in invasive carcinoma with oncocytic pattern[5,7-10].

The distinction of these IPMNs subtypes has prognostic relevance because outcome of patients affected to various IPMN subtypes is different: patients with colloid and oncocytic carcinoma in IPMN have a favorable outcome, with better 5-years survival rate than patients affected to tubular carcinoma in IPMN [8-13], associated with worse overall survival, not significantly different from that of pancreatic ductal adenocarcinoma.

Assessing the subtypes of invasive carcinoma as well as underlying IPMNs at the moment of clinical and Imaging diagnosis may provide useful information for different clinical management of patients affected to IPMN.
Gadolinium (GD)-enhanced Magnetic Resonance Imaging (MRI) and Magnetic Resonance Cholangio Pancreatography (MRCP) are Imaging techniques recommended for characterization of IPMNs thanks to high risk stigmata and worrisome features [11-13]. MRI/MRCP enables the identification of the most reliable signs associated with malignancy. In case of malignancy, MRI is a useful imaging modality for assessment of resectability and metastatic disease[12,13].

3.0-T MRI offers higher signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) than 1.5-T MRI and many abdominal application can benefit from 3.0-T MR Imaging, such as MRCP and MRI pancreatic study [14-16].

The aim of the study is to provide 3.0-T MR Imaging features correlated to IPMNs subtypes in our experience, in order to assess the capability of 3.0 -T MRI in predicting IPMNs and invasive IPMNs subtypes.
Methods and materials

Patient population

A search in our Institution's surgical records and radiological database, between January 2010 and January 2014, disclosed 40 patients with diagnosis of IPMNs to be considered for the inclusion in this retrospective study.

Inclusion criteria were: surgically resected IPMNs, preoperative 3.0-T MRI/MRCP examination performed at our Institution within the 3 months preceding surgery, histologically proven diagnosis of IPMNs and IPMNs subtypes (GT, IT, PBT, OT, TCT, CCT, OCT) and availability of surgical specimens.

Exclusion criteria were: previous pancreatic surgery (5 patients), lack of preoperative MRI/MRCP (5 patients), poor image quality (6 patients), specimen not available (4 patients).

Thus, our study population encompassed 20 patients, 8 females and 12 males, with a mean age of 65 years.

All patients underwent preoperative 3.0-T MRI/MRCP imaging and surgical procedure (10 pancreaticoduodenectomy: PD; 4 splenopancreasectomy: SP; 6 total pancreatectomy: TP). The median time interval between MRI/MRCP and surgery was 1.2 months (range 0.1-2.8 months).

MR Imaging

In all cases pancreatic MRI and MRCP were performed on a 3.0-Tesla field strength scanner (Magnetom Verio, Siemens, Erlangen, Germany) using a surphace phased-array body coil. Patients were asked to fast for 4-6 hours before the MRI examination. To eliminate overlapping fluid-containing organs on MRCP T2-weighted images, 50-150 ml of superparamagnetic iron oxide particles are administered 10-20 minutes before MRI examination. The MRI protocol included the following elements: a chemicalshift T1-weighted gradient-echo sequence with in- and out-of-phase echo times in the axial plane, axial fat-saturated T1-weighted sequence, a fat-saturated T2-weighted RARE sequence in the axial plane, and a T2-weighted half-Fourier RARE sequence in the coronal and axial plane. Sagittal and coronal oblique half-Fourier RARE sequences with appropriate angulation to depict the longest diameter of the pancreatic duct were performed to optimize depiction of the pancreatic duct system. Once the most appropriate plane in which to assess the bilio-pancreatic duct system was identified, MRCP was performed in all patients with a two-dimensional half-Fourier RARE heavily T2-weighted pulse sequence during breath holding along the most appropriate coronal or coronal oblique plane to best depict the pancreatic duct system, the biliary tree, both papillae, and the duodenum. In addition, in all cases respiratory-triggered 3D half-Fourier
RARE MRCP was also performed along the coronal oblique plane. The respiratory-triggered 3D half-Fourier RARE source images were analyzed and post-processed with a maximum intensity projection algorithm at a workstation. Dynamic imaging during Gd chelate injection was performed with a three-dimensional volumetric gradient-echo pulse sequence (referred to as the volumetric interpolated breath-hold examination) with fat saturation along the axial plane and use of parallel imaging. A quadriphasic dynamic examination was performed during intravenous injection of 0.1 mmol per kilogram of body weight gadolinium chelates with a power injector at a rate of 2-2.5 mL/sec; images were acquired in the precontrast, pancreatic (35-45 seconds after injection), portal venous (75-80 seconds after injection), and delayed (180 seconds after injection) phases.

DWI Imaging was obtained by a singol-shot spin-echo echo-planar sequence, performed with $b$ value of 0,50,600,1000 sec/mm2. An ADC map was calculated for each section automatically by the imager software.

**Imaging Analysis**

In retrospective study, MRI/MRCP images were independently analyzed by 2 blinded Radiologists who were aware of the diagnosis of IPMNs but unaware of the subtypes. Discrepancies were solved by final consensus.

In Qualitative imaging analysis we considered: GD-enhanced endoluminal solid defects (presence/absence; in MPD/BD), GD- enhanced ductal wall thickening #3mm (presence/absence; in MPD/BD), ductal dilatation (MPD :#10mm, BD: #30mm;presence/absence),non GD- enhanced mural noduls (presence/absence; in MPD/BD), vascular infiltration(superior mesenteric artery/superior mesenteric vein/celiac trunk;presence/absence), areas of high signal intensity from restricted diffusion at high $b$ value ($b$= 1000 sec/mm2) DW images (presence/absence).

In Quantitative imaging analysis we measured ductal maximum diameter (MPD/BD).

At histological specimen, 5/20 GT (all of them with low grade dysplasia), 4/20 IT (2 of them with high grade dysplasia and 2 of them with moderate dysplasia), 2/20 PBT (1 of them with carcinoma in situ and 1 with moderate dysplasia ), 2/20 OT (all of them with low moderate dysplasia), 7/20 TCT, 0/20 CCT and 0/20 OCT resulted.

A comparison of 3.0T-MRI/MRCP data with histological specimen results and statistical analysis with Fischer Test and Mann-Whitney Test were performed.
Results

GD-enhanced endoluminal filling defects were observed (FIG 1 E) in 1/5 GT (20%), 3/4 IT (75%), 1/2 PBT (50%), 1/2 OT (50%), 7/7 TCT (100%), with a significant absence in GT (p=0.03) subtype (FIG 1 A-B) and presence in TCT (p= 0.04) subtype (FIG 1C-D).

GD-enhanced thickened ductal wall #3mm (FIG 2 E) was absent (FIG 2A-B) in all GT (0%) and present in 4/4 IT (100%), 2/2 PBT (100%), 1/2 OT (50%), 7/7 TCT (100%: FIG 2 C-D); only its absence in GT subtype (FIG 2 A-B) was statistically significant (p =0.03).

MPD dilation #10mm (FIG 3B) in 0/5 GT (0%), 2/4 IT (50%), 1/2 PBT (50%), and OT (50%), 4/7 TCT (57%) and BD dilation #30mm (FIG 3C) in 1/5 GT (20%), 2/4 IT (50%), 1/2 PBT (50%), and OT (50%), 4/7 TCT (57%) were present respectively; only absence of MPD dilation #10mm in GT subtypes (FIG3A) resulted significant (p=0.05).

Non-enhanced mural nodules in 3/20 GT, 4/20 IT, 2/20 PBT, 1/20 OT, 6/20 TCT (FIG 4 A-C) and vascular invasion (FIG 4 D-F) in 1/20(TCT) were present; both parameters were not found significantly associated with any IPMN subtypes.

Areas of high signal intensity from restricted diffusion at high b value (b=1000 sec/mm2) DW images (FIG 5E) were absent in all GT and PBT (0%), present in 4/4 IT (100%), 2/2 OT (100%), and in 7/7 TCT (100%); their absence in GT (FIG 5A-B) subtype (p= 0.004) and presence in TCT (FIG 5C-D) subtype (p= 0.04) were significant.

The mean size of maximum diameter of MPD (FIG 3D) was 5.2 mm in GT, 11.25 in IT, 9.5 mm in PBT, 12.5 in OT, 20.28 in TCT. The mean size of maximum diameter of BD was 12.5mm in GT, 25.6mm in IT, 27.4 mm in PBT, 22.1 mm in OT, 42.4 in TCT. The comparison of mean size of maximum diameter of MPD and BD in various subtypes had no statistic value (Mann-Whitney Test: P = 0.098).
**Fig. 1:** FIG 1A-E. GD-enhanced endoluminal filling defects. Axial fat-saturated 3D volumetric Gradient Echo before (A,C) and after GD intra venous injection during late arterial/pancreatic phase (B,D) 3.0-T MR images. GD-enhanced endoluminal filling defects resulted significantly absent ($p=0.03$) in GT subtype (A-B) and present ($p=0.04$) in TCT subtype (C-D: arrows). The prevalence in % of GD-enhanced endoluminal filling defects in different IPMN subtypes in our series (E).

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**Fig. 2**: FIG 2A-E. GD-enhanced thickened ductal walls (#3mm). Axial fat-saturated 3D volumetric Gradient Echo before (A, C) and after GD intra venous injection during late arterial/pancreatic phase (B, D) 3.0 T MR images. GD-enhanced thickened ductal walls (#3mm) resulted significantly absent (p=0.03) in GT subtype (A-B), no significantly present in TCT subtype (C-D: arrow). The prevalence in % of GD-enhanced thickened ductal walls (#3mm) in different IPMN subtypes in our series (E).

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**Fig. 3:** FIG 3A-D. MPD (#10mm) and BD (> 30 mm) dilatation. 3.0-T MRCP. MPD dilatation (#10mm) resulted significantly absent (p=0.05) in GT subtype (A). The prevalence in % of MPD dilatation #10mm (B) and BD dilatation > 30 mm (C) in different IPMN subtypes in our series. Quantitative measurement of maximum diameter of MPD in different IPMNs subtypes of our series (D); the comparison between mean value of maximum diameter of MPD in GT and TCT didn't result significant in our series (p: 0.098).

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**Fig. 4:** FIG 4 A - F. Non GD-enhanced mural nodules (A-C) and vascular infiltration (D-F). Axial fat-saturated 3D volumetric Gradient Echo before (A) and after GD intra venous injection during late arterial/pancreatic phase (B) and venous phase (D,E) 3.0 T MR images. Non GD-enhanced mural nodules (A-B: arrows) and vascular infiltration of superior mesenteric vein (D-E: arrow) were significantly correlated with IPMN subtypes. The prevalence in % of both parameters, GD-enhanced mural nodules (C) and vascular infiltration (F) respectively in different IPMN subtypes in our series.

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**Fig. 5:** FIG 5A -E . Areas of high signal intensity from restricted diffusion at high b value (b= 1000 sec/mm²) 3.0- T MR DWI. DW axial images performed with b value of 0 (A,C) and 1000 (B, D) sec/mm². This finding resulted significantly absent (p=0.004) in GT subtype (A-B) and present (p= 0.04) in TCT subtype (C-D: arrow). The prevalence in % of this finding in different IPMN subtypes in our series (E).

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Conclusion

International consensus guidelines for the management of IPMN and MCN of the pancreas [12] and European experts consensus statement on cystic tumors of the pancreas [13] assessed MRI with MRCP is Imaging modality recommended to check for imaging signs associated with malignancy, represented by "high-risk stigmata", including enhanced solid ductal component and MPD size of 10 mm, and "worrisome features", including cyst of 3 cm in diameter, thickened enhanced cyst walls, non-enhanced mural nodules, MPD size of 5 e 9 mm, abrupt change in the MPD caliber with distal pancreatic atrophy, and lymphadenopathy.

All pancreatic cystic lesions with "worrisome features" and cystic lesions of >3 cm in diameter without "worrisome features" should undergo Endoscopic Ultra Sound (EUS), and all cystic lesions with "high-risk stigmata" should be resected.

If no "worrisome features" are present, no further initial work-up is recommended, although surveillance is still required [12,13].

In our experience, of six 3.0-T MRI and MCRP parameters analyzed, high-risk stigmata and worrisome features, three of them were correlated with invasive IPMN and underlying IPMN subtypes.

GD-enhanced endoluminal filling defects, GD-enhanced thickened ductal walls (#3mm), considered "high-risk stigmata and worrisome feature in Literature[12,13] respectively and presence of areas of high signal intensity from restricted diffusion at high b value (b=1000 sec/mm2) DW images, MRI feature recently reported with add value in predicting malignancy of IPMN [17], were strongly associated with different IPMNs subtypes in our study.

The absence of all there parameters was significantly correlated with gastric types (GT) of IPMN in our analysis. The presence of two parameters, GD-enhanced endoluminal filling defects and areas of high signal intensity from restricted diffusion at high b value (b=1000 sec/mm2) DW images was significantly correlated with tubular carcinoma subtype (TCT) in IPMN. The absence of MPD dilatation (#10mm), significantly correlated only with gastric type (GT), improved the prediction of this IPMN subtype.

None of others parameters analyzed, BD dilatation (#30mm), non-enhanced mural nodules and vascular invasion, showed statistic prevalence in different IPMN subtypes.

Our experience suggest 3.0-T MR/MRCP imaging may provide useful information and add value in predicting the two most different subtypes of IPMN. Assessing at 3.0-T MR imaging the absence of GD-enhanced endoluminal filling defects, GD-enhanced thickened ductal walls (#3mm), areas of high signal intensity from restricted diffusion at high b value (b=1000 sec/mm2) DW images and MPD dilatation (#10mm) suggest
the prediction of gastric type of IPMN (GT), reported in Literature as non invasive, low malignant pancreatic lesion[5, 7-10]. Assessing at 3.0-T MR imaging the presence of GD-enhanced endoluminal filling defects and areas of high signal intensity from restricted diffusion at high b value (b= 1000 sec/mm2) DW images, suggest the presence of tubular type carcinoma (TCT) in IPMN , the most malignant with worse survival type of IPMN [5, 7-10]. These information may help in treatment decision making and clinical management, both in patients fit for surgery, and in patients affected to comorbidities, where surgery is not indicated and radiological surveillance is recommended [10,11-13].

Finally, these 3.0 -T MR evaluations about IPMN subtypes could be useful also in pancreatic IPMNs occasionally found in individuals with a history of familial pancreatic cancer [17-20]. Some studies showed that a family history of pancreatic cancer is associated with a worse prognosis in patients with invasive IPMNs, with faster progression of IPMNs, and with a major risk for the development of other pre-neoplastic lesions in the remainder of the pancreas [17-20 ].

Our study has several limitation that the Authors are well aware of, mainly related to the retrospective design of the study: the most noticeable is a selection bias in the patient population, since we included in the study only patients with proven IPMN that underwent surgical procedure. Other limitation is a low number of cases, that makes a low statistic value of the study and explains the insufficiency of our data to evaluate the real and actual MR prediction of IPMN subtypes.

In conclusion, this study emphasizes the capability of 3.0-T MR Imaging in predicting IPMNs subtypes, in particularly the gastric subtype (GT), frequently non invasive and low grade malignant lesion, and tubular carcinoma subtype (TCT) frequently invasive and malign tumor with worse prognosis.

3.0- T MR imaging findings and the evaluation of biomarkers to preoperatively detect IPMN subtypes should improve the clinical practice and patient outcome.
References


