



Utility of gadolinium for identifying the malignant potential of pancreatic cystic lesions

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Abstract

Purpose To determine if gadolinium is necessary for the diagnosis of a pancreatic cystic lesion (PCL) as benign or malignant by assessing inter- and intra-observer agreement and diagnostic accuracy for the presence of worrisome features/high-risk stigmata on non-contrast MRI compared to MRI with and without contrast, with cytopathology as a reference standard.

Methods The institutional database was searched to identify consecutive patients that underwent EUS/FNA or surgical resection of an asymptomatic PCL performed from 01/01/2015 to 01/01/2019. Two abdominal radiologists independently evaluated PCLs on MRI with all sequences except for contrast-enhanced sequences followed by a second reading with data from the entire MRI including pre- and post-contrast sequences. Cyst size, growth, and the presence of worrisome features/high-risk stigmata were assessed for each cyst on both datasets.

Results There were 87 patients with 87 pancreatic cysts; 76(87.4%) were benign and 11 (12.7%) were malignant. The presence of any worrisome features/high-risk stigmata for reader 1 was concordant on both MRIs in 95.4% (83/87; $k=0.874$) of cases and for reader 2 was concordant in 96.6% (84/87; $k=0.920$) of cases. The diagnostic accuracy of the two datasets when the presence of any worrisome feature/high-risk stigmata was predictive of malignancy was identical for reader 1 (AUC = 0.622 for both; $p=1.0$) and similar for reader 2 (AUC 0.569 and 0.589; $p=0.08$) for both MRI datasets.

Conclusion The addition of gadolinium had no significant impact in the diagnosis of a benign versus malignant PCL, with similar intra-observer agreement and diagnostic accuracy for both readers when using contrast-enhanced and unenhanced MRI datasets.

Keywords IPMN · MRI · Gadolinium · Pancreatic cystic lesion

Introduction

Pancreatic cystic lesions (PCL) are commonly encountered at cross-sectional imaging [1]. These are detected more frequently on MRI than CT, likely due to the increased soft tissue contrast of MRI [2], with an incidental PCL prevalence as high as 41.6% in some abdomen MRI series [3]. Most

PCLs are mucin-containing lesions, with the majority being intraductal papillary mucinous neoplasms (IPMNs) [4]. The frequency of malignant transformation from PCL to adenocarcinoma is low [5, 6], allowing for conservative management algorithms. Various clinical societies, including the American College of Radiology (ACR) and International Consensus Fukuoka Guidelines have issued management guidelines for IPMNs [7–9]. Both guidelines consider cyst size, cyst growth, and additional imaging features such as the presence of an enhancing mural nodule, thickened cyst wall, or pancreatic duct dilatation in the diagnosis of cyst malignancy and overall management decision; either EUS/FNA, resection, or continued surveillance, with the length and frequency of surveillance varying between guidelines [7–9].

Although the ACR recommends either contrast-enhanced MRI or CT for PCL surveillance, MRI is often preferred due to the lack of ionizing radiation and superior performance

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for characterizing cystic lesions [10, 11]. Given the frequency and potential duration of surveillance, patients with PCLs that undergo MRI surveillance may be subject to multiple repeated administrations of gadolinium-based contrast agents. This is a point of concern for some patients and referring clinicians given reports of gadolinium deposition in various body tissues and the yet unknown clinical effects [12–14]. Two prior studies have assessed the need for intravenous contrast in the surveillance of PCLs by assessing the interobserver and intra-observer agreement for final management decision or cyst size/presence of mural nodule using MRI without contrast as well as MRI with and without contrast [10, 15]. However, there is a sparsity of studies evaluating whether contrast is needed in the diagnosis of a benign or malignant PCL by assessing individual worrisome features/high-risk stigmata against a cytopathology reference standard.

Therefore, the aim of our study is to determine if gadolinium is necessary for the diagnosis of a PCL as benign or malignant by assessing interobserver and intra-observer agreement and diagnostic accuracy for the presence of worrisome features/high-risk stigmata on non-contrast MRI compared to MRI with and without contrast, with cytopathology as a reference standard.

Material and methods

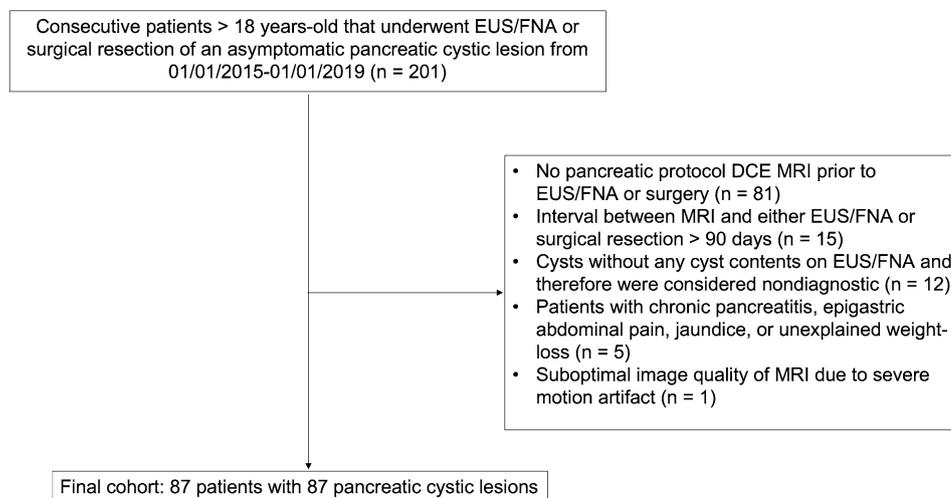
This Health Insurance Portability and Accountability Act–compliant study was approved by the institutional review board with a waiver of informed consent. In this single institutional retrospective study, the institutional database was searched to identify consecutive patients > 18-years-old that underwent EUS/FNA or surgical resection of an asymptomatic PCL performed from 01/01/2015 to 01/01/2019 (Fig. 1). Exclusion criteria were as follows: no dynamic

contrast-enhanced abdomen MRI prior to EUS/FNA or surgery ($n = 81$); interval between MRI and either EUS/FNA or surgical resection > 90 days ($n = 15$); cysts without any cyst contents on EUS/FNA and therefore were considered non-diagnostic ($n = 12$); patients with chronic pancreatitis, epigastric abdominal pain, jaundice, or unexplained weight loss ($n = 5$), as the management recommendation in these cases are based on clinical criteria and not imaging criteria; and suboptimal image quality of MRI due to severe motion artifact ($n = 1$). In patients with more than one pancreatic cyst that underwent EUS/FNA or resection, the largest lesion was chosen for inclusion in our study cohort.

Imaging technique

MR examinations were performed by using either 1.5-T or 3-T MR imagers: Magnetom Skyra, Trio, or Aera (Siemens Healthcare, Erlangen, Germany) or LX Signa Excite 2, (GE Healthcare, Milwaukee, Wis; HD, GE Healthcare). The MRI with and without contrast included the following sequences: axial and coronal breath-hold single-shot fast spin-echo T2-weighted sequence (repetition time ms/echo time ms, TR/TE: 1100–1100/80–85, matrix 320×256 , section thickness 5 mm, interslice gap 1 mm, acceleration factor of 1.5–2x), axial breath-hold three-dimensional dual-echo sequence (TR/TE 150/2.3 and 4.6 (1.5 T), 2.3 and 5.8 (3 T), matrix 288×230 , section thickness 3 mm, acceleration factor of 2x), axial diffusion-weighted images (b values of 0, 50, 800, TR/TR: 5900/52, matrix 134×134 , section thickness 5 mm, acceleration factor of 2x). 3D fat-suppressed T1-weighted sequence (TR/TE: 2.68/1.1, matrix 288×170 , section thickness 3 mm, acceleration factor 2x) before and after the administration of gadobenate dimeglumine (Multihance, Bracco Diagnostics, Princeton NJ; 0.1 mmol of gadolinium per kilogram of body weight) or gadobutrol (Gadavist, Bayer Pharma; 0.05 mmol of gadolinium per kilogram of body

Fig. 1 Flow diagram demonstrating patient selection and study flow. *EUS/FNA* endoscopic ultrasound/fine needle aspiration, *DCE* dynamic contrast-enhanced



weight) in the following phases: axial arterial phase (either 2 or 3 separate consecutive acquisitions obtained within a single breath-hold or single arterial phase); axial portal venous phase; coronal delayed phase, and axial equilibrium phase. Contrast was injected at 1 ml/s (gadobutrol) or 2 ml/s (gadobenate dimeglumine) followed by a 20 ml saline flush at 2 ml/s. MR cholangiopancreatography, when available, was performed with coronal respiratory-triggered three-dimensional fast spin-echo heavily T2-weighted sequence (4000/614; flip angle, 90°; section thickness, 1.8 mm) and coronal breath-hold thick-slab single-shot fast spin-echo T2-weighted sequence (6000/800; flip angle, 90°; section thickness, 30 mm).

Image analysis

All observations were reviewed by the study coordinator who was not involved in study readings (an abdominal imaging radiologist with 6 post-fellowship years of experience) and the series and image number of each PCL on T2-weighted imaging was recorded. Two fellowship trained abdominal radiologists (R1, R2) with 2 and 7 years of post-fellowship experience independently reviewed every pancreatic cyst on MRI. The readers were aware that patients had a pancreatic cyst, but were blinded to all clinical, pathologic data, and follow-up imaging. First, the two reviewers independently analyzed data from the MRI examination utilizing all sequences except for contrast-enhanced sequences [unenhanced T1-, T2-weighted, and DWI]. Following at least a 4-week interval to decrease recall bias [16], a second session was performed where the readers independently analyzed data from the entire MRI including pre- and post-contrast sequences.

Each reader evaluated the following features based on the International Consensus Fukuoka and the ACR Guidelines for the Management of IPMNs [8, 9]: cyst size in longest dimension, cyst growth, communication of cyst with the main pancreatic duct (MPD) and the following worrisome features/high-risk stigmata: the presence of non-enhancing mural nodule, enhancing mural nodule, thickened cyst wall, and pancreatic duct dilatation. A thickened cyst wall was defined as an enhancing or non-enhancing wall measuring > 2 mm. A non-enhancing or enhancing mural nodule was defined as any non-enhancing or enhancing solid protuberance into the cyst, respectively. The main pancreatic duct was measured as the maximal duct diameter anywhere in the gland and was considered dilated when ≥ 7 mm. Cyst growth was defined as: for cysts < 0.5 cm, a 100% increase in long-axis diameter; for cysts ≥ 0.5 cm and < 1.5 cm, a 50% increase in long-axis diameter; and for cysts ≥ 1.5 cm, a 20% increase in long-axis diameter as per the ACR guidelines on the management of pancreatic cysts [8]. All measurements were performed on axial or coronal images.

Reference standard

Fine needle aspiration with fluid analysis ($n=64$) or surgical resection ($n=23$) were used as the reference standard. For pancreatic cysts that underwent resection, the pathologic grades of IPMN were classified as low-grade dysplasia, intermediate-grade dysplasia, high-grade dysplasia, or invasive carcinoma associated with IPMN as per the World Health Organization guidelines [17]. Those with low- and intermediate-grade dysplasia were considered as benign and those with high-grade dysplasia and associated invasive carcinoma were malignant. For cysts that underwent EUS/FNA, cyst contents demonstrating high-grade dysplasia were considered malignant and cyst contents without evidence of high-grade dysplasia were considered benign. Those without evidence of cyst contents on cytology (and no histology available) were considered non-diagnostic ($n=12$) and were excluded as described above. Twenty-seven cysts that underwent EUS-FNA also underwent biopsy with results that were concordant with cytology.

Statistics

To evaluate the strength of interobserver and intra-observer agreement, weighted k value and intraclass correlation coefficient values were calculated for all features and interpreted as follows: 0.00–0.20, poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; and 0.81–1.00, excellent agreement. Receiver operating characteristic analyses were performed using the presence of any worrisome feature/high-risk stigmata as predictive of malignancy and the presence of cyst growth as predictive of malignancy. We compared the area under the receiver operating characteristic curve values of contrast-enhanced and non-contrast MRI datasets for both readers. A two-tailed $p < 0.05$ was considered to indicate statistical significance. All statistical analysis was performed by using SPSS (version 25; IBM, Armonk, NY) and R (version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria) software.

Results

Patients

The study cohort consisted of 87 patients with 87 pancreatic cysts (mean age 65.5 years+—13.2; 59 women, 28 men). Seventy-six cysts (87.4%) were benign, defined as low or moderate grade dysplasia. Eleven cysts (12.7%) were malignant and included 6 with high-grade dysplasia, 4 with invasive carcinoma, and 1 pancreatic neuroendocrine tumor. The mean interval between CT and MRI examinations and

surgery was 1.7 months (range, 2 days to 3 months). Sixty-six of the 87 patients (75.9%) had a prior contrast-enhanced CT or MRI at least 6 months prior to the baseline MRI to assess for cyst growth.

Interobserver agreement

Kappa coefficients to assess interobserver agreement for pancreatic cyst features is outlined in Table 1. For MRI without gadolinium, reader 1 and reader 2 agreed on the presence of any worrisome features/high-risk stigmata in 77/87 (88.5%; $k=0.722$) of cases and for MRI with and without gadolinium in 76/87 (87.4%; $k=0.739$) of cases. Reader 1 and 2 agreed on the presence of cyst growth in 61/66 (92.4%; $k=0.800$) of cases on MRI without gadolinium and in 61/66 (92.4%; $k=0.800$) of cases on MRI with and without gadolinium. Thickened cyst wall demonstrated the lowest interobserver agreement for both MRIs ($k=0.282$ and 0.274 respectively) and pancreatic cyst size demonstrated the highest interobserver agreement for both MRIs (ICC = 0.953 and 0.937 respectively).

Intra-observer agreement

Kappa coefficients to assess intra-observer agreement for pancreatic cyst features is outlined in Table 2. The presence of any worrisome features/high-risk stigmata for reader 1 was concordant on both MRIs in 95.4% (83/87; $k=0.874$) of cases and for reader 2 was concordant in 96.6% (84/87; $k=0.920$) of cases. In 2 cases, reader 1 recorded the presence of a worrisome feature on MRI without contrast that was not recorded on MRI with and without contrast (both nodule without enhancement), both cysts were benign on EUS/FNA. In two cases, reader 1 recorded the presence of

a worrisome feature on MRI with and without contrast that was not recorded on MRI without contrast (1 with thickened cyst wall and one with a nodule without enhancement), both cysts were benign on EUS/FNA. In 3 cases, reader 2 recorded the presence of a non-enhancing nodule on MRI without contrast that was not recorded to be present on MRI with and without contrast (Fig. 2), all three cysts were benign on EUS. The presence of cyst growth showed the greatest intra-observer agreement and was concordant in 100% (66/66; $k=1.0$) of cases for both readers. Communication with the duct demonstrated the lowest intra-observer agreement when using both datasets for reader 1 ($k=0.494$) and non-enhancing mural nodule demonstrated the lowest intra-observer agreement for reader 2 ($k=0.772$). Reader 1 recorded the presence of an enhancing mural nodule in 3 cases (2 of which were malignant on cytopathology), and reader 2 recorded the presence of an enhancing mural nodule in 5 cases (2 of which were malignant on cytopathology). In all cases where an enhancing nodule was recorded, the presence of a non-enhancing nodule on the same case on MRI without contrast was recorded for both readers.

Diagnostic accuracy

The diagnostic accuracy of MRI without and MRI with and without gadolinium for the diagnosis of a benign or malignant PCL, when the absence of any worrisome feature/high-risk stigmata is considered a true negative and the presence of any of these features is considered a true positive is outlined in Table 3. The diagnostic performance of the two MRIs when using the above criteria, for reader 1 was identical (area under the receiver operating characteristic curve (AUC), 0.622 [95% CI 0.44, 0.74] and 0.622 [95% CI 0.44, 0.74], respectively; $P=1.0$) (Fig. 3). The

Table 1 Interobserver agreement for imaging features between MRI without contrast and MRI with and without contrast

Imaging features	MRI without gadolinium	MRI with and without gadolinium
R1 vs R2	Kappa	Kappa
Communication with duct	0.338 (0.248–0.429)	0.310 (0.226–0.394)
Cyst size ≥ 3 cm	0.755 (0.675–0.835)	0.749 (0.665–0.833)
Non-enhancing mural nodule	0.580 (0.472–0.688)	0.493 (0.373–0.613)
Enhancing mural nodule	N/A	0.739 (0.563–0.915)
Thickened cyst wall	0.282 (0.142–0.422)	0.274 (0.146–0.402)
MPD dilatation	0.654 (0.570–0.738)	0.722 (0.642–0.802)
Cyst growth	0.800 (0.714–0.886)	0.800 (0.714–0.886)
Any worrisome feature or High-risk stigmata	0.722 (0.642–0.802)	0.739 (0.658–0.820)
*Cyst size	0.953 (0.928–0.969)	0.937 (0.905–0.958)

Unless otherwise indicated, data are in k values with 95% confidence intervals in parenthesis

MPD main pancreatic duct

*Data in intraclass correlation coefficients, with 95% confidence intervals in parenthesis

Table 2 Intra-observer agreement for imaging features between MRI without contrast and MRI with and without contrast

Imaging features	Reader 1	Reader 2
Communication with duct	0.494 (0.397–1.085)	0.972 (0.901–0.982)
Cyst size ≥ 3 cm	0.941 (0.900–0.982)	1.00 (1.00–1.00)
Non-enhancing mural nodule	0.893 (0.832–0.954)	0.772 (0.859–0.685)
Enhancing mural nodule	N/A	N/A
Thickened cyst wall	0.851 (0.705–0.997)	0.920 (0.864–0.976)
MPD dilatation	0.893 (0.841–0.915)	1.00 (1.00–1.00)
Cyst growth	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Any worrisome feature or high-risk stigmata	0.874 (0.813–0.935)	0.920 (0.875–0.965)
*Cyst size	0.990 (0.984–0.993)	0.987 (0.981–0.995)

Unless otherwise indicated, data are in k values with 95% confidence intervals in parenthesis

MPD main pancreatic duct

*Data in intraclass correlation coefficients, with 95% confidence intervals in parenthesis

diagnostic performance of MRI without and MRI with and without, when using the above criteria, for reader 2 was similar (AUC, 0.569 [95% CI 0.39, 0.71] and 0.589 [95% CI 0.40, 0.72], respectively; $P=0.08$) (Fig. 4). There were no false negative cases using MRI without contrast that were not noted on concurrent MRI with and without contrast for either reader. In three cases, reader 2 recorded the presence of a non-enhancing nodule on MRI without contrast that was not recorded for MRI with and without contrast, with

all three pancreatic cysts being benign on EUS/FNA, leading to the decreased specificity for reader 2 between the two datasets (68.4% vs. 72.4%).

The diagnostic accuracy of MRI without and MRI with and without gadolinium for the diagnosis of a benign or malignant pancreatic cyst, when the absence of cyst growth is considered a true negative and the presence of cyst growth is considered a true positive is outlined in Table 4. The diagnostic performance of the two MRIs when using the above criteria, was identical for reader 1 (AUC for both MRIs, 0.692 [95% CI 0.59, 0.80]) and identical for reader 2 (AUC for both MRIs, 0.735 [95% CI 0.56, 0.84]) ($p=1.0$).

The diagnostic accuracy of each additional individual worrisome feature/high-risk stigmata is present in Tables E1–E5 in Supplemental Material.

Discussion

We demonstrated excellent intra-observer agreement for the detection of worrisome features/high-risk stigmata, cyst size, and cyst growth for both readers using both MRI without and MRI with and without intravenous contrast ($k=0.851–1.00$). The diagnostic accuracy of the two datasets when the presence of any worrisome feature/high-risk stigmata was predictive of malignancy was identical for reader one (AUC = 0.622 for both) and similar for reader 2 (AUC 0.569 and 0.589) for both MRI datasets.

Asymptomatic pancreatic cysts are a common clinical problem and are being detected with increasing frequency

Fig. 2 66-year-old female with an incidentally detected pancreatic cyst in the pancreatic body. Axial and coronal single-shot fast spin-echo (SSFSE) T2-weighted image (a, c) and axial and coronal 3D gradient-recalled echo T1-weighted image (b, d) obtained during the portal venous phase shows a 16 mm cyst (arrows) in the pancreatic body. In this case, reader 2 recorded the presence of a non-enhancing mural nodule on MRI without contrast that was recorded as having no worrisome features/high-risk stigmata on MRI with and without contrast. Reader 1 did not record the presence of any worrisome features/high-risk stigmata for either MRI dataset. This patient underwent EUS/FNA demonstrating no evidence of high-grade dysplasia

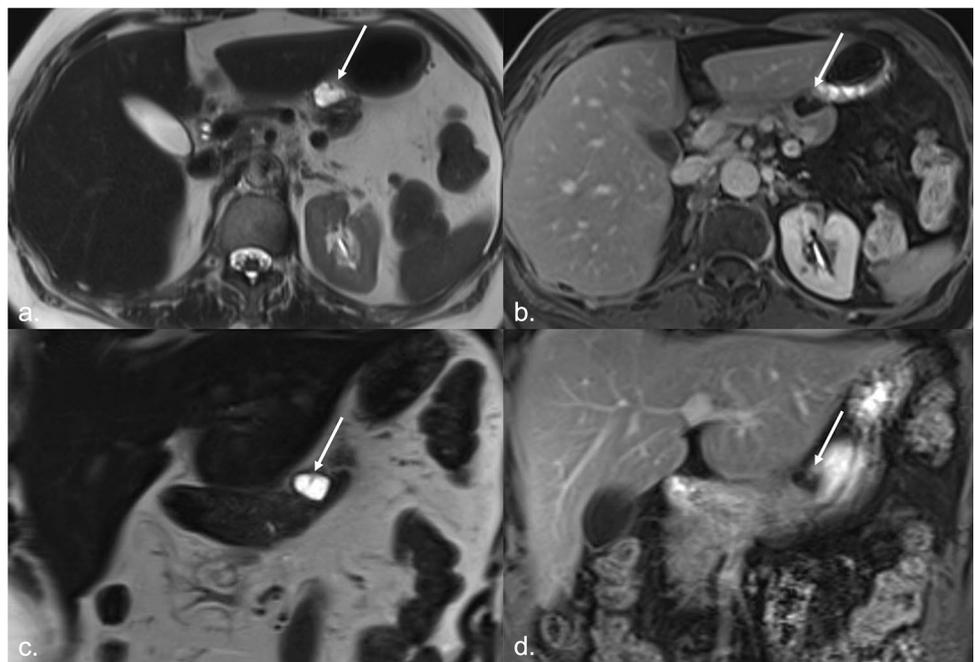


Table 3 Diagnostic performance of MRI without and MRI with and without contrast when the presence of any worrisome feature/high-risk stigmata is considered predictive of malignancy

MRI characteristic	TN	FP	FN	TP	Sensitivity (%)	Specificity (%)	Accuracy (%)
R1 MRI without contrast	60	16	6	5	45.4 (16.8, 76.6)	79.0 (68.1, 87.5)	74.7 (64.3, 83.4)
R1 MRI with and without contrast	60	16	6	5	45.4 (16.8, 76.6)	79.0 (68.1, 87.5)	74.7 (64.3, 83.4)
R2 MRI without contrast	52	24	6	5	45.4 (16.8, 76.6)	68.4 (56.8, 78.6)	65.5 (54.6, 75.4)
R2 MRI with and without contrast	55	21	6	5	45.4 (16.8, 76.6)	72.4 (60.9, 82.0)	69.0 (58.1, 78.5)

Data in parenthesis are confidence intervals

TN true negative, FN false positive, FN false negative, FP true positive

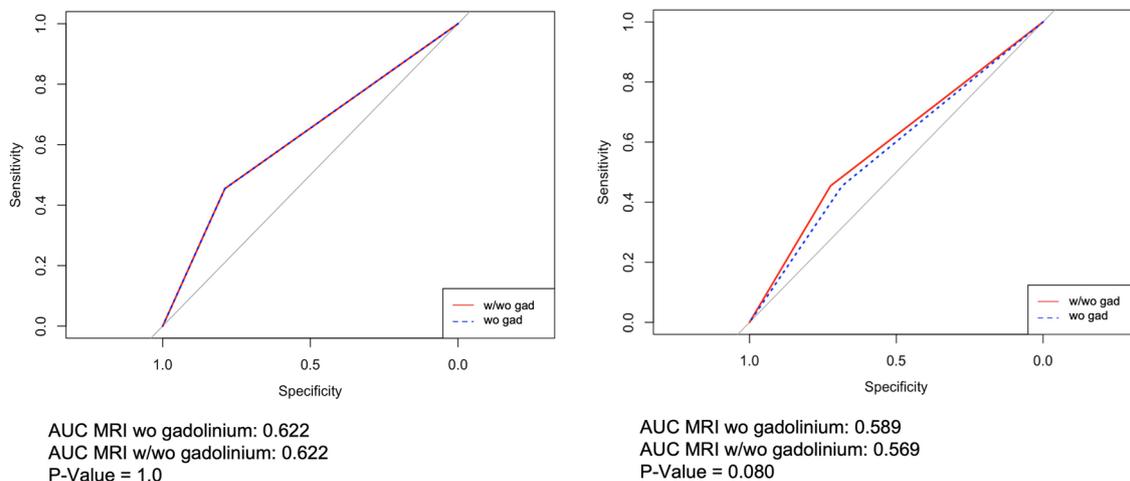


Fig. 3 Graph shows comparison of area under the receiver operating characteristic curve (AUC) between MRI without gadolinium and MRI with and without gadolinium for the diagnosis of benign

or malignant pancreatic cystic lesion for reader 1 and reader 2. wo gad = MRI without gadolinium. w/w/o gad = MRI with and without gadolinium

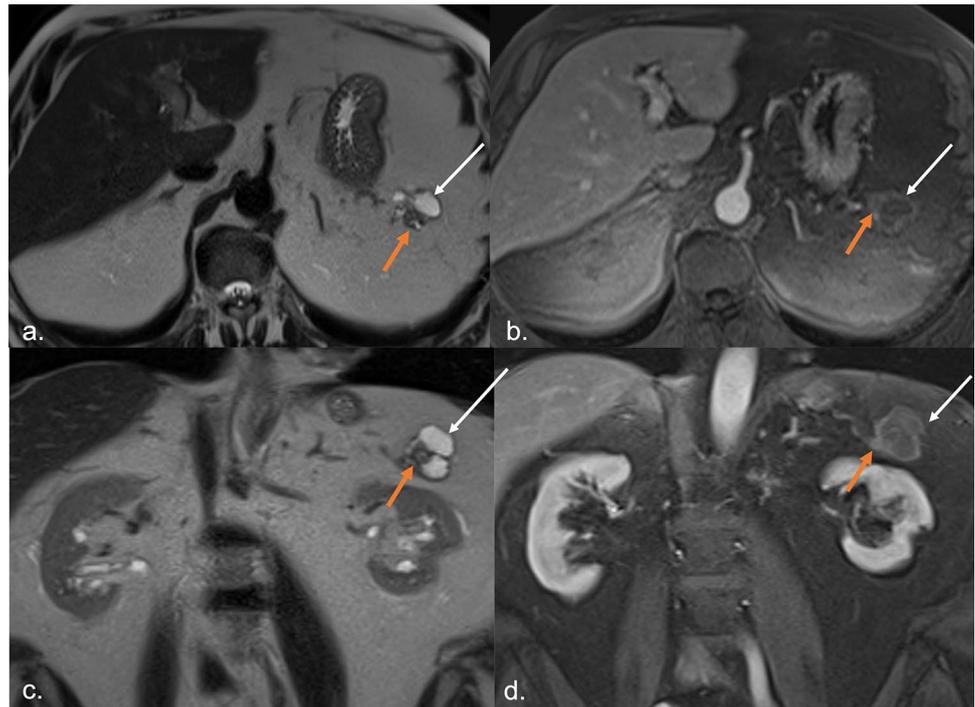
given the growing use of MRI in clinical practice [8, 18]. MRI offers several advantages for the detection and characterization of pancreatic cysts over CT, with the main benefit being in the superior contrast resolution [11, 19]. T2-weighted imaging allows assessment of cyst morphology, internal contents (including nodularity), presence of pancreatic ductal communication, and presence of ductal dilatation. Given these advantages, MRI is currently the preferred modality for surveillance of pancreatic cysts, and patients with pancreatic cysts often undergo annual MRI follow-up for several years, usually with intravenous contrast as recommended by the America College of Radiology Guidelines [8]. However, given the recent findings that gadolinium deposition in the brain is cumulative over a patient's lifetime [12], the necessity of repeat doses of GBCAs is being questioned [13, 14].

In our study, all high-risk stigmata and worrisome features demonstrated fair to excellent inter-reader agreement ($k=0.274$ – 0.953), for each dataset (MRI without contrast and MRI with and without contrast). Our results are in line with a prior study that also demonstrated good to moderate

interobserver variability for these features (kappa range 0.48–0.74) on MRI with and without intravenous contrast [20]. Like this prior investigation, our results also demonstrated that a thickened cyst wall had the lowest inter-reader agreement for both datasets ($k=0.282$ and 0.274 respectively) and cyst size demonstrated the highest agreement (ICC = 0.953 and 0.937 respectively). The presence of an enhancing mural nodule demonstrated moderate inter-reader agreement ($k=0.739$) in our study, which is also in line with this prior investigation ($k=0.66$) [20].

There was excellent intra-observer agreement when assessing both datasets for the evaluation of any worrisome features/high-risk stigmata for both readers (R1 k range = 0.851–1.00, R2 k range = 0.920–1.00). Interestingly, most of the discordance for both readers occurred as a worrisome feature/high-risk stigma that was noted on MRI without contrast that was not noted for MRI with and without contrast. This suggests that this discordance may be due to inherent intra-observer variability and not because contrast-enhanced sequences added any new information. Similarly, the intra-observer agreement for cyst size (R1 ICC = 0.941;

Fig. 4 79-year-old male with pancreatic cystic lesion within the tail incidentally detected on MRI. Axial and coronal single-shot fast spin-echo (SSFSE) T2-weighted image (a, c) and axial and coronal 3D gradient-recalled echo T1-weighted image (b, d) obtained during the portal venous phase show a 26-mm cyst (white arrows) in the tail of the pancreas. This cyst was not present on contrast-enhanced CT performed 14 months prior (not shown). In this case, both readers recorded the presence of an enhancing and non-enhancing mural nodule (red arrows), thickened cyst wall, and cyst growth on the MRI without as well as MRI with and without contrast. This patient underwent EUS/FNA and biopsy, both demonstrating pancreatic adenocarcinoma



R2 ICC = 1.0) and the presence of cyst growth (R1 $k = 1.0$; R2 $k = 1.0$) between the two datasets was excellent for both readers. A prior study by Nougeret et al. similarly evaluated the intra-observer agreement of MRI without and MRI with and without contrast for final pancreatic cyst classification as either benign, indeterminate, or malignant, also demonstrating high concordance between the two datasets of 94.6–96.4% [15]. Similarly, a study by Macari et al. evaluated the intra-observer agreement in overall management decision for pancreatic cysts on MRI without and with/without contrast, demonstrating similar high concordance of 95.5% ($k = 0.67$) between the two datasets [10]. However, in both studies, individual cyst features were not assessed and diagnostic accuracy with a cytopathology reference standard was not evaluated.

The presence of a non-enhancing mural nodule is considered a worrisome feature and an enhancing mural nodule is considered a high-risk stigmata as per the American

College of Radiology Guidelines on the management of IPMN [8]. However, as per the revised International Consensus Fukuoka Guidelines, the presence of a non-enhancing nodule is not considered a worrisome feature or high-risk stigmata [9]. In our study, we demonstrated relatively high specificity of non-enhancing mural nodule for predicting cyst malignancy for both readers (80.3–86.8%). However, the majority of the intra-observer variability between the two datasets was when a non-enhancing mural nodule was recorded for MRI without contrast that was not recorded for MRI with and without contrast. It is possible this was due to greater reader confidence in classifying a PCL as having no worrisome features/high-risk stigmata when contrast-enhanced sequences were available, although this was an uncommon occurrence in our cohort. In rare cases of uncertainty on MRI without contrast, we propose that it is reasonable for a patient to be recommended to return for

Table 4 Diagnostic Performance of MRI without and MRI with and without contrast when the Presence of Cyst Growth is Considered Predictive of Malignancy

MRI characteristic	TN	FP	FN	TP	Sensitivity (%)	Specificity (%)	Accuracy (%)
R1 MRI without contrast	44	14	3	5	62.5 (24.5, 91.5)	75.9 (62.8, 86.1)	74.2 (62.0, 84.2)
R1 MRI with and without contrast	44	14	3	5	62.5 (24.5, 91.5)	75.9 (62.8, 86.1)	74.2 (62.0, 84.2)
R2 MRI without contrast	49	9	3	5	62.5 (24.5, 91.5)	84.5 (72.6, 92.7)	81.8 (70.4, 90.2)
R2 MRI with and without contrast	49	9	3	5	62.5 (24.5, 91.5)	84.5 (72.6, 92.7)	81.8 (70.4, 90.2)

Data in parenthesis are confidence intervals

TN true negative, FN false positive, FN false negative, FP true positive

MRI with contrast prior to rendering a final management recommendation.

While few prior studies have evaluated intra-observer agreement [10, 21], there is a sparsity of investigations assessing diagnostic accuracy of the two imaging techniques for cyst malignancy against a cytopathology reference standard. The diagnostic accuracy of the two datasets when the presence of any worrisome feature/high-risk stigmata was considered predictive of malignancy was identical for reader one (AUC = 0.622 for both) and similar for reader 2 (AUC 0.569 and 0.589) for both datasets. Similarly, the diagnostic accuracy when using cyst growth as predictive of malignancy was identical for both readers for both datasets (R1: 0.692 for both datasets and R2: 0.735 for both datasets). The presence of worrisome features/high-risk stigmata (which is inclusive of cyst size ≥ 3 cm) and cyst growth are the primary features that dictate management recommendations for both the American College of Radiology and Internal Consensus Fukuoka Guidelines for the management of IPMNs [8, 15]. Therefore, the similar diagnostic accuracy of these features between the two datasets is reassuring.

There were no cases of malignancy in our cohort that were separate from the PCL. However, a widespread neoplastic field defect is believed to underlie the development of IPMNs [9, 22, 23] and therefore, the entire pancreatic parenchyma is at increased risk for synchronous or metachronous adenocarcinoma in these patients. This complicates radiologic screening in patients with pancreatic cysts, however, additional features on non-contrast MRI (not evaluated in this study) may alert the radiologist to the presence of a separate pancreatic malignancy, including pancreatic ductal dilatation with duct cut-off, a hypointense lesion on non-contrast T1-weighted sequences, and the presence of focal diffusion or T2-weighted signal abnormality. In fact, a prior study demonstrated no significant difference in diagnostic accuracy between the two MRI examinations (without contrast and with/without contrast) for the detection of pancreatic ductal adenocarcinoma [24]. However, further studies are needed to evaluate diagnostic accuracy between the two datasets for the detection of synchronous or metachronous pancreatic malignancy in patients with IPMNs.

Our study has several limitations. We aimed to simulate normal clinical practice, in which the majority of PCLs do not undergo surgical resection, using a combination of EUS/FNA and pancreatic resection as our reference standard. The utilization of an exclusively surgical cohort would skew the results to predominantly suspicious appearing lesions. Second, given the inherent infrequency of malignant PCLs in clinical practice, we had a relatively small number of malignant cysts, and therefore our study may have been under-powered to detect a difference in diagnostic accuracy between the two MRI imaging studies. As EUS/FNA was used as the reference standard in most cases,

we did not know the histology of most of the cystic lesions and some had microcystic morphology (suggesting serous cystadenoma), however, our aim was not to evaluate lesion characterization but to compare the diagnostic accuracy of MRI without and MRI with and without contrast for detecting malignant PCLs. Imaging prior to the baseline MRI to assess for cyst growth was only present for 76% of the patient cohort. We chose to include consecutive cases of PCLs on MRI, as inclusion of a cohort of only patients with follow-up imaging would possibly skew our population toward lesions that likely underwent cyst growth, prompting EUS or surgery, or lesions that had features on baseline imaging that warranted follow-up, as opposed to all-comer PCLs mimicking what is encountered on MRI in clinical practice.

In conclusion, our study showed that the addition of gadolinium had no significant impact in the diagnosis of a benign versus malignant PCL with similar intra-observer agreement and diagnostic accuracy for both readers when using contrast-enhanced and unenhanced MRI datasets.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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