Published in final edited form as:

J Comput Assist Tomogr. 2016 ; 40(4): 505–512. doi:10.1097/RCT.0000000000000403.

Diffusion-Weighted MR imaging in distinguishing between mucin-producing and serous pancreatic cysts

Chiara Pozzessere, MD^{1,2}, Sandra Luz Castaños Gutiérrez, MD¹, Celia Pamela Corona Villalobos, MD¹, Lorenzo Righi, MD³, Chunmiao Xu, MD¹, Anne Marie Lennon, MB PhD⁴, Christopher L. Wolfgang, MD PhD⁵, Ralph H. Hruban, MD⁶, Michael Goggins, MD^{4,6}, Marcia I. Canto, MD MHS⁴, and Ihab R. Kamel, MD PhD.¹

¹The Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins University, 1800 Orleans St., MRI 143, Baltimore, Maryland, 21287, USA.

² Department of Medical, Surgical and Neurosciences University of Siena, Viale Bracci 10, 53100 Siena, Italy.

³ Department of Molecular and Developmental Medicine, University of Siena, Via Aldo Moro 2, 53100 Siena, Italy

⁴Department of Medicine (Gastroenterology), The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins University, 401 North Broadway St., Baltimore, Maryland, 21287, USA.

⁵Department of Surgery, The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins University, 401 North Broadway St., Baltimore, Maryland, 21287, USA.

⁶Department of Pathology, The Sol Goldman Pancreatic Cancer Research Center, Johns Hopkins University, 401 North Broadway St., Baltimore, Maryland, 21287, USA.

Abstract

Objective—To evaluate the feasibility and the reproducibility of diffusion-weighted imaging (DWI) in distinguishing between mucin-producing and serous pancreatic cysts.

Methods—Forty-four pancreatic cysts (43 patients; 27 females; mean age 57 years-old; 26 mucin-producing cysts; 18 serous cysts) underwent histological examination or cyst analysis after DW-MRI were retrospectively reviewed. Three blinded readers independently evaluated SI and ADC. Intra-observer and inter-observer agreements were calculated. Fisher's exact test and Welch's t test were used to compare SI and ADC values respectively, to pathological results. ROC analysis was used to determine diagnostic accuracy of various thresholds for ADC. A *p* value < 0.05 was considered statistically significant.

Results—Mean ADC value of the mucin-producing cysts was 3.26×10^{-3} mm²/sec, 3.27×10^{-3} mm²/sec and 3.35×10^{-3} mm²/sec for the three readers, respectively. Mean ADC value of the serous cysts was 2.86×10^{-3} mm²/sec, 2.85×10^{-3} mm²/sec and 2.85×10^{-3} mm²/sec for the

Address of correspondence: Ihab R. Kamel, M.D., Ph.D., Russell H. Morgan Department of Radiology and Radiological Sciences, Johns Hopkins Hospital, 1800 Orleans St., MRI 143, Baltimore, MD 21287 Phone: 410- 955-4567, Fax: 410-955-9799, (ikamel@jhmi.edu).

Conflicts of Interest and Source of Funding: R.H. has received a grant (CA62924) from National Cancer Institute. For the remaining authors none were declared.

three readers, respectively. Difference in ADC values between the two cyst groups was 12.4%, 12.9% and 14.8% for the three readers, respectively ($p<0.001$). Intra-observer and inter-observer agreement was excellent. A threshold ADC of 3×10^{-3} mm²/sec resulted in correct identification of cysts in 77-81% of cases, with sensitivity and specificity ranging between 84-88% and 66-72%, respectively.

Conclusions—DWI may be a helpful tool in distinguishing between mucin-producing and serous pancreatic cysts.

Keywords

Diffusion Weighted MRI; Pancreatic cyst; Intraductal Papillary Mucinous Neoplasms; Mucinous Cystic Neoplasms; Serous Cystadenomas

Introduction

Pancreatic cysts are common in the general population and their incidence increases with age (1). With the widespread use of advanced imaging techniques, incidental pancreatic cysts are frequently detected (2,3). Three percent of asymptomatic individuals undergoing computed tomography (CT) of the abdomen have an incidental pancreatic cyst identified (2). The incidence is even higher (13–40%) on magnetic resonance imaging (MRI) due to its higher contrast-resolution (3-5). Pancreatic cystic lesions represent a wide spectrum of lesions varying from those with very low or no malignant potential, to those associated with invasive cancer. Goh and colleagues, in a study of 220 surgically treated patients, reported that 31% of pancreatic cysts can be considered neoplastic (6). Chernyak et al. reported a three times increased risk of both adenocarcinoma and overall mortality in patients younger than 65 years with an incidental diagnosis of pancreatic cyst (7).

Management of pancreatic cysts depends on their malignant potential. The three most common types of pancreatic cysts are serous cystadenomas (SCAs), mucinous cystic neoplasms (MCNs), and intraductal papillary mucinous neoplasms (IPMNs), which account for almost 80% of pancreatic cysts seen in multidisciplinary clinics (8). SCAs have an extremely low risk of malignant transformation, and do not require surgical resection in the absence of symptoms (9,10). IPMNs and MCNs are often grouped together as ‘mucin-producing cysts’ because they contain a thick, viscous, mucinous-type fluid. In contrast to SCAs, mucin-producing cysts have malignant potential. IPMNs are classified into main-duct (MD) and branch-duct (BD) IPMNs depending on their involvement of the main pancreatic duct. Surgery is recommended for MD-IPMNs and MCNs, as they are considered high risk lesions, and in cysts with “worrisome” features concerning for malignancy (11). BD-IPMNs have much lower malignant potential, but surveillance is suggested (11). Hence, differentiating between serous (almost no malignant potential) or mucin-producing cysts (some malignant potential) is mandatory.

Pathology is the gold standard in distinguishing between pancreatic cysts. However, preoperatively the type of pancreatic cyst may be assessed based on imaging features and cyst fluid analysis for cytology and carcinoembryonic antigen (CEA) (9). Imaging may show specific morphological features or “worrisome” signs of neoplastic transformation.

However, differentiating between the different cyst subtypes is often not possible (12-14). This was highlighted in a recent large surgical series of almost 900 surgically resected pancreatic cysts, where over 20% of those were found to be SCAs following surgical resection, while over 75% of surgically resected branch-duct IPMNs did not harbor high-grade dysplasia or invasive cancer, and could potentially have undergone surveillance (15,16). A report from a high-volume center showed an overall preoperative diagnostic accuracy in pancreatic cysts of only 68% (17). When imaging is not diagnostic cyst fluid analysis may be performed, which consists of cytological and fluid markers evaluation. Although a low overall accuracy, cytology detects malignant cysts with high specificity (around 100%) (18). SCAs can be identified for the presence of cuboidal epithelium and thin, 'serous' type fluid, mucin-producing cysts for columnar epithelial cells and mucinous fluid (18). CEA may be a helpful marker. A CEA above 192 ng/ml has high sensitivity and specificity for mucin-producing cysts whereas they may be excluded with a CEA below 5 ng/ml (9). However, cyst fluid analysis is an invasive procedure and the fluid sample is often inadequate (19).

Diffusion Weighted Imaging (DWI) is an MRI sequence sensitive to Brownian motions of the water in biological tissues, which can be quantitatively assessed by Apparent Diffusions Coefficient (ADC) maps (20). DWI has been highly effective in identifying malignancy in solid lesions, but its role in pancreatic cysts is not well determined (21-29). Prior studies have evaluated the feasibility of DWI in pancreatic cystic lesions, with conflicting results (21-28). Some authors reported no differences between mucin-producing and serous cysts (21,22). However, in these studies the sample size of serous cysts included was too small (2 and 5 SCAs, respectively). Other studies reported higher ADC values in serous compared to mucinous cysts (23,24). In addition to a limited sample of serous cysts (2 SCAs), in the study by Yamashita et al., low b values (b_0 ; 300) were used, and perfusion effects related to low b values could have affected the results (23). In the study by Schraibman, et al., significantly higher ADC values were found for non-mucinous cysts (32 SCAs, 6 pseudocysts, 1 GIST, 1 cystadenocarcinoma, 1 cystic hemangioma and 2 abscesses) when comparing to mucin-producing cysts (5 MCNs and 8 MCNs with associated invasive carcinoma) [$p<0.001$] (24). No specific values were reported for SCAs and results may be influenced by the other cystic lesions included in the non-mucinous group. Contrary to the studies mentioned above, other studies reported higher ADC values for mucin-producing cysts compared to serous ones (25-27). However, the difference in ADC values between the two groups was statistically significant only in the study by Boraschi et al. (26). As highlighted, the small sample size, particularly for serous cysts, is a main limitation of most of the previous studies (21-23, 25,26). Moreover, diagnosis was often assumed by imaging and/or follow up without pathologic confirmation of the cyst type (21,22, 24-26). However, as recently described, pancreatic cysts changes by imaging are not evident in a short-time follow-up (30). Given the limitations listed above, it is difficult to draw any conclusions regarding DWI in pancreatic cysts. Therefore, the aim of this study was to evaluate the feasibility and the reproducibility of DWI at distinguishing between mucin-producing and serous pancreatic cysts in patients who underwent histological examination or cyst analysis.

Materials and Methods

Patient Population

Our internal institutional review board (IRB) approved this retrospective study performed in compliance with the health insurance portability and accountability act (HIPAA) after obtaining a waiver for the informed consent. Patients with known pancreatic cystic lesions who underwent a complete MRI with DWI and either surgery or fine needle aspiration (FNA) followed by histologic examination or cyst analysis at our institution within 6 months between July 2009 and June 2014 were reviewed. Inclusion criteria were: mucin-producing cyst or serous cyst at pathological examination or cyst analysis (cytology and CEA as follow: columnar epithelial cells and mucin plus CEA >192ng/ml for mucin producing cysts; benign glandular epithelium plus CEA<5ng/ml for SCAs); cysts ≥ 5 mm on MRI to avoid partial volume averaging effects. The CEA cut-offs were chosen in agreement with AGA recommendations (9). Flow chart for patients included in this study is shown in Figure 1.

MR Imaging protocol

All MRIs were performed on Siemens (Siemens Healthcare, Erlangen, Germany) 3T Magnetom Trio Tim or 1.5 T Magnetom Avanto using a phased-array torso coil (31,32). The imaging protocol included T2-weighted turbo spin-echo images with and without fat suppression (repetition time 3000 ms; echo time 90 ms; matrix size, 256×256; slice thickness 5mm; intersection gap 2mm; received bandwidth 32 kHz), respiratory-triggered MR cholangiopancreatography (MRCP), three-dimensional, heavily T2-weighted fast spin-echo sequence (repetition time automatically adapted to the patient's breathing pattern; echo time 630ms; section thickness 1 mm; interslice gap 1 mm; field of view 35–45cm; matrix size 256×128) and breath-hold DW echo-planar images (repetition time 5000ms; echo time 70ms; matrix size 128×128; slice thickness 7mm; interslice gap 2mm; b value 50 and 750 s/mm²; receiver bandwidth 64 kHz). Breath-hold unenhanced and contrast-enhanced (0.1mmol/kg intravenous gadobutrol [Gadavist; Bayer HealthCare Pharmaceuticals, Wayne, NJ]) T1-weighted three-dimensional fat-suppressed spoiled gradient-echo images (repetition time 4.77ms; echo time 1.77ms; matrix size 192×160; section thickness 3mm; received bandwidth 64kHz; flip angle 10°) in the arterial (20 seconds), portal venous (70 seconds), and delayed (3 minutes) phases were also obtained.

MR imaging analysis and measurement of ADC

Image analysis was performed by 3 readers with 6, 4 and 1 year of experience in abdominal MR imaging. Readers were blinded to all patient data, including the results of histologic and cytological analysis. According to the location and size of the cysts, the readers identified and labeled the index lesion(s) by consensus on T2 weighted images in the axial plane. Subsequently, the three readers independently performed image analysis. Cysts were identified on the DWI $b750$ and ADC images with confirmation on the T2 and DWI $b50$ sequences. Cysts were analyzed qualitatively and quantitatively. Qualitatively, cysts were classified as hypointense, isointense or hyperintense to the surrounding pancreas both on the DWI $b750$ and on the ADC maps. For quantitative analysis, ROI (≥ 5 mm of diameter, covering the largest possible area of the cyst) was placed over the cyst on the axial ADC maps images. Readers avoided placing the ROI on the wall of the cyst as confirmed on T2

and DWI *b0* images. To assess intra-observer agreement, all three readers measured the ADC values a second time after a two-week interval to reduce recall bias. The first set of measurement for the 3 readers was used to calculate inter-reader agreement. The results of the three readers during the first ADC read were used to compare to the pathological examinations.

Statistical analysis

Statistical analysis was performed using STATA statistical software V.12.1 (StataCorp, Texas). The distribution of the quantitative variables was expressed as the mean and standard deviation of observations. Inter-observer agreement was performed using intraclass correlation coefficient. Lin's concordance correlation coefficient was used to evaluate intra-observer agreement. Fisher's exact test was used to compare DWI signal intensity to histological subgroups. The differences in the ADC values, between mucin-producing and serous pancreatic cysts were assessed by Welch's *t* test. Diagnostic accuracy of ADC measurements was assessed by using receiver operating characteristic (ROC) analysis. ROC curves were analyzed to determine the optimal cut-off value of ADC values of the three readers to differentiate between the two groups of cysts. A *p* value of less than 0.05 was considered statistically significant.

Results

Study Cohort

During the study period, one hundred forty-six patients with known pancreatic cystic lesions underwent MRI with DWI and either histologic examination after surgery or FNA followed by cyst fluid analysis at our institution. As shown in Figure 1, 103 patients were excluded, and demographics of the remaining 43 patients included in the cohort (27 females; 16 males; with a mean age of 57 years, range 34 - 89) are shown in Table 1. A total of 44 pancreatic cystic lesions were analyzed. Thirty-one patients (72.1%) had a solitary cyst. Twelve patients (27.9%) had multiple cystic lesions and a total of 13 of those cysts had pathological or cyst fluid analysis and were included in our analysis. The mean size of the cysts was 26.4 mm (range 10 – 64 mm). Whipple resection was performed in 8 patients (18.6%; 9 cysts) and distal pancreatectomy with splenectomy in 9 patients (20.9%). The remaining 26 patients (60.5%) underwent FNA. Histology reported 11 cysts (25%) as mucin-producing (2 MCN, 9 IPMN), and 7 (15.9%) as SCA. At cyst fluid analysis, cytology plus CEA suggestive for a mucin-producing cyst was found in 15 cysts (34.1%). Cytology plus CEA suggestive for serous cyst were found in 11 (25%). Twenty six mucin-producing cysts (59.1%) and 18 serous cyst (40.9) were analyzed by the three readers.

Qualitative MRI analysis

Out of 44 cystic lesions, twenty (45%) were reported as hyperintense (9/26 mucin-producing, 11/18 serous), 17 (38.6%) as isointense (11/26 mucin-producing, 6/18 serous), 7 (16%) as hypointense (6/26 mucin-producing, 1/18 serous) on DWI *b750* images. No statistically significant difference in SI was identified between mucin-producing and serous cysts (*p*=0.23). All cysts were classified as hyperintense on the ADC map.

Quantitative MRI analysis

Mean ADC value of the mucin-producing cysts was $3.26 \times 10^{-3} \text{ mm}^2/\text{sec}$, (range $2.74\text{--}4.09 \times 10^{-3} \text{ mm}^2/\text{sec}$), $3.27 \times 10^{-3} \text{ mm}^2/\text{sec}$ ($2.75\text{--}3.98 \times 10^{-3} \text{ mm}^2/\text{sec}$), and $3.35 \times 10^{-3} \text{ mm}^2/\text{sec}$ (range $2.84\text{--}4.07 \times 10^{-3} \text{ mm}^2/\text{sec}$) for the 3 readers, respectively (Figure 2). Mean ADC value of the serous cysts was $2.86 \times 10^{-3} \text{ mm}^2/\text{sec}$ (range $2.27\text{--}3.39 \times 10^{-3} \text{ mm}^2/\text{sec}$), $2.85 \times 10^{-3} \text{ mm}^2/\text{sec}$ (range $2.15\text{--}3.72 \times 10^{-3} \text{ mm}^2/\text{sec}$) and $2.85 \times 10^{-3} \text{ mm}^2/\text{sec}$ (range $2.19\text{--}3.33 \times 10^{-3} \text{ mm}^2/\text{sec}$) for the 3 readers, respectively (Figure 3). Mean ADC results by the three readers are reported in Table 2. In Figure 4 Box-and-Whiskers Plot for the three readers. There was a statistical significant difference of 12.4% 12.9% and 14.8% on ADC values between serous and mucin-producing cyst groups ($p < 0.001$) for the first, second and third reader, respectively. ROC analysis showed an area under the curve of 0.82 (0.69-0.94), 0.81 (0.67-0.94) and 0.85 (CI 0.69-0.95) for the three readers, respectively (Figure 5). Sensitivity and specificity rates using different cut-offs samples are reported in Table 3.

Intra and Inter Reader Agreement

Inter-observer agreement between the three readers was ICC=0.93 (95% CI, 0.90-0.96). The intra-observer agreement was $\rho=0.88$ (95% CI, 0.82 – 0.94), $\rho=0.87$ (95% CI, 0.81 – 0.93) and $\rho=0.89$ (95% CI, 0.83 – 0.95) for the first, the second and the third reader, respectively.

Discussion

In the current study of 44 pathologically examined mucin-producing (IPMNs and MCNs) and serous pancreatic cysts, we have found that DWI could differentiate between the two groups of cystic lesions. The difference in ADC value between mucin-producing and serous cyst was 12.4% ($3.26 \times 10^{-3} \text{ mm}^2/\text{sec}$ vs. $2.86 \times 10^{-3} \text{ mm}^2/\text{sec}$), 12.9% ($3.35 \times 10^{-3} \text{ mm}^2/\text{sec}$ vs. $2.85 \times 10^{-3} \text{ mm}^2/\text{sec}$) and 14.8% ($3.35 \times 10^{-3} \text{ mm}^2/\text{sec}$ vs. $2.85 \times 10^{-3} \text{ mm}^2/\text{sec}$) for the first, second and third reader, respectively ($p = 0.001$). In our cohort, between 77 to 81% of cysts would have been correctly classified by using a threshold of $3.0 \times 10^{-3} \text{ mm}^2/\text{sec}$ to differentiate mucin-producing from serous cysts, with sensitivity and specificity rates of 84-88% and 66-72%, respectively. Moreover, these ADC measurements were highly reliable and reproducible. We demonstrated an excellent intra-observer ($\rho=0.88$, 0.87 and 0.89 for the first, second and third reader, respectively) and inter-observer (ICC=0.93) agreement among readers with different expertise.

Our results demonstrated a trend of higher ADC values for mucin-producing cysts compared to serous cysts. Mucin-producing cysts are viscous due to their mucin content; consequently, we expected more restricted diffusion compared to serous cysts. However, although serous cysts may lack visible internal complexity, they have micro-septations that may restrict the movement of water molecules inside the cyst. Moreover, as Fatima et al., previously hypothesized, IPMNs fluid may move more freely due to the presence of ductal communication, and may result in unexpectedly high ADC values (28).

Similar results, with ADC values of mucin-producing cyst tending to be higher than serous ones, have been previously described (25-27). Ichikawa in a small unpublished sample

reported higher ADC values in IPMNs than SCAs (2.9×10^{-3} mm²/sec and 2.6×10^{-3} mm²/sec, respectively) (25). Sandrasegaran et al., also reported higher ADC values of mucin-producing lesions than serous cysts (2.99×10^{-3} mm²/sec vs. 2.31×10^{-3} mm²/sec, respectively), with no significant difference between the two groups ($p=0.06$) (27). Significantly higher ADC values of mucin-producing cysts than serous cysts (4×10^{-3} mm²/sec, 3.65×10^{-3} mm²/sec) were found by Boraschi et al. ($p < 0.05$) (26). As previously mentioned, contradicting results has also been reported (21-24). However, some methodological differences between the previous and the current studies should be mentioned. Unlike the current study, most of the previous studies relied on clinical and/or imaging features and lacked pathological confirmation (21,22, 24-26). Moreover, in some of the previous studies the sample size, particularly for serous cysts is relatively small (21-23, 25,26).

Our results suggest that DWI could be a helpful tool in differentiating between serous and mucin-producing cysts. MRI is routinely performed for characterization and follow up of pancreatic cysts. DWI is a non-invasive and fast sequence, doesn't require IV contrast administration, and can be easily added to the routine protocol. DWI could provide additional information and potentially increase the diagnostic performance of MRI in distinguishing between mucin-producing and serous cysts.

The current study has some limitations. First, this is a retrospective study with a relatively small sample size. However, all cases included in this cohort were pathologically proven, which increases our confidence in the results. Second, our study population did not include patients with certain types of cysts such as simple cysts and pseudocysts. However, we focused on the two most common cysts which are the most challenging ones, especially when it comes to treatment because their management is different due to different outcome. Third, studies from both 1.5T and 3T MR field strengths were included. Nonetheless, previous studies attempted to evaluate if ADC values from 1.5 T and 3T magnet can be compared. Two studies performed in vivo showed that ADC values between the two different strength fields by the same vendor were comparable (31,32). For this reason we included cases performed on both 1.5 and 3T magnets to increase the sample size of pathologically proven cysts. Lastly, normalized ADC, which has recently showed promising results in solid pancreatic lesions, was not calculated (33). However, despite that our ADC maps were not normalized, our results showed statistically significant differences when comparing mucin-producing and serous cysts as determined by absolute ADC values.

In conclusion, a threshold of 3×10^{-3} mm²/sec on the ADC maps could differentiate mucin-producing from serous cysts with an accuracy rate ranging between 77-81%, with good correlation to pathological results. DWI may be a useful tool in addition to the routine MRI protocol, providing additional information in differentiating between mucin-producing and serous cysts in indeterminate cases. Further prospective studies with DWI as complementary tool to MRI protocol and an increased number of cases are suggested to validate our results.

References

1. Gardner TB, Glass LM, Smith KD, et al. Pancreatic cyst prevalence and the risk of mucin-producing adenocarcinoma in US adults. *Am J Gastroenterol.* Oct; 2013 108(10):1546–50. [PubMed: 24091499]
2. Laffan TA, Horton KM, Klein AP, et al. Prevalence of unsuspected pancreatic cysts on MDCT. *AJR Am J Roentgenol.* Sep; 2008 191(3):802–7. [PubMed: 18716113]
3. De Jong K, Nio CY, Hermans JJ, et al. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. *Clin Gastroenterol Hepatol.* Sep; 2010 8(9):806–11. [PubMed: 20621679]
4. Lee KS, Sekhar A, Rofsky NM, et al. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. *Am J Gastroenterol.* Sep; 2010 105(9):2079–84. [PubMed: 20354507]
5. Girometti R, Intini S, Brondani G, et al. Incidental pancreatic cysts on 3D turbo spin echo magnetic resonance cholangiopancreatography: Prevalence and relation with clinical and imaging features. *Abdom Imaging.* Apr; 2011 36(2):196–205. [PubMed: 20473669]
6. Goh BK, Tan YM, Thng CH, et al. How useful are clinical, biochemical, and cross-sectional imaging features in predicting potentially malignant or malignant cystic lesions of the pancreas? results from a single institution experience with 220 surgically treated patients. *J Am Coll Surg.* Jan; 2008 206(1):17–27. [PubMed: 18155564]
7. Chernyak V, Flusberg M, Haramati LB, et al. Incidental pancreatic cystic lesions: Is there a relationship with the development of pancreatic adenocarcinoma and all-cause mortality? *Radiology.* Jan; 2015 274(1):161–9. [PubMed: 25117591]
8. Lennon AM, Manos LL, Hruban RH, et al. Role of a multidisciplinary clinic in the management of patients with pancreatic cysts: A single-center cohort study. *Ann Surg Oncol.* Oct; 2014 21(11):3668–74. [PubMed: 24806116]
9. Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. *Am J Gastroenterol.* Oct; 2007 102(10):2339–49. [PubMed: 17764489]
10. Khashab MA, Shin EJ, Amateau S, et al. Tumor size and location correlate with behavior of pancreatic serous cystic neoplasms. *Am J Gastroenterol.* Aug; 2011 106(8):1521–6. [PubMed: 21468008]
11. Tanaka M, Fernandez-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatol.* May-Jun; 2012 12(3):183–97. [PubMed: 22687371]
12. Kalb B, Sarmiento JM, Kooby DA, et al. MR imaging of cystic lesions of the pancreas. *Radiographics.* Oct; 2009 29(6):1749–65. [PubMed: 19959519]
13. Barral M, Soyer P, Dohan A, et al. Magnetic resonance imaging of cystic pancreatic lesions in adults: an update in current diagnostic features and management. *Abdom Imaging.* 2014; 39:48–65. [PubMed: 24263208]
14. Zaheer A, Pokharel SS, Wolfgang C. Incidentally detected cystic lesions of the pancreas on CT: review of literature and management suggestions. *Abdom Imaging.* 2013; 38(2):331–41. [PubMed: 22534872]
15. Valsangkar NP, Morales-Oyarvide V, Thayer SP, et al. 851 resected cystic tumors of the pancreas: a 33-year experience at the Massachusetts General Hospital. *Surgery.* Sep. 2012 152:S4–12. [PubMed: 22770958]
16. Sahora K, Mino-Kenudson M, Brugge W, et al. Branch duct intraductal papillary mucinous neoplasms: does cyst size change the tip of the scale? A critical analysis of the revised international consensus guidelines in a large single-institutional series. *Ann Surg.* Sep. 2013 258:466–75. [PubMed: 24022439]
17. Correa-Gallego C, Ferrone CR, Thayer SP, et al. Incidental pancreatic cysts: Do we really know what we are watching? *Pancreatol.* 2010; 10(2-3):144–50. [PubMed: 20484954]
18. Frossard JL, Amouyal P, Amouyal G, et al. Performance of endosonography-guided fine needle aspiration and biopsy in the diagnosis of pancreatic cystic lesions. *Am J Gastroenterol.* Jul. 2003 98:1516–1524. [PubMed: 12873573]

19. De Jong K, Poley JW, van Hooft JE, et al. Endoscopic ultrasound-guided fine-needle aspiration of pancreatic cystic lesions provides inadequate material for cytology and laboratory analysis: initial results from a prospective study. *Endoscopy*. Jul; 2011 43(7):585–90. [PubMed: 21611945]
20. Le Bihan D, Turner R, Douek P, et al. Diffusion MR imaging: clinical applications. *Am J Roentgenol*. 1992; 159(3):591–99. [PubMed: 1503032]
21. Irie H, Honda H, Kuroiwa T, et al. Measurement of the apparent diffusion coefficient in intraductal mucin-producing tumor of the pancreas by diffusion-weighted echo-planar MR imaging. *Abdom Imaging*. Jan-Feb;2002 27(1):82–7. [PubMed: 11740615]
22. Mottola JC, Sahni VA, Erturk SM, et al. Diffusion-weighted MRI of focal cystic pancreatic lesions at 3.0-tesla: Preliminary results. *Abdom Imaging*. Feb; 2012 37(1):110–7. [PubMed: 21512724]
23. Yamashita Y, Namimoto T, Mitsuzaki K, et al. Mucin-producing tumor of the pancreas: Diagnostic value of diffusion-weighted echo-planar MR imaging. *Radiology*. Sep; 1998 208(3):605–9. [PubMed: 9722835]
24. Schraibman V, Goldman SM, Ardengh JC, et al. New trends in diffusion-weighted magnetic resonance imaging as a tool in differentiation of serous cystadenoma and mucinous cystic tumor: A prospective study. *Pancreatol*. 2011; 11(1):43–51. [PubMed: 21412024]
25. Muhi, A.; Ichikawa, T. DW-MRI For Disease Characterization In The Abdomen.. In: Koh, DM.; Thoeny, HC., editors. *Diffusion Weighted MR Imaging: application in the body*. Springer Science and Business Media ed.; Heidelberg, DE: 2010. p. 117-142.
26. Boraschi P, Donati F, Gigoni R, et al. Diffusion-weighted MRI in the characterization of cystic pancreatic lesions: Usefulness of ADC values. *Magn Reson Imaging*. Dec; 2010 28(10):1447–55. [PubMed: 20864287]
27. Sandrasegaran K, Akisik FM, Patel AA, et al. Diffusion-weighted imaging in characterization of cystic pancreatic lesions. *Clin Radiol*. Sep; 2011 66(9):808–14. [PubMed: 21601184]
28. Fatima Z, Ichikawa T, Motosugi U, et al. Magnetic resonance diffusion-weighted imaging in the characterization of pancreatic mucinous cystic lesions. *Clin Radiol*. Feb; 2011 66(2):108–11. [PubMed: 21216325]
29. Barral M, Taouli B, Guiu B, et al. Diffusion-weighted MR Imaging of the Pancreas: Current Status and Recommendations. *Radiology*. Jan; 2015 274(1):45–63. [PubMed: 25531479]
30. Nougaret S, Reinhold C, Chong J, et al. Incidental pancreatic cysts: natural history and diagnostic accuracy of a limited serial pancreatic cyst MRI protocol. *Eur Radiol*. 2014; 24(5):1020–9. [PubMed: 24569848]
31. Rosenkrantz AB, Oei M, Babb JS, et al. Diffusion-weighted imaging of the abdomen at 3.0 Tesla: image quality and apparent diffusion coefficient reproducibility compared with 1.5 Tesla. *J Magn Reson Imaging*. Jan; 2011 33(1):128–35. [PubMed: 21182130]
32. Saremi F, Jalili M, Sefidbakht S, et al. Diffusion-weighted imaging of the abdomen at 3 T: image quality comparison with 1.5-T magnet using 3 different imaging sequences. *J Comput Assist Tomogr*. May-Jun;2011 35(3):317–25. [PubMed: 21586923]
33. Barral M, Sebbag-Sfez D, Hoeffel C, et al. Characterization of focal pancreatic lesions using normalized apparent diffusion coefficient at 1.5-Tesla: preliminary experience. *Diagn Interv Imaging*. 2013; 94(6):619–27. [PubMed: 23545001]

Figure 1.
Flowchart for patients included in this cohort

Figure 2. Branch-duct intraductal papillary mucinous neoplasm (BD-IPMN) diagnosed on pathologic analysis after surgery. The arrow shows the cyst on axial T2-weighted fat-saturated TSE (TR 4500 ms; TE 92 ms) (a); DWI (TR 4709 ms; TE 70 ms) b_{50} (b) and b_{750} (c). On ADC map (d) the value was $3.32 \times 10^{-3} \text{ mm}^2/\text{sec}$.

Figure 3. Serous cystadenoma (SCA) diagnosed on pathologic analysis after surgery. The arrow shows the cyst on axial T2-weighted fat-saturated TSE (TR 2000 ms; TE 90 ms); (a) DWI (TR

4741 ms; TE 74 ms) b_{50} (b) and b_{750} (c). On ADC map (d) the value was $2.66 \times 10^{-3} \text{ mm}^2/\text{sec}$.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 4. Box-and-Whiskers Plot for the three readers

The box-and-whiskers plot shows the distribution of the ADC values of mucin-producing and serous cysts for the first, second and third reader respectively. The ADC values of mucin-producing cysts were significantly higher than those serous cysts for all the three readers ($p < 0.001$). The optimal threshold of ADC value determined by ROC was $3.0 \times 10^{-3} \text{ mm}^2/\text{s}$ for differentiating between mucin-producing and serous cysts.

Figure 5. ROC curve for the three readers

The graph of the ROC curve for the ADC value for differentiating between mucin-producing and serous cysts shows an area under the curve of 0.82 (0.69-0.94), 0.81 (0.67-0.94) and 0.85 (CI 0.69-0.95) for the first, the second and the third reader, respectively.

Table 1

Characteristics of patients and pancreatic cysts.

Characteristics	All cysts (% or range)	Mucinous cysts (% or range)	Serous cysts (% or range)
<i>N patients</i>	<i>43</i>	<i>25</i>	<i>18</i>
Gender			
Female	27 (62.8)	15 (34.9)	12 (28)
Male	16 (37.2)	10 (23.2)	6 (13.9)
Solitary	31 (72.1)	16 (37.3)	15 (34.9)
Multiple	12 (27.9)	9 (21)	3 (6.8)
Mean age (years)	57 (34-89)	65 (34-89)	54 (38-65)
<i>N cysts</i>	<i>44</i>	<i>26 (59.1)</i>	<i>18 (40.9)</i>
Mean size (mm)	26.4 (10-64)	22.2 (10-64)	32.2 (15-59)
<30 mm	33 (75)	22 (50)	11 (25)
>30 mm	11 (25)	4 (9.1)	7 (15.9)
Location			
Uncinate process	3 (6.8)	2 (4.6)	1 (2.3)
Head/neck	16 (36.4)	11 (25)	5 (11.4)
Body	13 (29.5)	7 (15.9)	6 (13.6)
Tail	12 (27.3)	6 (13.6)	6 (13.6)
Pathological examination			
Histology	18 (40.9)	11 (25)	7 (15.9)
IPMN		9	-
MCN		2	-
SCA		-	7
Cyst fluid analysis	26 (59.1)		
Columnar epithelium, mucin, CEA>192		15 (34.1)	-
Benign glandular epithelium, CEA<5		-	11 (25)

IPMN: Intraductal Papillary Mucinous Neoplasm; MCN: Mucinous Cystic Neoplasm; SCA: Serous Cyst Adenoma; CEA: carcinoembryonic antigen. CEA values are in ng/ml.

Table 2

mean ADC values of 44 cysts by the three readers according to pathological analysis, difference between mucinous and serous cysts by the three readers, intra-observer and inter-observer agreement.

	Cyst type	Reader 1	Reader 2	Reader 3	Inter-observer agreement (ICC)
1 read	Mucinous	3.26 (2.74–4.09)	3.27 (2.75–3.98)	3.35 (2.84–4.07)	0.93 (95% CI 0.90-0.96)
	Serous	2.86 (2.27–3.39)	2.85 (2.15–3.72)	2.85 (2.19–3.33)	
2 read	Mucinous	3.14 (2.2–4.06)	3.24 (2.71–4.07)	3.24 (2.23–4.05)	
	Serous	2.87 (1.93–3.51)	2.9 (2.09–3.47)	2.79 (1.99–3.35)	
% difference between mucinous and serous cysts	/	12.4	12.9	14.8	/
<i>p</i> value	/	< 0.001	< 0.001	< 0.001	/
Intra-observer agreement (rho)	/	0.88 (0.82–0.94)	0.87 (0.81–0.93)	0.89 (0.83–0.95)	/

All the ADC values are expressed in $\times 10^{-3}$ mm²/sec (range).

Table 3

Sensitivity and specificity rates using different cut-offs by the three readers, with mucin-producing cyst considered “positive” and serous cysts considered “negative”.

ADC Cut-off ($\times 10^{-3}$ mm ² /sec)	Correctly classified (%)	Sensitivity (%)	Specificity (%)
3.4	54-59	23-31	100
3.2	50-65	42-65	61-83
3.0	77-81	84-88	66-72
2.8	66-77	92-100	28-44
2.6	63-66	100	11-16