Morphological Analysis and Differentiation of Benign Cystic Neoplasms of the Pancreas Using Computed Tomography and Magnetic Resonance Imaging

Morphologische Analyse und Differenzierung benigner, zystischer Neoplasien des Pankreas mittels Computertomografie und Magnetresonanztomografie

Zusammenfassung ▼

Ziel: Beurteilung morphologischer Charakteristika und die Etablierung eines standardisierten diagnostischen Algorithmus für die Differenzierung von benignen, zystischen pankreatischen Tumoren (CPTs) mittels Multidetektor-Computertomografie (CT) und Magnetresonanztomografie (MRT) bei Patienten ohne Pankreatitis.


Ergebnisse: Insgesamt wurden 62 Patienten mit insgesamt 64 CPTs (n=21 intradukrale papilläre muzinöse Neoplasien; n=10 muzinös-zystische Neoplasien; n=12 serös-mikrozystische Adenome; n=3 serös-oligozystische Adenome; n=6 solide pseudopapilläre Neoplasien; n=12 neuroendokrine Neoplasien) aus der chirurgischen Datenbank identifiziert. Die gemittelte Gesamtgenauigkeit für alle drei Befunder lag bei 89,9 % für die CT und 93,1 % für die MRT mit steigender Gesamtgenauigkeit längerer Erfahrung des Befunders (jeweils 88,2, 91,5 und 93,8 %; generalisierte Kappa-Wert=0,69 (CT=0,64; MRT=0,76; p<0,001). Die Genauigkeit des standardisierten diagnostischen Algorithmus lag bei 91,1 %.

Schlussfolgerung: Die Differenzierung benigner CPTs gelingt gut mittels MRT und CT, wobei die MRT der CT überlegen zu sein scheint. Die diagnostische Treffsicherheit ist erfahrungsabhängig. Der standardisierte Algorithmus könnte als Entscheidungshilfe dienen, sollte jedoch noch an einer weiteren Patientenpopulation getestet werden.

Abstract ▼

Purpose: To evaluate morphologic characteristics and establish a standardized diagnostic algorithm to differentiate benign cystic pancreatic tumors (CPTs) in non-pancreatitis patients using multidetector computed tomography (CT) and magnetic resonance imaging (MRI).

Materials and Methods: Patients with histopathologically proven CPTs who had undergone MRI and/or CT and subsequent tumor resection in our institution were retrospectively identified. Images were analyzed for morphology and enhancement patterns by three independent blinded observers. Preoperative image findings were correlated with histopathological results. Based on the evaluated morphologic parameters, a standardized diagnostic algorithm was designed to help characterize the lesions.

Results: A total of 62 consecutive patients with 64 CPTs were identified from the surgical database (21 intraductal papillary mucinous neoplasms; 10 mucinous cystic neoplasms; 12 serous microcystic adenomas; 3 serous oligocystic adenomas; 6 solid pseudopapillary tumors; 12 neuroendocrine neoplasms). The overall averaged accuracy for the 3 observers was 89.9 % for CT and 93.1 % for MRI with increasing overall accuracy in relation to the experience of the observer (88.2 %, 91.5 %, and 93.8 %, respectively). Overall, the generalized kappa value was 0.69 (CT, 0.64; MRI, 0.76; p<0.001). The accuracy of the standardized diagnostic algorithm was 91.1 %.

Conclusion: It is possible to characterize benign CPTs with MRI and CT, while MRI appears to be superior to CT. Diagnostic accuracy depends on the observer’s experience. The standardized algorithm can aid in the differential diagnosis but still needs to be tested in other patient populations.

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Introduction

Due to technical improvements and the widespread use of cross-sectional imaging techniques such as magnetic resonance imaging (MRI) and multidetector computed tomography (CT), benign primary cystic pancreatic tumors (CPTs) are being recognized with increasing frequency. The diagnostic and therapeutic management of primarily benign CPTs varies depending on the entity. The most common entities are serous cystic neoplasms (SCNs) (including serous microcystic adenoma [SMA] and serous oligocystic adenoma [SOA]) and mucinous tumors (including mucinous cystic neoplasm [MCN] and intraductal papillary mucinous neoplasm [IPMN]). SCNs are benign and are therefore usually treated conservatively if the patient is asymptomatic. Mucinous tumors may be premalignant and should therefore be treated surgically. Solid pseudopapillary tumors (SPNs) and cystic neuroendocrine neoplasms (NENs) are less common pancreatic tumors that may present as cystic lesions. SPNs predominantly affect young women. They have a low-grade malignant potential with an excellent prognosis after complete resection. The malignant potential of cystic NENs varies substantially and resection has to be considered individually [1]. Because of this variable behavior of primarily benign CPTs, the goal of radiologic imaging is not only the discrimination from malignant tumors but also differentiation between the benign entities [2]. Typical imaging findings are described in the literature for the differentiation of benign CPTs in CT and MRI. However, the differentiation of these lesions based on imaging is still a diagnostic challenge [1 – 11]. Therefore, the purpose of the present study was to retrospectively evaluate CT and MRI findings for the characterization of histopathologically confirmed benign CPTs and to establish a diagnostic algorithm to provide support when making decisions.

Patients and methods

Patients

A total of 62 consecutive patients fulfilling the prerequisites for inclusion (female: 44; male: 18; median age: 55.6; 25th percentile: 45.1 years; 75th percentile: 66.3 years) were identified from the institutional surgical database: digitally archived multidetector CT and/or MRI of the pancreas (at least biphasic contrast-enhanced imaging for both modalities and additionally for MRI unenhanced standard T1- and T2-weighted (T1w, T2w) sequences with and without fat suppression (FS); see below for further details of examination protocols), complete lesion resection with definitive histopathological diagnosis of a benign cystic tumor of the pancreas (search period 2001 – 2011). The exclusion criteria were a history or findings of pancreatitis such as pseudocysts and malignant lesions such as (cystic)-adenocarcinoma. The median interval between imaging and surgery was 21 days (25th percentile: 8 days; 75th percentile: 48 days). The institutional review board approved this retrospective study.

Imaging techniques

62 patients with a total of 84 examinations were evaluated (CT: n = 50; MRI: n = 34). Helical CTs were obtained with 4-row (n = 15), 6-row (n = 1), 8-row (n = 11), 16-row (n = 17), and 64-row (n = 6) CT devices according to the institutional standard protocols for abdominal CT and pancreatic imaging, which have evolved over time and differed between scanner types. All examinations were performed with an intravenous contrast agent (injected amount: 100 – 140 mL; iodine concentration: 350 – 400 mg/dL; flow rates: 2 – 4 mL/sec (automatic injection); saline flush: 40 mL) and were bi- or triphasic (bolus tracking was used in 50 % of cases) consisting of an arterial phase (20 – 40-second delay, performed in 80 % of cases), a portal venous phase (40 – 70-second delay, performed in 90 % of cases), and a venous phase (70 – 90-second delay, performed in 60 % of cases). Additional unenhanced scans were acquired in 69 % of cases. The minimal available reconstructed slice thickness varied from 1 to 3.75 mm. MRI data were obtained with 1.5 T systems (n = 34) using phased-array surface coils. The examination protocols comprised T2w standard 2D sequences with and without FS and T1w unenhanced 2D sequences with and without FS. Intravenous application of Gadolinium-based extracellular contrast agents (0.1 – 0.2 mmol/kg body weight according to the manufacturer’s recommendation for the different types of contrast agent; manual or automatic injection at approximately 1 – 2 mL/sec flow rate followed by 40 mL saline flush) was followed by at least two contrast phases (2D or 3D T1w sequences with FS in accordance with CT; arterial: 50 %; portal venous: 65 %; venous phase: 71 %). MRCP was performed in 27 (79 %) of all examinations with single-shot thick slab and/or 3D sequences.

Image analysis

A dedicated viewing workstation was used for image analysis (Centricity PACS RA1000, General Electric, Milwaukee, WI). MRI and CT images were reviewed separately in a randomized order blinded to clinical, histopathological, and surgical data by 3 independent observers with 4 (observer 1), 6 (observer 2), and 9 years (observer 3) of abdominal imaging experience. A definitive diagnosis had to be documented for each case by each observer during the blinded read. The histopathological report served as the reference standard. In a subsequent truth panel read by the observers, descriptive lesion analysis was performed collecting the following parameters: unifocal or multifocal lesion, number of lesions, location, maximum transverse diameter, predominantly solid or cystic or purely cystic, presence and thickness of a cystic wall/capsule and septa, presence of hemorrhage or calcifications, connection to/contact with the pancreatic duct, and contrast enhancement patterns differentiating early enhancement (i.e., highest contrast uptake during the arterial and/or portal venous phase) and late enhancement (i.e., highest uptake during the venous phase). The truth panel also determined the quality of the scans, which was evaluated with respect to image noise (minor, major, and non-diagnostic) and movement (or other) artifacts (minor, major, and non-diagnostic) affecting at least one examination component decisive for the evaluation of the lesion on a 3-point scale (1: good (minor image noise and moving artifacts); 2: sufficient (at least one major and no non-diagnostic category); 3: poor/ non-diagnostic (non-diagnostic image due to noise and/or artifacts)). The quality of contrast-enhanced dynamic imaging was assessed according to predefined criteria of phase-appropriate enhancement: early arterial phase: dominant arterial contrast filling with little pancreatic parenchyma enhancement; portal venous phase: strong portal venous contrast filling with strong pancreatic parenchyma enhancement; venous phase: complete contrast filling of inferior vena cava and liver veins with fading of pancreatic contrast enhancement. The contrast enhancement of the vessels and pancreatic parenchyma in each contrast phase was graded using a 5-point scale: 1: phase-appropriate and strong enhancement; 2: phase-appropriate but weak enhance-
Results

Image quality

The quality score for CT and MRI was 1 (96%) or 2 (4%) and 1 (85%) or 2 (15%), respectively. The quality of contrast enhancement for all available contrast phases was rated with a score of 1 in 75%, 2 in 23%, 3 in 2%, and 4 in 0% of cases for CT (contrast phases missing: 35) and with a score of 1 in 84%, a score 2 in 10%, 3 in 6%, and 4 in 0% of cases for MRI (contrast phases missing: 39).

Evaluated lesions

In the 62 patients, a total of 64 CPTs were identified and evaluated. The histopathological diagnoses of the CPTs are summarized in Table 1. (IPMN: adenomas: n = 7 (10.9%); borderline: n = 14 (21.9%); main duct: n = 2; branch duct: n = 7; Santorini’s duct: n = 1; mixed type: n = 11; MCN: adenomas: n = 7 (10.9%); borderline: n = 4 (6.3%); NEN: insulinoma: n = 7 (10.9%); glucagonoma: n = 2 (3.1%); non-functional: n = 3 (4.7%).) All pancreatic lesions were subject to histopathological confirmation.

Morphologic findings

Table 1 shows the evaluated morphologic criteria for the different pancreatic lesions.

IPMNs (Fig. 1) were mostly located in the pancreatic head (53%; p < 0.05) in older patients (median: 66 years; only 2 patients were younger than 58 years; p < 0.05), with macrocystic appearance (62%; p < 0.05) and contact/association with the pancreatic duct (62%); p < 0.05). The quality of contrast enhancement was rated with a score of 1 in 96%, 2 in 4% and 3 in 0% of cases for CT (contrast phases missing: 35) and with a score of 1 in 84%, a score 2 in 10%, 3 in 6%, and 4 in 0% of cases for MRI (contrast phases missing: 39).

Statistics

Statistical analyses were performed using the IBM SPSS software (version 21.0.0.1; SPSS Inc., IBM, Armonk, NY), the R software (version 2.13.2, R Foundation for Statistical Computing, Vienna, Austria) and SAS software (version 9.1.3, SAS Institute Inc., Cary, NC). Diagnostic parameters (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy) were calculated using the standard formulas. Sensitivities and specificities were tested according to the method of Bennett [12]. For the analysis of interobserver variability kappa statistics was used (Cohen’s and Fleiss kappa coefficient). Due to the small sample size, normality distribution was not assumed and non-parametric tests were consequently performed. The comparison of paired proportions was performed with the McNemar’s Chi-squared test with continuity correction. Unpaired proportions were compared using Fisher’s exact test. To compare the medians of two groups, we used the Mann-Whitney U-test. Significance was defined by p-values less than 0.05. Concerning the prediction of the different evaluated parameters, a univariate logistic regression model was used. Odds-ratio estimates, confidence intervals and p-values were calculated using the exact logistic regression model provided by the SAS software package.
creatic duct (62%; p < 0.05). A cystic wall/capsule and septae were present in 50% of cases (p < 0.05).

MCNs (● Fig. 2) were only found in female patients (100%; p < 0.05) without a predominant location (p > 0.05). The majority had a purely cystic (90%; p > 0.05) and macrocystic (90%; p > 0.05) presentation with the presence of a cystic wall (90%; p > 0.05) and septae (100%; p > 0.05) with contrast uptake of both in 80% of cases (p > 0.05).

SMAs (● Fig. 3) were found mostly in female patients (92%; p > 0.05) in the pancreatic head (67%; p > 0.05). A microcystic appearance was found to be significant (67%; p < 0.05). The vast majority of SMAs had a purely cystic presentation (83%; p < 0.05) with the presence of a cystic wall (92%; p > 0.05) and septae (100%; p > 0.05) with contrast uptake (100%; p > 0.05). Furthermore, calcifications were found in 50% (p > 0.05). SOAs (● Fig. 4) were all purely cystic (100%; p > 0.05) with the presence of a capsule with contrast uptake in 100% (p > 0.05). SPNs (● Fig. 5) were all found in female patients (100%; p > 0.05) with a mixed appearance of predominantly solid (50%; p > 0.05) and purely cystic (33%; p > 0.05) components without the presence of a cystic wall/capsule (0%; p < 0.05).

NENs (● Fig. 6) were significantly smaller than all other lesions (16 ± 8 mm; p < 0.05) and predominantly solid (92%; p < 0.05).

**Univariate logistic linear regression model**

Table 2 shows the univariate logistic linear regression model for predictors of different CPTs. For IPMNs, association with the pancreatic duct, a micro- or monocystic appearance and age were found to be predictive factors (p < 0.05). For MCNs, a location in the pancreatic corpus or tail and macrocystic appearance were found to be predictive (p < 0.05). For SMAs, a microcystic appearance with the presence of calcifications and septal en-
enhancement were found to be predictive (p < 0.05). For SPNs, only age was found to be predictive. For NENs, a solid structure and early enhancement were found to be predictive (p < 0.05). No predictive factors could be assessed for SOAs due to the small sample size (n = 3).

**Differential diagnosis by observers and algorithm**

Table 3 shows the accuracy and positive predictive values (PPV) of CT and MRI for the differential diagnosis of CPTs by the different observers and the algorithm. For all observers, the overall accuracy of MRI was slightly higher than the accuracy of CT (93.1% vs. 89.9%). The overall accuracy increased from the least to the most experienced observer (01/02/03: 88.2%/91.5%/93.8%). The standardized diagnostic algorithm achieved a high overall accuracy of 91.1% (MRI: 95.1%; CT: 88.5%; Fig. 7). In the subgroup of the 22 patients who underwent both MRI and CT, the accuracy of MRI was also slightly higher compared to CT (92.4% vs. 89.6%). However, this accuracy was not found to be significant for the different observers (observer 1: p = 0.727; observer 2: p = 0.125; observer 3: p = 1.0; all observers: p = 0.092) or the standardized diagnostic algorithm (p = 0.063).

The interobserver variability of different observers and the algorithm for the differentiation of benign CPTs is shown in Table 4. The generalized kappa value was 0.69 for all three observers (CT: 0.64; MRI: 0.76; p < 0.001). The generalized kappa value was 0.69 for all three observers and the algorithm (CT studies: 0.64; MRI studies: 0.76; p < 0.001).
Discussion

In the case of CPTs the challenge of diagnostic imaging with CT and MRI in non-pancreatitis patients is to determine the definitive diagnosis based on the imaging features of a lesion. Several image characteristics are described in the literature for the characterization of benign CPTs on CT and MRI [2–5, 7, 13–24]. In the present retrospective histopathologically validated study, univariate logistic regression revealed significant characteristics typical for different CPTs such as age, location, association with the pancreatic duct, macro- versus microcystic appearance, presence of calcifications, solid versus cystic structure, and early contrast enhancement, which match the parameters reported in the literature. As in the literature, we also observed overlaps of these criteria between the various (candidate) entities making differential diagnosis challenging.

In the present study, the accuracy of the imaging-based diagnosis of a CPT improved as the years of experience of the radiologist increased, i.e., the overall accuracy improved from the least to the most experienced observer (88.2 %, 91.5 %, and 93.8 %, respectively). According to the generalized kappa value for all three observers (overall kappa: 0.70), the use of MRI (kappa: 0.79) created a higher concordance among readers with different levels of experience than CT (kappa: 0.636). This could be explained by a diagnostic superiority of MRI. However, previous studies showed that CT and MRI have an equal diagnostic accuracy for the characterization of CPTs [22, 25]. Other authors rate MRI as more specific than CT due to a better depiction of septae and cyst contents as well as the pancreatic duct, especially with the use of MRCP [4, 26–30]. In the present study, MRI had a slightly better overall accuracy in comparison to CT (93.1 % vs. 89.9 %). As a limitation to this statement it has to be noted that a direct comparison of the performance of MRI and CT examinations was only possible in 22 of the 62 patients. In these patients, neither the overall accuracy (MRI: 92.4 %; CT: 89.6 %) nor the accuracy of single observers or the algorithm was found to be significantly different between the two examination modalities.
To lower interobserver variability as a result of different levels of experience, a standardized diagnostic algorithm was developed based on the most significant imaging criteria. This algorithm achieved a good overall accuracy (91.1%), which was superior to that of the least experienced observer. Thus, it appears to be helpful for inexperienced readers to apply this algorithm to CPTs on CT or MRI in order to increase the accuracy of the differential diagnosis. However, there are some limitations regarding this algorithm. The study population comprised the most frequent but not all of the possible CPT entities in non-pancreatitis patients. The definition of the discriminators used in the algorithm is somewhat subjective and requires training. The algorithm needs to be assessed in a further patient collective with CPTs to evaluate reproducibility. Furthermore, to meet the challenges of the daily routine, the algorithm should be extended to pseudocystic and malignant lesions such as cystadenocarcinomas, which were exclusion criteria in the present study. Moreover, the standardized diagnostic algorithm was developed for a common MRI and CT diagnostic workflow and the accuracy may be improved when separate algorithms optimized for MRI or CT are used. For example regarding MRI, this improvement can be achieved by introducing additional parameters, such as diffusion-weighted imaging, which are not available for CT [31 – 33].

Several limitations to our study have to be mentioned. Due to the retrospective study design and the long examination period (10 years), various MRI and CT scanners and scan protocols with varying contrast phases were used. A distinct quality assessment was performed for all examinations to partly outweigh this drawback revealing at least sufficient image quality regarding image noise, contrast timing, and motion artifacts. Furthermore, most patients were examined in our institution with equivalent examination protocols. Regarding the study population, only patients with histopathologically confirmed cystic benign lesions (IPMNs, MCNs, SCNs, SPNs, and NENs) were included in this study. This was necessary but may have resulted in a selection bias. Also, due to the rare incidence of some of the evaluated CPTs (e.g.,

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**Fig. 7** Diagnostic algorithm for assessing benign pancreatic cystic lesions.

**Abb. 7** Diagnostischer Algorithmus zur Beurteilung benigner, zystischer pankreatischer Läsionen.
resonance imaging (MRI) alone for the differentiation of benign cystic pancreatic tumors (CPT).\textsuperscript{1}

Table 3

<table>
<thead>
<tr>
<th>variable</th>
<th>OR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPMN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age</td>
<td>2.11</td>
<td>1.21 – 4.13</td>
<td>0.005</td>
</tr>
<tr>
<td>macrocystic</td>
<td>52.13</td>
<td>4.87 –</td>
<td>0.000</td>
</tr>
<tr>
<td>monocystic</td>
<td>12.02</td>
<td>2.06 – 130.08</td>
<td>0.003</td>
</tr>
<tr>
<td>association/contact with</td>
<td>29.93</td>
<td>5.34 – 323.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>the pancreatic duct</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age</td>
<td>0.28</td>
<td>0.09 – 0.63</td>
<td>0.000</td>
</tr>
<tr>
<td>SPN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>solid structure</td>
<td>29.23</td>
<td>4.87 – 246.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>arterial septal enhancement</td>
<td>8.14</td>
<td>1.4 – 52.54</td>
<td>0.017</td>
</tr>
</tbody>
</table>

\textsuperscript{1} IPMN: intraductal papillary mucinous neoplasm; MCN: mucinous cystic neoplasm; SMA: serous microcystic adenoma; SOA: serous oligocystic adenoma; SPN: solid pseudopapillary tumor; NEN: neuroendocrine neoplasm; n.a.: not assessable.

Table 2

Univariate logistic linear regression model for predictors of different cystic pancreatic tumors (OR: odds ratio; CI: confidence interval).\textsuperscript{1}

Table 3 Genauigkeit (acc.) und positiv prädiktive Werte (PPV) aller Untersuchungen (all) sowie der Multidetektor-Computertomografie (CT) und der Magnetresonanztomografie (MRT) alleine für die Differenzierung benigner zystischer pankreatischer Tumore (CPT).\textsuperscript{2}

SOAs and SPNs), the statistical conclusions may not be completely relevant (significant).

Conclusion

The characterization of benign CPTs is possible with MRI and CT, with MRI seeming to be superior to CT. The diagnostic accuracy depends on the observer’s experience. The standardized algorithm can aid in the differential diagnosis but still needs to be tested in other patient populations.
Table 4 Interobserver variability of different observers and algorithm for the differentiation of benign cystic pancreatic tumors.1

<table>
<thead>
<tr>
<th>observer</th>
<th>CT (kappa)</th>
<th>MRI (kappa)</th>
<th>All (kappa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1, O2*</td>
<td>0.69</td>
<td>0.72</td>
<td>0.71</td>
</tr>
<tr>
<td>O1, O3*</td>
<td>0.61</td>
<td>0.80</td>
<td>0.68</td>
</tr>
<tr>
<td>O2, O3*</td>
<td>0.62</td>
<td>0.76</td>
<td>0.67</td>
</tr>
<tr>
<td>O1, O2, O3+</td>
<td>0.64</td>
<td>0.76</td>
<td>0.69</td>
</tr>
<tr>
<td>O1, algorithm*</td>
<td>0.63</td>
<td>0.65</td>
<td>0.65</td>
</tr>
<tr>
<td>O2, algorithm*</td>
<td>0.67</td>
<td>0.85</td>
<td>0.74</td>
</tr>
<tr>
<td>O3, algorithm*</td>
<td>0.64</td>
<td>0.80</td>
<td>0.71</td>
</tr>
<tr>
<td>O1, O2, O3, algorithm+</td>
<td>0.64</td>
<td>0.76</td>
<td>0.69</td>
</tr>
</tbody>
</table>

1 O: observer; *: Cohen’s kappa coefficient; +: generalized Fleiss kappa coefficient; significance level p < 0.05 for all kappa values.
2 O. Untersucher, *Cohens Kappa Koeffizient, +generalisierter Fleiss Kappa Koeffizient, Singifikanzlevel p < 0.05 für alle Kappa Werte.

References

12 Bennett BM. On comparisons of sensitivity, specificity and predictive value of a number of diagnostic procedures. Biometrics 1972; 28: 793–800