Retrospective Study

Serous pancreatic neoplasia, data and review

Christoph F Dietrich, Yi Dong, Christian Jenssen, Valentina Ciaravino, Michael Hocke, Wen-Ping Wang, Eike Burmester, Kathleen Moeller, Nathan SS Atkinson, Paola Capelli, Mirko D’Onofrio

Christoph F Dietrich, Medizinische Klinik 2, Caritas-Krankenhaus Bad Mergentheim, 97980 Bad Mergentheim, Germany

Yi Dong, Wen-Ping Wang, Department of Ultrasound, Zhongshan Hospital, Fudan University, Shanghai 200032, China

Christian Jenssen, Department of Internal Medicine, Krankenhaus Märkisch Oderland Strausberg/Wriezen, 15344 Strausberg, Germany

Valentina Ciaravino, Department of Radiology, G.B Rossi University Hospital, University of Verona, 37129 Verona, Italy

Michael Hocke, Department of Internal Medicine 2, Helios Hospital Meiningen GmbH, 98617 Meiningen, Germany

Eike Burmester, Department of Internal Medicine I, Sana Kliniken, 23560 Luebeck, Germany

Kathleen Moeller, Sana Klinikum Lichtenberg, 10365 Berlin, Germany

Nathan SS Atkinson, Translational Gastroenterology Unit, Oxford University Hospitals NHS Foundation Trust, Oxford OX3 9DU, United Kingdom

Paola Capelli, Department of Pathology, G.B Rossi University Hospital, University of Verona, 37134 Verona, Italy

Mirko D’Onofrio, Department of Radiology, GB Rossi University Hospital, University of Verona, 37134 Verona, Italy

Author contributions: Dietrich CF is accepting full responsibility for the conduct of the study, he and all others had access to the data, all had control of the decision to publish; all authors planning the study, conducting the study, collecting and/or interpreting data, drafting the manuscript, and critical revision of the manuscript for important intellectual content Statistical analysis; each author made a statement that they approved the final draft submitted.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Data sharing statement: Each author gives permission to the graphic designers to alter the visual aspect of figures, tables, or graphs.

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Manuscript source: Invited manuscript

Correspondence to: Christoph F Dietrich, MD, PhD, MBA, Professor of Medicine, Chief, Medizinische Klinik 2, Caritas-Krankenhaus Bad Mergentheim, Uhlandstr 7, 97980 Bad Mergentheim, Germany, christoph.dietrich@ckbm.de
Telephone: +49-7931-582201
Fax: 49-7931-582290

Received: March 5, 2017
Peer-review started: March 7, 2017
First decision: April 11, 2017
Revised: June 8, 2017
Accepted: July 22, 2017
Article in press: July 24, 2017
Published online: August 14, 2017

Abstract

AIM
To describe the imaging features of serous neoplasms of the pancreas using ultrasound, endoscopic ultrasound, computed tomography and magnetic resonance imaging.
### INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the most common malignancy of the pancreas, accounting for about 90% of malignant pancreatic neoplasms. The most important imaging diagnosis to differentiate from PDAC are neuroendocrine tumours\(^1,2\). Most pancreatic cystic neoplasms are mucin producing including intraductal pancreatic mucinous neoplasia (IPMN) and mucinous cystic neoplasia (MCN)\(^3\). Other important pancreatic lesions to differentiate include metastases (e.g., of renal cell cancer), lymphoma and ectopic spleen. Comparatively less is known about serous pancreatic neoplasias (SPNs) and serous pancreatic cystadenomas (SCACs) were recorded (0.1%)\(^8\). Rare cases of synchronous or metachronous hepatic SPNs may represent multifocal occurrence rather than metastatic spread\(^9\). Frankly malignant behavior with metastases seems to be very rare. In a multinational study of 2622 patients with SPNs, only 3 serous cystadencarcinomas (SCACs) were recorded (0.1%)\(^8\). Therefore, SCAC is represented predominantly by a few sporadic case reports in the recent literature. Follow-up studies have not demonstrated proof of an adenoma-carcinoma sequence in SPN\(^9,10,11,15\).

The growth rate of SPNs is variably reported. In the largest series (\(n = 2622\)) it was found to be only 4 mm/year, and size was stable or decreased in as many as 63% of patients\(^8\). This was supported by another series (\(n = 214\)), where the doubling time was estimated at approximately 12 years, and was independent of tumour size\(^14\). In contrast, in another case series (\(n = 106\)) growth rate was reported to vary by tumor...
size, with the fastest growth (20 mm/year) observed in tumors ≥ 40 mm, compared to tumors < 40 mm (increasing 12 mm/year)\textsuperscript{16}. Finally, a fourth series (n = 145) found the fastest growth 7-10 years after diagnosis (60 mm/year) compared to the first 7 years (10 mm/year). Oligocystic or macrocystic appearance, a history of other tumors, and patient age were all significant predictors of more rapid tumor growth\textsuperscript{13}.

Diagnosis of SPN primarily is based on imaging (computed tomography (CT); magnetic resonance imaging (MRI); ultrasound (US); endoscopic ultrasound (EUS)). The classical microcystic SPN consists of innumerable very small cysts separated by thin, vessel-containing fibrous septae. Cysts may be microscopic or measure up to 10 mm. These features cause a honeycomb or sponge-like appearance with hypervascularity and distinct, sometimes lobulated, margins. Pertinent negatives include communication with the pancreatic duct, vascularized mural nodules, and a hypervascular capsule on contrast-enhanced imaging, whilst a central scar is visible in a third of cases and may contain calcifications\textsuperscript{17-20}. Pitfalls may arise from several factors: the macro- and oligo-cystic types of SPN can appear similar to pseudocysts or MCN. Rarely the solid form of SPN may be confused with other hypervascular well-circumscribed pancreatic tumors, in particular neuroendocrine tumors and solid pseudopapillary neoplasms\textsuperscript{18,19,26-28}. In contrast to the mentioned reports, an atypical appearance on CT was found in 61.1\% of cases in a study of 72 confirmed SPNs\textsuperscript{28}.

A correct diagnosis of SPN is challenging. The pre-operative diagnosis was wrong in 63\% of resected cases in a Japanese series\textsuperscript{12}, and in a large multinational study the indication for surgery was an uncertainty of diagnosis in 60\% of cases\textsuperscript{8}. To date, no large series describing typical and atypical US- and EUS-features of SPNs has been reported.

The aim of this retrospective study was to describe the imaging features of serous neoplasms of the pancreas using US, EUS, CT and MRI. The frequency of atypical imaging aspects by different imaging modalities will be estimated and the most common atypical features will be reported, particularly of US which is often the initial imaging modality employed.

MATERIALS AND METHODS

Patients
An international multicenter retrospective data collection of 287 histologically confirmed cases of SPNs was performed. The cohort was not uniform according to the resection criteria. No other exclusion criteria have been defined.

Examination technique
Conventional ultrasound and contrast enhanced ultrasound (CEUS) were performed in all patients with one of six ultrasound systems: Philips IU22 unit (Philips Bothell, WA, United States; C5-1 convex array probes, 1-5 MHz), or LOGIQ E9 (GE Healthcare, Milwaukee, WI, United States; C1-5 convex array probes, 1-5 MHz) or Hitachi (HI vision EUB-6500, Preirus, Ascendus; C715 convex array probes, 1-5 MHz), or SIEMENS (Acuson Sequoia or S2000), or Toshiba (Apio platinum 500; Apio CV, convex array probes 3-6 MHz). CEUS was performed using contrast harmonic real-time imaging at a low MI 0.05-0.30. The ultrasound contrast agent Sonovue was used at a dose of 1.5-2.4 mL, immediately followed by an injection of 10 mL sodium chloride solution. Images were recorded for 3 min after contrast agent injection.

Contrast enhanced EUS was performed using longitudinal echoendoscopes EG-3870 UTK and Hitachi platforms (Hitachi HI vision EUB-6500, Hitachi Preirus, Hitachi Ascendus)\textsuperscript{29-32}.

Imaging Evaluation (TUS, EUS, CEUS, ceEUS)
After identification of the pancreatic lesion by conventional B-mode US or EUS, contrast enhanced imaging was immediately performed. All examinations were interpreted according to the 2011 EFSUMB guidelines\textsuperscript{11}. CEUS features of pancreatic lesions were compared to the surrounding normal pancreatic parenchyma.

Final diagnoses, treatment and clinical follow up
Most patients (n = 249, 86.7\%) were diagnosed as SPNs by post-operative histopathology. 31 (10.8\%) cases were confirmed by EUS FNA and 7 (2.5\%) by transabdominal (percutaneous) ultrasound-guided core needle biopsy (18-gauge 20-cm single-use biopsy needles; Temno, Germany, or BioPince, Pflugbeil, Germany). Clinical follow-up for a minimum of 12 mo was established for all patients with SPN diagnosed by biopsy. Additional information on outcome data was not requested.

Statistical analysis
Statistical analyses were performed using SPSS Statistics 17.0 (SPSS Inc., Chicago, IL, United States). The χ² test and Fisher’s exact test were used to compare categorical parameters between the groups. Continuous parameters were presented as the mean ± SD, and Student’s t test was used. A P value of less than 0.05 was considered statistically significant.

RESULTS

Epidemiology
The average age of included patients was 57.3 ± 14.2 years (18-85 years). Fifty-eight patients were male and 229 were female (Table 1).

Conventional ultrasound
On conventional B mode ultrasound (BMUS) most SPN lesions (n = 113, 39.3\%) were detected in the head/neck of the pancreas. Most SPN lesions (97.9\%) were
In the arterial phase, most SPN lesions were hypoenhancing (1.7%) or isoenhancing (61.8%) (Table 3).

**DISCUSSION**

SPNs are less frequent than common pancreatic tumors such as solid ductal adenocarcinoma and cystic IPMN but recent estimates suggest SCAs represent about 20% of all cystic pancreatic lesions [33,34]. SPN typically present as a solitary multicystic lesion with a honeycomb architecture due to the presence of multiple microcysts. Thin walls and multiple thin septa orient toward the centre/scar of the lesion, without communication with the main pancreatic duct. In typical cases an imaging diagnosis can be made confidently. However, atypical presentations are commonly encountered in everyday clinical practice. Specifically, extremely multicystic SPNs are considered rare, resembling a solid lesion in conventional US, but in fact a solid component was seen in 55.7% of cases in our multicentre study. After contrast administration, these solid SPNs may resemble hypervascular solid lesions with homogeneous hyperenhancement, making differentiation from neuroendocrine neoplasms as difficult as it is crucial [35,36]. MRI may reveal a lesion’s true cystic nature [37]. The macrocystic variant must be differentiated from other macrocystic pancreatic lesions, such as pseudocyst, mucinous cystic neoplasms, side-branch and mixed type IPMNs, solid tumors (either adenocarcinomas or neuroendocrine) with cystic degeneration, and lymphangiomas [38-40].

**Epidemiology**

The mostly asymptomatic SPN is often a solitary lesion with multilocular cysts predominantly in the corpus and tail of the pancreas. SPNs are usually diagnosed single, though 6 (2.1%) patients had multiple lesions, and most lesions (97.9%) were hypoechoic on BMUS. With colour Doppler imaging (CDI), macrovessels were detected in 20.6% of lesions, among which the typical “spoke wheel” appearance was identified in 35.6% of lesions (Table 2).

**CEUS**

Transabdominal CEUS was performed in 173 (60.3%) lesions. After contrast agent injection, most SPN lesions displayed hyper- (36.5%) or isoenhancement (61.8%) in the arterial phase. During the late phase, most SPN lesions were hyper-enhancing (22.5%) or iso-enhancing (74.9%) (Table 3).

**EUS and contrast enhanced EUS**

EUS was performed in 61 patients diagnosed with SPN. Using CDI, macrovessels were detected in all 61 cases. Contrast enhanced endoscopic ultrasound (CE-EUS) was performed in 54 SPN lesions, demonstrating hyper-enhancement in all cases (Table 4).
in females in the 5th to 7th decade (female to male ratio 2-3:1) but with improved imaging methods the neoplasia may be diagnosed much earlier. Multiple lesions, including involvement of the entire organ, have been observed in patients with Von Hippel-Lindau disease. SPNs may present up to 20% of cystic pancreatic lesions.

Clinical symptoms
Sporadic and benign SPNs are most often an incidental finding without symptoms; jaundice is particularly uncommon. In our series only 5.2% of SPNs presented with symptoms. During the course of the disease, symptoms may be caused by growth of the lesion. The main pancreatic duct and or common bile duct may become entrapped in the lesion, especially if large in dimension. The reported growth rate has been estimated at 4 mm per year.

Pathology
The solitary well demarcated and multicystic SPN is a multilobular cyst forming epithelial neoplasia with a somewhat “honeycomb” architecture (Figure 1) without communication with the pancreatic duct. Histologically, monostratified cuboidal, glycogen rich epithelial cells typically without mitoses are observed. Centrally located fibrous tissue (a so called “scar”) with or without calcifications can be found, similar to focal nodular hyperplasia of the liver; therefore the lesion has been referred to as “FNH of the pancreas”. SPNs are typically hypervascular lesions, where septa are characterized by abundant subepithelial micro- and macro-vessels.

Size of single cysts
According to the size of the cysts, SPNs can be classified as real solid lesions (< 5%), pseudo-solid SPNs (cysts only detectable by microscopic evaluation), microcystic (< 10 mm), oligocystic (< 20 mm), and macrocystic appearance (30%). The cystic appearance can be described by thin multiple septa oriented toward the center of the lesion. Mixed forms (microcystic and macrocystic) are typical in large SPNs. Macrocytic giant SPNs are more commonly located in the pancreatic head, and a male preponderance was observed. The macrocystic variant may be indistinguishable from other macrocystic tumors of the pancreas.

Malignant transformation
SPN is typically a benign neoplasia but in a series of 257 resected SPNs, local expansion (5.1%) and malignant transformation with metastases (0.8%) have been described. Therefore, follow-up is recommended by means of ultrasound or MRI. Surgical treatment is recommended only for symptomatic patients or patients with growing lesions, usually larger than 4 cm.

Imaging
Ultrasound: Sonographically, SPN is a typically lobular cyst forming isoechoic neoplasia with centrally oriented thin walls (thin septae) without communication with the main pancreatic duct. A central hypoechoic spot (central fibrovascular scar) is characteristic.

Table 4: Endoscopic ultrasound and contrast enhanced endoscopic ultrasound imaging features of serous pancreatic neoplasia lesions (n = 61)

| Characteristic                  | SPN lesions (n = 61) |
|--------------------------------|----------------------|
| EUS Anechoic                    | 2 (3.3)              |
| Hypoechoic                      | 56 (91.8)            |
| Isoechoic                       | 3 (4.9)              |
| EUS-CDI vessel detectable       | 0                    |
| Avascular                       |                      |
| Macroversels detectable         | 61 (100)             |
| EUS-CDI vascular pattern (n = 61)|                      |
| Central artery                  | 26 (42.6)            |
| Typical spoke wheel appearance  | 15 (24.6)            |
| No specifics                    | 20 (32.8)            |
| CE-EUS (n = 54)                 |                      |
| Hyperenhancement                | 54 (100)             |
| Isoenhancement                  | 0                    |
| Hypoenhancement                 | 0                    |
| Final EUS-Diagnosis             |                      |
| “Eyecatcher”                    | 49 (80.3)            |
| Typical SCA                     | 5 (8.2)              |
| Unclear macrocyst               | 6 (9.8)              |

EUS: Endoscopic ultrasound; EUS-CDI: Endoscopic ultrasound color Doppler Imaging; CE-EUS: Contrast enhanced endoscopic ultrasound; SPN: Serous pancreatic neoplasia; SCA: Serous cystadenoma.

Figure 1 Macro- and micro-pathology (histology, cytology) of microcystic pancreatic adenoma. A: Typical microcystic appearance of serous cystadenoma with “honeycomb” architecture, and central scar with small calcification; B: Histology demonstrates the typical single layer of clear cuboidal epithelial cells lining the cysts.
the case of depictable cysts the content is anechoic. SPNs are typically hypervascular lesions since the septa are composed by abundant subepithelial micro- and macro-vessels\(^6,7\) (Figures 2 and 3).

As has been shown in a prospective study \((n = 12)\) using CE-EUS, hypervascularity, sharp delineation, fibrotic strands and typical vessel architecture are the predominant features of serous microcystic adenoma\(^47\) (Figures 4 and 5).

Solid SPNs may mimic neuroendocrine tumours, renal metastases, intrapancreatic accessory spleens and other hypervascular pancreatic tumours\(^35,36,45,48\).

Solid and pseudosolid SPNs are typically hypervascular and, therefore, hyperenhancing using CEUS\(^45,48,49,50\).

**EUS:** EUS is an accurate imaging modality to diagnose and exclude neoplasia of the pancreas\(^1,51-53\). The features are the same as described for conventional ultrasound\(^54\). SPN do not communicate with the main pancreatic duct but may show proximal duct dilatation due to compression, whereas IPMN usually showed distal or whole pancreatic duct dilatation\(^50,55\).

CE-EUS has been proven to be of value for many indications\(^29-32,56-60\). In our study EUS was able to detect macrovessels and hypervascularity by CDI contrast-enhanced imaging in 100% of cases, whereas percutaneous US with CDI delineated macrovessels only in 20.6% of cases.

**Endoscopic ultrasound fine needle aspiration:**
Endoscopic ultrasound fine needle aspiration (EUS-FNA) of SPN should target the largest cyst for fluid analysis\(^61,62\). The cyst fluid is watery (non-viscous) and colorless\(^63\). The cellularity is low with few cuboidal glycogen positive and mucin negative epithelial cells. CEA levels are usually but not always low (< 20 ng/mL). In the majority of cases, aspirated fluid will be hypocellular with few groups of bland cuboidal epithelial cells embedded in granular debris\(^64-67\). Round to cuboid serous epithelial cells with clear cytoplasm and small, round nuclei forming loose clusters or monolayered sheets are identified in only 20%-25% of cases\(^64,66,68\). Positive \(\alpha\)-inhibin immunocytochemistry

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**Figure 2** Typical microcystic serous pancreatic neoplasia using colour Doppler imaging. Note the centrally located artery.

**Figure 3** Typical microcystic serous pancreatic neoplasia using B-mode (A), colour Doppler imaging (B), and contrast enhanced ultrasound (C and D). Note the centrally located artery and the typical hyperenhancement.

**Figure 4** Typical oligocystic serous pancreatic neoplasia using endoscopic ultrasound.
may enhance the diagnostic accuracy of EUS-FNA in SPN. Promising cyst fluid markers with high sensitivity and specificity for SPN include VEGF-A and a molecular assay for KRAS, GNAS and VHL mutations. In one study, VEGF-A was markedly elevated in SPN when compared to pseudocysts and mucinous neoplastic cysts. The presence of KRAS and GNAS mutations is highly specific for IPMN and is never observed in SPN, whereas VHL deletions are found in almost all SPN.

Core biopsy: In solid and pseudosolid lesion we prefer histological evaluation which allows definite diagnosis.

MRI: The MRI features of SPNs are also represented by a typical lobular “honeycomb” shaped contour and architecture with thin walls less than 2 mm, in contrast to other cystic neoplasia of the pancreas. SPNs are homogeneously hypointense on T1-weighted MRI sequences. The cystic nature of the lesion can be easily demonstrated by a typical hyperintense signal on T2-weighted images. The hyperintense cysts are surrounded by hypointense septa and sometimes by a hypointense (pathognomonic) central scar. The central scar is a less sensitive (15%) but specific sign of SPN.

In contrast to EUS, the individual vessels cannot be displayed but contrast enhanced MRI using gadolinium chelates also reveal the hypervascular nature by diffuse hyperenhancement in pseudosolid SPN. However also in pseudosolid SPN, MRI remains highly accurate in showing the cystic nature of the lesion on T2-weighted images. The macrocystic types present features similar to other macrocystic tumors of the pancreas, but the lobulated contours, together with the absence of wall enhancement and wall thickness less than 2 mm, should suggest the correct diagnosis.

CT: CT is sometimes helpful for detection of SPN but
should in general not be used for the evaluation and differential diagnosis of cystic pancreatic lesions. CT might be helpful in the visualization of a centrally located calcified scar. SPN may mimic a hypervascular lesion\[17,39,46\].

**Differential diagnosis**

The presence of a unilocular lobulated cyst located in the pancreatic head with anechoic fluid and wall thickness less than 2 mm are indicative of SPN using all imaging methods and should be considered as a unilocular macrocystic SCA, until otherwise proven (Figures 6-8\[80\]).

**Pancreatitis:** A clinical history of pancreatitis is crucial for differentiating pseudocysts. Imaging findings of pancreatitis derived pseudocysts include signs of inflammation in the acute setting, calcifications, thin-walled duct dilation, pancreaticolithiasis, and atrophy and typical dilation of the pancreatic duct\[39,51,81,82\].

**Figure 6** Pseudo-solid serous pancreatic neoplasia, histologically demonstrated to have a microcystic structure. A: B-mode ultrasound shows a solid hypoechoic mass in the neck of the pancreas; B: Contrast enhanced ultrasound shows the lesion to hyperenhance with a hypoechoic defect in the center; C: Computed tomography shows the lesion as solid and inhomogeneously hyperenhancing.

**Figure 7** Large pseudosolid serous pancreatic neoplasia. A: With B-mode ultrasound a huge mass is visible appearing solid and inhomogeneously hypoechoic; B: Doppler shows large arterial vessels within the mass; C: With Computed tomography the lesion appears pseudosolid with inhomogeneous slight enhancement; D: Magnetic resonance imaging clearly shows the cystic nature of the mass with microcystic appearance.

Solid SPNs are often misdiagnosed as chronic (focal) pancreatitis, which is important to know.
A correct diagnosis of pancreatic cystic neoplasms (SPNs) is challenging. Serous pancreatic cystic neoplasms are infrequent neoplasms of the pancreas. A correct diagnosis of pancreatic cystic neoplasms (SPNs) is challenging. To date, no large series describing typical and atypical ultrasound (US)- and endoscopic ultrasound (EUS)-features of SPNs have been reported.

**Research frontiers**
The aim of this retrospective study was to describe typical and atypical imaging features of serous neoplasms of the pancreas using US, EUS, computed tomography and MRI.

**Innovations and breakthroughs**
This multicenter international collaboration reports on imaging features in one of the largest series of 287 histologically confirmed cases of SPNs.

**Applications**
Ultrasound B-mode descriptors and contrast enhanced ultrasound describing the vascular pattern and enhancement features are helpful to differentiate SPN from other neoplastic cystic lesions.

**Peer-review**
Very interesting study about the serous pancreatic neoplasia.

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