Typical Pancreatic Serous Cystadenomas: Should We Recommend Surgical Consultation for Asymptomatic Patients with Large Lesions?

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ABSTRACT **Background:** Gastroenterological guidelines consider pancreatic serous cystadenomas (SCAs) to have minimal malignant potential and generally do not recommend intervention or surveillance. In contrast, the American College of Radiology recommends surgical consultation for large SCAs (> 4 cm).

Objectives: To evaluate the association between initial SCA size and lesion growth during follow-up.

Methods: The final reports of all patients who underwent magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) at our institution between the years 2011 and 2021 were reviewed for the diagnosis of serous cystadenoma. Patients with typical microcystic serous cystadenomas who had at least two MRCP examinations were included. We collected clinical data from the patients during the follow-up period, including history, symptoms, and laboratory results. The primary and maximal cyst size diameters and additional radiological characteristics were collected.

Results: Our cohort included 35 patients (21 females, 14 males) with a median age of 68 years. The median follow-up period was 32 months. None of our patients developed malignant transformation. Nineteen lesions grew during follow-up. We found no connection between the lesion size at presentation and the enlargement during follow-up. In total, 21 patients had smaller lesions < 4 cm and 14 had larger lesions > 4 cm. There were no significant clinical or radiological differences between the smaller and larger lesions.

Conclusions: We investigated whether the current radiological recommendations for serous cystadenomas should be revised. Surgical consultation may not be needed for typical asymptomatic SCAs, regardless of the size.

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KEY WORDS: magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP), pancreatic serous cystadenoma (SCA), pancreatic cystic lesions guidelines, surgical consultation

Serous cystadenomas (SCAs) are benign cystic neoplasms of the pancreas. They have a predilection for older women and can be associated with Von-Hippel-Lindau disease. The risk of malignant transformation to serous cystadenocarcinoma is extremely low and estimated at around 0.1% of all SCAs [1]. On imaging, SCAs can be divided into several morphological patterns: microcystic (70%), macrocystic, mixed, honeycomb appearance, and solid variant. The typical microcystic pattern demonstrates multiple small cysts of less than 2 cm in size, separated by thin septations. Fine external lobulations and a fibrous central scar are characteristic. There is no communication between SCAs and the main pancreatic duct [2,3].

Several attempts have been made to establish a universally acceptable set of recommendations for the management of pancreatic cystic lesions [4]. The International Association of Pancreatology (IAP) has published several guidelines documents concerning pancreatic cystic lesions since 2006. These guidelines focus on defining high-risk lesions requiring surgery and on designing a follow-up plan for low-risk lesions. The latest document was published in 2024 [5] and included no specific guidelines regarding SCAs, similar to all the previous IAP guidelines [6]. In addition, SCAs did not appear in the guidelines of the American Gastroenterological Association for the diagnosis and management of asymptomatic neoplastic pancreatic cysts from 2015 [7]. The updated clinical guidelines of the American College of Gastroenterology (ACG) for diagnosis and management of pancreatic cystic lesions suggest that pancreatic SCAs have a very low risk of malignant transformation and, therefore, do not require treatment or further evaluation [8].

However, the guidelines of the European Study Group on Cystic tumors of the Pancreas from 2018 included several recommendations for patients with SCAs. For example. asymptomatic patients with a definite diagnosis of SCA should undergo one follow-up examination after one year. When the diagnosis is uncertain, patients should undergo follow-up like branch-duct intraductal papillary mucinous neoplasm (IPMN). Surgery is recommended in symptomatic patients with symptoms related to the compression of adjacent organs, like the bile duct or the stomach [9]. The white papers of the American College of Radiology (ACR) from 2010 and 2017 recommended surgical consultation for patients with symptoms or large lesions of over 4 cm [10].

Considering the different guidelines systems, particularly the ACR recommendations, the aim of this study was to compare growth patterns during follow-up between smaller and larger SCAs.

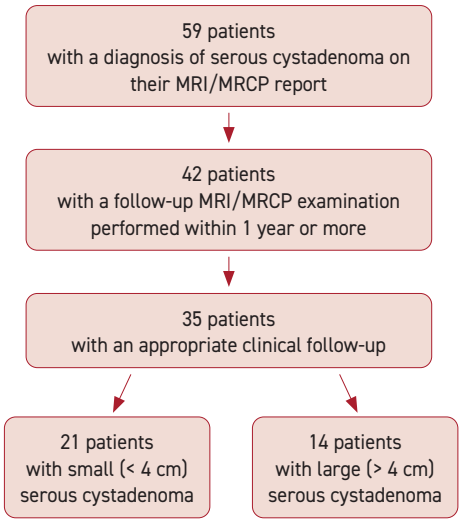
PATIENTS AND METHODS

PATIENTS

The final reports of all the magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) examinations performed at our institution between the years 2011 and 2021 were reviewed for the diagnosis of SCA. We included only patients who had two or more MRI/MRCP scans with at least one year between them. Exclusion criteria were age younger than 18 years and lack of appropriate clinical gastroenterological follow-up from the time of the MRI/MRCP ± one month [Figure 1]. This retrospective research was approved by the institutional review board.

Figure 1. Flow chart of the study population selection

MRI/MRCP = magnetic resonance imaging/magnetic resonance cholangiopancreatography



MRI EXAMINATION

All examinations were performed on a 1.5T or 3.0T Siemens MRI systems (Avanto®, Skyra®, Aera®, or VIDA®; Siemens Healthineers, Germany) with an abdominal radiofrequency coil. Our MRI/MRCP protocol includes several T2 sequences: axial and coronal Half-Fourier Acquisi-

Table 1. Comparison between the lesions that presented growth of 2 mm or more and the lesions that were stable on follow-up

	Non-enlarging lesions	Enlarging lesions
Age, median, months (IQR)	69.5 (9.8)	65 (12.3)
Sex (female)*	10	11
BMI, kg/cm^2, months, median (IQR)	29.5 (7.2)	27 (6)
H/O Smoking*	2	2
Diabetes mellitus*	9	10
H/O Pancreatitis*	0	1
H/O Liver disease*	0	1
H/O malignancy*	6	5
Family H/O pancreatic adenocarcinoma*	2	0
Abdominal symptoms**	6	4
Length of F/U in cm, median (IQR)	35 (12.5)	41 (17)
First max. cyst diameter in cm, median (IQR)	3 (1.85)	3.2 (2.9)
Large SCA > 4 cm*	6	9
Multiple SCAs*	1	4
Stellate scar*	2	4
Head location*	9	10
MPD dilatation*	3	3
Pancreatic divisum*	1	2
Cholelithiasis or s/p cholecystectomy*	1	2
IPMN*	7	9
Total number of cases	16	19

*Number of patients (frequencies)

**Abdominal symptoms: abdominal pain, nausea/vomiting, abdominal bloating

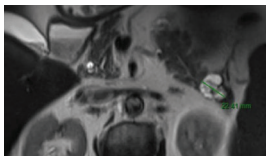
BMI = body mass index, H/O = history of, IPMN = intraductal papillary mucinous neoplasm, IQR = interquartile range, MPD = main pancreatic duct, SCA = serous cystadenoma

tion Single-Shot Turbo Spin-Echo (HASTE) T2 sequence of the entire upper abdomen in free breathing and with a slice thickness of 5 mm; axial HASTE T2 of the entire upper abdomen with inversion recovery in free breathing and with a slice thickness of 5 mm; axial, coronal, left anterior oblique, and right anterior oblique breath-hold HASTE T2 with a small field of view (focused on the pancreas) and a slice thickness of 3 mm. The MRCP portion includes two sequences of 3D respiratory triggered coronal single slab 3D turbo spin-echo T2, with and without minimal intensity projection. Diffusion-weighted images were acquired in free breathing with a slice thickness of 5 mm and b-values of 50, 400, and 800 s/mm^2. Out-of-phase and in-phase gradient-echo scans of the upper abdomen were acquired on the axial plane with a 3 mm slice thickness.

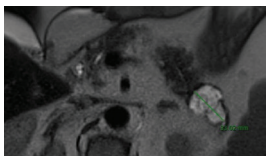
The last part of the examination included several volumetric interpolated breath-hold T1 scans of the upper abdomen, with a slice thickness of 3 mm, before and after intravenous contrast administration. The entire abdomen is scanned first before contrast administration, on the axial and coronal planes. We used 0.2 ml/kg gadoterate meglumine (Dotarem, Guerbet, France) as the contrast material for MRI/MRCP. The post-contrast scans were performed at 25 seconds, 55 seconds, 90 seconds, 3 minutes, and 5 minutes after contrast administration. A post-contrast coronal scan was performed 110 seconds after contrast administration. Subtraction sequences were created for each of the post-contrast scans.

Figure 2. HASTE T2 images of two patients

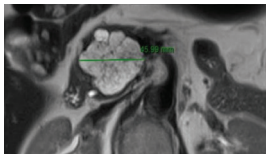
[A] A 70 year-old female with a typical serous cystadenoma in the tail of the pancreas, T2 axial image of the pancreas from the first examination of the patient. The lesion measured up to 2.2 cm.



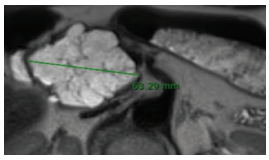
[B] A 70 year-old female with a typical serous cystadenoma in the tail of the pancreas, T2 axial image of the pancreas from the second examination of the patient. The lesion enlarged to the size of 3.3 cm (50% enlargement) during 4 years of follow-up.



[C] A 64 year-old female with a typical serous cystadenoma in the head of the pancreas, T2 axial image of the pancreas from the first examination of the patient. The lesion measured up to 4.6 cm.



[D] A 64 year-old female with a typical serous cystadenoma in the head of the pancreas, T2 axial image of the pancreas from the second examination of the patient. The lesion enlarged to the size of 6.3 cm (37% enlargement) during 4.5 years of follow-up.



DATA COLLECTION

The clinical data collection included demographic data, past medical history, gastrointestinal symptoms and laboratory results, which were collected from the time of the MRI/MRCP examinations ± 1 month. The radiological data collection included the number of SCA lesions in the pancreas, first and last maximal diameter of the largest lesion, location of the SCAs, presence of a central scar, presence of main pancreatic duct or common bile duct dilatation, and presence of any biliary or pancreatic pathologies including additional pancreatic cystic lesions (other than SCAs). If a patient had more than two MRI/MRCP examinations, we collected the information from the first and last examinations only. Pathological results from aspiration on endoscopic ultrasound were available for only 11 patients; therefore, they were not included in the final statistical analysis. The data were collected by a radiologist with 5 years of experience (YK) and reviewed by a fellowship-trained body radiologist with 13 years of experience (RK).

STATISTICAL ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 28 (SPSS, IBM Corp, Armonk, NY, USA). Four numerical size parameters were used for the evaluation of the lesions: first maximal diameter in cm, last maximal diameter in cm, lesion size progression in cm, and progression velocity, which is the enlargement in cm divided by number of months of follow-up. The study population was first divided according to the presence of progression on follow-up and a comparison between the groups was performed. Next, the population was re-divided according to the cutoff of the ACR guidelines into patients who had smaller lesions (< 4 cm) and patients who had larger lesions (> 4 cm). The clinical and radiological parameters were compared between the new groups.

The distribution of continuous variables was evaluated using histograms, and since none of the continuous variables followed a normal distribution, they were reported as medians with interquartile ranges (IQRs). Categorical variables were presented as frequencies. Chi-square test and Fisher's exact test were used for the comparison between categorical

variables and Mann–Whitney U tests were used for comparison between continuous variables. All calculations were 2-tailed, and $P < 0.05$ was considered statistically significant.

RESULTS

The lesions of 35 patients, 21 females (60%) and 14 males (40%), were included in our study. Initially, 59 cases were initially collected; however, 24 cases were subsequently excluded due to lack of follow-up MRI/MRCP, lack of clinical follow-up, or sub-optimal examination [Figure 1]. The median age was 68 (IQR 11) years, and the median follow-up period was 32 (IQR 15) months. None of our patients underwent malignant transformation during follow-up. One of our patients (a 70-years-old female) developed abdominal pain and biliary dilatation during follow-up and had to undergo a Whipple procedure.

The comparison between the lesions that presented growth of 2 mm or more (n=19) and the lesions that were stable on follow-up (n=16) is summarized in Table 1. We found no significant differences ($P > 0.05$) between enlarging and non-enlarging lesions, when comparing all the clinical parameters, including age; sex; body mass index; family history of pancreatic adenocarcinoma; abdominal symptoms; length of follow-up; and history of smoking, diabetes mellitus, pancreatitis, liver disease, and malignancy. Furthermore, the radiological parameters did not differ significantly ($P > 0.05$) between the groups, including first maximal diameter, initial size of over 4 cm, multiples lesions, stellate scar, head location, main pancreatic duct dilatation, pancreatic divisum, IPMN, cholelithiasis, or status post cholecystectomy. The comparison between the smaller lesions group (< 4 cm, n=21) and the larger lesions group (n=14) is shown in Table 2. There were no significant differences ($P > 0.05$) between the groups, except for lesion size. HASTE T2 images of two patients from our study are illustrated in Figure 2.

Table 2. Comparison between the smaller lesions group (of less than 4 cm) and the larger lesions group

	Small SCA (< 4 cm)	Large SCA (> 4 cm)
Age in months, median (IQR)	67 (11.5)	70.5 (8.5)
Sex (female)*	15	6
BMI, kg/cm^2, median (IQR)	27 (6)	29.5 (5.25)
Smoking*	4	1
DM*	11	8
H/O Pancreatitis*	1	0
H/O Liver disease*	1	0
H/O malignancy*	6	5
Family H/O pancreatic adenocarcinoma*	1	1
Abdominal symptoms*	4	5
Length of F/U in months, median (IQR)	36 (12.5)	32.5 (14)
First max. cyst diameter in cm, median (IQR)	2.4 (1.1)	6.95 (4.48)
Second max. cyst diameter in cm, median (IQR)	2.8 (1.2)	7.6 (2.6)
Growth in cm, median (IQR)	0.36 (0.3)	0.45 (1.25)
Cyst progression (growth of ≥ 2 mm)*	10	9
Multiple SCAs*	2	2
Stellate scar*	3	5
Head location*	11	8
MPD dilatation*	2	4
Pancreatic divisum*	1	2
Cholelithiasis or s/p cholecystectomy*	3	1
IPMN*	11	7
Total number of cases	21	14

*Number of patients (frequencies)

BMI = body mass index, H/O = history of, IPMN = intraductal papillary mucinous neoplasm, IQR = interquartile range, MPD = main pancreatic duct, SCA = serous cystadenoma

DISCUSSION

Our results revealed no clinical or radiological differences between smaller and larger typical microcystic SCAs. Since the size at diagnosis is a very important prognostic factor, we were surprised to see that the larger lesions group (> 4 cm) did not include more cases of cyst progression during follow-up. When comparing enlarging and non-enlarging lesions, the enlarging lesions group included more cases of large SCAs (> 4 cm); however, this finding was not statistically significant ($P = 0.35$).

Previous studies that evaluated the relation between lesion size at presentation and growth on follow-up of SCAs presented contradicting results. In their study from 2005, Tseng and colleagues [11] found that SCAs larger than 4 cm have a significantly higher growth rate compared to small lesions. Similarly, Menard and colleague [12] demonstrated in their study from 2011 a significant correlation between the largest diameter at presentation and growth rate of SCAs. Conversely, Malleo et al. [13] and Fukasawa et al. [14] showed that the size at presentation does not play a role in predicting the growth rate of SCAs. In their large multicenter study published in 2016, Jais and co-authors [15] found a significantly higher growth rate of large SCAs compared to smaller SCAs of less than 4 cm. Our results are consistent with those of El-Hayek and co-authors [16]. They compared the growth rates of large versus small SCAs, using a 4-cm cutoff and found no sig-

nificant difference between the groups. We believe that our results align with the pathophysiology of typical microcystic SCAs as benign, indolent lesions [17,18].

Due to the inconsistent findings across various studies, to the best of our knowledge, there are currently no universal surgical guidelines for the management of SCAs [3]. The current radiological guidelines from 2017 recommend surgical consultation for symptomatic patients or patients with lesions that are larger than 4 cm [6]. Based on our results, we suggest that future guidelines for SCAs should differentiate between the various types of lesions. More permissive guidelines should be considered for typical microcystic SCAs. In addition, the 4-cm cutoff should be re-evaluated in further studies.

Our study has several limitations. The first is the small sample size of the entire study population and the uneven group sizes, 14 and 21 patients, respectively. This size resulted in low statistical power to detect significant differences between groups. Consequently, the lack of statistical significance observed may be attributed to a type 2 error rather than the true absence of an effect. In addition, due to the small sample size, we were unable to identify a new cutoff size to replace the 4-cm threshold. The small sample size also undermines the external validity of our results. During the data collection, we had to exclude 24 patients due to lack of radiological or clinical follow-up. The exclusion of these patients may have introduced a selection bias. Another limitation of our study is the reliance on radiological diagnosis without pathological confirmation. However, a diagnosis of typical microcystic SCAs can often be made radiologically [19].

CONCLUSIONS

We showed no increased rate of growth in larger SCAs (< 4 cm). In fact, we did not find clinical or radiological differences between the smaller and larger typical SCAs, except for the size. While these findings should be interpreted with caution, our results raise the question whether the radiological guidelines for the management of SCAs should be revised. Larger studies are needed to verify our results.

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