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Tumor growth rate of pancreatic serous cystadenomas: Endosonographic follow-up with volume measurement to predict cyst enlargement

Federico Salom [a, b, *], William Piedra [a], Herbert Burgos [b]

[a] Departamento de Gastroenterología, Hospital México, San José, Costa Rica
[b] Gastroclinica WGO Training Center, Tibás, San José, Costa Rica

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ABSTRACT

Background: Serous cystadenomas are benign lesions of the pancreas. Usually they are diagnosed incidentally on cross-sectional imaging studies. Endosonography is a valuable tool in the diagnosis and follow-up of these cystic lesions. Given its benign nature, surgical resection is advised only in symptomatic patients. The interval and length of surveillance is not well established.
Methods: A retrospective single center study was done. All the patients with a pancreatic serous cystadenoma sent for an endosonographic evaluation, between December 2008 and December 2015 were included. The lesions were follow-up endosonographically at least once, in a 12 months interval. Volume was measured with the formula $\pi/6 \times$ (d1 x d1 x d2). Two groups were evaluated: patients with a volume under 10 mL (Group 1) and those with a volume of 10 mL or more at presentation (Group 2). Growth rate between these two groups was compared.
Results: Thirty-one patients were analyzed, with a mean age of 58.2 years. Patients were mainly women (87%). Twenty-four patients in Group 1 had a mean enlargement of 0.67 ml per year, whereas patients in Group 2 had a mean enlargement of 9.8 ml per year. The growth rate difference between these two groups was statistically significant ($p = 0.0001$).
Conclusion: Asymptomatic patients with pancreatic serous cystadenomas should be follow-up for enlargement. Small volume lesions have a low risk of enlargement compared with high volume and macrocystic serous cystadenomas. Volume at presentation is a feature to analyze when defining surveillance interval.

Introduction

Pancreatic cystic neoplasms are lesions that in recent years are diagnosed more frequently. As a consequence of an increased use of cross-sectional imaging studies (Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) scan), a larger number of patients with asymptomatic pancreatic cysts are diagnosed. The diagnostic prevalence of these lesions is between 1.2% and 19.6% [1]. In autopsies 25% of the pancreas harbor a pancreatic cystic neoplasm [2]. Studies have shown that once a pancreatic cystic neoplasm has been diagnosed, the risk of malignant transformation is 0.24% per year [3]. Only one in every 10000 cystic lesions diagnosed incidentally are invasive neoplasms [4]. Some of these lesions have a higher risk of malignant transformation than others. Since the life expectance of pancreatic cancer at 5 years is between 3% and 16%, finding and treating adequately a potential cancer precursor is crucial.

Many different types of pancreatic cystic neoplasms have been described. Four of them are the most frequently found: serous cystadenomas, mucinous cystadenomas, intraductal papillary mucinous neoplasms (IPMN), and solid pseudopapillary neoplasms. One can classify these lesions as mucinous and non-mucinous cystic neoplasms. Mucinous lesions (mucinous cystadenomas and IPMN) have a higher risk of malignant transformation compared with non-mucinous lesions, such as serous cystadenomas. That is why an adequate classification of each lesion is extremely important.

Thirty percent of all the pancreatic cystic neoplasms are

* Corresponding author. Departamento de Gastroenterología, Hospital México, 1641-2050, San José, Costa Rica.
E-mail address: fsalom@gastrocr.com (F. Salom).

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classified as serous cystadenomas [5]. These lesions are composed of cuboidal epithelium with cells rich in glycogen [6]. These cystic neoplasms are located more frequently in the body and tail of the pancreas. Usually they are solitary round lesions, composed of microcysts (each cysts measuring less than 2 cm in diameter), with a honeycomb pattern or a "cluster of grapes" appearance [7–9]. Most serous cystadenomas are exclusively microcystic lesions. A macrocystic variant is also possible but much less frequent. Four categories of serous cystadenomas have been described: a) Microcystic type, b) Macrocystic type, c) Mixed type (with a combination of microcysts and macrocysts), and d) Solid type; which is very difficult to recognize as a cystic structure by imaging studies [10,11]. Pancreatic serous cystadenomas have a benign behavior and the diagnosis is usually incidental. They are more frequently detected in women, between the sixth and seventh decade [12].

CT Scan and/or MRI are considered the standard procedures for the evaluation of pancreatic cystic neoplasms [1,13,14]. The capability of radiologists to establish an accurate diagnosis based on imaging varies from 23% to 95% [15,16]. To distinguish benign from malignant pancreatic cystic neoplasms, CT scan and MRI have equivalent accuracy [17]. CT Scan evaluation has a diagnostic accuracy of 61.4%, but raises up to 80.5% when CT scan and MRI are combined [18].

Endosonography is a valuable diagnostic tool in the evaluation of pancreatic cystic lesions. Its high frequency modality and the proximity to the pancreas through the stomach and duodenum wall, provides an exceptional image, which allows an adequate classification of the pancreatic cystic lesions [18,19].

The endosonographic image of a serous cystadenoma is usually a polycystic lesion composed of microcysts (cysts measuring less than 2 cm), with a thin wall and thin septa, with no connection with the pancreatic duct. Ten percent of these lesions could have a macrocystic variant. A central calcification is pathognomonic, but present only in 20% of the cases [20].

The diagnostic accuracy of endosonography for pancreatic cystic neoplasms classification based on morphologic evaluation is variable, ranging from 40 to 96% [21,22]. Fine needle aspiration (FNA) of these cystic lesions can provide useful information to distinguish mucinous from non-mucinous cystic pancreatic lesions [23]. It is a low risk procedure, with reports of adverse events in less than 2.5% of the cases [24–26]. FNA is very important for the macrocystic serous cystadenoma subtype, to ensure an adequate differential diagnosis with mucinous cystadenomas [27]. One of the most helpful markers is the measurement of Carcino Embryonic Antigen (CEA). Levels below 5 ng/ml are very specific for the diagnosis of non-mucinous lesions, such as serous cystadenomas [28]. Cytologic evaluation of the cystic fluid in serous cystadenomas has a high specificity (93%) but a very low sensitivity (30–54%) [29]. Usually the small number of cells obtained during FNA of the cystic fluid is the reason for its inadequate sensitivity.

The possibility of malignant transformation of serous cystadenomas is close to 0.1%. Since this risk is unremarkable, surgical resection is advised only in symptomatic patients [8]. Symptoms are uncommon and can include abdominal pain, jaundice and gastrointestinal obstruction. The development of symptoms depends mostly on the size of the lesion [21]. If an asymptomatic pancreatic serous cystadenoma is diagnosed it should be managed conservatively. Surveillance is advised to assess cyst enlargement and predict the risk of developing symptoms [30]. Since pancreatic serous cystadenomas are three-dimensional lesions, we propose that volume rather than diameter should be a more accurate way of measuring enlargement. The objective of this study was to measure cyst enlargement by volume quantification through endosonographic evaluation.

Methods

Institutional ethics research review board approval was obtained for this study. We performed a retrospective single center study at Hospital Mexico in San Jose, Costa Rica. Evaluation of all patients sent for endosonography, due to the existence of a cystic lesion in the pancreas classified as pancreatic serous cystadenoma, between December 2008 and December 2015 was done. To be included, all the patients should have a polycystic lesion either exclusively microcystic, macrocystic or mixed microcystic and macrocysitc, with a carcinoembryonic antigen level in the fluid evaluation of less than 5 ng/ml; have no mural nodules, no communication with pancreatic duct and no duct dilation. All the lesions were follow-up endosonographically at least once, in a 12 months interval by the same endosonographer. Only asymptomatic patients were included, since patients with symptoms were sent for surgery and no follow-up was done.

Volume of the cyst was measured with the formula $\pi/6 \times$ (d1 x d1 x d2) in each procedure. Endosonographic evaluation of cystic lesions is usually done with bidimensional images, in which cyst diameter is usually measured. In this formula d1 and d2 stand for two different diametric measurements. Two groups were evaluated. Those patients with a volume of less than 10 ml and those with a volume of 10 ml or more at presentation. Growth rate measurement between these two groups was compared. Variables were compared using two-sample Student *t*-test. Statistical significance was set at $P = 0.05$.

Results

Demographics

Thirty-one patients were included and follow-up for cystic enlargement, measuring their volume yearly. Mean age was 58.2 years and 87% of the patients were women. A summary of patient's demographics is presented in Table 1.

These cystic lesions were distributed throughout the pancreas, They were found more frequently in the neck (35.5%) and body of the pancreas (29%). Lesions located in the head (22.6%), tail (9.7%) and uncinated process (3.2%) were less frequent. Most of the lesions were microcystic (87%), and only 13% had a macrocystic variant.

Endosonography

Endosonography was done under deep sedation. The patient

Table 1
Patient features.

Features	Total Number	Percentage
Total	**31**	**100.0**
Gender		
Women	27	87.1
Men	4	12.9
Location		
Head	7	22.58
Body	9	29.03
Tail	3	9.68
Neck	11	35.48
Uncinated Process	1	3.23
Type		
Microcystic	27	87.1
Macrocystic	4	12.9

was placed on a left lateral position. An endosonographic evaluation of all the pancreatic gland was done with a linear endosonographic probe. Endosonographic features of the pancreatic cyst were analyzed. All the lesions were policystic lesions with thin septa, and no mural nodules. No communication or dilation of the pancreatic duct were found. The lesions were classified either as microcysitic or macrocystic, all of them having a CEA level below 5 ng/ml in the cystic fluid evaluation. All the FNA's were done with a 22 gauge needle, under direct endosonographic view, with no evidence of vessels in the puncture field. Only one puncture was done in each case. No complications were reported due to the endoscopic ultrasound or the FNA. The patients were follow-up endosonographically in a yearly interval and cystic volumes were measured and compared (Figs. 1 and 2).

Tumor growth

In all cystic lesions, volume was measured with the formula $\pi/6 \times$ (d1 x d1 x d2). The patients were follow-up endosonographically in a yearly interval (range 2–5 years). The mean follow-up period was 2.45 years. The mean volume of the lesions at diagnosis was 7.85 ml, going from 0.3 ml up to 48 ml. The mixture model analysis demonstrated that the slopes were clustered in two groups. Most of the patients were in the slow growing group (25 patients) with a mean growth rate of 0.45 ml per year (range: 0–3.37 ml). There were six patients in the fast growing group, with a mean growth rate of 17.34 ml per year (range 9–30 ml). All of the fast growing group patients had a volume of more than 10 ml at presentation. Patients were divided in two groups: those with a volume of less than 10 ml (Group 1) and those with a volume of 10 ml or more at presentation (Group 2). Twenty-four patients had a volume below 10 ml at the initial evaluation (Group 1). This group had a mean enlargement of 0.67 ml per year. Seventeen of these patients (70%) had no enlargement during surveillance. There were 7 patients in Group 2 with a volume of 10 ml or more at presentation. This group had a significant increase in their volume during surveillance compared with Group 1, with a mean enlargement of 9.8 ml per year. The difference in the pattern of enlargement between the two groups was statistically significant with a $p = 0.0001$. Growth patterns are shown in Fig. 3.

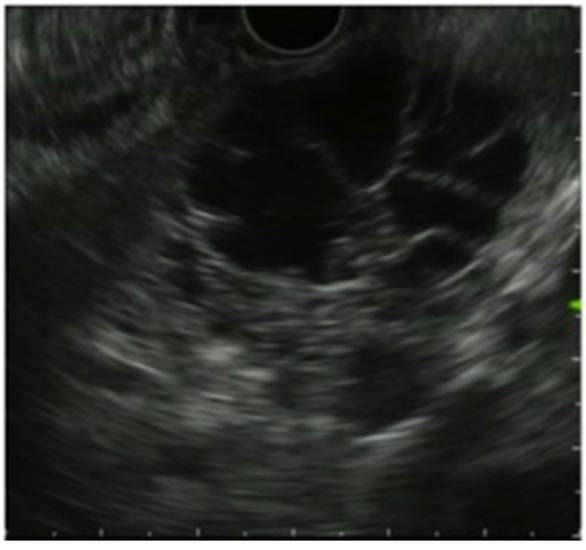

Fig. 1. Pancreatic serous cystadenoma endosonographic features: policystic lesion composed of microcysts, with thin septa and no mural nodules.

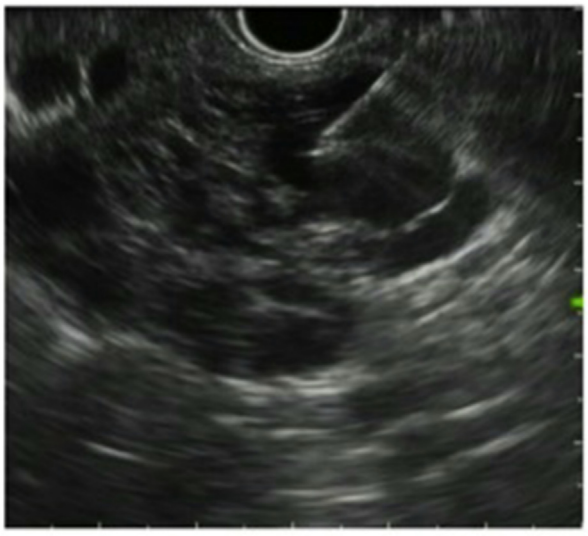

Fig. 2. Pancreatic serous cystadenoma: endosonographic evaluation and FNA for cystic fluid evaluation.

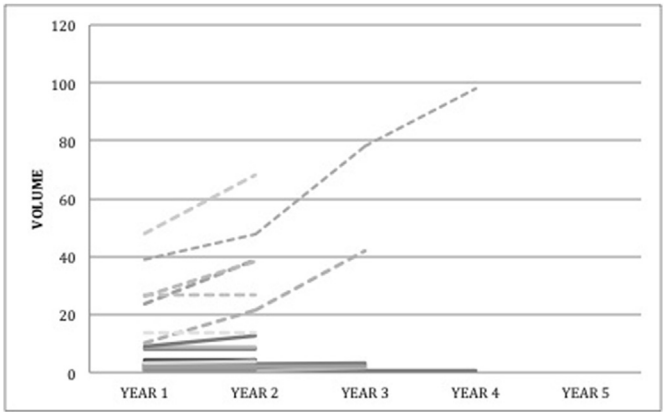

Fig. 3. Pancreatic serous cystadenomas: Follow-up with yearly volume measurement. Continuous lines represent low volume lesions with less that 10 ml at presentation. Dotted lines represent higher volume lesions with 10 or more ml at presentation.

Interestingly all the macrocystic lesions had more than 10 ml of volume at presentation. There were four patients (12.9%) with serous cystadenomas classified as macrocystic lesions. When we analyze the growth pattern of patients with macrocystic lesions compared with microcystic lesions, we found that patients with a macrocystic lesion had a mean annual enlargement of 11.2 ml. Patients with a microcystic lesion (87.1% of the lesions) had a mean annual enlargement of only 1.89 ml per year.

Discussion

Pancreatic serous cystadenomas are benign lesions with a very low risk of malignant transformation. Because of this indolent behavior, surgical resection is advised only in symptomatic patients. Symptoms related to this type of lesion depend mostly on size. Some authors have proposed surgical resection for cysts larger than 4 cm in diameter, since the larger the lesion the greater the risk of presenting symptoms. Nevertheless the risk of pancreatic surgery needs to be analyzed before sending a patient to the operating room. In high volume pancreatic surgery centers,

morbidity and mortality are not negligible. The mortality of this type of surgery, close to 3% and morbidity of 30% are factors to evaluate before proposing surgical resection [3].

In this study the female preponderance of serous cystadenomas has been confirmed. Most of them were diagnosed near the seventh decade, but with a mean age of 58.2 years. The decrease in the age of diagnosis is probably because only asymptomatic patients with an incidental diagnosis were included.

Some studies have been done regarding the natural history and growth pattern of pancreatic serous cystadenomas. El Hayek KM et al. analyzed prospectively the growth pattern of these cystic lesions. A growth pattern that increased at a steady rate over time, with an estimated doubling time of 12 years, regardless of the initial size, was described [30]. Tseng JF et al. analyzed all the serous cystadenomas in their center. One hundred and six patients were evaluated retrospectively in a time-length of 28 years. In their series tumors of less than 4 cm were less likely to be symptomatic than larger lesions (22% vs 72% $P < 0.001$). Mean growth for tumors smaller than 4 cm at presentation was 0.12 cm per year and tumors larger than 4 cm at presentation had a mean growth of 1.98 cm per year ($p = 0.0002$) [31]. Menard A et al. in their series of 31 patients analyzed specifically the microcystic subtype of serous cystadenomas. No difference was found in growth rate regardless of size at presentation [32]. Malleo G et al. estimated an overall mean growth rate of pancreatic serous cystadenoma of 0.28 cm per year. The growth curve evaluation showed a different trend between the first 7 years of follow-up with a growth rate of 0.1 cm per year and the subsequent period with a growth rate of 0.6 cm per year ($p < 0.0001$) [33]. Jais B et al. have the largest survey of pancreatic serous cystadenomas reported so far. In their study 2622 patients were included. The patients that were follow-up had a slow growing behavior with a growth rate of 4 mm per year. Interestingly 57% of the lesions did not grow during the 3 years follow-up [11].

Probably there is more than one variable involved in the risk of enlargement of a pancreatic serous cystadenomas. We have seen that size at presentation is the most frequently analyzed in the different studies that have been done. Since we are evaluating three-dimensional lesions, cystic volume measurement should be analyzed rather than diameter for surveillance of pancreatic cysts enlargement. It has been reported that morphological analysis of pancreatic cystic lesions based on a single diameter measurement is less accurate when compared with volume measurement [34]. Comparison of volume estimation between ultrasound and other cross-sectional imaging studies, have shown similar accuracy when extrapancreatic structures have been analyzed, for example prostate and cervical lesions [35–38].

Considering that we only included asymptomatic patients, most of the lesions were small volume cysts, with a mean volume at presentation of 7.85 ml. In our study small cysts with a volume under 10 ml, practically did not grow during the length of the study. As it has been reported in other series, in our study 70% of these small volume lesions did not grow at all during surveillance. Serous cystadenomas of more than 10 ml in volume had a greater increase in volume compared with lower volume lesions. Interestingly, macrocystic subtype serous cystadenomas, due to the presence of at least one cyst larger than 2 cm, have higher volume lesions and consequently a greater enlargement pattern during surveillance.

In conclusion small volume microcystic lesions have a low risk of enlargement during surveillance and consequently a low risk of producing symptoms. Since most of the pancreatic serous cystadenomas have an indolent behavior, follow-up for enlargement and development of symptoms seems to be the best clinical practice for these lesions. We propose that microcystic lesions with a volume of less than 10 ml at presentation should have a subsequent evaluation at one year. If no growth is identified during this interval, they could continue surveillance less frequently, since the risk of enlargement is low. For cystic lesions with volume greater than 10 ml at diagnosis or macrocystic subtype serous cystadenomas, a more frequent surveillance protocol for cyst enlargement should be proposed.

This study has some limitations including the retrospective evaluation of the information and the absence of histopathologic confirmation, since none of the patients were sent for surgery during the length of the study. Probably a longer period of surveillance would provide more information regarding the natural history and enlargement behavior based on volume measurement of pancreatic serous cystadenomas.

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