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ORIGINAL ARTICLE

# Serous cystic neoplasm of the pancreas: a multinational study of 2622 patients under the auspices of the International Association of Pancreatology and European Pancreatic Club (European Study Group on Cystic Tumors of the Pancreas)

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## ABSTRACT

**Objectives** Serous cystic neoplasm (SCN) is a cystic neoplasm of the pancreas whose natural history is poorly known. The purpose of the study was to attempt to describe the natural history of SCN, including the specific mortality.

**Design** Retrospective multinational study including SCN diagnosed between 1990 and 2014.

**Results** 2622 patients were included. Seventy-four per cent were women, and median age at diagnosis was 58 years (16–99). Patients presented with non-specific abdominal pain (27%), pancreaticobiliary symptoms (9%), diabetes mellitus (5%), other symptoms (4%) and/or were asymptomatic (61%). Fifty-two per cent of patients were operated on during the first year after diagnosis (median size: 40 mm (2–200)), 9% had resection beyond 1 year of follow-up (3 years (1–20), size at diagnosis: 25 mm (4–140)) and 39% had no surgery (3.6 years (1–23), 25.5 mm (1–200)). Surgical indications were (not exclusive) uncertain diagnosis (60%), symptoms (23%), size increase (12%), large size (6%) and adjacent organ compression (5%). In patients followed beyond 1 year (n=1271), size increased in 37% (growth rate: 4 mm/year), was stable in 57% and decreased in 6%. Three serous cystadenocarcinomas were recorded. Postoperative mortality was 0.6% (n=10), and SCN's related mortality was 0.1% (n=1).

## Significance of this study

### What is already known on this subject?

- Serous cystic neoplasm is a cystic neoplasm of the pancreas whose natural history is poorly known.
- Following guidelines, serous cystic neoplasm should be resected in patients with disabling symptoms or when the cyst diagnosis is uncertain.
- Several predictors of complications have been proposed: initial cyst size, growth rate, oligocystic/macrocystic variant, a history of other non-pancreatic malignancies and patients' age.
- There is no consensus about the strategical management between follow-up and surgery.

### What are the new findings?

- Serous cystic neoplasm is seldom symptomatic.
- It has a slow growth and is associated with a very low risk of new onset symptoms.
- Malignant progression is very rare.
- Disease-specific mortality of serous cystic neoplasm is almost nil.

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## Significance of this study

### How might it impact on clinical practice in the foreseeable future?

- It is important to achieve a complete workup including CT scan, MRI and endoscopic ultrasonography in order to get an accurate diagnosis of serous cystic neoplasm.
- Surgical treatment should be proposed in a minority of patients, only for uncertain diagnosis, significant and related symptoms or exceptionally when exists concern with malignancy.
- This study supports initial conservative management for the majority of patients with SCN.

**Conclusions** After a 3-year follow-up, clinical relevant symptoms occurred in a very small proportion of patients and size slowly increased in less than half. Surgical treatment should be proposed only for diagnosis remaining uncertain after complete workup, significant and related symptoms or exceptionally when exists concern with malignancy. This study supports an initial conservative management in the majority of patients with SCN.

**Trial registration number** IRB 00006477.

## INTRODUCTION

Due to the widespread use and increasing advances in cross-sectional imaging, the discovery of asymptomatic cystic tumours of the pancreas has increased. The prevalence is reported to be between 2.6% and 19.6%.[1 2]

Serous cystic neoplasm (SCN) represents 10–16% of cystic pancreatic lesions.[3 4] Mucinous neoplasms (mucinous cystic neoplasm and intraductal papillary mucinous neoplasm (IPMN)) are potentially malignant, whereas SCN is benign in nearly all the cases.[5] However, there is no consensus about the need for surgical resection or surveillance strategies for SCN. Some centres argue that SCN should undergo surgical resection due to the risk of malignant progression, the risk of mechanical complications due to their size and location.[6 7] In addition, a significant number of patients with SCN undergo resection as they are misdiagnosed as pre-malignant or malignant neoplasms.[8] In contrast, other centres, following guidelines, only recommend resection in patients with disabling symptoms due to the SCN or when the cyst diagnosis is uncertain.[5 9]

In order to improve SCN management, predictors of complications have been proposed: initial cyst size, growth rate, oligocystic/macrocystic variant, a history of other non-pancreatic malignancies and patient age.[10–12] The absence of consensus highlights the lack of knowledge about the natural history of SCN with a large number of cases and a sufficient follow-up. The goal of this study was to analyse a very large international cohort of surgically resected and non-resected SCNs in order to describe the natural history. In this setting, the primary objectives were to describe the disease-specific mortality, the growth rate during follow-up and the risk of malignancy.

## PATIENTS AND METHODS

### Study population

We conducted a retrospective, international and multicentre study under the auspices of the International Association of Pancreatology (IAP), the European Pancreatic Club (EPC) and the European Study Group on Cystic Tumors of the Pancreas. Members of the IAP and EPC were contacted via email.

Some of the recruited patients may have been previously published in series from participating centres.[12–14]

### Inclusion criteria

Inclusion criteria were all histologically or radiologically highly suspected SCN, diagnosed between 1990 and 2014.

Radiological and histological diagnostic criteria are detailed below. In cases where the diagnosis remained in doubt, endoscopic ultrasonography (EUS) diagnostic criteria (detailed below), with or without cyst fluid aspiration, were used. SCN data had to be filled between January 2013 and February 2014.

### Exclusion criteria

Patients with Von Hippel–Lindau disease, incomplete records, follow-up <1 year (in non-operative patients) and cases with unclear diagnosis were excluded. Unclear SCN diagnosis was defined as cases in which there was an uncertain radiological or histological diagnosis, or probable misdiagnosis not clarified after email requests for more precise data.

### Data collection and study groups

Data were collected through an online form. Two data points were scheduled: one at the first imaging study (DP1), the second at the last imaging study or at the time of surgical resection or death (DP2). Abdominal CT and/or abdominal MRI and/or EUS were requested at DP1, and also at DP2 for the non-operated patients.

Follow-up period extended between the first (DP1) and the last imaging study or surgery (DP2).

We divided the cohort into three groups. Group 1 (G1) included patients undergoing surgery less than a year after the diagnosis, group 2 (G2) included patients who underwent surgery >1 year after diagnosis and group 3 (G3) included non-operated patients with a follow-up >1 year. The duration of 1 year for groups 2 and 3 was chosen in order to have a minimum follow-up to observe morphological changes.

Demographic (age, gender), clinical (symptoms), radiographic and endoscopic (tumour size, location, cystic pattern, local compression), surgical (type of operation, location, surgical mortality) and pathological (tumour size, lymph node involvement, evidence of local aggressiveness and/or metastasis) data were collected. Surgical morbidity was not recorded since the study was retrospective.

### Radiological and endosonographic features

Four morphological SCN patterns were distinguished: microcystic, macrocystic, mixed microcystic and macrocystic and solid (figure 1).[13] Microcystic pattern was defined as multiple cysts measuring <2 cm separated by thin fibrous septa giving sometimes a honeycomb aspect.[15] Macrocystic type were cysts ≥2 cm.[16] Mixed microcystic and macrocystic type was defined by a combination of a microcystic and macrocystic pattern. Solid SCN was a tumour without cystic lesions distinguishable on cross-sectional imaging. In case of atypical imaging such as an unilocular macrocystic type, the following criteria were requested: polycyclic outlines, thin wall, no tubular structure or communication with pancreatic duct system.[17]

When multiple imaging studies were performed, the largest cyst size was chosen at DP1 and the more recent ones at DP2. Tumour growth was calculated by dividing the difference in size between DP2 and DP1 to the follow-up period (mm/year).

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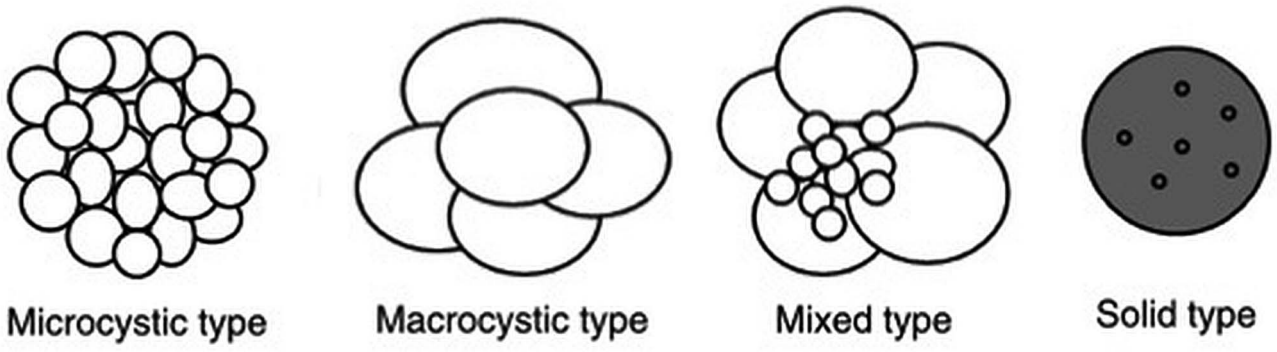


**Figure 1** Four morphological serous cystic neoplasm patterns were distinguished: microcystic, macrocystic, mixed microcystic and macrocystic and solid.[13]

The diagnosis of SCN at EUS was based on the presence of a myriad of microcysts (2 mm or less) separated by thin septa, which sometimes appear as 'layered' and a thin cyst outline wall.[18 19] In the absence of microcystic appearance, a low carcinoembryonic antigen (CEA) level in the cystic fluid was considered specific of SCN.[20] No central reviewing of imaging procedures was performed.

### Pathology

SCNs were histologically defined by the presence of cysts lined by a single, uniform layer of cuboidal, glycogen-rich 'serous cells'.[21]

Malignant SCN was defined by distant metastasis beyond pancreatic and peripancreatic bed.[21]

Considering Khashab *et al*'s[14] definition, we defined locally aggressive tumours as tumours that invaded surrounding structures, vessels and/or peripancreatic lymph nodes without distant metastasis.

No central reviewing of pathological specimen was performed.

### Statistical analysis

Qualitative variables are presented as frequencies (%) and continuous data as median (range) as appropriate. In case of missing data, 'n' indicates the number of patients with available data. Comparisons of qualitative data were performed using the $\chi^2$ or Fisher's test and continuous data were compared using the Mann–Whitney test. To determine whether initial size influenced tumour growth, a correlation of these two parameters was performed using the Spearman's test. To such end, we only took into account the lesions that actually grew. All tests were two sided. A p value $<0.05$ was considered significant. All statistical analyses were performed using SPSS V.19.0 (SPSS for Mac, IBM, Chicago, Illinois, USA).

## RESULTS

### General and imaging characteristics

–In total, 2799 cases were identified. Also, –177 cases were excluded because of incomplete data (n=75), follow-up <1 year for non-operated patients (n=67) and a doubtful diagnosis (n=35). Ultimately, 2622 patients from 23 countries and 71 centres (including 31 surgical centres) were included. Seventy-four per cent of the patients were women, and median age at diagnosis was 58 years (16–99) (table 1). The diagnosis was based on pathological analysis in 1590 cases, highly suspected diagnosis on radiological features in 785 cases and with the help of cyst fluid analysis in 247 cases. The morphological patterns in the whole population were microcystic in 45%, macrocystic in 32%, mixed microcystic and macrocystic in 18% or solid in 5% of cases. In the 785 cases where diagnosis relied only on radiological data, these percentages were respectively microcystic in 55%, macrocystic in 24%, mixed in 19% or solid in 2%. Cystic calcifications were present in 15%. The tumour was located in the head/uncinate process in 40%, in the body in 34% and in the tail in 26% of cases. SCN had a lobulated shape in 58%. Upstream dilated main pancreatic duct was present in 11% of cases.

### Medical or surgical treatment

Among the 2622 patients, 61% underwent surgical resection including 52% within 1 year following diagnosis (G1, n=1351) and 9% after 1 year of follow-up (G2, n=239, median follow-up: 3.0 years (1–20)). Conservative management was undertaken in 39% of the patients (G3, n=1032, median follow-up: 3.6 years (1–23)) (table 1). Sixty-seven per cent of G2+G3 patients (n=850) have been followed between 1 and

**Table 1** Baseline characteristics

| | Overall |
|---|---|
| Sex, n (%) | |
| Male | 683 (26) |
| Female | 1939 (74) |
| Median age at diagnosis, years (range) | 58 (16–99) |
| Symptoms, n (%) | |
| Asymptomatic | 1610 (61) |
| Symptomatic | 1012 (39) |
| Tumour location, n (%) n=2491 | |
| Head/uncinate | 985 (40) |
| Body | 860 (34) |
| Tail | 646 (26) |
| Schematic pattern, n (%) N=2516 | |
| Microcystic | 1127 (45) |
| Macrocystic | 814 (32) |
| Mixed microcystic/macrocystic | 455 (18) |
| Solid | 120 (5) |
| Initial median tumour diameter, mm (range) | 31 (1–238) |
| Management, n (%) | |
| Operated <1 year (G1) | 1351 (52) |
| Operated >1 year (G2) | 239 (9) |
| Non-operated (G3) | 1032 (39) |

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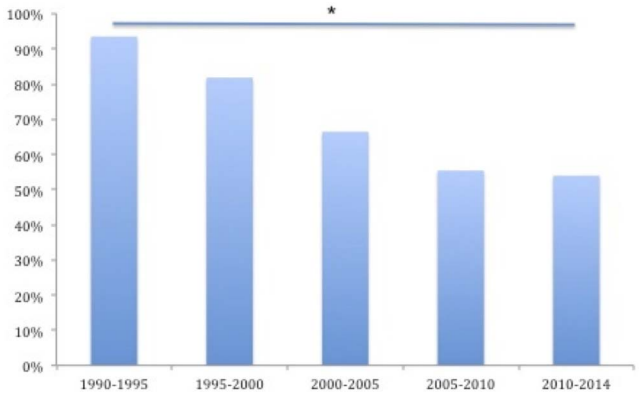


**Figure 2** The resection rate decreased over time from 94% between 1990 and 1995 to 54% between 2010 and 2014 (p<0.01).

5 years, 27% (n=342) between 5 and 10 years, 5% (n=63) between 10 and 15 years and 1.2% (n=16) between 15 and 20 years.

Among the 10 centres that included >40 cases, resection rate ranged from 24% to 93%. The resection rate decreased over time from 94% between 1990 and 1995 to 54% between 2010 and 2014 (p<0.01) (figure 2).

Among the operated patients (G1 and G2; n=1590), indications for surgery (more than one indication was possible) were unclear diagnosis (n=950; 60%), symptoms (n=370; 23%), increasing tumour diameter (n=193; 12%), initial large size (n=97; 6%) and adjacent organ compression (n=82; 5%).

In the group of patients operated for unclear diagnosis (n=951), the preoperative evaluation included CT, MRI and EUS in 13%, CT and MRI in 17%, CT and EUS in 15%, MRI and EUS in 2%, CT alone in 47%, MRI alone in 5% and EUS alone in 1%.

The remaining patients (53%) had only one cross-sectional imaging (CT or MRI or EUS) before surgery. When EUS was performed, fine needle aspiration (FNA) was associated in 30% of cases.

In the group of patients operated for symptoms (n=366), 242 (66%) presented with non-specific symptoms and 124 (34%) with pancreaticobiliary symptoms.

## Symptoms

At diagnosis, patients had non-specific abdominal pain (27%), pancreaticobiliary symptoms (9%), diabetes mellitus (5%), other symptoms (4%; abdominal mass, asthenia, nausea and vomiting) or were asymptomatic (61%). Patients were more frequently symptomatic in G1 compared with G2 and G3 (52% vs 31% and 23%, respectively; p<0.001) (table 2). With increasing cyst size, patients were more frequently symptomatic (including specific and non-specific symptoms) (p<0.001) (figure 3). However, there was no clear size cut-off associated with symptoms.

Among the 1271 G2 and G3 patients, 963 were asymptomatic at DP1. In this group, 104 (11%) became symptomatic at DP2 (non-specific abdominal pain (n=69), pancreaticobiliary symptoms (n=33) and/or diabetes mellitus (n=10)).

**Table 2** Symptoms, initial tumour diameter and tumour growth in operated patients less than a year after the diagnosis (group 1), in operated patients >1 year after diagnosis (group 2) and in non-operated patients (group 3)

| | G1 (n=1351) | G2 (n=239) | G3 (n=1032) | p Value* |
|---|---|---|---|---|
| Symptoms, n (%) | 704 (52)†‡ | 75 (31) | 233 (23) | <0.001 |
| Initial diameter, mm (range) | 40 (2–238)†‡ | 25 (4–140) | 25.5 (1–200) | 0.354 |
| Tumour growth, mm/year (range) | | 4 (0–41.5) | 1 (0–27) | <0.001 |

*Represents intergroup's p value.
†Represents significant (p<0.001) value for comparison between G1 and G2 groups.
‡Represents significant (p<0.05) value for comparison between G1 and G3 groups.

## Tumour size and growth rate

Overall initial median cyst diameter was 31 mm (1–238). The initial diameter was significantly higher in G1 than in G2 (40 mm vs 25 mm; p<0.001), and than in G3 (40 vs 25.5 mm; p<0.05) (table 2). Among the patients who underwent surveillance (G2 and G3; n=1271), 724 (57%) SCNs remained stable in size, 476 (37%) increased in size (tumour growth: 4 mm/year) and 71 (6%) decreased in size, most of the time after EUS FNA. Diameter at DP2 was 40 mm (0–170) and 29 mm (0–240) in G2 and G3, respectively.

Tumour growth was higher in G2 than in G3 (4 vs 1 mm/year; p<0.001). Tumour growth was correlated with initial tumour size (correlation coefficient=0.211; p<0.001) (figure 4). Tumour<4 cm (n=976) had a slower growth compared with those≥4 cm (n=295) (1.25 vs 2.7 mm/year, p=0.002). Tumour growth was not associated with radiological pattern (p=0.89) or age (p=0.08).

## Aggressive behaviour

Three serous cystadenocarcinomas (0.1%) were reported: two patients had liver metastasis (one synchronous, one metachronous) and one had distant hepatic artery lymph nodes metastases. These three patients were symptomatic (non-specific abdominal pain (n=2), jaundice (n=1)). The cystadenocarcinoma and the metastases were surgically resected for each patient. One patient was lost to follow-up after 1 year, one was still alive after 9 years then lost to follow-up. The last patient with lymph node metastases had adjuvant chemotherapy and was still alive at 1 year.

The diameter of serous cystadenocarcinoma was 71, 100 and 170 mm. Among 1590 operated patients, 18 patients with SCN were considered as locally aggressive, including 14 from one centre: invasion of regional organs (n=6), regional lymph node involvement (n=3), peripancreatic vessels (n=8) and perineural area (n=1).

## SCN-specific mortality and operative mortality

Among the 1032 non-operated patients, one died of pneumonia after an endoscopic retrograde cholangiopancreatography indicated for SCN-related jaundice. Disease-specific mortality was 0.1% in G3. If the three patients with malignant SCN were considered to have died, disease-specific mortality would have been 0.4%.

Reported operative mortality was 0.6%. Ten patients died within 30 postoperative days (all but one after 2000) from pneumonia (n=3), septic shock (n=2), colon perforation (n=1), retroperitoneal haemorrhage (n=1), hepatic failure (n=1) and two for unknown reasons. Whipple procedure mortality was 1.5% (7 deaths/461) and left pancreatectomy mortality was 0.2% (2/861). Mortality in G2 was 0.8% and in G1 0.6% (not significant).

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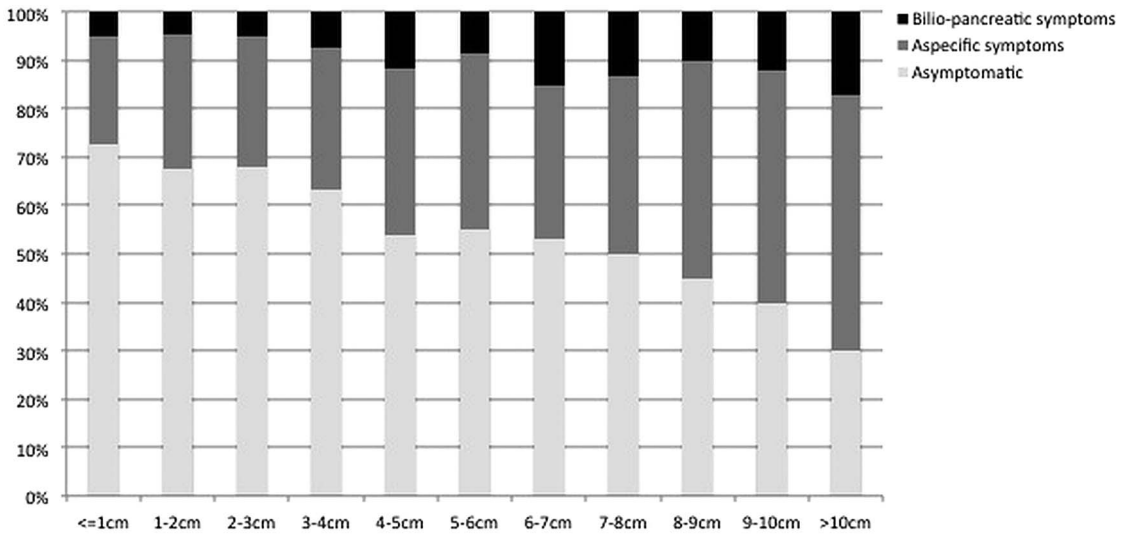


**Figure 3** With increasing cyst size, patients were more frequently symptomatic (including specific and non-specific symptoms) (p<0.001).

## DISCUSSION

This work, performed under the auspices of the IAP and EPC, is the largest cohort of histologically or radiologically proven SCNs. Although the way of recruitment and data records are opened to criticisms, the size of the cohort allows to draw some important conclusions. The main results underscore that SCN are benign in nearly all cases, indolent with slow growth and rarely become symptomatic. SCN-specific mortality is nearly nil.

Currently, the management of SCN remains controversial. The difficulty to have an accurate preoperative diagnosis, the presence of symptoms supposedly related to SCN, the risk of new onset symptoms and the risk of malignant transformation are the major arguments raised for surgical intervention.[6–8] On the other hand, the indolence of the tumour and the significant morbidity and mortality of pancreatic surgery are strong arguments in favour of a conservative attitude.

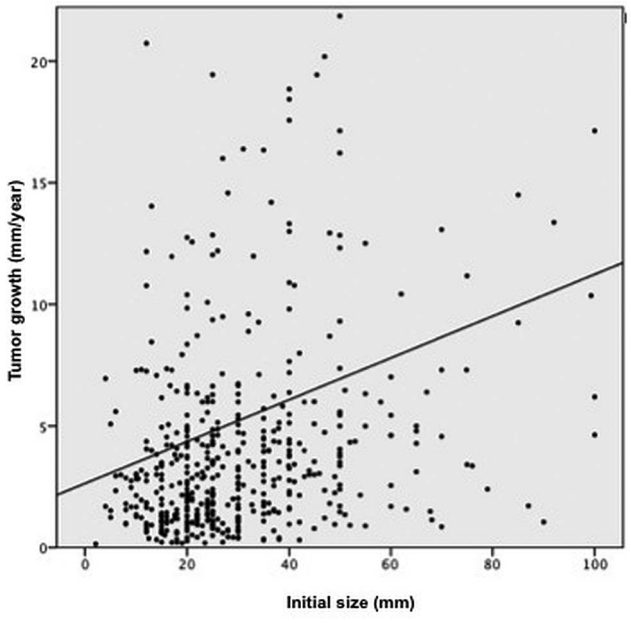


**Figure 4** Tumour growth was higher in G2 than in G3 (4 vs 1 mm/year; p<0.001). Tumour growth was correlated with initial tumour size (correlation coefficient=0.211; p<0.001).

The first and main issue in SCN management is to accurately diagnose them. CT and MRI are the two imaging modalities usually used for the diagnosis of pancreatic cysts. Despite knowledge and technological advances, establishing an accurate diagnostic can be difficult. In this study, the majority of patients were operated on because of diagnostic uncertainty (60%). But only 13% of patients in this group had CT, MRI and EUS performed, while 34% had two imaging studies. It is noticeable that these imaging procedures were not always available at the beginning of recruitment. Blinded studies have shown that diagnostic accuracy by CT and MRI for SCN ranged from 27% to 91%, while accuracy for pancreatic cysts ranged from 43% to 64%.[22–24] When cross-sectional imaging does not allow definitive diagnosis, EUS can provide supplemental information thanks to high-resolution images.[25–27] If a diagnostic doubt remains, the additional benefit of EUS resides with the ability to perform cyst FNA for a fluid analysis.[28] Low CEA levels with different thresholds had an excellent specificity for SCN diagnosis.[20 29 30] However, low cyst fluid CEA have also been reported in IPMNs and in neuroendocrine tumours.[31 32] Moreover, EUS-FNA is not always technically feasible and it can be difficult to obtain sufficient fluid for biochemical analysis.[33] In this study, FNA was performed with EUS in 30% of cases. Nowadays, surgery for uncertain diagnosis when the preoperative diagnosis workup is insufficient does not appear as an acceptable option. If there is no clear diagnosis after a CT and/or MRI, EUS should be performed. And if a doubt still remains, the association with FNA for cyst fluid analysis is necessary if technically feasible. Surgery is indicated if all investigations have been completed and there is still a doubt with a pancreatic neoplasm. The reduction of the resection rate with time underscores the progress in technology and knowledge of imaging semiology. It is likely that molecular genetic analysis of cyst fluid such as the presence of a VHL mutation, vascular endothelial growth factor dosage or confocal laser endomicroscopy could lead to a more accurate diagnosis.[34–36]

Even when an SCN is diagnosed preoperatively, centres have different approaches depending on cultural trends (surgical units vs medical ones), tumour size, presence of symptoms and risk of new onset of symptoms. Several centres select patients

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for surgery considering the tumour size and the growth rates. In a small monocentric series, tumours <4 cm had a slower growth rate than tumours ≥4 cm (1.2 vs 20 mm/year; p=0.0002).[10] Recent studies showed no correlation between tumour size and growth rate.[11 12] In the present study, growth rate was significantly higher for tumours ≥4 cm (2.7 vs 1.25 mm/year). The growth rate interpretation is limited by our short follow-up and the absence of more than one interval imaging. Moreover, this method assumed a linear growth rate instead of a curvilinear growth rate, which can better reflect the reality.[11] We also observed a slight increase of symptom rate in large SCN. The question of whether a large size per se or a slow-growing SCN are an indication for surgery remains open. Unlike a recent study, macrocystic variant and patients' age were not associated with higher growth rate.[12]

Some authors consider symptomatic SCN as an indication for surgery.[5] However, it is important to ensure that the tumour is responsible for the symptoms. In the present study, 27% of patients complained of non-specific abdominal pain. Only 9% of patients presented pancreaticobiliary symptoms directly related to the tumour. The risk of new onset symptoms was low as well, with only 11% of patients becoming symptomatic during follow-up.

The risk of malignant progression influences management. Since 1989, 28 cases of serous cystadenocarcinoma have been reported in the literature.[37] As of now, there is no consensus about the definition of serous cystadenocarcinomas. Considering Bosman *et al*'s[21] definition, malignant SCNs are characterised by distant metastasis beyond pancreatic and peripancreatic bed. Whether locally aggressive SCN defined by invaded surrounding structures should be considered as benign, malignant or intermediate stage still remains in debate.[14] Eighteen cases of locally aggressive tumours were recorded. Of these, 14 were provided from an unique centre. This might be explained by discrepant definition of these stages. It is the reason why we do not draw any conclusion about the prevalence of this entity in the entire cohort.

Three serous cystadenocarcinomas (0.2%) were recorded in the present study. The proportion of serous cystadenocarcinomas was lower than usually described in the literature (around 1–3%).[6 21] Tumour diameter was significantly larger compared with non-malignant group. Serous cystadenocarcinomas seemed to have a low aggressive behaviour with a monitoring up to 9 years. It is much lower than those for branch duct IPMNs for which international experts recommended surveillance in the absence of worrisomes.[38] When balanced with the operative risk of mortality and morbidity, these results suggest that the risk of malignant transformation should not be the sole indication for surgery.

Recently, some authors have advocated early active surgical strategy considering the risk of complications of an asymptomatic SCN and the improvement of pancreatic surgery.[7] This strategy implies the need to evaluate the risk–benefit balance between follow-up and surgery. Within the limits of a short median follow-up, we observed a very low specific mortality and rate of new onset symptoms. Operative mortality was much lower than reported in high-volume centres (around 1–3%) and was probably underestimated in this self-reporting study.[39 40] Moreover, short-term and long-term pancreatic surgical morbidity remains high with pancreatic fistulae, exocrine pancreatic insufficiency and/or diabetes mellitus in around one-third of cases.

Due to the very low rate of new events in patients with SCN, it is difficult to prospectively follow-up patients during a long time. We aimed at recruiting retrospectively a large number of patients from expert centres to answer as far as possible the most critical issues. Imaging studies and pathological slides were not centrally reviewed. We could not make sure that cyst measurements were uniform across all centres. Follow-up was short but similar to the other studies, except one.[12] Study strengths are the very large number of patients that included both operated and non-operated SCNs. If there was any essential missing information or diagnosis doubt, centres were systematically contacted and remaining doubtful cases were excluded.

In conclusion, we describe the natural history and specific mortality of SCNs in a very large cohort of patients from expert centres, with a median 3 years' follow-up in non-operated patients. This study suggests that SCN is almost always a benign and indolent tumour, seldom symptomatic, with slow growth and very low risk of new onset symptoms including malignant progression. Inside this interval of time, disease-specific mortality was almost nil. Surgical treatment should be proposed in a minority of patients, only for uncertain diagnosis remaining after complete workup including CT scan, MRI and EUS, significant and related symptoms or exceptionally when concern with malignancy exists. This study supports initial conservative management for the majority of patients with SCN.

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# Serous cystic neoplasm of the pancreas: a multinational study of 2622 patients under the auspices of the International Association of Pancreatology and European Pancreatic Club (European Study Group on Cystic Tumors of the Pancreas)

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