# Solid pseudopapillary neoplasm of the pancreas: distinct patterns of onset, diagnosis, and prognosis for male versus female patients

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**Background.** Solid pseudopapillary neoplasm of the pancreas is a distinctive pancreatic neoplasm with low metastatic potential. This study examines clinical differences and prognosis between male and female patients.

**Methods.** The medical records of 34 consecutive patients with pancreatic solid pseudopapillary neoplasms between 1990 and 2006 were reviewed. Whenever feasible, organ-preserving operation was performed. Statistical analysis was performed using chi-square and Student t test.

**Results.** There were 27 women (79%) and seven men (21%) with median age of 23 years. Mean diameter of the tumor was 7 cm. Tumor size tended to be smaller in patients treated in more recent years. Conservative surgery was possible in 11 patients including spleen-preserving distal pancreatectomy in 3, central pancreatectomy in 5, and enucleation in 3 patients. Median hospital stay was 11 days, morbidity rate was 62%, including 17 patients with grade A pancreatic fistula, and there was no operative mortality. Mean follow-up time was 84 months. Tumor recurred in 2 patients (6%). Overall late morbidity rate was 12%. At the time of diagnosis, age was ($\overline{x} \pm$ SD) higher among male patients ($25 \pm 2$ years vs $37 \pm 7$ years; $P < .05$) with no difference in tumor size. The neoplasms were more aggressive in male patients; therefore, conservative surgery was less likely. There was no correlation between tumor aggressiveness and age of the patient or size of tumor.

**Conclusion.** This is the first single center study to demonstrate that solid pseudopapillary neoplasms in male patients have distinct patterns of onset and aggressiveness when compared with female patients. Although valid prognostic criteria are still lacking, it appears that male patients may be best treated by more radical operation and should be observed more closely during follow-up. (Surgery 2008;143:29-34.)

Solid pseudopapillary neoplasm of the pancreas is an uncommon but distinct pancreatic neoplasm with low metastatic potential.[1] It accounts for 1-3% of all pancreatic malignancies, while the overall mortality rate of the tumor has been estimated to be around 2%.[2-4] Usually, 90% of patients are females and 85% of them are less than 30 years old with a reported average age of 24 years.[5,6]

In spite of histologic findings of malignancy, few of the neoplasm are locally aggressive with involve-

ment of major organs or blood vessels invasion requiring radical surgery.[7] Some authors report this aggressiveness to be related to the age of the patient.[8]

In contrast to ductal adenocarcinomas, most solid pseudopapillary neoplasms, although often large in size, are usually resectable and complete surgical resection may provide more than 95% cure rate.[1,7] It has been suggested that pathologic features, such as perineural and vascular invasion and an increased mitotic rate, are associated with metastasis and recurrence;[7] however, recurrence and metastasis cannot be excluded even in the absence of these findings, and, therefore, aggressive behavior is sometimes unpredictable.[7,9-11]

The prevalence of solid pseudopapillary neoplasm among women at the beginning of the reproductive period may suggest that it is a sex

hormone-dependent neoplasm. For this reason, the expression of sex hormone receptors is controversial. Progesterone receptors have been reported as positive in more than 80% of these patients, whereas estrogen receptors were usually negative.[12] A recent report from Geers et al[13] documented positive estrogen receptor using a refined technique in exploring the beta subtype of estrogen receptors.

Interestingly, we have noticed a high incidence among male patients in our series. This finding allowed us to perform a detailed analysis of clinical characteristics and prognosis of female and male patients. To our knowledge, this is the first study to analyze clinical differences and prognosis between male and female patients.

## PATIENTS AND METHODS

Thirty-four consecutive patients with solid pseudopapillary neoplasms of the pancreas between 1990 and December 2005 were studied. All specimens were reviewed by a senior pathologist, and only patients with a final diagnosis of solid pseudopapillary neoplasm were included. In this process, two patients with initial diagnosis of solid pseudopapillary neoplasm were excluded from the present analysis. The database included sex, location, size, portal vein invasion, metastasis, operative data, postoperative complications, and late results.

Whenever feasible, an organ-preserving operation was performed. For small tumors distant from the main pancreatic duct, enucleation was elected. For tumors located in the neck of the pancreas, central pancreatectomy with distal pancreatojejunostomy was performed. For tumors located in the body or tail of the pancreas, a spleen-preserving distal pancreatectomy was the procedure of choice.

**Genetic study.** It was possible to perform genetic analysis in 8 patients from this series. Genomic DNA was extracted from paraffin-embedded archival specimens and evaluated for both K-ras oncogene and p53 tumor-supressor gene. The method of Polymerase chain reaction-restriction fragment length polymorphism analysis was used for K-ras analysis and polymerase chain reaction-single stranded conformational polymorphism for p53 (exons 5 to 8). PCR products were eletrophoresed and analyzed by a photodocumentation system. Tissue sections were stained by the Feulgen method and assessed by image analysis using the WING software for the nuclear DNA-ploidy grade (version 1.1, Mcom Informátia, São Paulo).

**Immunohistochemical study.** Immunohistochemical analysis was performed in 16 patients in the present series. The technique used for this study was heat-induced-epitope retrieval and antigen retrieval. The samples were then exposed to the following antibodies: cytokeratin 7,8,14,19,20; cytokeratin high molecular weight 68,58,56,56.5,50 Kd; cytokeratin AE!, CA19-9, Chromogranin A and alfa amylase.

**Statistical analysis.** Summary data are formatted as mean ± standard deviation (SD) or number of patients (percentage of population). Statistical analysis was performed using chi-square or Fisher exact tests for categorical variables. For continuous variables, Student t test was used. All tests were 2-sided with $P < .05$ considered significant. Calculations and statistical analyses were completed using Prism 4 software (Graph Pad, San Diego, Ca).

## RESULTS

There were 27 women (79%) and seven men (21%) with a median age of 23 years (range, 10-72 years). The oldest patient in this series was a man receiving hormonal therapy for prostate cancer. Twenty-six (84%) were Caucasian. The neoplasm was single in all patients, and the most common localization was the body or tail (61%). Mean diameter of the tumor was 7 cm (1.5–15 cm).

The main clinical findings were abdominal pain (73%), nausea and vomiting (32%), and weight loss (18%). Seven patients (21%) were asymptomatic with the diagnosis made by an incidental finding on routine examination.

**Radiologic findings.** Computed tomography (CT) and/or magnetic resonance imaging (MRI) showed the typical features of solid pseudopapillary neoplasm in 79% of the patients. Usually, the tumor appeared as well-circumscribed lesions with a mixed cystic and solid component but was almost entirely solid or else cystic with thick walls (Fig 1).

**Surgical treatment.** Conservative resection was possible in 11 patients, including a spleen-preserving distal pancreatectomy in 3, a central pancreatectomy in 5, and enucleation in 3 patients. Distal pancreatectomy was performed in 12 patients and pancreaticoduodenectomy in 11. Five patients had spleno-mesenteric portal axis involvement and underwent venous resection and reconstruction.

Median hospital stay was 11 days (range, 7-18 days). There was no operative mortality. Surgical margins were free in all patients. Twenty-one patients developed at least 1 complication with operative morbidity rate of 62%. According to the International Study Group on Pancreatic Fistula,[14] 17 patients developed postoperative pancreatic fistula grade A, one patient grade B, and one patient grade C. Infectious complications occurred in 3 patients and intestinal obstruction in 2. Reopera-
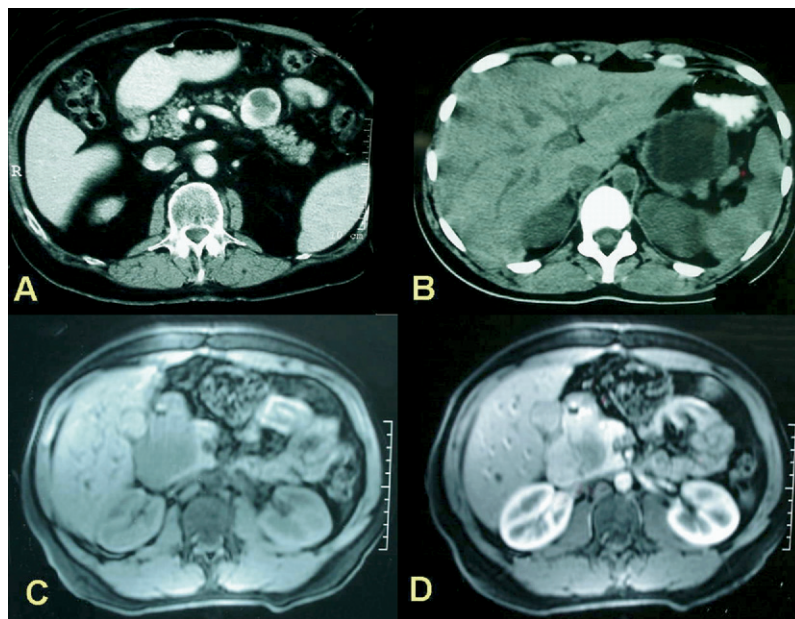
**Fig 1.** CT and MRI findings of a solid pseudopapillary neoplasm of the pancreas. (**A**) A well-circumscribed neoplasm with a mixed cystic and solid component. (**B**) A large neoplasm with predominant cystic component with thick wall. (**C**) MRI shows an almost entirely solid neoplasm. (**D**) MRI shows venous involvement by the neoplasm.

tion was necessary in two patients due to pancreatic abscess and intestinal obstruction, respectively.

One patient developed a persistent pancreatic fistula that required operative intervention during late follow-up. Mean follow-up time was 84 months (range, 3-170 months). Two patients developed recurrent disease. One patient developed an unresectable, local recurrence after duodenopancreatectomy and received systemic chemotherapy with combination of 5-FU and cisplatin, and was still alive 39 months after initial operation. The second patient, who had undergone subtotal pancreatectomy and resection of the portal vein, developed disseminated liver metastases and died of the disease 24 months after the initial procedure.

Overall late morbidity rate was 12%, with 2 patients developing peptic ulcer, 1 insulin-dependent diabetes, and 1 with disease recurrence who had 1 episode of upper gastrointestinal hemorrhage.

Looking further into our results, we found that 21% of our patients were males. At the time of diagnosis, mean age was older among male patients (37 vs 26; $P < .05$). In spite of this fact, the tumor size did not differ between sexes. There were no statistical difference among male and female patients regarding preoperative symptoms, radiologic findings, or tumor location (Table I). The neoplasm was an incidental finding in 5 women and 2 men. The neoplasms were more aggressive (greater

**Table I.** Patterns among male and female patients

| Clinicopathologic features | Female (n=27) | Male (n=7) | Total (n=34) | P value |
|---|---|---|---|---|
| Age (mean ± SD) | 25 ± 2.1 | 37 ± 7.4 | 28 ± 13 | <.05 |
| Tumor size (mean ± SD) | 7.3 ± 0.7 | 6.7 ± 1.7 | 7.2 ± 0.6 | NS |
| Head tumor | 11 | 3 | 14 | NS |
| Incidental finding | 5 | 2 | 7 | NS |
| Portal vein invasion | 3 | 3 | 6 | <.05 |
| Conservative surgery | 11 | 0 | 11 | <.05 |
| Tumor recurrence | 1 | 1 | 2 | NS |

incidence of portal vein involvement and/or development of metastases) in male patients; therefore, conservative surgery was less likely to be performed in the male patients. There was no correlation between tumor aggressiveness, defined by portal vein involvement and/or neoplasm recurrence, and age or size of tumor.

Tumor size tended to be smaller at the time of diagnosis in patients treated after the year 2000 (Table II). Other patient characteristics such as

**Table II.** Correlation between date of surgery and clinicopathologic features of patients

| Clinicopathologic features | Before 2000 (n=16) | After 2000 (n=18) | P value |
|---|---|---|---|
| Age (mean ± SD) | 24 ± 2.1 | 31 ± 3.9 | NS |
| Tumor Size (mean ± SD) | 9.2 ± 0.9 | 5.5 ± 0.7 | <.005 |
| Male Gender | 2 | 5 | NS |
| Conservative Surgery | 5 | 6 | NS |



**Fig 2.** Macroscopic features of solid pseudopapillary neoplasm of the pancreas. (**A**) Well-circumscribed neoplasm with predominant cystic (gelatinous content) and minimal solid component. (**B**) Well-circumscribed neoplasm with predominance of solid component and cystic cavity with clear liquid. (**C**) Well-defined neoplasm entirely cystic (gelatinous content). **D,** Invasive neoplasm with entirely solid component.

age, sex, and possibility of conservative surgery did not differ before and after 2000.

## PATHOLOGIC FINDINGS

**Macroscopic appearance.** Grossly, most neoplasms were well-circumscribed tumors with both cystic and solid components. The neoplasm ranged from entirely solid to entirely cystic. The cystic component had gelatinous or clear liquid content (Fig 2).
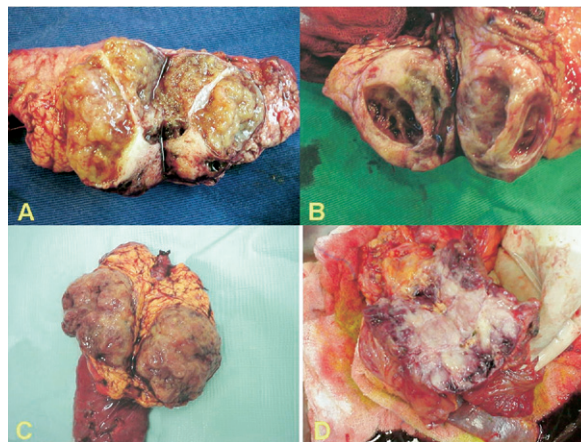
**Microscopic appearance.** Histologically, solid pseudopapillary neoplasm of the pancreas presented as small and uniform tumor cells with round nuclei with both solid and cystic growth patterns. Typical features included a pseudopapillary pattern with fibrovascular stalks (Fig 3). Perineural invasion was present in 5 patients, vascular invasion in 7, and extension into peripancreatic tissue in 1. No lymphatic invasion was present and no lymph nodes metastases were found. In 2 patients with recurrence, microscopic vascular invasion was demonstrated. One patient with extension into peripancreatic tissue developed local recurrence.

**Genetic study.** We detected a mutation in K-ras oncogene in only 1 patient (a male). There were no mutations in exon 5, 6, 7, and 8 of p53 gene. All analyses had normal DNA content (diploid). There was no correlation between K-ras mutation and development of metastasis.

**Immunohistochemical study.** Neoplastic cells displayed a wide spectrum of immunohistochemical markers. In most patients, acinar markers (ie, CK8 and amylase) were intermingled with markers, such as CA19-9, CK7, CK14, and CK19. CK 20 was found in 7 patients (44%), most often displayed by a small amount of cells. Chromogranin A was found in only 3 patients and, even then, restricted to scarce cells.

## DISCUSSION

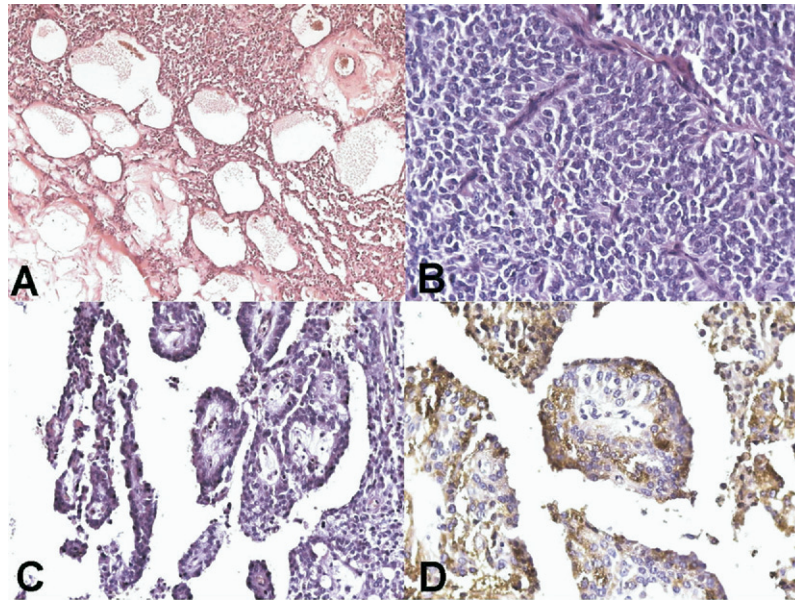Solid pseudopapillary neoplasms of pancreas are uncommon neoplasms with a low malignant poten-

tial, and resection remains the main therapeutic option.[1,6] The overall mortality of the disease has been estimated to be about 2%.[1,13] Recurrence rate is estimated in 10-15% of patients after resection.[13]

Advances in imaging modalities have led to more accuracy in the diagnosis of this neoplasm.[3,15] Indeed, the neoplasms detected after the year 2000 were smaller (P<.005) than those diagnosed before 2000. This finding is related clearly to the improvement in the imaging modalities and widespread use of CT and MRI in our department after 2000. Moreover, almost 80% of our patients had typical features on CT.

Solid pseudopapillary neoplasms have characteristic pathologic features. On gross analysis, they have a typical gelatinous content mixed with a solid component. Sometimes the neoplasm can be entirely cystic or solid. Histopathologically, these neoplasms are composed of small and uniform tumor cells with round nuclei and eosinophilic cytoplasm, and may have a typical pseudopapillary pattern with fibrovascular stalks. When entirely solid, it may be difficult to distinguish from acinar adenocarcinoma and islet cell neoplasm. Immunohistochemistry and a mutation in beta catenin gene have been used for differential diagnosis.[11,16]

After publication of the first cases in Brazil[17] in 1993, most gastroenterologists, radiologists, and pathologists became aware of this relatively rare neoplasm; and our department, a tertiary referral center, received several new patients for evaluation

**Fig 3.** Microscopic features of solid pseudopapillary neoplasm of the pancreas. (**A**) Small and uniform tumor cells with predominant cystic pattern. (**B**) Small and uniform tumor cells with round nuclei and eosinophilic cytoplasm demonstrating a solid growth pattern (HE). (**C**) Tumor cells have a pseudopapillary pattern with fibrovascular stalks (HE). (**D**) Immunohistochemical staining for alpha-1-antitrypsin of the pancreatic tumor. Almost all tumor cells are stained positively, and the reaction is strong in the cytoplasm.

and confirmation of the diagnosis. In this setting, almost 80% of patients had typical features on CT and/or MRI. Preoperative diagnosis was especially difficult in small tumors and in those without cystic component. This diagnosis should always be suspected in young women with a solid and/or cystic pancreatic mass.[11]

Despite the large tumor size or vascular involvement at the time of diagnosis, operative resection is usually possible and curative. Therefore, complete aggressive resection is the treatment of choice for these neoplasms even in the presence of metastases. Resection of distant metastases should be performed at the time of primary resection or even for recurrences. These neoplasms are usually large but rarely have local extrapancreatic invasion into adjacent organs, as occurred in only 1 patient of the present series. In this situation, the surgeon should always aim for complete, en bloc resection including adjacent structures, preferably with microscopically clear margins. Extensive lymphadenectomy is not necessary because none of the patients in this series had lymph node metastases. The rarity of nodal metastases is consistent with other reports.[18] In our series of 34 patients, 6 underwent portal vein resection to obtain free margins. This aggressive approach is supported by the present series because all but 2 patients were alive and disease-free at long-term follow-up even after ex-

tended resections. Although 1 patient of the present series received systemic chemotherapy with 5FU and cisplatin, there are no reliable data on adjuvant or neoadjuvant therapy for this low-grade malignancy.[11,19]

This neoplasm shows clear female predilection with very few reported cases in male patients. In our series, we found a greater proportion of male patients when compared to other reports.[6,20,21] This fact allowed us to compare tumor characteristics such as size and aggressiveness with the sex of the patient. The mean age of the male patients was greater than the female patients, but tumor size was similar. This observation suggests that the onset, not the diagnosis, occurs later in time among male patients. Tumor aggressiveness was more marked among the male sex and portal vein invasion was more frequent in those patients. When we compare age and aggressiveness, we did not find any correlation even when we stratified the patients under and over 30 years old.[8] Conservative, organ-preserving surgery was possible in 32% of patients; none of them in male patients. Recurrence occurred in only 2 patients and does not allow us to draw any conclusions.

These differences in incidence among males and females stimulated studies of sex hormones receptors.[5,12,21] Because of conflicting results of steroid receptor analysis, it seems that sex hormones

may play an important role; however, it is not clear whether they influence growth of the neoplasm or its pathogenesis.[5] Interestingly, the oldest patient of this series was a man who received hormonal therapy for prostate cancer.

In collective reviews, solid pseudopapillary neoplasms of the pancreas arising in older patients and in males are more likely to behave aggressively.[20] Our report is the first large enough single center study to be able to demonstrate that solid pseudopapillary neoplasms in male patients have distinct patterns of onset and aggressiveness when compared with female patients. The reasons for more aggressive behavior in male patients are not clear. The only difference is that male patients are older than females, but the clinical presentation (tumor location, incidental finding, and symptoms) were the same; the reason is not due to late presentation or delayed diagnosis because tumor size was equivalent or even smaller in male patients.

Although valid prognostic criteria are still lacking and the number of patients is not enough to draw any definitive conclusion, male patients with solid pseudopapillary neoplasms of pancreas may be best treated by a more radical resection, and should be observed closely during follow-up.

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