**Name of Journal:** *World Journal of Hepatology*

**Manuscript NO:** 71353

**Manuscript Type:** LETTER TO THE EDITOR

**Current highlights on solid pseudopapillary neoplasm of the pancreas**

Sibio S *et al*. Solid pseudopapillary neoplasm of the pancreas

Simone Sibio, Sara Di Carlo

**Simone Sibio,** Department of Surgery Pietro Valdoni, Sapienza University of Rome, Umberto I Hospital, Rome 00161, Italy

**Sara Di Carlo,** Minimally Invasive Surgery Unit, Tor Vergata Hospital, Tor Vergata University of Rome, Rome 00133, Italy

**Author contributions:** Both Sibio S and Di Carlo S contributed equally in revising current literature, writing the manuscript, and reviewing the drafts.

**Corresponding author: Simone Sibio, MD, PhD, Associate Professor, Surgical Oncologist,** Department of Surgery Pietro Valdoni, Sapienza University of Rome, Umberto I Hospital, Viale del Policlinico 155, Rome 00161, Italy. simone.sibio@uniroma1.it

**Received:** September 4, 2021

**Revised:** October 25, 2021

**Accepted: January 5, 2022**

**Published online:**

**Abstract**

Solid pseudopapillary neoplasm of the pancreas is a low-grade malignant tumor that predominantly affects young women in their third and fourth decade. Etiology and risk factors are unknown. Clinical symptoms are aspecific and most commonly due to mass effect. Diagnosis is made by computed tomography scan or magnetic resonance imaging and histological characterization is obtained by endoscopic ultrasound-guided fine needle biopsy. Microscopically, these lesions are composed by both solid and pseudopapillary structures with necrotic and hemorrhagic areas. Occasionally, the biological behavior is aggressive with tumor recurrence and distant metastasis. Usually, curative R0 surgical resection is the best option able to provide long term survival even in advanced disease. Unresectable disease is the main predictor of poor prognosis. Chemotherapy and radiotherapy regimens are not well standardized. However, they could be effective in reducing tumor size as neoadjuvant treatment or disease control in palliative setting. Although complete surgical resection provides a cure rate of > 95%, considering young age of the patients and morbidity associated to pancreatic surgery, further studies are needed to better investigate risk factors and responsiveness to hormones in order to allow early diagnosis and follow up strategies that could avoid unnecessary surgery in less aggressive disease.

**Key Words:** Pseudopapillary neoplasm; Pancreatic tumor; Pancreaticoduodenectomy; Distal pancreatectomy; Pancreas; Surgery

Sibio S, Di Carlo S. Current highlights on solid pseudopapillary neoplasm of the pancreas. *World J Hepatol* 2022; In press

**Core Tip:** This letter aims to underline the utmost importance of early diagnosis and standardization of treatment for a subset of rare pancreatic malignant tumors that affect young women and have good prognosis when curative surgery is performed. However, little is known about clinical behavior and hormonal responsiveness of such diseases and treatment option availability is still scarce for advanced, recurrent and metastatic disease so further investigation is claimed.

**TO THE EDITOR**

We read with great interest the review written by Omiyale[1] which outlines the clinical and pathological features of solid pseudopapillary neoplasm of the pancreas (SPN) including the epidemiology, molecular pathology, cytology, differential diagnosis, treatment and prognosis.

As already reported by the aforementioned author, this is a rare tumor of uncertain histogenesis, known with several names or as Frantz tumor (after the name of who first described it) which accounts for 0.3% to 2.7% of all pancreatic neoplasms[2].The author underlines the predominant incidence rate in young women.

Available data on this tumor behavior and prognosis are scarce and reported experiences are based on small number of patients or single case reports[3-7] even in high volume referral centers for pancreatic diseases. Nevertheless, no certain risk factors nor relationships with functional endocrine syndromes have been identified. SPN shows a bimodal incidence in women with two peaks at 28 years and 64 years and a unimodal behavior in men at 64 years[8]. Furthermore, recent studies described larger masses and more aggressive disease in men and post-menopausal women, suggesting an estrogen dependent behavior of these tumors[9,10]. These findings deserve further investigation in order to find out other possible non-surgical treatment options. It is very interesting to highlight that SPN are low-grade malignant tumors with an excellent overall prognosis and a curative rate of > 95% following complete surgical resection. It is worth emphasizing that although 10% to 15% of SPN have an aggressive behavior, the disease-free survival and overall survival are much better compared to other pancreatic tumors as long as R0 resection is achieved. Hao *et al*[11] in their review and metanalysis on a sample of 59 patients with aggressive SPN (one of the most consistent experiences available in literature) described a 5-year disease-free survival rate of 26.8% and a 5- and 10-year overall survival rates of 71.1% and 65.5%, respectively, with a recurrence or metastatic rate of up to 69.5%. This leads to the conclusion that about one third of patients affected by aggressive SPN will die of this disease. These consistent rates emphasize the outstanding importance of standardization of diagnostic tools and treatment procedures in order to guarantee early diagnosis and best therapy options to this small but challenging subset of patients[11]. Since the disease is often asymptomatic and symptoms are aspecific (mainly abdominal pain and distension) due to mass compression, the identification of homogeneous parameters able to predict an aggressive behavior is one of the major concerns in all the published studies. In fact, as reported by the author, diagnosis is mainly accidental and relies upon computed tomography (CT) scan and endoscopic ultrasound with fine needle biopsy for histological characterization. Often, SPN appears as a large (mean size 7.2 cm)[4] and heterogeneous mass (composed by both solid and cystic portions with fibrous septs, necrotic and hemorrhagic areas). A differential diagnosis of other exocrine or neuroendocrine pancreatic tumors can be challenging but crucial given the differences in clinical and prognostic behavior as well as treatment options. The tail of the pancreas seems to be the most frequent site of presentation although bifocal lesions have been sometimes reported. Based on these findings, Flores *et al*[8] proposed to classify SPN as follows: Unifocal SPN, referred to single lesions, bifocal SPN when there are two lesions and multifocal SPN when they are three[8].

Some authors emphasized the role of positron emission tomography-CT scan to better predict the aggressive pattern: An elevated standard uptake value seems to be correlated to higher Ki-67 expression (> 3%)[12,13] that is sometimes reported to be a sign of aggressiveness[14,15]. However, while the role of aberrant Beta catenin expression is well known, the real prognostic meaning of Ki-67 expression is still not confirmed by the literature[16].

Histogenesis remains unclear and, although no specific immunochemistry pattern has been identified, most lesions show loss of positivity for E-cadherin and positivity for β-catenin, vimentin, alpha-1-antitrypsin, alpha-1-antitrypsin, CD10, CD117 and progesterone receptors. These characteristics may be added to the clinical, imaging and histological findings to provide diagnosis[8].

Curative resection, as conservative as possible, with both open or laparoscopic approach, is the best treatment option[17-19] providing long term overall and disease-free survival even in node positive patients[20]. Surgical planning is crucial and the classification proposed by Flores *et al*[8] could be useful in this matter[8].

Although overall and disease-free survival is good even in locally advanced and metastatic patients after curative (*i.e.* R0) resection, unresectable disease remain the most important predictor of poor survival in all experiences[11]. Given the low-grade malignancy of these tumors and the prognostic efficacy of surgery, non-surgical therapies have been scarcely investigated and no standardized protocol exists for this subset of patients. Some studies suggested the use of various drugs, in monotherapy or combinations, such as cisplatin, 5-fluorouracil, gemcitabine with uncertain results in recurrent, unresectable or metastatic disease[21,22]. Radiotherapy has been reported to reduce lesion size in little case series[21,23,24]. Despite this evidence, no standardized chemotherapy or radiotherapy regimen has been identified for unresectable, metastatic or recurrent patients. From this point of view, investigation into the possible estrogen-depending behavior of SPNs could perhaps open the way to new non-surgical treatment strategies.

Finally, the author reported a cure rate of > 95% following curative resection for these tumors even for advanced, recurrent and metastatic disease. However, since some other experiences described worsen overall and have a low disease-free survival and high recurrence rates[10], considering the young age of the patients and the relevant morbidity associated to pancreatic surgery, we strongly think that further studies are needed to better understand etiology, risk factors and hormonal relationships of this disease. This could improve early diagnosis, standardization of medical regimens thus limiting treatment invasiveness and it will help to identify patients with less aggressive disease who could benefit just from a strict follow up.

**REFERENCES**

1 **Omiyale AO**. Solid pseudopapillary neoplasm of the pancreas. *World J Hepatol* 2021; **13**: 896-903 [PMID: 34552696 DOI: 10.4254/wjh.v13.i8.896]

2 **Chen H**, Huang Y, Yang N, Yan W, Yang R, Zhang S, Yang P, Li N, Feng Z. Solid-Pseudopapillary Neoplasm of the Pancreas: A 63-Case Analysis of Clinicopathologic and Immunohistochemical Features and Risk Factors of Malignancy. *Cancer Manag Res* 2021; **13**: 3335-3343 [PMID: 33883945 DOI: 10.2147/CMAR.S304981]

3 **Deniz K**, Arıkan TB, Başkol M, Karahan Öİ. Solid Pseudopapillary Neoplasm of the Pancreas. *J Gastrointest Surg* 2021; **25**: 322-324 [PMID: 32410181 DOI: 10.1007/s11605-020-04644-0]

4 **Farhat W**, Ammar H, Amine Said M, Mizouni A, Bouazzi A, Abdessaied N, Ben Mabrouk M, Ben Ali A. Solid pseudopapillary neoplasm of the pancreas: a report of 10 cases and literature review. *ANZ J Surg* 2020; **90**: 1683-1688 [PMID: 31989788 DOI: 10.1111/ans.15701]

5 **Lubezky N**, Papoulas M, Lessing Y, Gitstein G, Brazowski E, Nachmany I, Lahat G, Goykhman Y, Ben-Yehuda A, Nakache R, Klausner JM. Solid pseudopapillary neoplasm of the pancreas: Management and long-term outcome. *Eur J Surg Oncol* 2017; **43**: 1056-1060 [PMID: 28238521 DOI: 10.1016/j.ejso.2017.02.001]

6 **Antoniou EA**, Damaskos C, Garmpis N, Salakos C, Margonis GA, Kontzoglou K, Lahanis S, Spartalis E, Patsouras D, Kykalos S, Garmpi A, Andreatos N, Pawlik TM, Kouraklis G. Solid Pseudopapillary Tumor of the Pancreas: A Single-center Experience and Review of the Literature. *In Vivo* 2017; **31**: 501-510 [PMID: 28652415 DOI: 10.21873/invivo.11089]

7 **Torres OJM**, Rezende MB, Waechter FL, Neiva RF, Moraes-Junior JMA, Torres CCS, Fernandes ESM. PANCREATODUODENECTOMY FOR SOLID PSEUDOPAPILLARY TUMOR OF THE PANCREAS: A MULTI-INSTITUTION STUDY. *Arq Bras Cir Dig* 2019; **32**: e1442 [PMID: 31460602 DOI: 10.1590/0102-672020190001e1442]

8 **Flores RL**, Rossi R, Castiblanco A, Gallardo A, Schiappacasse G. Solid bifocal pseudopapillary neoplasm of the pancreas: A case report. *Int J Surg Case Rep* 2021; **84**: 106131 [PMID: 34182434 DOI: 10.1016/j.ijscr.2021.106131]

9 **Kotecha K**, Pandya A, Gill AJ, Mittal A, Samra J. Pancreatic solid pseudopapillary neoplasm: a single-institution study. *ANZ J Surg* 2021; **91**: 2453-2458 [PMID: 34427035 DOI: 10.1111/ans.17142]

10 **Wu J**, Mao Y, Jiang Y, Song Y, Yu P, Sun S, Li S. Sex differences in solid pseudopapillary neoplasm of the pancreas: A population-based study. *Cancer Med* 2020; **9**: 6030-6041 [PMID: 32578384 DOI: 10.1002/cam4.3180]

11 **Hao EIU**, Hwang HK, Yoon DS, Lee WJ, Kang CM. Aggressiveness of solid pseudopapillary neoplasm of the pancreas: A literature review and meta-analysis. *Medicine (Baltimore)* 2018; **97**: e13147 [PMID: 30544374 DOI: 10.1097/MD.0000000000013147]

12 **Kim JS**, Hao EI, Rho SY, Hwang HK, Lee WJ, Yoon DS, Kang CM. Clinical Pattern of Preoperative Positron Emission Tomography/Computed Tomography (PET/CT) Can Predict the Aggressive Behavior of Resected Solid Pseudopapillary Neoplasm of the Pancreas. *Cancers (Basel)* 2021; **13** [PMID: 33925678 DOI: 10.3390/cancers13092119]

13 **Park M**, Hwang HK, Yun M, Lee WJ, Kim H, Kang CM. Metabolic characteristics of solid pseudopapillary neoplasms of the pancreas: their relationships with high intensity 18F-FDG PET images. *Oncotarget* 2018; **9**: 12009-12019 [PMID: 29552289 DOI: 10.18632/oncotarget.23846]

14 **Watanabe Y**, Okamoto K, Okada K, Aikawa M, Koyama I, Yamaguchi H. A case of aggressive solid pseudopapillary neoplasm: Comparison of clinical and pathologic features with non-aggressive cases. *Pathol Int* 2017; **67**: 202-207 [PMID: 28208222 DOI: 10.1111/pin.12516]

15 **Reindl BA**, Lynch DW, Jassim AD. Aggressive variant of a solid pseudopapillary neoplasm: a case report and literature review. *Arch Pathol Lab Med* 2014; **138**: 974-978 [PMID: 24978926 DOI: 10.5858/arpa.2013-0184-CR]

16 **Tang LH**, Aydin H, Brennan MF, Klimstra DS. Clinically aggressive solid pseudopapillary tumors of the pancreas: a report of two cases with components of undifferentiated carcinoma and a comparative clinicopathologic analysis of 34 conventional cases. *Am J Surg Pathol* 2005; **29**: 512-519 [PMID: 15767807 DOI: 10.1097/01.pas.0000155159.28530.88]

17 **Torres OJ**, Moraes Junior JM, Moraes AM, Torres CC, Oliveira AT. Performance of Laparoscopic Pancreatoduodenectomy for Solid Pseudopapillary Tumor of Pancreas. *Am J Case Rep* 2016; **17**: 894-898 [PMID: 27890912 DOI: 10.12659/ajcr.900792]

18 **Eric D**, Milosavljevic V, Gonzalez-Urquijo M, Tadic B, Veselinovic M, Grubor N, Jelic D, Bjelovic M. Laparoscopic enucleation of Frantz's tumor of the pancreas: Case report and literature review. *Ann Med Surg (Lond)* 2021; **64**: 102221 [PMID: 33796288 DOI: 10.1016/j.amsu.2021.102221]

19 **Allam M**, Hidalgo Salinas C, Machairas N, Kostakis ID, Watkins J, Fusai GK. Solid Pseudopapillary Neoplasms of the Pancreas: a Single-Center Experience and Review of the Literature. *J Gastrointest Cancer* 2021 [PMID: 33877570 DOI: 10.1007/s12029-021-00638-6]

20 **Marchegiani G**, Andrianello S, Massignani M, Malleo G, Maggino L, Paiella S, Ferrone CR, Luchini C, Scarpa A, Capelli P, Mino-Kenudson M, Lillemoe KD, Bassi C, Castillo CF, Salvia R. Solid pseudopapillary tumors of the pancreas: Specific pathological features predict the likelihood of postoperative recurrence. *J Surg Oncol* 2016; **114**: 597-601 [PMID: 27471041 DOI: 10.1002/jso.24380]

21 **Soloni P**, Cecchetto G, Dall'igna P, Carli M, Toffolutti T, Bisogno G. Management of unresectable solid papillary cystic tumor of the pancreas. A case report and literature review. *J Pediatr Surg* 2010; **45**: e1-e6 [PMID: 20438906 DOI: 10.1016/j.jpedsurg.2010.02.045]

22 **Ansari D**, Elebro J, Tingstedt B, Ygland E, Fabricius M, Andersson B, Andersson R. Single-institution experience with solid pseudopapillary neoplasm of the pancreas. *Scand J Gastroenterol* 2011; **46**: 1492-1497 [PMID: 22050136 DOI: 10.3109/00365521.2011.627448]

23 **Dyas AR**, Johnson DT, Rubin E, Schulick RD, Kumar Sharma P. Yttrium-90 selective internal radiotherapy as bridge to curative hepatectomy for recurrent malignant solid pseudopapillary neoplasm of pancreas: case report and review of literature. *J Surg Case Rep* 2020; **2020**: rjaa325 [PMID: 33005321 DOI: 10.1093/jscr/rjaa325]

24 **Kodama R**, Koh Y, Midorikawa H, Yokota Y, Saegusa H, Ushimaru H. A case of recurrence of a solid pseudopapillary neoplasm of the pancreas effectively treated with proton beam radiotherapy. *Clin J Gastroenterol* 2021; **14**: 375-381 [PMID: 33052580 DOI: 10.1007/s12328-020-01262-w]

**Footnotes**

**Conflict-of-interest statement:** The authors declare no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** September 4, 2021

**First decision:** October 18, 2021

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** Italy

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): D

Grade E (Poor): 0

**P-Reviewer:** Jin ZD, Lima R, Omiyale AO **S-Editor:** Fan JR **L-Editor:** Filipodia **P-Editor:** Fan JR