ORIGINAL ARTICLE

Solid Pseudopapillary Neoplasm of the Pancreas: A Good Prognostic Tumor of the Bad Lucky Organ

Ergun Sefa[1], Tunc Emre[1], Batur Sebnem[2], Pekmezci Yasemin[1], Velidedeoglu Mehmet[1], Simsek Osman[1], Pekmezci Salih[1]

[1]Department of General Surgery, Faculty of Medical, Istanbul University Cerrahpasa, Turkey

[2]Department of Pathology, Faculty of Medical, Istanbul University Cerrahpasa, Turkey

ABSTRACT

Introduction Solid pseudopapillary neoplasm (SPN) of the pancreas is a rare clinical entity with low malignant potential and good clinical prognosis. It was first defined by Frantz Virginia in 1959 and was renamed solid pseudopapillary tumor by the World Health Organization (WHO) in 2010. SPN is more common in young women with an average age of 28-32 years and a female: male ratio of 3-10:1 in different publications. **Material & Method** The data were retrospectively analyzed for 26 patients whose pathology was compatible with SPN and operated on between 2003 and 2019 in the General Surgery Clinic at XXX. **Results** Of the patients, 25 (96.2%) were female and 1 (3.8%) was male; the mean age at diagnosis was 37.1 (range: 18-69, eight patients <30 years); mean body mass index was 28.8 kg/m^2. The most common reason for referral was abdominal pain (n=13, 50%); three patients (11%) had nausea and vomiting, and one patient (3.8%) had jaundice with mass at the head of the pancreas. Ten patients (38%) were asymptomatic and were diagnosed incidentally during examinations performed for other reasons. The most frequent tumor localization was the head and neck part of the pancreas (n=10, 38%); eight patients (31%) had body, and eight patients (31%) had tail localization. Ten patients (38%) had Whipple procedure (pancreaticoduodenectomy), 15 patients (53%) had distal pancreatectomy, and one patient had intra-abdominal mass excision and segmental small bowel resection operation in addition to distal pancreatectomy. Six (37%) of the 16 patients who underwent distal pancreatectomy had splenectomy too. One of the patients had laparoscopic distal pancreatectomy and splenectomy. The mean tumor diameter was 7.2 cm (range: 2-23 cm). **Conclusion** SPN is a rare tumor, and even though it is diagnosed late and in large sizes, it has prolonged survival when appropriate surgical resection is applied. The ability to perform surgery even in cases with relapse or meta stasis during the SPN follow-up reveals the importance of accurate diagnosis.

INTRODUCTION

Solid pseudo papillary neoplasm (SPN) of the pancreas is a rare clinical entity with low malignant potential and good clinical prognosis. After being first defined by Frantz Virginia in 1959, it has been called Frantz'stumor, Hamoudi's tumor, papillary and solid epithelial neoplasm, papillary cystic tumor, solid and cystic papillary tumor, and papillary cystic carcinoma before being designated as solid pseudo papillary tumor by the World Health Organization (WHO) in 2010.SPN is more common in young women with an average age of 28-32 years and a female: male ratio of 3-10:1 reported in various publications [1-3]. SPN constitutes 0.9 to 2.7% of all pancreatic exocrine neoplasm's. The tumor is located at the head (26-34%) or body and tail (66-74%) of the pancreas. Its incidence increased 7-fold since 2000 due to the advances in imaging methods and an increased awareness of surgeons and pathologists [3, 4]. Although abdominal pain is the most common reason for presentation, some of the cases are asymptomatic and can be detected incidentally; others have nonspecific complaints such as nausea, vomiting, dyspepsia, fever, weight loss, early satiety, and jaundice due to the space-occupying effect of the tumor. In SPN, tumor markers are mostly within the normal range [2, 5].

Ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), endoscopic US (EUS), and positron emission tomography (PET) are used in the imaging of SPN. CT is more commonly preferred and shows solid and cystic structures with well-defined encapsulated bleeding and cystic degeneration areas [2, 4]. Surgical resection is the preferred treatment with a good prognosis, and satisfactory results are obtained even in cases with relapse or metastasis. The choice of surgical technique is based on the location of the tumor. Pancreatic oduodenectomy is the preferred method for tumors localized to the pancreas' head, and distal pancreatectomy is preferred for those located in the body and tail [4, 6]. Here we present our experience with 26 patients who were diagnosed with SPN and operated in our clinic.

Material and Method

The data were retrospectively analyzed for 26 patients whose pathology was compatible with SPN and who were

Received May 18th, 2021; Accepted May 22nd , 2021
Keywords Pancreas tumor; Solid pseudopapillary neoplasm; Frantz's tumor; CD56; Beta Catenin
Correspondence Ergun Sefa
Department of General Surgery,
Faculty of Medical ,
Istanbul University Cerrahpasa, Turkey
Tel 90-5378935148
E-mail sefaergn@yahoo.com

operated between 2003-2019 in the General Surgery Clinic at XXX. The patients whose pathology report indicated other diseases than SPN and those who did not have available clinical and radiological data, although their postoperative pathology report which was compatible with SPN, were excluded from the study.

Patients' demographic information (i.e., age, gender, and BMI), clinical findings, laboratory tests, radiological examinations, surgical treatment, mortality and morbidity, and long-term follow-up and relapse data were obtained from the patient files and through control visits and phone calls. Post operative pancreatic fistula was defined according to the International Study Group of Pancreatic Surgery (ISGPS) classification; postoperative complications were categorized based on Clavien-Dindo classification. This study was approved by the Ethics Committee of Istanbul University Cerrahpaşa, Cerrahpasa Medical Faculty with the number 157085 dated 17.12.2020.

The quantitative variables were expressed as mean ± standard deviation; qualitative variables were expressed as frequency (%).

RESULTS

In 26 pancreatic tumor patients who were operated on between 2003 and 2019, whose the histo-pathological evaluations indicated SPN. Of these, 25 (96.2%) were female, and one (3.8%) was male. The average age at diagnosis was 37.1 years (range: 18-69, eight patients were younger than 30 years), and the average body mass index (BMI) was 28.8 kg/m^2. The most common reason for admission was abdominal pain (n=13, 50%); three patients (11%) had nausea and vomiting, and one patient (3.8%) had jaundice with mass at the head of the pancreas. Ten patients (38%) were asymptomatic and were diagnosed incidentally during the examinations performed for other reasons **(Table 1).**

On physical examination, two patients (7.6%) had palpable mass. All patients had abdominal CT performed preoperatively; eleven patients had abdominal MRI, and four patients had PET-CT. The evaluation of tumor markers (alpha-fetoprotein (AFP), Carcino Embryonic Antigen(CEA), carbohydrate antigen(CA) 125, and CA 19-9) have shown to be elevated at CA 19-9 levels only in one patient who had jaundice (CA19-9: 97.8).

The most frequent tumor localization was the head and the neck part of the pancreas (n=10, 38%); eight patients (31%) had body, and eight patients (31%) had tail localization. In two patients (7.6%) with the mass originating from the pancreatic tail, one tumor had a diameter of 15 cm and extended into the mesentery of the small intestine, and the other was 23 cm in diameter and extended into the mesentery of the large intestine and infiltrated the small intestines. Ten patients (38%) had Whipple procedure (pancreaticoduodenectomy), 15 patients (53%) had distal pancreatectomy, and one patient had intra abdominal mass excision and segmental small bowel resection operation in addition to distal pancreatectomy (**Figure 1**: Pancreaticoduodenectomy specimen of a huge tumor). Six (37%) of the 16 patients who underwent distal pancreatectomy had splenectomy too. One of the patients had laparoscopic distal pancreatectomy and splenectomy. The average tumor diameter was 7.2 cm (range: 2-23 cm).

The average length of hospital stay was eight days. In the postoperative follow-up period, seven patients (27%) developed pancreatic fistula and intra-abdominal collection. Pancreatic fistulas were Grade B according to the ISGPS classification; four of these recovered spontaneously; and three underwent radiological percutaneous drainage **(Table 2).**

Patients were followed up with CT annually, and MRI if there was any suspicion. The average long-term follow-up period was 98 months (range: 12-204). No recurrence was observed except for one patient, who had liver and intra abdominal metastases one year after the operation, underwent a debulking procedure, and died one year later.

DISCUSSION

Although SPN's patho-physiology is not fully understood, the fact that the disease is more frequently observed in women and regresses with menopause led to the hypothesis by several researchers that the disease originates outside the pancreas and develops from the multipotent stem cell in the ovarian fold. However, this relationship does not explain its occurrence in men. It is less common and usually detected at 5-10 years later in males than in females. Although it has not been shown to be associated with any ethnicity or syndrome, it has also been

Table 1: Demographic and clinical data's of patients with pancreas solid pseudo papillary tumor.

Datas	**n: number**	**% percent**
Age, mean	37.1	
BMI(body massindex) kg/m^2	28.8	
Female	25	96.2
Male	1	3.8
Clinical Presentation		
Abdominal pain	13	50
Nausea and vomiting	3	11.4
Palpable abdominal mass	2	7.6
Jaundice	1	3.8
Asmyptomatic	10	38.4

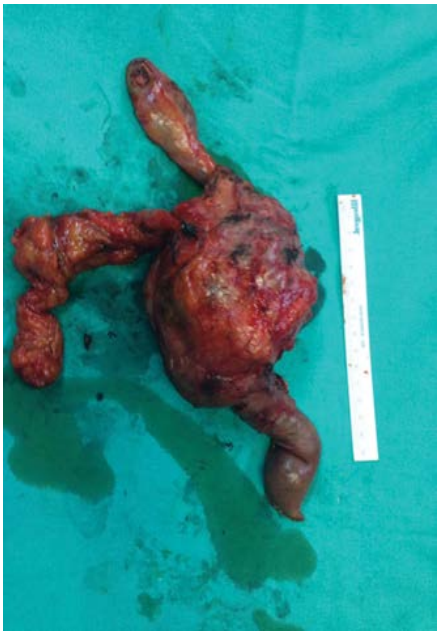

Figure 1. Pancreaticoduodenectomy specimen of huge solid pseudopapillary tumor.

Table 2: Tumor location and treatment data's of solid pseudo papillary tumor of pancreas.

	n: number	**% percent**
Tumor Size Mean (cm)	7.2	
Tumor Location		
Head	10	38.4
Body	8	31
Tail	8	31
Surgicaltreatment		
Pancreaticoduodenectomy	10	38.4
Distal pancreatectomy with spleen preservation	10	38.4
Distal pancreatectomy with splenectomy	6	23.2
Hospital stay mean (day)	8	
Postoperative complications	7	27
Long term follow-up (month)	98	

observed in some Familial Adenomatous Polyposis (FAP) patients [7]. Some publications suggested that hepatitis B virus (HBV)might have a role in the pathogenesis since HBV was present in 62.5% of the patients; However, this role has not been proven yet although it is supported by the stimulation of β-catenin over expression in tumor cells by HBV [3, 8]. In our study, 25 patients (96.2%) were women, and only two patients were HBV positive.

Although its diagnosis is delayed since 30% of the patients are asymptomatic and most of the symptoms are nonspecific, SPN can be diagnosed incidentally with imaging performed for other reasons [9]. In symptomatic patients, the most common symptoms are abdominal pain, a palpable mass in the abdomen, and nausea, vomiting, dyspepsia, and early satiety due to the tumor's compression on adjacent organs. There are also cases of jaundice due to a lesion located in the head of the pancreas. Although rare, cases with acute abdomen due to a tumor rupture associated with blunt abdominal trauma and spontaneous tumor rupture in a pregnant woman have also been reported in the literature [10, 11]. In recent years, studies have shown an increase in the number of patients diagnosed with SPN and a decrease in tumor size [12]. In our study, abdominal pain was the most common reason for admission (13 patients, 50%); two patients (7.6%) had palpable mass, and one patient (3.8%) had jaundice. Ten patients (38%) were asymptomatic. It has been shown that serum tumor markers CEA and CA19-9 are not useful in diagnosis and follow-up. In a study of 82 patients, Zhan et al. found that CA19-9 was high in three patients [12]. In our study, CA-19-9 was found to be elevated only in a patient with pancreatic head mass and jaundice.

Abdominal US, CT, MRI, EUS, and PET-CT are used for diagnosis although imaging is not entirely specific. SPN is seen as solid cystic lesions with smooth borders in the pancreas, containing hemorrhagic areas and calcification. Although it is reported in the literature as it is not always possible to distinguish SPN from other tumors found in the differential diagnosis of SPN such as duct aladenocarcinoma, neuroendocrine tumor, or other cystic tumors of the pancreas through radiological examination; Therefore, the final diagnosis is based on postoperative pathological examination [4, 12, 13]. In our experience we saw that SPN mostly does not invade adjacent organs and vascular structures even when it reaches very large sizes

because it grows not by infiltrating like an adenocarcinoma, but expansively by pushing surrounding structures **(Figures 2 and 3).** Pre-operative differential diagnosis of SPN from adenocarcinoma can be made by seeing this characteristic growth on CT and MRI radiological. In our clinic; while the being of 4-5 cm in size is a risk factor for adenocarcinoma inoperability , the average diameter of the SPN we operated on was 7.2 cm.

Although preoperative diagnosis can be made by EUS fine-needle aspiration (FNA) biopsy or percutaneous method, it is not preferred in some clinics. In a series of cases, Choi et al. reported a correct diagnosis rate of 65%with the help of EUS without causing peritoneal contamination; other studies have reported a rate of 91% [13, 14]. The efficiency of EUS and EUS-FNA depends on the operator, isolated cytological samples may be insufficient, and the procedure may cause tumor rupture and spread [15]. In our clinic, we prefer EUS-FNA for diagnosis in metastatic and un respectable cases rather than operable patients.

In macroscopic examinations, the tumor may be well-circumscribed and encapsulated and contain varying proportions of solid and cystic components. Smaller lesions tend to be more irregularly delineated and more solid. Although a fibrous pseudo capsule is observed in larger tumors, the cross-sectional face is speckled and friable. Signs of cystic degeneration and bleeding are more common in large tumors [16, 17].

In microscopic examination, solid, pseudo papillary, and cystic components are observed in the tumor. Solid islands which are formed by weak cohesive cells and which surrounded the blood vessels like a cuff are seen as a pseudo papillary structure. Tumor cells have a moderate amount of eosinophilic cytoplasm with visible large intracytoplasmic hyaline globules (diastases-resistant, periodic acid-Schiff positive) and perinuclear vacuoles. Nuclei are oval or round in shape and uniform in appearance and have thin chromatin, indistinct nucleoli, and characteristic longitudinal grooves. Oncocytic or clear cell changes can be seen **(Figure 4)** [16, 17].

Tumors have rare mitosis and low Ki-67 score. Immunohistochemistry results are positive for beta-catenin, alpha-1 anti-chymotrypsin, alpha-1 anti-trypsin, vimentin, cyclin D1, CD10, SOX11, androgen receptor, progesterone receptor, TFE3, LEF1, CD56, claudin 5, and claudin 7. Although focal positivity is observed with neuron-specific enolase (NSE)and synaptophysin, the positivity rate with cytokeratin is between 30% and 70%. Paranuclear dot-like staining can be observed with CD99. Chromogranin A, CEA, and estrogen receptor are negative. Loss of E cadherin is observed [16-18].

The SPN is considered a low-malignancy tumor due to the low rate of metastasis and vascular invasion. The rate of malignant SPN has been reported between 10% and 20% [13]. The 5- and 10-year survival rates are 97%

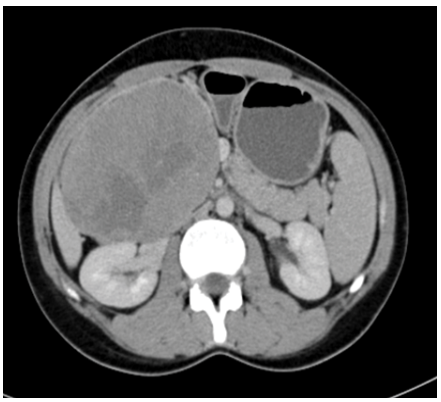

Figure 2. Lesion with heterogen density, cystıc / necrotıc hypodense areas in sıze of 101 x 112 mm, located at the pancreas head-uncınate process level and the lesıon extenses to the portal hilus and promotes the head of the pancreas forward and superıor and lean right renal vein and kidney posteriorly.

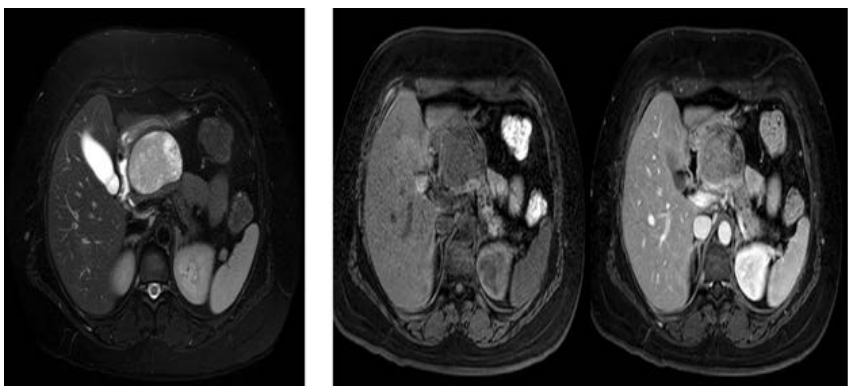

Figure 3. Lesion located at the neck of the pancreas with a dimensions of 68x44x56 mm with cystic areas in T2-weighted series, thick walled straight contrast mass lesion with heterogencontrast attachment in T1 weight series.

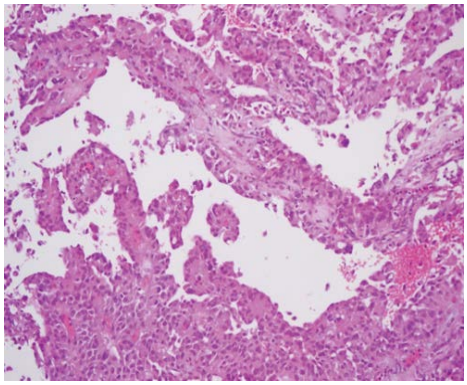

Figure 4. Pseudopapillae with vascular stalks surrounded by loosely cohesive cells (HEX200) HE – (Hematoksilen Eosin).

and 94%, respectively; indeed, the survival rates in R1 resections have been shown to be similar to those in R0 resections. Local invasion or distant organ metastasis, most commonly to the liver, mesentery, omentum, and peritoneum, has been reported in 15-20% of cases, and lymph node metastasis is very rare [3, 19, 20]. Malignant behavior is radiologically associated with pancreatic duct dilatation, vascular invasion with or without metastasis, peripancreatic invasion. It is histological associated with severe necrosis, nuclear atypia, high mitotic index and Ki-67 expression, and sarcomatoid areas [2, 18].

Although an association between tumor diameter and malignancy has been reported in some studies, Robertis et al. indicated that the atypical radiological appearance was significantly more common in tumors smaller than 3 cm and small tumors were detected at an older age, suggesting that there was no correlation between tumor size and malignancy [13].

The best treatment for SPN is early diagnosis and radical resection. SPN is suitable for minimally invasive surgery because it shows an expansive growth rather than infiltrating the surrounding tissues and is highly operable. Aggressive radical resections or debulking surgery can be applied, and the survival can be increased even in patients with locally advanced tumors or malignant tumors with liver or distant metastases [12, 21]. In our study, no recurrence or metastasis was observed in 25 (96.2%) of the patients during an average follow-up of 98 months. In one patient, liver and abdominal metastases were detected after one year, and the patient died two years later.

Function-preserving surgery (pancreaticoduodenectomy and distal pancreatectomy) or parenchymal-sparing resections (central resection and enucleation) are chosen in pancreatic SPNs depending on the location of the tumor. Although parenchymal-sparing surgeries were shown to have a shorter operative time, less bleeding, and the lower rates of exocrine failure and morbidity, some studies reported that there might be an increased risk of pancreatic fistula and tumor recurrence. Parenchymal-sparing surgeries are mostly recommended for small tumors located in the neck of the pancreas. Complete lymphatic dissections are not indicated due to the low rates of lymphatic spread [3, 22, 23]. In our study, function-preserving surgical methods were applied to all patients (pancreaticoduodenectomy in ten patients and distal pancreatectomy in 16 patients).

The effectiveness of chemotherapy and radiotherapy in SPN patients is not fully known; some publications recommended them only in recurrent and irresistible cases. Since the tumor may recur at a rate of 5-7% after surgery, it should be followed up regularly for an extended period, and surgical resection should be performed in the presence of an indication [3, 6, 22]. In our study, no patient received oncology treatment, except for one metastatic patient. Since it is a rare tumor, the low number of cases and the patients dropped out of the follow-up constitute our retrospective study's limitation.

CONCLUSION

SPN is a rare tumor, and the long-term survival which is possible with appropriate surgical resection although it is diagnosed late and large. The possibility of surgical treatment, even in relapse or metastatic cases during the follow-up of SPN, reveals the importance of correct diagnosis.

Conflicts of Interest

All named authors hereby declare that they have no conflicts of interest to disclose.

REFERENCES

1. La Rosa S, Bongiovanni M. Pancreatic solid pseudopapillary neoplasm: Key pathologic and genetic features. Arch Pathol Lab Med. 2020; 144: 829-837. [PMID: 31958381].

2. Dinarvand P, Lai J. Solid pseudopapillary neoplasm of the pancreas: A rare entity with unique features. Arch Pathol Lab Med. 2017; 141:990-995. [PMID: 28661210].

3. Farhat W, Ammar H, Amine Said M, Mizouni A, Bouazzi A, Abdessaied N, et al. Solid pseudopapillary neoplasm of the pancreas: A report of 10 cases and literature review. ANZ J Surg. 2020.

4. Torres OJM, Rezende MBD, Waechter FL, Neiva RF, Moraes-Junior JMA, Torres CCS, et al. Pancreatoduodenectomy for solid pseudopapillary tumor of the pancreas: A multi-institutionstudy. ABCD. Arq Bras Cir Dig. 2019; 32:e1442. [PMID: 31460602].

5. Chagas VL, Rosman FC, Carvalho MDGDC. Solid pseudopapillary neoplasia of the pancreas: A review. Revista da AssociaçãoMédica Brasileira. 2020; 66:87-94.

6. Coelho JC, da Costa MA, Ramos EJ, Torres AR, Savio MC, Claus CM. Surgical management of solid pseudopapillary tumor of the pancreas. JSLS. 2018; 22: e2018.00032. [PMID: 30740012].

7. Ye J, Ma M, Cheng D, Yuan F, Deng X, Zhan Q, et al. Solid-pseudopapillary tumor of the pancreas: Clinical features, pathological characteristics, and origin. J Surg Oncol. 2012; 106:728–35. [PMID: 22688864].

8. Yu PF, Hu ZH, Wang XB, Guo JM, Cheng XD, Zhang YL, et al. Solid pseudopapillary tumor of the pancreas: A review of 553 cases in Chinese literature. WJG. 2010; 16:1209-1214. [PMID: 20222163].

9. Cienfuegos J, Lozano MD, Rotellar F, Martí P, Pedano N, Arredondo J, et al. Solid pseudopapillary tumor of the pancreas (SPPT). Still an unsolved enigma. Rev Esp Enferm Dig. 2010 ; 102:722–8. [PMID: 21198316].

10. Tajima Y, Kohara N, Maeda J, Inoue K, Kitasato A, Natsuda K, et al. Peritoneal and nodal recurrence 7 years after the excision of a ruptured solid pseudopapillary neoplasm of the pancreas: Report of a case. Surg Today 2012; 42:776-780. [PMID: 22706721].

11. Huang SC,Wu TH, Chen CC, Chen TC. Spontaneousrupture of solid pseudopapillary neoplasm of the pancreas during pregnancy. Obstet Gynecol 2013; 121:486-488. [PMID: 23344418].

12. Zhan H, Cheng Y, Wang L, Su P, Zhong N, Zhang Z, et al. Clinicopathological features and treatment outcomes of solid pseudopapillary neoplasms of the pancreas: A 10-year caseseriesfrom a singlecenter. J Laparoendosc Adv Surg Tech. 2019; 29:600-607. [PMID: 30741591].

13. De Robertis R, Marchegiani G, Catania M, Ambrosetti MC, Capelli P, Salvia R, et al. Solid Pseudopapillary Neoplasms of the Pancreas: Clinicopathologic and Radiologic Features According to Size. Am J Roentgenol. 2019; 213:1073-1080. [PMID: 31310181].

14. Lam KY, Lo CY, Fan ST. Pancreaticsolid-cystic-papillary tumor: Clinicopathologic features in eight patients from Hong Kong andreview of the literature. World J Surg. 1999; 23:1045-50. [PMID: 10512945].

15. Virgilio E, Mercantini P, Ferri M, Cunsolo G, Tarantino G, Cavallini M, et al. Is EUS-FNA of solid-pseudopapillary neoplasms of the pancreas as a preoperative procedure really necessary and free of acceptable risks?. Pancreatology. 2014; 14:536-8. [PMID: 25227317].

16. Springer S, Wang Y, Dal Molin M, Masica DL, Jiao Y, et al. A combination of molecular markers and clinical features improve the classification of pancreaticcysts. Gastroenterology. 2015; 149:1501–10. [PMID: 26253305].

17. Gurzu S, Bara T, Sincu M, Gabos S, Vlad DM, Bara T, et al. Solid pseudopapillary neoplasm of the pancreas. Med. 2019; 98:e16455. [PMID: 31335701].

18. Tang LH, Aydin H, Brennan MF, Klimstra DS. Clinically aggressive solid pseudopapillary tumor of the pancreas: A report of two cases with components of undifferentiated carcinoma and a comparative clinicopathologicanalysis of 34 conventional cases. Am J Surg Pathol. 2005; 29:512–519. [PMID: 15767807].

19. Papavramidis T, Papavramidis S. Solid pseudopapillary tumors of the pancreas: Review of 718 patients reported in English literature. J Am Coll Surg. 2005; 200:965-972. [PMID: 15922212].

20. Estrella JS, Li L, Rashid A, Wang H, Katz MH, Fleming JB, et al. Solid pseudopapillary neoplasm of the pancreas: Clinicopathologic and survival analyses of 64 cases from a single institution. Am J Surg Pathol. 2014; 38:147-157. [PMID: 24418850].

21. Tipton SG, Smyrk TC, Sarr MG, Thompson GB. Malignant potential of solid pseudopapillary neoplasm of the pancreas. Br J Surg. 2006; 93:733-737. [PMID: 16609955].

22. Hansen CP, Kristensen TS, Storkholm JH, Federspiel BH. Solid pseudopapillary neoplasm of the pancreas: Clinical-pathological features and management, a single-center experience. Raretumors, 2019; 11:2036361319878513. [PMID: 31598207].

23. Lin X, Lin R, Lu F, Chen Y, Huang H. Surgical management of solid pseudopapillary neoplasms of pancreas: A single-center experience of 60 patients. Digest Surg. 2020; 37:348-354. [PMID: 31958791].