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**Unraveling the enigma: A comprehensive review of solid pseudopapillary tumor of the pancreas**

Xu YC *et al*. Solid pseudopapillary tumor of the pancreas

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**Abstract**

Solid pseudopapillary tumor of the pancreas (SPTP) is a rare neoplasm predominantly observed in young females. Pathologically, CTNNB1 mutations, β-catenin nuclear accumulation, and subsequent Wnt-signaling pathway activation are the leading molecular features. Accurate preoperative diagnosis often relies on imaging techniques and endoscopic biopsies. Surgical resection remains the mainstay treatment. Risk models, such as the Fudan Prognostic Index, show promise as predictive tools for assessing the prognosis of SPTP. Establishing three types of metachronous liver metastasis can be beneficial in tailoring individualized treatment and follow-up strategies. Despite advancements, challenges persist in understanding its etiology, establishing standardized treatments for unresectable or metastatic diseases, and developing a widely recognized grading system. This comprehensive review aims to elucidate the enigma by consolidating current knowledge on the epidemiology, clinical presentation, pathology, molecular characteristics, diagnostic methods, treatment options, and prognostic factors.

**Key Words:** Pancreas; Solid pseudopapillary tumor; β-catenin; Endoscopic ultrasound; Surgery; Recurrence; Liver metastasis; Prognostic prediction

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**Core Tip:** Solid pseudopapillary tumor of the pancreas (SPTP) is a rare neoplasm predominantly affecting young females. Pathologically, CTNNB1 mutations, β-catenin nuclear accumulation, and Wnt signaling pathway activation are key molecular features. Accurate preoperative diagnosis relies on imaging and endoscopic biopsies. Surgical resection is the main treatment, and prognostic models like Fudan Prognostic Index aid in prognosis assessment. Challenges in understanding its etiology, establishing treatments for unresectable/metastatic disease, and developing a standardized grading system persist. This comprehensive review aims to consolidate current knowledge on epidemiology, clinical presentation, pathology, molecular features, and treatment options for SPTP.

**INTRODUCTION**

Solid pseudopapillary tumor of the pancreas (SPTP), also known as solid pseudopapillary neoplasm (SPN) or solid pseudopapillary epithelial neoplasm (SPEN)[1], is a rare, low-grade malignant neoplasm that primarily affects young females[2,3]. Initially described by Frantz in 1959 as “papillary cystic tumors of the pancreas”[4], the World Health Organization (WHO) later adopted the term “SPTP” in 1996 to better reflect the tumor’s histological characteristics[5]. SPTP has limited malignant potential, and typically results in localized disease. Most cases are asymptomatic and are incidentally detected during routine imaging studies or investigations of other conditions.

Although the exact cause of SPTP is unknown, evidence suggests that it originates from pluripotent cells within the pancreas[6]. It typically presents as a combination of solid and cystic areas, with a central pseudopapillary structure formed by cell accumulation around blood vessels[7]. The disease is associated with a favorable prognosis, with a 5-year survival rate exceeding 95%[8]. Surgical resection is the preferred treatment, and complete tumor removal is curative in most cases[8-13]. In rare situations where the tumor is unresectable or has metastasized, chemotherapy or other anti-cancer therapies may be considered. Predicting the risk of postoperative recurrence can aid clinicians in identifying and closely monitoring patients who may benefit from adjuvant therapy.

In this comprehensive review, we delve into recent advances in understanding SPTP to unravel this enigma.

**Epidemiology**

The epidemiology of SPTP remains poorly defined due to lack of large-scale population-based studies. The exact global incidence varies depending on the region and population studied but is estimated to be less than one in a million per year. SPTP can affect individuals of all races[14]. It is important to note that available data on the geographic and ethnic distribution is limited. Further studies are needed to obtain a more accurate understanding of its distribution. However, due to its rarity, conducting large-scale epidemiological studies is very challenging, and even considered impossible.

There are no established risk factors or predisposing conditions associated with the development of SPTP. The gender and age predilection may be related to sex hormones[6]. Studies have suggested that progesterone may be involved in its pathogenesis[15]. Differential expression of estrogen and androgen receptors have also been observed, although these associations are not definitive[16-18]. Further research is needed to identify the underlying mechanisms.

**Pathogenetic Features**

Several molecular and genetic alterations that contribute to pathogenesis and malignant potential have been identified. The most common genetic alteration is a mutation in exon 3 of CTNNB1[7,19-23], which encodes β-catenin, a crucial component of the Wnt-signaling pathway. Activation of β-catenin has been shown to induce pancreatic tumorigenesis[24]. The Wnt/β-catenin pathway promotes carcinogenesis by influencing gene transcription in a regulated or deregulated manner[25,26]. It also interacts with the Hedgehog and androgen receptor signaling pathways, which trigger epithelial–mesenchymal transition[21]. The mechanism underlying its limited malignant potential is unclear, but may be related to the significant downregulation of BCL9/9L, a crucial transcriptional co-activator of β-catenin[25], and high expression of the cyclin D1 inhibitors p21 and p27[27].

In addition to β-catenin, which has been identified as a positive molecular marker for SPTP[28-30], negative markers such as KRAS, GNAS, RNF43, and chr18 Loss of heterozygosity have also been identified[28]; however, their implications remains poorly understood. Based on these complex molecular mechanisms, SPTP is typically characterized by slow growth and low malignant potential[31]. It is usually well-circumscribed, rarely invades neighboring structures or metastasizes to distant sites, and has a high R0 resection rate. However, an aggressive growth pattern with local infiltration and distant metastasis occurs in approximately 15% of the cases[32].

**Clinical Presentation**

An analysis of 1,072 cases of SPTP cases from several large cohort studies have shown that abdominal pain and discomfort were the most common symptoms, accounting for 43.5% of cases. More than 40% of patients had no symptoms, making it difficult to detect this tumor. An abdominal mass was the first finding in 14.8% of patients. Other clinical manifestations, with a prevalence of more than 1%, include dyspepsia, nausea, vomiting and back pain. Rare symptoms (< 1%) include obstructive jaundice, anorexia, fever, weight loss, and sinusoidal hypertension[3,9,11-13,32]. It is worth noting that the mechanism by which obstructive jaundice and sinistral portal hypertension occur in SPTP is different from that involved in pancreatic ductal adenocarcinoma. In SPTP, these symptoms are caused by external pressure on the surrounding structures, whereas in pancreatic ductal adenocarcinoma, they result from invasion of the biliary tract and portal vein system[12]. Due to advances in imaging techniques and increased health-consciousness, the proportion of asymptomatic cases has gradually increased in recent years as more people become aware of their health and undergo regular check-ups[3,13]. Nevertheless, the nonspecific symptoms and the absence of specific laboratory tests and tumor markers present difficulties in the accurate diagnosis of SPTP[26].

**Imaging techniques for detection and characterization**

Ultrasonography is often the initial test used for symptomatic patients and is also used for screening. Ultrasonically, an SPTP appears as a well-defined hypo-echoic cystic mass with few internal flow signals. Contrast-enhanced ultrasonography shows enhanced capsular boundaries with a nonenhanced central area. Additionally, iso/hypo-enhancement can be observed during the early and delayed parenchymal perfusion phases[33,34].

Computed tomography (CT) is the most widely used and sensitive test for the evaluation of pancreatic tumors. Multi-detector CT (MDCT) is recommended as the primary method for detecting SPTP and for assessing its resectability. Li *et al*[35] classified SPTP into five types based on their solid–cystic ratio. Types III, IV, and V were more common in females. The most prevalent type was type III (29.4%), which appeared as a well-circumscribed mass with mixed solid and cystic components, with no clear boundary between the cystic and solid regions. Interestingly, the solid–cystic ratio may decrease as the SPTP grows. Smaller SPTPs (less than 3 cm) tend to be predominantly solid, while larger SPTPs (more than 3 cm) show more cystic components[36]. On contrast-enhanced CT, noticeable enhancement of the solid area is observed during the arterial and portal venous phases, although it is lower than that of the pancreatic tissue[37]. Peripheral enhancement due to a fibrous pseudo-capsule is also a characteristic feature of SPTP[38]. Enhancement of fibrous components within cystic fluid resembles a “floating cloud” appearance[39]. Hemorrhage, necrosis, and calcification are important features[35].

SPTP exhibits greater heterogeneity on magnetic resonance imaging (MRI). MRI often reveals T2 hyperintensity and T1 hypointensity, as well as heterogeneous enhancement on contrast-enhanced T1-weighted images[35,40]. Although the role of MRI in SPTP has been less extensively studied than that of compared to CT scans, MRI is crucial for its detection due to its non-invasiveness and high diagnostic accuracy[41].

Endoscopic techniques provide methods for the preoperative pathological diagnosis of SPTP. Similar to abdominal ultrasound, SPTP appears as solid, cystic, or solid–cystic on endoscopic ultrasound (EUS)[42]. The application of artificial intelligence, such as the deep learning analysis of EUS images, has the potential to improve the diagnostic value of endoscopic techniques[43]. EUS-guided fine needle aspiration (EUS-FNA) is increasingly utilized in pancreatic tumor diagnosis, with both sensitivity and specificity exceeding 80%[44]. In addition to biopsy, EUS-FNA allows for the minimally-invasive collection of fluid samples, including pancreatic juice and cyst fluid[42,45]. Table 1 summarizes the results of cyst fluid analysis for various pancreatic cystic diseases[45-47]. Considering the predominant solid component in SPTP and the limited diagnostic accuracy of cyst fluid analysis, EUS-guided fine needle biopsy (EUS-FNB) can be a more valuable diagnostic tool. This method often provides a larger tissue sample for possible immunostaining needed for diagnosis and to exclude other tumors with different management such as pancreatic neuroendocrine tumor (PNET). A recent retrospective multi-center study showed an impressive preoperative diagnostic accuracy of 97.2% (103/106) for SPTP using EUS-guided biopsy[48]. However, EUS-guided biopsy demands specialized endoscopic skills and expertise, which may limit its availability on a global scale. Moreover, the learning curve is long, and low cellularity in sometimes encountered, which may limit its clinical utility. Additionally, the probability of biopsy-induced inflammation and needle tract seeding, while extremely low, does exist[42,49-51]. Additionally, EUS-guided needle-based confocal laser endomicroscopy (EUS-nCLE) has emerged as a novel diagnostic method, exhibiting high diagnostic accuracy[52,53]. The typical features of SPTP on EUS-nCLE include tiny round dark cellular clusters with white stroma bands[52,54].

Positron emission tomography/CT (PET/CT) complements routine imaging tests and provides insights into the histopathological composition of SPTP. One characteristic finding is the presence of strong focal fluorodeoxyglucose (FDG) uptake, which is indicative of metabolic activity[55]. Recent reports have suggested that fibroblast activation protein inhibitor (FAPI) activity can also be observed in cases where FDG uptake is negative[56]. This highlights the potential of FAPI as an alternative tracer in certain situations. Additionally, the standard uptake value, a quantitative measure of FDG uptake, has been shown to correlate with pathological features such as tumor cellularity, proliferative index, and histological malignancy[57]. PET/MRI is relatively rare used in the evaluation of SPTP. It combines the benefits of both PET and MRI, and provides detailed anatomical and functional information in a single imaging session. Similar to PET/CT, PET/MRI can also show focal FDG uptake, allowing for identification and localization of active tumor regions[58]. Both aid in staging, prognostication, and early detection of recurrence, and assist in treatment planning[59]. However, despite their clinical value, high costs may restrict their widespread application.

**Diagnosis**

Age and sex are essential factors to consider when diagnosing SPTP. If a solid pancreatic cystic tumor is detected in a young female, SPTP should be considered first. A definitive diagnosis is typically made using a combination of imaging studies. In cases where the differential diagnosis is difficult, a multidisciplinary approach, involving radiologists, gastroenterologists, and surgeons, is usually required to make an accurate diagnosis. Definitive diagnosis before surgery relies on biopsy and histopathological examinations. In the era of guidelines and EUS, the misdiagnosis rate of SPTP is markedly low, at only 6%, making it the lowest among pancreatic cystic neoplasms[60]. A flowchart of the SPTP diagnosis is shown in Figure 1.

Macroscopically, the majority of SPTPs appears as a well-circumscribed mass[61,62]. They often have a fine peripheral capsule, and hemorrhage and necrosis may also be visible[61]. Microscopically, SPTPs typically display characteristic histological features, including pseudopapillary structures, and areas of hemorrhage and necrosis[62]. Tumor cells usually have large round nuclei, with abundant eosinophilic or clear cytoplasm that can be vacuolated[63]. Wang *et al*[64] identified key cytological features of SPTP, such as myxoid stroma surrounding fibrovascular cores and discohesive epithelioid cells with deficient cytoplasm, pale chromatin, longitudinal nuclear grooves, and small nucleoli closely associated with the nuclear membrane. However, a definitive diagnosis cannot rely solely on morphological features. Immunohistochemistry helps to confirm the diagnosis and differentiate SPTP from other tumor types[63]. Several immunohistochemistry markers, such as CD56, CD10, and β-catenin, have been shown to be commonly expressed in SPTP[65,66]. Table 2[18,26,31,65,66,73-80] provides a list of useful immunohistochemical markers for SPTP. Although SPTP possesses distinct features, it has similarities and overlaps with other tumors, such as non-functional PNET[67] and acinar cell carcinoma[37]. A comprehensive differential diagnosis of SPTP is presented in Table 3[68-72].

**Malignant SPTP**

Until now, there has been no unified standard for defining malignant SPTP. Certain features, such as cell pleomorphism, prominent necrosis, perineural invasion, and the presence of multiple mitotic figures, may indicate malignant potential[81,82]. The 2010 WHO classification of tumors of the digestive system considered SPTP as a low-grade malignancy[83]. However, the updated system in 2019 introduced the concept of high-grade malignant SPTP, characterized by tumor cells exhibiting high levels of atypia and extensive mitotic figures throughout the tumor[84]. Previous studies defined malignant SPTP based on various criteria including lymph node or distant metastases, cellular atypia, capsule invasion, parenchymal infiltration, perineural or lymphovascular infiltration, or extrapancreatic infiltration in 18.3% of cases[31]. Fleming *et al*[85] defined malignant SPTP based on the American Joint Committee on Cancer (AJCC) 8th edition staging system, classifying T4 stage, lymph node metastasis, and distant metastasis as malignant, accounting for 13.4%[85]. Further research and collaboration are needed to establish a consensus for diagnosing malignant SPTP, which may require more aggressive treatments.

Liver metastasis of SPTP can occur synchronously or metachronously. Chen *et al*[9] showed that synchronous metastasis rates ranged from 0% to 4.3%, while metachronous metastasis rates ranged from 1.5% to 4.5%. Metachronous liver metastasis can be classified into three types: classical, indolent, and aggressive. In the classical type, metastases grow at a relatively slow rate. Small lesions appear as low-density on CT scan and may be single or multiple. As the lesions increase in size, peripheral enhancement may occur during the arterial and venous phase. With further growth, cystic degeneration and hemorrhagic necrosis may develop. Multiple lesions can even merge to form a larger lesion (Figure 2). The classical type aligns with the natural growth pattern of the primary SPTP lesion[86]. The indolent type exhibits a very slow growth rate, and the lesions are often small (less than 1 cm) when detected. During follow-up, these lesions typically only grow a few millimeters per year (Figure 3). It can be challenging to detect this type, and enhanced MRI has relatively high sensitivity. Treatment options for the indolent type may include observation or radiofrequency ablation (RFA). The aggressive type is usually asymptomatic and discovered incidentally during follow-up. If the metastases are unresectable, they may progress rapidly despite adjuvant therapy. In this condition, surrounding vessels such as splenic vein, portal vein, superior mesenteric vein, and even inferior vena cava can be involved, leading to tumor thrombus formation (Figure 4). The factors contributing to this type are unclear but may be associated with abdominal trauma[87,88]. The prognosis for the aggressive type is generally poor, and surgical intervention is often not possible.

**Treatment Approaches**

Observation is typically not recommended for SPTP because of its malignant potential[89]. However, a recent study examined 994 cases from the National Cancer Database between 2004 and 2018 and found that the incidence of lymph node metastasis was 0.5% in tumors ≤ 4 cm and 0% in those ≤ 2 cm[90]. This suggests that patients with cT1N0 Lesions should be closely monitored rather than undergoing immediate surgery. The benefit of observation is the avoidance of the morbidity and mortality associated with pancreatic resection[91]. With advancements in interdisciplinary approaches, EUS-guided RFA (EUS-RFA) has emerged as a potential treatment option for pancreatic tumors[92]. In a study by Choi *et al*[93], two patients with SPTP underwent EUS-RFA without experiencing any procedure-related adverse events, and one patient achieved a complete response. Coupier *et al*[94] subsequently reported on three SPTP patients who received EUS-RFA, and none of them experienced recurrence during a 2-year follow-up period. However, it should be noted that EUS-RFA is only suitable for individuals who are not eligible for surgical interventions, despite being less invasive. For T1N0 tumors, this treatment option can be discussed, but further data collection is necessary. Currently, R0 resection is the mainstay of treatment for SPTP.

It has been shown that the type of surgery has a limited impact on long-term survival[95]. Generally, for SPTP in the pancreatic head, enucleation, duodenum-preserving pancreatic head resection (DPPHR), and pancreaticoduodenectomy can be performed[96-98]. For tumors in the pancreatic body and tail, enucleation, central pancreatectomy, and distal pancreatectomy (with and without splenectomy) are available[3,31,32]. As depicted in Table 4, parenchyma-preserving pancreatectomies such as enucleation, central pancreatectomy, and DPPHR are increasingly performed[99-104]. They have been reported to reduce the incidence of pancreatic endocrine and exocrine insufficiencies without compromising short- and long-term outcomes[99]. Minimally invasive techniques, including laparoscopic and robotic surgery, may also be considered in both traditional and parenchyma-preserving procedures[32,104-107].

To date, no consensus on the optimal approach for the treatment of SPTP metastasis has been established[31,98]. Lymph node metastasis is relatively rare, occurring in approximately 1.0% to 7.9% of cases[8-10,32]. This finding indicates that extended lymphadenectomy may be unnecessary in most patients[108]. Liver-directed therapies, including metastasectomy, RFA, proton beam radiotherapy, chemosaturation, and liver transplantation, can be considered for liver metastasis[109-116]. Although not yet documented, EUS-RFA might prove to be effective for treating small recurrent metastases that are not amenable to surgical resection. It is important to note that the available information regarding therapy for metastasis is predominantly derived from case reports and lacks robust evidence. However, every effort should be made to perform curative resection, even in cases of vascular invasion or distant metastasis. The surgical algorithm that guides the treatment decisions is summarized in Figure 5.

In addition to surgical resection, other treatment options are available for malignant SPTP. Although chemotherapy was shown not to improve overall survival (OS) for both resected and unresected SPTP[85], several reports have shown that oxaliplatin- and gemcitabine-based chemotherapies are applicable for malignant SPTP[117,118]. Other antitumor methods included targeted therapy (mTOR inhibitor)[119-121] and endocrine treatment (tamoxifen)[122], both of which have been reported in individual cases; however, more data are needed to validate these approaches. A multidisciplinary approach should be adopted to develop individualized treatment plans for patients with metastatic SPTP.

**Prognostic Factors and Grading Systems**

The prognosis of SPTP is generally favorable due to its low malignant potential[32]. Previous studies have shown a 10-year recurrence-free survival (RFS) rate of 94.8% and an OS rate of 97.6%[8]. These results are consistent with other large-scale studies and meta-analysis[10-12,32,123]. Even in cases of relapse, the survival rate remains acceptable. In recent years, several risk factors for recurrence have been identified, including male gender, incomplete capsule, young age, high neutrophil-to-lymphocyte ratio, large tumor size, R1 resection, high Ki-67 index, lymphovascular invasion, and synchronous metastasis[9,31,108,124-128].

The traditional TNM staging system has limitations in predicting the prognosis of SPTP[8]. SPTP rarely invades surrounding arteries and has a low incidence of lymph node metastasis, resulting in few cases classified as T4 or N1/N2 tumors. No significant survival differences were reported between stage I and II[8,9]. The European Neuroendocrine Tumor Society staging system shares similar limitations[8]. However, the Fudan Prognostic Index (FPI), which takes into account tumor size and Ki-67 index, has been recently developed[8]. This index categorizes SPTP into three risk groups (Table 5) and shows that each group has a significantly different RFS[8]. The FPI outperforms other staging systems in predicting RFS[8], as demonstrated in both the Huashan and historical cohorts. It represents a groundbreaking study and is the first to report a novel grading system for SPTP[129]. Subsequent studies have further confirmed the value of FPI in predicting the prognosis of SPTP[9,61]. Based on the FPI, the Peking Union Medical College Hospital (PUMCH) risk model was developed by including lymphovascular invasion as an additional factor (Table 5)[9]. This model categorizes patients into low- and high-risk groups, and predicts RFS with an area under the curve of 0.791.

Both models have significantly enhanced clinicians’ understanding of prognosis for SPTP. Nevertheless, there is a difference in the distribution of patients in the intermediate/high risk groups between the two models. In the FPI cohort, only 21.2% of patients were classified as intermediate/high risk, while the PUMCH cohort had 64.1% classified as high-risk patients[8,9]. This suggests that the PUMCH risk model may result in overtreatment and excessive follow-up, potentially burdening patients psychologically. Additionally, the model poses challenges for pathologists due to the heavy workload for assessing lymphovascular invasion[9]. The FPI model allows for more detailed risk stratification. However, both models require further studies for external validation due to the relatively short follow-up time.

With the emergence of radiomics, big data and artificial intelligence, more predictive models are expected to be developed. To achieve this, it is crucial to establish standardized reporting criteria for radiology, histopathology, and immunohistochemistry to ensure accurate identification of predictive factors. Furthermore, large-scale, multicenter, and even multinational studies are necessary, along with the creation of big data cohorts. These efforts will contribute to advancing the development of more precise predictive models for SPTP.

**Postoperative follow-up strategy**

Due to the lack of guidelines, there is currently no consensus for postoperative follow-up for SPTP. Traditionally, patients undergoing SPTP surgery are advised to have regular check-ups every 3 to 6 months for the first two years, followed by 6-month to yearly intervals as necessary. However, with the availability of predictive models, follow-up protocols can be customized based on a patient’s risk profile. For low-risk patients, the follow-up period can be extended to minimize unnecessary use of medical resources. One the other hand, high-risk patients may require a more intensive and personalized follow-up protocol to detect any recurrence. Although there is limited data specifically on SPTP, enhanced CT and MRI scans are considered the optimal methods for identifying recurrence. In cases where routine imaging fails to define lesions, PET-CT or PET-MRI scans may be reasonable alternative options (Figure 6). With the increasing use of parenchyma-preserving pancreatectomy in managing SPTP, it is important to consider the possibility of pancreatic endocrine and exocrine insufficiency after traditional pancreatectomy. Therefore, regular follow-up for these patients should include monitoring of blood glucose level, glycated hemoglobin, and quality of life.

**CONCLUSION**

SPTP is characterized by distinct molecular and genetic changes, including mutations in CTNNB1, which activates the Wnt-signaling pathway and promotes tumor growth. Although biomarkers, such as beta-catenin, CD10, and CD56 can assist in diagnosis, they are not specific to SPTP. When evaluating pancreatic tumors, particularly in young women, SPTP should be considered in the differential diagnosis. This tumor is typically associated with favorable long-term outcomes, with low rates of recurrence and metastasis. Surgical resection is the preferred approach, even in patients with recurrence and metastasis. Factors such as large tumor size, high Ki-67 index, and lymphovascular invasion may affect RFS, and patients with these risk factors should undergo more frequent follow-ups. Further research is needed to gain a better understanding of the relationships among clinicopathological, molecular, and genetic factors and their impact on prognosis of patients with SPTP.

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**Footnotes**

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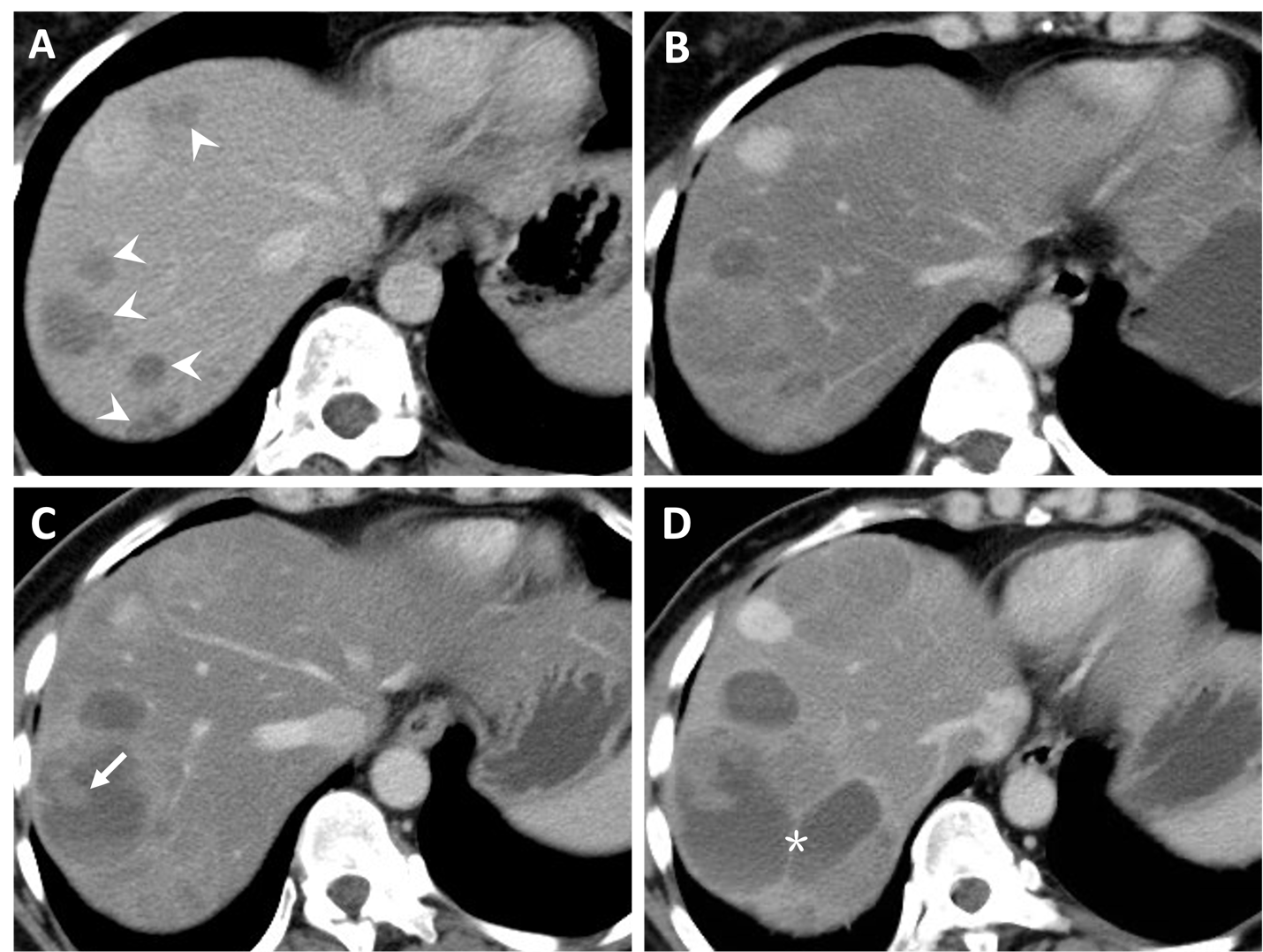
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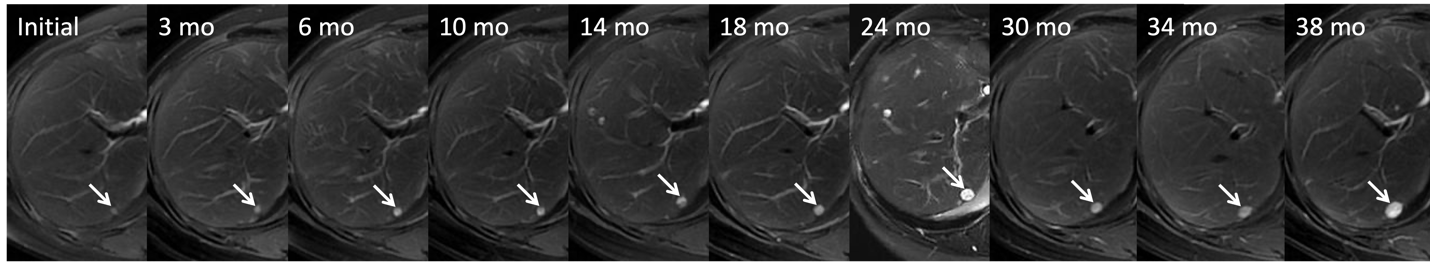
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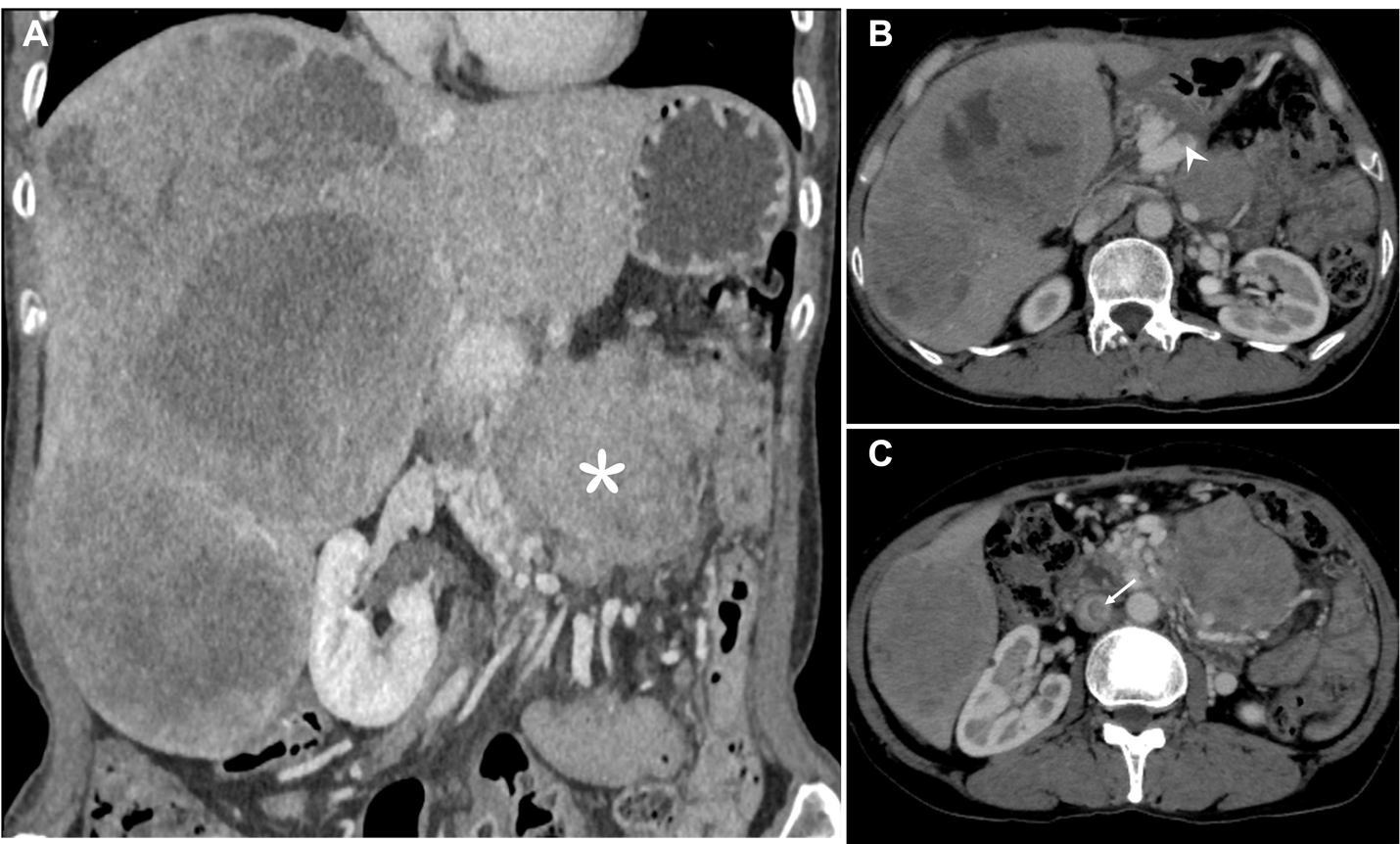
**Figure 1 Diagnosis algorithm for** **solid pseudopapillary tumor of the pancreas.** US: Ultrasound; CE-CT: Contrast enhanced computed tomography; MRI: Magnetic resonance imaging; SPTP: Solid pseudopapillary tumor of the pancreas; EUS-FNA: Endoscopic ultrasound guided fine-needle aspiration; EUS-nCLE: Endoscopic ultrasound guided needle-based confocal laser endomicroscopy; PET-CT: Positron emission tomography-computed tomography; PET-MRI: Positron emission tomography-magnetic resonance imaging.

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**Figure 2 Natural history (classical type) of liver metastasis from** **solid pseudopapillary tumor of the pancreas.** A and B:Multiple liver metastases (A, arrowheads) were detected 38 months after surgery. Five months later, the lesions increased in size gradually (B); C and D: Cystic change of the lesion with solid component (C, arrow) was shown after 10 months. Seventeen months later, the lesions continued increasing with septum-like structure detected (D, asterisk).

****

**Figure 3 Indolent type of liver metastasis from** **solid pseudopapillary tumor of the pancreas.** A 46-year-old woman, who had a history of surgery for malignant solid pseudopapillary tumor of the pancreas with Ki-67 of 1%, received serial magnetic resonance imaging scans as surveillance. T2WI showed a new-onset homogeneous high signal nodule in the liver segment 7 (arrows). During the 3-year follow-up, the lesion grew slightly.

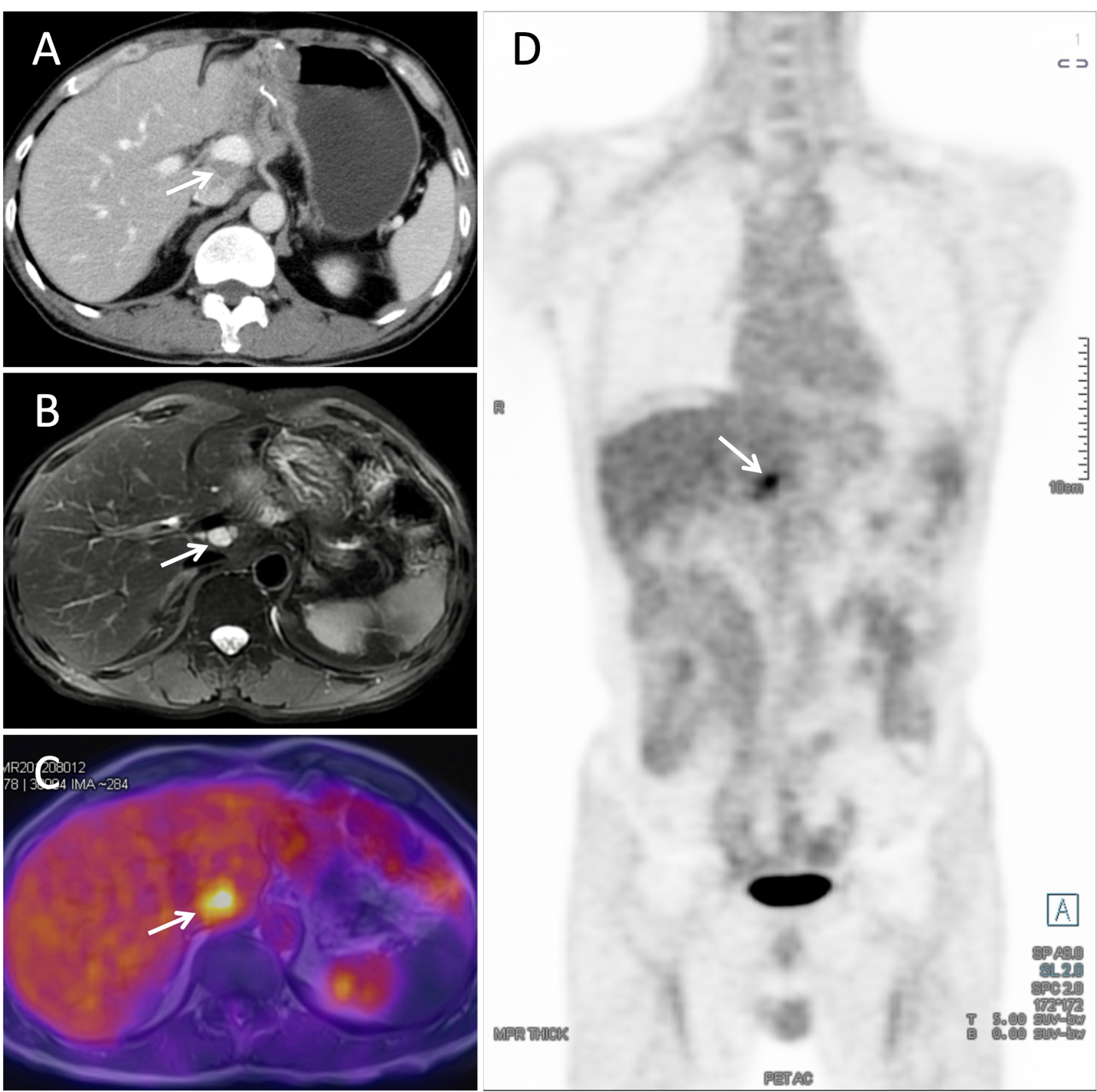
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**Figure 4 Aggressive type of liver metastasis from** **solid pseudopapillary tumor of the pancreas.** A 55-year-old woman, who underwent surgery for solid pseudopapillary tumor of the pancreas 6 years ago, presented with incidental detection of abdominal masses after abdominal blunt trauma due to an accidental fall. Computed tomography scan showed multiple heterogeneously enhancing masses with extensive central necrosis fused in the right liver, with a size of 26 cm × 17 cm. A-C: A retroperitoneal mass (A, asterisk) invading the superior mesenteric vein (SMV) was detected, with presence of collateral circulation, and tumor thrombi filling the SMV (B, arrowheads) and inferior vena cava (C, arrow).

**形状

中度可信度描述已自动生成**

**Figure 5 The algorithm for surgical treatment of** **solid pseudopapillary tumor of the pancreas.** SPTP: Solid pseudopapillary tumor of the pancreas; PPPT: Parenchyma-preserving pancreatectomy; MPD: Main pancreatic duct; CP: Central pancreatectomy; DP: Distal pancreatectomy; PD: Pancreaticoduodenectomy; DPPHR: Duodenal-preserving pancreatic head resection.

****

**Figure 6 Detection of recurrence in** **solid pseudopapillary tumor of the pancreas.** A: Abdominal enhanced computed tomography scan revealed a hypodense mass between the portal vein and inferior vena cava; B: T2WI magnetic resonance imaging (MRI) demonstrated a high signal mass located at the hepatic hilum; C and D: Axial-fused (C) and coronal-fused (D) positron emission tomography/MRI showed that the lesion had increased fluorodeoxyglucose uptake.

**Table 1 Pancreatic cyst fluid analysis based on endoscopic ultrasound-fine needle aspiration**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Type** | **SCN** | **MCN** | **IPMN** | **SPTP** | **Pseudocyst** |
| Viscosity | Low | High | High | NA | Low |
| Mucin | Low | High | High | NA | Low |
| Amylase | < 250 U/L | < 250 U/L | High | Low | High |
| Cytology | Negative or Glyogen containing cuboid cells | Mucin containing column cells | Papillary clusters of mucin column cells, atypia | Branching papillae cuboid or cylindric cells, high cellularity, myxoid stroma | Dirty material, macrophages, inflammatory cell |
| NGS | VHL; chr3 LOH | CEA | KRAS; GNAS; TP53; PTEN; CEA | CTNNB1 | NA |

SCN: Serous cystadenoma; MCN: Mucinous cystadenoma; IPMN: Intraductal papillary mucinous neoplasm; SPTP: Solid pseudopapillary tumor of the pancreas; NGS: Next-generation sequencing; LOH: Loss of heterozygosity; CEA: Carcinoembryonic antigen; NA: Not available.

**Table 2 Markers for diagnosing** **solid pseudopapillary tumor of the pancreas on immunohistochemistry analysis**

|  |  |  |
| --- | --- | --- |
| **Markers** | **Positive rate** | **Mechanisms/implications** |
| β-catenin[26,65] | almost 100% (nuclear) | Activating the Wnt-signaling pathway |
| CD200[73] | 100% (focal) | Marker of stem cell status |
| CD10[65,66,74] | 100% | Marker of SPTP; expressed in immature lymphocyte |
| CD56[66] | 100% | Marker of SPTP |
| AMACR[75] | 96.2% | Marker of SPTP |
| LEF1[18] | 94.7% | Regulating the Wnt-signaling pathway |
| TFE3[76] | 94.7% | Activating and regulating the Wnt-signaling pathway |
| CD99[77] | 78.4% (paranuclear dot-like) | Differentiating from PNET |
| E-cadherin[65,78] | 0% | Differentiating from PNET |
| CgA[26] | 0% | Differentiating from PNET |
| Trypsin[26,79] | 0% | Differentiating from ACC |
| BCL10[26,79] | 0% | Differentiating from ACC |
| Ki-67[31,80] | Mostly 1-2% | Predicting prognosis |

CD: Cluster of differentiation; PNET: Pancreatic neuroendocrine tumor; SPTP: Solid pseudopapillary tumor of the pancreas; LEF1: Lymphoid enhancer-binding factor 1; TFE3: Transcription factor E3; AMACR: α-methylacyl-CoA racemase; CgA: Chromogranin A; ACC: Acinar cell carcinoma; BCL10: B-cell lymphoma-10.

**Table 3 Differential diagnosis of** **solid pseudopapillary tumor of the pancreas**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Disease** | **Female** | **Age (yr)** | **Marker** | **Clinicopathological features** |
| SPTP | 90% | 20-40 | β-catenin | Well-circumscribed; < 3 cm: Mainly solid; > 3 cm: Solid-cystic; myxoid stroma enveloping fibrovascular cores; discohesive epithelioid cells |
| Non-functional PNET | 50% | 50-60 | CgA | Solid: Obviously enhanced with capsule ring-like enhancement; solid-cystic: Mural nodule, uneven wall; high rate of G2 and G3 |
| ACC | < 50% | 60 | AFP | Enhanced solid with large mass having hypodense areas; heterogeneous enhancement; full of large polygonal cells with background necrosis, zymogen-rich and granular cytoplasm, cherry-red nucleoli |
| SCN | 75% | 55-70 | NA | Honeycomb appearance, central scar; stellate scar in the center of the cyst cavity; clear serous fluid |
| MCN | > 95% | 40-60 | NA | Mucin secretion; disconnection from pancreatic duct; ovarian-like stroma; intracellular mucin |
| IPMN | 50% | 60-80 | NA | Communication with pancreatic duct; absence of ovarian-like stroma; mucin |
| Pseudocyst | ≤ 25% | Any | NA | History of pancreatitis or pancreatic trauma; high amylase in pancreatic juice |
| PBL | NA | < 10 | AFP | Hypodense mass; central mass; squamous nest; well-defined margin; heterogeneous; enhanced; circumscribed, plump spindly cell whorls with squamous morules |

SPTP: Solid pseudopapillary tumor of the pancreas; PNET: Pancreatic neuroendocrine tumor; CgA: Chromogranin A; ACC: Acinar cell carcinoma; AFP: Alpha-fetoprotein; SCN: Serous cystic neoplasms; MCN: Mucinous cystic neoplasms; IPMN: Intraductal papillary mucinous neoplasms; PBL: Pancreatoblastoma; NA: Not available.

**Table 4 Reported parenchyma-preserving pancreatectomy for** **solid pseudopapillary tumor of the pancreas**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Country** | **F/M** | **Median/mean age** (yr) | **Surgery type** | **Median/mean follow-up** (mo, range) | **R/M** |
| Li *et al*[100] | China | 129/37 | 32.5 (10-68) | 11 EN, 22 CP | 49 (24-102) | 2 |
| Wang *et al*[103] | China | 84/17 | 31.7 (10-65) | 31 EN | 46.1 (12-101) | 0 |
| Tjaden *et al*[101] | Germany | 44/8 | 29 (8-71) | 4 EN, 5 CP | 54 (2-230) | 2 |
| Cho *et al*[102] | Korea | 56/10 | 14.5 ± 5.8 | 15 EN, 4 CP | 24.9 (10-76) | 1 |
| Gao *et al*[99] | China | 49/13 | 31.76 ± 10.19 | 15 EN, 47 CP | 31 (3-69) | 0 |
| Chen *et al*[104] | China | 8/2 | 44.6 (32-57) | 10 CP | 22.9 (3-48) | 0 |
| Guo *et al*[11] | China | 71/16 | 31.3 ± 13.1 | 6 EN, 4 CP | 46 (13-97) | 0 |
| Wang *et al*[13] | China | 85/12 | 31.6 ± 13.92 | 15 EN, 20 CP, 2 DPPHR | 54 (7-121) | 0 |

F: Female; M: Male; EN: Enucleation; CP: Central pancreatectomy; R/M: Recurrence/metastasis; LR: Local resection; DPPHR: Duodenal-preserving pancreatic head resection.

**Table 5 Current models to predict the risk of recurrence of solid pseudopapillary tumor of the pancreas**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Tumor size** | **Ki-67 index** | **LVI (extratumoral)** | **Classification** |
| **Fudan Prognostic Index[8]** | ≤ 10 cm | < 3% | - | Low risk |
| > 10 cm | < 3% | - | Intermediate risk |
| Any | 3-20% | - |
| Any | > 20% | - | High risk |
| **PUMCH risk model[9]** | ≤ 9 cm | ≤ 1% | Negative | Low risk |
| > 9 cm | Any | Any | High risk |
| Any | > 1% | Any |
| Any | Any | Positive |

LVI: Lymphovascular invasion; PUMCH: Peking Union Medical College Hospital.