Pancreatic Resection for Solid Pseudopapillary Neoplasms

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Abstract

Pancreatic solid pseudopapillary neoplasms (SPNs) are rare and relatively benign tumors, with a malignancy ratio of 10–15%. The utility of multiple imaging modalities, combining with age and gender profile, is crucial for the diagnosis of SPNs. At present, surgery remains the only curative method for SPNs. While opinions towards surgical procedures are highly divided due to its rarity, minimally invasive procedures for SPNs are gradually recommended, whether extent of resection or surgical path. Although patients with SPNs always have a favorable prognosis, postoperative follow-ups remain essential. In general, we mainly discussed the diagnosis, treatment, and follow-up for patients with SPNs.

Pancreatic solid-pseudopapillary neoplasms (SPNs) are rare, accounting for 1–2% and 5% of pancreatic exocrine neoplasms and pancreatic cystic neoplasms, respectively [1]. SPNs are relatively benign neoplasms with a malignancy rate of 10–15% [2]. The mutation of *CTNNB1*, present in over 90% of cases, is a molecular hallmark of the disease, leading to the activation of Wnt/β-catenin signaling pathway [3, 4]. SPNs are mostly found in younger women [5], with a female to male ratio of 10:1 [6]. The symptoms are not well-defined, but the most common symptom is abdominal discomfort, which is present in over half of patients [7]. In addition, about a third of patients are asymptomatic. There is no significant difference in presentation between men and women [8], nor in symptom and tumor characteristics between children and adults [9, 10].

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Radiological examinations are important for SPNs diagnosis. Computed tomography (CT) is the most commonly used imaging modality, followed by ultrasound (US) and magnetic resonance imaging (MRI) [7]. The combination of imaging manifestations of US, CT, and MRI is crucial for the diagnosis of SPNs [11]. However, the CT imaging features of SPNs are different between males and females, such as tumor shape and tumor composition. Tumor imaging in male patients always features a solid mass with lobulated margin and progressive enhancement [12]. Compared to symptomatic SPNs, asymptomatic ones have significantly smaller tumor size and may lack the typical features [13, 14]. The characteristic imaging manifestation combined with age and gender profile may be sufficient for most SPNs diagnosis [15]. EUS-guided fine-needle aspiration (FNA) is a accurate diagnosis method with sensitivity and specificity as high as 91% and 94%, respectively. However, the procedure of FNA may entail certain risks, such as hemorrhage, pancreatitis, pancreatic fistula, gastrointestinal perforation, and even tumor cells dissemination [15]. Previous studies recommended that laparoscopic biopsy should be avoided due to the risk of tumor recurrence and peritoneal dissemination [16–18]. In addition to diagnosis, the preoperative imaging workups are helpful for discriminating between potentially malignant and benign tumors to guide clinical treatment options. Previous studies have indicated that preoperative CT imaging may be helpful to discriminate aggressive SPNs from non-aggressive tumors [12]. Incomplete capsule, ill-defined margin, and absence of bleeding feature in CT imaging are risk factors for aggressive SPNs, which could be used to guide the preoperative selection of surgical procedure. In addition to radiographic results, researchers have also found that preoperative neutrophil-to-lymphocyte ratio (NLR) is predictive of malignant SPNs [19].

At present, surgical resection remains the mainstay of treatment for SPNs, which is recommended by the 2017 International Association of Pancreatology (IAP) and the 2018 European Pancreatic Club guidelines [20–22]. The

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common surgical procedures for SPNs generally include enucleation, segmental pancreatectomy, and pancreaticoduodenectomy, which depend on the location of the tumor [23]. Tumors located in the head or uncinate of the pancreas require enucleation, or pancreaticoduodenectomy with or without pylorus-preserving. For tumors located in the neck or body of the pancreas, surgeons could resect the midportion of the pancreas or perform enucleation. Distal pancreatectomy (DP) with or without splenectomy is often performed for SPNs located in the body or tail of the pancreas [2, 15, 24]. However, there is currently no uniform standard on the selection of surgical procedures. The procedure may be performed either laparoscopically or by open surgery and could be aggressive or function-preserving. The lack of a golden standard is partially due to the rarity of SPNs, and that the current experience is mostly based on the small-scale studies or case reports.

Due to the favorable prognosis and low-grade malignancy of SPNs, pancreatic function and adjacent organ preserving surgery has been proposed by multiple studies [25]. Deficient residual volume of the pancreas is correlated with pancreatic functional deficiency [26]. Previous studies have shown that enucleation could be performed for SPNs located within the head, neck, or body of the pancreas, especially with no indications of dilated pancreatic duct and/or common bile duct [23]. However, opinions regarding such a surgical procedure are highly divided. Some studies maintained that enucleation is indicated for smaller tumors [24], while others considered that it should not be performed because of the increased risk of dissemination, recurrence, and pancreatic fistula [2, 27]. For SPNs in children, enucleation may be a safe and effective surgical procedure if taking tumor size and location into consideration, but it correlates with increased risk of prolonged fasting times and development of pancreatic fistula [28]. Enucleation may be more beneficial for children than adults with SPNs, because it could preserve the exocrine and endocrine functions of the pancreas to the greatest extent. However, because age < 13.5 is associated with a higher risk of recurrence [29], surgeons should balance the benefits and risks of enucleation. Whether enucleation should be performed on patients with SPNs and the selection of patients for enucleation require future researches.

Patients undergoing Whipple's procedure experience significantly longer postoperative hospitalization and increased unadjusted mortality than segmental pancreatectomy, while with no significant difference in postoperative complication rates [30]. Compared to conventional DP, spleen-preserving distal pancreatectomy (SPDP) may reduce the risk of overwhelming post-splenectomy infection, without increasing the complication rate and prolonging postoperative hospitalization [31, 32]. It appears that function or organs preserving surgery is superior to invasive surgery. The function or organ preserving surgery could preserve the function of digestive system, pancreas, or spleen to a large extent, which is crucial for the life quality of patients, especially for younger ones. However, some studies have indicated that parenchyma-preserving surgical procedure is associated with an increased risk for postoperative recurrence due to the incomplete resection [33].

When it comes to the surgical path, laparoscopic surgery is recently becoming more prevalent with the improvement of surgical techniques. Shorter time to diet and postoperative hospitalization, lower intraoperative blood loss and transfusion requirement, and lower complication rates have been previously observed in minimally invasive pancreatectomy (MIP) for SPNs than open groups [34, 35]. However, laparoscopic management may be correlated with a higher risk of local or disseminated recurrence than open laparotomy [36].

There is a growing body of literature that recommends function-preserving and laparoscopic surgery for SPNs due to low-grade malignancy, but routine lymphadenectomy is not indicated because of the rarity of metastasis [15]. However, patients with preoperative imaging workups or histopathological examination showing high-grade malignancy, such as locally advanced tumors or distant metastasis, require more aggressive surgical procedures [37, 38]. For instance, patients with portal-superior mesenteric vein (PV/SMV) and/or adjacent organ involvement, who underwent en bloc primary tumor excision with synchronous PV/SMV and/or adjacent organ resection could obtain a good prognosis [39]. The principle of surgical management for patients with distant metastasis is to resect both the primary and metastatic tumors as completely as possible [40]. But for patients with unresectable tumors of SPNs, adjuvant radiation, chemotherapy, vascular resection and reconstruction, and liver transplantation may be acceptable options, but the evidence level is relatively low [41–44].

Although patients with SPNs always have a favorable prognosis, with the 5-year survival rate of more than 95% [15, 45], postoperative follow-ups remain essential. The majority of recurrences or metastases occur within 5 years after surgery. However, in a small but significant number of patients, recurrence or metastasis has been seen between 5 and 10 years. Long-term follow-ups are needed to examine the outcome of surgery for patients with SPNs. About 2% of patients who underwent surgical resection experience recurrence after surgery [46]. Over the last decades, the factors suggesting malignant potential of SPNs have been broadly explored, which could predict surgical outcome and guide postoperative follow-ups. Extensive researches have shown that tumor size and microscopic malignant features are significant prognostic factors for postoperative recurrence [47–49]. Besides, multiple large-scale studies have demonstrated that blood vessel invasion and larger tumor size may be associated with high-grade malignancy [48, 50, 51]. However, previous studies have shown differences in predictive ability

and cut-off value of tumor size to predict recurrence [52, 53]. Recently, Yang et al. have shown that the combination of Ki-67 and tumor size is helpful to predict postoperative recurrence, superior to the current American Joint Committee on Cancer (AJCC) and European Neuroendocrine Tumor Society (ENETS) staging systems [54]. Negative surgical margins are essential to avoid recurrence, and the intraoperative frozen section could be used for validation [55, 56]. On the other hand, a meta-analysis study that summarized the studies analyzing the relationships between clinicopathological factors and SPNs malignancy has found no reliable factor [57]. In addition to the clinicopathological characteristics, Cohen et al. analyzed the miRNA patterns among normal pancreas, primary tumors, and metastatic tumors through miRNA array. They found that lower expression of miR-375, miR-217, and miR-200c and higher expression of miR-184, miR-10a, and miR-887 are associated with metastasis [58]. However, even if patients relapsed at follow-up, reoperation could still result in long-term survival [24].

We herein summarize the diagnosis, treatment, and postoperative follow-up for patients with SPNs. Yet, the current literature regarding SPNs mostly come from case reports and studies by an isolated center with low levels of evidence. Regardless, minimally invasive procedures are increasingly being recommended for the treatment of SPNs, not only for the extent of resection but also as surgical path. Meanwhile, future studies should establish methods for more accurate preoperative diagnosis and malignant markers. Large-scale multicenter studies are urgently needed to verify and update the current understanding of SPNs.

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