Reviewer 1:

1, Please show how to select papers in this review.

Ans: All reference articles were included in references section at the end.

2, Please impact new findings from this review.

Ans: In our review article we proposed algorithms for pathogenesis and management in addition to histology and morphology, immunohistochemistry, clinical presentation and diagnosis of SPN using the existing current literature. we discussed about EUS-FNA and EUS-FNB in preoperative diagnosis of SPN. SOX11, LEF1, TFE3, and AR that can be putative diagnostic markers in SPNs are discussed. Overall, this review article is comprehensive and guides in management of SPN

3, Please summarize figures

Ans: figures are summarized

4, How do the authors define malignant SPN?

Ans: Angioinvasion, perineural invasion and deep invasion of adjacent surrounding pancreatic parenchyma are considered potentially malignant SPN.

Reviewer 2:

1) The authors described the risk of peritoneal carcinomatosis after EUS-FNA, especially in the case of pancreatic ductal adenocarcinoma (PDAC). However, I think that peritoneal dissemination of tumor cells more likely occur after EUS-FNA (or percutaneous needle biopsy) in the case of cystic tumor, since intratumoral pressure is supposed to be higher in the cystic tumor than in solid tumor like PDAC. Therefore, the authors had better describe the risk of peritoneal dissemination after EUS-FNA in the case of cystic tumor, using the literatures. Or, the authors had better the EUS-FNA method (puncture point, puncture direction, or postpuncture compression) to avoid the peritoneal dissemination.

Ans: It is possible that peritoneal dissemination of tumor cells occurs more likely after EUS-FNA in case of cystic tumors because of increased intratumoral pressure. However, there are very few case reports in the literature. Hirooka et al. described a case report of peritoneal dissemination after EUS-FNA of IPMN located in pancreatic body. They concluded

that pancreatic lesions located in the body/tail have more risk because of needle passage through lesser sac. Kita et al. described another case report of needle tract seeding (NTS) in posterior wall of stomach after EUS-FNA of pancreatic cancer located in pancreatic body. They concluded that NTS is rare in pancreatic head lesions as the needle passage is through duodenum and usually they undergo pancreaticoduodenectomy which includes needle tract (duodenal bulb). However, pancreatic lesions located in body/tail have higher risk of NTS as the needle passage is through transgastric (lesser sac) and they usually undergo distal pancreatectomy which doesn't include needle tract (lesser sac). Hence, there is more risk of peritoneal dissemination with transgastric than transduodenal approach. Sakamoto et al. described a case report of NTS after EUS-FNA of pancreatic adenocarcinoma located in pancreatic tail. They mentioned about slow-pull technique with/without side-hole. Slow-pull technique can increase cytological diagnostic accuracy with less blood contamination. Also, application of low suction during EUS-FNA decreases the blood contamination and increases the diagnostic accuracy. The technique involves the stylet where it is slowly withdrawn from the needle and in and out motion is performed with in the target lesion. When the needle is pulled out without suction, the tissue enters through the side hole thus replacing the existing tumor inside the needle. After the strokes, when the needle is pulled out too far or because of difficult recognition of the side hole on EUS-images, the tissue collected can exit out of the needle hole and there is potential for NTS. Hence, they concluded that slow-pull technique with side-hole needle should be avoided in cases scheduled for resection of pancreatic body/tail cancer to prevent NTS.

2) SPN occasionally recurs very lately after surgery (see "A systematic review of solid-psuodopapillary neoplasms: are these rare lesions?", Pancreas 2014, 43(3): 331-7. In this paper, the median time to recurrence is reported to be 50.5 months). The authors had better describe the importance of long-term observation after resection.

   Ans: The above study suggests a minimum follow up of atleast 5yrs after surgical resection. There are no specific guidelines for follow up after surgery but SPN with pathologic features indicative of aggressive behavior like diffuse growth pattern, high mitotic activity, nuclear atypia, tumor necrosis and component of sarcomatoid carcinoma may require extended period of follow up. Estrella Et al. showed that muscular vessel invasion (tumor cells in the luminal spaces of blood vessels with circumferential smooth muscle layers), tumor (T) stage by European Neuroendocrine tumors society (ENETS) classification, ENETS stage grouping and stage grouping by the American joint committee on cancer (AJCC) were important predictors in disease specific survival of patients with SPN after surgical resection. Recurrence rate was 5/39 (13%) after a median follow up of 76 months. 10-year disease specific survival was 96% and metastatic/recurrent disease was significantly associated with large tumor size ($P<0.001$). Papavramidis showed that 31/467 (6.6%) had recurrence after 1-10 years of

follow up and the most common site of metastasis is liver and lymph nodes. S.G Tipton et al. showed 2/14(14%) had recurrence after a median follow up of 3months to 20 years. Machado et al. showed 2/34(6%) had recurrence after a mean follow up of 84 months.

3) "Computed tomography" in the introduction part in Page 2 had better be "computed tomography" (small letter).
Ans: changed to "computed tomography"

4) "Beta-catenin" in the introduction part in Page 2 had better be "beta-catenin" (small letter). Also, "Mutations in Beta-catenin gene" had better be "Mutations in beta-catenin gene". The authors use the word "beta-catenin" and "β-catenin". They should be unified.
Ans: changed to "beta-catenin"

5) "exon-3 mutations" in the introduction part in Page 2 had better be "exon-3 mutations in beta-catenin gene".
Ans: changed to exon-3 mutations in beta-catenin gene.

6) "The aberrant Protein expression" in the introduction part in Page 2 had better be "The aberrant protein expression" (small letter). Similarly, many capitalized words, such as Pancreatic endocrine tumor, Acinar cell carcinoma, Renal cell carcinoma, exist in the manuscript.
Ans: changed to "The aberrant protein expression"

7) "lead to Wnt signaling" in the introduction part in Page 2 had better be "lead to Wnt signaling activation".
Ans: changed to "lead to wnt signaling activation".

8) The authors use words "p21" and "p21" ("p27" and "p27") in the sentences. They should be unified.
Ans: p21 and P27 are used.

9) The words "Cytoplasmic nuclear expression" in page 4 may cause the readers' confusion. Therefore, I recommend switch the sentence "Cytoplasmic nuclear expression of β-catenin and loss of E-cadherin" to "Nuclearβ-catenin expression and membranous E-cadherin loss". At the same time, the readers would not understand why E-cadherin loss occurs after nuclear translocation of beta-catenin. Therefore, the authors had better explain the mechanism (I know the fact that beta-catenin acts as anchoring of E-cadherin to the membrane.)

Ans: changed to “Nuclearβ-catenin expression and membranous E-cadherin loss”
E-cadherin is a transmembrane protein that mediates cell adhesion through interactions with catenins and it is linked to the actin skeleton. The exact mechanism for the loss of E-cadherin expression is not clear. Tang etal, proposed that loss of E-cadherin is a result of promoter silencing and overexpression of transcription repressors such as Snail.

Reviewer 3:

Are there any previous review articles regarding SPN like this paper? If so, please clarify any differences between this paper and former reports. If not so, please describe it in this paper.

Ans: To our knowledge, from the literature search we came across one review article which summarized the molecular pathogenesis and clinical features of SPN. In our review article we proposed algorithms for pathogenesis and management in addition to histology and morphology, immunohistochemistry, clinical presentation and diagnosis of SPN using the existing current literature. we discussed about EUS-FNA and EUS-FNB in preoperative diagnosis of SPN. SOX11, LEF1, TFE3, and AR that can be putative diagnostic markers in SPNs are discussed. Overall, this review article is comprehensive and guides in management of SPN.

Reviewer 4:

1) I do not fully agree with the algorithm. Even if the suspicion is high at CT/MRI I would prefer an EUS/FNA performed in order to have histological verification of the lesion.
   Ans: Agree, changed to EUS/FNA in order to have histological verification of the lesion.

2) On which data do the authors suggest 5 yrs follow up?

Ans: There are no specific guidelines for follow up after surgery.

Law JK, Ahmed A, Singh VK, Akshintala VS, Olson MT, Raman SP, Ali SZ, Fishman EK, Kamel I, Canto MI, Dal Molin M, Moran RA, Khashab MA, Ahuja N, Goggins M, Hruban RH, Wolfgang CL, Lennon AM. A systematic review of solid-pseudopapillary neoplasms: are these rare lesions? Pancreas. 2014 Apr;43(3):331-7

The above study showed that mean time for recurrence of tumor was just over 4years and hence they suggested a minimum follow up for atleast 5years.

3)The ENETS suggest 10 yrs f/u for the pancreatic NETs.

Ans: Yes, agree that ENETS suggest 10yrs f/up.

4) SOX11, LEF1, TFE3, and AR that can be putative diagnostic markers in SPNs are not discussed.

Ans: Kim et al. identified androgen receptor (AR), lymphoid enhancer-binding factor 1 (LEF-1) and transcription factor for immunoglobulin heavy-chain enhancer 3 (TFE3) as putative diagnostic markers of SPN in addition to beta-catenin. This study showed that the sensitivity and specificity of beta-catenin in SPN were 98.9% and 97% respectively. when beta-catenin, LEF-1 and TFE3 were combined, the sensitivity and specificity of SPN diagnosis increased to 100% and 91%, respectively (34). They concluded that when these markers are incorporated in to immunohistochemical panel, they can help differentiate SPN from pancreatic adenocarcinoma and neuroendocrine tumor. LEF-1 is a member of the lymphoid enhancer binding factor 1/T-cell factor (LEF1/TCF) complex and it acts as a regulator of the Wnt/CTNNB1 signaling pathway. when LEF-1 interacts with mutant CTNNB1 it leads to upregulation of LEF-1 in SPN. CTNNB1 is primarily located in the cytoplasmic plasma cell membrane and it plays a key role in the Wnt signal transduction pathway. Singhi et al. analyzed the immunohistochemical staining for LEF-1 and CTNNB1 in pancreatic tumors. They concluded that abnormal CTNNB1 accumulation with nuclear LEF-1 expression was found in both SPN and pancreatoblastoma but with diffuse nuclear LEF-1 expression in SPN (35).

TFE3 is a member of the microphthalmia(MiT) family of transcription factors. MiT transcription factors regulate cellular proliferation, survival, motility, metabolism, melanocyte development by binding to target promoters (36). These are deregulated during oncogenic process. TFE3 is expressed in 74.7% of SPN (34). Park et al. showed activation of androgen receptor signaling pathway in SPN and they demonstrated increased AR expression at transcriptional and translational levels (37). This study confirmed high level of nuclear androgen receptor expression in all SPN (14/14,100%). Kim et al. showed AR expression in 81.3% of SPN (34).

SOX-11 is a member of the SOX (SRY-related HMG-box) family of transcription factors. They play an important role in cell differentiation, sex determination, development of the central nervous system, hematopoietic, and other organ systems by regulating lineage and tissue-specific gene expression (38). SOX proteins have been shown to be key modulators of Wnt/beta-catenin signaling pathway. However, the interaction between SOX-11 and Wnt/beta-catenin signaling is not reported so far. Harrison et al. showed a sensitivity and specificity of 100% and 84%, respectively in expression of SOX-11 in SPN (39). They concluded that immunohistochemistry with beta-catenin, SOX-11 and TFE3 should be combined to achieve optimal sensitivity and specificity in SPN. Foo et al. evaluated the nuclear reactivity of SOX-11 in SPN and they showed that the sensitivity and specificity was 100%, respectively in EUS-FNA specimens (40).

Minor points:

5) I suggest that the word solitary will be added at the title.

Ans: sorry, we prefer to keep our original title.

6) Not all the pancreatic NETs are immunostained with chromogranin A (eg insulinomas). Please rephrase.
Ans: Agree. However, chromogranin is positive in 50-70% of both functioning and nonfunctioning PanNET.

7) References 30, 47. Not all the letters are of same size.
Ans: changed

8) Reference 34. The name of the journal is missing where this reference was published (J Gastroenterol Hepatol).
Ans: changed

9) I suggest that representative microphotographs with β-catenin immunohistochemistry to be included.
Ans: included

10) Introduction. Please add a space between the abbreviation (SPN) and pseudopapillary neoplasm.
Ans: changed

11) Last two lines of the Pathogenesis (Figure 1). Instead of () please use []
Ans: changed

12) Please make it more clear about E-cadherin IHC.
Ans: **E-**cadherin is a transmembrane protein that mediates cell adhesion through interactions with catenins and it is linked to the actin skeleton. The exact mechanism for the loss of E-cadherin expression is not clear.

13) The authors use two abbreviations and two terms for pancreatic endocrine/neuroendocrine (PanNETs/PET) tumors. Please consider only one.
Ans: Changed to PanNET

14) Last line at the immunohistochemistry part. Please consider immunohistochemical staining or immunostaining and not immune histochemical staining.
Ans: changed to immunohistochemical staining

15) Clinical presentation at diagnosis please add a space between Type 3.
Ans: added space to Type 3

16) Anastomotic and not anastomatic leak.
Ans: changed to anastomotic leak.

17) Space between pancreaticoduodenectomy and (PPD).
Ans: changed space between pancreaticoduodenectomy and PPD.

18) Lymph node and not lymphnode.
Ans: changed to lymph node

19) Space between 2/14(6%) and 2/34(6%).
Ans: changed.

20) The authors use abbreviations in terms that are used only once or twice, they should consider omitting these abbreviations.
Ans: changed.