Dear Dr. Yuan Qi, dear reviewers,

Thank you very much for your revision of our paper "Simultaneous occurrence of autoimmune pancreatitis and pancreatic cancer in patients resected for focal pancreatic mass" (ESPS manuscript NO: 32196). We have taken all your comments seriously, we have addressed all of them as outlined below and appropriate changes have been made in the manuscript. We think that the reviewers' comments and suggestions improved our paper and we hope you will now find it suitable for the audience of your journal.

Please see below a detailed point by point response to the reviewers:

Reviewer #1 (00503444)

1. The sentence in the terminology section should be modified: "Pancreatic cancer is usually an adenocarcinoma derived from pancreatic ductal cells".
2. Anyway, the section "terminology" is a repetition of sentences contained in the introduction section.
3. This sentence "Proper diagnosis of AIP is an indication for immunosuppressive therapy, but failure to recognize AIP results in surgical treatment, which is then deemed unnecessary." is a general comment because in this case series the main problem is that AIP patients having pancreatic ductal adenocarcinoma were not recognized before the surgical approach. Please revise.
4. The high incidence of pancreatic cancer in patients with AIP is an intriguing finding that draws attention to the eventuality of synchronous presence of PC in patients with proven AIP: this sentence is not clear for physicians and should be reworded.
5. Discussing the accuracy of IgG4 serum levels, please add a comprehensive meta-analysis on this topic (Morselli-Labate AM, Pezzilli R. Usefulness of serum IgG4 in the diagnosis and follow up of autoimmune pancreatitis: A systematic literature review and meta-analysis. J Gastroenterol Hepatol. 2009 Jan;24(1):15-36.)

Response to Reviewer 1:

1. **The sentence was changed according to your suggestion.**
2. **We shortened the terminology section to avoid repetition of already written statements.**
3. **The sentence was changed as suggested.**
4. **The sentence was rewarded for better understanding.**
5. **The content of the meta-analysis is now discussed in the manuscript and the paper is referenced.**

Reviewer #2 (02650654)

The paper is interesting. I suggest to give more discussion about the severity of jaundice in case of pancreatic head cancer, to specify the most frequent localization of the cancer, if in the head, body or tail. It would be important to show some Ct or MR pictures, demonstrating the most important signs of this association. A flow-chart of the diagnostic procedure could help in reading the article

Response to reviewer 2:

We agree that the presence and severity of jaundice may possibly be an interesting issue. We show in our Results section that there was not a statistically significant difference in the presence of jaundice between the two groups of patients. However, due to the retrospective character of the study, we were unable to provide a meaningful comparison of severity of jaundice since in some of our jaundiced patients, exact bilirubin levels were not available (some of those referred from other hospitals). Furthermore, the severity of jaundice is significantly influenced by the time between disease development and patient's presentation and may thus not reflect solely the disease type/extent. Nevertheless, we at least mention the issue in the text now.

Information about localization of the cancers was added to the results section of the paper.

We agree with you that showing a CT/MR picture is important and we now include it in the revised manuscript.

As this was a retrospective study, the diagnostic process in our patients did not follow a specific flow-chart. We do provide, though, information about what diagnostic procedures our patients had.

Reviewer #3 (03316921)

Dear authors: Your work is very interesting; congratulations. I only have an observation: when you describe that an experienced pathologist reviewed the cases, it is subjective to say "experienced". So it would be helpful to add the number of AIP or PC cases reported by the pathologist, before the cases reported within the period of time described.

Response to reviewer 3:

We appreciate the encouraging feedback. The pathologist who reviewed the cases is our hospital expert on pancreas pathology. The hospital serves as a tertiary center for pancreatic diseases and pancreatic surgery. We now specify in the text that our pathologist had had experience with hundreds of pancreatic cancer and chronic pancreatitis cases prior to our study.

Reviewer #4 (02529835)

1. Given the different treatment option, separating PC from AIP is a clinical necessity. The differential approach, apparently not simple and straightforward, is of clinical significance which is the value of this study and has been explored and discussed to some extent, but not thoroughly. To me, the value we can draw from this study is to find all possible pre-surgery clues to separate PC from AIP. Authors are clearly aware of the limitation of their study, including small case number and incomplete pre-surgery workup. As said, among the 15 AIP patients in the study, none of them had a prior surgery diagnosis. For a retrospective study, one helpful suggestion is to analyze all AIP patients who received a definite diagnosis without surgery during the same period. Try to find more clues in the pre-surgery workup and prognosis to improve the diagnostic sensitivity and specificity. Maybe after comparison, some clues will emerge.
2. It will be helpful to provide a flow chart to demonstrate how to differentiate AIP from AIP+PC.
3. The author provided the highest count of IgG4 in patients with AIP and PC. Is the IgG4 expression patchy, multifocal or diffuse?
4. Complete data including AIP patients should be provided in table 3 which can be listed as type 1 (AIP, AIP+PC) and type 2 (AIP, AIP+PC).
5. The observation of different weight loss is interesting. Although there is no statistical significance in the absolute weight loss, is there any difference in the weight loss percentile compared to the baseline? Will it be different?
6. Other minor comments, add the initial of the pathologist who reviewed the cases in method.
7. In table 1, provide the normal range of Ca 19-9.

Response to reviewer 4:

1. **We fully agree with the reviewer that one of the main values of the study is finding pre-surgery clues to separate AIP and PC. We have been able to do this by finding three differences (age, weight loss, diabetes). We further agree that making a comparison to a third group of patients with pre-surgery diagnosis of AIP could possibly provide additional clues. However, we have to admit that we were able to make a pre-surgery diagnosis of AIP in the same time period only in 3 patients, a number that does not allow a meaningful comparison. It needs to be noted that the time period of our study started in the year 2000, when the awareness of AIP was very limited.**
2. **We feel that having a flow chart that would demonstrate how to differentiate AIP from PC would be very helpful for clinical practice. However, we think that the aim of our study, its retrospective character and the results do not allow for such a chart. Producing such a flow chart was possible for example in the studies by Chari et al. (Chari ST, A diagnostic strategy to distinguish autoimmune pancreatitis from pancreatic cancer, Clin Gastroenterol Hepatol 2009;7:1097-1103) or Kamisawa T et al (Strategy for differentiating autoimmune pancreatitis from pancreatic cancer. Pancreas 2008;37:e62-e67). These studies were designed with the aim to find features distinguishing AIP and PC. They**

used a retrospective analysis of high quality prospectively obtained data, used appropriate statistical analyses and a validation cohort of patients.

3. **Only patients with diffuse distribution of IgG4+ plasma cells were included in the study. We mention this in paragraph 4 of the Discussion section.**
4. **Table 3 was changed as suggested.**
5. **Unfortunately, we cannot assess the weight loss percentile in all of our patients because of the retrospective data acquisition. Even though the absolute weight loss is available in all patients, the exact body weight is not available in the medical history of some of them. However, after changing the statistical method used for evaluating the differences in weight loss (Mann-Whitney test as suggested by reviewer 5), the weight loss difference became statistically significant.**
6. **Initials of the pathologist were added to the Method section as suggested.**
7. **The normal range of Ca 19-9 is now provided in table 1.**

Reviewer #5 (03475317)

1. The term IgG4 systemic sclerosing disease should be changed by IgG4 related sclerosing disease. It's used more commonly.
2. You should include in the characteristics of type 1 AIP the presence of autoantibodies and extrapancreatic lessions.
3. It's wrong that focal pancreatic enlargement is more common than diffuse pancreatic elargement in AIP. Diffuse enlargement of the pancreas is more typical and specific of AIP.
4. The diagnosis of AIP should have been done according to the ICDC criteria not only based on the histological findings.
5. Statistical analysis should be improved: Which software have been used for the data analysis? The Mann-Withney U non-parametric test should be used for the comparation of quantitative data.
6. To complete the study, serum IGg4 levels should be measured in all patients, because it have been reported in several studies that increased serum IgG4 levels is useful to differentiate AIP (referred to type 1 AIP) from PC. The presence of autoantidodies and extrapancreatic lessions should have been evaluated in all patients.
7. Expression of data is confusing and are not presented properly. Data should be expressed as Median (Range).
8. In the Table 2 you should include Data are expressed as.. at the bottom.
9. The results included in the Table 2 regarding to the histopathological findings, should be explained more clearly, because the description is quite confusing.
10. Focal pancreatic lesions are less frequent than diffuse enlargement of the pancreas in AIP.
11. I`m not agree with this sentence: " Serum markers of AIP and pancreatic cancer are often not hepful in the diagnosis of either conditions". Several studies

supported that increased serum IgG4 levels and some autoantibodies (Such as, serum anti-carbonic anhydrase II and anti-α amylase antibodies) are useful to differentiate AIP from pancreatic cancer. Additionally to give this conclusion, you should have determined this serological markers in your patients.

12. Could you give some appropriate explanation of this sentence? " It is likely that many patients with AIP-not otherwise specified (NOS) would be reclassified as AIP Type 2 after examination of their histological materials".
13. The high incidence of pancreatic adenocarcinoma in your patients with AIP, could be explained only by the design of the study because you have select only the patients with focal lesions.
14. The sentence in the discussion "AIP type 1 as a paraneoplastic phenomenon" is purely conjectural. The conclusion of the study is too long and confusing, you should give a more precise conclusion.

Response to reviewer 5:

1. **The term was changed as requested.**
2. **The presence of other organ involvement in patients with AIP type 1 is noted in the Results section, paragraph 3, and also in table 1. We agree about the importance of serum markers in AIP type 1 patients, however due to the retrospective nature of the study, they are not available in all of them.**
3. **It is obvious that the disease can present in both forms, that is as diffuse or focal. It is very likely that the proportion of the two forms varies among studies and patient populations. It seems, however, from the literature that the focal form is overall more frequent.**
   Frulloni et al., Am J Gastroenterol. 2009 (PMID 19568232) - focal-type AIP was diagnosed in 63% and diffuse-type in 37% of patients.
   Maire et al., Am J Gastroenterol. 2011 (PMID 20736934) - imaging showed pancreatic mass in 21 patients (47%) and diffuse pancreatic enlargement in 15 (34%) patients with AIP.
   Furthermore, it was shown that focal lesions are more common in patients with AIP type 2.
   Sah et al., Gastroenterology. 2010 (PMID 20353791) - diffuse swelling vs focal features: type 1 AIP, 40% vs 60%; type 2 AIP, 16% vs 84%.
   Kamisawa et al., Pancreas. 2011 (PMID 21747310) - patients with LPSP (AIP type 1) were more likely to have diffuse swelling of the pancreas (40% vs 25%) compared to IDCP (AIP type 2) patients.
   Fritz et al., Br J Surg. 2014 (PMID 25047016) - 30 of 32 patients with AIP type 2 were found to have a localized tumour-like pancreatic mass and underwent pancreatectomy, compared with only 16 of 40 with type 1.
   We cite now more studies in the revised manuscript to support this statement.
4. **All patients with definitive type 1 and type 2 AIP were diagnosed according to the ICDC criteria (level 1 histology evidence + indeterminate parenchymal imaging) (Methods section, paragraph 2, page 6). In a retrospective manner, the**

non-histology ICDC criteria were applied whenever possible and were met by no patient (Results section, last paragraph, page 8).

5. **We thank the reviewer for this very valuable comment. We agree that Mann-Whitney test is more appropriate. A new statistical analysis was performed by a professional statistician as suggested by the reviewer, and the difference in weight loss between AIP and AIP+PC groups reached statistical significance. We also added information about the statistical software used in the Methods section.**
6. **We agree that having serum levels of IgG4 in all patients would be very valuable for the study. However, this is a retrospective study and the values are not available in most of our patients, as they were referred to our center for pancreatic surgery with a suspicion of pancreatic cancer. We regret that it cannot be done ex post, as all patients with AIP+PC already died.**
7. **Quantitative data are now expressed as median (range).**
8. **Table 1 description was changed as suggested.**
9. **We agree that the histopathology definitions may be a little cumbersome, however we wanted to stick to the official terms used in the ICDC criteria.**
10. **Please see paragraph 3.**
11. **We agree that the sentence is confusing and that serum markers (notably serum IgG4) are helpful in distinguishing AIP from PC. We wanted to point out that elevation of serum IgG4 might be present in patients with PC. We changed this paragraph in the revised manuscript.**
12. **This sentence might be confusing when it is out of context. We omitted the sentence in the revised manuscript.**
13. **We are aware that the high incidence of PC in our AIP patients may be caused by selection bias and may not reflect the situation in the general population of AIP patients. However, we believe that it still allows us to point out the possible co-occurrence of the two diseases.**
14. **The relationship between AIP and PC (if there is any) is not known. We discussed possible explanations for this finding. AIP being a paraneoplastic phenomenon is just one of hypotheses proposed by some Japanese authors. We stated that this observation was not confirmed by further studies. Regarding the conclusion of the paper, it was revised as suggested.**