Dear Reviewers,

Thank you very much for taking your time to review our manuscript. We believe our manuscript is greatly improved thanks to your constructive comments. Our answers are appended below, and the changes in the manuscript are highlighted in yellow.

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The manuscript is well-written and very informative for the readers. – Thank you!

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This is an interesting minireview that aims to to describe the microscopic, immunohistochemical and molecular features that can help distinguish PDAC and benign mass-forming entities, especially CP,according to the latest World Health Organization (WHO) classification of digestive system tumors.However, the author reviewed a few subtypes of non-conventional PDAC that may further confound the diagnosis with their differing morphologies. It's very promising that the molecular markers of PDCA would be favored to distinguish CP. – Thank you!

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Manuscript Number: 63890 Title: Benign Versus Malignant Pancreatic Lesions: Molecular Insights to an Ongoing Debate The authors describe the microscopic, immunohistochemical and molecular features that can help distinguish pancreatic ductal adenocarcinoma (PDAC) and benign mass-forming entities, including chronic pancreatitis (CP), autoimmune pancreatitis (AIP), and paraduodenal pancreatitis (PDP). The authors describe the histological characteristics of three benign diseases similar to pancreatic cancer. In order to make it easier for readers to understand the histological characteristics of these three benign pancreatic

diseases and to distinguish them from those of pancreatic cancer, the author should summarize and list them in the same table. – Table 1 is added as suggested.

Chronic pancreatitis is also an important risk factor for pancreatic cancer, so the similarities and differences between the two diseases at the time of clinical diagnosis should be described in more detail. – Paragraphs regarding risk factors, clinical presentation and imaging findings of PDAC and CP are added in the respective sections.

When clinically diagnosed, autoimmune pancreatitis can easily be misdiagnosed as pancreatic cancer, thus leading to unnecessary surgery on the patient. The authors should elaborate on autoimmune pancreatitis and pancreatic cancer, especially the clinical features that are prone to misdiagnosis. – We agree this is an important point to add. We re-iterated clinical presentations and imaging findings (presentation as a mass lesion) of AIP that are similar to PDAC in the beginning of the section.

In addition, this review lacks the prospect of conclusion. The author should summarize the content of this paper and provide some important guidance and suggestions for future readers. – A conclusion paragraph is added.

Overall, I think this is an interesting study that has important implications for the diagnosis of pancreatic cancer and other clinically similar benign pancreatic diseases. The manuscript can be accepted and published in World Journal of Gastrointestinal Surgery after major revision. – Thank you!

Reviewer #4:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: I want to congratulate the authors for this review on a difficult topic. The authors have done an admirable work summarizing the relevant literature about the challenging task in differentiating benign mass forming pancreatic lesions, sometimes presenting as chronic pancreatitis from pancreatic ductal adenocarcinoma (PDAC). – Thank you!

A rationale algorithm with a microscopic, immunohistochemical and molecular workup is finally outlined and to help clinicians for a definitive diagnosis and therapy. I want to remark a few critical points and suggest something which can be usefully added in this review: 1. Autoimmune pancreatitis (AIP): the Authors have correctly stated that the clinical presentation of AIP and PDAC can be strikingly similar and the finding of a normal pancreas on imaging does not preclude AIP which require in most cases further histologic investigation. In my opinion, the Authors should briefly add to conclusions in the paragraph of AIP that the diagnostic approach of AIP is complex and requires a combination of clinical, laboratory, radiological examinations and typical pathological findings when available. Most clinicians consider the so-called HISORt criteria which combine multiple information from Histology, Imaging, Serology, Other organ involvement, and Response to therapy. – We agree. We added concluding remarks in the AIP section as suggested. Thank you for bringing up HISORt criteria.

2. Figure 8. “An algorithm outlining the steps for the work up of pancreatic ductal adenocarcinoma (PDAC) vs chronic pancreatitis (CP)”. I would probably specify in the legend before work up “microscopic, immunohistochemical and molecular work up”. – The legend is modified as suggested. Thank you.

3. I would suggest the Authors add a comprehensive table that summarize all the main specific features of benign form of chronic pancreatitis and the different types of PDAC with their essential characteristics and features (microscopic, immunohistochemical and molecular). – Table 1 and Table 2 are added. There is no immunohistochemical difference between differing subtypes of PDAC, therefore immunohistochemistry is not included in Table 2. But we included morphologic features and altered genes of the PDAC subtypes. Thank you for your suggestions.