Dear editor and reviewers, we appreciate the comments to our manuscript and the opportunity to be considered for publication in the World Journal of Gastrointestinal Oncology.
According to the reviewer´s and editor suggestions we have edited the manuscript.

1. We sent the manuscript for English language editing and provide the correspondent certificate.
2. WE use the RCA system to update and select new evidence and information requested by the reviewers.

Reviewer 1.

Specific Comments to Authors: This article described current diagnostic limitations of diagnosis among AIP, PDAC and MFCP and highlighted the disease specific imaging, serological and histological characteristics which may play a significant role in the differentiation of pancreatic mass of uncertain diagnosis after an initial diagnostic approach.

1. The following question should be concerns. New Imaging Techniques in Pancreas, such as Perfusion CT, Dual-energy CT and low-voltage tube techniques, MRI elastography, etc. might provide useful information that would increase our capability to differentiate benign from malignant pancreatic masses. It is suggested to add the typical imaging of "New Imaging Techniques in Pancreas", and its disctintive radiological features of AIP. MFCP and PDAC in Table 1.

We appreciate your comment. As you suggested, we have added information on those new imaging techniques, so we modified the main manuscript and table 1 accordingly, also we found potentially useful add a paragraph about the potential utility of liquid biopsy.

Introduction

…. The advent of new techniques such as the dynamic-MRI, that calculates and evaluates perfusion parameters may increase the diagnostic yield and seems to provide relevant information regarding chemo sensibility to standard and antiangiogenic therapies for PDAC. Perfusion CT, dual-energy CT and MRI elastography diagnostic performance report are encouraging; pending of further research, so far, they seem to produce relevant information that would improve our current capacities, to differentiate distinct malignant and benign pancreatic masses [1]. In addition to the former imaging techniques, serologic

markers, histologic examination, and in some cases, therapeutic trials (e.g., steroid trial for presumed AIP) can be entertained.

Section on New imaging techniques in the main manuscript.

New Imaging Techniques in Pancreas

Some recently developed techniques might provide useful information that would increase our capability to differentiate benign from malignant pancreatic masses.

Perfusion CT is a modality that is not widely available but seems to differentiate between MFCP and PDAC. Yadav et. al [82] Aslan et al. [83] assessed the characteristics histology proven PDAC and MFCP on perfusion CT. Blood flow (BF) and blood volume (BV) were the best parameters that differentiated both entities from each other. Although both presented low values in BF and BV compared with normal pancreatic parenchyma, the lowest ones were more frequent in PDCA. A cut off value of 19ml/100 ml/min for BF and a value of 5 ml/100 ml for BV had a 100 % and 92 % sensitivity and 73 % and 68% specificity respectively to differentiate PDAC from MFCP.

These results are encouraging but they still need to be replicates and validated in larger studies.

On the other hand, dual-energy CT and low-voltage tube techniques have become the modality of choice for pancreatic cancer imaging and has shown good performance in detecting < 2 cm or isoattenuating lesions. This methods allows a more precise characterization of the solid or cystic nature/components of a given pancreatic lesion as well as a better visualization of de pancreatic duct and surrounding vascularity [14,86].

Low voltage generated images increase the probability of detecting a hypodense lesion embedded in normal pancreatic parenchyma compared with those obtained with a high voltage equipment. Such distinction becomes more evident during the portal contrasted phase. [87]. Low voltage CT has higher sensitivity in diagnosing PDCA compared to high voltage imaging using iodine contrast (86).

PET/CT has limited and low diagnostic yield when discriminating between benign inflammatory masses and malignant ones[8,87].

MRI elastography is a new tool with high diagnostic accuracy differentiating PDAC from AIP by assessing and comparing the tissue rigidity related to either an inflammatory process and a malignant one……

Paragraph on liquid biopsy.

Liquid Biopsy

Liquid biopsy identifies circulating tumor DNA, micro RNA, and cells, and has shown to be feasible and efficient in diagnosing different malignant neoplasms at early stages (e.g., lung, breast, colon and liver cancer). It also has been suggested that it could be a reliable confirmatory test and possibly repalce the need for tissue biopsy [92].

Information in pancreatic cancer is scarce but promising, it could not only aid in the diagnosis, but also may provide information related to potential therapeutic targets as well as about prognosis [93,94,95]. Its reported sensitivity and specificity in diangosing PDAC range between 33-100% and 27-81% respectively [93]. Liquid biopsy could also be applied in the study and diagnosis of benign conditions such as AIP and CP.

Pancreatic cancer (PDAC) is one of the most lethal malignancies and it is on course to become the 2nd cause of cancer-related death. Often, PDAC´s clinical and radiological presentation may be mirrored by other inflammatory pancreatic masses such as autoimmune pancreatitis (AIP) and mass-forming chronic pancreatitis (MFCP) making its diagnosis challenging. Differentiating autoimmune pancreatitis and mass-forming chronic pancreatitis from PDAC is vital due to significant therapeutic and prognostic implications. Current diagnostic criteria and tools allow to precisely differentiate benign form malignant masses most of times, however diagnostic accuracy is not perfect. It has been reported that major pancreatic resections have been performed in AIP cases under initial suspicion of PDAC, after an initial diagnostic approach failed to provide an accurate diagnosis…….

Reviewer #2:

Specific Comments to Authors: The article discusses the challenges in accurately diagnosing pancreatic ductal adenocarcinoma (PDAC), which has a low survival rate. Other pancreatic masses such as autoimmune pancreatitis (AIP) and mass-forming chronic pancreatitis (MFCP) can be mistaken for PDAC, making it important to differentiate them due to different treatment and prognostic implications. Current diagnostic tools have limitations and may not always provide a clear diagnosis, leading to major pancreatic resections being performed unnecessarily. The article highlights disease-specific characteristics that can aid in accurate diagnosis, such as clinical, radiological, serological, and histological hallmarks.

1. I would suggest to slightly restructure the manuscript to allow the reader efficiently catch the bulletts.
   Here is a possible outline for systematically reviewing the topic of accurately diagnosing pancreatic masses, including PDAC, AIP, and MFCP: I. Introduction Background information on pancreatic masses, including PDAC, AIP, and MFCP Importance of accurate diagnosis due to different treatment and prognostic implications Overview of current diagnostic tools and their limitations II. Methods Systematic search strategy for relevant studies in multiple databases Inclusion and exclusion criteria for studies Quality assessment of included studies III. Results Summary of studies that evaluated the accuracy of different diagnostic tools for distinguishing

between PDAC, AIP, and MFCP Description of disease-specific clinical, radiological, serological, and histological characteristics that can aid in accurate diagnosis Discussion of the limitations and challenges of current diagnostic tools, including cases where major pancreatic resections were performed unnecessarily IV. Discussion Implications of accurate diagnosis on treatment and prognosis for patients with pancreatic masses Recommendations for improving diagnostic accuracy, such as incorporating disease-specific characteristics and using multiple diagnostic tools in combination Future research directions, including the development of new diagnostic tools and the evaluation of novel biomarkers V. Conclusion Summary of key findings and recommendations for improving diagnostic accuracy in pancreatic masses VI. Limitations Limitations of the systematic review, such as the quality and quantity of included studies, as well as potential publication bias Suggestions for future research to address these limitations

Answer: *Thank you for your comments and suggestions. We agree that the different topics discussed in the manuscript are worthy for one or more systematic review and even a meta analysis. However our aim was a Literature review. We did not try to answer a specific questions and did not perform a more comprehensive search using different tools and databases.*

A review article is a comprehensive and reliable analysis and detailed and systematic exposition of the research history, current situation, progress, and future trend of a certain field or research topic. Its purpose is to draw structural, trend, forward-looking, and guiding conclusions and to reasonably point out existing problems and future research directions. Most review articles are written by leading or distinguished experts in a field or industry[1].

The aim of our study was to reasonably describe current situation of existing diagnostic limitations that hinder our ability to reach an accurate diagnosis among AIP, PDAC, and MFCP and to highlight those disease-specific clinical, radiological, serological, and histological characteristics that could support the presence of any of these three disorders when facing a pancreatic mass with uncertain diagnosis after an initial diagnostic approach has been unsuccessful. Trying to suggest or unveil future research directions.

In trying to conduct a systematic review, means to start a new project with a specific design trying to answer a specific question which will require a longer time to achieve, as it would be an entirely new project. Our current information discusses different aspects, clinical, biochemical, imaging from different populations and statistical designs, rises not one by different questions that need to be

independently answered, also the consulted literature is vast and would introduce a high heterogeneity to the sample and we consider that the number of manuscripts that may be included in the current form would be very low. However we will plan on designing a systematic review and eta analysis that could answer on of the many questions raised by our manuscript.

We rephrased the abstract and manuscript trying to highlight and present with more clarity the current limitation in the differential diagnosis of pancreatic masses using current clinical, biochemical and imaging data, also we try to highlight the importance of an accurate differential diagnosis as well as to clearly present those highly disease specific clinical and imaging findings that may help in the differential.

2. As the authors tried to, Incorporating case reports within the review can help provide real-world examples of the challenges faced in accurately diagnosing and treating pancreatic cancer. One approach could be to include a separate section dedicated to case reports, where a few representative cases are summarized and discussed in relation to the main themes of the review. The selected cases could highlight the difficulties in accurately differentiating pancreatic ductal adenocarcinoma (PDAC) from other pancreatic masses, the impact of genetic alterations on treatment decisions and outcomes, and the challenges posed by the tumor microenvironment in achieving effective treatment. By incorporating case reports that illustrate key points of the review, readers can gain a better understanding of the real-world implications of the challenges in diagnosing and treating pancreatic cancer. CARE (CAse REport) guidelines are a set of internationally recognized guidelines developed to improve the accuracy, transparency, and completeness of case reports. These guidelines provide a standardized approach to writing and reporting case reports, with the aim of ensuring that all relevant information is included and that the report is of high quality. The CARE guidelines consist of a 13-item checklist covering different aspects of the case report, including the title, abstract, introduction, case description, discussion, and conclusion. The guidelines recommend that case reports include a clear description of the patient's history and presentation, details of the diagnostic evaluation, treatment, and outcomes, and any relevant ethical considerations.

Answer: Thank you for your recommendation, However our aim was a Literature review. We think that incorporating a section of case reports is out of our manuscript´s scope and would not add in our opinion more information, however we do incorporate and provide the citation reference of clinical cases or case series to be consulted by those reader that may be interested.

3. Previously published manuscript contributing to the understanding of pancreatic cancer and the need for accurate diagnosis and effective therapeutic strategies to improve the prognosis and survival rates of patients with this disease should be discussed. Indeed, the tumor microenvironment, which includes blood vessels, plays a crucial role in pancreatic cancer progression and immune evasion. Endothelial cells in blood vessels can act as immune checkpoints, controlling immune patrolling and affecting the response to immunotherapy. In pancreatic cancer, the tumor microenvironment is known to be immunosuppressive, making it difficult for immune cells to infiltrate and attack cancer cells. Therefore, understanding the role of blood vessels and endothelial cells in the tumor microenvironment and their relationship with key mutations (i.e. K-RAS) can help in developing effective treatment strategies for pancreatic cancer, including targeting the immune checkpoint molecules expressed by endothelial cells (PLEASE refer to PMID: 33918146 and expand accordingly).

   Answer: Thank you for your recommendation. Considering the comment, we added a paragraph on liquid biopsy and its potential utility in approaching pancreatic masses.
   The scope of our literature review is to comment on the limitations of current clinical, biochemical and imaging diagnostic tools in the differential of different pancreatic masses. The reviewer´s suggestion makes to consider a specific review on oncogenesis, tumor markers, tumor microenvironment. And although all of them explain some clinical scenarios, it is not with in the intention of our manuscript. But considering the comment, we added a paragraph on liquid biopsy and its potential utility in approaching pancreatic masses.