Dear Editor:

Thank you so much for your great suggestions and comments to our manuscript NO: 49159 titled "Apparent-Diffusion-Coefficient-based Histogram Analysis Differentiates Histological Subtypes of Periampullary Adenocarcinoma". Based on your suggestions, we have revised the manuscript and responded point-by-point to the comments. The clean and annotated versions are attached. If you have any questions about the paper, please do not hesitate to contact me.

Best regards

Point-by-point response to the comments of the reviewer :

1.Title: -Please consider starting with "MRI-based" or similar so as to better orient the reader (at face value). The title might be changed to something like: "MRI-based Volumetric ADC Histogram Analysis Differentiates Histological Subtypes of Periampullary Carcinoma"

Answer: Thanks for your great suggestion. Based on your comments and combined with the editor's request, we changed the title to "Diffusion-weighted-imaging -based Histogram Analysis Differentiates Histological Subtypes of Periampullary Carcinoma"

2. Abstract: In the sentence, "However, the classification of histological subtypes is difficult before surgery", it might read better to include the words "to determine" after the word "difficult".

Answer: Thanks for your great suggestion. We have revised this sentence and it refers to P3 in the revised version.

3. Please include in the introduction section what the underlying imaging modality of ADC is (MRI, CT, either) as pertinent to this study.

Answer: Thanks for your great suggestion. We have introduced DWI and

ADC in more detail and explained the value of this functional MRI modality. It refers to P6 in the revised version.

4. In the aim section can remove the word "the" for improved readability.

Answer: Thanks for your great suggestion. We have revised this sentence and it refers to P3 in the revised version.

5. The terms "periampullary neoplasm" and "periampullary adenocarcinoma" are both used; is this intentional? (e.g. do the authors mean to ascribe distinct meanings?) Also, further down in the text, the term "periampullary tumor" is used, further adding to what seems to be heterogeneity in nomenclature.

Answer: Thanks for your great suggestion. We have revised it and make them the same to avoid ambiguity. Periampullary adenocarcinoma is one part of periampullaty carcinoma, which is included in the malignant epithelial tumours of the periampullary regions. The aim of this study is to distinguish two subtypes of the periampullary adenocarcinoma. To avoid misunderstanding, we also converted the word "carcinoma" to "adenocarcinoma" in title.

6. Introduction: "No significant survival benefit has been proven in periampullary adenocarcinomas after receiving chemotherapy, indicating the histological heterogeneity of the periampullary malignancy" seems to not make sense and/or is out of place. Please revise.

Answer: Thanks for your great suggestion. We reviewed the latest literature and modified our expression. It refers to P5 in the revised version.

7. This series of sentences is quite choppy and needs better transitions/revisions for readability:

"The median overall survival was 71.7 months for IPAC and 33.3 months for

PPAC [6]. PPAC is prone to show a greater response to gemcitabine-based therapies, while the IPAC responds better to fluoropyrimidine [9]. Tumor histology was recommended for driving therapeutic strategies [5,10]."

Answer: Thanks for your great suggestion. We have modified these sentences to make them more fluent and easier to understand. It refers to P5 in the revised version.

8. "At present, the classification of histological subtypes mainly relies on standardized dissected PD specimens." What of EUS-FNA, biliary brushings, and endoscopic biopsies? Are they not adequate to perform histological classification, at least in a subset/certain percentage of patients?

Answer: Thanks for your great suggestion. The classification of the histological subtype requires a standard procedure including evaluation of all important anatomic structures (main and accessory pancreatic duct, ampulla of Vater, minor papilla, common bile duct, pancreatic head) [Carcinoma of the ampulla of Vater: comparative histologic/immunohistochemical classification and follow-up[J]. Am J Surg Pathol, 2004,28(7):875-882]. EUS-FNA, biliary brushings, and endoscopic biopsies could not provide adequate histological information and has not been used as a gold standard in the literature that has been studying histological classification of periampullary adenocarcinoma. [BMC Cancer,2008,8:170; Radiology,2010,257(2):384-393; Am J Surg Pathol,2012,36(11):1592-1608; JAMA Surg,2017,152(1):82-88]

9. In the sentence, "Bi et al [15] found a combination of a progressive enhancement pattern and low ADCmin values (b800)…", ADC should be defined (rather than defining the abbreviation further along in the Intro).

Answer: Thanks for your great suggestion. We have defined ADC and ADC_{min} in this paragraph. It refers to P6 in the revised version.

10. "In addition, the use of gadolinium-based contrast agents is limited in

patients with impaired renal function." This is true; however, if contrast can improve diagnostic performance in those who do not have impaired renal function (the majority of patients in most settings), it would be useful to study this.

Answer: Thanks for your great suggestion. The enhancement pattern of the two subtypes is worth to deep investigate. We will focus gadolinium-based enhancement in near future.

11. Methods: (b) patents histopathologically confirmed with lesions other than IPAC or PPAC"; change "patents" to "patients".

Answer: Thanks for your great suggestion. We have revised the word. It refers to P7 in the revised version.

12. Please provide an overview of what b values mean/indicate. Also, why would one expect differences at a b value of 1,000 but not at 800? Some biological basis should exist/be explained (if not in the methods, than in the intro or discussion).

Answer: Thanks for your great suggestion. We have added an equation in the method section which could explain what b values is and how ADC is calculated. It refers to P8 in the revised version. The ADC value will change with the b value. In the acquisition of DWI, different b value is adopted for different tissue. The choice of b value has been explained in the discussion section. It refers to P11-12 in the revised version.

13. Results: -Perhaps one of the biggest limitations of the study, as shown in the flow diagram, is that it includes less than 10% of the n=476. The drop for 476 to 125 is of considerable magnitude; could the authors further break this down? E.g. how many didn't undergo MRI, how many underwent MRI but at lower Tesla, etc.

Answer: Thanks for your great suggestion. Among the 476 patients, 165

patients underwent MRI at 1.5 T. Among those underwent MRI at 3 T, 147 patients did not underwent DWI. We have added this part in the flow chart. It refers to Figure 1 in the revised version.

14. Discussion: -Need to discuss the limitation/bias associated with the fact that the patients included in the study represent a very small proportion of the patients with suspect periampullary tumors (in addition to being a small number overall)

Answer: Thanks for your great suggestion. We have added this limitation in the discussion. It refers to P13 in the revised version.