

Point by point reply:

We are pleased that the editorial team and reviewers found merits in our review and have given us the opportunity to respond to their concerns and to revise the manuscript. We have attempted to deal with all the issues/questions raised by the reviewers, and we hope that the revised manuscript is now suitable for publication on World Journal of Gastroenterology.

➤ Reviewer #1

We thank the referee for the comments and suggestions to ameliorate our manuscript and for the constructive criticisms.

Comments:

GENERAL 1) at least ONE sketch encompassing the differentiation of the mesoderm into a biliary and/or pancreatic bud would be most welcome.

REPLY:

We provided a sketch regarding the common embryology.

GENERAL 2) Examples of pathohistology and/or Spyglass (direct cholangioscopy/pancreaticoscopy) would be instructive.

REPLY:

We provided histological images of peribiliary glands and pancreatic duct glands (Figure 1), BillIN/PanIN (Figure 2) and IPNB/IPMN (Figure 3). Moreover, we cited the diagnostic indications of Spyglass in biliopancreatic neoplasms.

SPECIFIC 1) I cannot fathom the fact that there is not a single word on KRAS when writing about the intraepithelial neoplasia. This must be mended. Prior to the KRAS activation/mutation the sonic hedgehog pathway is engaged

REPLY:

We wrote about the role of KRAS and the activation of sonic hedgehog pathway in the section on intraepithelial neoplasms in both BillIN and PanIN, with the presence of SHH also in the Table 1.

SPECIFIC 2) Great efforts have been undertaken during recent years to subtype PDAC (via RNA expression profiling). Few but some data exist for the biliary neoplasias. There is not a single word on this in the entire manuscript

REPLY:

We investigated and inserted the recent data regarding genomic profiling and RNA sequencing studies in the section of cholangiocarcinoma and pancreatic ductal adenocarcinoma.

➤ Reviewer #2

We thank the referee for the positive comments on our manuscript and for the suggestions:

Major comment: My only issue with the review is that it needs many images, especially since it is a narrative review

REPLY:

We now provide histological images of peribiliary glands and pancreatic duct glands (Figure 1), BillIN/PanIN (Figure 2) and IPNB/IPMN (Figure 3).

➤ Reviewer #3

We very appreciate the positive comments of the referee on our manuscript

➤ Reviewer #4

We very appreciate the positive comments of the referee on our manuscript:

Comments:

- 1) I also recommend these papers. P3 25lines; Nakanuma Y, Sasaki M, Sato Y, Ren X, Ikeda H, Harada K. Multistep carcinogenesis of perihilar cholangiocarcinoma arising in the intrahepatic large bile ducts. World J Hepatol. 2009 Oct 31;1(1):35-42 P10 10lines; Moschovis D, Bamias G, Delladetsima I. Mucins in neoplasms of pancreas,

ampulla of Vater and biliary system. World J Gastrointest Oncol. 2016 Oct 15;8(10):725-734. Review. PubMed PMID: 27795812

REPLY:

These suggested references have been added

- 2) During human development, the hepatic diverticulum emerges from the foregut
[Please insert a cited thesis]. Put a space at the beginning of the line. P2 11lines,
P4 26lines, P5 19lines, P7 23lines, P10 12lines, P11 2lines P10 21lines: cytokeratin
7 → cytokeratin-7

REPLY:

This has been now corrected. Thanks.