

Dear Editor and Reviewers

Thank you for your expert and helpful review of our manuscript. We have responded to each query in a point-by-point manner below and will include a marked-up copy and a clean copy of the revised manuscript. We reviewed the entire manuscript for grammatical mistakes and corrected accordingly. We also provided the PMID and DOI of references.

Thank you for your time and consideration.

Muhammad Nadeem Yousaf, MD

Responses to reviewer's comments:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: The article reviews the ERCP-guided interventions for the management of pancreatic cancer. The topic of this article is very interesting to gastroenterologists because it focus on not only diagnosis, but also therapeutic roles of ERCP for pancreatic cancer patients. The manuscript is well-written and comprehensive. I have one major comment. The authers described on endoscopic stenting for gastric outlet obstruction (GOO) during the course of pancreatic cancer. I think endoscopic enteral stenting for GOO should not be included in ERCP-guided intervention because it is a procedure that allows stent insertion using a forward-viewing endoscope instead of the duodenoscope.

Response:

We disagree with the removal of GOO section from our review. We think ERCP still has role in the palliation and management pancreatic cancer which may results in simultaneous GOO and biliary obstruction. Infact we added more data as suggested by other reviewers and cited a recent review (Dig Endosc. 2017;29:16-25) on role of ERCP in managing combined GOO and MBO. Furthermore, we also cited (Surg Endosc. 2013;27:1243-8.), (Dig Dis Sci. 2014;59:1931-8.) and

commented on ERCP-stenting has poor clinical outcomes in some patients, and EUS-BD can be a treatment option.

Reviewer #2:

Scientific Quality: Grade E (Do not publish)

Language Quality: Grade A (Priority publishing)

Conclusion: Rejection

Specific Comments to Authors: This article is a review article on ERCP-guided interventions in the management of pancreatic cancer.

However, almost all of the topics on the management of pancreatic cancer mentioned by the authors are no different from those on the management of malignant biliary stricture by cholangiocarcinoma.

Response:

This is a review article in which we provided the overview of role of ERCP in the management of pancreatic cancer. Obviously, there will not be new information whatever already been published in the original studies, however, we tried to provide the concise summary on this topic by combining all relevant studies.

The table 2, 3, and 4 do not show the results of studies confined to pancreatic cancer, but rather show the overall results of malignant biliary strictures, mainly including those of bile duct cancer. Therefore, these tables do not fit the purpose of this paper. –

Response:

In tables, we only recorded data on pancreatic cancer, however it was impossible to separate the data of pancreatic cancer from cholangiocarcinoma in fewer studies because of combined pathology.

Yes, in the tables, we provided the overall results of the studies (median value of results). Again, we wrote a review article in which overview of ERCP role in the management of pancreatic

cancer was provided. We did not intend to write a meta-analysis which usually require data-analysis and interpretation of data.

The authors described ERCP-guided intraductal radiofrequency ablation(RFA). However, the authors did not just describe ERCP-guided intraductal RFA, but mostly the thermal ablative technique of RFA used to treat solid pancreatic tumor mass. Furthermore, most of the references they quoted were not about ERCP-guided intraductal RFA, but about the thermal ablative technique of RFA used to treat solid pancreatic tumor mass.

Response:

Although there is an increasing role of EUS-RFA, several studies continue to demonstrate the utility of ERCP-RFA especially in stage III and IV pancreatic cancer using a specialized catheter and probe compatible with ERCP or EUS duodenoscope. We added a reference doi: [10.4253/wjge.v9.i2.41](https://doi.org/10.4253/wjge.v9.i2.41) that was published in WJGE in 2017. we are going to remove the section of RFA from this manuscript because ERCP-RFA data is not strong enough.

The authors described role of ERCP in gastric outlet obstruction. However, stent placement for gastric outlet obstruction is not the role of ERCP, but the role of GI endoscopic intervention.

Response:

We disagree with the removal of GOO section from our review. We think ERCP still has role in the palliation and management pancreatic cancer which may results in simultaneous GOO and biliary obstruction. Infact we added more data as suggested by other reviewers and cited a recent review (Dig Endosc. 2017;29:16-25) on role of ERCP in managing combined GOO and MBO. Furthermore, we also cited (Surg Endosc. 2013;27:1243-8.), (Dig Dis Sci. 2014;59:1931-8.) and commented on ERCP-stenting has poor clinical outcomes in some patients, and EUS-BD can be a treatment option.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Overall the topic of the review is comprehensive and relevant. Please check whether the included literatures in TABLEs are up to date.

Response:

We double check the literature in the table and its uptodate.

Reviewer #4:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

This is a comprehensive review of ERCP for pancreatic cancer.

ERCP-GUIDED DIAGNOSTIC INTERVENTIONS

1. Approach to distal biliary stricture including pancreatic cancer is well summarized in the recent international consensus (J Gastroenterol Hepatol. 2020;35:967-979.). Please cite this consensus.

Response:

We added the data in relevant sections of our review from consensus guideline and commented on the selection of stents. We added the new reference.

2. Intrinsic (biliary tract cancer) and extrinsic (pancreatic cancer) stricture need different approach (Cancer Med. 2017;6:582-590.). Please give some comments.

Response:

We commented on the different diagnostic approaches for intrinsic and extrinsic biliary strictures under ERCP diagnostic interventions. We cited the above study.

3. For diagnosis of early pancreatic cancer, ERP might be better than EUS such as SPACE technique (Diagnostics (Basel). 2019;9:30.).

Response:

We added a new section on ENPD and SPACE techniques with appropriate references.

ERCP-guided preoperative biliary drainage (PBD) for resectable pancreatic cancers

4. Stent selection (SEMS vs. PS) should be discussed.

Response:

We discussed the factors guiding stent selection in the PBD section, specifically for patients undergoing both preoperative and neoadjuvant therapy.

ERCP-guided biliary drainage in neoadjuvant treatment of pancreatic cancer

5. Again, stent selection (CSEMS vs. USEMS) should be discussed (Gastrointest Endosc. 2019 Oct;90(4):602-612.).

Response:

As addressed under point 4.

ERCP-guided intraductal radiofrequency ablation

6. ERCP-RFA included mostly patients with biliary tract cancer. RFA for pancreatic cancer is often performed at laparotomy, or recently EUS-guided.

Response:

Although there is an increasing role of EUS-RFA, several studies continue to demonstrate the utility of ERCP-RFA especially in stage III and IV pancreatic cancer using a specialized catheter and probe compatible with ERCP or EUS duodenoscope. We added a reference doi: [10.4253/wjge.v9.i2.41](https://doi.org/10.4253/wjge.v9.i2.41) that was published in WJGE in 2017. we are going to remove the section of RFA from this manuscript because ERCP-RFA data is not strong enough.

Role of ERCP In Gastric Outlet Obstruction

7. Combined GOO and MBO is well reviewed in Dig Endosc. 2017;29:16-25. Please cite this paper. Furthermore, ERCP-stenting has poor clinical outcomes in those patients (Surg Endosc. 2013;27:1243-8.), and EUS-BD can be a treatment option (Dig Dis Sci. 2014;59:1931-8.).

Response:

We added the data in our review from this study and cite the paper with combined GOO and MBO (Dig Endosc. 2017;29:16-25).

8. EUS-GJ has been increasingly reported. Please add some comments.

Response:

We briefly commented on the EUS-GJ under GOO. As our focus is on ERCP interventions, we mentioned it briefly in cases of failed standard endoscopic treatment EUS GJ is increasingly utilized. We added a new reference as well.

9. For duodenal stenting, a meta-analysis comparing covered vs. uncovered stent was published recently (Dig Endosc. 2017 ;29:259-271.). Table 4. Ref 96 and 98 appeared to be a same study (preliminary data and final data).

Response:

We added the data in our review from this study and added a new reference.

We removed reference 98, which was preliminary data of same study.