

## EUS Guided Biliary Drainage: Are We There Yet?

Pawa et al.

Thank you for the reviewer's comments and the opportunity to address these comments. Our point-by-point response is provided below, as well as references to the specific sections and page numbers where changes to the manuscript can be identified. We believe we have been responsive to the comments and that the manuscript is stronger as a result of the review process.

Comment	Response
<b>ID 05260804</b>	
First of all, congratulation for your comprehensive EUS BD review, I have some comment in this review. Could you please mention about this paper for EUS HGS, e.g. plastic stent for HGS, intra-scope channel stent release technique, liver impaction technique to prevent shearing of the guidewire.	Thank you for the comment. We have outlined and addressed the specific comments below.
1) Gastrointest Endosc. 2015 Aug;82(2):390-396.e2. doi: 10.1016/j.gie.2015.02.041. Epub 2015 May 1. A newly designed plastic stent for EUS-guided hepaticogastrostomy: a prospective preliminary feasibility study "Plastic stents reduce the frequency of adverse events, such as segmental cholangitis or liver abscess caused by peripheral bile duct obstruction"	A paragraph highlighting this novel plastic stent was added to the EUS-HGS section (Citation 64).
2) VideoGIE. 2020 Aug; 5(8): 355–358. Published online 2020 May 15. doi: 10.1016/j.vgie.2020.04.003, Novel combination of a 0.018-inch guidewire, dedicated thin dilator, and 22-gauge needle for EUS-guided hepaticogastrostomy	The technique using a 22 gauge needle and 0.018 guidewire was highlighted in the EUS-RV portion, and we elected to defer adding this case report to EUS-HGS in an attempt to avoid repetition.
3) Uchida D, Kawamoto H, Kato H, Goto D, Tomoda T, Matsumoto K, et al. The intra conduit release method is useful for avoiding migration of metallic stents during	A section highlighting this technique was added to the EUS-HGS portion of the review (Citation 62).

EUS-guided hepaticogastrostomy (with video). J Med Ultrason (2001).2018;45:399–403.	
4) Miyano A, Ogura T, Yamamoto K, Okuda A, Nishioka N, Higuchi K. Clinical impact of the intra-scope channel stent release technique in preventing stent migration during EUS-guided hepaticogastrostomy. J Gastrointest Surg. 2018;22:1312–8 “Stent release inside the scope channel can prevent intraperitoneal stent deployment”	The study highlighting this technique was added to the EUS-HGS portion of the review (Citation 63).
5) Ogura T, Masuda D, Takeuchi T, Fukunishi S, Higuchi K. Liver impaction technique to prevent shearing of the guidewire during endoscopic ultrasound-guided hepaticogastrostomy. Endoscopy. 2015;47:E583–E584 “use the “liver impaction technique.” First, the guidewire is pushed adequately into the peripheral bile duct, and the FNA needle is pulled back into the hepatic parenchyma. Because the tip of the FNA needle is then within the hepatic parenchyma, shearing becomes less likely”	This technique was added to the EUS-HGS portion of our review (Citation 56).
Are We There Yet? You need to mention about learning curve of EUS BD and training EUS Model. Thanks	We have added a portion about the learning curve of EUS-BD in our conclusion (Citation 92). Due to lack of objective evidence in the various EUS training models, we have not included them in our review.
<b>ID 03474794</b>	
Pawa et al. describes the current view of EUS-guided biliary drainage. They mention a variety of approach into the bile ducts and the gall bladder very meticulously, and sites representative papers for each procedure. The review is understandable and important to figure out the entire concept of the complexing	Thank you for the review and comments! We have addressed the specific comments below.

procedure, there are several issues which seem to be modified.	
1) I agree with the LAMS is an appropriate device for the EUS-CDS, the stent has been mainly used for EUS-guided cystic drainage and has not been spread to use in the EUS-CDS, because it is expensive, and the primary or distal flange may be unexpectedly deployed between the bile duct wall and duodenum wall. In some countries, furthermore, it has even been prohibited to be used for EUS-CDS or Gallbladder drainage unless the IRB in the institution has been approved. I would suggest to write the additional comment to describe the usage of the LAM for EUS-BD can be acceptable while the real use of the LAMS should be careful because of its price and the adverse effect.	We have now commented in the LAMS portion of EUS-CDS section about limitations with LAMS given cost and expertise.
2) In the session of EUS-Guided Choledochoduodenostomy, a unique plastic stent named X-T stent, TYPE IT, Gadelius Medical Co., Tokyo, Japan) should be described (Gastrointestinal Endoscopy 82(2); DOI: 10.1016/j.gie.2015.02.041) as an alternative stent for the procedure.	The article (Umeda J, Itoi T, Tsuchiya T, Sofuni A, Itokawa F, Ishii K, Tsuji S, Ikeuchi N, Kamada K, Tanaka R, Tonozuka R, Honjo M, Mukai S, Fujita M, Moriyasu F. A newly designed plastic stent for EUS-guided hepaticogastrostomy: a prospective preliminary feasibility study (with videos). Gastrointest Endosc. 2015 Aug;82(2):390-396.e2. doi: 10.1016/j.gie.2015.02.041. Epub 2015 May 1. PMID: 25936451.) described using this stent for EUS-HGS. This has been added to the EUS-HGS section (Citation 64)
3) EUS-AG can be described in the session of EUS-RV as well to make it understandable more clearly.	We have added description of EUS-AG technique in the EUS-RV section. Thank you for the suggestion.
4) Authors mentions that adverse events in the EUS-HGS are higher	This study has been added to the EUS-CDS vs EUS-HGS segment (Citation 77)

<p>than the ones in the EUS-CDS. However, it is controversial now and a meta-analysis states EUS-CDS and EUS-HGS have equal efficacy and safety (J Clin Gastroenterol. 2018 Feb;52(2):123-130.). Moreover, EUS-HGS can avoid the severe adverse events such as portal vein or CBD injury. Please describe the opposite opinions as a review.</p>	
<p>Minor 1) In the Abstract, "Risk of procedure-related complication, such as bleeding, bile leak and stent occlusion, is not negligible." Should be "Risk of procedure-related complication, such as bleeding, bile leak and stent occlusion, are not negligible."</p>	<p>We have changed "is" to "are" in this sentence. Thank you for the suggestion.</p>
<p>Minor 2) I think the headquarter of Covidien/Medtronic is in Durbin, Ireland. Otherwise, the operational headquarter in the US is in Minneapolis, MN. Please check the location of the company.</p>	<p>We have updated the headquarters to Covidien/Medtronic world headquarters of Dublin, Ireland.</p>
<p>Minor 3) In the session of EUS-guided Choledochoduodenostomy versus EUS-guided Hepaticogastrostomy, ", likely to due a number of factors including the precise puncture of smaller caliber intrahepatic bile ducts" should be "likely due to a number of factors including the precise puncture of smaller caliber intrahepatic bile ducts".</p>	<p>We have corrected "to due" to "due to".</p>
<p><b>ID 05548747</b></p>	
<p>Comment to the Authors This is a review article of EUS-BD. Many EUS-BD reports are being considered. This is a very interesting subject for an endosonographer, and I have a number of queries for the authors.</p>	<p>Thank you for the review! We have addressed the individual comments below.</p>
<p>1) The text discusses uncovered SEMS with EUS-CDS, but is there currently any report of EUS-CDS</p>	<p>We came across a letter to the editor (Haseeb A, Freeman ML, Amateau SK. Distal malignant obstruction managed by</p>

<p>with UC-SEMS? How are the results of those reports?</p>	<p>EUS-guided choledochoduodenostomy by use of an uncovered self-expanding metal stent. <i>Gastrointest Endosc.</i> 2019 Oct;90(4):696-697. doi: 10.1016/j.gie.2019.03.013. PMID: 31540636) describing 20 patients undergoing EUS-CDS with an UC-SEMS. No adverse events were reported in these patients. The authors hypothesized that regional inflammation, adhesion of bile duct to the duodenal wall from malignancy, and the retroperitoneal nature of the fistula creation obviates bile leakage. However, we have not referenced this article as most articles we reviewed advocate using a FC-SEMS. We have modified the text accordingly.</p>
<p>2) Stent patency in EUS-CDS and EUS-HGS has not been studied, but what is the reported patency in both SEMS and PS?</p>	<p>1. The stent patency in EUS CDS vs EUS HGS has been studied in some studies below.</p> <p>a) Khashab MA, Messallam AA, Penas I, et al. International multicenter comparative trial of transluminal EUS-guided biliary drainage via hepatogastrostomy vs. choledochoduodenostomy approaches. <i>Endosc Int Open.</i> 2016;4(2):E175-E181. doi:10.1055/s-0041-109083. Stent patency duration between the two groups was not statistically significant (p=0.228). This was added to the EUS-CDS vs EUS-HGS section.</p> <p>b) EUS clinical practice guidelines Isayama H, Nakai Y, Itoi T, et al. Clinical practice guidelines for safe performance of endoscopic ultrasound/ultrasonography-guided biliary drainage: 2018. <i>J Hepatobiliary Pancreat Sci.</i> 2019;26(7):249-269. doi:10.1002/jhbp.631.</p> <p>There is no significant difference in the</p>

	<p>stent occlusion rate between CDS (19%) and HGS (13%) as reported in this article.</p> <p>2) The stent patency for FCSEMS in EUS-CDS was reported by Nakai et al. (Citation 37) with the median cumulative time to RBO being 11.3 months. We have added this to the review.</p> <p>3) Hara et al. (Citation 34 and 35) was added to compare rates of stent occlusion between PS and FCSEMS in EUS-CDS</p>
3) Recently, there have been many reports of EUS-BD in combination with duodenal stents. Please discuss the results of the reports with double stenting (duodenal stenting and EUS-BD).	A case series describing this technique has been added to the EUS-CDS section. (Citation 50). Thank you for this suggestion.
4) Is it correct to recognize EDGE as EUS-BD	We feel it is appropriate to mention EDGE in our review on EUS-BD as this technique involves creation of a GG fistula under EUS guidance in patients with Roux-en-Y gastric bypass (RYBG) anatomy. ERCP can then be performed through the fistulous tract.
<b>ID 05226039</b>	
Congratulations on this great review. It has been a pleasure to review the text.	Thank you for the comment and review!
<b>ID 05190212</b>	
I read with interest the paper by Pawa et al., presenting a complete review regarding EUS-guided biliary drainage. The manuscript is well-written and methodologically valid, providing a detailed description of the indications to EUS-guided biliary drainage, of the available techniques to perform it and of the procedures' technical and clinical success and of the possible complications. The abstract summarize and reflect the work described in the manuscript.	Thank you for the extensive review! We have addressed the comments individually below.

However the paper has some criticisms that should be modified:	
In the citation 13-14, after “fewer adverse events” I would add “and better quality of life”.	We have added “and better quality of life” to this section.
After the end of Introduction I would add a paragraph titled “ EUS-guided biliary drainage procedures” and consider the following titles as sub-paragraphs.	At the end of the introduction, Table 1 outlines the EUS-guided BD procedures. We feel this is appropriate prior to describing these techniques in detail.
Maybe the term “branch” would be better than “radical” (even in the Figure 2).	We have changed the word “radical” to “branch”.
Please correct 0.025 or 0.035 inch (instead of in).	We have corrected “in” to “inch”.
When you cite reference [18], after “in the trans-hepatic group” please add “and longer duration of hospitalization (2.52 vs 0.17 days; p =0.0015). So the extra-hepatic route should be preferred for EUS-RV in patients with distal CBD obstruction when both access routes are technically feasible.” Add citation: Tsuchiya T, et al. Endoscopic ultrasonography-guided rendezvous technique. Digestive Endoscopy 2016; 28 (suppl. 1); 96-101.	We have added the “longer duration of hospitalization” association with the transhepatic group in the Dhir et al. study.  We have mentioned a few articles (citation 16, 17 and 18) all of which favour the extrahepatic approach over transhepatic approach. We feel adding this additional citation may be redundant.
What did you mean with “while in the biliary system”?	We have changed this to “in the biliary tree” to make it more clear.
Change “which allows” with “allowing”.	We have changed “which allows” to “allowing”.
When you cite Lee et al. instead of “undergoing precut papillectomy alone” put “in which only precut papillectomy was available for failed cannulation”.	We have changed the language in this paragraph to reflect the recommended changes.
Before citation [24], “... due to high success rate in high-skilled in ERCP endoscopists, and lack of .....”	We have added “with experienced endoscopists” to this sentence to reflect the recommended change.
Add to “The conventional technique” “, defined as Multi Step Technique, involves...”	We have removed “conventional” to simplify the sentence to only “this technique involves”.
“Plastic stent were commonly used in the first cases” (instead of “in early cases”.	We have changed to “were initially used for biliary drainage...”
I would delete the entire sentence	We came across a letter to the

<p>“Furthermore..... with UC-SEMS”, as the uncovered SEMS are not indicated in this setting in which a fistulous tract must be covered by a stent.</p>	<p>editor (Haseeb A, Freeman ML, Amateau SK. Distal malignant obstruction managed by EUS-guided choledochoduodenostomy by use of an uncovered self-expanding metal stent. Gastrointest Endosc. 2019 Oct;90(4):696-697. doi: 10.1016/j.gie.2019.03.013. PMID: 31540636.) describing 20 patients undergoing EUS-CDS with an UC-SEMS. No adverse events were reported in these patients. The authors hypothesized that regional inflammation, adhesion of bile duct to the duodenal wall from malignancy, and the retroperitoneal nature of the fistula creation obviates bile leakage. However we have not referenced this article as most articles we reviewed advocate using a FC-SEMS.</p> <p>We have deleted this sentence and reworded it, to further convey that UC-SEMS are generally avoided as initial stents in EUS-CDS.</p>
<p>At the end of the page, It would be better to anticipate the sentence “A prospective study of.... .... and functional success (100%).” before the sentence “Despite achieving....”</p>	<p>We have made these changes as recommended.</p>
<p>Maybe the technique of realising LAMS should be better described, for example free-hand or use of guidewire...</p>	<p>The free hand technique with use of electrocautery-enhanced delivery system and the use of guidewire and multiple exchanges have been described in our review.</p>
<p>After citation [42], the high clinical success of the study population is influenced by the limited follow-up; in fact 27 patients have a follow-up &lt; 4 weeks and were not evaluated in terms of clinical success and need of biliary re-intervention.</p>	<p>We have made the recommended additions.</p>
<p>Modify the sentence “The transduodenal LAMS did not impede surgery thereby</p>	<p>We have added “even” to the line before “in patients” with resectable</p>



suggesting that EUS-CDS can be performed in patients with resectable malignancy" with "The transduodenal LAMS did not impede surgery thereby suggesting that EUS-CDS can be performed EVEN in patients with resectable malignancy".	malignancy.
"After confirmation of needle placement into the duct" please add "by aspiration of bile and cholangiogram".	We have added "by aspiration of bile and cholangiogram" to the sentence.
When you describe the DH group of the Park study please describe in detailed the device (7 Fr, etc).	We have described the device used in the DH group in detail.
The study by Cho et al. using a. novel hybrid metal stent is not present among the references and it must be cited.	Thank you for this comment, the citation for Cho et al. has been added.
Please describe this hybrid metal stent. Are the authors sure that this stent is available only in Korea and not currently available worldwide, because as far as we know it should be available in Europe.	We have described the stent further, and we removed the sentence saying the stent is only commercially available in Korea.
Please continue the sentence "However, 33% of patients eventually suffered RBO requiring re-intervention", with "... due to the hyperplastic ingrowth of the uncovered flange".	We have added "due to the hyperplastic ingrowth of the uncovered flange".
Please cite "especially bile leakage" among the adverse events. The higher rate of reintervention is not statistically significant (p = 0.25) and it should be underlined.	We have added a line highlighting the bile leak as an adverse event. We have re-worded the sentence regarding rate of re-intervention to convey that the difference was not statistically significant.
In the final part of HBO, please add after "Both techniques are challenging and only a small number of cases have been reported to date <sup>[66]</sup> " " only in referral center".	We have added "performed in referral centers" to this line.
In the third line invert "to" and "due".	We have corrected from "to due" to "due to"

<p>"The choice between .....site of obstruction, OPERATOR EXPERTICE and location of biliary dilation".</p>	<p>We have added operator expertise to the to sentence.</p>
<p>The authors say that "EUS-CDS is not feasible in patients with proximal MBO or GOO." This affirmation is not always true for GOO, because if the stricture is localized in the second portion of duodenum, leaving the duodenal bulb free and not preventing to create a choledocho-duodenal fistula. Please argue this issue.</p>	<p>We have removed GOO as EUS-CDS can be feasible based on the location of the obstruction.</p>
<p>It is not clear if the cases described in the figure have been managed by the authors.</p>	<p>The cases in the figures have been managed by the authors. We have addressed the specific comments below.</p>
<p>Figure 1. Could the authors explain the reason to place a double pigtail inside the LAMS? The procedure is described and used for EUS-HGS to prevent the migration of FC-SEMS (as in Figure 2). It is not clear the rational in EUSCDS using LAMS. Please argue this aspect.</p>	<p>The rationale for using a double pigtail stent inside a LAMS for EUS-CDS is to prevent injury to the opposite bile duct wall from the LAMS following decompression of the biliary tree.</p>
<p>Figure 2. Could the authors explain the cause of biliary strictures?</p>	<p>The distal bile duct stricture described in figure 2 was an inflammatory stricture secondary to stone disease. This patient had stones cleared from the biliary tree followed by stricture management with balloon dilation and stenting.</p>
<p>Figure 3. EUS-guided gallbladder. D. The patency of cystic duct should be evaluated before LAMS placement, to avoid an ineffective gallbladder drainage.</p>	<p>This patient had a CT scan of the abdomen/pelvis done prior to procedure which was suggestive of a patent cystic duct.</p>