

Dear Editor:

Please find enclosed the edited manuscript in Word format (Malignant Biliary Obstruction Review v4 [Editor's Revisions].doc).

Title: Managing Malignant Biliary Obstruction in Pancreas Cancer: Choosing the Appropriate Strategy

Author: Brian R Boulay MD MPH, Mayur Parepally MD

Name of Journal: World Journal of Gastroenterology

ESPS Manuscript NO: 6874

The manuscript has been improved according to the suggestions of reviewers. Each of the 4 reviewers' comments are reprinted with our responses in italics below:

1 Format has been updated with addition of page numbers and correction of references to include PMID numbers.

2 Revision has been made according to the suggestions of the reviewers

(1) "please check 1) the format of references according to the WJG instruction, 2)English spelling & grammar issues."

PMID numbers have been added to the references. Both authors believe the spelling and grammar are acceptable and both are native English speakers.

(2) " Major points 1. Authors may want to add a flowchart for the selection of appropriate biliary drainage. 2. As authors discussed, the advancement of chemotherapy, especially neoadjuvant chemotherapy, has drastically changed clinical management of pancreatic cancer. Please discuss the effects of chemotherapy on biliary stenting. 3. In addition to biofilm/sludge formation, duodenobiliary reflux is also one of the major causes of stent occlusion. Please discuss the association of duodenal invasion with stent patency, as well as the role of anti-reflux stent. 4. Combined malignant biliary obstruction and gastric outlet obstruction is an important issue in the management of cancer in the head of pancreas. There are various strategies including double stenting, double bypass, or EUS-BD and duodenal stenting. The authors should discuss their advantages and disadvantages in detail. Minor 1. Kitano et al. recently published an RCT of covered vs. uncovered EMS (Am J Gastroenterol. 2013;108:1713-22). Please discuss their paper since a clinical trial limited to pancreatic cancer patients is rare."

MAJOR POINT 1: A flowchart has been added as suggested.

MAJOR POINT 2: We did not find high-quality literature on the direct effect of chemotherapeutic agents on stents, other than the risk of occlusion during the prolonged period of medication and recovery in a neoadjuvant setting.

MAJOR POINT 3: Discussion of duodenobiliary reflux was added on page 5 and anti-reflux stents are discussed on pages 11-12.

MAJOR POINT 4: Management of duodenal and biliary obstruction is now discussed on pp 17-18.

MINOR POINT 1: The Kitano trial is now discussed on pp 9-10.

(3) No revisions suggested by Reviewer 3.

(4) "To authors. 1. The pages are not numbered and should. Numbering would facilitate review and corrections. Palliative stenting 2. Cost-effectiveness is cited as an indication for choosing plastic stents for patients surviving ≤ 4 months. The paper gives no guideline for this determination. Two randomized trials (Kaassis 2003, Soderlund 2006) have both identified the presence of distant metastases could be a criteria for choosing plastic stents. Suggest authors adding these 2 references to their review. Other methods for biliary drainage 3. It is true that percutaneous external biliary drain and bag are cumbersome. However, most biliary drainages for palliative treatment are internalized and offer both internal and external drainage capabilities. Internalization is attempted in all cases except in case of sepsis when internalization is delayed until after sepsis is controlled. Metallic stents can be inserted after internalization or at the initial insertion of biliary drainage. Exclusive, cumbersome external drainage is rarely encountered for prolonged periods. Suggest describing the current practice in most centers and de-emphasizing the occasional use of exclusively external drainage. Percutaneous stenting is an alternative to endoscopic stenting (Pinol 2002). 4. Reference #34 (Speer AR et al 1987) is a prospective randomized study published in 1987 and is quoted to support the use of ERCP for stenting. This article compares plastic stent insertion by percutaneous and endoscopic methods in the very debilitated and sick patients. The conclusion has been inappropriately applied to all patients in all clinical settings. A more up-to-date but similar prospective randomized was also published (Pinol, 2002); it reported a different result and conclusion. This publication should be included in this review to reflect the current status of clinical practice. 5. "Other endoscopic alternatives are being used for relieving malignant biliary obstruction not amenable to stent placement via ERCP." These new techniques have not been formally evaluated against traditional methods such as percutaneous stenting which is highly successful where ERCP is not. They also require skills in both ERCP and endoscopic ultrasound and only limited data on its safety are currently available. These

experimental new procedures are clinically indicated when both ERCP and percutaneous approaches have failed and need on-going evaluation. 6. Surgical bypass vs endoscopic stenting: The review recognizes the shortcoming of older publications which compare biliary stenting with surgical bypass. Plastic stents were used in many of the older studies. The outcome would likely be different if SEMS had been used instead. The paper should emphasize that it is uncertain if surgical bypass is superior to metallic stenting. In the case of concomitant duodenal and biliary obstruction, endoscopic duodenal and biliary stenting can be both carried out, eliminating the need for surgical bypass. For patients with poor prognosis, this may offer an effective palliation. Conclusion: 7. The first paragraph can be deleted as it repeats the introduction. 8. The last paragraph should be changed to reflect the conclusion of a recent prospective randomized trial that indicates "Placement of a percutaneous self-expanding metal stent is an alternative to placement of an endoscopic polyethylene endoprosthesis in patients with malignant biliary obstruction" (Pinol 2002) Reference Soderlund C, and Linder S. Covered metal versus plastic stents for malignant common bile duct stenosis: a prospective, randomized, controlled trial. GASTROINTESTINAL ENDOSCOPY 2006;63:986-995 Kaassis M, Boyer J, Dumas R, Ponchon T et al., plastic or metal stents for malignant stricture of the common bile duct? results of a randomized prospective study. gastrointest endosc 2003;57:178-82. Pi?ol V, Castells A, Bordas JM, Real MI, Llach J, Monta?à X, et al. Per"

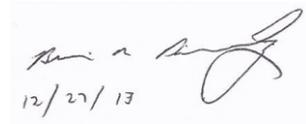
1. *Pages are now numbered.*
2. *Both references for using distant metastases as a prognostic indicator for stent choice have now been added on page 13.*
3. *A discussion of internalization of internal-external drains and use of percutaneous stent placement has now been added to the paper on pp 14-15.*
4. *The paper by Pinol (2002) has been added (citation 45) as a counterpoint to the Speer article, as suggested by the reviewer.*
5. *The lack of long-term experience and limitation to expert centers for EUS-guided biliary drainage is now mentioned on page 18.*
6. *A passage describing the lack of direct comparison of SEMS to surgical bypass has been added on page 17. A description of concomitant duodenal and biliary SEMS placement has now been added on page 17-18.*
7. *While respecting the opinion of the reviewer, I believe reiteration of the introduction at the article's conclusion is appropriate. I will defer to the wishes of the editor regarding the inclusion of this paragraph.*

8. *The use of percutaneous methods is now described in the conclusion as well, with citations as suggested by the reviewer.*

Thank you again for publishing our manuscript in the World Journal of Gastroenterology.

Regards,

Brian R. Boulay MD, MPH

A handwritten signature in black ink, appearing to read "Brian R. Boulay", is written over the date "12/27/13". The signature is fluid and cursive.

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