Format for ANSWERING REVIEWERS

September 25, 2013

Dear Editor,

Thank you for taking the time to review our paper titled 'Imaging Pancreatobiliary Ductal System with OCT: A Review'**.** We are in general agreement with the reviewers, and feel that the review process has strengthened our work. Please find enclosed the edited manuscript in Word format.

Title: Imaging Pancreatobiliary Ductal System with Optical Coherence Tomography (OCT): A Review

Author: Mohammad S. Mahmud, Gray R. May, Mohammad M. Kamal, Carry Sun, A. Vitkin, Victor X. D. Yang.

Name of Journal: ***World Journal of Gastrointestinal Endoscopy***

ESPS Manuscript NO: 3864

The manuscript has been improved according to the suggestions of reviewers:

Changes in accordance with first Reviewer's comments:

Q1. Although the article analysis a new topic and new technology-methodology**,** it is written in a technical way that may confuse average endoscopists' reader. It is plain text-presentation that doesn't highlight the topics of interest. However, it can be substantially improved if they shorten the introduction.

Ans 1: We modified the abstract and include this sentence: "Results show that OCT can improve quality of images of pancreatobiliary system during ERCP (Endoscopic Retrograde Cholangio-pancheatography) procedure, which may be important in distinguishing between neoplastic and non-neoplastic lesions".

We agree with the reviewer. Therefore, shorten 'Introduction' section in the revised manuscript.

Q.2. Clarify the structure of the paper. It is impossible to understand what is coming up after the last sentences of the intro that describes the structure of the paper. Should be modified.

Ans 2: We structured our revised manuscript and briefly described it in page 2, paragraph 2 in the introduction section 1 as: "In this review, we focused on the feasibility of OCT approach that improves the diagnostic accuracy of the ductal epithelial changes, with a potential to diagnose neoplastic and non-neoplastic lesions as well as pancreatic cysts. An introduction of the OCT imaging system has been discussed in section 2.1. Pancreaticobiliary ductal OCT images are divided into two categories: normal pancreatico-biliary ductal system is introduced in section 2.2, followed by the pathological (/neoplastic) ductal structure in section 2.3. Diagnosis of various pancreatic cysts with OCT is highlighted in section 2.4".

Q.3. Both in the sections of normal pancreatobiliary ducts examination and most of all in the section of

pathologies, please summarize the results of the presented studies in Tables that will include number of patients (animals), control examination, main outcome, accuracy (SEN, SPEC, PPV, NPV, where available), adverse events etc.

Ans 3: General criteria (accuracy, sensitivity and specificity, positive and negative predictive values) of different imaging methods used to diagnose biliary duct strictures (malignant and/or benign) is summarized in Table1.

Table1: Imaging methods for diagnosis of bile duct strictures.

Methods	SEN (%)	SPEC (%)	PPV (%)	NPV (%)	Accuracy %
BC/FNA	30(30-60)	95(90-100)	100(90-100)	28(28-50)	48(30-50)
Forceps Biopsy	43(40-70)	90(90-100)	95(90-100)	31(30-50)	48(30-70)
BC+FNA+Biopsy	62(60-75)	90(90-100)	96(90-100)	39(35-60)	55(45-75)
ERCP/MRCP	70(67-90)	75(70-80)	80(68-90)	88(70-95)	70 (50-80)
ERCP-BC/BX	43(36-60)	80 (75-100)	95 (94-100)	90(56-100)	70 (60-80)
EUS	80 (70-100)	80 (75-100)	80(76-100)	80(54-90)	80 (78-90)
EUS-FNA	85 (80-100)	95(90-100)	95(95-100)	80 (60-90)	85(80-90)
IDUS	90 (85-100)	85 (80-100)	85(80-100)	90(80-100)	90 (83-90)
IDUS+ERCP/Biopsy	91(90-100)	93(90-100)	94(84-100)	90 (84-95)	92 (90-100)
OCT	79 (75-90)	69(65-90)	75(70-90)	73(70-90)	74 (70-85)
OCT-BC/BX	84(80-90)	69(70-90)	76(70-90)	78(70-100)	77 (70-90)

BC= brush cytology, BX= intraductal/forceps biopsy, FNA= Fine-needle aspiration, ERCP = Endoscopic retrograde cholangiopancheatography, MRCP = Magnetic resonance cholangiopancreatography, EUS-FNA= Endoscopic ultrasound-guided FNA biopsy, IDUS= Intraductal ultrasonography, OCT = Optical Coherence Tomography. Sensitivity, specificity, positive predictive values and negative predictive values were calculated as [54]: SEN = TP/(TP+FN), SPEC=TN/(TN+FP), PPV=TP/(TP+FP), NPV=TN/(TN+FN). True positive (TP) and true negative (TN) represent the accurate diagnosis of biliary and non-biliary strictures respectively. False positive (FP) reflects the incorrect diagnosis of non-malignancy, whereas, false negative (FN) reflects incorrect diagnosis of the benign strictures.

Q.4. Present the available OCT systems and summarize in a table their technical characteristics focusing in those of clinical-endoscopy interest.

Ans 4: Three different types of OCT systems are currently used in various research and clinical applications. These systems are compared and are listed in Table 3.

Table 3: Comparison of different types of OCT systems.

Parameters	TD-OCT	SD-OCT	SS-OCT/OFDI
Mechanism	Interference signals are detected as a function of optical time delay between obj. & ref. arm.	Interference signals are detected with a camera as a function of optical frequency.	Spectral fringes are mapped to time domain by use of a swept laser & are measured with a detector as a function of time.
Major components	Broadband laser, optical delay line and a detector	Broadband laser, spectrometer and camera	Tunable laser, digitizer and a balanced detector.
Spectrum	800nm, 1000nm, 1300nm	800nm, 1000nm, 1300nm	800nm, 1000nm, 1300nm

Imaging Depth	1-3 mm	1-3 mm	1-3 mm
Resolution	≥ 10µm	1-10µm	1-10µm
Imaging Speed (Axial scan rate)	Slow (≤ 5 kHz)	Fast (20 -150 kHz)	Fairly Fast (20-400 kHz)
SNR*	Low	High	High
Image quality	Moderate	Fairly High	High
Sensitivity	Low (70-90 dB)	High (85-105 dB)	High (≥ 100 dB)
Phase stability	Low	High	Moderate
Portability	Yes	yes	Yes
System Cost	Low	High	Moderate

*SNR= Signal-to-noise Ratio, dB= decibel, TD-OCT = Time domain OCT, SD-OCT = spectral-domain OCT, ODFI = Optical frequency domain imaging, SS-OCT = Swept Source OCT.

Q.5.Present data on the availability, on the cost of the system and on the cost of the examination.

Ans 5: There are over fifteen commercially available OCT system manufacturers with different capabilities and price ranges. Companies that produce OCT systems are: Novacam, Bioptigen, Heidelberg Engineering, Alcon/LenSx, Canon/Optopol, Volcano Crop, Optovue, Thorlabs, Topcon, Imalux, Nidek, Tomey, Schwind, Wasatchphotonics, OptiMedica, Optos/OTI, Volcano Crop, LightLab Imaging, Shenzhen Moptim Imaging, Technolas Perfect Vision, and Carl Zeiss Meditec.

It is difficult to estimate accurate costs of an OCT system, as cost varies with imaging engines (consisting of an interferometer, light source, and detector) and imaging devices (or OCT probes). However, an average cost of an OCT system ranges from $20,000−$80,000 and cost per correct diagnosis (or procedure cost) is approximately $100 (100-200).

This information has included in page 5, first paragraph of section 2.1 in the revised manuscript.

Q.6. Present date of the learning curve of the method.

Ans 6: We introduced section 2.1 (Introduction to OCT imaging system) in our revised article where we explain the principle of OCT technology, learning curve and compare different types of currently available imaging systems for research and clinical applications.

Q.7. Summarize in a table the advantages and disadvantages of OCT compared to MRCP, ERCP + biopsy/cytology, EUS+biopsy/cytology, IDUS

Ans 7: We compare advantages and disadvantages of different imaging modalities and results are listed in Table 2**.**

Table 2: Comparison of various imaging modalities.

Imaging modality	**PTC**	**ERCP**	**MRCP**	**US/HFUS‡ /EUS/IDUS**		**CT**	**OCT**
Projection/ Tomograph	Projection	Projection	Projection or Tomographic	Tomographic		Tomographic	Projection or Tomographic
Resolution	1-2 mm	1-2 mm	**Fairly Poor 3-5 mm**	**US/EUS** 100-250µm	**HFUS/IDUS** 50-100µm	300-500 µm µCT: 3-125µm	**Fairly High 1-10 µm**

Imaging Depth	1 - 5 mm	5 - 60 mm	Entire biliary tree	US/EUS: 5- 10 cm HFUS/IDUS : 1-3 cm		Entire biliary tree	1 - 3 mm
Tissue sampling	**++**	**+++**	**–**	**US** **+**	**EUS** **+++**	**+**	**–**
Portability	**–**	**+**	**–**	**US** **+++**	**EUS** **++**	**–**	**++**
Therapy	**+++**	**+++**	**–**	**US** **–**	**EUS** **+**	**–**	**+**
System Cost*	**++**	**++++**	**+++**	**US** **–**	**EUS** **++**	**++**	**++**
Operator dependence	**High**	**High**	**Low**	**Very High**		**Low**	**Low**
Staging of malignancy	**–**	**–**	**++**	**US** **+**	**EUS** **+++**	**+++**	**–**
Safety	**–**	**+**	**+++**	**++**		**++**	**+++**
Experiment Duration	2−4 hours	30−120 min	10−30 min	20−40 min		15−30 sec	5−10 min
Complications	**+++** Risk (5-10%) of Infection, bleeding and bile leaks.	**++** Risk (<5%) Bleeding, perforationp ancreatitis cholangitis.	**–** Claustrophobia in some patients	**+** Risk (1%) of failure rate, bleeding and perforation.		**–** Rare allergic reaction (<1%) to iodinated agents	**–** No complication.
Comments **Pros:**	+ Diagnosis & therapeutic (treatment) procedure.	+ Diagnosis & treatment procedure.	**Non-invasive** + No ionizing radiation. + Relatively operator -independent.	**Usually Non- invasive (sedation).** + Diagnosis tool combined with tissue and/or lesion sampling.		**Non-invasive** + Faster method. + High resolution. + Operator -independent.	**Non-invasive** + No ionizing radiation. + High resolution. + Faster method. + Operator-independent.
Cons:	**Invasive** **−Ionizing radiation**. − Operator-	**Invasive** **− Ionizing radiation**. − Operator	− Expensive. **− Poor resolution.** − Solely diagnostic method.	− **Operator dependent**. −Highly motion sensitive		**− Ionizing radiation.** − Solely diagnostic method	**− Low Imaging depth ~3mm**. − Motion

	dependent.	dependent.	– Motion sensitive. – Claustrophobia	– Thermal effects and cavitations.		sensitive.

PTC= percutaneous transhepatic cholangiography, ERCP= Endoscopic Retrograde Cholangiopancheatography, MRCP = Magnetic resonance cholangiopancreatography, US = Clinical Ultrasound, EUS = Endoscopic ultrasound, HFUS= High Frequency Ultrasound (>10MHz), IDUS=Intraductal ultrasonography, CT= Computed Tomography, OCT= Optical Coherence Tomography.

Q.8. Respect the requirements of the journal regarding the format of the submitted paper. Extensive revision is required on this field, including the description of authors' contribution (e.g. what was the contribution of the author from the 5th affiliation?)

Ans 8: We agree with the reviewer. We formatted our manuscript according to the requirement of the journal.

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Changes in accordance with second reviewer 's comments:

Q: Authors have to assume that the general endoscopists will have little knowledge of OCT. Therefore in the title, it should be explained that OCT stands for optical coherence tomography. In addition, there should be a line explaining what OCT is.

Ans: We agree with the reviewer. We modified the abstract to include: "Optical coherence tomography (OCT) is a noninvasive, high-resolution (1-10μm) emerging optical imaging method with potential for identifying microscopic subsurface features in the pancreatic and biliary ductal system."

Q: The authors should comment on the potential cost, length of time of the procedure, and learning curve.

Ans: We introduce a new section 2.1 (Introduction to OCT imaging system) where we explain in detail principle of OCT technology, learning curve and compare different types imaging systems currently available for research and clinical applications. It is difficult to estimate accurate costs of an OCT system, as there are wide verity of imaging engines (consisting of an interferometer, light source, and

detector) and imaging devices (or OCT probes). However, average cost of an OCT system ranges from $20,000−$80,000 and the procedure itself lasts about 5-10 mins.
This information has been included in page 5, first paragraph of section 2.1 in the revised manuscript.

Q. What is OCT technique likely to be used for? Diagnosis of biliary or pancreatic strictures? Diagnosis of pancreatic cysts? At present this review mixes strictures with cysts and it would be useful to separate the data for the two conditions.
Ans: An OCT modality can be used for diagnosing biliary and pancreatic strictures (Endoscopy 2009; 41: 696–701, Dig. & Liv. Dis. 2006, 38:688–695) as well as for detecting pancreatic cysts (Bio. Opt. Exp,2011,2:2372–82). We agree that old article mixes biliary duct strictures with pancreatic cysts. Therefore, we revised the manuscript and separated data into section 2.3 and 2.4 respectively.

Q. A table comparing the different modalities to diagnose the aetiology of a bile duct stricture would be useful. This could include number of studies, number of patients, accuracy, complications, cost, ease of use, etc.

Ans: We compare different imaging modalities to diagnose biliary duct strictures in Table1.
Table1: Imaging methods for diagnosis of bile duct strictures.

Methods	SEN (%)	SPEC (%)	PPV (%)	NPV (%)	Accuracy %
BC/FNA	30(30-60)	95(90-100)	100(90-100)	28(28-50)	48(30-50)
Forceps Biopsy	43(40-70)	90(90-100)	95(90-100)	31(30-50)	48(30-70)
BC+FNA+Biopsy	62(60-75)	90(90-100)	96(90-100)	39(35-60)	55(45-75)
ERCP/MRCP	70(67-90)	75(70-80)	80(68-90)	88(70-95)	70 (50-80)
ERCP-BC/BX	43(36-60)	80 (75-100)	95 (94-100)	90(56-100)	70 (60-80)
EUS	80 (70-100)	80 (75-100)	80(76-100)	80(54-90)	80 (78-90)
EUS-FNA	85 (80-100)	95(90-100)	95(95-100)	80 (60-90)	85(80-90)
IDUS	90 (85-100)	85 (80-100)	85(80-100)	90(80-100)	90 (83-90)
IDUS+ERCP/Biopsy	91(90-100)	93(90-100)	94(84-100)	90 (84-95)	92 (90-100)
OCT	79 (75-90)	69(65-90)	75(70-90)	73(70-90)	74 (70-85)
OCT-BC/BX	84(80-90)	69(70-90)	76(70-90)	78(70-100)	77 (70-90)

BC= brush cytology, BX= intraductal/forceps biopsy, FNA= Fine-needle aspiration, ERCP = Endoscopic retrograde cholangiopancheatography, MRCP = Magnetic resonance cholangiopancreatography, EUS-FNA= Endoscopic ultrasound-guided FNA biopsy, IDUS= Intraductal ultrasonography, OCT = Optical Coherence Tomography. Sensitivity, specificity, positive predictive values and negative predictive values were calculated as [54]: SEN = TP/(TP+FN), SPEC=TN/(TN+FP), PPV=TP/(TP+FP), NPV=TN/(TN+FN). True positive (TP) and true negative (TN) represent the accurate diagnosis of biliary and non-biliary strictures respectively. False positive (FP) reflects the incorrect diagnosis of non-malignancy, whereas, false negative (FN) reflects incorrect diagnosis of the benign strictures.

We compare advantages and disadvantages of different imaging modalities and results are listed in Table 2**.**
Table 2: Comparison of various imaging modalities.

Imaging modality	PTC	ERCP	MRCP	US/HFUS‡ /EUS/IDUS	CT	OCT
Projection/ Tomograph	Projection	Projection	Projection or Tomographic	Tomographic	Tomographic	Projection or Tomographic

Resolution	1-2 mm	1-2 mm	**Fairly Poor 3-5 mm**	**US/EUS** 100-250µm	**HFUS/IDUS** 50-100µm	300-500 µm µCT: 3-125µm	**Fairly High 1-10 µm**
Imaging Depth	1 - 5 mm	5 - 60 mm	Entire biliary tree	US/EUS: 5- 10 cm HFUS/IDUS : 1-3 cm		Entire biliary tree	1 - 3 mm
Tissue sampling	**++**	**+++**	**–**	**US** **+**	**EUS** **+++**	**+**	**–**
Portability	**–**	**+**	**–**	**US** **+++**	**EUS** **++**	**–**	**++**
Therapy	**+++**	**+++**	**–**	**US** **–**	**EUS** **+**	**–**	**+**
System Cost*	**++**	**++++**	**+++**	**US** **–**	**EUS** **++**	**++**	**++**
Operator dependence	**High**	**High**	**Low**	**Very High**		**Low**	**Low**
Staging of malignancy	**–**	**–**	**++**	**US** **+**	**EUS** **+++**	**+++**	**–**
Safety	**–**	**+**	**+++**	**++**		**++**	**+++**
Experiment Duration	2−4 hours	30−120 min	10−30 min	20−40 min		15−30 sec	5−10 min
Complications	**+++** Risk (5-10%) of Infection, bleeding and bile leaks.	**++** Risk (<5%) Bleeding, perforationpancreatitis cholangitis.	**–** Claustrophobia in some patients	**+** Risk (1%) of failure rate, bleeding and perforation.		**–** Rare allergic reaction (<1%) to iodinated agents	**–** No complication.
Comments **Pros:**	+ Diagnosis & therapeutic (treatment) procedure.	+ Diagnosis & treatment procedure.	**Non-invasive** + No ionizing radiation. + Relatively operator -independent.	**Usually Non- invasive (sedation).** + Diagnosis tool combined with tissue and/or lesion sampling.		**Non-invasive** + Faster method. + High resolution. + Operator -independent.	**Non-invasive** + No ionizing radiation. + High resolution. + Faster method. + Operator-independent.

Cons:	**Invasive** **−Ionizing radiation**. − Operator-dependent.	**Invasive** **− Ionizing radiation**. − Operator dependent.	− Expensive. **− Poor resolution.** − Solely diagnostic method. **−** Motion sensitive. **−** Claustrophobia	**−** Operator dependent. −Highly motion sensitive − Thermal effects and cavitations.	**− Ionizing radiation.** − Solely diagnostic method	− **Low Imaging depth ~3mm**. − Motion sensitive.

PTC= percutaneous transhepatic cholangiography, ERCP= Endoscopic Retrograde Cholangiopancheatography, MRCP = Magnetic resonance cholangiopancreatography, US = Clinical Ultrasound, EUS = Endoscopic ultrasound, HFUS= High Frequency Ultrasound (>10MHz), IDUS=Intraductal ultrasonography, CT= Computed Tomography, OCT= Optical Coherence Tomography.

Q: Section 2.2.1, last paragraph: This is too superficial. It mentions the role of OCT in differentiating between benign and malignant lesions but this seems to be for non GI organs and should be clarified. ·
Ans: OCT shows great potential for differenting between benign and malignant lesions for both non-GI organs (*Radiology* 2007, 244: 865–74, *Chest* 2010, 138:984–8, *Gastrointest Endosc 2007,* 65:50–56, *Cancer Research 2010*,70:2579–84) and for GI organs (Endoscopy 2009; 41: 696–701, Dig. & Liv. Dis. 2006, 38:688–695, Bio. Opt. Exp 2011, 2:2372–82). However, imaging non-GI organs with OCT is out of scope of our study and we particularly focused on imaging pancreatobiliary ductal system with OCT in this review. We eliminate confusion by removing the last paragraph with non-GI refrences in our revised manuscript.

Q. Section 2.2.1, last paragraph: "for imaging an endoscopic OCT probe was inserted into the cut surface of the pancreatic cysts". Presumably these studies described are in animal studies and should be clarified. The authors should list the human studies that have been done to date. There are presumably small studies and could be listed in a table with the relevant findings of the studies.
Ans: Iftimia *et al.* (Bio. Opt. Exp, 2:2372–82,2011) showed that OCT modality can be used for diagnosing human pancreatic cysts. Fresh pancreatic specimens (pancreatic cysts) from patients were made available immediately after surgery and then examined with OCT. Images were able to reveal specific morphologic features of pancreatic cysts and thus to differentiate between low risk (i.e. serous cyst adenomas) and high risk (i.e., mucinous cystic neoplasms and intraductal papillary mucinous neoplasms) pancreatic cysts with over 95% sensitivity and specificity. This *ex vivo* pilot study suggests that OCT could be used by clinicians in future to more reliably differentiate between benign and malignant pancreatic cysts.

Q: Conclusion: I think that the authors are overstating it when they say that OCT can be used to diagnose early ductal changes and accurately differentiate between the neoplastic and non neoplastic lesions.
Ans: We agree with the reviewer. The sentence has been revised as: "OCT can improve the quality of images obtained during ERCP, which may be important in distinguishing between the neoplastic and non-neoplastic lesions".

Q: Conclusion: Authors mention a list of new OCT developments in passing. In a review, if there are data on these developments, they should be mentioned in a separate section with references, not at the end of a concluding paragraph.
Ans: We agree with the reviewer. Description of different generation of OCT systems has been deleted

from conclusion in the revised manuscript.

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

Sincerely yours,
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On behalf of all co-authors.