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Manuscript NO: 75504: Machine Learning in EUS and the Pancreas: The New Frontier?

Dear Editors-in-Chief,

Thank you for allowing us to revise our manuscript for Artificial Intelligence in Gastroenterology. We would like to extend the utmost gratitude to the editor and reviewers for the time taken to review our manuscript.

As suggested, we have revised the table, introduction and conclusion sections. We have also added a new figure based on the reviewers' comments.

We appreciate the positive feedback. We hope that we have adequately addressed your concerns, and that you find this new optimized version suitable for publication in your esteemed journal.

Sincerely yours,

Cem Simsek, MD
Linda S. Lee, MD

Comments from Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: This manuscript is a mini review of the literature on the use of AI in the diagnosis of pancreatic diseases when using EUS, divided into visual recognition classification, procedure assistance and training. The listing procedure for review is thought to be correct. I would also say that it provides a sufficient amount of information in the content. However, since the papers listed in Table 1 are not numbered as references, the reader may not be able to refer to them without bibliographic information. All references in Table 1 should be numbered.

Response: We appreciate the reviewer's kind comments. The references for the studies included in the table are added as below:

Table 1. Summary of included machine learning studies on EUS in pancreatic disease.

Field	Author	Reference	Year	Study Population Used for Training	Task	Machine learning method	Performance (in test population if available)
Pancreatic Cysts	Kuwahara	[1]	2019	Benign IPMN (n=27) Malignant IPMN (n=23)	Differentiate benign from malignant IPMN	Convolutional neural network	AUC = 0.98
	Springer	[2]	2019	Mucinous cystic neoplasms (n=153) Serous Cystic Neoplasms (n=148) IPMN (n=447) Malignant cysts (n=114)	Guide clinical management by classify into three risk groups: No risk of malignancy Low risk of progression High-risk of progression or malignant	Not available	First group: 100% specificity, 46% sensitivity. Second group: 54% specificity, 91% sensitivity Third group: 30% specificity, 99% sensitivity.
	Kurita	[3]	2019	Mucinous cystic neoplasms (n=23) Serous Cystic Neoplasms (n=15) IPMN (n=30) Other cyst types (n=17)	Differentiate benign from malignant cyst	Multi-layered perceptron	AUC = 0.96, sensitivity: 95%, specificity: 91.9%
	Nguon	[4]	2021	Mucinous cystic neoplasms (n=59) Serous Cystic Neoplasms (n=49)	Differentiate mucinous cystic neoplasm and serous cystadenoma	Convolutional neural network	AUC = 0.88
Pancreatic Cancer	Saftouiu	[5]	2008	PDAC (n=32) Normal pancreas (n=22) Chronic pancreatitis (n=11) Pancreatic neuroendocrine tumor (n=3)	Differentiate benign from malignant masses	Multi-layered perceptron	AUC = 0.96
	Zhang	[6]	2010	PDAC (n=153) Chronic pancreatitis (n=43) Normal pancreas (n=20)	Differentiate cancer from non-cancer pancreas	Support Vector Machine	Accuracy: 97.9%, sensitivity: 94.32%, and specificity: 99.4%.
	Saftoiu	[7]	2012	PDAC (n=211) Chronic pancreatitis (n=47)	Differentiate cancer from benign masses	Multi-layered perceptron	AUC = 0.94

	Zhu	[8]	2013	PDAC (n=262) Chronic pancreatitis (n=126)	Differentiate cancer from non-cancer pancreas	Support Vector Machine	Accuracy: 94.2%, sensitivity: 96.2%, and specificity: 93.3%.
	Ozkan	[9]	2016	PDAC (n=202) Normal pancreas (n=130)	Differentiate cancer from normal pancreas	Multi-layered perceptron	Accuracy: 87.5%, sensitivity: 83.3%, and specificity: 93.3%.
	Udristou	[10]	2021	PDAC (n=30) Chronic pancreatitis (n=20) Pancreatic neuroendocrine tumor (n=15)	Diagnose focal pancreatic mass	Convolutional neural network and long short-term memory	Mean AUC = 0.98 (Includes PDAC, CP and PNET)
	Tonozuka	[11]	2021	PDAC (n=76) Chronic pancreatitis (n=34) Control (n=29)	Differentiate pancreatic cancer from chronic pancreatitis and normal pancreas	Convolutional neural network and pseudo-colored heatmap	AUC = 0.94
Autoimmune pancreatitis	Zhu	[12]	2015	AIP (n=81) Chronic pancreatitis (n=100)	Differentiate AIP from chronic pancreatitis	Support Vector Machine	Accuracy: 89.3%, sensitivity: 84.1%, and specificity: 92.5%
	Mayra	[13]	2021	AIP (n=146) PDAC (n=292) Chronic pancreatitis (n=72) Normal pancreas (n=73)	Differentiate of AIP from PDAC	Convolutional neural network and pseudo-colored heatmap	AUC for AIP from all other = 0.92
Procedural assistance	Iwasa	[14]	2021	Pancreatic mass (n=100)	Segmentation of pancreatic masses	Convolutional neural network	Intersection over unit = 0.77
	Zhang	[15]	2020	EUS Videos (n=339)	Recognition of stations, and segmentation of anatomical landmarks	Convolutional neural network	Accuracy for classification of stations (average) = 0.824, Dice coefficient for segmentation of pancreas (average) = 0.715

AUC: Area under the receiver-operator characteristic curve, AIP: Autoimmune pancreatitis, IPMN: Intraductal papillary mucinous neoplasm, PDAC: Pancreatic adenocarcinoma; CP: chronic pancreatitis; PNET: pancreatic neuroendocrine tumor

Comments from Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: The overall quality of the manuscript is good

Response: We thank the reviewer for the positive comment.

Comments from Reviewer #3:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Minor revision

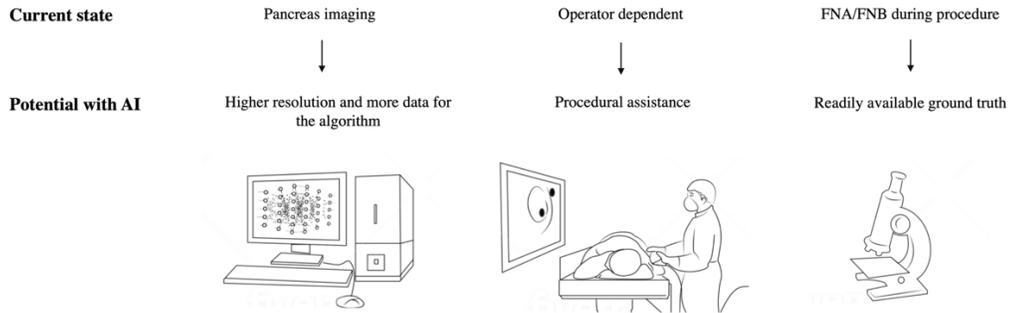
Specific Comments to Authors: *This is a mini review to summarize the recent advance in machine learning in endoscopic ultrasonography for pancreatic diseases. Machine learning techniques and detailed applications are systematically written. Also, some limitations are given from the author's point of view. So, I recommend accepting after minor revision.*

Comment 1. *The term machine learning in the Introduction and Conclusion Sections mentioned need more. Merely discuss AI is not enough which expands the scope of this paper. -Recommended the authors make a schematic diagram to illustrate the advantages of machine learning or AI, compared to CT and MRI and transabdominal ultrasonography. The corresponding discussion needs to be written in the Introduction section.*

Response: We thank the reviewer for the comment. We have added the following discussion to the introduction section. We have also added a figure summarizing the discussion:

- In this regard, utilization of artificial intelligence (AI) with EUS has emerged as a promising strategy (Figure 1). Although EUS has better performance than the alternative radiology imaging methods, it is also more operator dependent. The endosonographer's experience and skills can significantly alter the diagnostic or therapeutic outcomes of an EUS procedure. AI may decrease this operator dependency as it can provide assistance to the endosonographer in several tasks that include, but are not limited, to identifying anatomical landmarks, detecting lesions, interpreting sonographic findings, and guiding obtaining optimal tissue biopsy with higher diagnostic yield. Because AI algorithms use higher resolution EUS imaging data, they might distinguish patterns and identify details from the images which may not be recognizable with human detection alone currently. Finally, AI research with EUS is more convenient because imaging data used to train the AI models often have readily available definitive histologic diagnoses.

Advantages of AI in EUS



Comment 2. *Introduction: This part is logically confusing. Suggest to first introduce pancreatic diseases, then introduce diagnostic methods including EUS, then introduce AI, then introduce machine learning, and finally highlight the uniqueness of this review. -*

Response: We thank the reviewer for the insightful comment regarding the introduction section. We agree with the reviewer and adjusted the flow of the introduction as requested.

Comment 3. *Conclusion: Recommended to replace the subtitle “Conclusion” with “Conclusion and Prospects”, as the last paragraph also points out the limitations of this technology.*

Response: We appreciate the reviewer’s suggestion. “Conclusion” section is changed to “Conclusion and Prospects” as recommended.