



PEER-REVIEW REPORT

Name of journal: Artificial Intelligence in Gastroenterology

Manuscript NO: 62911

Title: Artificial Intelligence for Pancreatic Cancer Detection: Recent Development and Future Direction

Reviewer's code: 02528808

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Assistant Professor, Chief Doctor, Doctor

Reviewer's Country/Territory: Spain

Author's Country/Territory: United States

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Reviewer chosen by: AI Technique

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

Nowadays, the use of AI in the field of medicine is essential. This is a clear, concise and well-structured review, which summarizes the advances and limitations of the application of AI in the diagnosis of pancreatic cancer. I agree with the publication of the article.



PEER-REVIEW REPORT

Name of journal: Artificial Intelligence in Gastroenterology

Manuscript NO: 62911

Title: Artificial Intelligence for Pancreatic Cancer Detection: Recent Development and Future Direction

Reviewer's code: 02445461

Position: Editorial Board

Academic degree: FACS, FRCS (Hon), MD

Professional title: Professor

Reviewer's Country/Territory: France

Author's Country/Territory: United States

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Reviewer chosen by: Lian-Sheng Ma

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input checked="" type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
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SPECIFIC COMMENTS TO AUTHORS

Manuscript summary This manuscript presents a survey for research on the detection and diagnosis of pancreatic cancer in medical images (CT, MR, EUS) and biomarker information using machine learning. The emphasis is focused on EUS and biomarkers in serum and cystic fluids. The field of machine learning applied to pancreatic cancer detection is progressing at a rapid pace and it is of high interest to the community. Therefore a survey of recent progress is important. The manuscript covers some key areas and it finishes with some perspectives for the future. However, I found that the manuscript has some major limitations. I break these down into 7 issues in the following section. These issues are not small: to correct them would require significant modifications. Manuscript limitations Major issue 1: Limited novelty and no discussion about other survey papers There are several recent survey papers on exactly this topic already and several are published within the last year. The authors should have referenced at least some of the good ones and then discussed what new aspects this manuscript brings to us. Example survey articles include (but are not limited to): [1] Lin et al., Application of artificial intelligence for the diagnosis, treatment, and prognosis of pancreatic cancer, *Artificial Intelligence in Gastroenterology*, 2020 [2] Gorris et al., Artificial intelligence for the management of pancreatic diseases, *Digestive endoscopy*, 2020 [3] Tonozuka et al., The Role of Artificial Intelligence in Endoscopic Ultrasound for Pancreatic Disorders, 2020 [4] Lakshmi et al., A Survey on Detection of Pancreatic Cancer using Deep Learning Techniques, *International Journal of Grid and Distributed Computing* Vol. 13, No. 1, (2020), pp. 2753– 2763 [5] Cazacu et al., Artificial intelligence in pancreatic cancer: Toward precision diagnosis, *Endoscopic Ultrasound* 2019 [6] Kuwahara et al., Current status of artificial intelligence analysis for endoscopic ultrasonography, *Digestive endoscopy* 2020 [7] Pereira et al., Early detection of



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pancreatic cancer, Lancet Gastroenterol Hepatol, 2020 [8] Akshintala et al., Artificial intelligence in pancreaticobiliary endoscopy, Gastroenterology and hepatology, 2021 These works cover very similar grounds as the manuscript. In the case of EUS, which seems to be the primary focus of this manuscript, [3] and [6] do better jobs both in terms of paper organization (see below) and completeness. For CT and MR, [2] does a better job in terms of these aspects. [7] includes a review of detection biomarkers in addition to using social media for detection and predictive models using electronic health records. It is not clear what value this manuscript brings in light of these survey papers. The authors should, after conducting a systematic review of survey papers/meta-reviews, be clear about what is missing from these previous (but very recent) reviews and how the manuscript fills the gap.

Major issue 2: Poor organization The manuscript is organized by imaging modality CT, MR, EUS which is fine. But fundamental aspects are not clarified. The distinction of computer-assisted detection (CADE) and computer-assisted diagnosis (CADx) is not covered. From the FDA definitions: a CADE device is “intended to identify, mark, highlight or otherwise direct attention to portions of an image that may reveal abnormalities during interpretation of images by the clinician.” A CADx device is “intended to provide information beyond identifying abnormalities, such as an assessment of disease.” It is very important to classify research and AI systems as CADE or CADx because they serve different purposes, performance requirements for real clinical use can be substantially different and patient risk changes. The manuscript mixes everything together and ‘detection’ is often confused with ‘diagnostics’. Indeed the review of AI for EUS pancreatic cancer analysis in [2] separates works into CADE and CADx, and it is more comprehensive and systematic than the manuscript. EUS AI systems can also be categorized according to the modality used e.g. elastography, colour doppler, contrast enhancement, standard b-mode or combinations. Contrast enhancement and elastography is mentioned but it is not clear surveyed papers



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use only b-mode. The section on CT and MR is also quite poor with few references. Radiomics is not even mentioned but it is a large topic for CADe and CADx in CT and MR. Most of the discussion in CT is on pancreas segmentation, which is not very relevant for CADe or CADx for which there are many works see e.g. [2] and other survey papers. Major issue 3: Survey methodology is not described The manuscript is missing a section on survey methodology. How were papers discovered? Why were they included? Major issue 4: Performance of papers are reported with metrics (usually sensitivity and specificity) but other details are missed. We know that the quality of the evaluation methodology of an AI system is fundamental. Results from papers are presented with performance metrics but we lack evaluation details and there is no real comment on the quality of the evaluation (a critical aspect). This manuscript would have much better value in my opinion (and differentiate it from other survey papers) if it also covered aspects such as: 1. Dataset size (test and training) 2. How datasets were divided into training and test sets 3. Dataset access (open or private) 4. Study type (retrospective/prospective, single-centre/multi-centre etc.) 5. AI models Note that [6] did something like this already for some papers for AI+EUS. Major issue 5: Abdominal US was not discussed There exists several works for pancreatic cancer detection with abdominal US see e.g. [6]. Why was abdominal US not included? Unlike EUS, it is non-invasive and it is considered one of the first imaging modalities to consider. Major issue 6: Future directions was quite weak For EUS, the suggested future directions are quite light: to develop AI systems capable of real-time performance and evaluation on larger datasets. But there are so many other important future directions and unsolved challenges that are not mentioned. I was hoping to read about the authors' insights into them such as: 1. How to systematically record and standardize EUS data, required for large-scale deep learning? Unlike CT and MR, this is much harder for EUS. 2. How do we motivate centres to systematically record and share EUS data? 3. How to train AI



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systems that handle the inherent operator-dependence of EUS and variable image/procedure quality? 4. How to make AI models interpretable and explainable, so that they are not just working in a 'black box' manner. This is a known issue in AI-based CADx and CADE systems today. What is particularly relevant when it comes to pancreatic cancer? 5. What are likely to be the fundamental limits of AI and EUS? We cannot expect AI to work magically. It has limits on diagnostic capabilities because of limits in the information contained in an EUS video/image. e.g. highly accurate differential diagnostics of IPMNs, SCNs and MCNs in b-mode may not be possible. There are no comments on the limits of AI. 6. What EUS modalities are likely to be important for use for CADE and CADx? What could we expect to achieve with b-mode compared to b-mode + elastography, or b-mode + elastography + contrast enhancement? 7. What other factors are preventing good results presented in papers from translating to clinical use? 8. How to combine data with CT, MR, biomarkers and electronic health records to make better predictions? Are there examples for pancreatic cancer or can we draw inspiration from work in other cancer types. Major issue 7: No figures or tables Figures in previous survey papers can convey useful information such as EUS images of pancreatic lesions, diagnostic trees, decision processes (both by clinician and AI systems). The fact that this manuscript has no figures is a major weakness. Furthermore, the fact that this manuscript has no tables to systematically summarize works is also a major limitation. Summary Overall I found that this manuscript presented a fairly superficial overview of progress in pancreatic cancer detection/diagnostics with machine learning. The review on progress in CT, MR and EUS analysis is not comprehensive nor particularly well organized compared to other recent survey papers. It is therefore not clear what the value or purpose of this manuscript is. As a survey paper, this falls short because it is not comprehensive nor well structured. Other survey papers do a better job. As a paper giving insights into the future of AI and pancreatic cancer, there were limited



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contributions and the comments were quite obvious (combining information sources, real-time EUS video processing). In the conclusion, a statement such as “The accuracy of AI aided EUS for pancreatic cancer diagnosis is high” is simply too vague and not accurate. The statement needs to be qualified by the detection/diagnostic problems being attempted by current AI systems. Diagnostic accuracy can vary from good in simplified problem cases (e.g. differentiating an EUS image of healthy pancreas parenchyma from an image of a pancreatic cyst), to complex e.g. differentiation of chronic pancreatitis from solid tumours with only b-mode, to extremely complex (e.g. differentiation of cystic lesion types). These details are important and glossed over in the manuscript. In summary, I do not think the manuscript can be accepted for publication in its current form. As a survey paper, It is not comprehensive nor well structured and it does not bring much compared to other survey papers published in the last year. It is also not giving genuinely novel insights into the future directions of the use of AI in pancreatic cancer. I just feel that this manuscript falls into a middle ground of neither being a strong survey paper nor giving interesting new insights about the treatment of pancreatic cancer with AI and how we can translate AI research to clinical use.



RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: Artificial Intelligence in Gastroenterology

Manuscript NO: 62911

Title: Artificial Intelligence for Pancreatic Cancer Detection: Recent Development and Future Direction

Reviewer's code: 05526270

Position: Peer Reviewer

Academic degree: BPharm, MS

Professional title: Pharmacist, Research Fellow

Reviewer's Country/Territory: Ireland

Author's Country/Territory: United States

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS



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The authors revised the manuscript carefully. No further comments.