Response letter

Manuscript Number: 89548

Journal: World Journal of Gastrointestinal Oncology

Title: A CT-Based Radiomics Diagnostic Approach for Differential Diagnosis between Early- and Late-stage Pancreatic Ductal Adenocarcinoma

Dear editors and reviewers,

We sincerely thank the editors and all reviewers for the critical review and the chance for revision. Your comments are highly insightful and constructive. We have revised the manuscript accordingly and marked the changes with yellow color. We hope the revised manuscript has been improved to the quality that is suitable for publication now. We will be happy to edit the text further, based on helpful and valuable comments from both editors and reviewers. We are looking forward to your favorable final decision.

Best regards.

Reviewers' comments:

Reviewer #1:

Conclusion: Major revision

Authors built a radiomics model using CT datasets from a single institution to distinguish early-stage and late-stage pancreatic ductal adenocarcinoma. It is unclear though what the intended application would be for such a model. If the model only stages as early or late, can any clinical decision be made without TNM staging? On the other hand, if TNM staging is available, what is the value to the present model?

Authors response: We thank the reviewer for the constructive and valuable comments. Pancreatic cancer remains one of the most dismal types of cancers worldwide, characterized by a poor prognosis and a low 5-year survival rate [1]. Pancreatic ductal adenocarcinoma (PDAC) constitutes more than 90% of all pancreatic cancer cases. One of the primary reasons for the dismal survival rates in PDAC is that most patients are usually diagnosed at late stages when the disease is already metastatic. Current estimates indicate that only 10-15% of PDAC patients are diagnosed with a

resectable or borderline resectable disease [2]. These data highlight the urgent unmet clinical need to identify and develop diagnostic methods that could precisely detect PDAC at its earliest stages when the disease is still confined to within the pancreas and while there is still an opportunity for the surgical resection of the tumor [3]. Over the past few years, radiomics has facilitated the development of processes for the conversion of digital images into mineable data and further analysis of the data for decision support [4]. In this study, we aimed to develop a radiomics-based diagnostic approach with a robust noninvasive diagnostic potential for identifying patients with early-stage PDAC.

References:

1.Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023;73(1):17-48.

2.Versteijne E, van Dam JL, Suker M, et al. Neoadjuvant Chemoradiotherapy Versus Upfront Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Long-Term Results of the Dutch Randomized PREOPANC Trial. J Clin Oncol 2022;40(11):1220-1230.

3.Xu C, Jun E, Okugawa Y, et al. A Circulating Panel of circRNA Biomarkers for the Noninvasive and Early Detection of Pancreatic Ductal Adenocarcinoma. Gastroenterology 2024;166(1):178-190.e16.

4.Amaral MJ, Oliveira RC, Donato P, Tralhão JG. Pancreatic Cancer Biomarkers: Oncogenic Mutations, Tissue and Liquid Biopsies, and Radiomics-A Review. Dig Dis Sci 2023;68(7):2811-2823.

Minor suggestions: 1) "included into the study" -> "included in the study"? 2) Line 5 of Page 2: "by reason of" -> "due to"? 3) Line 26 of Page 2: "and-or"->"and/or"? 4) Line 11 of Page 3: "making... management" -> "making... management decision"? 5) Line 21 of Page 3: Why was "biopsy proved PDAC" excluded? Weren't all cases pathologically PDAC? 6) Line 24 of Page 3: close parenthesis 7) Page 4, Line 12: "Following... features" -> "The following... features"? 8) Page 5, Line 3: "and portal venous phases" -> "and 396 from portal venous phases"? 9) Page 5, Line 11: Please define abbreviation RF here as it's referred to later in the manuscript. 10) "was showed" -> "was shown"; "were showed" -> "were shown" 11) Page 6, Lines 11--12: Please define abbreviations GLCM, GLSZM, and RLM. 12) Page 6, Line 31: remove "with which"? 13) Page 7: Should Ref. [16] be cited after Lines 15--17 instead of Lines 17--18? 14) Page 7, Lines 27--29: Does this statement deliver any useful

information? Isn't the definition that M1 is Stage IV (thus late stage)? 15) Page 7, Lines 29--30: Please fix this sentence as well. Stage III does not allow distant metastasis by definition. 16) Page 8, Line 3: "support-vector machine based on CT texture analysis" -> "CT texture analysis based on support vector machine"? 17) Page 8, Line 19: remove "regarding"? 18) Page 8, Line 24: The readers are referred to the documentation of the code, which is NOT intrepretability! 19) Page 8, Line 30: "radiomiscs"->"radiomics"; remove "And"? 20) Page 8, Lines 33--34: grammar; "it only uses CT which is fast, low cost, and widely available"? 21) "dismal metastasis" -> "distal metastasis"? 22) Line 15 of Page 6 and Line 10 of Page 8: "Among which" -> "Among those" / "Among them"? 23) Line 22 of Page 6: remove ", respectively"? 24) Please label x and y axes of Fig. 3. 25) Fig. 4: How was “importance” defined? 26) Fig. 4C: Please show the color bar indicating how the colors correspond to values.

Authors response: We feel great thanks for your professional review work on our article. We are sorry for our carelessness. Based on your comments, we have made the corrections to our previous draft. Sentences with inappropriate expression or grammatical errors, which have been pointed out in the light of your valuable and merticulous comments, have been revised accordingly (No. 1-4, 6-23).

Line 21 of Page 3: Why was "biopsy proved PDAC" excluded? Weren't all cases pathologically PDAC?

Authors response: The staging of PDAC and evaluation of surgical resectability become critical in the management of this deadly disease [1]. The recent 8th edition American Joint Committee on Cancer (AJCC) revealed that the tumor, node, and metastases (TNM) system is the preferred system for staging of PDAC [2]. The significance of tumor size was further emphasized in the latest version of AJCC, especially for further grouping of T1-stage PDAC [3]. In addition to being useful for more accurate staging of tumors, it is also important for the accurate tumor measurement and delineation to improve outcomes in PDAC with effective treatment planning and decision-making on surgery, chemotherapy, and radiation therapy, which are usually used in clinical practice [4]. Large discrepancies in the PDAC measurements on CT or MRI compared with pathologic specimens have been reported in previous studies [5, 6]. Therefore, staging of PDAC is based on pathological TNM system in our study.

References:

1. Ma C, Yang P, Li J, Bian Y, Wang L, Lu J. Pancreatic adenocarcinoma: variability in measurements of tumor size among computed tomography, magnetic resonance imaging, and pathologic specimens. Abdom Radiol (NY) 2020; 45(3):782-788.

2. Amin MB, Edge SB, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asar EA, Madera M, Gress DM, Meyer LR. AJCC Cancer Staging Manual. 8 ed. 2017, New Yor: Springer. 337-406.

3. Huguet F, Girard N, Guerche CS, Hennequin C, Mornex F, Azria D. Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: a qualitative systematic review. J Clin Oncol 2009; 27:2269-2277.

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5. Legrand L, Duchatelle V, Molinié V, Boulay-Coletta I, Sibileau E, Zins M. Pancreatic adenocarcinoma: MRI conspicuity and pathologic correlations. Abdom Imaging 2015; 40:85-94.

6. Kassardjian A, Stanzione N, Wang HL. Comparative Accuracy of Tumor Size Assessment and Stage Analysis by Imaging Modalities Versus Gross Examination for Pancreatic Ductal Adenocarcinoma. Pancreas 2019; 48: 223-227.

24) Please label x and y axes of Fig. 3.

Authors response: We have labeled x and y of Fig. 3 as suggested.

25) Fig. 4: How was “importance” defined?

Authors response: Thank you very much for your concern. The feature importance plot was provided by the random forest methods as soon as the model train procedure completed. The importance of the feature was computed from permuting out-of-bag (OOB) data. As described in the introduction of the random forest package, "for each tree, the prediction error on the out-of-bag portion of the data is recorded (error rate for classification). Then the same is done after permuting each predictor variable. The differences between the two are then averaged over all trees, and normalized by the standard deviation of the differences."

26) Fig. 4C: Please show the color bar indicating how the colors correspond to values.

Authors response: Thank you very much for your constructive comment. We added color bar to Fig. 4C.

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Best regards.

Reviewer's comments:

Conclusion: Minor revision

Thanks for your effort in responding to my questions. For some of them, however, I can't see the direct answer to my question in your response. 1) MATERIALS AND METHODS, Patients: Why was "biopsy proved PDAC" excluded? One of your inclusion criteria was "pathologically proved PDAC". What is the difference between "biopsy proved" and "pathologically proved" ?

Authors response: We thank the reviewer for the insightful and constructive comments. Pancreatoduodenectomy is performed for both pancreatic cancer and periampullary non-pancreatic cancer (i.e. distal cholangiocarcinoma, ampullary cancer, duodenal cancer). Each of these cancers differ in terms of prognosis and (neo)adjuvant treatment [1, 2]. Based on recent randomized trials [3, 4], preoperative chemo(radio) therapy is increasingly used in the treatment of pancreatic cancer, but not recommended for periampullary cancers according to the current guidelines [5]. Therefore, certainty about the diagnosis prior to pancreatoduodenectomy is important, as it determines the pretreatment strategy and, as such, has direct clinical

consequences. A research by Dr. van and colleagues has evaluated the accuracy of the diagnosis prior to pancreatoduodenectomy based on all available information incorporating clinical presentation, laboratory tests, radiological characteristics and, preoperative cytology/histology [6]. As a result, of all patients with a final diagnosis of periampullary (non-pancreatic) cancer, 21% (116/565) were preoperatively incorrectly diagnosed as pancreatic cancer. Of all patients with a final diagnosis of pancreatic cancer, 13% (87/679) were preoperatively misdiagnosed as distal cholangiocarcinoma (n = 41, 6.0%), ampullary cancer (n = 27, 4.0%) duodenal cancer (n = 16, 2.4%), or other (n = 3, 0.4%). Therefore, we excluded PDAC proved by biopsy in our study. Additionally, staging of PDAC is based on pathological TNM system instead of clinical TNM system since large discrepancies in the PDAC measurements on CT or MRI compared with pathologic specimens have been reported in previous studies [7, 8].

References:

1. He J, Ahuja N, Makary MA, et al. 2564 resected periampullary adenocarcinomas at a single institution: trends over three decades. HPB (Oxford). 2014;16(1):83-90.

2. Tol JA, Brosens LA, van Dieren S, et al. Impact of lymph node ratio on survival in patients with pancreatic and periampullary cancer. Br J Surg. 2015;102(3):237-245.

3. Jang JY, Han Y, Lee H, et al. Oncological Benefits of Neoadjuvant Chemoradiation With Gemcitabine Versus Upfront Surgery in Patients With Borderline Resectable Pancreatic Cancer: A Prospective, Randomized, Open-label, Multicenter Phase 2/3 Trial. Ann Surg. 2018;268(2):215-222.

4. Versteijne E, Suker M, Groothuis K, et al. Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial. J Clin Oncol. 2020;38(16):1763-1773.

5. Tempero MA, Malafa MP, Chiorean EG, et al. Pancreatic Adenocarcinoma, Version 1.2019. J Natl Compr Canc Netw. 2019;17(3):202-210.

6. van Roessel S, Soer EC, Daamen LA, et al. Preoperative misdiagnosis of pancreatic and periampullary cancer in patients undergoing pancreatoduodenectomy: A multicentre retrospective cohort study. Eur J Surg Oncol. 2021;47(10):2525-2532.

7. Legrand L, Duchatelle V, Molinié V, Boulay-Coletta I, Sibileau E, Zins M. Pancreatic adenocarcinoma: MRI conspicuity and pathologic correlations. Abdom Imaging 2015; 40:85-94.

8. Kassardjian A, Stanzione N, Wang HL. Comparative Accuracy of Tumor Size Assessment and Stage Analysis by Imaging Modalities Versus Gross Examination for Pancreatic Ductal Adenocarcinoma. Pancreas 2019; 48: 223-227.

2) Fig. 3: Can you please indicate what "x" and "y" axes mean? The readers need to know what quantities are plotted, and the unit, if applicable.

Authors response: We thank the reviewer for the valuable comments. The X-axis indicates the gray level (HU). The Y-axis indicates the number of voxels. We added the definition of "x"and "y" as suggested.

3) Please include the definition of "importance" in the manuscript.

Authors response: We thank the reviewer for the constructive comments. We included the definition of "importance" in the revised paper as suggested.