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March 9, 2021.

Ms. Li Ma
Vice Editor-in-Chief
Baishideng Publishing Group

Dr. Subrata Ghosh, AGAF, FCAHS, FRCP (C), FRCPC, FRCPE, MD
Dr. Andrzej S Tarnawski, DSc, MD, PhD
Editors-in-Chief
World Journal of Gastroenterology

Dear Editor:

I wish to re-submit the manuscript titled “**Large-duct pattern invasive adenocarcinoma of the pancreas – a variant mimicking pancreatic cystic neoplasms: A minireview.**” The manuscript ID is 63338.

We thank you and the reviewers for your thoughtful suggestions. The manuscript has benefited from these insightful suggestions. I look forward to working with you and the reviewers to move this manuscript closer to publication in the *Baishideng Publishing Group*.

The manuscript has been rechecked and the necessary changes have been made in accordance with the reviewers’ suggestions. The responses to all comments have been prepared and attached herewith/given below.

The major modifications in the text are highlighted (light blue) for easy recognition of our revision. We also made some minor edits in the main text (underlined). Our detailed point-by-point responses to your comments and those of the referees as well as additional data are provided in a separate file.

Thank you for your consideration. I look forward to hearing from you.

Sincerely,
Hiroki Sato, MD
Department of Medicine, Asahikawa Medical University
2-1-1-1 Midorigaoka-Higashi, Asahikawa, Hokkaido 078-8510, Japan
Email: hirokisato@asahaikawa-med.ac.jp

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 63338

Title: Large-duct pattern invasive adenocarcinoma of the pancreas – a variant mimicking pancreatic cystic neoplasms: A minireview

Reviewer's code: 05106105

Position: Editorial Board

Academic degree: MD

Professional title: Chief Technician, Professor

Reviewer's Country/Territory: China

Author's Country/Territory: Japan

Manuscript submission date: 2021-01-28

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-01-30 02:49

Reviewer performed review: 2021-01-31 10:04

Review time: 1 Day and 7 Hours

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 Grade E: Do not publish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
Re-review	<input checked="" type="checkbox"/> Yes <input 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

In your review, you describe all conditions underlying the large-duct type variant, a unique subtype of pancreatic ductal adenocarcinoma (PDA) with cystic features, which has not been reviewed in the literature. Your reference documentation is very comprehensive and the review concludes almost all conditions that may have something to do with mucin profile and genetic alterations in distinguishing large-duct PDA from IPMNs. I can imagine how much work you have done for this professional review. A flaw in this otherwise perfect writing is that there are some sloppy grammatical issues. I recommend that you give a final polish to your writing to keep your message as concise as possible. Overall, the abundant information from this review contribute to our understanding of large-duct pattern invasive carcinoma of the pancreas. I really appreciate your great work and it's my great honor to read this paper.

Author response:

Thank you for your appraisal of our work. Moreover, thank you for reviewing our manuscript and providing insightful comments, which significantly helped us in revising the manuscript. We provided our manuscript to a professional editing service for proofreading according to your suggestion (see attached certificate of English editing by Editage).

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 63338

Title: Large-duct pattern invasive adenocarcinoma of the pancreas – a variant mimicking pancreatic cystic neoplasms: A minireview

Reviewer's code: 02510721

Position: Peer Reviewer

Academic degree: MD

Professional title: Full Professor

Reviewer's Country/Territory: Italy

Author's Country/Territory: Japan

Manuscript submission date: 2021-01-28

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-01-29 07:32

Reviewer performed review: 2021-02-02 15:17

Review time: 4 Days and 7 Hours

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

SPECIFIC COMMENTS TO AUTHORS

To Authors The Title and Abstract are correct and correspond to the content and aim of the study. The Introduction develops clearly the topic of the histological and genetic alterations of PDA and the perspective of the differentiation from the cystic pancreatic tumors and the detection of cystic subtype of PDA.

In the minireview the Authors report organically the data from the literature of all the patients suffering from large-duct PDA. The data analysis is very accurate: epidemiology, tumor location and symptoms, imaging findings, pathology with immunohistochemistry, genetic alterations, treatment and prognosis. The Conclusion is appropriate with the development and results of the study. The References are up-to-date and complete. The Figures and the Tables are clear and completely integrate the text.

In summary this is an excellent study that provides a valuable and fundamental contribution to the definition of the new large-duct subtype of PDA.

Author response:

Thank you very much for your comments on our manuscript. I sincerely appreciate your comprehensive comments.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 63338

Title: Large-duct pattern invasive adenocarcinoma of the pancreas – a variant mimicking pancreatic cystic neoplasms: A minireview

Reviewer's code: 03251562

Position: Editorial Board

Academic degree: MD

Professional title: Associate Professor, Doctor

Reviewer's Country/Territory: United States

Author's Country/Territory: Japan

Manuscript submission date: 2021-01-28

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-02-04 22:24

Reviewer performed review: 2021-02-04 22:38

Review time: 1 Hour

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
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input type="checkbox"/> Anonymous <input checked="" type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

Sato and colleagues, write an excellent review on Large-duct pattern invasive adenocarcinoma of the pancreas. Overall this is very interesting topic in pancreatic cancer with overall limited understanding. Review is in-depth and summarizing published literature very nicely. Authors have done an excellent job in highlighting various features of large duct type adenocarcinoma macroscopically as well as in pathology.

Author response:

Thank you very much for your comments on our manuscript. I sincerely appreciate your comprehensive comments.

PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 63338

Title: Large-duct pattern invasive adenocarcinoma of the pancreas – a variant mimicking pancreatic cystic neoplasms: A minireview

Reviewer's code: 01558248

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Professor, Surgeon

Reviewer's Country/Territory: Taiwan

Author's Country/Territory: Japan

Manuscript submission date: 2021-01-28

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2021-01-29 02:19

Reviewer performed review: 2021-02-07 09:11

Review time: 9 Days and 6 Hours

Scientific quality	<input checked="" 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 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 checked="" type="checkbox"/> Accept (High priority) <input 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

SPECIFIC COMMENTS TO AUTHORS

The question and suggestion as following: 1. How to define the large duct and main PD or the same. 2. If the branch duct PDA closed to the main PD, and how to classify? 3. In the section of "endoscopic findings"highly challenging (see the "PATHOLOGY" section below for more details)..Please take a consideration as ...highly challenging which will be described well in the section of "Pathology".... 4. Are the figure 3 and 4 taken from the same patient? 5. This is a suggestion that do you think the difficulty to give a subtype for PDA and why? Therefore, please take the next consideration of cellular origin of carcinogenesis about the PDA arisen form main PD to the terminal PD through the pathway of the differentiation and trans-differentiation between the pancreatic duct and glandular stem cells in your future.

Author response:

Thank you for carefully reviewing our manuscript and acknowledging our study's novelty. We apologize for any inadvertent mistakes in the original manuscript.

Our comments to your questions/suggestions and comments are described below:

1. How to define the large duct and main PD or the same.

Response: There is no evidence that the main PD and large-duct PDA developed from the same origin. The normal PDA was undeveloped as a result of acinar-to-duct metaplasia, which occurred in the early stage of multistage carcinogenesis. I added this discussion in the GENETIC ALTERATIONS section. (Page 13, line 17–page 14, line 11)

2. If the branch duct PDA closed to the main PD, and how to classify?

Response: To distinguish branch-duct PDA from the main-duct PDA, the

Elastica–Masson immunohistochemistry (IHC) may be helpful. The normal main PD is positive for elastin fibers, whereas branch duct PDA is negative for elastin fibers. We included statements regarding the discussion in the PATHOLOGY (Immunohistochemistry) section (Page 13, lines 10–14).

3. In the section of "endoscopic findings"highly challenging (see the "PATHOLOGY" section below for more details)..Please take a consideration as ...highly challenging which will be described well in the section of "Pathology"

Response: We appreciate the recommendation. We have revised the manuscript accordingly, and new sentences were added as follows:

Thus, drawing a distinction between large-duct PDA and IPMN-associated cancer using EUS-FNA can become highly challenging, which will be explained well in the "Pathology" section. (Page 10, lines 16–18)

4. Are the figure 3 and 4 taken from the same patient?

Response: Indeed, Figures 3 and 4 are from the same patient. However, the patient's personal information should be kept confidential for publication; thus, we did not declare that the figures are from the same patient in the main text.

5. This is a suggestion that do you think the difficulty to give a subtype for PDA and why? Therefore, please take the next consideration of cellular origin of carcinogenesis about the PDA arisen form main PD to the terminal PD through the pathway of the differentiation and trans-differentiation between the pancreatic duct and glandular stem cells in your future.

Response: Thank you very much for this crucial point. The cellular origin of carcinogenesis of the large-duct PDA remains unclear. Extensive genomic and expression analyses may reveal the cellular origin and particular pathways developing



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the large-duct PDA, when a large number of cases will be collected.

We therefore added this discussion in the GENETIC ALTERATIONS section (page 13, line 17–page 14, line 11).