

To the Editor:

Attached, please find the resubmission of our revised manuscript (file name: WJG 6942-review.doc) for the *World Journal of Gastroenterology*. The details of our manuscript are as follows:

Title: Strategies for early detection of resectable pancreatic cancer

Author: Keiichi Okano, Yasuyuki Suzuki

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6942

Thank you for your earlier letter (January 2, 2014) regarding our manuscript. We greatly appreciated your comments and those of the reviewers. These comments have helped us to improve our manuscript considerably. We have revised the manuscript to meet each of the reviewers' suggestions. Point-by-point responses to these suggestions can be found on the following pages. Additionally, please note that the manuscript has been proofread again by a professional editing service (Editage Co., Ltd.).

We thank the reviewers for their insightful commentary, and we hope that the revised version of our manuscript is now acceptable for publication in the *World Journal of Gastroenterology*. We certify that this manuscript is original, has not been published previously, and is not under consideration by another journal.

Thank you for reconsidering our manuscript.

Respectfully yours,

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Reviewer 1

The manuscript by Okano et al, reviewed the strategy for screening high risk groups in the frame of pancreatic cancer. Although the review requires minor English revision, the manuscript is well written and can be of potential interest of WJG readers.

Comments: The paragraph entitled "Other potential biomarkers" is too short.- Although the authors reviewed the potential biomarkers that are able to predict the pancreatic cancer onset, I suggest to add other biomarkers (hENT1, Mesothelin etc..etc...) which are able to predict the chemotherapy end point.- Paragraph: proteomic: The authors wrote that "The application of proteomics in studying pancreatic cancer is still in its early stage and remains challenging; however, as an emerging technology it has already provided fundamental information to improve the understanding of disease mechanism and potentially offer solutions for early detection of the cancer". The possible solutions are not mentioned by the authors. Please speculate about them.

We thank Reviewer 1 for providing such helpful and insightful comments, and for the careful attention that he or she has paid to our manuscript.

Although it is not yet clear how hENT1 and mesothelin specifically relate to the early diagnosis of pancreatic cancer, they may be clinically useful for treatment selection. Per your suggestion, we have incorporated text regarding other potential biomarkers (including hENT1 and Mesothelin) in the section, "Other potential biomarkers" (p17~).

In addition, we have added a description of how proteomics approaches may aid in the early detection of pancreatic cancer (please see the subsection on proteomics, p14).

The revised manuscript has been edited by a professional editing service, and we have attached the corresponding English editing certificate.

To Reviewer 2

In this article, the authors summarize the current approaches for the early detection of pancreatic cancer. This is a subject of great importance, since early detection is crucial for patients with pancreatic cancer, who's only chance for cure is the complete surgical resection of the tumor at an early stage. However, the article has a narrative character especially in the first half, and its structure lacks of a logical flow. Especially the subsections "new-onset diabetes" and "dilatation of the pancreatic duct" should be

revised. Additionally, the authors should add a conclusion regarding the value of these clinical signs for the early diagnosis of pancreatic cancer. What are the consequences of the presented results for clinicians? I would prefer to read about a more pragmatic, clinical approach and the authors view and suggestions, rather than a listing of study results. The chapter about new imaging modalities for the early detection of pancreatic cancer is better structured and easier to read.

Moreover, there are quite a lot of grammatical errors and typos, which further interrupt the text-flow. Not all abbreviation are introduced at first use.

We thank Reviewer 2 for providing such helpful and insightful comments. Based on your comments, we have extensively revised the entire the manuscript. The subsection on dilation of the pancreatic duct was revised with especial care, and moved to the subsection on MDCT (under the heading “3. Imaging”).

The revised manuscript has been edited by a professional editing service, and we have attached the corresponding English editing certificate. Further, we have edited the text so that all abbreviations are introduced at first use.

Major comments to the authors

- 1. It would be interesting to mention what the current criteria for „resectability“ are in the first place, and how these are evaluated in clinical practice*

We agree with the reviewer’s comment. Accordingly, we have included the most recent version (2014) of the associated National Comprehensive Cancer Network (NCCN) guidelines in our manuscript (p5~).

- 2. A conclusion is missing regarding the diagnostic value of the discussed screening parameters*

Per your suggestion, we have added a conclusion at the end of the section on screening (p11).

- 3. The article should be shortened and edited by a native English speaker*

We attempted to shorten the manuscript as much as possible. Further, the

manuscript was edited by a native English speaker.

Minor comments to the authors

Chapter 1: Screening

- *Page 2: rather say „tumor resectability“ than „disease resectability“*

Thank you for pointing this out. In response to your comment, we have edited the text so that it refers to “tumor resectability” rather than “disease resectability”.

- *Page 4: typo: current smoker (not smokers)*

In response to your comment, we have revised the text to “current smoker”.

- *Page 7: the second sentence is very hard to read, consider to rephrase*

In response to your comment, we have revised the sentence as follows (p8~):

The CAPS consortium specifically agreed that the following individuals were candidates for screening: first-degree relatives (FDRs) of patients with pancreatic cancer in a familial pancreatic cancer kindred with at least two affected FDRs; patients with Peutz-Jeghers syndrome; and carriers of *p16*, *BRCA2*, and hereditary non-polyposis colorectal cancer (HNPCC) mutations with at least one affected FDR.

- *Page 8 ff.: in this section there is a lot of repetition, it could be shortened and structured more logically. In the last paragraph the word ‚have‘ is missing : „overall, it appears that nearly half of the patients who HAVE (or with) early stage resectable tumors also have diabetes. The following sentence is also grammatically incorrect.*

In response to your comment, we have substantially revised this section.

- *Page 9 ff.: in this section there is some repetition and lack of logical structure, too. What is the consequence of the presented findings?*

The subsection on dilation of the pancreatic duct was revised and moved to the subsection on MDCT (p21, a subsection of “3. Imaging”).

- *The next section is called “identify precancerous neoplasia”, maybe “identification of precancerous lesions” would fit better. The same applies for the first sentence, which is grammatically incorrect as it stands. The whole section needs revision of language.*

We have revised this section per your comments.

Chapter 2: Biomarkers

- *Page 11 at the bottom: I don’t agree that “biomarker screening is generally necessary to identify early lesions”*

In response to your comment, we have revised the sentence to “Biomarker screening is one possible approach for identifying these early lesions.” (p11)

- *Page 13: what do you mean by ‘subradiographic unresectable pancreatic cancer’?*

To make this text clearer, we have revised it to, “unresectable pancreatic cancer that could not be recognized in diagnostic images.”

- *I would try to reduce the number of subheadings in this section*

We have reduced the number of subheadings in response to your comment.

- *Page 14: I don’t understand the first sentence “attempt to improve the performance of CA19-9...”*

In response to your comment, we have revised the sentence as follows (p13): “Carbohydrate antigens of mucin-1 (MUC-1) have been investigated as potential means of improving on the performance of CA19-9.”

- *Page 15: grammar of sentence 2*

- Page 17: second paragraph: *"with improvements IN (not 'to') the technology.."*
same mistake on page 20

Chapter 3: Imaging

- Page 20: *see above*
- Page 21: *replace 'must' with 'be' in the last sentence of the first paragraph*
- *The last sentence of the conclusion could be rephrased to be more comprehensible*

In response to your comments, we have revised theses grammatical issues, as well as the last sentence of the conclusion.

Thank you for your detailed and thoughtful comments. We have carefully revised the manuscript in response to your comments and hope that this new draft addresses all of your concerns.

We thank both reviewers for their precise and insightful comments, and for the careful attention that they have paid to our manuscript.