17 February, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format.

Title: Preoperative high level of D-dimers in pancreatic head cancer raises the suspicion of occult liver metastases.

Author: Adam Durczynski, Anna Kumor, Piotr Hogendorf, Dariusz Szymanski, Piotr Grzelak, Janusz Strzelczyk

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 9288

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated
2 Revision has been made according to the suggestions of the reviewer

Reviewer:

1. **Such a simple and cheap lab test, like D-dimer test is very useful to decide by operability in case of pancreatic cancer. If hepatic micrometastases occur the life expectancy is lower so the major operation (ie Whipple) should be avoided. This test could be one of the part of triage in decision. I advice to controll platelet count as well, because it is also a very good prognostic marker.**

We thank the Reviewer for this comment.

2. **Dear Authors, Congratulations for this study. This laboratory test may be of interest to predict the resectability of pancreatic cancer. There are some considerations about the manuscript. Key words: In addition, ?pancreatic cancer" must be a key word Abstract - Aim: The main aim of the study must be in relation to the title. In the title the relation of the D-dimers is with the occult liver metastases and not with resectability of the pancreatic cancer. The authors must change the tittle because the metastases are not the only cause of the lack of resectability in pancreatic cancer. Abstract - Conclusion: The conclusion must talk about the predictive value of the D-dimers and its relation with the resectability. Comments: A critical aspect of the study is the low rate of resectability at the operation. May the authors explain if the CT-scan was the only preoperative study?. Why they don't perform in any case a biliary magnetic resonance or a vascular image exploration?**

The Reviewer gives us a very important comments and it is absolutely helpful for the quality improvement.

"Pancreatic cancer" was added to key words.

The title of article and conclusion have been changed according to Reviewer's advice.

All our patients underwent spiral CT with intravenous contrast enhancement, since it remains the single most useful method for diagnosis and staging of pancreatic adenocarcinoma. It has been added in Material and Methods section.

3. **This is an interesting paper assessing the potential predictive role of a common lab test such as D-dimers in the metastatic spread of pancreatic cancer. The concept of the study is simple and straightforward and the results - if verified by subsequent studies - could have practice-changing implications. I recommend publication of the manuscript.**

We thank the Reviewer for this comment.

4. **Comments for the authors… Thank you for your manuscript, which presents the value of D-dimer level in determining resectability of pancreatic cancer. Although the idea of manuscript is nice, the content may not rich, and there are serious problems. Although the title has mentioned the relation between D-dimers and liver metastases, in the section of abstract especially for results, we could find any comments for liver metastases. Just as the authors presented (in the section of introduction) that the aim of this study was to assess the value of the D-dimers in determining unresectability of pancreatic cancer, however, in the last paragraph, the author made the conclusion that the D-dimers might be used in the diagnostic for hepatic metastases. In the section of material and methods, the resectability standard may be too simple. If the final decision of resectability was confirmed by different surgeons with different experience? If all the incisal edges of pancreatic cancer were confirmed negative by pathology? The author should present more clinic information about all enrolled patients. In the section of results, among the unresectable population, there were 20 patients without liver metastases. Is there still significant difference between these 20 patients and the patients with resectable pancreatic cancer for D-dimers level? To our surprise, with the developments of imaging technology (enhanced MRI or PET), why so many patients with liver metastases could not be diagnosed before operation? After all, diagnostic laparoscopy and/or laparoscopic ultrasound may not better than enhanced MRI for early detecting liver metastases.**

According to Reviewer's advice the title of article and conclusion have been changed to better correspond one another. Conclusion in Abstract section has been made more precise.

All surgeries and all decisions of tumor resectability were performed by one experienced pancreatic surgeon. This crucial information has been added in Material and Methods section.

In resectable cases (n=29) the final pathological examination confirmed tumor-free margins. Authors explained this aspect in Results section.

Analysis in subgroups proposed by Reviewer has been added in Results section. It revealed considerably higher peripheral D-dimers level in patients with liver metastases (2470,7 ± 3028,8, p<0,001), and moderately higher in locally advanced tumors (904,2 ± 662,9, p=0,013) when compared to resectable disease (630,9 ±593,8).

All our patients underwent spiral CT with intravenous contrast enhancement, since it remains the single most useful method for diagnosis and staging of pancreatic adenocarcinoma. It has been added in Material and Methods section.

5. **The paper is really clear and well written. The item is intriguing and of great praticial impact.**

   We thank the Reviewer for this comment.

6. **This study investigates the potential use of D-dimer level in several biological fluids of patients with pancreatic cancer to assess their prognostic values for the resectability of the cancer and the post-operative outcome for the patients. For the study, 64 patients with pancreatic cancer were recruited. The presented results indicate higher mean D-dimer value in peripheral and portal blood of patients with unresectable pancreatic cancer, suggestive of the presence of hepatic metastases undetectable by other diagnostic tools. The study appears to be properly conducted. and the conclusion is validated by the data presented in the manuscript. A couple of point should be better address to enhance the significance of the reported data. 1. the authors should clarify the concept of D-dimers and their significance for people less versatile on the field. 2. Do the authors have any additional hepatic (e.g. conjugated and non-conjufgated bilirubin levels, prothrombin time, alkaline phosphatase, etc.) and non hepatic (e.g. CEA and CA biomarkers) parameters that could help in**

supporting the presence of hepatic metastases? 3. a few typos need to be emended and English revised (e.g. page 7, line 7 from bottom: remove of before resectability; page 7, line 6 from bottom metastases instead of metastatic disease; page 8, line 9 from bottom: ratio instead of ration; page 8: the sentence starting at line since from bottom is too long and unclear)

We thank Reviewer for invaluable advices.

1. The concept of D-dimers has been extended in Introduction Section.
2. All surgeries were performed by experienced pancreatic surgeon and all hepatic metastases were confirmed intraoperatively. Authors have additional parameters including tumor markers concentration in peripheral and portal blood of patients with pancreatic cancer but it is the part of another study (still not published).
3. Article language was revised by native speaker according to advices.

Furthermore:

1. Article language was revised by native speaker
2. The Columns of this manuscript was determined.
3. Material and Methods in Abstract section was changed.
4. References numbers were reformatted.
5. Pubmed and DOI citation numbers were added.
6. COMMENT section was added.