

## Format for ANSWERING REVIEWERS

April 26, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 2429-review.doc).

**Title:** Diffusion-weighted imaging of pancreatic cancer

**Author:** Riccardo De Robertis, Paolo Tinazzi Martini, Emanuele Demozzi, Flavia Dal Corso, Claudio Bassi, Paolo Pederzoli, Mirko D'Onofrio.

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 16728

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

(1) *In the IDENTIFICATION section the sentence: 'At this regard, Lemke[21] reported that the IVIM-derived  $f$  value, which quantifies blood microcirculation, was significantly higher in the healthy pancreas (mean  $25.0 \pm 6.2\%$ ) than in PDACs (mean  $8.59 \pm 4.6\%$ ): this reflects the true histologic nature of PDACs, which typically present a very low microvascular density (MVD) as compared to healthy pancreatic parenchyma' needs to be changed. Is really pancreatic ductal adenocarcinoma an hypovascular tissue as compared to healthy pancreatic parenchyma? To this regard several published studies suggest that pancreatic ductal adenocarcinoma present an high MVD as compared to peritumoral tissue or normal pancreatic tissue (for example: High microvessel density in pancreatic ductal adenocarcinoma is associated with high grade, Virchows Arch. 2013 May;462(5):541-6. doi: 10.1007/s00428-013-1409-1, Bar?u A et al.; Inflammatory cells contribute to the generation of an angiogenic phenotype in pancreatic ductal adenocarcinoma, Clin Pathol 2004;57:630-636, Esposito I et al.).*

Pancreatic ductal adenocarcinoma is characterized by glandular structures embedded in desmoplastic stroma. Very few vessels can be found within the fibrous stroma, and this accounts for the typical poor perfusion of this tumor at imaging examinations. All ductal adenocarcinomas are associated with more or less developed fibrosclerotic and inflammatory changes in the adjoining non-neoplastic pancreas, due to carcinomatous duct obstructions (obstructive chronic pancreatitis) [Bosman FT WHO Classification of tumors of the digestive system, IARC press 2010].

Numerous reports have described the microvascular density of ductal adenocarcinoma. However, these reports vary with regard to the methods of assessing MVD, both in the antibodies used and in the counting methods. As a result, measured values for MVD show considerable variation. Esposito and Barau have used the hot-spot method, i.e. counting MVD in the areas with highest microvascular density ("each section was scanned at  $\times 40$

magnification to identify the five areas (hot spots) with the highest number of [...] neo-vessels (CD34 staining)" [Esposito]; "Areas with the highest CD31-defined microvascular density (vascular hot spots) were selected [...]. Vascular hot spots were identified at a low optical power using ×4 and ×10 objectives. Five equal areas of high vascularization were photographed with a ×20 objective (magnification, ×200). Immunoreactive cell groups clearly distinguishable from the background were counted as one vessel" [Barau]. These authors found that the MVD of ductal adenocarcinoma measured in hot-spot areas is high: a probable explanation is that hypoxia stimulates neoangiogenesis in the inner areas of this tumors; peri-tumoral parenchyma, instead, tend to present a lower MVD as compared to the tumor. It can be therefore assumed that the overall vascularization of pancreatic ductal adenocarcinoma is low as compared to other pancreatic tumors, as neuroendocrine neoplasms, because PDACs are mainly composed of fibrotic stroma with few vessels; MVD may be relatively higher when evaluated in hot-spot areas, as a consequence of neoangiogenesis induced by hypoxia. Probably, imaging methods are not sufficiently accurate in detecting MVD differences at a microscopic level.

Please note that the term "MVD" has been changed ("which typically present fewer vessels as compared to healthy pancreatic parenchyma").

(2) *The review is lacking of the REFERENCES section.*

Ok, references section has been added.

(3) *In the EDITING CERTIFICATE there are several Co-Authors that are not listed in the manuscript. Please ceck.*

Ok.

(4) *More words of differentiation from other pancreatic malignancies are suggested to underline its specificity.*

Some specific sentences have been added ("Pancreatic adenocarcinoma is usually hypointense to the normal pancreas on T1-weighted fat-suppressed sequences, shows hypoenhancement during arterial phase, and shows progressive enhancement on delayed sequences. These features, and particularly the hypointense appearance on pancreatic phase images, are distinctive of this tumor<sup>[32]</sup>"; "These findings are consistently related to the histologic nature of PDACs, which are fibrous tumors with very few internal vessels, as compared to the healthy parenchyma and to PanNETs").

(5) *The authors are suggested to concentrate in the description of pancreatic cancer, and nodal metastasis does no help for the claim of accuracy of early diagnosis.*

Please note that all sentences regarding nodal metastases are in the "staging" section.

(6) *It is necessary to compare this method with other image modalities such as enhanced computer tomography. The rates of false and true positivity of cancer by this method could be provided to prove its negative prognostic value.*

Please note that some data comparing CT and DWI have been added ("The sensitivity of computed tomography (CT) in revealing PDAC is high, ranging between 89% and 97%<sup>[11]</sup>. MRI offers better soft tissue contrast compared with CT; PDACs are usually well

recognized on T1-weighted and DW images, owing to differences between the histological components of the tumor and the circumstant parenchyma. There is however no significant diagnostic advantage of MRI over contrast-enhanced CT for the identification of PDAC<sup>[12]</sup>". "Some old studies have suggested that T1-weighted spin-echo images with fat suppression and dynamic gradient-echo MR images enhanced with gadolinium could be superior to CT for detecting small pancreatic carcinomas<sup>[27,28]</sup>". "A meta-analysis by Niekel et al [51] reported sensitivity estimates of CT, MR, and FDG-PET on a per-lesion basis of 74.4%, 80.3%, and 81.4%, respectively, whereas on a per-patient basis, the sensitivities of CT, MR, and FDG-PET were 83.6%, 88.2%, and 94.1%, respectively. For lesions smaller than 10 mm, the sensitivity estimates for MR were higher than those for CT". "DWI is a reliable method to detect liver metastases, with a sensitivity and specificity higher than both CT and conventional MR sequences<sup>[51]</sup>". ).

(7) Please correct typo and edit errors. Grammatical errors exist.  
Language editing has been performed.

(8) References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Riccardo De Robertis, MD  
Department of Radiology  
G.B. Rossi Hospital – University of Verona  
Piazzale L.A. Scuro 10  
37134 – Verona, Italy  
[Riccardo.derobertis@hotmail.it](mailto:Riccardo.derobertis@hotmail.it)  
Phone: +39-045-8124301  
Fax: +39-045-8027490