Replies to the Reviewers

We would like to thank the reviewers for their thorough work and we have revised the manuscript accordingly. Please see point-by-point replies below.

After dealing with the reviewers´ pertinent comments, we believe that the quality of the manuscript is much better and we hope that it is now suitable for publication.

# Reviewer A

**1. Imaging techniques: there are too many general information about the imaging techniques but they are not focused in PNETs characteristics.**

***Reply:*** *We agree with the Reviewer A that there is a lot of general information about the imaging techniques that is not exclusively focused on PNETs imaging characteristics. However, neither the well-established techniques nor the more recent advances in imaging of PNETs are, unfortunately, PNET-specific, with the exception of SRS-imaging for the pancreatic neuroendocrine tumors.*

*Furthermore, as a prerequisite before going into details on “advancements” (in the Section “Applications”), it is, in our opinion, necessary to firstly introduce a comprehensive explanation of the corresponding basic technique (in the Section “Imaging techniques”). We, therefore, believe that although our presentation of the technicalities of each modality is fairly extensive, it is of benefit for the reader. For example, to describe advances of DWI without previously explaining what DWI is or which of its components it is possible to calculate would result in a less comprehensive and not as didactic text. Similarly, it would be incomplete to go into details on vascular and ductal encasement by tumors without previously providing some hints about the techniques that are available for such evaluations (e.g. MIP, VRT).*

*However, we have nevertheless somewhat shortened this section in the manuscript (Please see function “show changes/deleted” in the Section “Imaging Techniques”).*

**2. There are also many details about functional imaging. Emphasis should given at those tracers that are clinically available.**

***Reply:*** *Here as well, we believe that the details in the text are of benefit for the reader but we have somewhat shortened this section. We removed the text about the tracers that are not yet clinically available.*

*(Please see function “show changes/deleted” in the Section “Imaging Techniques”)*

**3. More details should be given about the clinical impact of perfusion and DWI parameters and their clinical role, since this review is to be read by clinicians.**

***Reply:*** *More details about the clinical role of perfusion and DWI parameters have been provided in the corresponding subsections in Section “Imaging Techniques”*

**4. Scintigraphy: The term PNET should be kept along the document-replace NET.**

***Reply:*** *The term “NET” was replaced by “PNET “ in Subsections “Nuclear Medicine Imaging” and “Therapy monitoring and prediction of response”.*

**5. A paragraph must be added regarding the impact of dual energy CT in detection of PNETs [Lin XZ, EJR 2011] as it represents a novel development in CT imaging.**

***Reply:*** *Relevant information about dual-energy CT was added in Sections “Imaging techniques” and “Applications”, as well as the corresponding references.*

Applications:

**6. Author should describe CT and MRI characteristics of PNETs beyond the contrast uptake.**

***Reply:*** *The PNETs features at CT and MRI beyond contrast enhancement have been added in the Subsection “Primary tumor detection”.*

**7. A differention diagnosis of hypervascular pancreatic lesion should be given.**

***Reply:*** *The differential diagnosis of hypervascular pancreatic lesions has been added in the Subsection “Primary tumor detection” and the corresponding reference.*

**8. Primary tumor detection: the references 30-32, 34-36 are quite old and they are referred to the impact of spiral CT in detection of PNETs. The performance of MDCT should be mentioned in comparison with other modalities and not that of spiral CT.**

***Reply:*** *We agree with Reviewer A that the references 30-32 and 34-36 are old and refer to the impact of spiral CT and not MDCT. However, to the best of our knowledge, in the current literature there are only two references regarding the impact of MDCT in the detection of PNETs:*

*In the first of them [Rappeport ED, et al. Multidetector computed tomography and neuroendocrine pancreaticoduodenal tumors. Acta Radiol. 2006 Apr;47(3):248-56]; there were only three patients with PNETs included and because of that, we do not consider it appropriate to include this reference in this review.*

The second of them, which was already included in the corresponding EUS paragraph [*Versari A , et al. Ga-68 DOTATOC PET, endoscopic ultrasonography, and multidetector CT in the diagnosis of duodenopancreatic neuroendocrine tumors: a single-centre retrospective study. Clin Nucl Med 2010;****35****:321-328*], has now been added even in the corresponding CT paragraph.

**9. Tumor staging and grading: The role of MDCT and MRI in the evaluation of tumor resectability and surgical planning should also be mentioned.**

***Reply:*** *The role of MDCT and MRI in the evaluation of tumor resectability and surgical planning has been added in the Subsection “Tumor staging and grading”.*

# Reviewer B

It is a very interesting review paper, well written, containing recent imaging advances.

***Reply:*** *We would like to thank Reviewer B for his/her kind remarks!*

Some additions are proposed.

The paper addresses most of the current indications of available imaging techniques. The authors should discuss also on the following subjects:

**10. What about the early arterial phase? Should this be omitted?**

 ***Reply:*** *This is a very interesting issue. According to the 2009 ENETS’ Consensus statement [Sundin A, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: radiological examinations. Neuroendocrinology. 2009;90(2):167-83.], the early arterial/CT angiographic phase is routinely not necessary as the contrast-enhancement of arteries is deemed sufficient during the late arterial phase.*

*To the best of our knowledge, there is only one recent study assessing the value of the single CT phases of a triple-phase protocol vs. 68Ga-DOTATOC PET/CT [Ruf J, et al. 68Ga-DOTATOC PET/CT of neuroendocrine tumors: spotlight on the CT phases of a triple-phase protocol. J Nucl Med. 2011 May;52(5):697-704.]. The authors included various NETs in the abdominal region, among them PNETs, and conclude that for all lesions, the sensitivity and accuracy of the early arterial phase is lower compared to the other two subscans; the difference however, is due mainly to a clear inferiority of the early arterial phase in detecting liver lesions as it is demonstrated in Table 2. In the same table, it is shown that for PNET, all three subscans show identical results; however, the number of PNETs was only 17 and the authors themselves recommended cautious interpretations of these results.*

*To conclude, it is our opinion, that the available data in the literature are not robust enough to support the use of an early arterial phase, especially considering the radiation risk penalty that such a paradigm shift would result in.*

*A clarification about that point, i.e. the use or not of early arterial phase, was added accordingly in the Subsection “Computed Tomography”.*

**11. What diffusion may add concerning the prediction of malignancy?**

 ***Reply:*** *As stated in Subsection “Tumor staging and grading”, DWI may be helpful in differentiating PNETs G1 from PNETs grade 2/3 [Jang KM, et al. The value of gadoxetic acid-enhanced and diffusion-weighted MRI for prediction of grading of pancreatic neuroendocrine tumors. Acta Radiol 2014;****55****:140-148.*

*Wang Y, et al. Diffusion-weighted MR imaging in pancreatic endocrine tumors correlated with histopathologic characteristics. J Magn Reson Imaging 2011;****33****:1071-1079.]. To the best of our knowledge, there are no further data in the current literature concerning the role of DWI in the prediction of malignancy.*

**12. What are the perfusion techniques’ applications in the estimation of the therapeutic effect?**

 ***Reply:*** *To the best of our knowledge, there are no studies available on the usefulness of CT- or MRI-perfusion in the estimation of therapeutic effect on treatment of PNETs.*

**13. What are the possible limitations of EUS (e.g. ectopic tumors or located distally in the tail)?**

 ***Reply:*** *The possible limitations of EUS are added in the Subsection “Ultrasonography” and the corresponding reference.*

**14. What are the main differences between different SSAs in scintigraphy and the advantages or limitations?**

 ***Reply:*** *The mainstay for SSA imaging is scintigraphy with 111In-labeled octreotide (Octreoscan™) but there are also 99mTc-labeled preparations (99mTc-EDDA/HYNIC-SSA ), that are used in some centers; however, they have not been able to compete with Octreoscan and therefore are of considerably less interest to include in this review. Regarding SSA-PET/CT, which is of considerably higher interest, because the technique is believed to, within a few years, in many centers replace Octreoscan, we have in this review listed the by far most frequently used preparations 68Ga-DOTATOC, 68Ga-DOTANOC and 68Ga-DOTATATE which, from an imaging point of view have not yet shown significant differences for clinical use.*

**15. What is the importance of imaging not only concerning the definition of resectability but also on the selection of the type of surgery (pancreatectomy vs enucleation)?**

***Reply:*** *The role of MDCT and MRI in the evaluation of tumor resectability and surgical planning has been added in the Subsection “Tumor staging and grading”.*