January 31, 2013

Dear Editor,

Please find enclosed the revised manuscript in Word format (file name: 1241-review.doc).

Title: Combined laparoscopic spleen-preserving distal pancreatectomy and islet autotransplantation for benign pancreatic neoplasm

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We thank the Referee for the interest in our work and for the helpful comments. We thank the Editor to give us the opportunity to clarify our research objectives and results. As indicated below, we have checked all the general and specific comments provided by the Referee and we have made the necessary changes accordingly.

- 1.Doesnt really however discuss the risks of the procedure should the "benign "diagnosis be incorrect. Mentioning the lack of mural nodules, the tumour marker levels in the methods is interesting however in patient 3 the patient had mural nodules and a raised Ca19.9, concerning for potential malignancy.

We agree with the concern of the reviewer about the possible malignancy of a cystic lesion with such characteristics. Nevertheless, a careful evaluation of MR images showed no involvement of the surrounding pancreatic parenchyma, with a well demarcated cystic capsule and no dilation of the main pancreatic duct. We presumed that the cystadenoma was benign with high probability level (as it was confirmed by histologic diagnosis) and we decided to performed a conservative resection, with an intraoperative frozen section examination of the cyst wall. This confirmed the diagnosis of mucinous cystoadenoma. In the revised text we have inserted a note on the lack of involvement of surrounding parenchyma and on intraoperative frozen section examination of the cyst wall, to rule out malignancy

- 2. The discussion should include an extensive discussion of the diagnostic methods used to exclude malignancy, risks of seeding from these diagnostic methods and some discussion of the series of laparoscopic pancreatectomy where early series had a 25% unsuspected malignancy rate.

We thank the reviewer for this comment. Actually, the finding of 25% unsuspected malignancy is exceptional and it differs from what reported by all high-volume pancreatic surgery Institutions. In 2012 three large series have been published on spleen-preserving distal pancreatectomy (SPDP), accounting for > 200 patients (see references below). Malignancy was reported in only 2/213 patients (< 1%). In our Institution malignancy is excluded by strict preoperative assessment including CT or MRI and endoscopic ultrasonography. Since 2000 we have performed 95 SPDP (26 of them were performed laparoscopically in the last 4 years) and in no case an unsuspected malignancy was revealed by histologic examination.
We have included in discussion a description of the diagnostic tools commonly used to excluded malignancy.
We have included also a note about the dissemination risk after Endoscopic FNA.

References
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- 3.There should also be discussion of the risks of seeding from processing the and any evidence that the 1cm margin from tumour to processed pancreas is safe.

We understand the comment of the reviewer and we are aware that any possibility of malignancy must be excluded before processing the specimen. Pre- and intraoperative work up is essential to select adequate cases for autotransplantation. This series of three cases is part of a larger series of 33 patients that received islet autotransplantation in our Institution for indications other than chronic pancreatitis. The article describing the outcome of the whole series was submitted to Annals of Surgery.
In this series of 33 patients the presence of a pancreatic malignant disease was not an exclusion criterion *per se,* while patients who met any of the following criteria were not eligible: presence of any multifocal pancreatic neoplasm at preoperative imaging or intraoperative evaluation, including multifocal benign intraductal-papillary mucinous neoplasm (IPMN); a diagnosis (suspected or ascertained) of Multiple Endocrine Neoplasm. Seventeen out of 33 patients had malignancy; nevertheless, at a median follow-up of 546 d, none of them developed liver metastases.

In the case series retrospectively analyzed by F. Ris (cited at #17 in references) 3 mm margin has been considered safe to exclude the risk of dissemination and that was testified by 90 months disease free follow up. We increased the safety margin to 1 cm to allow the pathologist to precise exclude any presence of malignancy and to be sure of having enough tissue for the analysis, given that the margin could be easily damaged or cauterized by the surgical procedure/manipulation.

- 4.Most of the studies on auto transplantation have been on patients with chronic pancreatitis. Is the risk of diabetes as great in these patients who presumably will have a normal head and neck?

The risk of diabetes onset after pancreatic resection is substantially higher for patients suffering from chronic pancreatitis compared to patients carrying benign neoplasm. However the risk rate of pancreatogenic diabetes after resection is certainly underestimated, as shown by data on living donor transplantation, as reported in the manuscript. Further, since patients operated for benign disease have long life-expectancy, it is important to consider not only the early diabetes onset after surgery but the actual risk during long term follow up which is still under investigation.

- 5.The ultimate aim as noted by the authors is to reduce morbidity without compromising patient safety. They have not demonstrated any benefit in either patient length of stay or early morbidity and with such a small series it is impossible to quantify any benefit from auto transplantation over the traditional laparoscopic or open approach. This is an interesting study looking at feasibility which they have demonstrated and the emphasis of the article should be on this whilst dealing with the other issues noted above.

We have revised the discussion accordingly with this suggestion by highlighting the concept of feasibility.

- References and typesetting were corrected

- All the changes in the revised manuscript were highlighted, deleted types were marked by strikethough, new inserted types were red coloured.

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

Sincerely yours,

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