

ANSWERING REVIEWERS



June 17, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: revision 3441.doc).

Title: Biliary tree gastrinomas as underestimated site in Multiple Endocrine Neoplasia type 1.

Author: Francesco Tonelli, Francesco Giudici, Gabriella Nesi, Giacomo Batignani, Maria Luisa Brandi .

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 3441

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 reviewers

reviewer 1: the title of the manuscript has been changed according to your suggestion. We differentiated the tumors according to the eventually present preoperative clinical syndrome with the blood exams (basal hormones and after stimulation with secretin) and with a meticulous postoperative pathological examination (immunohistochemically performed for all lesions) as is actually described in M&M section accordingly. The first case we described underwent TP because of the concomitant presence of a non functioning neuroendocrine tumor of the pancreatic tail as you correctly supposed: we modified the case to make it clearer. The discussion section has been shortened accordingly and table 1 and 2 have been merged in a single table and figures 1,2,3 have been removed, while fig 4 and 5 have been merged.

reviewer 2: 1. all patients had all preoperative imaging available at the time of operation at our hospital and patient number 3 had SSRS before the first operation but it was negative for biliary tree lesions at that time. 2. Ki67 index is now reported for all cases. 3. "abdominal" has been changed with "brain" accordingly, thank you. 4. the manuscript was shortened accordingly.

reviewer 3: 1. discussion about sporadic ectopic gastrinomas is reported in the first part of discussion section (page 12-13-14). 2. and 4. We operated 10 patients affected by insulinoma actually (we published on *Pancreas* during 2012 our experience about the first eight patients), however we modified the first paragraph of results section to make it clearer, accordingly. 3. about intraoperative serum gastrin we referred to our previous manuscript published on *Ann Surg* 2006 (reference n°4). 5. total pancreatectomy was performed because of the associated presence of a non functioning pancreatic tumor of more than 3 cm in diameter we found in the pancreatic tail, as it is clearer reported in the description of case 1 (page 9 line 6). 6. the ectopic lesion found in the case n° 3 was inside the glissonian sheet of the anterior sectional pedicle and not in the liver parenchyma (as visible in figure 5). Therefore, we think that the lesion grew primarily from the biliary tree and did not develop as a metastatic liver nodule. 7. non functioning pancreatic neuroendocrine tumors were found in all our MEN1 patients, as it is now better described in the results section (first paragraph), it is well known that in MEN1 patients NF PETs have higher prevalence than functioning tumors and they are characterized by malignant

behavior in relationship with the increasing of their diameter (as previously reported also by Triponez F et al. Ann Surg 2006). 8. discussion section has been shortened accordingly. 9. we think that meticulous analysis of preoperative imaging, intraoperative transillumination and palpation with intraoperative imaging (as IIOUS) could be useful to better identify ectopic biliary tree gastrinomas, but the first thing is to think about it: this is the reason why we wrote this manuscript, and because we think this study is important. 10. we think it is better to report the figures of all cases, because ectopic biliary tree gastrinomas are till now considered as rare entity so it is important to clearly show their presence at pathological study in all 3 cases.

3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Tonelli', with a stylized, cursive script.

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