Author's response to reviews

Title: Results of a prospective multicenter neuroendocrine tumor registry reporting on clinicopathologic characteristics of Greek patients

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Author's response to reviews:

Dear Editor of BMC Endocrine Disorders,

Many thanks for considering our manuscript for publication to your journal.

Please find a point by point reply to the reviewers’ fair comments that have improved our manuscript considerably.

Reviewer 1

‘The authors should describe the multiple endocrine neoplasia specifically and say whether it is MEN1, MEN2, VHL, etc.’

REPLY: All patients with hereditary syndrome in our study had ###1. The specific information requested is now described in page 7, last paragraph.

Reviewer 2

1st Comment

‘The authors described the demography, clinical manifestation, diagnostic procedures, histopathological characteristics, therapeutic intervention and observed death of NET patients from gastroenterology, oncology and endocrinology department in eight hospitals in Greek. The result can only represent a hospital based study. It is not appropriate to represent or estimate the incidence of NET in Greek from this study. It may explain the difference of NET incidence from the other countries in US and Europe.’

REPLY: We have removed the term incidence from our data and the appropriate changes have been made to describe the occurrence of NETs as presented in the eight participating centers. The phrase estimating the incidence of NETs in Greece was completely removed.
2nd Comment

‘The results provided the percentage of manifestation, diagnostic tools used, therapeutic intervention and pathologic classification, such as Ki-67 in this study but provided limited information for the risk factor, prognosis, or treatment of NET from the registry data analysis.’

REPLY When the registry was designed by all investigators the consensus was to record the provided information as described in the materials and methods section. At this time we are preparing a new database to include more centers and more information regarding the risk factor/prognosis and treatments as the reviewer has indicated.

3rd Comment

‘Needs some language corrections before being published’

REPLY: We have made a point by point language check and errors have been found and corrected.

Reviewer 3

1st Comment

‘Data acquisition, second paragraph. Patients’ initials, date of birth. Is there a data protection law in Greece that accepts this? In other european countries, even with the acceptance of the ethics committee and the informed consent of the patient, this is not acceptable and data have to be anonymized.’

REPLY: Given the different specialties involved we wanted to exclude the possibility of more than one recordings of the same patient in the database so we allowed the insertion of the initials and date of birth during data acquisition by trained doctors. Once the duplicates were removed this information was excluded from the analyses that was totally anonymized. This information is now added in the second paragraph, page 6.

Minor essential revisions comments

1. NEN (Neuroendocrine neoplasia) instead of neuroendocrine tumors is suggested.

REPLY: The term neuroendocrine tumors was substituted by neuroendocrine neoplasia in text and tables.

2. Introduction second paragraph. Ki 67 is only used for GEP neuroendocrine neoplasia (not lung or paraganglioma/pheochromocytoma)

REPLY: this is now specified

3. Patient inclusion. Date of diagnosis after October 2010.

REPLY: this is now included in inclusion criteria

4. Results fourth paragraph. Specify MEN 1 and 2

REPLY: This is now addressed – same as 1st comment-reviewer 1.

5. Clinical manifestations. First paragraph Specify if the patients had diarrhea
and flushing at the same time
REPLY: this information is now added
6. Where there no gastrinomas, insulinomas, vipomas...? and
7. Diagnostic procedures second paragraph. Insulin, gastrin, VIP??
REPLY: This information is now added
REPLY: This was a histopathological feature indicating infiltrative front of the tumor instead of pushing front. It is an indication of more aggressive biology and is independent of T stage.
9. Therapeutic interventions. Last paragraph I do not understand what you mean by this
REPLY: The last paragraph addressed the lack of significant-differences between the two genders. However since this paragraph does not contribute significantly to the results it was removed to avoid further confusion.
10. Discussion. 9th paragraph. Locally advanced tumors are not considered unknown primary
REPLY: Cancers of unknown primary are by definition metastatic, however a group of patients with local bulky lymphadenopathy is a rare subset of CUPs with better prognosis. An appropriate reference has been added.
11. Small mistakes in English
REPLY: We have made a point by point language check
12. As the authors state small number of patients and short follow up, but these data are the only data that we have on Greek patients
REPLY: More data may arise when the registry continues
13. Specify if they continue with the registry
REPLY: The 8 centers continued until the end of the 1st phase of the registry (Q4 2014)
14. Table 2 This table is a bit confusing.
For head and neck MTC and paraganglioma should be separated.
REPLY: Table 2 was re-structured to indicate number of performed diagnostic procedures (and the relevant positive yield). For Head and neck category, MTCs and paragangliomas are now indicated. The total number of head and neck was 44 of which 41 was myeloid thyroid cancer and 3 were paragangliomas.
We do not know which kind of PET scan was performed
REPLY: In our country only 18FDG PET is available. We have now added 18FDG in all cases to clarify this.
We do not know in how many patients the diagnostic procedure was performed so when we say 0% for example for MIBG it could either be that it was not performed or that the result was negative in all of the patients in which it was
used.

15. Table 3. This table is also confusing. Head and neck should be separated by paraganglioma and MTC. Total number of patients in each localization should be specified at the top. In an unknown primary what is local infiltration?

REPLY: For Head and neck category, MTCs and paragangliomas are now indicated. Total number of patients in each localization was specified at the top. In an unknown primary, local infiltration was a feature described in the histopathology report of the biopsy of five patients.

16. Table 4. Put total numbers on the left

REPLY: This information has now been added

17. Table 5. Specify number of patients on each category on the left

REPLY: This information has now been added