

Peer Review File

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Peer review comment:

The most important information are including in the text of this publication but I have some of the comments which could have been including in the paper

1. Calcitonin (CTN) level exceeding 100 pg/mL before operation indicates medullary thyroid cancer. (but remember: rare neuroendocrine tumours may secrete calcitonin, eg. lung cancer.) For the high rate of suspicious malignancy the CTN level in the aspirate from FNAB helps to state MTC diagnosis.

Reply 1: we have modified our text as advised (see Page 4, lines 59-62)

Changes in the text: Nevertheless, elevated serum CTN levels is not an exclusive characteristic of MTC and may be present in other malignancies (neuroendocrine tumors, lung cancer, etc.); the measurement of CTN levels in the fine needle aspiration biopsy (FNAB) aspirate helps confirming the diagnosis of MTC

2. CTN stimulation test allows for selection of doubtful cases and increases the effectiveness of MTC preoperative diagnostics and its follow-up.

Reply 2: We have modified our text as advised (see Page 4, lines 58-59)

Changes in the text: In doubtful cases, a CTN stimulation test might be necessary to confirm the diagnosis

3. MTC - clinically apparent (the presence of a thyroid nodule and a positive result of FNAB and CTN level) : total thyroidectomy accompanied by central neck dissection, both in hereditary and sporadic MTC are recommended .

Reply 3: We have modified our text as advised (see Page 4, lines 74-75)

Changes in the text: patients with diagnosed MTC (thyroid nodule with FNAB diagnostic for MTC and elevated serum CTN levels).

4. The extent of lateral neck lymphadenectomy depends on the presence of lymph node metastases in neck ultrasound and serum CTN level.

Reply 4: We believe that information is already provided (see Page 5, lines 76-85). Please let us know if there is anything that needs clarification.

5. There are no unequivocal indications for lateral neck lymphadenectomy if no enlarged lymph nodes have been found and simultaneously preoperative serum CTN concentration is < 200 pg/mL.

Reply 5: We have modified our text as advised (see Page 5, lines 86-92)

Changes in the text: There is no consensus on how to proceed in patients with normal neck US: while some endocrinologists and surgeons believe that preoperative neck US should guide the decision and do not advocate lateral compartment lymph node dissection in negative preoperative neck US, others consider it indicated if basal serum CTN levels are between 20 pg/mL and 50 pg/mL. Moreover, some authors believe that cervical contralateral lateral compartment lymph node dissection is indicated in patients with a cervical negative US when basal serum CTN levels are >200 pg/mL.

6. Follow-up of MTC patients : CTN - normalization of a postoperative concentration is the best indicator of the radicalness of surgery and a positive prognostic factor.

Reply 6: We believe that statement is already provided in the text “Normalization of serum CTN levels after optimal surgery, together with disease burden at diagnosis, are considered the most important prognostic factors in patients with MTC that have undergone surgery with a curative intent” (see Page 6, lines 117-119). Please let us know if there is anything that needs clarification.

7. We recommended CTN evaluation at 3, 6 12 months after initial surgery and serum CTN doubling time is very usefulness prognostic and predictive value. Further MTC follow-up involves: neck ultrasound, serum CEA level (only when CTN is elevated), diagnostic imagine tests only when serum CTN level is > 150 pg/mL.

Reply 7: As regards follow up after initial surgery, we have stuck to the ATA recommendations, that recommend measurement of serum CTN and CEA levels 3 months postoperatively and, if undetectable or within the normal range, they should be measured every 6 months the first year and yearly thereafter. As regards imaging techniques during follow up, the ATA guidelines believe they are unnecessary in patients with biochemical cure after surgery, and they should be reserved for patients without biochemical cure or when serum CTN or CEA levels start to increase after initial normalization. Postoperative serum CTN levels <150 pg/ml indicate residual or recurrent disease confined to the neck, so physical examination and US of the neck must be performed and, if negative, they should be repeated every 6 months; b) postoperative serum CTN levels >150 pg/mL indicate high probability of distant metastases, so whole-body imaging examinations should be performed in order to rule them out, which may include neck US, chest and abdominal CT-scan, bone scintigraphy and MRI of the pelvis and axial skeleton.

As regards the importance of “CEA and CTN doubling times” we have modified our text as advised.

Changes in the text: (Pages 9-10, Lines 225-228): Follow-up, as recommended by the ATA Guidelines (1), differs depending on postoperative serum CTN levels, which together with serum CEA levels must be measured every 6 months in every case in order to determine their doubling time, which reflects the MTC growth and progression rates

8. We agree with the Dralle publication: CTN level of 150 pg/mL one should be aware

of a possible false negative result in the localization of cancer foci by imaging tests. In the patients with CTN level > 500–1000 pg/mL the chance for the localization of cancer foci is growing but always should be consider that a common reason of the increase in serum CTN level (>500 pg/ml) is liver micrometastases.

Reply 8: We have modified our text as advised (see Page 12, lines 267-271)

Changes in the text: Imaging techniques have a considerable high rate of false negative results as regards the localization of metastatic foci when serum CTN levels are <150 pg/mL. The sensitivity of imaging techniques in recognizing distant metastasis is higher when serum CTN levels are >150 pg/mL (PET-CT) and >500-1000 pg/mL (CT, MRI). In every case, liver micrometastasis should always be suspected.

9. Surgery is a basic treatment of a local and locoregional recurrence and if local/locoregional recurrence is accompanied by distant metastases, the indications for surgery should be consider.

Reply 9: We believe that information is already provided in the text (see Page 11-12, Lines 236 - 261). Please let us know if there is anything that needs clarification.

10. Could you tell me about alternative kind of therapy : classical chemotherapy, radiotherapy, effectiveness of somatostatin analogues, the use of tyrosine kinase inhibitors, immunotherapy

Reply 10: The purpose of our narrative review is the role of surgery in MTC patients with locoregional recurrent disease and distant metastases. We therefore believe that an extensive review of the alternative oncologic therapies exceeds the purpose of our paper. Nevertheless, we have included some information about non-surgical oncologic treatment (see page 5-6, lines 99-106)

Changes in the text: No medical curative treatment has proven effective in the treatment of locally advanced or metastatic MTC, being surgery the only curative option. Chemotherapy and external beam radiation have limited response rates. Vandetanib and cabozantinib are the only tyrosin kinase inhibitors (TKIs) approved for the treatment of locally advanced and metastatic MTC non-amenable to surgery, having demonstrated an improved progression-free survival but without an impact on overall survival. Immunotherapy with PD-L1 inhibitors (pembrolizumab), or peptide receptor radionuclide therapy (PRRT) are other therapeutic options that are being evaluated and might prove effective in selected cases.