Author’s response to reviews

Title: New insight into ectopic thyroid glands between the neck and maxillofacial region from a 42-case study

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Author’s response to reviews:

Reviewer #1:

1. Did the patients have any other developmental problems?

Answer: Most of the patients had no other developmental problems while only a 9-year-old boy with lingual thyroid was found to suffer from first and second branchial arch syndrome as well.

2. It will be great to know the locations of the "dual ectopic" and "others".

Answer: In all five dual ectopic cases, the first location was lingual and the second was sublingual (one in the floor of the mouth, and four in anterior neck region).

In three other type cases, the ectopic thyroids located substernal.

These have been added in page 7, line 1.

3. What were the criteria of "sublingual-type thyroid"? Were there any thyroglossal duct lesions? Did this group of patients have orthotopic thyroid tissue?

Answer: According to Raju A. Gopal (Gopal RA, et al. Clinical profile of ectopic thyroid in Asian Indians: a single-center experience. Endocr Pract. 2009), sublingual means below the tongue. In our article, the ectopic thyroids below the tongue and located in the anterior neck region other than the place of normal thyroid were defined as a sublingual thyroid. There were no thyroglossal duct lesions in our study. Five patients with sublingual thyroid had orthotopic thyroid.

4. Were there any studies to demonstrate if patients had normal 4 parathyroid glands clinically? PTH IHC is not sensitive if there is no gross or microscopic evidence of parathyroid tissue. Fig 4E is not necessary, since there is no parathyroid tissue morphologically.
Answer: Thank you for your kind suggestion. To our knowledge, there were no studies to demonstrate if patients had normal parathyroid glands with the ectopic thyroids yet. We agree with your suggestion and delete Fig 4E.

5. Page 9, line 31: TTF-1 is essential for thyroid morphogenesis and differentiation. Authors found that TTF-1 was highly expressed in ectopic tissue. Were there any differences of TTF1 expression between lingual thyroid and sublingual thyroid (and other locations).

Answer: 21 paraffin fixed specimens (15 lingual thyroids, 4 sublingual thyroids and 2 dual ectopic thyroids) are available for histological study. In view of the small number of the cases, we did not make statistical analysis to compare TTF1 expression between lingual thyroid and sublingual thyroid.

6. How many slides (percentage of total blocks submitted) did you use for calcitonin IHC?

Answer: 21 slides of ectopic thyroid, 21 slides of orthotopic thyroid and one slide of medullary thyroid carcinoma were used for calcitonin IHC.

7. Fig 3A: The lesion appears to be a follicular adenoma.

Answer: Fig 3A just showed a part of the lesion. Thyroid adenoma generally have complete capsule. In this case, capsule was incomplete maybe due to damage in surgery. The diagnosis given by our Department of Oral Pathology was lingual thyroid with local adenomatous hyperplasia. And the lesion was diagnosed adenoma clinically.

8. Page 5, line 9-26: This part is too long, please shorten it.

Answer: Thank you for your advice. We have shortened the part you mentioned.

9. Page 9, Line 12: Could you list published reports for ectopic thyroid as references?

Answer: Thank you for your kind reminding. We have added published reports as references where you mentioned.

Reviewer #2:

1. The description of the genetic studies in the discussion should be summarized.

Answer: Thanks. We have revised the paragraph following your advice (page 8, paragraph 3).

2. In the Immunohistochemistry section are reported the number of patient (n=23) who underwent to surgical excision of the ectopic lesions. It should be clarified which type of ectopic lesion has been subjected to surgical removal.
Answer: Thank you for your kind reminding. Sixteen patients with lingual thyroid, five with sublingual-type thyroid and two with dual ectopic thyroid underwent surgical excision. We have added this information to the manuscript (page 4, paragraph 4).

3. At the beginning on page 11, the authors suggest that the possibility of ectopic thyroid tissue to develop cancer is for ectopic locations different from cervical and maxillofacial regions.

However, lingual thyroid carcinoma has an estimated incidence about 1% with 52 reported cases. Pre-surgical diagnosis is often difficult do to the histopathological features typical of ectopic tissue and to the low sensibility of cytological studies.

Therefore it seems useful to revise the sentences (Please cite: Sturniolo G. et al. Differentiated thyroid carcinoma in lingual thyroid. Endocrine 2015)

Answer: Thank you for your point. We have revised the sentences and cited the article.

4. At page 11 of the Discussion, the authors say that “no accompanying parathyroid was followed by ectopic thyroid”. Nevertheless, the detection of one or more ectopic parathyroid in presence of an orthotopic thyroid is not a rare occurrence. So the sentence, “These results indicate that no accompanying parathyroid could be followed by ectopic thyroid.” should be modified in “Our results may indicate that no accompanying parathyroid could be followed by ectopic thyroid.”

Answer: We have changed the sentence as your suggestion. Thank you very muc