

Peer Review File

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Review Comments

In their manuscript, Zhou and coworkers tried to establish whether a positive titer of thyroid peroxidase antibody (TPOAb) and/or thyroglobulin antibody (TgAb) was correlated with a higher (or lower) risk of lymph node metastasis (LNM) from differentiated thyroid carcinoma.

To this aim, the clinical records of 2352 patients submitted to total thyroidectomy in 2018 at a single institution were retrospectively reviewed. Patients (n = 806) with a final diagnosis of thyroid malignancy and available data concerning TPOAb and TgAb levels were finally included in the study.

The article is clearly written; nevertheless, some points need to be clarify (see below). Besides, the interest of the study could be enhanced in case some additional data could be collected.

- a) From what it is reported in the Material and Methods section is not clear if the initial population of 2302 patients who underwent "thyroidectomy" were all treated for thyroid carcinoma. In lines 99-100 it is written that "Prophylactic central neck dissection was performed for almost all patients", a concept with apparently suggests that all patients were cytologically diagnosed with thyroid carcinoma. Yet (see lines 113-115 and Figure page 20), among the 1101 patients with available ant-thyroid antibodies data, only 806 presented with "thyroid malignancy". This seems to indicate that surgical referral for a fraction of patients was not due to thyroid cancer. This point should be clarified.

Reply 1: Thank you very much for your valuable suggestion. In fact, the initial population of 2302 patients who underwent "thyroidectomy" were treated for all kinds of thyroid diseases, and thyroid carcinoma. Of which, only 806 patients diagnosed with thyroid cancer with available data of both TPOAb and TgAb were finally included in the present study. In lines 99-100, it is true that "Prophylactic central neck dissection was performed for almost all patients", however, only part of patients was cytologically diagnosed with thyroid carcinoma, the rest patients were diagnosed by frozen section pathology. So, some patients who received thyroid surgery for suspected thyroid carcinoma turned out to be finally diagnosed with benign thyroid disease.

Changes in the text: add: "For suspected thyroid cancer patients" and "diagnosed with thyroid cancer."

we have modified our text as advised (see the part of “Subjects and Methods”, line 98-101).

b) Strictly connected with the previous point, one could argue that among the population with positive anti-thyroid antibodies, a higher fraction of incidental thyroid microcarcinomas could be expected (a fraction of patients could have been referred to surgery due to Graves' disease with a final histological diagnosis of carcinoma). Interestingly, the notion that (lines 149-150) "tumor size in TPOAb+ and/or TgAb+ groups tend to be smaller compared to control" is in accordance with this hypothesis.

Of course, if this is the case, the results of the study could be biased: incidental tumors found at histology are usually smaller and less invasive. Again, "significantly less extrathyroidal invasions were identified in TPOAb-/TgAb+ group in comparison to control group" (lines 151-152). This issue underlines the importance of providing more information concerning the reason why the patients were referred to surgery.

Reply 2: Thank you very much for your valuable suggestion and the information you provided. Indeed, in the present study “incidental tumors found at histology are usually smaller and less invasive” seems to be true, although could be biased. The patients were referred to surgery for all kinds of thyroid diseases, as stated in reply 1.

Changes in the text: no.

c) The histological profile of the patients should be better detailed. Alternatively, the vast majority of the patients (Table 2) had a papillary thyroid carcinoma: wouldn't the authors consider the opportunity of limiting their study to this histological type only?

Reply 3: Thank you very much for your valuable suggestion. We added the detailed histological profile of the patients in the text. Indeed, previously, many authors focused on thyroid antibody levels and papillary thyroid carcinoma only but not all thyroid cancer. However, it may be more reasonable to explore the effect of thyroid antibody levels on all kinds of thyroid cancer at first. In the future, maybe we will further explore the relationship thyroid antibody levels and papillary thyroid carcinoma only. Again, thank you very much for your valuable suggestion.

Changes in the text: we have modified as advised (see the part of “table 2”, words in red).

d) It would be quite interesting to evaluate the correlation between positivity of TPOAb and TgAb levels and histological evidence of autoimmune thyroiditis in the study population. Could the authors provide some data on this long-discussed issue?

Reply 4: Thank you very much. Indeed, theoretically positivity of TPOab and Tgab levels and histological evidence of autoimmune thyroiditis are highly correlated, we also wish to present this part of data in the present study. Unfortunately, for some unknown reasons pathologists in our hospital usually don't report autoimmune thyroiditis on the histological report, maybe simply due to short of hands, they focused mainly on thyroid cancer and lymph node metastasis in routine clinical work.

Changes in the text: no.

e) Preoperative neck ultrasound (lines 99-100) was performed in most ,if not all, patients. Are there any data available on the ultrasound (US) pattern of thyroid texture detected in anti-thyroid positive patients as compared to the control group? As for the histological evidence of autoimmune thyroiditis, it would be quite interesting to know to what extent the positivity of serum markers of thyroiditis was corroborated by US signs of chronic inflammation (and vice-versa).

Reply 5: Thank you very much. It is a very interesting question. It seems that there will be some kind of “diffuse lesions” based on the description of US report for patients with autoimmune thyroiditis. As we mainly focused on the effect of thyroid antibody status on lymph node metastasis of thyroid cancer, maybe we will further explore this correlation in the future.

Changes in the text: no.

f) The introduction should be profitably shortened and made more focused to the major endpoint of the article.

Reply 6: Thank you very much.

Changes in the text: delete “The most common site of nodal metastases for thyroid cancer is in the central neck and LNM in this area usually appear normal on preoperative imaging study and even when inspected at the time of surgery.”

we have modified our text as advised (see the part of “introduction”, line 57-60).

g) Minor language pitfalls should be amended (e.g. "committed" surgery).

Reply 7: Thank you very much.

we have modified our text as advised (see the part of “abstract”, line 24;

“Subjects and Methods”, line 94).