

Peer Review File

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Reviewer A

The revised manuscript, “Thyroid Lobectomy is Enough for Patients with Intermediate-Risk Differentiated Thyroid Cancer: Comparison of Oncologic Outcomes,” addresses most major concerns from the original study, but there are still some issues that should be addressed prior to publication.

Major concerns

1. To better address the need for completion thyroidectomy in intermediate risk DTC, it would be ideal to assess recurrence rate in patients with any feature of intermediate risk DTC instead of 2 features. Also, some features are challenging to assess, it would be nice to include vascular invasion and aggressive histology since these should be available on pathology. If these are not available, the reason that they are not included and why only 2 features of intermediate risk DTC are used should be discussed.

Reply 1: We very much agree with your opinion. Unfortunately, the pathology department of our institution did not describe vascular invasion in the report; therefore, it was impossible to confirm. Additionally, most of the enrolled patients had conventional type PTC, and only three patients had the diffuse sclerosing type; hence, we concluded that the comparative analysis was not meaningful. Therefore, we revised the conclusion stating that lobectomy alone was sufficient in patients with an upgraded risk after surgery (see Page 15, lines 322 and 323).

Changes in the text: Page 15, lines 322-323

2. Vascular invasion, aggressive histology, and RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan should be added to intermediate risk features in the introduction.

Reply 2: This has been included in the introduction (see Page 5, lines 84 and 85)

Changes in the text: Page 5, lines 84 and 85

3. Power calculations should be included in the results to determine if the lack of statistical significance in RFS between A1 and B is because the study is not adequately powered to detect a difference.

Reply 3: We have included the following statements in the discussion section. “When

we calculated the statistical power, it was 0.363. Assuming a power of 0.8 and significance level of 0.05, the required sample sizes were 2918 and 1646, respectively. Since the progression of DTC is slow and the recurrence rate is low, the 10-year follow-up duration of our study may be rather short. To compensate for this, a larger number of patients or a longer follow-up will be needed in the future.” (see Page 14, lines 278-282)

Changes in the text: Page 14, lines 278-282

4. Discussion as to why the following paper is different from the authors should be included. <https://doi.org/10.1159/000510620>

Reply 4: We have addressed this by including the following statements in the text. “Matthieu et al. demonstrated that recurrence rate of intermediate-risk PTC was higher than low-risk PTC in patients who underwent TL (28.6 vs. 7.1%) (50). However, they included aggressive histologic cancer types like poorly-differentiated cancer and diffuse sclerosing PTC. Also, there was no mention of central LN dissection, and they did not analyze central LN metastasis. We thought that this may have affected the recurrence rate.” (see Page 13, lines 254-259).

Changes in the text: Page 13, lines 254-259

5. Conclusions should be changed to TL can be considered for DTC with > 5 central LN or capsular invasion (not ATA intermediate risk DTC).

Reply 5: We agree with your opinion and have modified our conclusion. “In conclusion, TL with prophylactic CCND is sufficient for patients with DTC whose risk was upgraded after surgery, because they have a good prognosis at long-term follow-up. Larger-scale randomized clinical trials are required to confirm our findings.” (see Page 15, lines 322-324)

Changes in the text: Page 15, lines 322-324

Minor concerns

1. The syntax in the following sentences is problematic:

This retrospective study was designed to proper surgical methods by comparing the oncologic outcomes and long-term prognosis (assessed through serial follow-up) of ATA low-risk and intermediate-risk groups of patients who underwent TL with prophylactic central compartment neck dissection (CCND) at a single medical center.

Reply 1: We have modified the sentences (see Page 6, lines 94-96).

Changes in the text: Page 6, lines 94-96

Reviewer B

The manuscript has been greatly improved and the data are presented in a better way. The data are interesting, and the series of patients is large. These are strengths in the study. However, my main concern from the previous review remains the same: The authors go too far in their interpretation of the data and in the conclusions. Specifically, they cannot extrapolate their findings to conclude about the treatment for intermediate risk cancer patients in general, because they study a selected group within the intermediate risk category.

All patients in the study were potential low risk and treated with lobectomy and lymph node dissection. All patients with clinical LN metastasis, or T3 tumors, were treated with total thyroidectomy and are not part of the study population. Therefore, a significant proportion of intermediate risk patients in the authors' clinic is actually treated with total thyroidectomy. No data for this group is presented, which is ok, but it is not possible to know if lobectomy is enough for the intermediate risk group in general. The authors should make a more moderate conclusion along the following lines: Patients initially perceived as clinical low risk, and treated as such, but later upgraded to intermediate risk because of capsular invasion or >5 LN mets, do not need completion thyroidectomy. This is still an interesting finding, without making conclusions about intermediate risk patients in general. The recurrence rate of 2 %, very low compared to other studies of intermediate-risk DTC is indirect proof of this selection bias that group B harbors only the "best part" of intermediate risk patients.

The main conclusion must be modified.

There is yet another reason that Group B has a selection bias to the lower end of the intermediate risk group. In another institution they may have been treated without CND and remained low risk because nobody saw micrometastasis. The argument against this is that all patients in group B had capsular invasion, and none in Group A, so they would still be upgraded to intermediate risk. We are then left with a single histopathological finding that the story is all about: Patients that are otherwise low risk should not be selected for completion thyroidectomy only because of capsular infiltration. I think you should change your conclusions and rather argue that incidentally found micrometastasis, and capsular invasion in particular, should not warrant completion thyroidectomy.

The authors go far in extrapolating their results to ATA intermediate-risk DTC, especially in the discussion. For example, in line 257-259. Please remember that these are patients first selected as possibly low risk that were treated with lobectomy and CND and upgraded to intermediate risk by histology. The same goes for line 282-284 and the main conclusion line 60-63 and 302-304. You have not presented

data for the entire group of intermediate-risk DTC, only a selected subset, probably those with the best prognosis and cannot conclude for patients with ATA intermediate risk in general.

Reply 1: We fully agree with your opinion. Unfortunately, the pathology department of our institution did not describe vascular invasion in the report; therefore, it was impossible to confirm. Additionally, most of the enrolled patients had conventional type PTC, and only three patients had the diffuse sclerosing type; hence, we concluded that the comparative analysis was not meaningful. Therefore, we revised the conclusion stating that lobectomy alone was sufficient in patients with an upgraded risk after surgery (see Page 15, lines 322 and 323).

Changes in the text: Page 15, lines 322 and 323

In Figure 1 and 2 it looks like there is a difference in recurrence after about 12 years. Could the lack of statistically significant effect be because the observation time is too short? We all know the disease grows slowly. This should be discussed in the last part of the discussion for example. This is as a weakness that has directly to do with the data supporting the main conclusion. Also, I do not understand line 296: “The recurrence rate of the enrolled patients was high”

Reply 2: We agree with your opinion. We have added a statement about the short observation time (see Page 14, lines 280 and 281). Additionally, we modified the sentence at line 296 (see Page 15, line 315). It now reads “The recurrence rate of the enrolled patients was higher than that of those lost to follow-up”.

Changes in the text: Page 14, lines 280 and 281, Page 15, lines 315 and 316

Line 41: underwent thyroid lobectomy and ipsilateral central node dissection?

Reply 3: As you advised, we have modified the sentence (see Page 3, lines 41 and 42).

Changes in the text: Page 3, lines 41 and 42