

Peer Review File

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Reviewer A

I would like to congratulate the authors for their excellent, and very relevant manuscript. The paper is very well written. However I would like further expansion on the discussion section.

In particular the way I read these data, it appears that addition of PCND did not change overall recurrence. It solely changed the site of recurrence from the central compartment to the lateral compartment. One may argue that PCND takes away a natural line of defence, allowing the disease to spread to the lateral nodes. Whether or not this is a favourable or unfavourable outcome could be argued either way.

Clearly going back in the scarred central compartment could be associated with some major complications. On the other hand resection of lateral recurrence seems to be a more straight forward procedure at least in the trained hands. However theoretically taking away a line of defence just to allow for a more pleasant subsequent surgery does not appear to be oncologically sound!

Reply:

Thank you for comments related to further expansion ideas from original manuscript. As the reviewer pointed out, there are several hypotheses about the role of lymph nodes related to cancer spread. Lymph nodes may act as a first line of defense, preventing cancer metastasis, while providing a pathway through which cancer spreads. However, these theories are still debatable.

Forty-two percent of patients in pCCND group had occult lymph node metastasis and generally the rate of occult lymph node metastasis in PTC has been reported up to 82% as we mentioned in introduction. It is assumed that the remnant metastatic lymph nodes were expressed as cancer recurrence over time, considering the high prevalence of occult lymph node metastasis of PTC.

It is difficult to study the effect of occult lymph node metastasis on thyroid cancer recurrence because it is impossible to determine whether lymph node metastasis exists without pCCND in clinically N0 patients with thyroid cancer. Moreover, 5840 patients in a prospective trial would be necessary to have sufficient statistical power to prove positive effects of pCCND on recurrence rate as we mentioned in discussion section (line 240-243). There are no long-term follow-up studies related to this. We were able to observe the natural cancer recurrence from occult lymph node in central compartment during a relatively long term follow up period (117.4 months \pm 44.7 [9-191]), although we did not prove the protective effect of pCCND to oncologic outcome.

However, we added your comments into line 247-258 on discussion section and more references (reference 30,31,32)

Changes in text :

line 247-258 on discussion section.

Because there are conflicting studies about the role of lymph nodes in cancer recurrence, there may also be disagreements about the need for lymph node resection. In several studies, lymph nodes may play a role as education centers of the immune system and anti-tumor immunity (30,31). According to these studies, it seems that removal of lymph node has adverse effect on oncologic outcome. In the other hands, according to recent research, lymph node colonization can induce cancer metastasis (32). However, it is difficult to study the effect of occult lymph node metastasis on thyroid cancer recurrence because it is impossible to determine whether lymph node metastasis exists without pCCND in clinically N0 patients with thyroid cancer. Forty-two percent of patients in pCCND group had occult lymph node metastasis in this study and generally the rate of occult lymph node metastasis in PTC has been reported up to 82% (2-8). Considering this, we may estimate that undissected-occult lymph nodes induced local recurrence in central compartment in non-pCCND group.

Line 377-382 on reference section

30. von Andrian UH, Mempel TR. Homing and cellular traffic in lymph nodes. Nat Rev Immunol 2003;3:867-78.

31. Binnewies M, Mujal AM, Pollack JL, et al. Unleashing Type-2 Dendritic Cells to Drive Protective Antitumor CD4(+) T Cell Immunity. Cell 2019;177:556-71 e16.

32. Reticker-Flynn NE, Zhang W, Belk JA, et al. Lymph node colonization induces tumor-immune tolerance to promote distant metastasis. Cell 2022;185:1924-42 e23.

Reviewer B

This is a one-center retrospective study that includes a large cohort of patients. However, there are some sources to bias, especially when the numbers differs for the different groups and when there are different surgeons consequently treating the patients differently.

1. The surgeons who did not do routine pCLND, did they ever peri-operatively encounter lymph nodes that made them change their surgical plan and do a CLND? Where these patients excluded then?

Reply :

We could not sure whether the plan of CCND was changed or not during procedure in this retrospective design. Dividing into two group (non-pCCND and pCCND) was determined according to the final operation record. However, patients with incidentally removed lymph

nodes belonged to non-pCCND group. The related explanation was mentioned in the introduction section, line 135-140.

Changes in text : none

2. I notice that micro-PTC are included in this study, how do you usually treat these patients in your hospital? Are they also treated with total thyroidectomy and given RAI? It would be interesting to see the numbers with the micro-PTC excluded as well.

Reply :

We retrospectively reviewed the records of patients with PTC who underwent thyroidectomy between 2006 and 2012. The treatment guidelines for thyroid cancer was more aggressive at that time. Even micro-PTC were often treated with total thyroidectomy and RAI, especially in cases with capsular invasion (minimal invasion) or multiple nodules. Currently, total thyroidectomy or RAI are no longer performed for micro PTC in our institutions.

Of total patients (n=2902), 2254 patients (77.7%) had micro PTC. Of these patients, 608 patients underwent unilateral thyroid lobectomy and 1646 patients underwent total thyroidectomy with followed RAI. When comparing the recurrence rate by cancer size group, the recurrence rate was 1.8% (40/2254) for tumors less than 1 cm, 3.3% (18/548) for tumors greater than 1 cm and less than 2 cm, and 9% (9/100) for tumors greater than 2 cm and less than 4 cm.

The majority of the cohort in this study consisted of micro-PTC (77.7%). It was difficult to analyze data except those micro-PTC patients because the number of recurrence cases decreased and statistical analysis was difficult. Further study of cancer larger than 1cm is performed, the effect of pCCND on recurrence will be better analyzed.

Changes in text: none

3. I would be careful to make conclusions with such small differences between groups, even if the differences are significant, as this might not be clinically relevant.

Reply :

Thank you for your comment. In our study, we tried to figure out the differences in recurrence pattern according to whether pCCND was performed, not the necessity of pCCND. The difference between two groups may be due to remained-occult lymph node metastasis on central compartment. There were few cases with recurrent thyroid cancer in this cohort and it was not clear to demonstrate the effect of pCCND on oncologic outcome. This small difference may be due to the large proportion of early stage cancer (T1a, 77.7%) in this cohort. So, if more cases between T1b and T2 with long term follow up are included, more definitive results can be expected.

Changes in text : none

4. You suggest in the conclusion section, that patients not subjected to pCLND should be

followed carefully to identify any recurrences in the central compartment. Based on your data, with a recurrence of 1,2 percent in the central compartment, is this clinically defensible? How would you do this follow-up as ultrasound is not a very sensitive method to identifying central lymph node metastasis.

Reply :

The recurrence rate in central compartment was rare as your comment. As we mentioned on introduction, the occult lymph node metastasis on central compartment is common as much as 24%-82%, which means that it is difficult to detect the metastatic lymph node before lymph node dissection in thyroid cancer.

However, post-operative ultrasonography is useful and high sensitivity tool for detecting node metastasis after surgery (1). It is also useful for detecting persistent disease in N1-PTC patient. Sensitivity, specificity, NPV, and PPV of post-operative ultrasonography for the detection of the 121 PD were 82.6, 87.4 95.6, and 60.6% respectively (2).

According to our results, more detailed evaluation of central compartment is necessary for patients without CCND performing in thyroid cancer when we consider re-operation because of recurrence.

- (1) Torlontano M, Crocetti U, Augello G, D'Aloiso L, Bonfitto N, Varraso A, Dicembrino F, Modoni S, Frusciante V, Di Giorgio A, Bruno R, Filetti S, Trischitta V: Comparative evaluation of recombinant human thyrotropin-stimulated thyroglobulin levels, 131I whole-body scintigraphy, and neck ultrasonography in the follow-up of patients with papillary thyroid microcarcinoma who have not undergone radioiodine therapy. *J Clin Endocrinol Metab* 2006;91:60-63.
- (2) Charlotte Lepoutre-Lussey, Dina Maddah, Jean-Louis Golmard, Gilles Russ, Frédérique Tissier, Christophe Trésallet, Fabrice Menegaux, André Aurengo, Laurence Leenhardt: Post-operative neck ultrasound and risk stratification in differentiated thyroid cancer patients with initial lymph node involvement. *Eur J Endocrinol*. 2014 Jun;170(6):837-46.

Changes in text : none

5. Please state in the table legend what the numbers are (ie mean or median and sd or sem)

Reply : we appreciated your thoughtful comments. With your consideration, we stated the type of representative value (Mean±SD [Min-Max]) in the table 1.

Changes in test :

Table 1

Age (Mean±SD [Min-Max])

Tumor size (cm)

(Mean±SD [Min-Max])

No. of lymph node retrieved

(Mean±SD [Min-Max])

Follow up period (months)
(Mean±SD [Min-Max])

Reviewer C

According to the result of this study, prophylactic central neck dissection seems to reduce central compartment recurrence compared to the non-pCND group. However, it is not possible to conclude that the omission of pCCND was related to worse recurrence in the central compartment or pCND is recommended for T1-T2 cN0 PTC based on the results of this study. Reoperation for recurrence in the non-dissected central lymph nodes might be easy compared to recurrence in the dissected central compartment. So, central compartment recurrence in the non-pCND group might not be a worse recurrence. Also, the total recurrence rate did not differ between the pCND and non-pCND groups; the reason for the difference in recurrence pattern is not determined. It is a retrospective, non-randomized study. Therefore, there is inevitable bias.

The authors need to mention these issues and controversies in the Discussion.

Reply:

Thank you for comments. Our main conclusion of this study could not be a necessity of pCCND. Even if pCCND is effective in preventing the recurrence in the central compartment, as you mentioned, it is easier to operate non-dissected central lymph nodes, so it is not possible to conclude that pCCND is safe or useful for the patients in thyroid cancer. However, the point of our study is to report of recurrence pattern difference according to whether pCCND was performed.

Forty-two percent of patients in pCCND group had occult lymph node metastasis and generally the rate of occult lymph node metastasis in PTC has been reported up to 82% as we mentioned in introduction. According to this, we estimated that there could have remnant-occult lymph node metastasis in non-pCCND group and these were expressed as recurrence lesion later. However, as long as it remains undissected, there is no way to find out whether the occult lymph node metastasis existed or not.

We elaborated further about these arguments at line 264-267. Also please note the another line 255-258 in discussion section.

Changes in text

Inserted sentence in line 264-267

Considering these non-different results and the easier accessibility to the non-dissected central compartment lymph node during the re-operation rather than to the dissected area, it seems impossible to conclude that pCCND is necessary to patients with thyroid cancer to improve overall outcome.