

Reviewer A

Comment 1:

This study is looking at rates of spread of PTC and MTC to levels IIa and IIb in the lateral neck. I have a few major issues with this study. First, I can find no data to support the contention that level II should not be dissected when doing a therapeutic lateral neck dissection. The citations the authors list all support including level IIa when doing a therapeutic lateral neck dissection. The paper by Dr. Hartl, which suggests that level II is not often involved with occult disease, is in the context of a prophylactic lateral neck dissection of levels III and IV, not in a therapeutic context. When levels III and IV were positive, there was a high rate of involvement of level II as well. All of the other cited studies show a high rate of spread to level II in patients who have lateral neck disease.

Reply 1: The level II remains not always performed for therapeutic lateral neck dissection, and it is for this reason that therapeutic selective neck dissection, frequently reported in thyroid carcinoma, is distinguished from therapeutic (complete) comprehensive neck dissection (cf ref 19-21,23).

In addition, in multidisciplinary staff, we observed that some surgeons reported performing complete therapeutic neck dissection, but there are only few lymph nodes at histopathological analysis!

Changes in the text to clarify terms of therapeutic LND:

p. 1: lines 2,10, 20

p.2: lines 37, 38

p. 3: lines 50,51, 52, 53, 56, 57, 63,64, 71

p. 4: lines 91,92

p. 8: lines 185,186

p. 9: line 203 (the ref Hartl has been deleted)

p. 11, line 232

p. 11: line 255

Comment 2:

Additionally, the authors include MTC and PTC. These are two very different disease processes and including both together I think is inappropriate and limits any conclusions that could be drawn from the data.

Reply 2: We include MTC, since, like DTC, some surgeons perform a selective therapeutic LND and not a complete comprehensive LND.

Changes in the text: cf page 3, line 65, we add “also”, p. 5 lines 91-92. It was also pointed out in the discussion (cf page 9, lines 196-200), but we have made some changes and the word “complete LND” has been deleted)

Reviewer B

This is a retrospective study supporting the necessity of performing comprehensive LND for thyroid carcinoma. Although I agree with the author that comprehensive LND should be preferred over selective LND when LND is indicated, some of the aspects of this study needs additional consideration.

Comment 1. Authors of this study support comprehensive LND for several reasons. It is provided that IIA/IIB shows higher rate of involvement, and lower level LN groups (III/IV/V) were involved whenever upper level LN groups (IIA/IIB) show positive occurrence. Moreover, number, size is higher and ECS is more frequent in upper level LN groups. Although numbers presented for data's above (concerning table 2 and 3) do show trends supporting statements above, but just by presenting the trend does not clearly offer the evidence since results are lacking statistic approval. Therefore, it seems to be inappropriate to conclude that IIA/IIB LN involvement show “higher rate of involvement compared to” III/IV/V level LNs (p.10 line 8-10). ”This also applies to the statement that “average number and size of positive lymph nodes was higher” in upper LN group “compared to” the lower III/IV/V groups, and ECS among positive IIA/IIB groups “is higher than” III/IV/V groups. I suggest a proper statistical analysis for the results of table 2 and 3, or at least mention the lack of statistical analysis as a limitation in the discussion.

Reply 1: We understand the comment, and changes were performed

Changes in the text:

- page 8, lines 166-168
- page 10, line 226

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- page 11, lines 245-246, 248
 - page 12: line 258

Comment 2. Involvement of level IIA/IIB are compared with lower lymph node groups of level III/IV/V in this study. However, this study could provide more clinical implication if lower lymph node groups are further categorized as level III/IV and level V. A similar analysis regarding level V lymph node groups as conducted to level IIA/IIB is suggested.

Reply 2: It is a really difficult since the classification of Robbins has evolved and since the nodes of the level V are difficult to distinguish from the group III/IV (see page 3, lines 59-62). We usually remove all of nodes posteriorly to the III/IV levels, and we have included these nodes with the levels III/IV for pathological analysis in this study.

Changes in the text: page 10, lines 218-222

Comment 3. The patient characteristics provide information of T staging in primary lesion. This study could provide more clinical implications if relevant findings of the primary lesion such as T staging or presence of extrathyroidal extension are suggested, since it is widely accepted and applied in clinical practice that the primary lesion size and extrathyroidal extension are relevant to conducting CND or LND. Thus, univariable and multivariable regression analysis regarding patient factors of sex and age, T staging, ETE, with CND, and LND should be conducted to determine the predicting factors of level II LN metastasis.

Reply 3: No predicting factors of level II LN metastasis have been studied since it was not the aim of the study, and since the lack of statistical analysis due to the number of cases studied.

Changes in the text: page 11, line 245-246,248

Comment 4. This article needs English editing. Moreover, some of the numbers are not consistent, such as presenting 26 total patients with 14 males and 10 females. Meticulous minor revision is also required.

Reply 4: We understand the comment, and changes have been performed, and the manuscript was English reviewed. Some other changes have been performed in the

abstract (therapeutic, p. 1, lines 1,10) and in the main text (p. 3, lines 55/56; p. 4, lines 91-95; p. 5 line 95; p.9, lines 199-200; and number of reference since one has been deleted, p. 16/17: ref 26-28).

The text has been English revised.

Changes in the text:

- page 6, line 131
- table 2: page 18, line 389

Reviewer C

Although lateral neck dissection (LND) may be indicated in thyroid carcinoma, the cervical lymph node groups IIA and IIB, according to Robbins classification, are often not removed. In the manuscript “High rate of IIA/IIB neck groups involvement supports complete lateral neck dissection in thyroid carcinoma”, authors determined the relevance of complete comprehensive LND in thyroid carcinoma.

Couple questions are required to be answered before accepted.

(1) There was similar report (Head Neck. 2018 Feb;40(2):242-250) in the PubMed.

What is the novel idea in the paper? Please elaborate in the introduction.

Responses: Following revisions 2 and 3, introduction and objectives of the paper have been modified, and also to clarify terms of therapeutic LND. In the introduction, the study objectives (session 1.3 Study objectives in therapeutic LND) are more pointed out. In comparison to previous studies, the originality is to compare upper to lower groups involved in thyroid carcinoma. The study of Lombardi et al in 2018 evaluated nodal involvement without grouping upper and lower groups of lymph nodes involved.

In this version we add this sentence, in the 1.3:

“The extent of therapeutic LND, selective or comprehensive, has been subject to debate over the past 40 years. In several series with LND performed, including also MTC, selective resection of only lower groups III/IV and V (16,24), were preferred to limit the surgical morbidity. The aim of our work was to study the relevance of dissection of all lateral groups by performing a comprehensive LND, when therapeutic LND is indicated in thyroid carcinoma, removing levels IIA/IIB, III, IV, and V. The originality was to make comparison between lower III/IV/V groups to upper IIA/IIB involvement. Analysis of histopathological results of LND according to upper IIA/IIB or lower III/IV/V groups, was conducted in order to support subsequent complete comprehensive LND instead of selective LND (lower groups) in thyroid carcinoma.

(2) The figure 1 was not clear enough. Please replace it with a new.

Response: It has been performed on the R3 figure

(3) In the paper, the case samples were too small. Whether the results can support the conclusion?

Responses: We have modified the limits of this study in the discussion

‘The limits of the present study where a poor number of patients with a lack of statistical evidence, and the type of study which is a retrospective analysis. Nevertheless, our study is original in comparing the upper IIA/IIB and the lower III/IV/V cervical lymph nodes groups involved in thyroid carcinoma. Predicting

factors of level IIA/IIB metastasis, impact of complete comprehensive LND on survival rate and on modulation of postoperative radioactive iodine treatment remains to be studied in a larger prospective analysis, keeping into account that cosmetic and functional sequels remain a real challenge in view of oncologic benefits.”

Responses: We have also modulated our conclusions

“A high prevalence of positive involvement of IIA/IIB groups during therapeutic LND for thyroid carcinoma may support to perform complete comprehensive LND including the upper IIA/IIB groups, instead of selective lower III/IV/V groups. These results should be studied in a larger population to confirm results and to evaluate impact on survival for patients.”

(4) In the introduction, please enrich the progress of the treatment for thyroid carcinoma. Why to focus on LND in the paper? Based on what to choose LND?

Please supplement in the introduction.

Responses: The LND needed in thyroid carcinoma has been more precise in the introduction, in the background and in the paragraph 1.2 (the particular features of neck dissection in thyroid carcinoma).

(5) Up to now, in common clinical treatment, whether LND is needed in thyroid carcinoma?

Responses: We point out that the aim of this study was not to discuss indications of LND (cf discussion as following in the discussion).

“The aim of this study was not to discuss indications of LND in thyroid carcinoma (3,5,7,12,16,17), but to study the relevance of a dissection including all levels of lateral cervical nodes when LND is indicated (i.e. comprehensive LND, including groups VA/VB since dissection of levels III/IV was performed until the posterior cervical roots). The choice to further analyse the involved cervical nodes by upper or lower level was appropriate since we aimed to study the location of cervical metastasis in thyroid carcinoma, according to Robbins classification (1,2).”

(6) How to make a difference between DTC and MTC? What are the exclusion criteria for enrolled cases?

Responses: Criteria of inclusion and of exclusion were clarified in the final version.

We have also precised why we have include DTC and MTC in this study (cf introduction (cf 1.3) and in discussion (“Patients with MTC were accordingly included in the study since the aim was to analyse the levels of nodes involved in thyroid carcinoma, and like in DTC, some surgeons don’t perform complete comprehensive LND in MTC, although LND is indicated (6).”)

(7) It is better to provide representative HE staining images of lymph node.

Response: We have added in this R4 version, a Figure 2 (HE staining).

Figure 2. Lymph node metastasis of a papillar thyroid carcinoma with extracapsular spread. HES staining. Digital slide scanned, magnification x10.

a: normal lymph node tissue, b: metastasis of papillary thyroid carcinom, c: lymph

node's capsule, d: extracapsular invasion of lymph node.