

Peer Review File

Article information: <http://dx.doi.org/10.21037/gs-20-712>.

REVIEWER A

Comment 1

1. The cohort size is very small. It is difficult to assess efficacy of thyroid lobectomy compared to total thyroidectomy

Reply 1

Thank you for this comment. We fully agree with this statement by the reviewer and acknowledge it in the paragraph on study limitations in the Discussion section. Limitations in sample size and follow-up time, as it is also stated in comment #2, are common in retrospective studies like ours. On the other hand, it was not our objective to compare the results of lobectomy with those of total thyroidectomy, since for this we would need a second group of patients with this last surgical procedure. Our study only intended to study the clinical outcomes of a nationwide multicenter cohort of patients with DTC, treated by lobectomy, and to quantify the proportion of patients who required completion of thyroidectomy and who exhibited tumor recurrence. In brief, we had no intention to compare total thyroidectomy with lobectomy. Our aim was to reflect what is the real practice in our country. Therefore, according to this suggestion and that in comment #2, we have added a brief paragraph in the new version of the Discussion.

Changes in the text

Please, see the section on limitations in the Discussion of the revised version of the manuscript.

The limitations derive from a relatively small sample size and duration of follow-up. This may be probably due to the fact that TL has had little diffusion among Spanish surgical departments. Our study does not allow to compare the outcomes of patients

undergoing TL with those treated by total thyroidectomy, since the latter were not included. To compare thyroid lobectomy to total thyroidectomy, a larger sample size and a long-term follow up period should be needed. Most of the patients...

Comment 2

2. Collection period of patients is unclear. Before 2015 ATA guidelines or After 2015 ATA guidelines? and What is the average duration of follow up?

To compare thyroid lobectomy to total thyroidectomy, long term follow up period should be needed.

Reply 2

Thanks for the suggestion. Indeed, all patients were recruited by the researchers after the publication of the ATA 2015 guidelines. The recruitment period of the different participating hospitals was between 2017 and 2019. We have added a sentence clarifying these dates in the Methods section of the revised version.

The average duration of follow-up was 45.4 (23.4-67.1) months for the entire cohort, 47.2(24.1-70.7) months for female patients, and 34.8 (20.4-55.9) months for male patients. These data are detailed in table 1. As noted by Reviewer B, duration of follow-up was shorter in men than in women, but without reaching statistical significance. In the new version of the article, we have included a brief sentence highlighting this finding pointed out by the reviewer. See the second paragraph of Results

We also agree with the reviewer's statement about the short period of follow-up of our study and we acknowledge this in the paragraph dedicated to study limitations (see comment 1).

Changes in the text

Please, see the section Patients new version of the manuscript.

Data collection was carried out in the participating hospitals between 2017 and 2019.

For the comment on duration of follow up, see table 1 and the second paragraph of Results.

Duration of follow-up was shorter in men than in women, but without reaching statistical significance (34.8 [20.4-55.9] vs. 47.2[24.1-70.7] months, P=0.132). All the other...

For the limitation of the study in comparison of lobectomy with total thyroidectomy, see the section Discussion.

The limitations derive from a relatively small sample size and duration of follow-up. This may be probably due to the fact that TL has had little diffusion among Spanish surgical departments. Our study does not allow to compare the outcomes of patients undergoing TL with those treated by total thyroidectomy, since the latter were not included. To compare thyroid lobectomy to total thyroidectomy, a larger sample size and a long-term follow up period should be needed. Most of the patients...

Comment 3

3. I think authors should give contents of dynamic risk stratification to readers.

Reply 3

Thank you for your comment. The system used to classify patients into the four types of response is described in the Methods section, according to criteria accepted in recent literature (refs. 16,17 and 19), that is: excellent (stable Tg level <30 ng/ml and negative TgAb and negative imaging), biochemical incomplete (Tg >30 ng/ml or increasing Tg levels or increasing TgAb levels and negative imaging), structural incomplete (evidence of disease regardless of Tg or TgAb), and indeterminate response (nonspecific findings on imaging studies or TgAb levels stable or declining in the absence of structural disease).

The absolute data of the patients with the different types of response in the dynamic risk stratification at 12 months and at last visit appear in Figure 1. We think that it is illustrative to show the readers the changes in DRS. Following the recommendation of the reviewer, we have expanded the information on these responses by constructing a new table (Table S1) that collects the number and percentage of the four types of responses in the evaluation carried out at 12 months (available in 148 subjects) and at the last visit (available in the total cohort of patients).

Changes in the text

For description of the criteria for each of the four types of responses, please see the Methods section.

For quantitative information, please see Table S1 in the supplementary material of the revised version of the manuscript.

Comment 4

4. The definition of chronic lymphocytic thyroiditis is unclear. laboratory diagnosis or pathologic diagnosis or ultrasound diagnosis?

Reply 4

Thanks for this observation. The definition of chronic lymphocytic thyroiditis was exclusively pathological, that is, this diagnosis was considered when it was explicitly included in the pathological report of the specimen. Following this recommendation of the reviewer and to clarify this point to the readers, we have added a brief comment in the Study design section, in which the diagnostic criteria for chronic lymphocytic thyroiditis are clearly stated. We have also made a clarifying change in the section on the results of Dynamic risk stratification.

Changes in the text

Please, see section Study design.

histopathological data (histology type, tumor size, multifocality, invasiveness, incidental finding, extrathyroidal extension, presence of chronic autoimmune thyroiditis in non-tumor thyroid);

Please, see section Dynamic risk stratification.

Patients with persistent disease exhibited a higher proportion of chronic autoimmune thyroiditis demonstrated in histopathological study than patients in remission (42.9% vs 19.7%), with...

Comment 5

5. Page 8, line 24-25, 122 (74.4 %) patients were in remission and 42 (25.6%) were not cured. 'not cured' is inappropriate. 'not in remission' may be suitable.

Reply 5

Thanks for this observation. We have amended this error in the text.

Changes in the text

Please, see section Dynamic risk stratification in the new version.

At last visit, 122 of 164 patients (74.4%) were in remission and 42 (25.6%) were not in remission.

Comment 6

6. Central lymph node dissection was performed in only 5 cases. There is a definitive limitation in this study.

Reply 6

The reviewer is right. This is a limitation of the study and it is included in the Discussion of this revised version. Given the indolent nature of these small PTC, the current practice in some hospitals is not to perform central lymph node dissection in

every patient.

Changes in the text

Please, see the new version of the Discussion.

...our results cannot be extrapolated to populations with higher risk tumors. Besides, central lymph node dissection was performed in only 5 cases. The retrospective nature...

Comment 7

7. The reasons of completion thyroidectomy is uncertain. Did you perform the fine needle aspiration biopsy before completion thyroidectomy?

Reply 7

Thanks for this comment. FNAC was performed in most patients before undergoing thyroidectomy completion. There were three patients in whom we did not have this information. In the remaining 5 patients, in whom satisfactory thyroid cytopathology was obtained, this examination confirmed malignancy in 2 cases (patients 7 and 8, in table 5). Cytology showed benign characteristics in the remaining 3 patients (patients 4, 11 and 12).

Changes in the text

We have added a brief comment on this point in the section Results of the new version of the manuscript.

Fine needle aspiration cytology was available in 5 patients before thyroidectomy completion. Results confirmed malignancy in two of these patients.

Furthermore, we have included the above mentioned information in detail in table 5, where we have added a new column.

Comment 8

8. Normal range of anti-Tg ab should be presented.

Reply 8

Thanks for this observation. As this was a multicenter study, each hospital used the TgAb assay from its corresponding clinical laboratory. The methods used were chemiluminescence assays from different suppliers (Siemens, Roche, Beckman and Abbott). The thresholds for considering the patients under investigation to be positive or negative varied according to the method used. Due to this great diversity of numerical data, we estimated that it was reasonable to consider the variable TgAb as qualitative of two categories (positive, negative). The cut-off points for each assay ranged from 4 to 60 U/ml, so the data from the different instruments were not comparable. Following the reviewer's recommendation, we have added a short sentence in the methods section that indicates the different cut-off points used.

Changes in the text

Please, see the new version of the section Methods.

. For the quantification of TgAb, the most used appliances were Immulite and Advia Centaur (Siemens), Cobas (Roche), Access (Beckman) and Architect (Abbott). The cutoffs for TgAb positivity were different in the several employed assays, ranging between 4 and 60 U/ml in the participating hospitals. Given the diversity of methods, only the presence of positive or negative TgAb values was considered. In patients with positive TgAb, the serum Tg value was not considered.

REVIEWER B**Comment 1**

1: The authors should consider adding p values to results presented in tables.

Reply 1

Thank you for this comment. The P value has been added to Tables 1, 2, 4 and S1 (now table S2 in the new version of the article).

Changes in the text

Please, see the tables and supplementary material in the new version of the manuscript.

Comment 2

2: Pg 9 line 16: there appears to be a computing error: there are 164 patients in the study, however the number of patients who had contralateral nodules (60) and no nodules (109) adds up to 169.

Reply 2

Thank you for detecting this mistake. Indeed, it is a misprint. There were 60 patients with nodules in the remnant lobe and 102 without nodules. In two patients this information was not available. We have corrected the typo and made the paragraph more complete to make it easier to understand.

Changes in the text

Please, see the section Ultrasound examinations in the new version of the manuscript.

During follow-up, ultrasound tests showed nodules in the remnant contralateral thyroid lobe in 60 patients (36.6%) and absence of nodules in 102 (62.2%). This information was not available in 2 patients (1.2%).

Comment 3

3: Pg 9, line 17-19: Potential computing error. The number of completions here adds up to 7 however the rest of the manuscript discusses 8 patients who had a completion thyroidectomy

Reply 3

In fact, the wording can be misleading and lead the reader to think that there are only 7 completions instead of 8. There is one patient who is not mentioned. This is a patient in the group that did not exhibit nodules during follow-up. In this patient, the result of the thyroidectomy was a recurrence of papillary cancer. We have added a sentence to clarify these points.

Changes in the text

Please, see the section Ultrasound examinations in the new version of the manuscript.

A further thyroidectomy was performed in one subject from the group of 102 patients without nodules during follow-up, also resulting in tumor recurrence (Figure S2).

Table 4 shows...

Comment 4

4: Pg 12, line 20: is CDT a typo for DTC? Please clarify

Reply 4

It is a typo, indeed. Thanks for pointing it out.

Changes in the text

Please, see the Discussion of the new version of the manuscript.

However, in a low-mortality disease such as **DTC**, it is essential...

Comment 5

5: Pg 12, line 21: Please provide the meaning of MCPT as the acronym is not defined elsewhere in the manuscript

Reply 5

Thank you for this comment. MCPT is a typo for PTMC (papillary thyroid

microcarcinoma). The meaning of this acronym has now been defined in the new version of the article. The typo has been amended

Changes in the text

Please, see the seventh paragraph of the revised manuscript.

However, in a low-mortality disease such as **DTC**, it is essential to analyze, not only survival, but also the risk of recurrence. In a cohort of 2014 **patients with papillary thyroid microcarcinoma (PTMC)**, after a propensity...

Comment 6

6: Table 1: It is interesting that males had a substantially shorter follow-up time than females. Are males who undergo lobectomy more likely to be lost to follow-up?

Reply 6

Indeed, as the reviewer points out, patient follow-up was shorter in men than in women. However, the difference between men and women in the duration of follow-up was not significant ($P=0.132$). We have not found reasons to think that there is a greater loss to follow-up in men than in women. In fact, of the 8 patients who underwent thyroidectomy completion, 3 were men (37.5%), while in the whole studied cohort there was a lower percentage of men (36 of 164, 22%).

Changes in the text

In the new version of the article, we have included a brief sentence highlighting this finding pointed out by the reviewer. See the second paragraph of Results.

Duration of follow-up was shorter in men than in women, but without reaching statistical significance (34.8 [20.4-55.9] vs. 47.2[24.1-70.7] months, $P=0.132$). All the other clinical and histopathological characteristics that appear in Table 1, were similar in both sexes.

Comment 7

7: Since this study involves postoperative surveillance following lobectomy, the authors should consider providing some information on surveillance intervals for US and labs for the patients.

Reply 7

Thank you for this comment. In accordance with this suggestion of the reviewer, we have added a short paragraph describing the sequence of imaging and laboratory tests followed in the hospitals that participated in the study. As this was a retrospective study, there were no previously defined time intervals for complementary tests, but most of the centers followed similar protocols.

Changes in the text

Please, see section on Laboratory and imaging tests in the revised version of the manuscript.

Although the protocols of each center were not identical, in most patients, laboratory (serum Tg and TgAb) and imaging tests (neck ultrasound) were performed every 3-6 months for the first year and then annually or every 2 years. Serum Tg and TgAb levels...