Peer Review File

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Reviewer A:

I read this paper with great interest. The authors' efforts in this work are well-recognized. However, the way ideas are structured and conveyed are at times confusing, and many sentences lack descriptive accuracy. The results are interesting in the way that clinico-pathologic prognosticator of recurrence correlated with BRAF positivity; whereas recurrence rate itself did not. The authors are requested to kindly consider the following major remarks:

1. The article requires revision by a native speaker or an editorial service provider.

➔ The article was revised by a German interpreter for English

2. Disease recurrence reflects behavioral aggressiveness of cancer. Therefore, this makes the title in its current form inaccurate. replace "tumor aggressiveness" with "aggressive clinico-pathologic features". In the title as well substitute 10 years for 10-year …

➔ Thank you very much for this comment. We changed the title accordingly

3. The abstract is poorly written. The outcomes of interest are too generic; the clinico-pathologic features of cancer need to be detailed, as these are the basis for the ATA-risk stratification system (capsular invasion, lymphovascular invasion, aggressive histologic variants, extrathyroidal extension, …). The same thing should be applied in the main text.

➔ You are right of course. We changed the abstract accordingly

4. Significant differences in the abstract should be supplemented with p-values. The presence of significant p-values in the abstract increase readership of the article.

➔ We changed the abstract accordingly

5. An informed consent is typically waived in retrospective studies. There is no need to describe the process of how the study cohort was obtained. Figure 1 should be omitted. A study cohort of 285 could have been used instead of 186.

➔ Here we actually have a different view, perhaps because of German regulations. The BRAF testing was not part of the usual diagnostics in our clinic. As this meant that the processing and testing of the resected, genetically

traceable specimen went beyond the use agreed with the patient as part of his treatment, we had to obtain a declaration of consent from the patients for BRAF testing. We added the following sentence to clear this up: Written consent was needed, because BRAF analysis exceeded the typical diagnostics, and because of handling specimen containing genetic material.

6. Prior to 2017, tumor registries implemented the 7th edition of the AJCC/ TNM staging system. This study appropriately implements the 8th edition. However, this is not demonstrated in the methodology. It would also be worthwhile to demonstrate the influence of the new edition on down-staging cases (provide a brief comparison), and highlight any conclusions in the context of BRAF mutation positivity.

➔ The aim of this study was not the comparison of the 7th and 8th different TNM-editions. Therefore, the used TNM classification was adapted to the actual edition. Nevertheless, it must be admitted that a comparison of the TNM editions would be interesting, but would go too far regarding our research question in our opinion.

7. Several subheadings in table 1 lack p- values.

➔ Yes. But this is intended. We have included the relevant variables to fully describe our patient population. However, since it was irrelevant to our research question whether the groups differed with respect to these variables, no tests were performed for these variables in order to keep the number of tests low. The more statistical tests are performed, the higher is the probability of making a 1st type error. Therefore, we wanted to keep the number of tests low, although of course we also corrected for multiple testing using the Benjamini-Hochberg method. We have added the following sentences to the statistics section to make this clear: No tests were performed for variables describing patient characteristics irrelevant to our research question in order to keep the number of tests low. We corrected for multiple testing using the Benjamini-Hochberg method.

8. The authors do not describe their policy in dealing with the central nodal compartment (prophylactic vs therapeutic). Furthermore, the sentences provided in the abstract and the results are confusing. Kindly amend bearing in mind the following: in the latest edition of the AJCC/ TNM staging system N1a and N1b are similar in the way they influence staging. Furthermore, nodal prognosticators that increase the likelihood of recurrence have been well demonstrated in the literature (Randolph et al. 2012 Thyroid).

➔ This information is added (line 175 - 181)

Minor considerations:

1. BRAF V600E mutation should be written in this way; not BRAF V600E.

➔ We corrected it accordingly

2. In “Key words” use BRAF V600E mutation instead of BRAF mutation. Also, add “Papillary thyroid cancer.

➔ We added this.

Reviewer B:

This is interesting work but there are some issues that need to be addressed and further clarified.

1) Please be careful about citing old references. The rule of thumb is to go back at most five to six years. Roughly 85% of all cited works should be less than five years old. However, in this article, most of the references are too old to cite.

➔ Thank you very much for this comment; we update the literature with the following references:

2) On page 3, “With 60-80% of cases, the papillary thyroid carcinoma is the most common subtype” The figures (percentages) are too low to reflect the latest statistics.

➔ We changed the respective sentence accordingly: The incidence of thyroid carcinoma has increased worldwide in recent years, with papillary thyroid carcinoma (PTC) representing the highest proportion (1, 2).

3) In “extracapsular growth”, extracapsular should be changed into “extrathyroidal”. Does it mean “gross extrathyroidal extension”?

➔ We changed the term accordingly

4) The results of multivariate logistic regression analysis should be shown in the table.

➔ We added the respective data as table 3

5) To address the clinical outcomes of PTC patients with BRAF mutation, the analysis of disease-free survival should be performed.

➔ We basically agree with this. However, this is not possible due to the retrospective nature of the study. We do not have any information on whether someone did not respond to our letter because he/she died, or simply because he/she had no interest in contact. This increases the uncertainty of the analysis

to such an extent that it would be essentially meaningless.

6) Abbreviations should be defined at first mention. Please check the abbreviations throughout the manuscript. Ex) In line 198, papillary thyroid carcinoma (PTC)

➔ Thank you. We corrected this oversight accordingly.

7) In this study, complication rates, recurrent laryngeal nerve injury and hypocalcemia seem higher than expected. Please discuss the reason.

➔ Again, this is due to the retrospective character of this study. We added the following paragraph at the results section on tumor therapy: It should be mentioned that due to the retrospective character of this study a differentiation between persistent and transient laryngeal nerve palsy and an information to postoperative hypoparathyroidism due to lack of routinely determined parathormone values cannot be made.

8) In table 2, please convert the symbols into text.

➔ Here we are of a different opinion, as we find this type of presentation very clear. We would like to keep it that way, at least if the other reviewers and/or the editor agree. If not, we would of course be happy to change that.

9) Editing of the English language and style is strongly required.

➔ The article was revised by a German interpreter for English

10) The manuscript is not formatted correctly. The whole manuscript is written in a way not to be scientific enough.

➔ Due to comments of reviewer A, we changed the abstract of the manuscript, since we agree, that this was indeed not scientific enough. However, we are unsure about the other parts. But perhaps this problem has also been solved by the fact that we have now adhered very strictly to the STROBE checklist?

Reviewer C:

The authors reported clinicopathological significance of BRAF V600E mutation in papillary thyroid carcinoma (PTC). While the overall significance of BRAF mutation is still controversial, this study provides precious evidence regarding aggressiveness and recurrence risk related to BRAF mutation based on 186 cases with 5-year follow up data. To provide further clinically meaningful information, the authors are encouraged to update the following points.

1. Previous reports showed that Hashimoto's thyroiditis was negatively associated with BRAF mutation. The authors should provide autoantibody information of the cases.

➔ This is not possible, due to the retrospective character of the study. Furthermore, the autoantibodies were not determined routinely in the preoperative diagnostic in all cases.

2. In this study, the vast majority of the cases were treated by total thyroidectomy followed by RAI. In the world-wide context of de-escalation in the surgical management for PTC, many early cases have been treated by lobectomy, but not by total thyroidectomy. Given that BRAF-positive PTC can have multifocal characteristics reported in this study, theoretically, BRAF-positive cases can have stronger indication for total thyroidectomy rather than lobectomy. The authors are encouraged to discuss potential impact of BRAF mutation on extent of thyroidectomy.

➔ An additional section at the end of the discussion has been added.