

Peer Review File

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Reviewer A:

The present paper for review attempted to evaluate the potential association between multifocality and survival of patients with thyroid cancer and found multifocality to be a surprisingly protective factor using data from SEER database. I have the following questions:

Comment 1: it appears the authors are unfamiliar with the thyroid pathology as it is not an exocrine gland, thus the malignancies arising from this organ cannot be adenocarcinoma since these cancers do not arise from glandular epithelial cells

Response 1:

Thank you for pointing out this critical issue. The thyroid is indeed an endocrine gland, and its malignancies, such as papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), originate from follicular epithelial cells. However, based on the American Cancer Society, these cancers are also called papillary adenocarcinoma and follicular adenocarcinoma (ref: [https://www.cancer.org/cancer/types/thyroid-cancer/about/what-is-thyroid-cancer.html#:~:text=Papillary%20thyroid%20cancer%20\(also%20called,lymph%20nodes%20in%20the%20neck.\)](https://www.cancer.org/cancer/types/thyroid-cancer/about/what-is-thyroid-cancer.html#:~:text=Papillary%20thyroid%20cancer%20(also%20called,lymph%20nodes%20in%20the%20neck.))) Such identification is also applied to the SEER database which is the nationwide cancer registration in USA. Detailed classification of the “thyroid adenocarcinoma” is not provided in the SEER database.

To clarify the confusion, we will clearly modify the definition of "thyroid adenocarcinoma" in the manuscript to "differentiated thyroid carcinoma or thyroid carcinoma," which accurately encompasses PTC and FTC.

Changes in the text: throughout the manuscript.

Comment 2: It is not clear why the specific interest in multifocality. As it reads now, I venture to guess that the authors used the SEER data as a hypothesis finding tool, which is often done, and stumbled upon this finding.

Response 2:

The focus on multifocality stems from its clinical relevance as a prognostic factor in thyroid cancer. Multifocality has been associated with an increased risk of lymph node invasion and recurrence, yet its impact on cancer-specific survival (CSS) and overall survival (OS) remains unclear. Furthermore, there is limited evidence on whether this relationship varies across ethnic groups, which has motivated us to explore this question. The SEER database was used not as a purely hypothesis-generating tool but as a resource to test a pre-specified hypothesis regarding

the prognostic impact of multifocality. We will revise the introduction to better articulate the clinical rationale for studying multifocality and its potential implications for ethnicity-specific patient management.

Changes in the text: Page 3 Line 40-43

Comment 3: The ICD codes do not correlate with thyroid malignancies. Would advise checking the included patient population. Also, would advise focusing on tumors of follicular origin such as PTC and FTC due to their significant differences.

Response 3:

We appreciate this important comment. The ICD-O-3 codes are used for patient selection. In our analysis, we included codes 8140–8389 together with an important ICD-O-3 behavior code (“Malignant” in SEER database) to capture thyroid malignancies. We have clarified this in our methodology section.

Changes in the text: Page 3 Line 53-54

Comment 4: If the event numbers are low, why separate the cohorts instead of analyzing race/ethnicity as a variable? May increase the power. Would advise consulting your stat team regarding validity

Response 4:

Thank you for your statistical suggestion. Our primary reason for separating cohorts by race/ethnicity was to investigate potential differences in the prognostic impact of multifocality across populations given the different genetic backgrounds. We have added the combined analyses to the results section. Briefly, the results remain significant (modified in the results section). The statistical section was also reviewed by the statistical team from the University of Hong Kong (our collaborative group) accordingly.

Changes in the text: Table 2 and Page 4 Line 82-99

Comment 5: For thyroid cancer of follicular origin, it is unclear what the tumor differentiation means. De-differentiated PTCs behave more like anaplastic cancer and may not be appropriate to be analyzed together with more indolent variants.

Response 5:

In our current analysis, tumor differentiation was included as a covariate, categorized into well-differentiated, moderately differentiated, and poorly differentiated groups. This is a parameter provided by the database. We re-analyzed the data to exclude de-differentiated variants to ensure accurate interpretation. The new results are shown in Tables and results section.

Changes in the text: Table 3, Table 4 and Page 4 Line 82-99, Page 5 Line 101-105

Comment 6: The method section should report rates of missing data and how these were

handled as it can influence the results significantly and thus the interpretation of data.

Response 6:

We acknowledge that missing data can significantly influence results. In our study, tumor stage had higher rates of missingness. Although imputation is an optional way to provide simulation results for the missing data, it is not necessary for the current research. For example, treatment information was completed, and it was highly correlated with the tumor stages (patients with higher tumor stage would be more likely to receive combination treatment). A retrospective study is currently being conducted by our team to further investigate this topic. We have mentioned this statement in our discussion section.

Changes in the text: Page 6 Line 154-165

Comment 7: aside from the variables reported, tumor types, lymphovascular invasion, macroscopic extracapsular extension, and LN positivity also influence survival. Although LN is implied in staging.

Response 7:

Thank you for your insightful comments. We agree that variables such as lymphovascular invasion, macroscopic extracapsular extension, and lymph node positivity are significant predictors of survival. Unfortunately, the SEER database does not provide granular details on these variables. While lymph node status is partially addressed through staging, we have explicitly acknowledged the absence of these factors as a limitation in our discussion.

Changes in the text: Page 6 Line 162-165

Comment 8: the 2nd paragraph of the discussion is very confusing. The studies were cited and critiqued without much context.

Response 8:

We have rephrased this paragraph and cited more informative literature to make it clearer.

Changes in the text: Page 5 Line 122-139

Comment 9: there are many limitations to this study. Retrospective nature, using large database without granular details. Missing data specifically pertinent to thyroid cancers such as radiation exposure, BRAF status, etc

Response 9:

These limitations were well noted and mentioned in the discussion section. Given the setting of the SEER database, we are unable to cover every risk factors and prognostic factors in the present study.

Changes in the text: Page 5 Line 154-165

Reviewer B:

The authors analyzed SEER data from 2000-2016 for thyroid cancer and studied CSS and OS with respect to multifocal disease. Their conclusion is that multifocal cancer is associated with better CSS and OS than solitary cancer in Non-Hispanic White patients.

Comment 1: Adenocarcinoma is mentioned. I presume that authors studied papillary thyroid cancer?

Response 1:

Thank you for pointing out the issue with terminology. We agree that the majority of cases studied are papillary thyroid carcinoma (PTC), along with some follicular thyroid carcinoma (FTC). To align with standard terminology, To clarify the confusion, we have clearly modified the definition of "thyroid adenocarcinoma" in the manuscript to "differentiated thyroid carcinoma or thyroid carcinoma," which accurately encompasses PTC and FTC.

Changes in the text: throughout the manuscript.

Comment 2: Multiple primary cancer were excluded: by what criteria? What is the difference with multifocal cancer in the SEER database?

Response 2:

We excluded cases of multiple primary cancers based on the definition: patients with two or more distinct primary malignancies diagnosed at different sites or times. This exclusion ensures that our analysis focused solely on primary thyroid cancers without confounding influences from other malignancies. In short, we want to make sure that thyroid cancer is the only cancer that the patients have.

Changes in the text: Not applicable.

Comment 3: Is tumor diameter taken into account?

Response 3:

Tumor diameter is a critical factor in thyroid cancer prognosis and is included in the SEER database. In our study, tumor diameter was used as part of the staging variables which was already evaluated in the analyses. However, its specific contribution to outcomes was not separately provided by the database.

Changes in the text: Not applicable.

Comment 4: Chronic lymphocytic thyroiditis is not mentioned: do the authors have those data? If not, please discuss, see reference 3 below.

Response 4:

Thank you for raising this point. Unfortunately, the SEER database does not provide

information on coexisting chronic lymphocytic thyroiditis (CLT). However, the relationship between CLT and thyroid cancer, particularly multifocal PTC, is well-documented in the literature. As suggested, we have discussed this potential association and its implications, referencing relevant studies.

Changes in the text: Page 5 Line 145-152

Comment 5: The authors discuss their data but do not come up with a reasonable explanation. Only hereditary factors are mentioned such as MEN2A (RET) which seems not relevant in the context of the study (PTC).

Response 5:

We appreciate this feedback. We acknowledge that these are more relevant to medullary thyroid carcinoma (MTC) rather than PTC. To improve the discussion, we focused on other potential explanations for the observed association between multifocality and better survival in PTC, including genetics, tumor biology and microenvironmental factors. We have also integrated findings from suggested references, such as Lin et al. (2008) and Bansal et al. (2013), to provide a more comprehensive perspective.

Changes in the text: Page 5 Line 145-152

Comment 6: Please also discuss other reliable literature which seems to contradict the current results.

Response 6:

Thanks for your suggestions. We have added relevant discussions.

Changes in the text: Page Line 126-128