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Reviewer A

The authors propose a nomogram model to predict the overall survival of patients with conjunctival melanoma. They have used public data derived from the Surveillance, Epidemiology, and End Results (SEER) database of patients diagnosed with conjunctival melanoma from 2000 to 2019. The study included 272 patients. A nomogram was developed using age and TNM stage as variables. Major and minor comments can be made.

Major comments

Comment 1: Generally, the authors have validated the 6th edition of the AJCC clinical TNM staging system for conjunctival melanoma. However, the AJCC TNM staging system has by now been adapted and has evolved to the 8th edition, making the conclusions of less relevance to be clinically applied in relation to newly diagnosed patients. It is essential to reassess the AJCC TNM staging data and update these to the current edition. Especially since multiple publications have validated the 8th edition AJCC TNM staging for conjunctival melanoma since publication: *Am J Surg Pathol* (2019) 43(12):1701–10.; *JAMA Ophthalmol* (2019) 137(8):905–11.; *Br J Ophthalmol* (2020) 105(10):1358–64.; *Ophthalmology* (2022)129(7):771-780.

Reply 1: Many thanks for this important comment. The AJCC TNM staging of conjunctival melanoma has been updated to the 8th edition. While the N and M stages remain unchanged, the T staging has been modified.

We attempted to reclassify cases from the SEER database that were staged according to the 6th edition T staging to the 8th edition T staging, in accordance with the reviewer's valuable suggestion. However, the SEER database lacks precise T sub-stages (e.g., T3a, b, c), making it impossible to reassess the 6th edition T staging to the 8th edition T staging.

If we directly use the 8th edition TNM staging data already in the SEER database to build a model, the number of patients is not sufficient (less than 50). We are actively collecting such patients and will update it in the future.

We acknowledge the limitations of relying on the 6th edition TNM staging system. However, it's worth noting that the N and M stages from the 6th edition remain consistent with the 8th edition. Of the four factors used to construct the nomogram, three are not affected by the TNM staging updates (N stage, M stage, and age). Although T staging has changed, it still follows the trend of local invasion ranging from T1 to T4 lesions. Given the limited number of cases for this disease, the use of the 6th edition TNM staging system, while having its limitations, still holds significance.

Comment 2: Results, page 5, lines 103-106: age was determined as a significant prognostic factor. However, it is not explained how the cut-off at 65 was obtained. This is an essential issue since it is the only extra factor introduced apart from the well-established AJCC TNM factors.

Reply 2: Many thanks to the reviewer for pointing this out. We apologize for the oversight. We set the cutoff at 65 according to a previous study. The authors initially divided conjunctival melanoma patients into two groups based on age, specifically those aged over 65 and those under 65. We adopted this age grouping during the initial model design, and through univariate analysis, we found that the distinction between the over-65 and under-65 age groups was a significant prognostic factor. This reference has been added in the article. Thank you again for your valuable comment.

Changes in the text: We have added the source for the cut-off at 65 to the study and added the

reference (see Page 4, line 74-75).

Comment 3: Results, page 6, lines 113-116: rather than using an independent database the authors have chosen a less desirable statistic approach using the data of the discovery cohort to validate their findings. It would be advisable to either use a different cohort of their own institute or seek collaboration with a third party to perform such validation.

Reply 3: Many thanks to the reviewer for pointing this out. The data for external validation is currently being collected, but due to the low incidence rate of conjunctival melanoma, we have only collected five cases so far. This number is currently too limited to validate the nomogram and we hope to accomplish this important task in the future.

Minor comments

Comment 4: Abstract, page 2, line 25: “CM exhibits obvious tumor heterogeneity” it is not clear why this is mentioned here. Please delete.

Reply 4: Thanks for your suggestion. We have deleted the sentence.

Changes in the text: we have modified our text as advised (see Page 2, line 25).

Comment 5: Abstract, page 2, lines 25-26: “Currently, there is no reliable method to predict the overall survival of patients with CM.” this is not true, the AJCC TNM has been validated in several independent cohorts for this purpose.

Reply 5: Thank you for pointing this out. We have removed this sentence and rewritten the background section of the abstract.

Changes in the text: we have modified our text as advised (see Page 2, lines 25-26).

Comment 6: Introduction, page 3, lines 43-47: the references provided are rather old or secondary sources. Moreover reference 2 seems inappropriate.

Reply6: Thank you for pointing this out. We have updated the references and replaced the inappropriate reference.

Changes in the text: we have updated the references as advised (see Page 3, lines 43-47).

Comment 7: Introduction, page 3, line 47: “CM patients have heterogeneity and local invasion and diffusion tendency” it is not clear what the authors mean to convey here. Please reformulate.

Reply 7: Thank you for pointing this out. We have deleted the sentence.

Changes in the text: We have deleted the sentence as advised. (see Page 3, line 47).

Comment 8: Discussion, page 6, line 125: please remove the word “but”

Reply8: Thanks for your suggestion. We have removed the word “but”.

Changes in the text: We have removed the word as advised (see page 6, line 128).

Comment 9: Discussion, page 6, line 127: “So far, no effective prediction model exists for the prognosis of CM” please remove this sentence, see comments above.

Reply 9: Thanks for your suggestion. We have removed the sentence.

Changes in the text: We have removed the word as advised (see page 6, line 131).

Reviewer B

Comment 1: Overall I think the manuscript would benefit from editing by an English native speaker or translator.

(see page 3 line 50 uncontrolled disease metastasis, page 4 line 53 some literatures, page 4 line 67

survival time fewer than one month for example and past en present tenses used randomly).

Reply 1: Thank you for your important suggestions. We have checked the grammar and the correct use of English in this manuscript.

Changes in the text: We have modified our text as advised (see Page 3 line 50, Page 4 line 53, Page 4 line 67).

Comment 2: Page 5 line 97 “Most are white” is not very precise. Although this subject is surrounded by sensitivities a controversy in melanoma and ocular melanoma literature ethnicity or ancestry are of significance. Could you be more precise? This remark also raises the question of the origin of the SEER data and on the way data on ethnicity or ancestry where gathered. Could you elaborate on that?

Reply 2: Thank you for your suggestion. We have modified our text about the race data from SEER database.

Changes in the text: we have modified our text (see Page 5, lines 98-100).

Comment 3: Page 5 Patient characteristics Could you comment on duration of follow up?

Reply 3: Thank you for your suggestion, we have added the follow up to our text.

Changes in the text: We have modified our text (see page 5, lines 95-96)

Comment 4: Page 6 line 125-127 You state that there surgery is an effective treatment. There is massive proof in literature that ancillary treatment with irradiation or chemo eyedrops reduces the chances of local recurrence. Please rephrase.

Reply 4: Thank you for your suggestion. We have rephrased our text and added the references.

Changes in the text: We have rephrased our text (see Page 6, lines 129-130).

Comment 5: Page 6 line 26 you state that prognosis is poor for conjunctival melanoma patients with metastasis. Current treatment modalities available for skin melanoma are often available for these patients aswell now and have changed their chances drastically over the last couple of years. It also makes mutation status of the tumour of importance. You mention treatment options and mutations in your discussion page 8 line 168 but not in relation to the years studied. The cohort studied spans the years 2000 to 2019 so I think this should be mentioned.

Reply 5: Thank you for your suggestion. We have modified our text.

Changes in the text: we have modified our text as advised (see Page 8, lines 175-178).

Comment 6: Page 6 line 133 by eye melanoma do you mean uveal melanoma?

Reply 6: Thank you for pointing this out. We apologize for this ambiguous expression. Eye melanoma here refers to both uveal melanoma and conjunctival melanoma. We have modified our text.

Changes in the text: We have modified our text (see Page 6, line 136)

Comment 7: On page 6 line 118 it is explained that the validation of the nomogram was done by performing bootstrap resampling. On page 7 line 161 you state the nomogram is a robust tool. Also

in the abstract page 2 line 38 you stat that OS can accurately be predicted and I wonder if it should not be externally validated to make a statement this bold.

Reply 7: Many thanks for this important comment. We apologize for this incorrect statement. We have modified our text.

Changes in the text: we have modified our text (see Page 7, line 160), and deleted the word “accurately” (see Page 2 line 38 and Page 8 line 193).