Peer Review File

Article information: https://dx.doi.org/10.21037/cco-23-16

Reviewer A

Comment 1: Methodology: please report a time frame of the conducted search (from 2000 to 11/2022). Please also include inclusion and exclusion criteria here (export from table 1).

Reply 1: As suggested, the timeframe and the inclusion and exclusion criteria have now been added to the main body of the text (see Methodology, page 7).

Changes in the text:

"The time frame of the conducted search was from 01/01/2000 to 01/11/2022. All studies included were peer-reviewed and available in the English language."

Comment 2: Results: even if this is a narrative review, please report how many studies were found and how many were included in the review (flow-chart).

Reply 2: Given that this is indeed a narrative review and not a systematic review, the authors believe that a flowchart (e.g. PRISMA flowchart) is not appropriate nor likely to be informative, as we did not code the reasons for exclusion for each paper. However, we have now indicated in the text the number of unique titles that we identified (n = 444), of which 108 specific titles focused on MMHN epidemiology (n = 14), staging (n = 28), and treatment (n = 66) were included (see Results, page 8).

Changes in text:

"From the literature review, 444 unique titles were identified, of which 108 specific titles focused on MMHN epidemiology (n = 14), staging (n = 28), and treatment (n = 66) were included. A brief summary of the included studies is provided in Supplementary Table 1."

Comment 3: Also, a short summary (in a table) of the included studies should be provided (i.e.: Author, year, type of study, patients, methods, main findings). Reviews should be excluded (as this article should contain "new" information) and results should be based on clinical studies (cross-sectional, observational, case-control…).

Reply 3: As suggested by the reviewer, a table including a brief summary of the included studies has been prepared. Given its length, it has been included as a Supplementary Table.

Changes in text:

See Supplementary Table 1, page 36.

Comment 4: Epidemiology: you state that MMHN does not share etiological factors with cutaneous melanoma. Which etiological factors of MMHN can be found?

Reply 4: As suggested by the reviewer, potential etiological factors for MMHN including smoking, and ingested/inhaled carcinogens have now been mentioned in the review (see Epidemiology, page 8).

Changes in the text:

Whereas for cutaneous melanomas exposure to UV light is a well-established risk factor, aetiological factors for mucosal melanomas remain largely undefined. Although epidemiological studies currently suggest that smoking, ill-fitting dentures, and ingested/inhaled carcinogens including tobacco and formaldehyde are potential causative factors for MMHN, strong evidence for these correlations is lacking(15, 19, 20).

Comment 5: Management: please provide literature on the extent of clear surgical margins. Rest is very good.

Reply 5: The dearth of studies which report surgical margins beyond 'clear' or 'positive' margin status in MMHN (as opposed to studies of cutaneous melanomas) has now been addressed (see Management, *Surgical resection,* page 15).

Changes in the text:

"Despite substantial and ongoing research seeking to establish the optimal width of excision margins for cutaneous melanomas(61), there remains a dearth of studies which report surgical margins beyond clear or positive margin status for MMHN(59). As for most head and neck cancers, the NCCN currently recommends a 1.5-2.0 cm surgical margin for MMHN (62)."

Comment 6: The only recommendation I suggest to the authors is to broaden the introduction by clarifying and stressing how the data (epidemiology, staging, and therapy) on mucosal melanomas are difficult to interpret since the works often analyze mixed cases with mucosal and cutaneous melanomas, mucosal melanomas of different sites (however to be considered as different diseases) but also because the same mucosal melanomas of the H&N region would seem to have many differences depending on the site (sinonasal, palate, etc.). Even if the latter are grouped together, they are to be considered for all intents and purposes as different diseases and numerous evidences suggest that they also differ from a pathogenetic and molecular point of view. Below are some references that analyze this aspect and that I suggest to add to the article (doi: 10.3390/jcm10030478; doi: 10.1038/s41379-022-01122-7, doi: 10.1097/PAS.0000000000001166, doi: 10.1097/PAS.0000000000002032).

Reply 6: We thank the reviewer for this suggestion and for the references recommended. As suggested, a paragraph has now been added to address the difficulties in interpretation of data pertaining to MMHN (Introduction, page 6). This paragraph explores how MMHN is often analysed as mixed cases alongside MM of other anatomical sites or with cutaneous melanomas (impeding extraction of data specific to MMHN). It also explains how analysis of MMHN is further complicated by the different pathogenetic backgrounds underlying MM of different subsites (e.g. nasal versus oral cavity).

Changes in text:

"Due mainly to the relative rarity of the disease, mucosal melanoma is poorly understood and data on MMHN remain particularly difficult to interpret. This is because studies investigating MMHN often do not analyse them separately from mucosal melanomas arising at other anatomical sites (including gynaecological, urological, and gastrointestinal tract) or even from cutaneous melanomas, impeding the extraction of data specific to MMHN. Furthermore, mucosal melanomas arising at different subsites even within the head and neck region have been shown to differ from a pathogenetic point of view(11, 12), complicating analyses of the aetiology and mechanisms underlying the natural history of this heterogeneous group of malignancies."

Reviewer B

Comment 1: Please define ECOG/MSS/RFS/HR/ICI upon first use in the Main Text.
Reply: The terms ECOG, MSS, RFS, HR, and ICI have now all been defined upon first use in the Main Text.
Changes in the text:
ECOG – defined in Staging, page 12.
MSS – defined in Staging, page 12.
RFS – defined in Introduction, page 5.
HR – defined in Management, *Radiation therapy,* page 17.
ICI – defined in Staging, page 12.

Comment 2: "Penel et al. reported a 21-fold increased risk of death associated with positive margins, while Lee et al. demonstrated a significantly increased rate of distant metastasis (14%–71%) and decreased OS associated with failure to achieve local control (16, 59, 60)."
There are two articles mentioned in the above sentence, but 3 references were cited. Please confirm.
Reply: Thank you for pointing out this error. Article 16 (López et al.) has now been removed from the text (*Management*, page 14).
Changes in the text:
Penel et al. reported a 21-fold increased risk of death associated with positive margins, while Lee et al. demonstrated a significantly increased rate of distant metastasis (14%–71%) and decreased OS associated with failure to achieve local control (59, 60).

Comment 3: In Table 1, we suggest revising Timeframe to "01/01/2000 to 01/11/2022" to be consistent with the Main Text.
Reply: The timeframe in Table 1 has been revised as suggested.
Changes in the text: Please see Table 1, page 26.

Comment 4: There is another table under Table 2. Please confirm whether it should be included in this article. If yes, please number it as Table 3 and cite it in the Main Text.
Reply: The table under Table 2 has now been numbered as Table 3, and cited in the text.
Changes in the text: Please see Table 3, page 28. Table 3 has also been cited in text on page 10.

Comment 5: Supplementary Table 1: Multiple column headers are not allowed. SurgT/SurgST can not be identified in the table. Please confirm whether they can be removed. CI/LPFS/RFS/IMT/wks/c-KIT/NR should be defined in the explanatory legend. We suggest numbering all the studies as references.

Reply: As suggested by the reviewers, all column headers excluding the first header have now been removed. The abbreviations “SurgT” and “SurgST” have now been removed from the abbreviations list, and the terms CI, LPFS, IMT, wks, c-KITi, and NR have all now been defined in the explanatory legend. Finally, all studies in the table have now been referenced.

Changes in the text: Please see Supplementary Table 1, page 42.