Peer Review File

Reviewer A

The authors aimed to establish the risk factors for distant metastasis (DM) derived from oral cancer and to establish a protocol for early DM detection. The study is interesting, but the authors must clarify in the Introduction its originality in comparison to other studies cited in the literature, as was done in Discussion.

General point:

A STROBE checklist must be applied in the manuscript. Some sections of STROBE were not clearly presented in the text.

   - Authors reviewed the paper and the STROBE checklist was applied to the paper

MM

Details about inclusion and exclusion criteria must be inserted.

   - A paragraph of inclusion and exclusion criteria was inserted by the author

Results

A flowchart illustrating the protocol suggested by the authors for early DM detection must be inserted. The risk factors associated to DM must be shown in the figure, as well as the image exams and the patient management before and after the surgery and adjuvant therapies.

   - We agree with the reviewer suggestion and a flowchart illustrating the protocol for the early detection of distant metastasis was added to the paper

Discussion

A conclusion must be inserted at the end of the Discussion section.

   - A conclusion section was added to the paper

References

The references must be updated. Some studies were published in 2020 and 2021.

   - References were updated

Reviewer B

This manuscript is about risk factors for distant metastases in oral cancer.

The authors focusses on clinical, radiological and pathological risk factors and emphasizes that pretreatment factors are important for treatment planning.

Why do they not use number of lymph node metastases, one of the most important risk factors? Same for low jugular lymph node metastasis (Level IV) and level V.

- An explication of why we did not use the number of lymph node metastasis and its location was added to the paper from line 184 to 191.

"One of the weak points of this study is represented by the fact that authors did not analyze the exact number and the location of lymph node metastases. These could represent extremely important variables for the developing of distant metastasis as suggested by Peters et al (21). However, these factors were not analyzed in our study because neck dissection specimen was not specifically marked and oriented in some of the patients included in this study. It could be very useful to analyze these variables in future studies to facilitate a better understanding of the impact of these factors in the developing of distant metastasis."

Title. I do not think that the manuscript covers 'strategy for early detection' good enough to put in the title.

- The title of the paper was modified to "Risk factors for distant metastasis in oral cancer and strategy preoperative detection."

Base of tongue is part of oropharynx. Several times the authors describe it like it is part of oral cavity. E.g. line 40, line 55). Please correct.

- Authors agree with the reviewer and modified this item

Please use PET and CT with capitals.

- PET and CT were corrected and used with capital

Line 60. Why is 5th edition originally used. It is from 1997 and inclusion is from 2009.

The authors uses tumor thickness and categorize like in TNM. Is it thickness or depth of invasion? Please discuss why used and the difference.

- An explication of why authors used the 5th edition of TNM was added to the paper from line 49 to 51.

"The clinical and pathological stage of the primary tumor was initially determined by using the recommendations of the fifth edition of the UICC TNM classification of malignant tumors because it was the classification commonly used by the pathology department of our institution at when the patients analyzed in this study underwent surgery"

- The differences between tumor thickness and depth of invasion and the reason for using TT for this analysis was added from line 191 to 198.

"Another bias of this study could be represented by the fact that only TT, and not depth of invasion (DOI), is analyzed to predict the probability of developing distant metastasis. TT considers the depth diameter of each tumor. However, DOI consider the is measured from the basement membrane of the epithelium from which the tumor

Please do not use 3 decimal places like in 11.833 years

- Authors corrected this item

Line 163/4. Indeed if patients present during follow-up with distant metastases it is likely that they were already present during screening, but below detection limit. This is particularly true if there is locoregional control. Please add.

- This suggestion was added to the paper

In discussion.

The authors suggest that chest CT is more cost-effective than PET. It has been shown that addition of PET is cost effective (Uyl-de Groot Cet al. J Nucl Med. 2010 Feb;51(2):176-82)

Other studies on risk factors should also be discussed. Peters et al. Oral Oncol. 2015 Mar;51(3):267-71. van der Kamp et al. Eur Arch Otorhinolaryngol. 2021 Jan;278(1):181-190.

- These references was added to the paper