

Peer Review File

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Reviewer Comments

1)The reviewer's comment: The background needs to indicate the clinical needs for this review and the clinical questions to be addressed or reviewed in this study.

The authors' answer: Thank you very much for your comment. We appreciate your professional comments and advices. According to your suggestion, we have revised the manuscript as follows.

“Background and Objective: Penile cancer is a kind of urogenital system tumour that seriously affects patients. The status of lymph node metastasis is closely related to the treatment and survival of patients. Accurately predicting lymph node metastasis has been the focus of many clinicians. In this review, we hoped that it can help to systematically understand the influencing factors of lymph node metastasis in clinical practice.”

2)The reviewer's comment: The methods need to briefly describe the key words for literature search and how the data from the literature were analyzed. The results need to list the identified prognostic factors including biomarkers, as well as the predictors in the predictive models and the accuracy of the predictive models. The conclusion needs to have comments on the prognostic performance of the prognostic biomarkers and factors and the predictive accuracy of existing predictive models, as well as comments for the future work in need to improve the prediction of lymph node metastasis.

The authors' answer: Thank you very much for your kindly advises. We all quite agree with your standpoint and proposal. According to your suggestion, we have revised the manuscript.

“Methods: In this study, we searched PubMed select English-language articles during wenty years (1992/01/01–2022/10/01). The following MeSH term was searched in [Title/Abstract]: penile cancer, penile tumor, penile neoplasm, penile squamous cell carcinoma, prognostic factors, prognosis, lymphatic metastases, lymph node

metastasis, lymph node metastases.”

3)The reviewer’s comment: Second, in the introduction of this review, the authors need to describe the methods for detecting the lymph node metastasis in PSCC and what the limitations and difficulties of the gold method are. It is also necessary to have comments on the clinical importance of the early prediction of lymph node metastasis and the prognostic factors including biomarkers.

The authors’ answer: Thank you very much for your comment. We appreciate your professional comments and advices. According to your suggestion, we have revised manuscript and added some information in the revised manuscript as follows.

“Therefore, the timely and accurate prediction of patients' LNM status can significantly reduce overtreatment, and promote active treatment to improve patient survival(9-11). However, different prediction factors have different prediction values. From initial single clinical pathological factors, haematological indices, immunohistochemical indices, and molecular indices to multifactor joint prediction models, there is still no consensus on the criteria for predicting lymph node metastasis.”

4)The reviewer’s comment: Third, in the main text of the review, please have a table to summarize these imaging, clinical, and biological prognostic markers with their prognostic effects as indicated by their OR/HR values and P values. The authors need to review the predictive accuracy of the prediction models and the predictors used.

The authors’ answer: Thank you for your comment and advises. We all quite agree with your standpoint and proposal. Due to the lack of randomized clinical research and large sample data validation, the level of evidence in the literature included in this paper is low. However, the literature still comprehensively analyzes various indicators and provides a lot of literature support. The value of each study is different, which is not suitable for summary and the predictive accuracy of the prediction models and the predictors used in table 4. We decide to maintain the original text after discussed again with each other and careful consideration.

Thank you for your comment again.

5) The reviewer's comment: We suggest that the authors add a separate paragraph about "Methods" after "Introduction" in the text, including the date of search, timeframe, databases, search terms, inclusion and exclusion criteria, and selection process.

The authors' answer: Thank you very much for your comment. We appreciate your professional comments and advices. According to your suggestion, we have revised manuscript and added some information in the revised manuscript as follows:

“At present, clinicopathological factors, such as the staging and grading of the primary lesion, are still important factors for predicting LNM. These factors are also important components of prediction models, especially nomograms. To date, the exploration of prediction models for LNM has mainly focused on clinicopathological factors or immunohistochemical factors. There is still no unified prediction model, and the prediction value of current models still lacks clinical confirmation in large samples. In addition, because there are many factors included in these prediction models, they are still difficult to evaluate. These deficiencies limit their clinical application. The exploration of noninvasive haematological indicators is one of the important research directions for future preoperative research. The use of single or combined haematological indicators can achieve an accurate prediction before the treatment of the primary tumour and surgery, which will greatly improve the treatment accuracy of patients and facilitate the rational use of medical resources. At present, the molecular indicators of penile cancer are in the preliminary exploration stage. With increasing cell line construction and molecular mechanism research, molecular indicators will also be potential molecular indicators, but their value still needs further clinical confirmation.”

Again, we really appreciate your detailed and useful comments and suggestions.