Peer Review File

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Reviewer A

This is an excellent review of staging, surgical options, and chemotherapy by a renowned expert in one of the countries with the highest incidences of penile cancer. Although the content is appropriate for the title, it does not match the objective in lines 74-76 where the manuscript states "The objective of this review is to search the current literature for the best treatment options for patients undergoing lymphadenectomy with a diagnosis of positive lymph nodes."

Reply 1

First, I would like to thank the reviewer for the opportunity to respond to criticism that helped improve this review.I changed to: The objective of this review is to search the current literature for the best treatment options for patients undergoing lymphadenectomy with advanced inguinal lymph node disease.

The authors have ignored the growing literature on the role of radiotherapy in the curative management of squamous cell cancer. Granted, the majority of this literature involves squamous cell cancer of other sites, such as the vulva, anal canal, head and neck, and cervix, but there is growing experience in penile cancer, as well. The oft-cited EAU guidelines are 5 years old and the updated version will be available in a few months and will reflect this change in approach.

The authors make a plea for cooperative international trials, but do not cite InPACT, which is accruing well and will provide level 1 evidence on how to best combine surgery, radiotherapy, and chemotherapy in management of node positive penile cancer.

Reply 2

I included the topic 3.6.3 Adjuvant concurrent radiotherapy and chemotherapy

Although chemoradiation is used in the initial treatment of patients with locally advanced squamous cell carcinoma of the head and neck, anal canal and vulva, evidence to support its application in penile cancer is lacking. The lack of studies regarding penile cancer was the basis for the international cooperation to develop InPACT (58): the International Penile Advanced Cancer Trial in 2017 in order to prospectively determine the potential benefits of chemotherapy or chemoradiation following lymph node dissection in patients with clinical evidence of inguinal lymph node metastases. InPACT is accruing well and will provide level 1 evidence on how to best combine surgery, radiotherapy, and chemotherapy in management of node positive penile cancer.

However, several current studies suggest that adjuvant radiotherapy has a role to play in the treatment of men with pN3 penile squamous cell carcinoma. (59,60,61).
In another study carried out with patients with nodal positivity limited to the inguinal region, adjuvant RT was shown to be superior to chemotherapy (62).

Another study compared patients who received adjuvant radiotherapy plus chemotherapy with patients who received only adjuvant chemotherapy. In conclusion, adjuvant radiotherapy + adjuvant chemotherapy was associated with improved cancer-specific survival in patients with penile cancer who had extracapsular nodal extension after inguinal surgery (63).
Regarding pelvic lymph nodes, inguinopelvic radiotherapy may benefit for regional control in patients with positive pelvic lymph nodes, but this appears to be limited to those without extranodal extension (64).
Furthermore, another study showed an advantage in using adjuvant pelvic radiotherapy to treat patients with penile cancer and positive pelvic lymph nodes. The use of radiotherapy improved survival and decreased recurrence in this population. (65).
However, according to Yuan Z et al. (66), similarly to primary penile lesions, most nodal metastases are genomically radioresistant with significant heterogeneity. According to these authors, optimal therapeutic gain can be achieved by stratifying the combination of clinical-pathological parameters, genomic heterogeneity, and radiation dose prescription based on its genome-based radiosensitivity index.

Specific Comments

Line 36 – should be downstaged, not downgraded

Reply 3
I changed downgraded to downstaged

Line 66 – It is worth mentioning that the route of spread is generally inguinal nodes to pelvic nodes and then distant.

Reply 4
I included: Therefore, the route of spread is usually via the inguinal nodes to pelvic nodes and then to distant sites.

Line 94 – T1a vs T1b is based on lymphovascular invasion, not perineural invasion.

Reply 5
I included: The 8th AJCC-TNM staging system also includes presence of lymphovascular embolization, perineural invasion, and the degree of differentiation into the T1 category, as a prognostic indicator, thus separating T1b from T1a stages.

Line 118 – The authors defined FNAC and then refer to FNAB. I presume this is fine needle aspiration biopsy, but this actually should be FNAC, since fine needles are only used for cytology and not biopsy.

Reply 6
I have defaulted to FNAC

Line 124 – What is PAAF?

Reply 7
I modified to FNAC

Line 219 – The authors state “lymphadenectomy is indicated for all patients”. They need to qualify this since it is not indicated for all patients with penile cancer, but only those with significant risk of lymph node metastases.

Reply 8
I changed to: Immediate lymphadenectomy is therefore indicated for all patients with significant risk of lymph node metastases.

Line 246-271 – Palliative surgery is grossly excessive. The authors should consult publications by J. Tward. Chemoradiation can be very effective in palliation and local regional control.

Reply 9
I included the topic 3.6.3 Adjuvant concurrent radiotherapy and chemotherapy

Line 322 – The author needs to include adjuvant radiotherapy, which is potentially curative as opposed to adjuvant chemotherapy. I would suggest including the following references:
Jaipuria, Urologic Oncology, 2020;
Johnstone, European Urology Focus, 2019;
Ager, BJU International, 2021;
Tang, Urologic Oncology, 2017;
Yuan, Urologic Oncology, 2022;
Bandini, European Urologic Oncology, 2022;
Choo, Minerva Urology and Nephrology, 2020.

Reply 10
I included the topic 3.6.3 Adjuvant concurrent radiotherapy and chemotherapy

Line 388 – Should state when there is a high risk of local recurrence and/or systemic spread, patients may benefit from adjuvant chemotherapy and/or radiotherapy.

Reply 11
I changed to: When there is a high risk of local recurrence and/or systemic spread, patients may benefit from adjuvant chemotherapy and/or radiotherapy.

The manuscript needs a major revision to include radiotherapy, an important modality in managing this disease.

Reply 12
I included the topic 3.6.3 Adjuvant concurrent radiotherapy and chemotherapy

Reviewer B

A really well written review article. With the limited available studies in this topic at present, the authors have done a good compilation and review. We do need to give more importance in this topic, due to aggressiveness of the disease, and I agree with the authors that a conclusion cannot be made regarding adjuvant chemotherapy due to the low patient volume or the limited number of studies

Reply: Thanks to the reviewer for agreeing with what was written in this review.