Peer Review Overview

**Manuscript Title:** Management of lymph node-positive penile cancer: a systematic review

1st Decision letter

**Reference:** EURUROL-D-22-01386

**Title:** Management of lymph node-positive penile cancer: a systematic review

**Journal**: European Urology

**Reviewer #1**

This is a systematic review of lymph-node positive penile cancer done by a large group of authors in a process of development of the 2023 EAU-ASCO guideline. This is a topic with very low high-quality evidence as stated by the authors which makes writing a systematic review quite difficult. The authors should be commended for attempting to provide the best possible evidence to create guidelines uro-oncologists can follow, despite the lack of sufficient evidence.

Comments:

1.Introduction: In a systematic review published in a high-yield urology journal it is important that data regarding the epidemiology and rates of metastasis to lymph nodes are provided. The scope of this disease and specifically of this stage of disease that is being addressed should be discussed and elaborated.

2.Perhaps some data (even in the form of a table) should be given regarding the current and updated disease TNM staging.

3.Results: When dealing with surgery and lymph node dissection in penile cancer I think it would benefit readers to have some data on the possible complications and their rates. More detail should be given on this.

4.Results: More discussion should be given regarding current recommendations regarding when neoadjuvant/adjuvant chemotherapy and radiotherapy should be given in a summarized manner.

5.Discussion: The authors should elaborate more on the implications for clinical practice. What has changed and what should we do going forward? Please provide a summary of changes that this review brings.

6.Discussion: It would be impactful to have a figure/algorithm of proposed management plan for patients with lymph-node metastatic penile cancer to help summarize new findings.

7.Disscussion: As trials in penile cancer are so rare, more details should be given on the InPACT trial and its endpoints.

8.A general grammatical review should be done for this manuscript.

**Reviewer #2**

Well done systematic review on lymph node positive penile cancer by a multinational group of experts in this specific disease space. Methods are sound. Reads well. The last systematic review on this all-inclusive topic was in 2017.

Comments:

1.Title: at first reads well but then a bit ambiguous and I assume purposefully so as it lymph node "positivity" can be interpreted as either clinically positive on imaging or exam, and confirmed by pathology or biopsy proven positive lymph nodes, or clinically suspicious but not necessarily confirmed on pathology. Can authors comment in methods if this was elucidated in their search/review of studies? And if all can agree, perhaps specifying in their title?

2.Figures: Figure 1, please adjust the arrows so it is aligned appropriately to the reasons for exclusion box. Figure 2, it would be helpful to re-label assessment of RCTs as (A) and (C) as this is how it presented in the text of results to be consistent.

3.Tables: why did the authors choose to highlight minimally invasive techniques in Table 1 which in the text follows 6 supplemental tables??? If the results presented in supplemental tables is truly supplemental, perhaps rearranging the sections would help the reader to reorient to what is important.

**Reviewer #3**

Sachdeva, et. al., perform a systematic review on the management of node positive penile cancer as part of an upcoming EAU-ASCO guideline. This group is to be commended for a thorough review of a broad topic.

Comments:

1.One of the a priori confounders was co-existing metastatic disease. The management of M1 penile cancer is not the same as N1 penile cancer, so it is unclear why studies including these patients would be a part of this review.

2.The bulk of patients in this review came from case-series and observational cohort studies. While the authors report a high RoB for the majority of studies, it would be important to also comment on the low quality of evidence. This was briefly mentioned in the limitations section, but could be highlighted in the Discussion section, especially where the authors make recommendations about treatment.

3.The authors could be clearer about what type of nodal staging (clinical or pathologic) is used throughout their manuscript and tables.

4.How were summary statistics estimated for the composite/pooled survival outcomes? Was a meta-analysis performed? This was not described in the method section.

5.It could be informative to include a summary of studies that report the risk of pN+ among patients with cN+ and initial approaches to cN+ disease.

6.Section 3.4.1.2,

a. Were patients of all clinical nodal stages (including cN0) combined for these survival statistics, or are the cumulative survival only reported for patients with pN+ regardless of their clinical staging? cN0 patients with either pN0 or low-volume inguinal metastasis generally have a very good prognosis after ILND, and are not necessarily the same as patients with bulky bilateral lymph nodes. It may not be appropriate to combine all patients into a single survival estimate.

b. The authors could expand on the discussion of immediate ILND vs. delayed ILND at the time of cN+ for patients with cN0 groins.

7.Section 3.4.1.2.4: there is substantial selection bias in which patients are chosen for minimally-invasive LND compared to open LND. I would hesitate to make declarative statements about less saphenous vein sparing and using more "morbid maneuvers" with open LND.

8.Section 3.4.1.3: if there is no survival advantage for N1/N2 disease with NACT compared to immediate ILND, is there one for N3 disease? If so, this would be relevant to highlight.

9.Section 3.4.1.4.2: this section includes patients with inguinal and pelvic nodal disease. This is redundant but also confusing given the section on Management of Pelvic Nodal Disease. I would discuss only adjuvant therapy for inguinal node disease in this section.

10.Section 3.4.2: The authors report that PLND vs no surgery in N2-3 disease has 3-year DSS of 39.6% vs. 39%, but then say that PLND is superior to no PLND for pN2-N3 disease using the same study reference. This is inconsistent and confusing.

11.Tables 2 and 3: the columns of "patient characteristics" and "selection criteria for treatment" seem redundant.

1st Author Response Letter

Response to comments from Editors and Reviewers:

**Reviewer #1**

**This is a systematic review of lymph-node positive penile cancer done by a large group of authors in a process of development of the 2023 EAU-ASCO guideline. This is a topic with very low high-quality evidence as stated by the authors which makes writing a systematic review quite difficult. The authors should be commended for attempting to provide the best possible evidence to create guidelines uro-oncologists can follow, despite the lack of sufficient evidence.**

**Comments:**

**1.Introduction: In a systematic review published in a high-yield urology journal it is important that data regarding the epidemiology and rates of metastasis to lymph nodes are provided. The scope of this disease and specifically of this stage of disease that is being addressed should be discussed and elaborated.**

Reply: We have added additional information in the introduction section. This now reads:

“Penile cancer (PeCa) is a rare malignancy with incidence of 1/100,000 males but has favourable survival when organ confined. Around a third will have metastasis to inguino-pelvic lymph nodes (LN), which is prognostic for mortality. Up to 25% of those with impalpable nodes will harbour micro metastasis whilst those with palpable nodes have high rates of metastasis. Therefore, the European Association of Urology (EAU) recommends treatment of both the primary lesion and LN to improve survival [1].”

**2.Perhaps some data (even in the form of a table) should be given regarding the current and updated disease TNM staging.**

Reply: We have included the following paragraph in the discussion section describing each nodal stage according to the 8th edition AJCC TNM criteria. We hope this will provide the reader sufficient background to interpret data described in our review:

“According to the latest 8th edition AJCC TNM criteria, pathological nodal staging is defined as follows, pN1: ≤ 2 unilateral ILN metastases without extra-nodal extension (ENE); pN2: ≥ 3 unilateral or bilateral ILN metastases without ENE; and pN3: ENE of ILN metastases or pelvic LN metastases.

In addition, the following text already included within section 3.4.1.2 highlights the change in the 2017 AJCC TNM staging:

“It is worth noting in 2017 the AJCC updated the TNM staging altering pN1 from one node to ≤2 unilateral nodes thus contemporary series may report lower survival.”

**3.Results: When dealing with surgery and lymph node dissection in penile cancer I think it would benefit readers to have some data on the possible complications and their rates. More detail should be given on this.**

Reply: Such data regarding complication rates of inguinal lymph node dissection have already been described in supplementary table 6 and summarized in section 3.4.1.2.3 of the main text.

**4.Results: More discussion should be given regarding current recommendations regarding when neoadjuvant/adjuvant chemotherapy and radiotherapy should be given in a summarized manner.**

Reply: We thank Reviewer 1 for this suggestion. We strongly believe that providing a summary of recommendations, is beyond the scope of this study. In contrast, EAU/ASCO panel members will use the findings of this systematic review and the GRADE approach and methodology will rate the quality of evidence to provide clinical recommendations. These recommendations will be implemented in the relevant section of the EAU guidelines both in paper format and online. However, the main findings of the review are discussed in the section on implications for clinical practice.

**5.Discussion: The authors should elaborate more on the implications for clinical practice. What has changed and what should we do going forward? Please provide a summary of changes that this review brings.**

Reply: We thank the reviewer for this suggestion, and in response have included the following text in section 4.2 implications for clinical practice.

Surgery is the mainstay of treatment of LN positive PeCa. Current guidelines suggest minimally invasive ILND is feasible in small series with no firm recommendations regarding their use. Our review confirmed the promise shown in reducing wound-related morbidity but lymphatic complications remain an issue and more data is needed to confirm oncological safety when applied in cN+ disease. This field is likely to continue to evolve and we expect further studies to be published advocating its use which may inform future guidelines. A previous systematic review cautioned against use of ART in pN3 disease [112] This review informed current EAU guidelines which only advocate ART use in clinical studies. However, more recent data suggests ART may indeed improve recurrence-free and overall survival and can thus now be considered in pN2-3 patients. Our review has demonstrated that adjuvant radiotherapy can be safely used outside of clinical studies for pN2-3 disease whilst minimally invasive iLND can be considered.

Furthermore, we would like to draw the reviewer’s attention to the last paragraph in this section (see below) where we additionally highlight current challenges to address which additional work is required.

Current challenges regarding the use of multimodal therapies are represented by the following: (i) identification of the most suitable patients and timing of chemotherapy (neoadjuvant vs adjuvant); (ii) patient selection and timing for the addition of RT, and (iii) better defining the added benefit versus toxicity on efficacy and patient quality of life.

**6.Discussion: It would be impactful to have a figure/algorithm of proposed management plan for patients with lymph-node metastatic penile cancer to help summarize new findings.**

Reply: Though a management algorithm would be of significant interest to the community, the authors respectively believe that such guidance does not fit within the explicit remit of this systematic review. It is anticipated that such an algorithm will be devised as part of the next iteration of the EAU-ASCO guidelines.

**7.Disscussion: As trials in penile cancer are so rare, more details should be given on the InPACT trial and its endpoints.**

Reply: As recommended by the reviewer, we have now added additional details regarding the InPACT trial in section 4.3 “Implications for further research”, as below.

The ongoing International Penile Advanced Cancer Trial (InPACT, NCT02305654) is an Phase III trial with a Bayesian design compares incorporating two sequential randomisations aiming to recruit 200 patients with inguinal and/or pelvic metastases. The first randomisation will test the role of neo-adjuvant therapies (NACT vs, CRT) before and ILND [113] for inguinal and/or pelvic metastases. Following ILND, further randomisation will evaluate oncologic benefit of PLND and or ACRT. The primary outcome measure is overall survival, with recruitment ongoing.

**8.A general grammatical review should be done for this manuscript.**

Reply: We have again reviewed our manuscript text and addressed any grammatical errors.

**Reviewer #2**

**Well done systematic review on lymph node positive penile cancer by a multinational group of experts in this specific disease space. Methods are sound. Reads well. The last systematic review on this all-inclusive topic was in 2017.**

**Comments:**

**1.Title: at first reads well but then a bit ambiguous and I assume purposefully so as it lymph node "positivity" can be interpreted as either clinically positive on imaging or exam, and confirmed by pathology or biopsy proven positive lymph nodes, or clinically suspicious but not necessarily confirmed on pathology. Can authors comment in methods if this was elucidated in their search/review of studies? And if all can agree, perhaps specifying in their title?**

Reply: We thank Reviewer 2 for this comment and we agree that this is a potential area of confusion within the available data. We therefore specifically focussed on review on patients with clinical node positive penile cancer (cN+). However, there was heterogeneity within included studies on the reporting of cN+ and pN+ disease, with little available data regarding pathological confirmation of cN+ disease. Where detail regarding cN and pN status were available, we have sought to stratify our findings accordingly.

The title of this review has been proposed by the EAU-ASCO panel members and approved by EAU Methods Committee and PROSPERO, to study lymph node-positive disease and enclose both clinical and pathologically positive patients and stratify them accordingly.

**2.Figures: Figure 1, please adjust the arrows so it is aligned appropriately to the reasons for exclusion box. Figure 2, it would be helpful to re-label assessment of RCTs as (A) and (C) as this is how it presented in the text of results to be consistent.**

Reply: We have now made these recommended changes

**3.Tables: why did the authors choose to highlight minimally invasive techniques in Table 1 which in the text follows 6 supplemental tables??? If the results presented in supplemental tables is truly supplemental, perhaps rearranging the sections would help the reader to reorient to what is important.**

Reply: Minimally invasive lymphadenectomy is a recent advance in LN management in penile cancer, and therefore believed to be an area of topical interest. Whilst surgeons seek to embrace this approach, it is important to be cognizant of the available evidence base including the risk of complications. We have therefore included these data in table 1. Given the relatively small body of evidence, we sought to summarise data were available, which we have included in the manuscript text. We felt it was prudent to provide the source data in an easy-to-access summarized manner for the reader who wishes to seek further details. These data were therefore placed in the supplemental section and allowed us to focus on the key interests of broad general interest within the main manuscript.

**Reviewer #3**

**Sachdeva, et. al., perform a systematic review on the management of node positive penile cancer as part of an upcoming EAU-ASCO guideline. This group is to be commended for a thorough review of a broad topic.**

**Comments:**

**1.One of the a priori confounders was co-existing metastatic disease. The management of M1 penile cancer is not the same as N1 penile cancer, so it is unclear why studies including these patients would be a part of this review.**

Reply: Given the scarcity of data regarding management of M1 disease, some studies reported findings for both N1 and M1 disease in the same report. We agree with the reviewer that management of M1 penile cancer differs significantly from N1 disease, and therefore sought to identify this potential risk of bias in included studies. Bearing this in mind, we exclusively focussed our review on data from M0 patients included within such studies.

**2.The bulk of patients in this review came from case-series and observational cohort studies. While the authors report a high RoB for the majority of studies, it would be important to also comment on the low quality of evidence. This was briefly mentioned in the limitations section, but could be highlighted in the Discussion section, especially where the authors make recommendations about treatment.**

Reply: We thank the reviewer in highlight this important point. In response, we have now included additional comments regarding the quality of evidence in section 4.2: Implications for clinical practice.

Most studies in this review are case series or observational studies thus the overall evidence quality is deemed low. Due to this, new firm recommendations are difficult to prescribe however some themes differing from current guidance are emerging and worthy of discussion. Surgery remains the mainstay of treatment of LN positive PeCa. Current guidelines suggest minimally invasive ILND is feasible in small series with no firm recommendations regarding their use. Our review confirmed the promise shown in reducing wound-related morbidity, but lymphatic complications remain an issue and more data is needed to confirm oncological safety when applied in cN+ disease. This field is likely to continue to evolve and we expect further studies to be published advocating its use which may inform future guidelines Given limited data and low-quality evidence, the optimal indication and order of multimodal treatment strategies is difficult to discern. Therefore, potential treatment strategies should be discussed in an experienced multidisciplinary team, balancing the potential benefits against toxicity. NACT should be reserved for fixed/bulky LN disease followed by completion surgery if feasible and can be considered in other N2-N3 cases. Adjuvant therapy may provide benefit in pN2-N3 disease.

**3.The authors could be clearer about what type of nodal staging (clinical or pathologic) is used throughout their manuscript and tables.**

Reply: Where data were available, we have specified type of nodal staging as either clinical (cN) or pathological (pN).

**4.How were summary statistics estimated for the composite/pooled survival outcomes? Was a meta-analysis performed? This was not described in the method section.**

Reply: Variations in outcome measurement and reporting precluded a meta-analysis. We therefore state in section 2.7 (data analysis) that a quantitative synthesis (ie meta-analysis) was not appropriate. Where pooled outcomes are reported, a range is provided supported by data in tables.

**5.It could be informative to include a summary of studies that report the risk of pN+ among patients with cN+ and initial approaches to cN+ disease.**

Reply: Though we agree with the reviewer that summary of available data regarding concordance between cN+ and pN+ status would be beneficial, such data were rarely available within the included studies and falls outside of the scope of our review. An ongoing systematic review by the EAU-ASCO guidelines panel is currently evaluating nodal staging and should provide more robust data in this regard.

**6.Section 3.4.1.2,**

**a. Were patients of all clinical nodal stages (including cN0) combined for these survival statistics, or are the cumulative survival only reported for patients with pN+ regardless of their clinical staging? cN0 patients with either pN0 or low-volume inguinal metastasis generally have a very good prognosis after ILND, and are not necessarily the same as patients with bulky bilateral lymph nodes. It may not be appropriate to combine all patients into a single survival estimate.**

Reply: We agree with Reviewer 2 that outcomes differ drastically between cN0 and cN+ disease. Therefore, we explicitly prespecified cN+ disease as part of the inclusion criteria within our review protocol. We have clarified this further by making the following amendment in Section 2.3 ‘Types of participants included’:

PeCa patients at any stage, diagnosed with clinically-apparent (cN+) or pathologically-confirmed (pN+) inguinal and/or pelvic LN disease, who received treatment with any intent.

The calculations of survival outcomes, including cumulative means, were based on N+ data. Where available, we have further stratified our analyses based upon pN status for clarity.

**b. The authors could expand on the discussion of immediate ILND vs. delayed ILND at the time of cN+ for patients with cN0 groins.**

Reply: As per our review protocol (CRD42021290784), this review was focussed on patients with cN+ disease, and therefore studies reporting outcomes for patients with cN0 groins were not included.

**7.Section 3.4.1.2.4: there is substantial selection bias in which patients are chosen for minimally-invasive LND compared to open LND. I would hesitate to make declarative statements about less saphenous vein sparing and using more "morbid maneuvers" with open LND.**

Reply: We thank the reviewer for highlighting this point and have amended the text (in red font) to highlight selection bias. Minimally-invasive ILND was utilised mainly in cN0 patients, with most having high pN0 rates which may reflect a selection bias. Only two series used VEIL in proven LN disease [100, 101]. Therefore, it is early to draw conclusions about oncological safety of VEIL in node positive patients. Moreover, some studies, using open-ILND as a comparator, occasionally included steps associated with increased risk of complications such as sartorius transposition and saphenous vein sacrifice that were not performed in minimally-invasive procedures.

**8.Section 3.4.1.3: if there is no survival advantage for N1/N2 disease with NACT compared to immediate ILND, is there one for N3 disease? If so, this would be relevant to highlight.**

Reply: We have clarified this point below:

“There remains little evidence for survival improvements for NACT in N1/N2 disease however in inguinal cN3 disease not imminently surgically resectable NACT may induce a response rate to allow subsequent iLND.”

**9.Section 3.4.1.4.2: this section includes patients with inguinal and pelvic nodal disease. This is redundant but also confusing given the section on Management of Pelvic Nodal Disease. I would discuss only adjuvant therapy for inguinal node disease in this section.**

Reply: We thank the reviewer’s input in helping clarify this section. Given that the available data does not report outcomes stratified by inguinal pN3 vs pelvic pN3 disease, in line with the reviewer’s recommendation we have amended the text (in red font below) in this section to remove data for pelvic nodal involvement, and instead focus on inguinal nodal disease alone.

Six studies used ACT after LN dissection [13-15, 17, 44, 46]. The largest published series included cohorts of ACT, NACT and NACT + ACT patients [13]. Patient selection and chemotherapy regime varied between centres. Most patients were pN2-3 (83%) with bilateral inguinal involvement (43%) and PN involvement (36%). The chemotherapy regimen comprised taxane-platinum-5-fluorouracil (FU) or platinum-5FU in 75%. Outcomes favoured ACT with non-significantly longer OS and significantly longer RFS. This may be due to more cN3 patients in the NACT cohort (48% vs 24%) although after LN dissection 55% of ACT patients were upstaged. The addition of RT, given in 36% of the ACT cohort, showed no survival or recurrence benefit. No difference was shown between chemotherapy regimens, but numbers were small. ACT patients reported lower incidence of grade 3-4 toxicity compared with NACT or NACT + ACT (21% vs 57% vs 100%).

In 47 patients treated with NACT (for cN3 disease) or ACT (≥pN2 after LND) using TPF, the ACT group had more pelvic involvement (58%) and ENE disease (74%)[14]. Despite this neither OS nor RFS were significantly different. Toxicity was lower with ACT (Grade ≥3 53% vs 85%).

**10.Section 3.4.2: The authors report that PLND vs no surgery in N2-3 disease has 3-year DSS of 39.6% vs. 39%, but then say that PLND is superior to no PLND for pN2-N3 disease using the same study reference. This is inconsistent and confusing.**

Reply: We thank the reviewer in highlighting this potential area of confusion. To clarify this point, we have removed the following paragraph from Section 3.4.2:

A NRCS compared bilateral PLND with no surgery in N2-3 disease after bilateral ILND reporting 3-year DSS of 39.6% without PLND (vs 39.0% in PLND group); although 40% of this group received adjuvant treatment [18]. Those with pN2 after ILND without PLND had a 3-year DSS of 50% whilst those with ENE after ILND had 3-year DSS of 25%.

In addition, as part of this revision, we have taken the opportunity to appraise the manuscript alongside the EAU guidelines 2023, which has already undergone two independent rounds of rigorous peer review. Consequently, we have identified an inconsistency in the risk of pelvic nodal involvement in this manuscript. This has been re-evaluated and an amendment made in section 3.4.2 to reflect the available data and bring the manuscript into line with forthcoming EAU guideline for penile cancer 2023. The revised section 3.4.2 now reads as follows:

3.4.2 Management of pelvic lymph node disease

Pelvic lymph node (PLN) metastases follow inguinal LN spread and carries worse prognosis (17% vs 62% 5-year DSS) compared to those without [52]. The presence of ENE and the number of positive inguinal LNs were predictive of ipsilateral PLN metastasis (1–2 nodes vs. ≥3 nodes; 0–6.5% and 33–67% respectively) Number of positive inguinal LNs (≥2 vs 1) and presence of ENE were predictive of ipsilateral PLN metastasis [52-54]. Multivariate analysis shows OS of patients with bilateral PLN disease is worse than unilateral involvement and the number of positive PLN is a predictor of poor survival [19, 52, 57]. Presence of ≥4 bilateral positive inguinal LNs was the only independent predictor of bilateral PLN metastasis (OR: 14.0, 95% CI 1.71-115) [57], however p53 immunoreactivity, LN density >30% and the primary tumour grade were additional predictors of PLN involvement [53, 72].

For consistency, the above has also been reflected in the appropriate paragraph of section 4.1 Principal Findings which now reads:

After ILND, ≥32 positive nodes or presence of ENE are predictors for PLN involvement and remain indication for PLND which improves outcomes in pN2 disease, but benefit is less clear for pN3. Both ACT and CRT show modest improvement in recurrence and survival outcomes after PLND.

**11.Tables 2 and 3: the columns of "patient characteristics" and "selection criteria for treatment" seem redundant.**

Reply: In Tables 2 and 3, the column “patient characteristics” defines the whole patient cohort included in each study and the “selection criteria for treatment” specifically describes the disease characteristics used to determine either neoadjuvant (table 2) or adjuvant (table 3) treatment selection, as only a subset of included patients received treatment. We believe that these data provide valuable information to the reader regarding the evidence base.

2nd Decision letter

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**Title:** Management of lymph node-positive penile cancer: a systematic review

**Journal**: European Urology

**Reviewer #1**

All reviewer points have been addressed appropriately.

**Reviewer #2**

Thank you for addressing my comments.

**Reviewer #3**

1.Please keep precision of estimate rates consistent with guideline 4.1 bullet 2.

2nd Author Response Letter

Response to comments from Editors and Reviewers:

**Author:**

**We thank the reviewers for their comments. We believe we have now fully addressed the single minor comment below. Amendments to the text are included in the ‘tracked changes’ version of the revised manuscript. Please not what we also made additional minor formatting changes and grammatical corrections in the revised manuscript with tracked changes.**

**Reviewer #1**

**All reviewer points have been addressed appropriately.**

**Reviewer #2**

**Thank you for addressing my comments.**

**Reviewer #3**

**1.Please keep precision of estimate rates consistent with guideline 4.1 bullet 2.**

Reply: We thank the reviewer for highlighting this issue. We have now amended the text, tables and supplementary tables as per recommendations in Guideline 4.1 Bullet 2 based on *Guidelines for Reporting of Statistics for Clinical Research in Urology* (Assel et al, European Urology 2019).

Accept Letter

Dear Dr. Plass,

We are pleased to inform you that your above-mentioned revised manuscript has been accepted for publication in EUROPEAN UROLOGY. We will forward it to our Publishing Department, which will undergo a desk editing process to ensure the highest quality publication.

If you have not already, you will soon receive a letter detailing the modifications made by the copyeditor and those that need to be addressed when you receive the proofs from the Publishing Department.

We at the Editorial Office of EUROPEAN UROLOGY would like to personally thank you for your interest and support to the Journal, and we do hope that you continue submitting valuable manuscripts to us in the future.

Thank you again for your interest and collaboration with European Urology, The Platinum Journal.

Yours sincerely,

James Catto Sarah P. Psutka
Editor-in-Chief Associate Editor

*-------- End of Review Comments --------*