Peer Review File

Article information: http://dx.doi.org/10.21037/tau-20-1044.

Reviewer A: The authors have used the SEER database and did a retrospective query with the aim to compare survival after chemoradiotherapy to chemotherapy (without radiotherapy) for advanced penile cancer.

Although the question what the best (adjuvant) treatment for patients with N2-N3 penile cancer is, is one of the most pressing current questions in the management of penile cancer, I'm afraid this article does not help elucidate this dilemma due to some intrinsic problems and potential causes of bias.

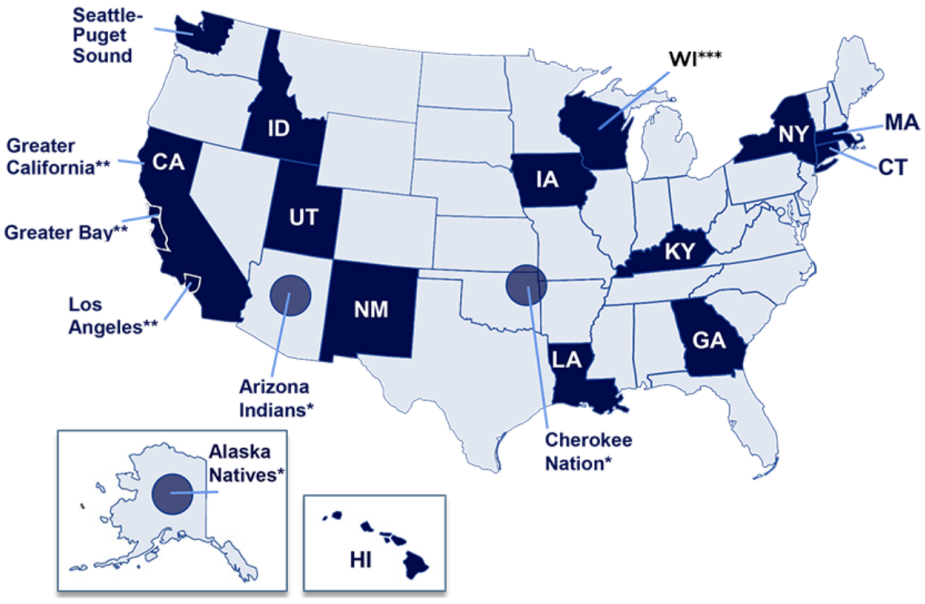
General response to the comments: We thank the reviewers for the valuable suggestions to improve our manuscript. We have carefully revised the manuscript according to these suggestions and believe that it has been significantly improved. The following are our point-by-point responses to the specific comments.

Comment 1: patients were selected between 2004-2015. The authors state that the 6th AJCC TNM staging was used. In 2010, the 7th edition of the American Joint Committee on Cancer (AJCC)-tumour-node-metastasis (TNM) staging system for penile cancer was published with two major changes in the N category. This might mean that all patients between 2010-2015 can not be compared with the earlier patients unless the N stage was corrected. Can the authors comment on this.

Reply 1: Thank you for your question. As we designed this study, we have considered this question and known that inevitable version changes. Therefore, we used the criteria from the American Joint Committee on Cancer (AJCC) 6th versions from 2014-2015. It is necessary to tell the reviewer that there were both AJCC6^{th} and AJCC^{7th} stage information after 2010 in SEER databases, but only AJCC^{6th} stage information between 2004 to 2010. Therefore, to avoid the question you mentioned, we have to use the relatively old version to carry out this study.

Comment 2: The study is not useful without more details on: 1) chemoradiotherapy protocol. Which chemo? how many gray? on which areas? only nodes inguinopelvic? or also primary tumour? 2) chemotherapy regimens. 3) was this adjuvant treatment? primary treatment? or neodadjuvant? Without this data the groups are too small to compare, there is too many potential bias.

Reply 2: Thanks for your questions. As for a huge database (SEER began collecting data on cancer cases on January 1, 1973, in the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii and the metropolitan areas of Detroit and San Francisco-Oakland. Since then, the SEER Program has been expanded to cover numerous additional areas (see map below)), it is hard to provide specific information you mentioned. Therefore, the aim of this study is to uncover the potential benefit of adding radiotherapy and cause the widespread concern of urologists, so as to explore a better treatment program for advanced penile cancer patients.



Changes in the text: we have modified our text as advised (see page 14, line 3-9).

Firstly, our study lacked specific information on chemotherapy, radiotherapy and surgery (e.g. chemotherapy regimens, radiotherapy strategy, lymph node dissection range…). What we got is that most chemotherapy regimens were based on Cisolatin and Radiotherapy was provided at the discretion of the attention radiation oncologist.

Therefore, it is necessary for us to research of our own patients in order to get more powerful evidence.

Comment 3: looking at table 1: there where 49 N0 patients who received chemotherapy? why? there is totally no indication for this. This is one of the examples that makes me wonder how reliable this dataset is.

Reply 3: Thank you for your question. All the data used in our study were extracted from the SEER database through SEER*Stat software V.8.3.5, which covers approximately 28% of the population in the USA (https:// seer. cancer. gov/, accession numbers 13693- Nov2015 and lh8N79l2). In the current literature, there were many studies based on this database, which reflecting the reliable of this dataset. As for the question you mentioned about the 49 N0 patients, we could only explain that it is the decision of patients and their doctors (may be affected by religion, economy or other specially disease condition) and we really do not know the specific information. This is the biggest limitation of using a public database, therefore, the next step of our group is to carry out a multi-center research in China.

1.Qian Y, Johannet P, Sawyers A, et al. The ongoing racial disparities in melanoma: an analysis of the Surveillance, Epidemiology, and End Results database (SEER) database (1975-2016). J Am Acad Dermatol, 2020. DOI：10.1016/j.jaad.2020.08.097.

2.Florindez JA, Alderuccio JP, Reis IM, et al. Splenic marginal zone lymphoma: A US population-based survival analysis (1999-2016). Cancer, 2020. DOI：10.1002/cncr.33117.

3.Yang Y, Tu Z, Cai H, et al. A predictive nomogram for lymph node metastasis of incidental gallbladder cancer: a SEER population-based study. BMC Cancer, 2020, 20: 828. DOI：10.1186/s12885-020-07341-y.

4. Su XH, Wu KH, Wang S, et al. The impact of orthotopic neobladder vs ileal conduit urinary diversion after cystectomy on the survival outcomes in patients with bladder cancer: A propensity score matched analysis. Cancer Med, 2020. DOI：

10.1002/cam4.3404.

5.Roberts AW, Eiffert S, Wulff-Burchfield EM, et al. Opioid use disorder and overdose in older adults with breast, colorectal, or prostate cancer. J Natl Cancer Inst, 2020. DOI：10.1093/jnci/djaa122.

Comment 4: It is unclear if N3 patients had N3 based on pelvic lymph nodes, or extranodal extension. this is an important distinction.

Reply 4: Thanks for your question. What you are talking about is the pN stage information in AJCC 7th. However, in this study, we used the N stage information in AJCC 6th. The following figures are two versions of AJCC Cancer Staging Manual about penis cancer.

AJCC 6th :

DEFINITION OF TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
Ta	Non-invasive verrucous carcinoma
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades corpus spongiosum or cavernosum
T3	Tumor invades urethra or prostate
T4	Tumor invades other adjacent structures

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single superficial, inguinal lymph node
N2	Metastasis in multiple or bilateral superficial inguinal lymph nodes
N3	Metastasis in deep inguinal or pelvic lymph node(s) unilateral or bilateral

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

AJCC 7th:

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Ta	Noninvasive verrucous carcinoma*
T1a	Tumor invades subepithelial connective tissue without lymph vascular invasion and is not poorly differentiated (i.e., grade 3–4)
T1b	Tumor invades subepithelial connective tissue with lymph vascular invasion or is poorly differentiated
T2	Tumor invades corpus spongiosum or cavernosum
T3	Tumor invades urethra
T4	Tumor invades other adjacent structures

Regional Lymph Nodes (N)

*Clinical Stage Definition**

cNX	Regional lymph nodes cannot be assessed
cN0	No palpable or visibly enlarged inguinal lymph nodes
cN1	Palpable mobile unilateral inguinal lymph node
cN2	Palpable mobile multiple or bilateral inguinal lymph nodes
cN3	Palpable fixed inguinal nodal mass or pelvic lymphadenopathy unilateral or bilateral

* *Note*: Clinical stage definition based on palpation, imaging.

*Pathologic Stage Definition**

pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in a single inguinal lymph node
pN2	Metastasis in multiple or bilateral inguinal lymph nodes
pN3	Extranodal extension of lymph node metastasis or pelvic lymph node(s) unilateral or bilateral

**Note*: Pathologic stage definition based on biopsy or surgical excision.

Comment 5: The authors mention 5 year survival rates, yet the median follow up was <5 years (25months, IQR 15-45). so I believe 5 year PCSS can not be concluded for all patients.

Reply 5: thanks for your suggestion. What you mentioned is reasonable and rigorous. Therefore, we have changed the 5-year PCSS to 2-year PCSS.

Changes in the text: we have modified our text as advised (see page 3, line 13-14; page 9, line 12-13; page 9, line 17-19).

The median follow-up time was 25 months, the 2-year PCSS was 52.98 % in the chemoradiotherapy group and 55.81% in the chemotherapy group.

The 2-year PCSS was 52.98% in the chemoradiotherapy group and 55.81% in the chemotherapy group.

In the N3 setting, the 2-year PCSS was 51.23% in the chemoradiotherapy group and 23.90% in the chemotherapy group and the log-rank test P value was 0.031.

Comment 6: In studies describing (adjuvant) therapies like radiotherapy, chemoradiotherapy, or chemotherapy, for which prospective evidence is lacking, it is also important to consider side effects and morbidity of these treatments. I'm afraid the authors can probably not provide this. Can the authors comment on this.

Reply 6: Thanks for your questions. There is not enough literature focus on describing (adjuvant) therapies like radiotherapy, chemoradiotherapy, or chemotherapy and we did not find any study of prospective research, due to the relatively rare penile cancer cases. Therefore, it is our significance to carry out this study, in order to got more evidences to support the applying of the chemoradiotherapy. As for the side effects and morbidity, no serious or fatal complications have been reported in the current literature. The SEER database can not provide such information, and therefore we added this limitation in the limitation section.

Changes in the text: we have modified our text as advised (see page 12, line 15-20; page 14, line 15-17).

According to the current literature, the most common side effect is skin acute skin

toxicity, which occurring in 83% of the patients received radiotherapy. Besides, some studies also reported the complication of lymphoedema and groin telangiectasia/fibrosis. Until now, no serious or fatal complications have been reported, which may reflect the safety of chemoradiotherapy. More researches focusing on toxicity should be carried out.

Fourthly, it was difficult to evaluate the complications and the specific morbidity, because it was conducted using the SEER database which lacking related information.

Comment 7: in general the article is poorly written in terms of English grammar.

Reply 7: Thanks for your comment about grammar in this manuscript.

Reviewer B: The authors present a revised manuscript of their secondary American Surveillance, Epidemiology, and End Results (SEER) program analysis, highlighting that chemoradiotherapy improved penile cancer specific survical in patient with a N3 status. Furthermore, the authors stated that their analysis 'demonstrated a significant correlation of chemoradiotherapy with improved cancer-specific survival of PeCa in N3 patients.'

Considering the rarity of penile cancer and the paucity of data, in particular on patients with advanced N stages, the reviewers welcomes this important work. Although the reviewer has not seen the initial submission, the reviewers would like to highlight two major and multiple minor points that should be addressed.

General response to the comments: Thank you very much for your interest in the subject of our article and for your recognition of our work. Your comments on our article are taken very seriously, and are detailed in the response below.

Major points:

Comment 1: The discussion is very brief and could benefit from a wider comparison with the current literature.

For example, a recent systematic review by the EAU penile cancer guidelines panel highlighted that there is a lack of good-quality evidence on adjuvant radiotherapy following ILND and therefore, cannot be recommended. [1] Chipollini and colleagues [2] evaluated the cancer specific survival (CSS), overall survival (OS) and progression-free survival (PFS) of a cohort with 330 patients with positives lymph nodes (N1-3) who either had lymph node dissection alone or underwent systemic treatment (adjuvant, neoadjuvant or both). However, none of the systemic treatment options significantly improved CSS, OS and PFS. Ottenhof and colleagues [3] reported disappointing 1-year (50%) and 2-year (26%) OS with low toxicity in a cohort of 34 patients with T3/4 N2/3 stages who underwent chemoradiation. In another study presented at the 2019 EAU annual meeting, Ager and colleagues [4] retrospectively assessed 151 patients with an N3 stage. Those who completed radiotherapy (with or without chemo sensitisation, n=124) had a higher 5-year CSS (47% vs. 31%) compared to patients who did not (n=27). [4] Finally, Johnstone and colleagues [5], who also retrospectively analyzed patients (n=93) with an N3 stage, found improved OS [postoperative chemotherapy (p=0.038); inguinopelvic radiotherapy (p=0.037)] and relapse-free survival [groin (p=0.016) or inguinopelvic radiotherapy (p=0.006)] in patients without extranodal extension (ENE). However, no beneficial effect of chemo- or radiotherapy was

observed in those with ENE. [5] Unfortunately, tumor differentiation was associated with worse CSS (with ENE only) and relapse-specific survival (with or without ENE). [5]

These are only a few suggestions of studies that could be incorporated into discussion

1. Robinson, R., Marconi, L., MacPepple, E., Hakenberg, O. W., Watkin, N., Yuan, Y., Lam, T., MacLennan, S., Adewuyi, T. E., Coscione, A., Minhas, S. S., Comperat, E. M.,Necchi, A. 2018. "Risks and Benefits of Adjuvant Radiotherapy After Inguinal Lymphadenectomy in Node-positive Penile Cancer: A Systematic Review by the European Association of Urology Penile Cancer Guidelines Panel." Eur Urol 74(1): 76-83.

2. Chipollini, J., Necchi, A., Spiess, P. E. 2018. "Outcomes for Patients with Node-positive Penile Cancer: Impact of Perioperative Systemic Therapies and the Importance of Surgical Intervention." European Urology 74(2): 241-242.

3. Ottenhof, S. R., Doodeman, B., Vrijenhoek, G. L., Djajadiningrat, R. S., Horenblas, S.,Pos, F. J. 2019. "497 - Chemoradiation in the treatment of loco-regionally advanced penile cancer." European Urology Supplements 18(1): e655.

4. Ager, M., Njoku, K., Serra, M., Pickering, L., Afshar, M., Beesley, S., Robinson, A., Crellin, P., Vyas, L., Kayes, O., Elmamoun, M., Eardley, I., Ayres, B., Henry, A., Tree, A.,Watkin, N. 2019. "492 - Results of a 10 year multicentre experience of adjuvant radiotherapy for pN3 squamous cell carcinoma of the penis (SCCp)." European Urology Supplements 18(1): e649.

5. Johnstone, P. A. S., Boulware, D., Djajadiningrat, R., Ottenhof, S., Necchi, A., Catanzaro, M., Ye, D., Zhu, Y., Nicolai, N., Horenblas, S.,Spiess, P. E. 2019. "Primary Penile Cancer: The Role of Adjuvant Radiation Therapy in the Management of Extranodal Extension in Lymph Nodes." European urology focus 5(5): 737-741.

Reply 1: Thank you very much for your contribution for this manuscript and we do not know how to express our gratitude for your kindness. Besides, we have downloaded and read these studies you suggested and gained a lot. Finally, we adjusted the order and added this content in the manuscript.

Changes in the text: we have modified our text as advised (see page 11, line 22 to page 12, line 21).

In a study presented at the 2019 EAU annual meeting, Ager et al. retrospectively assessed 151 patients with an N3 stage. Those who completed radiotherapy (with or without chemo sensitisation, n=124) had a higher 5-year PCSS (47% v.s. 31%) compared to patients who did not (n=27). This conclusion is consistent with the findings of other two studies12-13. On the contrary, there were some literatures which suspected the effective role of radiotherapy or chemoradiotherapy. Ottenhof et al. reported disappointing 1-year (50%) and 2-year (26%) OS with low toxicity in a cohort of 34

patients with T3/4 N2/3 stages who underwent chemoradiotherapy. Chipollini et al. evaluated the PCSS, OS and progression-free survival (PFS) of a cohort with 330 patients with positives lymph nodes (N1-3) who either had lymph node dissection alone or underwent systemic treatment (chemotherapy with or without radiation or radiation alone based on time of ILND). However, none of the systemic treatment options significantly improved PCSS, OS and PFS. Besides, Johnstone et al., who also retrospectively analyzed patients (n=93) with an N3 stage, found improved OS [postoperative chemotherapy (p=0.038); inguinopelvic radiotherapy (p=0.037)] and relapse-free survival [groin (p=0.016) or inguinopelvic radiotherapy (p=0.006)] in patients without extranodal extension (ENE); however, no beneficial effect of chemotherapy or radiotherapy was observed in those with ENE. At present, a recent systematic review by the EAU penile cancer guidelines panel highlighted that there is a lack of good-quality evidence on adjuvant radiotherapy following ILND and therefore, cannot be recommended in EAU guidelines.

Comment 2: The variable surgery, table 1 (p=0.026) highlights a significant difference between chemotherapy vs. chemoradiotherapy. However, the authors do not discuss this different at all.

Reply 2: We thank the reviewers for your reminding. We have added this part in limitation section.

Changes in the text: we have modified our text as advised (see page 14, line 11-15).

Thirdly, the rate of surgery in chemoradiotherapy group was higher than chemotherapy group; it is may due to the more serious condition of patients in chemoradiotherapy group. Maybe this different distribution would affect the result. However, in this study, surgery did not improve the PCSS through the results of multivariate analysis in our collected patients.

Minor points:

Comment 3: The authors cite that ethical approval and patient consent are not applicable. The reviewer cannot understand how both are not applicable. Data has been extracted from a database. Hence, both are apparently available and should be reported. Furthermore, the authors do not report whether any conflict of interest is present or not. Note: No funding is reported.

Reply 3: Thank you for your question. We have added the ethics statement in the method section.

Changes in the text: we have modified our text as advised (see page 8, line 4-8).

We were granted permission from the National Cancer Institute USA to access the SEER dataset for research purposes only (reference number: 21111-Nov2018). All the data from the SEER database were de-identified, and the extracted data did not require informed consent.

Thank you for your interest in the SEER Research Data. Your signed Research Data Agreement is on file at SEER. Your username and password have been generated for Internet access and they are shown below. Please note that both the username and password are case sensitive.

Username: 21111-Nov2018
Password: [redacted]

These will allow you to utilize the SEER*Stat client-server system and/or download the files which make up the SEER Research Data. These options are described at the following URL:

http://seer.cancer.gov/data/options.html

You can change your password once you log into SEER*Stat from the "Client Server User Information" option located under the Profile menu.

Radiation treatment variables have been removed from the public research database starting with the November 2016 data submission. These variables are available through a custom data request process after signing an additional data use agreement that describes the completeness of the radiation treatment variable and the potential biases associated with use of the radiation data. To request access to radiation treatment data, go to https://seer.cancer.gov/data/treatment.html

Send questions or comments to:
- seertrack@imsweb.com -- regarding access to SEER Research Data
- seerstat@imsweb.com -- for SEER*Stat technical support
- seerweb@imsweb.com -- general questions regarding SEER or SEER data

Thank you,
SEER*Stat Technical Support
IMS, Inc.

Reply to all the details you mentioned: Thank you for your hard work on this manuscript, and we really appreciate you. we have revised and verified all the detail you put forward.

Abstract

P3-lines 5/6: It is unclear for the reviewer to what database the authors refer to (Name, Country, Registry including number)?

Changes in the text: we have modified our text as advised (see page 3, line 6-9).

Data were obtained from the Surveillance, Epidemiology, and End Results database (SEER*Stat software V.8.3.5; USA; Accession numbers: 13693- Nov2015 and lh8N79l2), and the survival curves were conducted using the Kaplan-Meier method.

P3-line 8: PCSS is not explained.

Changes in the text: we have modified our text as advised (see page 3, line 9-11).

Univariate and multivariate cox regression models were performed in order to determine the hazard ratios (HRs) with 95% confidence intervals (CIs) for penile cancer-specific survival (PCSS).

P3-line 11: spelling c not C in chemoradiotherapy and chemotherapy

Changes in the text: we have modified our text as advised (see page 3, line 13-14).

The median follow-up time was 25 months, the 2-year PCSS was 52.98 % in the chemoradiotherapy group and 55.81% in the chemotherapy group.

P3-lines 13/14: improved PCSS in N3 but compared to …?

Changes in the text: we have modified our text as advised (see page 3, line 16-18).

In subgroup analysis, chemoradiotherapy improved the PCSS in N3 patients compared to these patients without therapy of radiotherapy (HR = 0.54, 95% CI = 0.30-0.98, P =0.043).

P3-line 15: "significant correlation" but where are the stats to confirm that (i.e. method sections)?

Reply: Thanks for your question. In result section, I have mentioned that "chemoradiotherapy improved the PCSS in N3 patients (HR = 0.54, 95% CI = 0.30-0.98, P =0.043, Figure 3)". We do not know if you are finding this.

P3-line 16: PeCa is not explained.

Changes in the text: we have modified our text as advised (see page 3, line 19-21).

Our study demonstrated a significant correlation of chemoradiotherapy with improved cancer-specific survival of penile cancer (PeCa) in N3 patients.

Introduction

P4-line 15: SEER is not explained.

Changes in the text: we have modified our text as advised (see page 5, line 15-18).

Recently, Burt et al. conduct a research using the data from Surveillance, Epidemiology, and End Results (SEER) Program database and frustratedly found that radiotherapy had neither a beneficial nor harmful effect for cancer-specific survival in the multivariable analysis.

P5-line 3: OS and IQR are both not explained

Changes in the text: we have modified our text as advised (see page 6, line 3-6).

In recent years, Sharma et al. concluded chemotherapy is associated with improved overall survival (OS) in patients undergone the treatment of LND (median OS months [Inter Quartile Range (IQR)]: 21.7 [11.8–104] vs 10.1 [5.6–48.1], P = 0.048).

P5-line 8: SEER should have been explained on page 4.

Changes in the text: we have deleted our text as advised.

P5-line 11: STROBE is not explained.

Changes in the text: we have modified our text as advised (see page 6, line 20-21).

We present the following article in accordance with the strengthening the reporting of observational studies in Epidemiology (STROBE) reporting checklist.

Methods

Out of curiosity, was there a specific reason for the selection of patients between 2004 and 2015?

Reply: As you can see, the AJCC 6^{th} were effective after 2003 and the AJCC 8^{th} were publicized after 2016. Therefore, we tried to maintain the version consistency of AJCC and chose the AJCC 6^{th} as a standard to compare the PCSS or OS of patients from 2004 to 2015.

Editions of the AJCC *Cancer Staging Manual*

The publication dates and effective dates for past editions of the AJCC Cancer Staging Manual are:

Edition	Publication Year	Effective Year	Resources
1	1977	1978	AJCC 1st Ed Cancer Staging Manual
2	1983	1984	AJCC 2nd Ed Cancer Staging Manual
3	1988	1989	AJCC 3rd Ed Cancer Staging Manual
4	1992	1993	AJCC 4th Edition Cancer Staging Manual
5	1997	1998	AJCC 5th Ed Cancer Staging Manual
6	2002	2003	AJCC 6th Ed Cancer Staging Manual Part 1 AJCC 6th Ed Cancer Staging Manual Part 2
7	2009	2010	AJCC 7th Ed Cancer Staging Manual
8	2016	2018	Purchase Here

P6-line 6: TNM is not explained.

Changes in the text: we have modified our text as advised (see page 7, line 7-9).

All patients have the information about age, race, grade, cancer tumor node metastasis (TNM) stage on criteria from the American Joint Committee on Cancer (AJCC) 6th versions, the first course of treatment (i.e. surgery, radiotherapy, chemotherapy or several of them), cause of death and survival months.

P6-line 16: PCSS is not explained.

Changes in the text: we have modified our text as advised (see page 7, line 19-21).

Univariate and multivariate cox regression models were performed in order to determine the hazard ratios (HRs) with 95% confidence intervals x(CIs) for penile cancer-specific survival (PCSS).

Results

P7-chapter 1: Why were non-parametric stats used? There are no explanation for that in methods!

Changes in the text: we have modified our text as advised (see page 7, line 14-15; page 9, line 3-4).

We used descriptive statistics to summarize the patients' clinical characteristics and continuous variables expressed as mean± standard deviation.

294 patients were included in the analysis. All patients' median age was 59.3 ± 11.7 years.

P7-lines 7/8 and 12/13, page 8-lines 2/3: Again (like in the abstract), spelling c not C in chemoradiotherapy and chemotherapy. Please be consistent throughout the manuscript.

Changes in the text: we have modified our text as advised.

P7-lines 17: Please use abbreviation PCSS

Changes in the text: we have modified our text as advised (see page 9, line 17-19).

In the N3 setting, the 2-year PCSS was 51.23% in the chemoradiotherapy group and 23.90% in the chemotherapy group and the log-rank test P value was 0.031(Figure 2E).

P7-lines 21/22: Please be more specific on "in order to further determine the effect of adding radiotherapy on PCSS) in different patients"

Changes in the text: we have modified our text as advised (see page 9, line 21-22).

Subgroup analyses were conducted in order to further determine the effect of adding radiotherapy on PCSS in different patients (< 60, >= 60; N0, N1, N2, N3; M0, M1).

Discussion:

Out of curiosity, did the authors (or are planning to do) any analysis of Chinese patients to compare with American patients?

Reply: Due to the small group of patients in just one hospital, we are planning to conduct a multi-center analysis.

P9-line 3: Please use abbreviation PCSS and PeCa only.

Changes in the text: we have modified our text as advised.

P9-line 4-6: Please rephrase sentence by including (45.21%) and (41.11%) directly after with and without in order to cut this sentence short.

Changes in the text: we have modified our text as advised (see page 11, line 4-5).

There was a similar 2-year PCSS rate in all patients group with or without combined radiotherapy (52.98 % v.s. 55.81%).

P9-line 7: improved not could improve

P9-line 8: PCSS not specific survival

Changes in the text: we have modified our text as advised (see page 10, line 5-7).

For patients with stage N3, chemoradiotherapy improved the PCSS, while chemoradiotherapy did not benefit PCSS for patients with stage N0, N1 and N2.

P9-line 11: ILND is not explained.

Changes in the text: we have modified our text as advised (see page 10, line 10-11).

Despite current treatment strategies, patients with advanced PeCa after inguinal lymphadenectomy (ILND) still have a poor prognosis.

P9-line 15: PPLN is not explained.

Changes in the text: we have modified our text as advised (see page 11, line 11-13).

some studies had demonstrated that chemotherapy could both decrease recurrence and improve the survival in patients diagnosed as primary PeCa with positive pelvic lymph nodes (PPLNs).

P10-line 9: NCCN is not explained.

Changes in the text: we have modified our text as advised (see page 13, line 9-12).

In addition, the National Comprehensive Cancer Network (NCCN) guidelines suggest to using adjuvant chemoradiotherapy in pN2–3 patients from the successful experience of treating other squamous cell carcinoma's.

P10-lines 14/17: usually limitations are mentioned and discussed before drawing conclusions.

Changes in the text: we have modified our text as advised (see page 14, line 18 to page 15, line 2).

In summary, in this population-based retrospective study, we investigated whether adding radiotherapy based on chemotherapy can effectively improve the prognosis of patients. Our study demonstrated a significant correlation of chemoradiotherapy with

improved cancer-specific survival of penile cancer (PeCa) in N3 patients. However, the effectiveness of treatment of chemoradiotherapy needs to be proven in many ways and prospective international multicenter studies are necessary in order to improve prognosis for patients with advanced penile cancer.

Table 1:

The variable surgery (p=0.026) highlights a significant difference between chemotherapy vs. chemoradiotherapy. However, the authors do not discuss this different at all.

Reply: Thank you for your reminding. We have added this part in limitation section.

Changes in the text: we have modified our text as advised (see page 14, line 11-15).

Thirdly, the rate of surgery in chemoradiotherapy group was higher than chemotherapy group; it is may due to the more serious condition of patients in chemoradiotherapy group. Maybe this different distribution would affect the result. However, in this study, surgery did not improve the PCSS through the results of multivariate analysis in our collected patients.

Table 2:

No information is provided on what constitute to the multivariate analysis compared to the univariate analyses. Please provide further information (i.e. age, sex, race, grade, T stage, etc.)

Changes in the text: we have modified our text as advised (see table 2 legends).

Table2 Univariate and multivariate analysis for cancer-specific survival in all patients.

*Including American Indian/AK Native, and Asian/Pacific Islander

Some variables (age at diagnosis, N stage, M stage, Surgery and radiotherapy) constitute to the multivariate analysis.

Reviewer C: Thank you for inviting me to evaluate the article titled "Adding radiotherapy based on chemotherapy can improve cancer-specific survival in N3 penile cancer: a SEER-based study".

In this retrospective cohort, the authors showed the data which indicates chemoradiotherapy is effective for N3 penile cancers using SEER database. The authors provide useful foresights, however, corrections of following points are required.

General response to the comments: We thank the reviewers for the valuable suggestions to improve our manuscript. We have carefully revised the manuscript according to these suggestions and believe that it has been significantly improved. The following are our point-by-point responses to the specific comments.

Major points:

Comment 1: In the introduction part, the authors suddenly pointed out that they supposed that adding radiotherapy based on chemotherapy can improve cancer-specific survival in N3 penile cancer. Please state the rationale for the literature.

Reply 1: Thank you for your suggestion.

Changes in the text: we have modified our text as advised (see page 6, line 9-15).

Recently, Yuan et al. reported that adjuvant chemoradiation therapy can improve locoregional control of PeCa. Besides, a retrospective study of Choo et al. was conducted for a total of 23 patients with regional lymph node metastasis and suggested a potential benefit of chemoradiotherapy for patients with extensive regional lymph node metastasis. Therefore, more and more urologists pay attention to the combination of radiotherapy and chemotherapy.

Comment 2: In the discussion part, the authors used a term of "a series of complication"(p.10, line 12). Please describe its meaning in detail.

Reply 2: Thanks.

Changes in the text: we have modified our text as advised (see page 13, line 15-20).

According to the current literature, the most common side effect is skin acute skin

toxicity, which occurring in 83% of the patients received radiotherapy. Besides, some studies also reported the complication of lymphoedema and groin telangiectasia/fibrosis. Until now, no serious or fatal complications have been reported, which may reflect the safety of chemoradiotherapy. More researches focusing on toxicity should be carried out.

Comment 3: In the discussion part, the authors use cited references to show that the incidence of hospitalization-related complications in the chemoradiotherapy group was significantly higher than that in surveillance. In this study, it was thought that it was difficult to evaluate the presence or absence of complications because it was conducted using the SEER database. The authors should state this fact as a limitation.

Reply 3: Thank you for your suggestion. We did not find the part of "incidence of hospitalization-related complications in the chemoradiotherapy group was significantly higher than that in surveillance", but we added what you suggested in the limitation section.

Changes in the text: we have modified our text as advised (see page 14, line 15-17).

Fourthly, it was difficult to evaluate the complications because it was conducted using the SEER database which lacking related information.

Comment 4: In this study, it is not clear what criteria chemoradiotherapy is used for. For example, the number of chemoradiotherapy performed in N0 penile cancer is too small. Therefore, there may be a bias towards chemoradiotherapy for N2-3 penile cancer, and the authors should mention this fact in the discussion part.

Reply 4: As for the question you mentioned about the N0 patients, there is no clear indication for these patients, but a small group of patients really accepted chemoradiotherapy. The specific information about the chemoradiotherapy criteria was not provided, as a limitation due to this big database. Therefore, subgroup analyses were conducted in order to further determine the effect of adding radiotherapy on PCSS in different patients, especially with different N stages, trying to decrease this bias.

Changes in the text: we have modified our text as advised (see page 13, line 1-5).

In this study, chemoradiotherapy had neither a beneficial nor harmful effect for PCSS while it improved the PCSS in patients with N3 stage. This may be due to the fact that adding radiotherapy based on chemotherapy has not obvious effect on N0-2 patients, but it occupies a certain proportion in the total patients, which obscures the beneficial effects of chemoradiotherapy for N3 patients.

Comment 5: The details of lymph node dissection (dissection range) in N + cases are unknown, even when the surgical rate for penile cancer is high, around 80% in both chemoradiotherapy and chemotherapy groups. Without knowing this detail, it is difficult to discuss survival rates. This fact should be mentioned as a limitation.

Reply 5: Thanks for your suggestion. The details of dissection range were not provided in this database, as a big database in American. Therefore, it is necessary to carry out our own research by multi-center cooperation in China.

Changes in the text: we have modified our text as advised (see page 14, line 3-9).

Firstly, our study lacked specific information on chemotherapy, radiotherapy and surgery (e.g. chemotherapy regimens, radiotherapy strategy, lymph node dissection range…). What we got is that most chemotherapy regimens were based on Cisolatin and Radiotherapy was provided at the discretion of the attention radiation oncologist. Therefore, it is necessary for us to research of our own patients in order to get more powerful evidence.

Minor points:

Comment 6: The second half of the discussion part is insufficient. After describing the limitations, the significance of conducting this research should be emphasized a little more. For example, if this report is the first to have a significant difference in N3 penile cancer, it should be emphasized.

Reply 6: Thanks. As you mentioned, we have found the lack of content of discussion

part, therefore we added some contents in the revised manuscript. Besides, we also mentioned the significance in the first paragraph in the discussion.

Changes in the text: we have modified our text as advised (see page 11, line 7-9).

As we known, this is the first study to describe the difference Curative effect between different N stages by using public databases, which may guide our future treatments in PeCa patients.

Comment 7: Because there is no description of the conclusion, please add it.

Reply 7: Thank you for your reminding and we have added this paragraph.

Changes in the text: we have modified our text as advised (see page 14, line 18 to page 14, line 2).

In summary, in this population-based retrospective study, we investigated whether adding radiotherapy based on chemotherapy can effectively improve the prognosis of patients. Our study demonstrated a significant correlation of chemoradiotherapy with improved cancer-specific survival of penile cancer (PeCa) in N3 patients. However, the effectiveness of treatment of chemoradiotherapy needs to be proven in many ways and prospective international multicenter studies are necessary in order to improve prognosis for patients with advanced penile cancer.