Original Article

Adding radiotherapy based on chemotherapy can improve cancer-specific survival in N3 penile cancer: a SEER-based study

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Background: Controversial effectiveness of chemotherapy and still poor prognosis prompt us to find better treatment options. This study targeted at investigating whether adding radiotherapy based on chemotherapy can effectively improve the prognosis of patients, especially for advanced penile cancer.

Methods: 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. 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). Subgroup analysis via multivariate Cox models were conducted to discovery the different effect in population with different features.

Results: 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. In multivariate analysis of all patients, combined chemoradiotherapy was not associated with PCSS (HR =0.90, 95% CI: 0.63–1.29, P=0.572). 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).

Conclusions: Our study demonstrated a significant correlation of chemoradiotherapy with improved cancer-specific survival of penile cancer (PeCa) in N3 patients. Prospective international multicenter studies are necessary in order to improve prognosis for patients with advanced penile cancer.

Keywords: Penile cancer (PeCa); chemotherapy; radiotherapy; prognosis; SEER

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Introduction

Penile cancer (PeCa) is relatively rare in most western countries (i.e., USA and Europe) (1), while the incidence can account for 1–2% of malignant diseases in men in Africa, South America or some other parts of the world (2). The histology of 95% penile cancers are squamous cell (3). Generally, more than 80% of cases can be cured if PeCa is diagnosed early. But when lymphatic metastasis occurs, it is a dangerous disease (4). Current research has validated that regional lymph node spread range is a key prognostic indicator in patients with PeCa, and patients have an especially poor long-term survival with pelvic lymph node (PLN) involvement (5). Pandey *et al.* (6) reported patients with pelvic nodal metastasis (21cases) had a poor prognosis.

As for patients with regional lymph nodes metastasis, the

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current European Association of Urology (EAU) guidelines recommended the treatment of radical lymphadenectomy (LAD) (4). However, outcomes were not satisfactory, leading to the development of adjuvant treatment including radiotherapy and chemotherapy. Recently, Burt *et al.* (7) 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. Besides, Franks *et al.* (8) reported some side effects after radiotherapy (i.e., skin toxicity, scrotal/penile or lower limb lymphedema and groin telangiectasia/fibrosis). On the contrary, Tang *et al.* (9) believed adjuvant pelvic radiation is associated with decreased recurrence and improved survival in patients with PeCa with positive PLNs. Due to this argue of effect, radiotherapy cannot be suggested for the treatment of lymph node metastasis in PeCa in the latest EAU Guidelines (4). Additionally, adjuvant chemotherapy after LAD in node-positive patients has been reported in some small studies. In recent years, Sharma *et al.* (10) 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}. Necchi *et al.* (11) showed the OS of patients with the stage cN0-2 and N3 could not be improved with neoadjuvant chemotherapy and adjuvant chemotherapy. Controversial effectiveness of chemotherapy and still poor prognosis prompt urologist to find better treatment options. Recently, Yuan *et al.* (12) reported that adjuvant chemoradiation therapy can improve locoregional control of PeCa. Besides, a retrospective study of Choo *et al.* (13) 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.

In this study, we used data from the American SEER program to investigate whether adding radiotherapy based on chemotherapy can effectively improve the prognosis of patients, especially for advanced PeCa. We supposed that adding radiotherapy based on chemotherapy can improve cancer-specific survival in N3 PeCa. We present the following article in accordance with the strengthening the reporting of observational studies in Epidemiology (STROBE) reporting checklist (available at http://dx.doi.org/10.21037/tau-20-1044).

Methods

Data source and patient selection

Our data were obtained from the National Cancer Institute's SEER program through SEER*Stat software V.8.3.5, which covers approximately 28% of the U.S. population (https://seer. cancer. gov/, accession numbers 13693-Nov2015 and lh8N79l2). In this study, we selected patients diagnosed with primary PeCa between 2004 and 2015. 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. Our exclusion criteria included (I) with other cancer diagnosis experience; (II) without chemotherapy. The specific selecting process could be seen in *Figure 1*.

Statistical analyses

We used descriptive statistics to summarize the patients' clinical characteristics and continuous variables expressed as mean± standard deviation. Clinicopathologic features were compared between the chemoradiotherapy group and chemotherapy group using Student's *t* test and Pearson's chi-square test. The survival curves were plotted using the Kaplan-Meier method and the log-rank test was conducted. 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). Subgroup analysis via multivariate Cox models were conducted to discovery the different effect in population with different features. All statistical tests were 2-sided, and the significance level was P<0.05. Data were analyzed using the statistical package R (the R foundation; http://www.r-project.org;version3.4.3).

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and 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

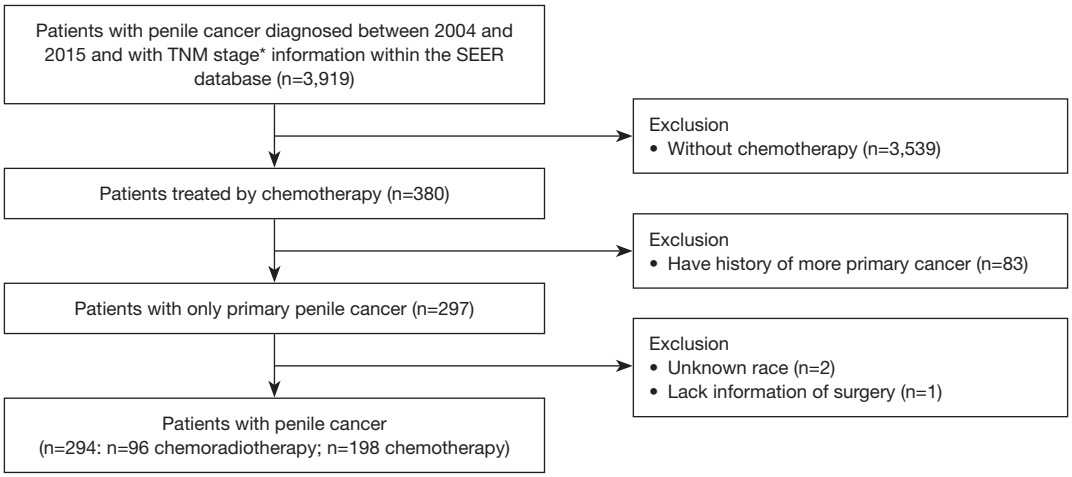

Figure 1 Flow-chart of the participants' selection. *TNM stage on criteria from the AJCC 6th versions. SEER, Surveillance, Epidemiology and End Results; TNM, Tumor node metastasis; AJCC, American Joint Committee on Cancer.

did not require informed consent.

Results

Demographic and tumor characteristics

Two hundred and ninety-four patients were included in the analysis. All patients' median age was 59.3±11.7 years. The demographics and tumor characteristics are presented in *Table 1*. Surgery and race information was missing in 3 (1.01%) patients and our analysis showed that these data met the "missing at random" hypothesis. There were no significant differences in age at diagnosis, race, grade, TNM stage variables between the chemoradiotherapy group and chemotherapy group (P>0.05), except that surgery situation were significantly different (P=0.026).

Association of combined chemoradiotherapy and PCSS

The median follow-up time was 25 months (IQR: 15–45 months), and 145 men died of PeCa. The 2-year PCSS was 52.98% in the chemoradiotherapy group and 55.81% in the chemotherapy group. Kaplan-Meier analysis illustrated that all patients who received combined chemoradiotherapy had a similar PCSS compared with patients who only received chemotherapy; the log-rank test P value was 0.914 (*Figure 2*). In multivariate analysis, combined chemoradiotherapy was not associated with PCSS (HR =0.90, 95% CI: 0.63–1.29, P=0.572) (*Table 2*). 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 2*).

Survival analysis for subgroups

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). Chemoradiotherapy improved the PCSS in N3 patients (HR =0.54, 95% CI: 0.30–0.98, P=0.043, *Figure 3*). There was no significant difference of survival in N0, N1 and N2 patients between the chemoradiotherapy group and chemotherapy group (HR =0.51, 95% CI: 0.12–2.27, P=0.381, *Figure 2B*, *Figure 3*; HR =1.62, 95% CI: 0.64–4.11, P=0.307, *Figure 2C*, *Figure 3*; HR =1.12, 95% CI: 0.60–2.09, P=0.725, *Figure 2D*, *Figure 3*).

Discussion

In this study, we used SEER database in order to investigate the impact of adding radiotherapy based on chemotherapy on PCSS in PeCa patients with stage N0 to N3. There was a similar 2-year PCSS rate in all patients group with or without combined radiotherapy (52.98 % *vs.* 55.81%). For patients with stage N3, chemoradiotherapy improved the PCSS, while chemoradiotherapy did not benefit PCSS for patients with stage N0, N1 and N2. As we known, this is the first study to describe the difference Curative effect between different N stages by using public databases, which

Table 1 Demographic and tumor characteristics between chemoradiotherapy group and chemotherapy group

Variables	Chemotherapy (N=198)	Chemoradiotherapy (N=96)	P value
Age at diagnosis	58.9±11.7	60.2±11.9	0.441
Race			0.386
White	165 (83.3%)	85 (88.5%)	
Black	16 (8.1%)	7 (7.3%)	
Other‡	17 (8.6%)	4 (4.2%)	
Grade			0.101
1	21 (10.6%)	13 (13.5%)	
2	86 (43.4%)	37 (38.5%)	
3	51 (25.8%)	35 (36.5%)	
4	40 (20.2%)	11 (11.5%)	
T*			0.625
T1	67 (33.8%)	24 (25.0%)	
T2	53 (26.8%)	28 (29.2%)	
T3	53 (26.8%)	31 (32.3%)	
T4	14 (7.1%)	8 (8.3%)	
Tx	11 (5.6%)	5 (5.2%)	
N			0.079
N0	49 (24.7%)	11 (11.5%)	
N1	32 (16.2%)	17 (17.7%)	
N2	60 (30.3%)	35 (36.5%)	
N3	47 (23.7%)	30 (31.2%)	
Nx	10 (5.1%)	3 (3.1%)	
M			0.128
M0	162 (81.8%)	77 (80.2%)	
M1	26 (13.1%)	18 (18.8%)	
Mx	10 (5.1%)	1 (1.0%)	
Surgery			0.026
No	44 (22.2%)	11 (11.5%)	
Yes	154 (77.8%)	85 (88.5%)	

Continuous variables expressed as mean ± SD (interquartile range). ‡Including American Indian/AK Native, and Asian/Pacific Islander. *Cancer TNM stage according to criteria from the AJCC 6th versions. SD, standard deviation; TNM, tumor node metastasis; AJCC, American Joint Committee on Cancer.

may guide our future treatments in PeCa patients.

Regional lymph node spread range is a key indicator of prognosis. Widely metastatic lymph nodes often mean poor prognosis (5,14). Despite current treatment strategies, patients with advanced PeCa after inguinal lymphadenectomy (ILND) still have a poor prognosis. The discovery of chemotherapy was a significant technique to improve the prognosis of kinds of cancer patients nowadays,

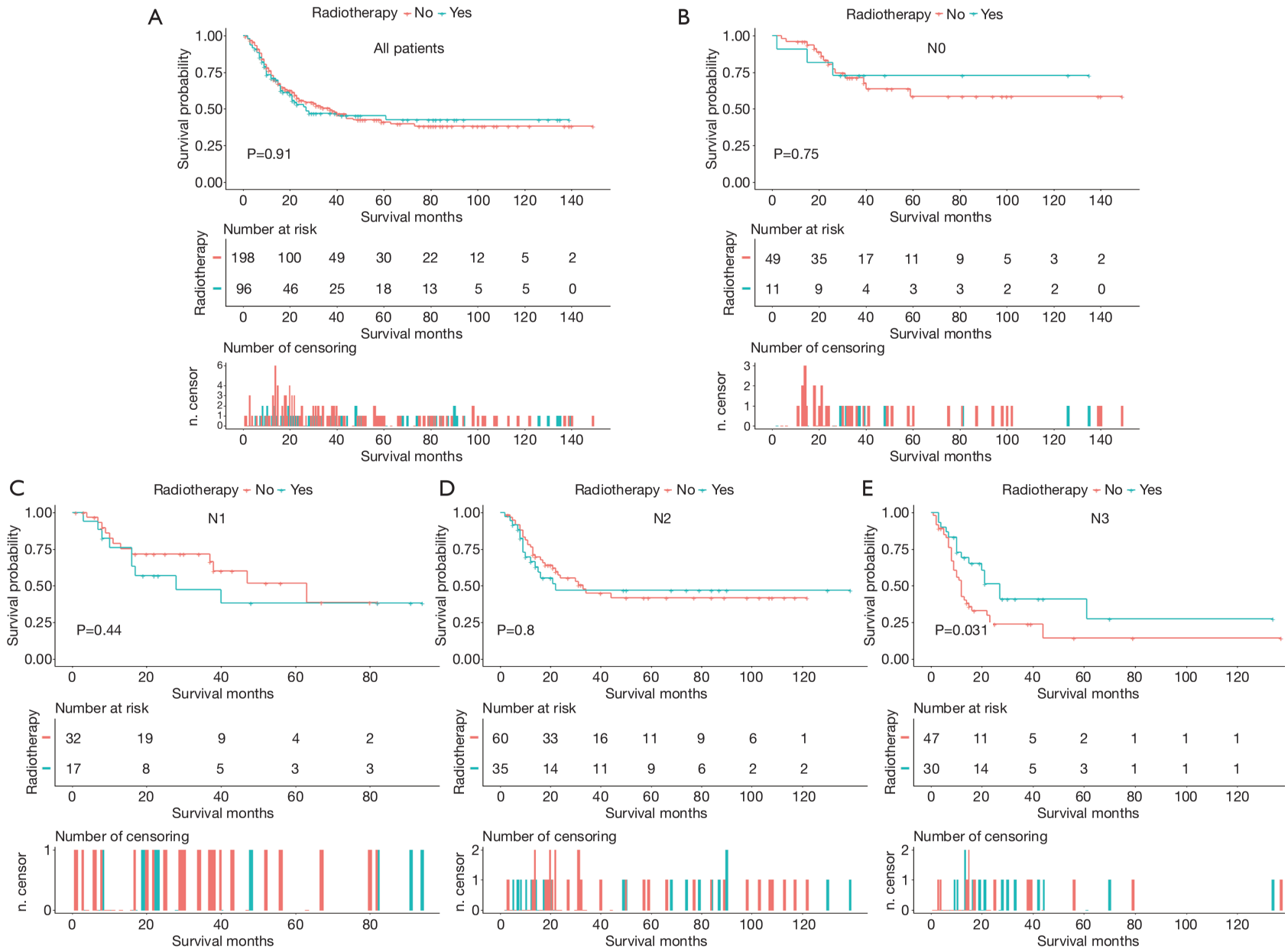

Figure 2 Survival curve in N0-N3 penile cancer patients combined with and without radiotherapy. (A) The survival curve in all penile cancer patients combined with and without radiotherapy. (B) The survival curve in N0 penile cancer patients combined with and without radiotherapy. (C) The survival curve in N1 penile cancer patients combined with and without radiotherapy. (D) The survival curve in N2 penile cancer patients combined with and without radiotherapy. (E) The survival curve in N3 penile cancer patients combined with and without radiotherapy.

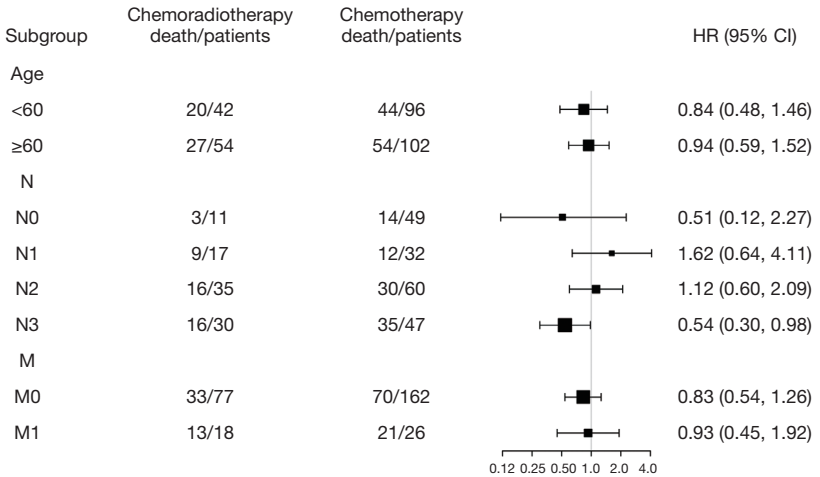

Figure 3 The forest plot for HR comparing cancer-specific survival between the Chemoradiotherapy group and Chemotherapy group according to different variables. HR, hazard ratio; CI, confidence interval.

and 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) (10).

However, even under the treatment of surgery and chemotherapy, the 5-year survival rate of advanced patients is still not satisfactory. Therefore, it is necessary to explore a better treatment program.

Recently, there are successive articles discussing the treatment of combined chemoradiotherapy. In a study presented at the 2019 EAU annual meeting, Ager *et al.* (15) 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% *vs.* 31%) compared to patients who did not (n=27). This conclusion is consistent with the findings of other two studies (12,13). On the contrary, there were some literatures which suspected the effective role of radiotherapy or chemoradiotherapy. Ottenhof *et al.* (16) 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.* (17) 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.* (18), 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 (19) 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.

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. N3 patients whose multiple or bilateral superficial lymph nodes have been attacked have a higher tumor burden and possibly higher risk of recurrence and metastasis than those of patients with N0-2 stage. Adding radiotherapy based on chemotherapy may be more effective and thorough for killing lymphatic metastatic tumor cells. In addition, the National Comprehensive Cancer Network (NCCN) guidelines (20) suggest to using adjuvant chemoradiotherapy in pN2–3 patients from the successful experience of treating other squamous cell carcinoma's (21,22). Therefore, further study is needed to validate the benefit of chemoradiotherapy. Besides, radiotherapy can not only kill tumor cells, but also cause damage to patients with a series of complications.

Table 2 Univariate and multivariate analysis for cancer-specific survival in all patients

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age at diagnosis				
<60	Reference		Reference	
≥60	1.22 (0.88, 1.69)	0.236	1.31 (0.93, 1.84)	0.123
Race				
White	Reference			
Black	1.28 (0.74, 2.24)	0.375		
Other‡	0.84 (0.43, 1.65)	0.613		
Grade				
1	Reference			
2	1.11 (0.64, 1.93)	0.707		
3	1.20 (0.68, 2.14)	0.524		
4	1.26 (0.68, 2.35)	0.465		
T*				
T1	Reference		Reference	
T2	1.78 (1.12, 2.82)	0.015	1.54 (0.96, 2.47)	0.076
T3	1.78 (1.13, 2.83)	0.014	1.43 (0.89, 2.29)	0.139
T4	3.24 (1.77, 5.94)	<0.001	2.83 (1.49, 5.36)	0.001
Tx	2.03 (1.00, 4.14)	0.0516	1.14 (0.43, 3.01)	0.787
N				
N0	Reference		Reference	
N1	1.86 (0.98, 3.53)	0.057	1.58 (0.82, 3.06)	0.174
N2	2.18 (1.25, 3.80)	0.006	1.96 (1.11, 3.46)	0.020
N3	3.99 (2.30, 6.94)	<0.001	2.57 (1.40, 4.71)	0.002
Nx	5.06 (2.31, 11.08)	<0.001	3.35 (1.23, 9.07)	0.018
M				
M0	Reference		Reference	
M1	3.36 (2.27, 4.98)	<0.001	2.79 (1.80, 4.32)	<0.001
Mx	1.98 (0.96, 4.06)	0.064	1.27 (0.40, 4.08)	0.688
Surgery				
No	Reference		Reference	
Yes	0.69 (0.47, 1.03)	0.066	0.86 (0.56, 1.33)	0.503
Radiotherapy				
No	Reference		Reference	
Yes	1.02 (0.72, 1.44)	0.915	0.90 (0.63, 1.29)	0.572

‡Including American Indian/AK Native, and Asian/Pacific Islander. *Cancer TNM stage according to criteria from the AJCC 6th versions. Some variables (age at diagnosis, TNM stage, Surgery and radiotherapy) constitute to the multivariate analysis. TNM, tumor node metastasis; AJCC, American Joint Committee on Cancer; HR, hazard ratio; CI, confidence interval.

According to the current literature, the most common side effect is skin acute skin toxicity, which occurring in 83% of the patients received radiotherapy (8). Besides, some studies also reported the complication of lymphoedema and groin telangiectasia/fibrosis (8,23). 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. In this study, the benefit was not found in N0-3 patients, which may suggest that the unnecessary recommendation of adding radiotherapy in PeCa groups of mild lymphatic metastasis due to the unclear efficacy and potential complications. More studies should be carried out to confirm this finding.

There are some limitations in our study. 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. Secondly, due to the rarity of penile cancer, our study sample size is limited, which still needs more evidences to prove effectiveness of combined chemoradiotherapy. Thirdly, the rate of surgery in chemoradiotherapy group was higher than chemotherapy group; it may be 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. Fourthly, it was difficult to evaluate the complications and the specific morbidity, because it was conducted using the SEER database which lacking related information.

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.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tau-20-1044

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau-20-1044). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and 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.

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