Original Article

Comparing T2-T3 staging of penile cancer according to the American Joint Committee on cancer 8th edition with two modified staging systems in predicting survival outcome: A single-center experience

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ABSTRACT

Introduction: Penile cancer is a rare malignancy of the genitourinary tract. We aimed to validate the recent changes in the T2 and T3 stages of penile cancer in the American Joint Committee on Cancer (AJCC) 8th edition and to compare its predictive ability with two other modified staging systems for survival outcomes.

Methods: This is a retrospective study of patients diagnosed with penile cancer from June 2015 to March 2020. The AJCC 8th edition and two other newly proposed systems by Li *et al.* and Sali *et al.* were used for staging the tumor. All variables were categorized and correlated with lymph node (LN) metastases and overall survival (OS).

Results: Fifty-four patients were eligible for this study. The mean age was 58 years (range 46–72 years). The tumor stage ($P = 0.016$), clinical LN stage ($P = 0.001$), the involvement of the spongiosa ($P = 0.015$) and the cavernosa ($P = 0.002$), lymphovascular invasion (LVI) ($P = 0.000$), and PNI ($P = 0.021$) were found to be the significant predictors of LN metastases. When the 5 year OS was compared between the T2 and T3 stages of the AJCC 8th edition, Li staging and the Sali staging systems, it was 91% and 50.1% ($P = 0.001$), 97.5% and 10.3% ($P = 0.000$), 94.4% and 14.7% ($P = 0.000$), respectively. The presence of LVI ($P = 0.001$) was the most significant independent predictor of OS.

Conclusions: The recent changes in the AJCC 8th edition pertaining to the T2-T3 stage are relevant, although the other two newly proposed staging systems were more precise in predicting the survival outcomes.

INTRODUCTION

Penile cancer is one of the rarest malignancies of the genitourinary tract and has a heterogeneous worldwide distribution. The guidelines for the staging of penile cancer are still evolving. The American Joint Committee on Cancer (AJCC) updates its tumor-node-metastases (TNM) staging system periodically and the most recent update, the AJCC 8th edition, classified the invasion of corpora spongiosa (CS) as pT2 and that of corpora cavernosa (CC) as pT3, irrespective of the urethral involvement among the other changes. These changes were based on the results of a few studies which showed that urethral involvement has no effect on the prognosis and the difference in the survival rates between the pT2 and pT3 patients, when classified according to the previous version of AJCC, was minimal.[1] However, the new AJCC 8th system has not been validated widely and many recent studies could not replicate the results.[2-4] Some authors have even proposed

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modified staging systems which may have superior accuracy in predicting the survival outcomes.[2,3]

Hence, in this study, we aimed to validate the modifications in the T2 and T3 stages of penile cancer in the AJCC 8th edition and compared its accuracy in predicting the survival outcomes with the two other newly proposed staging systems.

MATERIALS AND METHODS

A retrospective analysis of the patients diagnosed with carcinoma penis who underwent treatment at our institute from June 2015 to March 2020 was performed after obtaining clearance from the Institutional Ethics Committee (IEC code: 2021-222-MCh-EXP-42 date: October 13, 21). The data were collected from the hospital records and outdoor visits. All patients with incomplete medical records, advanced disease not amenable to surgery, or with distant metastases were excluded. The diagnosis of penile carcinoma was made on the histopathological examination of the specimens sent after excisional or incisional biopsy of the penile growth. For those patients who were diagnosed elsewhere and were referred to our institute, the histopathology examination (HPE) slides were reviewed at our pathology department to confirm the diagnosis. All patients then underwent primary surgery either in the form of an organ-sparing surgery (glans resurfacing, glansectomy, wide local excision, and partial penectomy) or radical penectomy with perineal urethrostomy, according to the stage of the tumor.[5] Computed tomography scan of the pelvis and abdomen was obtained in patients with palpable inguinal lymph nodes (LN) as a part of metastatic workup and was followed by radical inguinal lymphadenectomy. In patients without palpable inguinal LN and a high risk of LN metastasis (>T1G2), bilateral modified inguinal lymphadenectomy was performed either as an upfront or an interval procedure[6] via open or in a few cases minimally invasive video-endoscopic approach. The follow-up schedule was 3 monthly for the first 2 years and then 6 monthly for 5 years.

The data regarding the demography, tumor morphology, size, location, clinical tumor stage, LN stage, HPE subtype, HPE grades (WHO/International society of Urological Pathology grade),[7] invasion of the CS, CC, or urethra, presence of lymphovascular invasion (LVI), perineural invasion (PNI), surgical procedure, postoperative complications, LN yield, LN density (LND), need for adjuvant therapy and the follow-up were compiled. At first, the latest AJCC 8th edition was used to stage the tumors. For those patients who were admitted before 2018, their HPE reports were reviewed by our pathology department and the disease was reclassified according to the latest AJCC update. Subsequently, we stratified our data into two more groups according to the newly proposed staging systems by Li *et al.*[2] and Sali *et al.*[3] In the Li staging system, T2 includes the involvement of the CS and/or CC without LVI, whereas T3 includes CS and/or CC involvement with LVI. Similarly, in the Sali staging, T2 is CS and/or CC involvement without LVI/PNI/grade III component and T3 is CS and/or CC involvement with LVI/PNI/Grade III component. Subsequently, all the variables were categorized and correlated with LN metastases and the overall survival (OS). The follow-up time was calculated from the time of the surgery until the time of the last follow-up visit or the death of the patient.

All continuous variables were analyzed using one-way ANOVA test and the categorical variables by the Chi-square or the Fisher's exact tests. The Kaplan–Meier and the multivariate Cox regression techniques were used for survival analysis and the receiver operating characteristic (ROC) curves were generated to find the efficacy of the staging systems to predict LN metastases and OS using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY., USA).

RESULTS

After exploring the hospital database, 71 patients with penile cancer were identified, out of which 54 patients were eligible, and 17 patients were ineligible for this study. The mean age of the patients was 58 years (range 46–72 years). The clinical and pathological variables are described in Table 1. The most commonly performed surgery was partial penectomy (63%) and in almost 70% of the cases, lymphadenectomy was performed. Skin necrosis was the most common postoperative complication (a total of 4 patients, i.e., 7.4%). Adjuvant chemotherapy in the form of three cycles of cisplatin and 5-fluorouracil or cisplatin and capecitabine was given to 17 patients who had biopsy-proven LN metastases. The mean follow-up period was 40 ± 17 months.

The tumor stage ($P = 0.016$), clinical LN stage ($P = 0.001$), involvement of the spongiosa ($P = 0.015$) and cavernosa ($P = 0.002$), LVI ($P = 0.000$), and PNI ($P = 0.021$) were found to be significant predictors of LN metastases [Table 1].

The 5 year OS of the whole cohort was 77.2%, but in those with LN metastases it was 11.8%. In the absence of LN metastases, the 5 year OS was 100%, thus proving it to be an efficient indicator of poor survival. When the 5 year OS between the T2 and T3 stages as per the AJCC 8th edition, Li *et al.* and Sali *et al.* staging systems were compared, it was found to be 91% and 50.1% ($P = 0.001$), 97.5% and 10.3% ($P = 0.000$), and 94.4% and 14.7% ($P = 0.000$), respectively [Figure 1]. Thus, the T2 and T3 classification as described by the AJCC 8th edition and by the two modified staging systems indeed show a statistically significant

Table 1: Clinical and pathological variables in relation with lymph node metastases

Variable	Total (%)	Lymph node negative (−)	Lymph node positive (+)	*P*
Total Patients	54	37	17	
Tumor stage (AJCC 8th)				
T1a	19 (35.2)	17	2	0.016
T1b	4 (7.4)	3	1	
T2	12 (22.2)	9	3	
T3	18 (33.3)	8	10	
T4	1 (1.9)	0	1	
Clinical lymph node stage				
cN1	1 (1.9)	0	1	0.001
cN2	14 (25.9)	8	6	
cN3	6 (11.1)	1	5	
Histopathology				
Sarcomatoid	2 (3.7)	2	0	0.476
Basaloid	1 (1.9)	1	0	
Keratinizing SCC	51 (94.4)	51	0	
Grade				
I	35 (64.8)	27	8	0.148
II	16 (29.6)	8	8	
III	3 (5.6)	2	1	
Spongiosa involved	25 (46.3)	13	12	0.015
Cavernosa involved	19 (35.2)	8	11	0.002
Urethra involved	11 (20.4)	5	6	0.081
LVI present	13 (24.1)	3	10	0.000
PNI present	9 (16.7)	3	6	0.021

AJCC=American Joint Committee on Cancer, SCC=Squamous cell carcinoma, LVI=Lymphovascular invasion, PNI=Perineural invasion

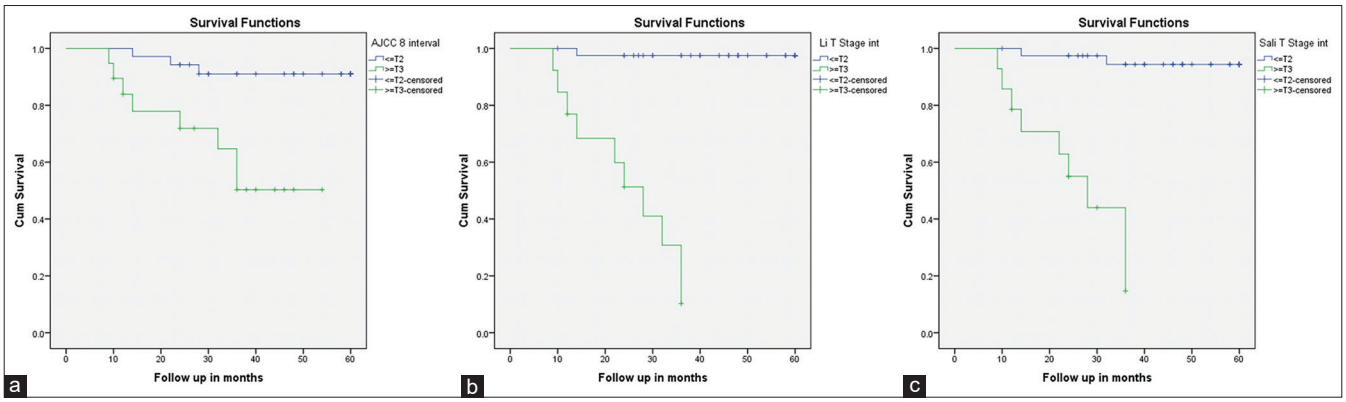

Figure 1: Kaplan–Meier analysis of overall survival according to (a) AJCC 8th T stage, (b) Li *et al*. T stage, and (c) Sali *et al*. T stage. AJCC = American Joint Committee on Cancer

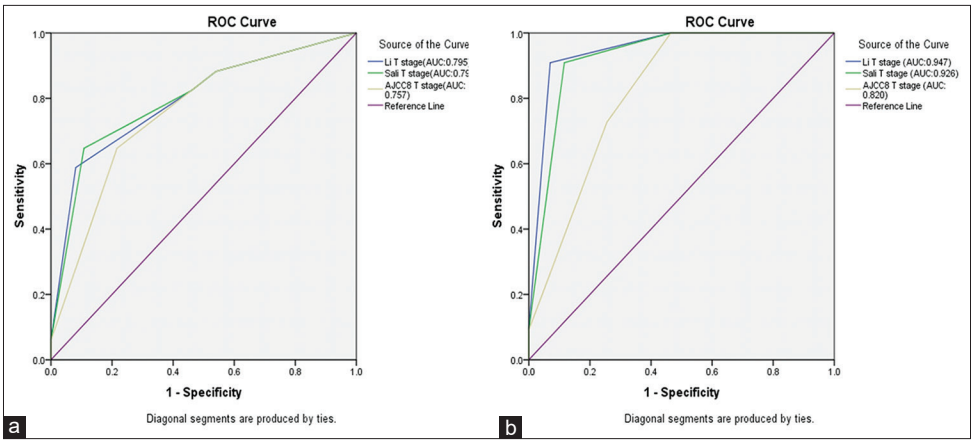

Figure 2: ROC curve analysis predicting (a) LN metastases and (b) overall survival among AJCC 8th and Li *et al*. and Sali *et al*. T stages. ROC = Receiver operating characteristic, LN = Lymph node, AJCC = American Joint Committee on Cancer

Table 2: Cox regression analysis of overall survival

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	Adjusted HR	95% CI	*P*
AJCC (≤pT2 *vs.* ≥pT3)	0.153	0.041–0.578	0.006			
Pelvic lymph node metastases	0.139	0.042–0.463	0.001			
Grade (≤G2 *vs.* ≥G3)	0.561	0.071–4.42	0.584			
LVI+	0.048	0.010–0.225	0.000	0.042	0.005–0.341	0.003
PNI+	0.111	0.032–0.390	0.001			
Lymph node density (<15% vs. ≥15%)	0.203	0.042–0.981	0.047			

HR=Hazard ratio, CI=Confidence interval, AJCC=American Joint Committee on Cancer, LVI=Lymphovascular invasion, PNI=Perineural invasion

difference in the survival outcomes of the patients with penile cancer.

All the variables mentioned in Table 1 were further sub grouped and evaluated by multivariate cox regression analysis. Eventually, only LVI (P = 0.001) was found to be the most significant independent predictor of OS [Table 2].

The area under curve (AUC) obtained from ROC analysis for predicting LN metastases for the AJCC 8th staging system was 0.757 (95% confidence interval [CI], 0.617–0.897), for the Sali staging system was 0.798 (95% CI, 0.661–0.935) and for the Li staging system was 0.795 (95% CI, 0.657–0.932) while the AUC for predicting the OS for AJCC 8th, Sali and Li staging system was 0.820 (95% CI, 0.706–0.935), 0.926 (95% CI, 0.853–1.000), and 0.947 (95% CI, 0.883–1.000), respectively [Figure 2].

DISCUSSION

Tumor staging is an integral part of cancer management as it predicts the outcomes and dictates the treatment options. The most popular staging system adopted worldwide for staging the penile cancer is the AJCC-TNM classification which has been instrumental in classifying, prognosticating, and guiding the treatment since its inception in 1968 through various revisions and modifications. With no exception, the latest edition of AJCC (8th) which was published in 2016 and clinically implemented since 2018, has also brought a few valuable changes such as subdividing T1 into two prognostic groups based on the presence of LVI, PNI, and Grade III.[8] The T2 and T3 stages were also redefined according to the presence of spongiosal and cavernosal invasion, respectively, renouncing the importance of urethral invasion.[9] However, some authors still believe that there is a room for improvement because a significant difference in the prognosis in patients with T2 and T3 disease was not evident after a multivariate analysis in their respective studies[4] and hence, they proposed their modified staging systems incorporating various pathological variables into different subgroups.[2] Several pathological variables have been described as independent risk factors for predicting either LN metastases or poor outcomes in patients with carcinoma penis. As LN metastasis is an established parameter and indicates poor survival,[9,10] many times, it is used as a surrogate for the latter in research.

Like several other studies, we also found T stage, clinical LN metastases, invasion of CS and CC, LVI, PNI, and LND as the significant predictors of LN metastases and poor OS (P < 0.05).[10] Several studies have reported that the invasion of CS is associated with better survival and lower incidence of LN metastases when compared with the invasion of CC (33%–35.8% vs. 48.6%–52.5%).[8-10] This may be the rationale of reclassifying these two entities into separate prognostic T stages in the AJCC 8th edition. Our findings also showed similar findings for LN metastases (CS vs. CC invasion is 48% vs. 57.9%). LVI and PNI are the other two factors commonly associated with early LN metastasis and poor survival.[11] LVI, defined as the invasion of lymph or blood vessels by the tumor cells, is also associated with higher T stage, advanced grade, and distant metastases.[12] We also found LVI to be the only significant independent variable predicting OS after multivariate cox-regression analysis [Table 2]. However, the tumor grade was not found to be significant prognostic marker in our study in contrast to the published literature.[13,14] The importance of urethral invasion in staging was questioned after it was found that small distal lesions in the glans invariably involve the urethra but spare CC without any significant prognostic effects,[15] similar to the findings of our study. LND ≥15% (often defined as the percentage of metastatic LN retrieved after lymphadenectomy) has also been regarded as an independent prognostic factor for recurrence-free survival and OS,[16] but in our study its significance could not be replicated after the multivariate analysis [Table 2].

Li *et al.*,[2] in their study of 411 patients in the training cohort and 436 patients in the external validation cohort found an overlapping OS in the T2 and T3 stages according to the AJCC 8th system. Similar to our study, they also found LVI as the most significant factor determining the survival after the multivariate analysis. Hence, they proposed a modified pathological staging system in which the T2 represents an invasion of the CS and/or CC and/or urethra and T3 includes the presence of LVI in addition to the aforementioned parameters and reported high accuracy in predicting the prognosis.

Similarly, when Sali *et al.*[3] in their study of 142 patients, were unable to validate the AJCC 8th staging system, they proposed a modification of the Li *et al.* staging system[2] and incorporated PNI and/or Grade III into T3 over and above the existing parameters.

In the present study, we stratified our patients into three groups according to the AJCC 8th, Li *et al.*, and the Sali *et al.* staging systems. We then compared the results of OS obtained by the Kaplan–Meier survival plots and calculated the AUC from the ROC curves to validate the efficacy of each of these staging systems.

Among the three groups, we found that Sali staging system was more efficacious for predicting the LN metastases as it had the highest AUC of 0.798 (95% CI, 0.661–0.935) followed by the Li system (0.795 [95% CI, 0.657–0.932]) and the AJCC 8th system (0.757 [95% CI, 0.617–0.897]). Kearns *et al.*[4] in 2019, also analyzed their data according to the AJCC 8th edition for LN metastases and reported an AUC of 0.77 (95% CI, 0.73–0.80) which is almost similar to our study.

In contrast, we found the Li staging system to be slightly more efficient in predicting the OS (AUC = 0.947 [95% CI, 0.883–1.000]) followed by the Sali staging system (AUC = 0.926 [95% CI, 0.853–1.000]) and finally the AJCC 8th system (AUC = 0.820 [95% CI, 0.706–0.935]) [Figure 2].

Similarly, when Li *et al.*[2] analyzed their data for predicting the survival of patients with penile cancer, they found that the AUC of their proposed staging system was significantly higher than the AJCC 8th staging system. They reported an AUC of 0.743 in the training cohort and 0.765 in the external validation cohort whereas the AUC of the AJCC 8th was only 0.691 and 0.698 in the training and the external validation cohort, respectively.

However, the value of the AJCC 8th staging system still cannot be ignored, as, like many other studies, ours also showed significant differences in OS between the T2 and T3 stages (P = 0.001) by the Kaplan–Meier survival analysis [Figure 1].

The main limitation of our study is that it is a retrospective study performed at a single centre with small a sample size and requires further validation.

CONCLUSION

Staging of penile cancer is still evolving and new modifications and inclusions are still being made. However, the recent changes in the AJCC 8th edition related to the T2-T3 stages are relevant and can be validated satisfactorily. Besides, the recently proposed staging systems are also helpful in predicting the survival outcomes with greater conviction and have the potential to get incorporated into the future AJCC updates.

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