Contemporary management of penile cancer: greater than 15 year MSKCC experience

Kelvin A. Moses, MD,[1] Andrew Winer, MD,[1] John P. Sfakianos, MD,[1] Stephen A. Poon, MD,[1] Matthew Kent, BS,[2] Melanie Bernstein, BA,[1] Paul Russo, MD,[1] Guido Dalbagni, MD[1]

[1]Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

[2]Department of Epidemiology and Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, New York, USA

MOSES KA, WINER A, SFAKIANOS JP, POON SA, KENT M, BERNSTEIN M, RUSSO P, DALBAGNI G. Contemporary management of penile cancer: greater than 15 year MSKCC experience. *Can J Urol* 2014;21(2):7201-7206.

Introduction: *Penile cancer is a rare malignancy, and few guidelines are available to define treatment paradigms. For greater understanding of the natural history of surgically treated penile cancer, we analyzed the experience at our institution.*

Materials and methods: *Using an institutional database, we identified 127 patients treated for squamous cell carcinoma of the penis from 1995-2011. Cancer-specific survival (CSS) was calculated using the Kaplan-Meier method. Survival data were compared using the log-rank test. The difference in risk of cancer-specific death by lymph node status and histological grade was determined by univariate Cox regression analysis.*

Results: *Five year CSS for pTis, pT1, pT2, and pT3/4 was 100%, 84% (95% CI 58%-95%), 54% (95% CI 33%-71%), and 54% (95% CI 25%-76%), respectively (p ≤ .005). Three year CSS for patients with N0, N+, and Nx disease was 90% (95% CI 47%-99%), 65% (95% CI 47%-79%), and 86% (95% CI 73%-93%), respectively (p = .03). The receipt of neoadjuvant chemotherapy did not change per 5 year period over the 16 years of our study. Median follow up was 2.8 years.*

Conclusions: *Penile cancer patients with advanced disease had poor survival. Tumor stage and nodal status were significant predictors of CSS. Penis-sparing approaches may be considered for most patients; however, pathological stage and grade dictate the management and ultimate outcome. Further studies are necessary to clarify the benefits of chemotherapy in this disease.*

Key Words: penile cancer, surgery, squamous cell carcinoma, cancer-specific survival, recurrence

Introduction

Penile cancer is a rare malignancy in North America and Europe, with approximately 1600 estimated new cases in the United States in 2014,[1] though it is one of the most common malignancies in South America, Asia, and sub-Saharan Africa.[2,3] Some of the known risk factors include uncircumcised status, chronic inflammatory conditions, and a history of condyloma acuminata, smoking, and possibly human papillomavirus exposure.[4-6] There are a few randomized trials exploring treatment options for penile cancer, but due to the small numbers of patients, management is typically based on retrospective reviews from large referral centers. Consequently, guidelines for treatment, such as those recently published by the European Association of Urology, are based on low grade

Accepted for publication January 2014

Address correspondence to Dr. Kelvin A. Moses, Department of Urologic Surgery, Vanderbilt University, A-1302 Medical Center North, Nashville, TN 37232 USA

recommendations.[6] In order to provide a contemporary perspective to the existing literature on the management of primary penile cancer, we retrospectively reviewed our institution's surgical experience over a greater than 15 year period and report the cancer-specific survival (CSS) based on tumor classification, nodal status, and histological grade.

Materials and methods

After obtaining Institutional Review Board approval, we retrospectively queried the Memorial Sloan-Kettering Cancer Center (MSKCC) surgical database to identify all patients treated for primary squamous cell carcinoma of the penis. We identified 127 patients who underwent surgery for penile cancer from January 1995 to September 2011. We assessed the differences in cancer-specific survival (CSS) by tumor TNM classification, nodal status and histological grade for patients with penile cancer. Additionally, we determined the difference in clinical characteristics between patients who received chemotherapy and those who did not, as well as between surgical approaches.

Demographic and clinical data were collected for each patient, and pathological data were reviewed. All patients gave a complete history and underwent physical examination, with attention to the inguinal region and skin. Radiological staging included a chest x-ray (CXR), and computed tomography (CT) and/or magnetic resonance imaging (MRI) based on the stage of the disease and physician discretion. Neoadjuvant, adjuvant or salvage chemotherapy and/or radiotherapy were also administered according to the discretion of the treating physician. Settings in which chemotherapy was considered included bulky and/or unresectable nodal disease, pelvic lymphadenopathy or metastatic disease, palliative treatment, or patient preference. Inguinal lymphadenectomy was considered in patients with high grade T1 disease or ≥ T2 disease with clinically negative nodes. Additionally, patients with palpable lymphadenopathy deemed resectable were considered for lymphadenectomy, and those with positive inguinal nodal disease were also considered for pelvic lymphadenectomy. Patients who were eligible for lymphadenectomy and did not undergo surgery had excessive comorbidity (n = 1), underwent palliative treatment for extensive disease (n = 3), refused surgical therapy (n = 10), or were lost to follow up prior to recommended lymphadenectomy (n = 3). Clinical and pathological staging was reported according to the 2009 American Joint Committee on Cancer (AJCC) 7th edition Cancer Staging Manual. Patients underwent a follow up schedule based on National Comprehensive Cancer Network (NCCN) guidelines. All patients received a physical exam of the penis and inguinal area. For patients with metastatic nodal disease on surveillance underwent chest imaging (CXR or CT) and abdominal and pelvic CT or MRI.

Chi-square analysis was used to describe the differences in clinical T, N, and M classifications by chemotherapy status. CSS was calculated using the Kaplan-Meier method, which was stratified by lymph node status (positive versus negative), histological grade (1, 2, or 3/4), or pathological tumor classification (in-situ [Tis], T1, T2, or T3/4). CSS data were compared using the log-rank test. Survival time was calculated from the time of surgery to death or censored at the date of most recent follow up for patients who were alive. Univariate Cox regression analysis was used to determine the difference in risk of cancer-specific death by lymph node status and histological grade. All statistical analyses were performed using Stata 12.0 (StataCorp, College Station, TX, USA).

Results

Table 1 summarizes the characteristics and treatment type for the 127 patients surgically treated for penile cancer, and Figure 1 demonstrates the disease-specific survival of the cohort (3y-79%; 5y-73%). Median age was 61 years (IQR 51, 72). In total, 24 patients died of their disease. The median follow up for surviving patients was 2.8 years. Sixty-six (52%) patients presented with ≤ T1 disease, while 59 (46%) had invasive or locally advanced disease. The majority of patients had no clinical evidence of nodal (n = 74/126, 59%) or metastatic disease (n = 112/126, 89%). One hundred thirteen patients (89%) were managed with penis-sparing surgical approaches, while radical penectomy was utilized in 14 patients (11%).

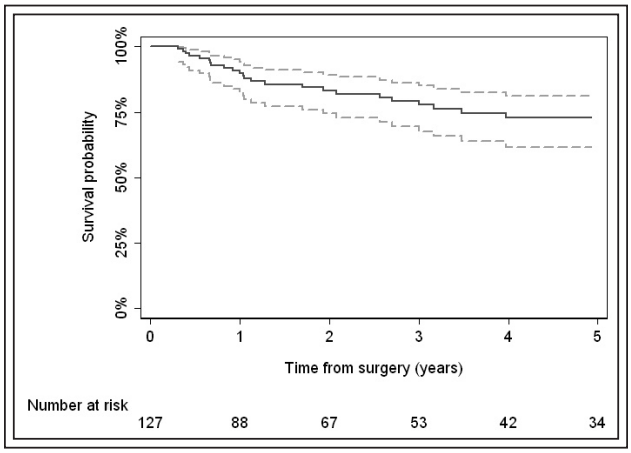

Figure 1. Cancer-specific survival of the entire cohort.

TABLE 1. **Patient demographics and clinical characteristics (n = 127)**

	Number (%)
Age (years)	
< 40	9 (7)
40-49	18 (14)
50-59	34 (27)
60-69	28 (22)
70-79	28 (22)
≥ 80	10 (8)
Race	
White	108 (85)
Black	6 (5)
Other	13 (10)
Body mass index, median (IQR)	29.0 (26.9, 33.2)
Circumcised	20 (16)
Current Smoker	72 (57)
Surgical approach	
Excisional biopsy/ circumcision	42 (33)
Partial penectomy	71 (56)
Radical penectomy	14 (11)
Pathological T classification	
Tis	32 (25)
T1	34 (27)
T2	42 (33)
T3	17 (13)
T4	1 (1)
Tx	1 (1)
Clinical N classification	
N0	74 (59)
N1	23 (18)
N2	20 (16)
N3	6 (5)
Nx	3 (2)
Pathological N classification	
N0	20 (16)
N1	12 (9)
N2	12 (9)
N3	17 (13)
Nx	66 (53)
Clinical M classification	
M0	112 (89)
M1	13 (10)
Mx	1 (1)

1 patient with missing clinical N classification data
1 patient with missing clinical M classification data

Among the 42 patients who had excisional biopsy/ circumcision, 3 patients had local recurrence, all with T1 disease. Of the 3 patients, 2 were found to have a positive surgical margin. None of these 42 patients experienced regional or distant recurrence, nor did they have node dissection.

Of the 71 patients who underwent partial penectomy, 4 experienced local recurrence and 18 had regional/ distant recurrence. Of the 4 patients with local recurrence, 3 were pT2 and one was pT3 with all but 1 patient receiving a node dissection at time of surgery. All 4 patients with local recurrence had negative margins. Of the 18 patients with regional/distant recurrence, 3, 11, 3, and 1 patient(s) were pT1, pT2, pT3, and unknown pathology, respectively. Fourteen patients had an inguinal lymph node dissection and 1 patient underwent excision of a groin mass. None of the 14 patients who had radical penectomy experienced local recurrence, while 6 had regional/ distant recurrence. Of these 6 patients, 4 were pT2, 1 was pT3, and 1 was pT4. Two patients underwent a node dissection and one had excision of a groin mass.

Compared to patients who did not receive chemotherapy, patients who received chemotherapy were more likely to have a T3 or T4 cancer (30% versus 11%, $p < .0005$), have positive nodes (85% versus 30%, $p < .0005$), and have distant metastases (35% versus 6%, $p < .0005$). We analyzed the trend in receipt of neoadjuvant chemotherapy over time and did not note a difference per 5 year period (1995-2000: 7 patients; 2000-2005: 5 patients; 2005-2010: 5 patients; 2010-Sept 2011: 3 patients). Figure 2 shows the Kaplan-Meier curve for CSS of patients with T2 or greater disease

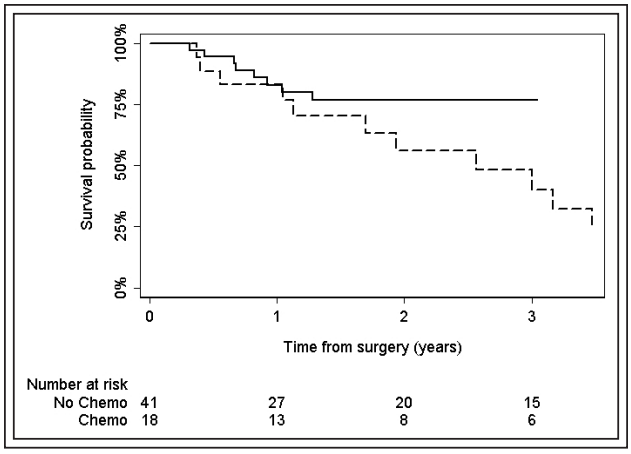

Figure 2. Cancer-specific survival in patients with clinical T classification ≥ T2 according to receipt of chemotherapy (no chemotherapy: solid line, chemotherapy: dashed line).

who did or did not receive chemotherapy. The 3 year survival probability differed significantly between the no chemotherapy group (77%; 95% CI 59%-88%) and the chemotherapy group (48%; 95% CI 22%-71%) (p = .004).

The CSS according to pathological T classification and N classification are shown in Figure 3. Disease-specific survival significantly decreased as pathological T-classification increased, see Figure 3a. The 5 year survival for Tis, T1, T2, and T3/4 disease was 100%, 84% (95% CI 58%-95%), 54% (95% CI 33%-71%), and 54% (95% CI 25%-76%), respectively, representing an absolute disease-specific survival difference of 46% from Tis to T2-4 disease (p = 0.005).

Sixty-one patients underwent lymph node dissection for clinically palpable nodes and/or high-grade pT1 disease or higher. Nine patients had unilateral inguinal lymphadenectomy, 49 had bilateral inguinal lymphadenectomy, 39 of these patients had a bilateral pelvic lymphadenectomy along with their inguinal node dissection, and 3 underwent sentinel lymph node biopsy. We found positive lymph nodes in 37 (60.6%) of patients; specifically 17, 15 and 5 patients had a final pathology of N1, N2 and N3, respectively. The 3 year CSS for patients with N0, N+, and Nx disease was 90% (95% CI 47%-99%), 65% (95% CI 47%-79%), and 86% (95% CI 73%-93%), respectively (p = .03), Figure 3b. There was a statistically significant difference in survival between patients with positive and negative lymph nodes, with a 5 year CSS of 90% for patients with negative lymph nodes vs 57% for patients with positive lymph nodes (p < .001).

Kaplan-Meier analysis of 3 year CSS according to histological grade for the 96 patients for whom this information was available showed a significant difference in survival between patients with histological grades 1, 2, and 3/4 disease, namely 82% (95% CI 44%-95%), 79% (95% CI 63%-88%), and 51% (95% CI 27%-72%), respectively (p = .001).

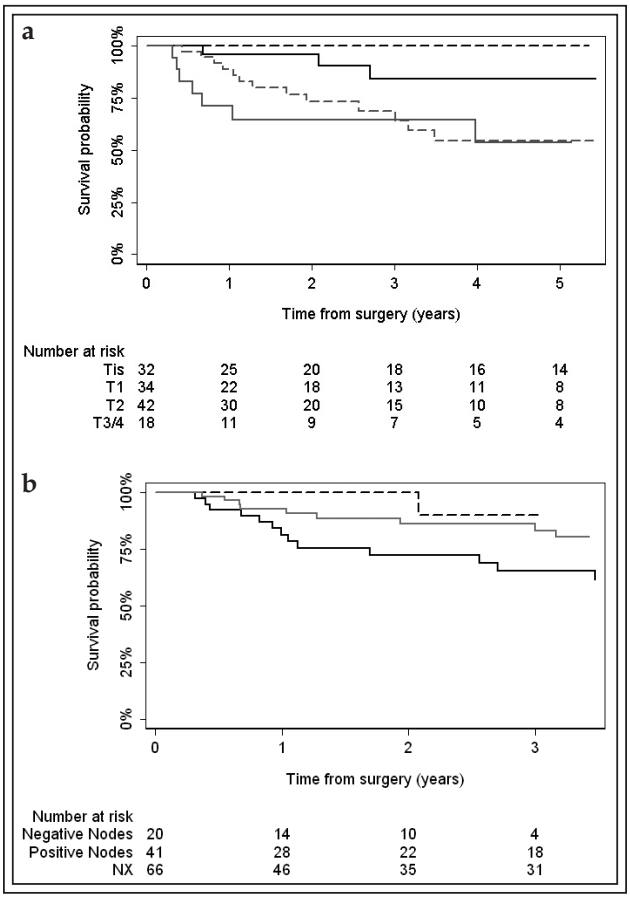

Figure 3. Cancer-specific survival in patients according to: **a)** pathological T classification (Tis: dashed line, T1: solid black line, T2: dashed grey line, T3 & T4: solid grey line); **b)** pathological N classification (N0: dashed line, N+: solid black line, Nx: solid gray line).

Discussion

We identified 127 patients over a greater than 15 year period who were treated for penile cancer with almost 3 years of follow up in surviving patients. Differences in pathological tumor classification, nodal status, and histological grade demonstrated significant reductions in CSS. The results shown here should be interpreted in the context of variations in administration of chemotherapy. Neoadjuvant chemotherapy is not routinely given at our institution, as described in other series,[7] and the majority of patients with a tumor deemed completely resectable underwent surgery prior to any other therapy.

Most patients were managed with penis-sparing surgical approaches, via excisional biopsy/circumcision or partial penectomy. The goal of penis-sparing approaches is to gain local control of the primary tumor while leaving an adequate amount of penile length for normal voiding and sexual function. The 3 year CSS in patients who underwent excisional biopsy/circumcision was 100%, while CSS in the partial and radical penectomy groups was 71% and 57%, respectively. Presumably, this reduction is not due to the surgical approach, but rather because patients who are receiving more aggressive treatment likely have worse disease (nodal or metastatic), which negatively impacts survival. Additionally, we identified recurrence in 29 patients, with local recurrence in 7 patients who underwent penis-sparing surgery. Our results are similar to those described by Leijte et al

from two medical centers in the Netherlands.[8] In their analysis of 700 patients, 130 patients experienced local recurrence, with a cumulative risk of recurrence at 3 years of approximately 18%. Of the 415 patients who underwent penile-sparing surgery, 115 patients experienced local recurrence. In a prior report from MSKCC, Korets et al identified 32 patients who underwent partial penectomy, revealing 1 patient with local recurrence 4 months after initial surgery.[9] In this cohort, the surgical margin was typically 1 cm from the palpable tumor. There is no consensus regarding the optimal margin distance, though a recent review of the literature suggests that a surgical margin within millimeters of the tumor is likely safe.[10] Patients with isolated local recurrence still have a 5 year CSS > 90%;[9-11] however, those with regional or distant recurrence have poor outcomes.

A significant proportion of patients presented with locally advanced or metastatic disease. Patients with higher-stage, node-positive or metastatic disease were more likely to receive chemotherapy in our study, and patients with clinical T2 or greater disease who received chemotherapy had significantly lower 3 year CSS than those who did not receive chemotherapy (48% versus 77%, respectively; p = .004). As was seen with our CSS data for surgical radical penectomy, this reduction in survival in the group that received chemotherapy likely reflects selection of patients with worse disease, and not necessarily a negative impact of chemotherapy.

Adjuvant chemotherapy for locally advanced and metastatic disease has not shown durable responses, and early experience with regimens such as methotrexate, bleomycin, and cisplatin (CMB) had significant toxicity with few complete responses.[12,13] In the few patients who underwent primary chemotherapy, the best responses were found in those able to undergo consolidative surgical resection. The disappointing results from adjuvant trials have led groups to identify better drug combinations administered in a neoadjuvant fashion. Leijte et al reviewed 20 patients over a 33 year period who were treated with various regimens of neoadjuvant chemotherapy, ranging from single-agent bleomycin to combination therapy with CMB.[14] Responders had a 5 year survival of 56%, whereas all patients who were non-responders died within 9 months of initiation of therapy. Eight of 9 patients who were responders and had consolidative surgery demonstrated long-term survival at follow up of 20.4 months. Surgery to gain local control in patients who were non-responders did uniformly poorly. Investigators from MD Anderson identified 10 patients with metastatic penile cancer who had neoadjuvant chemotherapy followed by surgical resection for stable, partial, or complete response.[15] Half of the patients received ifosfamide, paclitaxel, and cisplatin chemotherapy (TIP). Three patients were N0 after chemotherapy (all received TIP regimen), and the 5 year survival was 40%. Additionally, the authors demonstrated a more favorable toxicity profile in comparison to prior studies, which primarily used CMB. These findings served as the basis for a non-randomized, phase II clinical trial from MD Anderson utilizing neoadjuvant TIP in patients with advanced nodal disease and no distant metastasis.[7] Fifty percent of men had an objective response to therapy, 20% had disease progression, and 73% of men underwent consolidative surgery. Patients who achieved an objective response had a significant improvement in time to progression and overall survival (OS), and median OS for 20 patients who died was 17.1 months. The chemotherapy regimen was relatively well tolerated and there were no chemotherapy-related deaths. As noted in the introduction, however, these numbers of patients are too small to reach well-established guidelines.

We found an overall 3 and 5 year disease-specific survival of 79% and 73% in our cohort of 127 patients. There were significant differences in CSS by tumor classification, nodal status, and pathological grade. Patients with Tis and T1 disease had 5 year CSS of 100% and 84%, respectively, while higher-stage disease had predictably worse survival. Approximately 32% of patients had pN+ disease, and node-positivity conferred an absolute 33% reduction in CSS at 5 years, with a significantly increased risk of death (HR = 5.6). Well- and moderately-differentiated disease had similar 3 year CSS (82% and 79%), while poorly- and undifferentiated disease survival was significantly lower (51%). The ability to identify pathological factors that predict positive inguinal and/or pelvic lymphadenopathy is important in light of the poor outcomes of patients with node-positive disease. Slaton et al retrospectively examined numerous pathological variables in 30 node-negative and 18 node-positive patients who had surgical resection for primary penile cancer.[16] They found that pathological stage ≥ T2, lymphovascular invasion, and > 50% poorly differentiated cancer were significantly associated with nodal metastasis. Several groups have devised nomograms to determine CSS after treatment for penile cancer with minor variations in the number of variables used for calculation.[17-19] To date, the simplest and most accurate nomograms utilize a combination of tumor stage and grade based on Surveillance, Epidemiology, and End Results (SEER), AJCC, or TNM classifications,

with accuracy of predicting cancer-specific mortality of approximately 70%-80%.[18,19] Clearly, patients with invasive tumors are at risk for regional or distant disease and cancer-specific mortality, and merit close follow up after treatment of the primary tumor.

Limitations of this study include a relatively small number of patients and heterogeneous management of patients who received chemotherapy. This precluded any meaningful analysis or conclusions regarding the impact of these therapies. However, small numbers of patients are common in studies regarding penile cancer due to its overall rarity in the United States. Additionally, MSKCC is a tertiary/quaternary center, which represents a potential referral bias towards higher-grade or more widely disseminated disease, which potentially skews survival data. In particular a major limitation of our study is our median follow up time of 3 years for surviving patients, which likely reflects the fact that low stage patients may return to their original treating physician while advanced stage patients remain under our care. Nevertheless, our study represents one of the largest contemporary series of management of penile cancer, and even in a contemporary series tumor classification, grade, and node positivity remain the most significant factors in determining CSS.

Conclusion

Penile cancer is a rare malignancy in the United States and Europe that is primarily managed surgically, with neoadjuvant or adjuvant chemotherapy used for patients with advanced disease. The majority of patients can be managed with penis-sparing approaches with acceptable recurrence rates and excellent survival, at least within the short term. Efforts to combine institutional databases and perform prospective trials are necessary to standardize and optimize treatment of penile cancer. □

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin* 2014;64(1):9-29.
2. Misra S, Chaturvedi A, Misra NC. Penile carcinoma: a challenge for the developing world. *Lancet Oncol* 2004;5(4):240-247.
3. Bleeker MC, Heideman DA, Snijders PJ, Horenblas S, Dillner J, Meijer CJ. Penile cancer: epidemiology, pathogenesis and prevention. *World J Urol* 2009;27(2):141-150.
4. Dillner J, von Krogh G, Horenblas S, Meijer CJ. Etiology of squamous cell carcinoma of the penis. *Scand J Urol Nephrol Suppl* 2000;(205):189-193.
5. Daling JR, Madeleine MM, Johnson LG et al. Penile cancer: importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. *Int J Cancer* 2005;116(4):606-616.
6. Pizzocaro G, Algaba F, Horenblas S et al. EAU penile cancer guidelines 2009. *Eur Urol* 2010;57(6):1002-1012.
7. Pagliaro LC, Williams DL, Daliani D et al. Neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy for metastatic penile cancer: a phase II study. *J Clin Oncol* 2010;28(24):3851-3857.
8. Leijte JA, Kirrander P, Antonini N, Windahl T, Horenblas S. Recurrence patterns of squamous cell carcinoma of the penis: recommendations for follow-up based on a two-centre analysis of 700 patients. *Eur Urol* 2008;54(1):161-168.
9. Korets R, Koppie TM, Snyder ME, Russo P. Partial penectomy for patients with squamous cell carcinoma of the penis: the Memorial Sloan-Kettering experience. *Ann Surg Oncol* 2007;14(12):3614-3619.
10. Solsona E, Bahl A, Brandes SB et al. New developments in the treatment of localized penile cancer. *Urology* 2010;76(2 Suppl 1): S36-42.
11. Philippou P, Shabbir M, Malone P et al. Conservative surgery for squamous cell carcinoma of the penis: resection margins and long-term oncological control. *J Urol* 2012;188(3):803-808.
12. Corral DA, Sella A, Pettaway CA, Amato RJ, Jones DM, Ellerhorst J. Combination chemotherapy for metastatic or locally advanced genitourinary squamous cell carcinoma: a phase II study of methotrexate, cisplatin and bleomycin. *J Urol* 1998;160(5):1770-1774.
13. Hakenberg OW, Nippgen JB, Froehner M, Zastrow S, Wirth MP. Cisplatin, methotrexate and bleomycin for treating advanced penile carcinoma. *BJU Int* 2006;98(6):1225-1227.
14. Leijte JA, Kerst JM, Bais E, Antonini N, Horenblas S. Neoadjuvant chemotherapy in advanced penile carcinoma. *Eur Urol* 2007;52(2):488-494.
15. Bermejo C, Busby JE, Spiess PE, Heller L, Pagliaro LC, Pettaway CA. Neoadjuvant chemotherapy followed by aggressive surgical consolidation for metastatic penile squamous cell carcinoma. *J Urol* 2007;177(4):1335-1338.
16. Slaton JW, Morgenstern N, Levy DA et al. Tumor stage, vascular invasion and the percentage of poorly differentiated cancer: independent prognosticators for inguinal lymph node metastasis in penile squamous cancer. *J Urol* 2001;165(4):1138-1142.
17. Kattan MW, Ficarra V, Artibani W et al. Nomogram predictive of cancer specific survival in patients undergoing partial or total amputation for squamous cell carcinoma of the penis. *J Urol* 2006;175(6):2103-2108; discussion 2108.
18. Zini L, Cloutier V, Isbarn H et al. A simple and accurate model for prediction of cancer-specific mortality in patients treated with surgery for primary penile squamous cell carcinoma. *Clin Cancer Res* 2009;15(3):1013-1018.
19. Thuret R, Sun M, Abdollah F et al. Tumor grade improves the prognostic ability of American Joint Committee on Cancer stage in patients with penile carcinoma. *J Urol* 2011;185(2):501-507.