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ORIGINAL ARTICLE **CME**

Squamous Cell Carcinoma of the Penis: Fourteen-year Experience from a Tertiary Institution

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ABSTRACT

Objective: *Penile cancer is a rare disease and more than 95% of the disease is squamous cell carcinoma (SCC). This study aimed to report data of penile SCC from a regional institution in Hong Kong.*

Methods: *Patients with histologically confirmed SCC of the penis who were referred to our institution between January 2000 and December 2013 were retrospectively identified from our institutional patient database. Clinical, pathological, treatment, and survival data were collected and subsequently analysed.*

Results: *During the study period, 30 cases of SCC of the penis were identified. The median age of patients was 73 years. Most patients presented with T1-T3 disease and around one-third were node-negative. Radical surgery was performed in 18 patients, of whom two received adjuvant radiotherapy. A further patient received radical brachytherapy and another underwent radical external beam radiotherapy. For those who received radical surgery, 44.4% developed locoregional recurrence. The 5-year disease-free survival and overall survival was 32.8% and 43.8%, respectively. Both patients who received radical radiotherapy developed recurrence. The median overall survival of all the patients was 22 months.*

Conclusion: *Optimal upfront radical treatment and salvage surgery is vital for survival. Adjuvant treatment may improve survival but further randomised trials are needed to evaluate the optimal treatment strategies for patients with SCC of the penis.*

Key Words: *Penis neoplasms; Prognosis; Radiotherapy; Surgery; Therapeutics*

中文摘要

陰莖鱗狀細胞癌：一所提供第三層醫療服務的醫院的14年經驗分享

司徒安頤、鄭海清、吳惠敏、顏繼昌

目的：陰莖癌是一種罕見的疾病，95%以上的病例均屬於鱗狀細胞癌。本研究旨在報告香港一所分區醫院有關陰莖鱗狀細胞癌的數據。

方法：從病人數據庫中找出2000年1月至2013年12月期間到上述醫院並由病理學證實患有陰莖鱗狀細胞癌的病人紀錄。搜集並分析其臨床、病理、治療結果和存活數據的資料。

結果：研究期間陰莖鱗狀細胞癌共有30例。患者年齡中位數73歲。大多數患者屬T1至T3期，三分之一為淋巴結陰性。18例接受根治性手術，其中兩人接受輔助放療。1例接受根治性近距離放療，另1

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例接受根治性體外放療。接受根治性手術的患者中44.4%有局部復發。五年無病生存率為32.8%，五年總生存率為43.8%。接受根治性放療的兩名患者均有復發。所有患者的總生存中位數為22個月。

結論：對於陰莖鱗狀細胞癌，接受根治性治療和挽救手術至關重要。輔助治療可能可以提高存活率，但還須要進一步的隨機試驗以評估陰莖鱗狀細胞癌患者的最佳治療策略。

INTRODUCTION

Penile cancer is a rare malignant disease. The annual incidence of squamous cell carcinoma (SCC) of the penis is approximately 1.0 per 100,000 men in Hong Kong and the number of new cases in year 2012 was 32.[1] More than 95% of penile cancer is SCC. It originates from the epithelium of the inner prepuce or the glans. Penile cancer is common in regions with a high prevalence of human papillomavirus (HPV) and at least one-third of cases are attributed to HPV-related carcinogenesis. The incidence of penile cancer increases with age and peaks at the sixth decade of life.[2] We report our institutional experience of SCC of the penis over 14 years.

METHODS

Patient database of our institution were reviewed to identify patients treated for primary SCC of the penis from January 2000 to December 2013. We identified 30 patients with primary SCC of the penis. Demographic, clinical, and pathological data were reviewed retrospectively from patients' case records. All cases were restaged using the 2010 American Joint Committee on Cancer (7th edition) staging criteria; if surgery was not performed, clinical staging was applied. Follow-up and survival data were calculated from the date of histological diagnosis to most-recent visit or death.

Descriptive analyses were used for patient demographics and clinicopathological characteristics. Statistical analyses were conducted using the Statistical Package for the Social Sciences (Windows version 21.0; SPSS Inc, Chicago [IL], USA). The Kaplan-Meier method was used to calculate overall and disease-free survival.

RESULTS

Demographics and Staging

Between January 2000 and December 2013, 30 patients who had primary SCC of the penis were identified (Table 1). All patients, except one, were Chinese. The median age at diagnosis was 73 years (range, 33-91 years) and 80% (24/30) were aged >60 years. Overall stage at presentation was I (0%), II (23.3%), III (16.7%), or IV (26.7%). Most patients in our series presented with T1-T3 disease and one patient presented with clinical T4

Table 1. Demographics, and clinical and pathological characteristics of patients (n=30).

Characteristic	No. (%*) of patients†
Age (years)	
<60	6 (20.0)
60-70	7 (23.3)
71-80	10 (33.3)
>80	7 (23.3)
Stage	
I	0
II	7 (23.3)
III	5 (16.7)
IV	8 (26.7)
Unknown	10
T-stage	
T1	7 (23.3)
T2	8 (26.7)
T3	9 (30.0)
T4	1 (3.3)
Unknown	5
N-stage	
N0	11 (36.7)
N1	4 (13.3)
N2	1 (3.3)
N3	6 (20.0)
Unknown	8
M-stage	
M0	19 (63.3)
M1	1 (3.3)
Unknown	10
Grade	
I	10 (33.3)
II	8 (26.7)
III	4 (13.3)
Unknown	8
Lymphovascular invasion	
Yes	8 (26.7)
No	9 (30.0)
Unknown	13
Margin	
Clear	17 (56.7)
Close (<5 mm) / involved	2 (6.7)
Unknown	1
Not applicable (surgery not done)	10
Smoking history	
Yes	18 (60.0)
No	8 (26.7)
Unknown	4

* %s were calculated based on total number of patients in this series.

† Because of rounding, not all percentages total 100.

disease with direct invasion of the pubic symphysis. Among the eight patients with unknown clinical or pathological node status, five underwent local surgery to the primary tumour only, one had palliative radiotherapy to the pelvis, and two passed away shortly after histological confirmation. Although no HPV testing was performed in any of our patients, seven (23.3%) patients had a history of phimosis or paraphimosis and 18 (60.0%) were current or ex-smokers.

Treatment

Radical Treatment

Radical treatment was administered to 20 patients, of whom 18 underwent curative surgery, one patient underwent brachytherapy, and one received local external beam radiotherapy.

Among those who underwent radical surgery, one (5.5%) underwent circumcision only, six (33.3%) underwent either partial or total penectomy, four (22.2%) underwent penectomy with ipsilateral inguinal lymph node dissection, six (33.3%) underwent penectomy with bilateral inguinal lymph node dissection, and one (5.5%) underwent radical circumcision and was scheduled for sequential lymph node dissection (Table 2).

Two patients received adjuvant external beam radiotherapy: one patient was given adjuvant radiotherapy to true pelvis and bilateral groins (50 Gy in 25 daily fractions over 5 weeks then electron boost to left groin with 9 Gy in 3 daily fractions over 3 days) due to positive left inguinal lymph node after total penectomy and left inguinal lymph node dissection. The other patient received adjuvant radiotherapy to the right groin only (58 Gy in 29 daily fractions over 6 weeks) due to prior suboptimal inguinal lymph node surgery consisting of right inguinal lymph node excision only together with partial penectomy and left inguinal lymph node dissection.

Table 2. Treatment modalities.

Treatment modality*	No. (%) of patients
Radical treatment (n = 20)	
Surgery	18 (100)
Circumcision only	1 (5.5)
Partial / total penectomy	6 (33.3)
Penectomy with ipsilateral inguinal lymph node dissection	4 (22.2)
Penectomy with bilateral inguinal lymph node dissection	6 (33.3)
Others	1 (5.5)
Radiotherapy	2 (100)
External beam radiotherapy	1 (50)
Brachytherapy	1 (50)
Palliative treatment (n = 7†)	
Penectomy	2 (28.5)
Radiotherapy	6 (85.7)
Chemotherapy	1 (14.2)

* 3 Patients died shortly after histological diagnosis and thus were not given any form of oncological treatment.

† Some patients may have received more than one palliative treatment for carcinoma of penis in their lifetime.

None of the patients in this series received neoadjuvant or adjuvant chemotherapy.

Palliative Treatment

Seven patients received palliative oncological treatment while three patients died shortly after histological diagnosis. Among the seven patients who received palliative treatment, two received palliative penectomy; six received palliative radiotherapy, of whom three refused surgery due to advanced age and three had locally and regionally advanced disease; one received one cycle of palliative chemotherapy with cisplatin and 5-fluorouracil (PF). Some patients received more than one modality of palliative treatment in their lifetime. The various treatments received by these patients are summarised in Table 2.

Of the two patients who received palliative penectomy, one patient had cN3 disease at presentation and was scheduled for staged surgery. Total penectomy was performed but the patient then refused further inguinal lymphadenectomy and received two courses of palliative haemostatic radiotherapy to the right inguinal and pelvic regions. The other patient was found to have multiple lung metastases at presentation. No inguinal lymph node was detected in staging imaging and thus only palliative partial penectomy was performed. Palliative chemotherapy was offered but the patient refused any systemic treatment after surgery and opted for hospice care.

Six patients received palliative radiotherapy. Radical surgery was refused by three patents due to advanced age and multiple medical comorbidities. The remaining three patients had locally and regionally advanced disease and radical surgery was not feasible.

Treatment Outcome

Radical Surgery

Among the 18 patients who underwent radical surgery, the 5-year disease-free survival and 5-year overall survival was 32.8% and 43.8%, respectively (Figure

1). At the time of data collection, 10 (55.6%) patients had documented disease recurrence: two (11.1%) developed local recurrence, five (27.8%) developed regional recurrence, one (5.6%) developed locoregional recurrence, and two (11.1%) developed metastatic disease. All recurrences occurred within the first 4 years following radical treatment. The median time to relapse was 10 months (range, 1-41 months). The outcomes of all 18 patients who underwent radical surgery are summarised in Table 3.

Table 3. Outcomes of 20 patients who underwent radical treatment.

Outcome after radical treatment	No. (%) of patients
Patients with radical surgery	18
Local recurrence	2 (11.1)
Regional recurrence	5 (27.8)
Locoregional recurrence	1 (5.6)
Metastatic disease	2 (11.1)
No recurrence	8 (44.4)
Patients with radical radiotherapy	2
Local recurrence alone	1 (50.0)
Regional recurrence alone	1 (50.0)

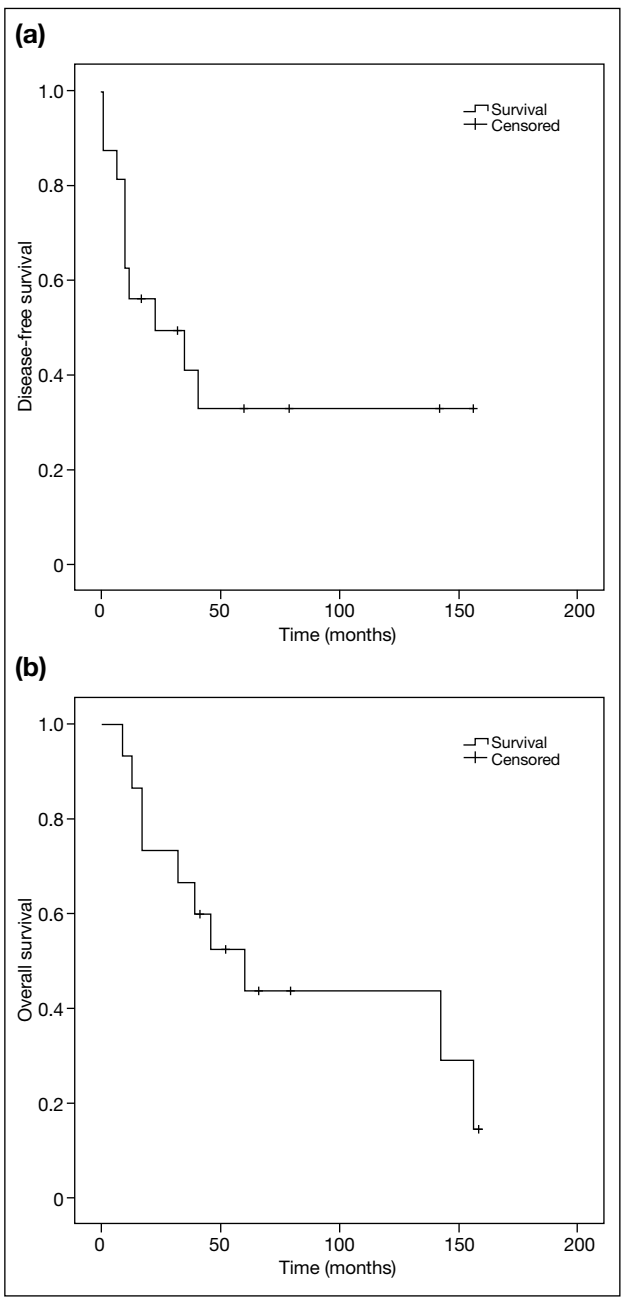

Figure 1. (a) Disease-free and (b) overall survival of patients who underwent radical surgery.

The two patients who developed local recurrence underwent surgery, of whom one developed a second locoregional recurrence at the penile stump and left inguinal lymph nodes 8.4 years later. He underwent total penectomy followed by bilateral radical inguinal lymph node dissection as salvage treatment. The other patient underwent pelvic exenteration and partial ostectomy of pelvic bone with flap reconstruction. Both patients were disease free at the time of data collection.

Among the five patients who developed regional relapse, one patient underwent pelvic and bilateral inguinal lymphadenectomy but he developed right inguinal relapse 2 months after radical surgery. He was then given 5 cycles of palliative chemotherapy (PF) and achieved static disease. Further palliative radiotherapy with electrons (10 Gy single fraction) was given to the right groin mass. He was lost to follow-up after radiotherapy. Two patients with regional relapse were given radical radiotherapy to the pelvis and bilateral inguinal regions (one with 50.4 Gy in 28 daily fractions over 5.5 weeks and the other with 50 Gy in 20 daily fractions over 4 weeks). Neither patient developed any further recurrence and were still alive at the time of analysis. One of the patients who developed metastatic disease at recurrence was given palliative radiotherapy for pain control. All other patients who developed disease recurrence were referred for hospice care.

Radical Radiotherapy

The patient who received primary radical brachytherapy developed local recurrence 30 months later and partial penectomy and bilateral modified inguinal lymph node dissection was performed. He was still alive with no further recurrence at the time of analysis. The patient who underwent primary radical external beam radiotherapy to the penis alone developed bilateral pelvic and inguinal lymph node recurrence 2

months after completion of radiotherapy. He refused further treatment and passed away 6 months later. The outcomes of the two patients treated with radical radiotherapy are also summarised in Table 3.

Overall Outcome

Overall 20 patients had died at the time of data collection. The median overall survival for all 30 patients included in this report was 22 months (range, 2-173 months; Figure 2), including deaths from other causes. Of the 20 deaths, nine were penile cancer-related.

DISCUSSION

Primary penile cancer is uncommon. Several risk factors for penile cancer have been identified. Established aetiological and epidemiological risk factors are phimosis, chronic penile inflammation, smoking, HPV infection, sporalene and ultraviolet A phototherapy for various dermatological conditions, multiple sexual partners, and early age of first intercourse.[3,4] In our series of 30 patients, one patient had a history of sexually transmitted disease, five had a history of phimosis, two had a history of paraphimosis, and 18 had a smoking history.

The majority of patients in this study presented late with advanced stage disease (stage III and IV) with operable or inoperable inguinal involvement. This is in keeping with other studies in other countries.[2] One reason for this late presentation in our series may be due to under-referral to a tertiary oncology centre. Most patients with early-stage penile cancer were followed up by a surgeon or urologist. The mean referral rate is around two to three cases per year according to our series but the incidence reported in the Hong Kong Cancer Registry is much higher.[1]

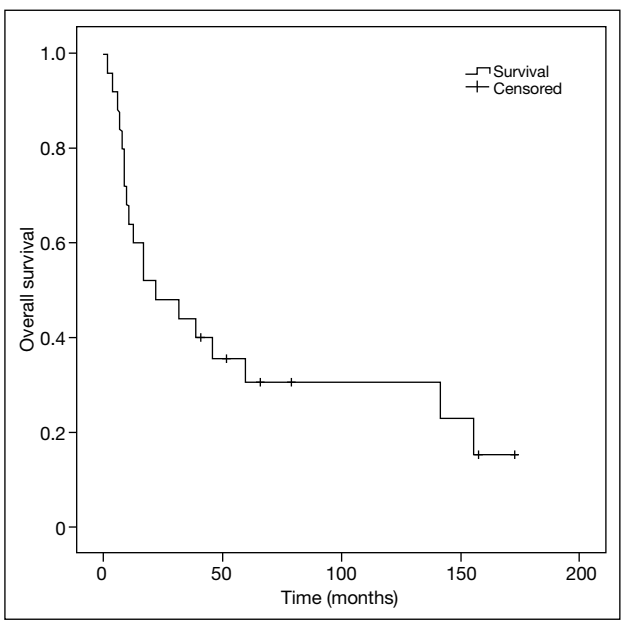

Figure 2. Overall survival of all patients.

The treatment modalities for penile cancer include surgery, chemotherapy, and radiotherapy. Primary treatment of penile cancer aims at complete tumour removal with as much organ preservation as possible; achieving negative margins to reduce the risk of local recurrences; and pathological staging of the tumour and inguinal lymph nodes.[5] There are no randomised controlled trials or observational studies for surgical treatment options of localised disease, nor studies comparing surgical and non-surgical modalities. Treatment choice depends on tumour size, histology, stage, grade, and patient preference. In our patient series, surgery was the most common modality of treatment for patients with SCC of the penis. In this series, inguinal lymphadenectomy was performed in 55.6% (10/18) of patients after penectomy, of whom six patients presented with clinically detectable lymph nodes before operation. Four patients underwent ipsilateral inguinal lymphadenectomy and six patients underwent bilateral inguinal lymphadenectomy. According to the recommendation of the European Association of Urology in 2015,[6] patients with clinically N0 disease and local staging of more than T1 and grade 2 disease are encouraged to receive invasive lymph node staging by bilateral modified inguinal lymphadenectomy or dynamic sentinel node biopsy. Patients with palpable inguinal lymph nodes (cN2/cN3) are advised to undergo radical inguinal lymphadenectomy and those with pN2 or pN3 disease are advised to undergo ipsilateral pelvic lymphadenectomy. According to current standards, nine of our patients should have undergone radical bilateral inguinal lymphadenectomy and three should have undergone ipsilateral pelvic lymphadenectomy.

The reported local and regional recurrence rates after radical surgery, irrespective of T-stage and nodal status, were 4% to 13% and 14% to 19%, respectively. The reported local recurrence rate after brachytherapy was 10% to 30%.[6,7] In our series, 55.6% (10/18) patients who underwent radical surgery developed disease recurrence, of whom two (11.1%) developed local recurrence, 5 (27.8%) developed regional recurrence, one (5.6%) developed local and regional recurrence,

and two (11.1%) developed distant metastases. Both patients (100%) who received radical radiotherapy developed disease recurrence. The high recurrence rate may partially be due to the small patient number, the relatively more advanced stage disease in our patients, and the suboptimal surgical resection.

Neoadjuvant chemotherapy is an attractive option for patients with locally advanced disease or bulky lymph node disease. It allows down-staging of the lymph nodes and early treatment of the likely systemic disease. Several phase II trials have suggested the response rate of neoadjvuvant chemotherapy to be 25% to 50%.[8-11] Adjuvant chemotherapy has been proposed to improve disease-free survival. A few small and heterogeneous series reported long-term disease-free survival of 39% to 53% after three to four cycles of adjuvant chemotherapy in patients with pN2-3 disease.[9,12,13] Different chemotherapeutic agents were administered including vincristine, bleomycin and methotrexate; PF; and cisplatin, 5-fluorouracil plus paclitaxel or docetaxel. None of our patients were offered neoadjuvant or adjuvant chemotherapy.

There are very limited published data for the use of radiotherapy to treat regional lymph nodes. In our series, two patients with regional disease recurrence were given radical radiotherapy to the pelvis and bilateral inguinal regions. Both remained disease-free after radiotherapy with a follow-up of 52 months and 39 months after salvage treatment. Radical radiotherapy for clinically detectable inguinal lymph nodes may be a treatment option but further studies are needed to define its role in treatment for patients with SCC of the penis.

Adjuvant radiotherapy has been administered following inguinal lymphadenectomy. According to a study based on the National Cancer Institute Surveillance, Epidemiology and End Results Program that compared patients with penile cancer treated with either surgery alone or surgery and external beam radiotherapy, results from the multivariate analysis showed that the addition of adjuvant radiotherapy conferred neither a harmful nor a beneficial effect on the cause-specific survival.[14] It is not generally recommended but may be considered in patients with high-risk factors such as involved resection margin, inadequate lymph node dissection, pelvic lymph node metastases, extranodal extension, bilateral inguinal lymph node involvement, or lymph nodes of >4 cm.[15] Two of our patients received adjuvant radiotherapy, of whom one remained disease-free until he died and the other patient developed regional relapse and died shortly after histological confirmation of disease recurrence. Given the proven curative efficacy of radiotherapy with or without chemotherapy in squamous cell malignancies in the head and neck regions, female genitalia and anus, and with penile SCC sharing a similar pathology, adjuvant radiotherapy may be considered. The role of postoperative adjuvant radiotherapy, or even chemoirradiation, in the treatment of patients with penile cancer has yet to be defined.

The most common long-term side-effect after radical penectomy and brachytherapy was meatal stenosis. In our series, six (31.6%) out of 19 patients who underwent penectomy developed meatal stenosis that required repeated dilatation. This complication rate is higher than that reported by other authors of approximately 3% to 9%.[16,17] None of our patients developed significant side-effects after radical radiotherapy.

The choice of chemotherapeutic agents for metastatic SCC of the penis varies. Several two- or three-drug regimens have been studied prospectively but no randomised trial has been performed and thus no single drug combination has yet been proven to be significantly superior to other regimens.[18] Systemic treatment for metastatic SCC of the penis is mainly cisplatin-based chemotherapy, building on the results from a study conducted by the Southwest Oncology Group on cisplatin monotherapy.[19] With the introduction of taxanes in penile cancer treatment, the efficacy and activity of the regimens used seemed to have been enhanced with response rates of up to 35% to 50%.[8,20] In our series, two of our patients received palliative chemotherapy with PF. One patient progressed after one cycle of PF and the other attained static disease after five cycles of PF.

This series included only patients who were evaluated and treated at a single institution, and may not reflect the whole population in this locality. Despite this limitation, this study has provided local data to supplement existing evidence of this disease in our local population.

CONCLUSION

SCC of the penis is a rare male malignancy in the Hong Kong population. Our series suggested that for our patients who present with advanced disease, a reasonable long-term survival can be achieved with aggressive local and regional treatment. More prospective studies will help refine the treatment

strategies and adjuvant treatment for patients with SCC of the penis.

REFERENCES

1. Hong Kong Cancer Registry, Hospital Authority. Available from: http://www3.ha.org.hk/cancereg/e_b2.asp. Accessed Sep 2015.
2. Favorito LA, Nardi AC, Ronalsa M, Zequi SC, Sampaio FJ, Glina S. Epidemiologic study on penile cancer in Brazil. Int Braz J Urol. 2008;34:587-93. cross ref
3. Dillner J, von Krogh G, Horenblas S, Meijer CJ. Etiology of squamous cell carcinoma of the penis. Scand J Urol Nephrol Suppl. 2000;205:189-93. cross ref
4. Tsen HF, Morgenstern H, Mack T, Peters RK. Risk factors for penile cancer: results of a population-based case–control study in Los Angeles County (United States). Cancer Causes Control. 2001;12:267-77. cross ref
5. Graafland NM, Lam W, Leijte JA, Yap T, Gallee MP, Corbishley C, et al. Prognostic factors for occult inguinal lymph node involvement in penile carcinoma and assessment of the high-risk EAU subgroup: a two-institution analysis of 342 clinically node-negative patients. Eur Urol. 2010;58:742-7. cross ref
6. Hakenberg OW, Comperat E, Minhas S, Necchi A, Protzel C, Watkin N. Guidelines on penile cancer. European Association of Urology; 2015. Available from: http://uroweb.org/wp-content/uploads/12-Penile-Cancer_LR1.pdf. Accessed Sep 2015.
7. 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 two-centre analysis of 700 patients. Eur Urol. 2008;54:161-8. cross ref
8. Nicholson S, Hall E, Harland SJ, Chester JD, Pickering L, Barber J, et al. Phase II trial of docetaxel, cisplatin and 5FU chemotherapy in locally advanced and metastatic penis cancer (CRUK/09/001). Br J Cancer. 2013;109:2554-9. cross ref
9. Giannatempo P, Paganoni A, Sangalli L, Colecchia M, Piva L, Catanzaro M, et al. Survival analyses of adjuvant or neoadjuvant combination of a taxane plus cisplatin and 5-fluorouracil (T-PF) in patients with bulky nodal metastases from squamous cell carcinoma of the penis (PSCC): Results of a single high-volume center [abstract]. J Clin Oncol. 2014;32(Suppl 4):abstr 377.
10. Leijte JA, Kerst JM, Bais E, Antonini N, Horenblas S. Neoadjuvant chemotherapy in advanced penile carcinioma. Eur Urol. 2007;52:488-94. cross ref
11. Hussein AM, Benedetto P, Sridhar KS. Chemotherapy with cisplatin and 5-fluorouracil for penile and urethral squamous cell carcinomas. Cancer. 1990;65:433-8. cross ref
12. Pizzocaro G, Piva L. Adjuvant and neoadjuvant vincristine, bleomycin, and methotrexate for inguinal metastases from squamous cell carcinoma of the penis. Acta Oncol. 1988;27:823-4. cross ref
13. Noronha V, Patil V, Ostwal V, Tongaonkar H, Bakshi G, Prabhash K. Role of paclitaxel and platinum-based adjuvant chemotherapy in high-risk penile cancer. Urol Ann. 2012;4:150-3. cross ref
14. Burt LM, Shrieve DC, Tward JD. Stage presentation, care patterns, and treatment outcomes for squamous cell carcinoma of the penis. Int J Radiat Oncol Biol Phys. 2014;88:94-100. cross ref
15. NCCN guidelines. Penile Cancer Version 3; 2015.
16. Chalya PL, Rambau PF, Masalu N, Simbila S. Ten-year surgical experiences with penile cancer at a tertiary care hospital in northwestern Tanzania: a retrospective study of 236 patients. World J Surg Oncol. 2015;13:71. cross ref
17. Carver BS, Mata JA, Venable DD, Eastham JA. Squamous cell carcinoma of the penis: a retrospective review of forty-five patients in northwest Louisiana. South Med J. 2002;95:822-5. cross ref
18. Pagliaro LC. Role of chemotherapy in treatment of squamous cell carcinoma of the penis. Curr Probl Cancer. 2015;39:166-72. cross ref
19. Gagliano RG, Blumenstein BA, Crawford ED, Stephens RL, Coltman CA Jr, Costanzi JJ. Cis-Diamminedichloroplatinum in the treatment of advanced epidermoid carcinoma of the penis: a Southwest Oncology Group Study. J Urol. 1989;141:66-7.
20. Pagliaro LC, Williams DL, Daliani D, Williams MB, Osai W, Kincaid M, et al. Neoadjuvant paclitaxel, ifosfamide, and cisplatin chemotherapy for metastatic penile cancer: a phase II study. J Clin Oncol. 2010;28:3851-7. cross ref