Penile carcinoma: a single institution experience

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KEY WORDS
penis ◗ penile cancer ◗ treatment

ABSTRACT

Introduction. Penile cancer is known to be a rare entity in developed countries with an incidence established to be less than 0.6%. The aim of this study is to describe our experience with penile cancer regarding demographics, clinical data, risk factors and, recurrence.
Methods. We retrospectively evaluated our experience in treating penile cancer between 1996 and 2008. Demographic data, associated risks factors, history of circumcision, presence of HPV, and HIV status were documented. Clinical stage at presentation was recorded. Follow-up consisted of clinical and/or radiographic evidence of recurrence.
Results. We identified 34 patients who were treated for carcinoma of the penis. Mean patient age was 57 years (32-84). Of the 34 patients, 19 (56%) were Hispanic, 21 (62%) were uncircumcised, 8 (24%) had pathologic evidence of HPV, and 6 (18%) were HIV-positive. A total of 28 patients (82%) were available for follow-up. The majority of the lesions were low-grade (Tis, T1). The treatment goal for low-stage, low-grade tumors was organ preservation. Eight lymphadenectomies were performed. Three patients presented with positive lymphadenopathy. Nine patients (26%) developed a post-operative complication. At a mean of 47 months follow-up, 7 of 28 patients (21%) had clinical and/or radiologic evidence of recurrence. Four of these patients had T1 disease at diagnosis.
Conclusion. In our experience, a significant number of patients were found to be HIV-positive as well as having other known risks factors of penile cancer, including evidence of HPV and history of circumcision. The recurrence for T1 disease was high, particularly for patients treated with organ sparing techniques, and several patients were lost to follow-up. Overall, our experience highlights many of the unique characteristics involved in the management of penile cancer.

INTRODUCTION

Penile cancer is known to be a rare entity in developed countries, including the United States, with an incidence established to be less than 0.6% [1, 2]. This disease is typically diagnosed in older men, and has been shown to be associated with numerous risk factors, such as those that contribute to an inflammatory state [4-6]. Current treatment guidelines are dichotomized on the presence or absence of lymphadenopathy. In addition, options exist for local treatment.

Penile neoplasm presents a challenge for the physician since rigorous follow-up is required and is highly dependent of patient compliance. The situation is confounded by the fact that patient denial is not uncommon.

Our 12-year experience in the Bronx will be reviewed. Our institution is unique in that it serves a diverse patient population, including a high percentage of Hispanic patients, a demographic that historically has a higher incidence of penile cancer [1-3].

METHODS

A total of 51 cases of penile cancer were identified at our institution between 1996 and 2008. Of the 51 patients, 34 were available for retrospective review and were included in the study. The presence of potential risks factors for penile cancer, including HPV, HIV, and circumcision was recorded. A pre-treatment biopsy was performed in 33 (97%) of the patients. Patients were staged according to the TNM classification, based on physical examination and/or pre-operative imaging (CT, MRI) [7]. Tumor grade was assigned using Broder's classification system, and was confirmed by an attending pathologist [8]. For the purposes of this study, we used the following definitions: G1 was considered to be well differentiated, G1-G2 to be well to moderately differentiated, G2-G3 to be moderately to poorly differentiate, and G3 to be poorly differentiated. Tumor grade was unavailable in 2 cases.

Treatment options included local excision (including circumcision), partial or total penectomy, local topical therapy, and adjuvant chemotherapy and radiation therapy. Radiation and/or chemotherapy were never utilized as primary treatment options. The decision to proceed with a lymphadenectomy was individualized to each patient according to current standardized recommendations.

The remaining patient, for whom no biopsy was performed, presented with a large fungating mass that comprised the entire glans and was subsequently treated with a distal partial penectomy.

Postoperative complications were recorded and were distributed by type of initial treatment. Patient follow-up consisted of clinical and/or radiologic evaluation, and presence of disease recurrence was recorded.

RESULTS

Mean patient age at time of diagnosis was 57.8 years (range 32-84). Of the 34 patients, 19 (56%) were of Hispanic origin, 21 (62%) were uncircumcised, 8 (24%) had evidence of HPV positivity, and 6 (18%) were HIV-positive. Of note, 8 (38%) of the uncircumcised men were HIV-positive, as were 4 (50%) of the HPV-positive men. Additionally, 7 of the 8 (87%) patients with evidence of HPV were uncircumcised. Follow-up was available for 28 (82%) of the patients, with a mean follow-up time of 42.8 months (range 2-108).

Patient histopathologic information is listed in Table 1. Of the 21 patients with T1 or higher stage disease, there was no documented grade available for 2 of the patients. Of these 2, one had verrucous subtype and the other had TxN+ disease; for the TxN+ patient, the biopsy showed evidence of invasive squamous cell carcinoma. A total of 1 (3%) patient was diagnosed with Kaposi Sarcoma.

Of the 4 (11.8%) patients who presented with clinically positives nodes, none (0%) underwent a therapeutic dissection. The first patient, staged as $T2N^{+}M_{x}$ G2-3, was scheduled for a lymph node dissection following partial penectomy but was subsequently lost to follow-up. This patient later presented to the emergency department with eroded inguinal nodes. The second patient died shortly after the lymph node biopsy, which was performed after this patient presented to the emergency department with suppurative draining lymphadenopathy bilaterally. This patient was noted to have a concomitant penile lesion. The third patient, who was ventilator dependant, was also lost to follow-up after undergoing a partial penectomy for a large Tis exophytic papillary mass. The final patient underwent a total penectomy and was then admitted more than a month later after surgery for a pulmonary embolism. His clinical status precluded him for having any further surgical intervention.

A total of 12 (35%) patients were diagnosed with Tis disease, 11 (32%) with T1, 5 (15%) with T2, and 4 (11.8%) with T3. There were no patients who were initially diagnosed with T4 disease. The various treatments for each of these stages are listed in Table 2.

Overall, a total of 7 (21%) patients had evidence of disease recurrence, including 2 cases of local recurrence, 4 cases of regional lymph node disease, and 1 of distant metastasis (Table 3). The patient with Tis who had a recurrence underwent a local re-excision and was subsequently lost to follow-up. Another patient with Tis disease who had palpable lymph node and was ventilator dependant was also lost to follow-up. Overall, 4 patients (36%) with T1 disease had a recurrence. Three of these presented with unilateral nodal disease after primary therapy, and all 3 were treated with delayed therapeutic bilateral node dissection. In addition, 2 of the 3 also underwent adjuvant chemotherapy and radiation. Of the 4 patients with T2 disease, 2 (50%) developed recurrences - one nodal and one with evidence of distant metastasis. The first patient initially had a negative prophylactic superficial lymph node dissection, but presented 6 months later with a right inguinal mass. Although he was treated with bilateral deep and pelvic node resection and adjuvant radiation, the patient subsequently progressed to T4 disease with a scrotal skin lesion and eventually developed eroded inguinal nodes. The second patient ($T2N^{+}$) was found to have fulminant metastatic disease after failing to show up for a therapeutic lymph node dissection. This patient presented to the Emergency Department with bilateral inguinal nodes that were eroded and bleeding; a bone scan confirmed metastatic spread to the thigh. The patient was unable to complete a course of radiation and chemotherapy secondary to his rapidly deteriorating clinical status. There no recorded recurrences on patients with T3 lesions.

A total of 9 patients experienced a postoperative complication. Of the 13 penectomies performed, 3 (23%) developed urethral stricture. One patient underwent a phalloplasty and subsequently developed a fistula, which was successfully repaired. One patient developed meatal stenosis after circumcision. Four patients devel-

Table 1. Patient demographics, clinicopathologic characteristics, and treatments.

Patients (n)		34
Mean age (range)		57.8 (32-84) years
Follow-up (months)		
	Median	42.77
	Mean (±SEM)	47.8 (2-108)
Clinical Stage (%)		
Tis		12 (35%)
T1		11 (32%)
	G1	3
	G1-2	2
	G2	3
	G2-3	2
	G3	0
	Unavailable	1
T2		5 (15%)
	G1	1
	G1-2	0
	G2	2
	G2-3	1
	G3	1
T3		4 (12%)
	G1	1
	G2	2
	G2-3	1
T4		0 (0%)
Kaposi's Sarcoma		1 (3%)
TXN+		1 (3%)
Lymphadenectomy		
	Prophylactic	4
	Therapeutic	0
	Delayed therapeutic	4

Table 2. Pathologic stage and initial treatments.

	Patients (n)	PP	TP	Local excision/ Circ.	Local Excis. +5-FU	5-FU	LND
Tis	12	1	0	5†	4	2	0
T1	11	6	0	5	0	0	0
T2	5	5	0	0	0	0	3
T3	4	2‡	2±	0	0	0	1

Abbreviations: PP=partial penectomy, TP=total penectomy, 5-FU=5-flourouracil, LND=lymph node dissection
† Includes 1 patient with Moh's Micrographic Surgery
‡ For 1 of these patients, a total penectomy was performed at a later date due to positive margins on final pathology
± Nodal dissection refused by 1 patient, but presented no evidence of recurrence at 1 year follow-up. One patient developed pulmonary embo-lism, preventing nodal dissection
circ. = circuncision

oped complications after lymphadenectomy, including 2 with lymphedema, 2 with DVT, 1 with a lymphocele, and 2 with wound erosions. Four patients died of the disease and 1 patient was living in a palliative care facility at the time of last follow-up.

DISCUSSION

Penile cancer is an uncommon entity, responsible for less than 1% of all malignancies seen in men [1, 2]. However, it is known to occur at a higher incidence in certain populations, such as Hispanic men, where the incidence is reported to be as high as 7% [3]. We reviewed data from 34 patients who were treated at our institution for penile cancer over a 12-year period. This cohort is similar in size to those reported from other regions in the United States for the given time frame. Our mean age at time of diagnosis, 57 years, is also similar to other published series [4, 9, 10]. The majority of the patients (56%) in our cohort were of Hispanic origin, paralleling the results from an epidemiological study by Goodman et al., which found Hispanic men had an almost doubled risk of developing penile cancer, relative to non-Hispanic men [3].

Reported risk factors for penile cancer include lack of circumcision, presence of HPV, history of a sexually transmitted disease, history of smoking, and poor hygiene [5, 6]. Misra et al. found the prevalence of phimosis and poor hygiene in men with penile cancer to be 25-75%, while that of HPV to be 15-80% [6]. In our series, 62% of the patients were uncircumcised, including 7 of the 9 males (88%) with HPV. Similarly, the overall percentage of men with HPV was 24%. This is slightly lower than other series that report the prevalence of uncircumcised patients and those with HPV to be as high as 89% and 42%, respectively [10, 11].

HIV has also been shown to be associated with the development of penile cancer. Poblet et al. proposed that HIV works synergistically with HPV to reduce the time between initial infection and the presentation of the cancer [12]. Frisch et al. found an increased rate of HPV associated malignancies in persons with HIV [13]. Our series included a high number of HIV-positive patients, of which 67% also had HPV. Of note, 0% of the HIV-positive patients were circumcised, perhaps affirming the results of Reynolds et al. who showed circumcision to be protective against HIV [14].

Another interesting finding is that the single case of Kaposi's Sarcoma was found in an HIV-negative, non-immunocompromised patient. This is uncommon but had been reported in the literature [15]. This patient with Kaposi's initially presented with a small lesion at the distal end of the penis. The patient refused surgery and was subsequently seen by the dermatology department, without evidence of progression.

Of the 34 patients, 18% were lost to follow-up, most likely due to a combination of patient denial and poor compliance in this population. The single patient who presented with advanced disease and bilateral eroded lymph nodes supports this phenomenon of poor compliance and a delay in diagnosis, which has previously been noted in the literature [16, 17]. Another example of poor compliance can be seen from the fact that two of the four patients who presented with positive lymph nodes were lost to follow-up. This can have catastrophic outcomes for patients presenting with advanced disease, and one of these patients ultimately died of diseases before any therapeutic measures could be instituted. Nevertheless, the majority of the patients presented with Tis and T1 lesions, which are early stage lesions. Similarly, the majority of tumors consisted of well and moderately-differentiated grades. Likewise, 82% of the tumors were of the usual subtype, as opposed to verrucous and warty subtypes, which parallels the findings of Cubilla et al [18].

The initial management for the majority of Tis lesions was local excision and adjuvant topical chemotherapy, which is considered standard of care. Interestingly, one patient with Tis who was initially treated with a partial penectomy had clinically positive nodes. This is an uncommon sequelae of Tis disease. One of the management goals for the T1 lesions was organ preservation, and almost half of the cases were treated with local excision/circumcision.

Table 3. Recurrences by T stage.

	Number of patients	Time to Recurrence	Type	Treatment
Tis	1		Local	Local excision
T1	4			
-T1G2		5 months	Local, Tis	Initial: local excision+5-FU
-T1G2		4 years	Nodal mass	Initial: local excision/ circ. recurrence: RILND, Chemotx, Brachytx
-T1G2-G3		18 months	Nodal	Initial: P.P. recurrence: PLND+BILND, Chemotx, Radiation tx
-T1G2-G3		3 years	Nodal	Initial: P.P. recurrence: ILND
T2	2			
-TG2		6 months	Nodal	Initial: P.P. + SILND recurrence: PLND+DILND
TG2-3		4 months	Nodal/ distant	Initial: partial penectomy recurrence: unable

5-FU = Fluorouracil, ILND = ilioinguinal node dissection
Chemotx = Chemotherapy, P.P. = partial penectomy,
Brachytx = Brachytherapy, PLND = pelvic lymph node dissection,
BILND = Bilateral ILND, SILND = Superficial ILND,
DILND = Deep ILND

Interestingly, none of the T1 patients underwent a lymph node dissection despite the controversy that exists over the appropriate management of T1 high grade lesions with clinically negative nodes. In our series only two patients were G2-G3. Some series have suggested that the ideal candidate for active surveillance of clinically negative nodes are those with well and moderately-differentiated lesions, for whom there is a less than 10% rate of metastatis [19, 20]. However, in our series, 2 of 9 (22%) of these patients (T1, G1-G2) developed nodal metastasis after primary treatment, similar to the value reported by Theodorescu et al. [21]. Yet, other series suggest that lymph node staging should be routine at the G2 level since the progression of T1N0 disease to nodal disease can be as high as 43% [22, 23].

A similar approach has been employed in regard to selecting the ideal candidate for organ-sparing surgery for the initial treatment. Namely, low-grade patients should be considered for organ-sparing surgery due to the low risk of nodal metastasis. However this was not observed in our series, where patients with low-grade disease developed nodal metastasis after partial penectomy and organ sparing surgery. Thus, the ideal approach is individual-dependant and requires careful evaluation of the characteristics of the primary lesion. On one hand, conservative surgical techniques provide adequate control when compared to formal amputation, while on the other hand these patients require strict follow-up, which is an important factor to consider among different populations. As described earlier, poor compliance was responsible for delayed treatment in some of our patients. This resulted in a more

aggressive approach to the initial management of poorly-compliant patients with T1 disease, especially since these patients had a greater rate of recurrences than those with higher stages.

With regard to T2 lesions, the incidence of nodal metastasis ranges from 50-70% [21, 23]. Therefore all T2 lesions in our series were treated with amputation. Interestingly, one patient who underwent a prophylactic superficial lymph node dissection later progressed to nodal disease, and ultimately to T4 disease.

All four of the patients with T3 lesions were treated with a penectomy. Despite the clear indication for a staging lymphadenectomy, only one patient with positive margins during the initial partial penectomy underwent nodal resection. Two patients did not undergo nodal resection, as previously described, and neither had evidence of disease recurrence. The last patient was scheduled to have surgery, but was admitted more than 30 days after total penectomy with a pulmonary embolism. His clinical condition precluded him from having further surgery.

The major etiology of post-operative complications in the treatment of penile cancer results from performing lymphadenectomies. Specific complications include: lymphedema, lymphocele, wound necrosis, infection, and scrotal edema. In our experience, three main complications were observed. There was a 29% incidence of lymphedema and a 14% incidence of a lymphocele requiring percutaneous drainage. These rates are similar to other published series [24-26]. In addition, deep vein thrombosis occurred in two patients. Our post-operative management plan involves an initial period of bedrest. In addition, we do not give patients heparin post-operatively in order to prevent the development of lymphoceles [16]. This is in contrast to Bradford et al. who advocate early ambulation, as quickly as 8 hours postoperatively, and report a 0% incidence of DVT and/or PE [26]. This is an important factor to consider and the benefits and risks should be further evaluated.

CONCLUSIONS

We sought to describe our experience with penile cancer. Despite the limited amount of patients, this is a significant study population for such a rare entity. The different approaches for each of the stages were thoroughly described, including primary and secondary treatments. Our results were also compared to other published series. Overall, our experience highlights various characteristics of penile cancer, including the association between known risks factors and HIV, the prevalence of penile cancer in the Hispanic population, poor patient compliance, and the fact that there may be a higher than expected rate of recurrence for >T1 lesions.

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