Non-squamous cell carcinoma of the penis: single-center, 15-year experience

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Abstract

Purpose Penile cancer is a rare malignancy with less than 5 % being non-squamous cell carcinoma (SCC) primary malignancies. We report our 15-year experience of treating non-SCC penile cancer at a tertiary care cancer center.

Methods We identified 12 patients with non-SCC of the penis from 1996 to 2012. Demographic and clinical data were abstracted, including histological type, surgical treatment, adjuvant therapy, and clinical course.

Results Five patients had sarcoma (three leiomyosarcoma, one spindle cell carcinoma, and one epithelioid sarcoma), four had melanoma, two had extramammary Paget's disease (EPD), and one had sebaceous carcinoma. Median follow-up was 37.5 months (mean 45.8 months). Tumor staging for melanoma was pT1aN3, pTisNx, pTxNxM1b, and pT3bN0. Patients with melanoma were treated with penile sparing surgery; two are alive without disease, one is alive with disease, and one patient with metastasis at presentation died of disease at 16.3 months. The patients with sarcoma and deep-seated or node-positive disease died of disease at a mean of 49.7 months. Two patients with EPD were treated with wide local excision of the lesions and were both pT1Nx. The remaining patient

had sebaceous carcinoma treated with excisional biopsy and was free of disease at 32.0 months.

Conclusions Non-SCC of the penis is primarily treated surgically, with the goal of complete excision at the time of treatment. The utilization of lymphadenectomy is less clear in these malignancies, but aggressive approaches should be considered in appropriate patients. Tumor stage and nodal status are important in determining patient outcomes.

Keywords Penile cancer · Melanoma · Sarcoma

Abbreviations

EBRT	External beam radiation therapy
EPD	Extramammary Paget's disease
ILND	Inguinal lymph node dissection
NED	No evidence of disease
SCC	Squamous cell carcinoma
WLE	Wide local excision

Introduction

Penile cancer is a rare malignancy that will affect approximately 1,500 men in the USA in 2012 and will account for over 300 deaths [1]. Greater than 95 % of penile cancers are squamous cell carcinoma (SCC), while non-SCC penile cancers are exceedingly rare. Several case reports and small series are published for non-SCC malignancies; however, due to small numbers, there is no consensus regarding the optimal management of these rare cancers. Melanomas and sarcomas have been the most commonly reported penile malignancies, with series published from our center, as well as others [2–4]. Herein, we describe our single-center, 15-year experience with

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primary noninvasive and invasive non-SCC of the penis, including treatment and outcomes for four patients with melanoma, five patients with sarcoma, two patients with extramammary Paget's disease (EPD), and one patient with sebaceous carcinoma.

Methods

After obtaining Institutional Review Board approval, we reviewed the Memorial Sloan-Kettering Cancer Center database to identify patients treated for primary penile cancer from January 1996 to August 2011. We identified 141 patients, 12 of whom had non-SCC of the penis. Demographic and clinical data were collected for each patient, and pathological data were reviewed. For patients with melanoma, TNM staging was performed according to the 2010 AJCC/UICC staging criteria [5]. Patients with sarcoma were staged according to the AJCC 7th edition for soft tissue sarcomas [6]. Patients with EPD and sebaceous carcinoma were classified according to the AJCC 7th edition TNM system for penile carcinoma [6]. All patients had a history and physical examination, with attention to the inguinal region and skin, and chest X-ray. CT and/or MRI was performed at the discretion of the treating physician, most commonly in patients with higher-stage disease. Patients were surgically treated by means of either a WLE, with the corpora cavernosa acting as the deep surgical margin and a margin of skin determined to be negative by frozen section, or partial penectomy, which included resection of the corpora cavernosa and the urethra. Lymphadenectomy was performed at the discretion of the treating physician; this is due to the lack of guidelines for these rare subtypes of penile cancer. Lymphadenectomy was approached using a sentinel lymph node sampling in one patient, while the remainder of the patients had either ipsilateral or contralateral superficial and/or inguinal node dissection. Adjuvant or salvage chemotherapy and radiotherapy were administered according to the discretion of the treating physician. Follow-up was calculated from the time of diagnosis to most recent visit or date of death, and time to recurrence was calculated from the time of surgical resection to the date of recurrence.

Results

Table 1 summarizes the clinical data for patients treated for primary penile melanoma. All four patients were Caucasian, with a mean age of 74.5 years (range 65–80). Mean follow-up was 40.1 months (range 1.0–104.7). All four patients presented with a pigmented lesion, with three presenting on the glans penis and one at the distal penile

shaft. Two patients underwent excisional biopsy of the lesion. Patient 1 had a lesion 0.76 mm thick and palpable inguinal lymphadenopathy. He subsequently had bilateral inguinal and pelvic lymph node dissections yielding a total of five positive nodes out of 28, with a final pathology of pT1aN3. This patient had pelvic recurrence at 11.9 months and was alive with disease at the follow-up of 38.6 months. Patient 2 was pTisNx with negative margins and had no evidence of disease at 1-month follow-up. The remaining patients were treated with partial penectomy. Patient 3 had a lesion of undetermined thickness and no evidence of metastatic disease at presentation; however, he had evidence of early local recurrence at the urethra and metastatic disease in the lungs. He underwent salvage chemotherapy with dacarbazine and vinblastine, however succumbed to disease at 16.3 months. Patient 4 had a 3.3-mm-thick lesion and underwent concurrent sentinel lymph node biopsy, which was negative. Final pathology was pT3bN0, and the patient has remained disease free at the follow-up of 104.7 months.

Data for patients with nonmelanoma and non-SCC of the penis are summarized in Table 2. Five patients had sarcomas of the penis (three leiomyosarcoma, one epithelioid sarcoma, and one spindle cell sarcoma). Mean age of the sarcoma patients was 38.8 years (range 22–66), and all patients were Caucasian. Four of the patients presented with lesions of the penile shaft at a mean size of 3.4 cm, while the patient with epithelioid sarcoma had a lesion of unknown size on the glans penis. Mean follow-up for this group was 46.7 months (range 29.4–70.1). Patient 5 had a deep-seated grade 1 primary lesion and local recurrence, as well as metastasis to the liver. He underwent several salvage chemotherapy regimens, of which only temozolomide showed any objective radiographic response. This patient ultimately succumbed to disease at 79.1 months. One patient with leiomyosarcoma (Patient 7) had excisional biopsy with a positive margin that was subsequently re-resected, and he remains free of disease at 37.5-month follow-up. Four of the five patients underwent partial penectomy. Patient 8 had bilateral inguinal lymph node dissection (0/62 nodes), and Patient 9 had left inguinal lymph node dissection (one positive node). Four of five patients experienced local and/or distant recurrence at a mean of 15.0 months. Overall, three patients died of disease, one patient was alive with disease when lost to follow-up at 47 months, and one patient is NED. The three patients who died of disease recurred within 1 year and had either deep-seated tumors or node positivity.

Two patients presented with EPD, with lesions of unknown size at the base of the penile shaft. They were aged 101 and 74 and were Caucasian and Chinese, respectively. The patients both underwent WLE for pT1Nx disease. Patient 10 had adjuvant EBRT for a positive

Table 1 Clinical data of patients with primary penile melanoma

Patient age at diagnosis (years)	Circumcised	Presentation	Depth of invasion	Treatment and margin status	2010 AJCC TNM classification	Recurrence (time)	Salvage treatment	Outcome (FU in months)
1–65	Unknown	Pigmented lesion on glans penis, palpable inguinal adenopathy	0.76 mm	WLE (positive margin), B ILND, B PLND	pT1aN3	R pelvis (11.9 months)	None	AWD (38.6)
2–78	Yes	Pigmented lesion on glans penis for 2–3 months	In situ	WLE (negative margin)	pTisNx	None	N/A	NED (1.0)
3–80	No	Pigmented lesion on distal penile shaft	Unknown	Partial penectomy (unknown margin)	pTxNxM1b	Urethra, lungs (1.3 months)	DTIC/Vinblastine	DOD (16.3)
4–75	No	Pigmented lesion on glans penis for 2 years	3.3 mm	Partial penectomy (negative margin), L sentinel node biopsy	pT3bN0	None	N/A	NED (104.7)

B ILND bilateral inguinal lymph node dissection, *B PLND* bilateral pelvic lymph node dissection, *DTIC* dacarbazine, *AWD* alive with disease, *DOD* dead of disease, *NED* no evidence of disease, *WLE* wide local excision

margin and died of other causes at 5.6 months. Patient 11 is NED at 118.5-month follow-up. The final patient is a 60-year-old Caucasian man who presented with a 2.4-cm lesion at the base of the penis. Excisional biopsy revealed a sebaceous carcinoma which was superficial (no lymphovascular or corporal invasion) and moderately to well differentiated (grades 1–2). This patient is NED at 32-month follow-up.

Discussion

We present our series of primary non-SCC penile cancer over a 15-year period at a tertiary care center. Non-SCC penile cancer represents <5 % of all penile cancer, and due to this rarity, the literature is limited to retrospective case series. We identified 12 patients who fell into four general categories, namely melanoma, sarcoma, EPD and sebaceous carcinoma. As with SCC of the penis, prognosis is dependent on the tumor and nodal stage.

Melanoma

Although potentially curable when recognized early, advanced melanoma progresses rapidly with a reported median survival of only 6–9 months [7]. In recent years, however, significant advances in understanding the disease biology have resulted in new and clinically effective therapeutic strategies. Presently, therapeutic approaches that are being offered to patients with metastatic melanoma include surgical resection of metastatic deposits, chemotherapy,

immunotherapy, and targeted therapy. One study by Chang et al. [8] using the National Cancer Database demonstrated 5-year survival rates of 55 % with regional lymphadenectomy compared with 27 % without a node dissection in patients with metastatic melanoma of unknown primary. Numerous other studies have shown similar findings demonstrating survival benefit from metatarsectomy or lymph node dissection for distant melanoma if the disease is completely resected [9, 10]. Less morbid procedures such as lymphoscintigraphy for sentinel node identification and biopsy have been suggested; however, the experience in penile melanoma is limited, lymphatic drainage in melanoma is unpredictable, and the learning curve for this approach is significant [11, 12]. Finally, several chemotherapeutics and monoclonal antibodies are now approved for the treatment of advanced melanoma, including dacarbazine, vemurafenib, ipilimumab, and IL-2, and are beginning to show promise in clinical trials [13]. Treatment strategies for metastatic melanoma may bring insight into treating patients with advanced penile melanoma, but because of the rarity of the disease, pooled-type prospective trials will be important.

In our series of four patients with penile melanoma, two patients underwent WLE for tumors that were <pT2. Conversely, partial penectomy was utilized for higher-stage disease in two patients, one of whom had early evidence of distant metastasis and died of disease. We cannot make recommendations regarding partial versus total penectomy for melanoma in this small series; however, obtaining a negative margin should be the ultimate goal as this is potentially important in reducing recurrence and improving long-term survival.

Table 2 Demographic and clinical data of patients with sarcoma, extramammary Paget's disease, or sebaceous carcinoma

Patient age at diagnosis (years)	Histology	Circumcised	Size and location of tumor	Treatment	Stage and grade	Recurrence (time)	Adjuvant/salvage treatment	Outcome (FU in months)
5–34	Leiomyosarcoma	Yes	4.7 cm, base of penile shaft	Partial penectomy (positive margin)	Stage IA (pT1bNx, grade 1)	Penile shaft, groin, liver (8.0 months)	Gemcitabine and docetaxel, sorafenib, doxorubicin, and dacarbazine, temozolomide	DOD (79.1)
6–42	Leiomyosarcoma	Unknown	1.7 cm, penile shaft	Partial penectomy (negative margin)	Stage IIA (pT1bNx, grade 3)	Lung (11.1 months)	None	DOD (29.4)
7–30	Leiomyosarcoma	Yes	3.0 cm, penile shaft	Wide local excision (positive margin)	Stage IIA (pT1aNx, grade 3)	None	N/A	NED (37.5)
8–22	Epithelioid sarcoma	Unknown	4.0 cm, penile shaft	Partial penectomy (positive margin), B ILND	Stage IIA (pT1bN0, grade 3)	Suprapubic region, L spermatic cord (37.2 months)	Unknown, lost to FU	AWD (47.0)
9–66	Spindle cell sarcoma—uncertain tissue type	No	Unknown size, glans penis	Partial penectomy (negative margin), L ILND	Stage III (pTxN1, grade 3)	L groin, distal penis (3.6 months)	None	DOD (40.6)
10–101	EPD	No	Unknown size, base of penile shaft	Wide local excision	Stage I pT1Nx	None	Adjuvant EBRT 4,000 Gy	DOC (5.6)
11–74	EPD	No	Unknown size, base of penile shaft	Wide local excision	Stage I pT1Nx	None	N/A	NED (118.5)
12–60	Sebaceous carcinoma	Yes	2.4 cm, base of penile shaft	Excisional biopsy	Stage I pT1Nx, grade 1–2	None	N/A	NED (32.0)

B ILND bilateral inguinal lymph node dissection, *B PLND* bilateral pelvic lymph node dissection, *EPD* extramammary Paget's disease, *EBRT* external beam radiation therapy, *AWD* alive with disease, *DOC* dead of other causes, *DOD* dead of disease, *NED* no evidence of disease

There are several important prognostic factors in melanoma, including Breslow thickness and Clark depth of invasion [14]. In the seventh edition of the AJCC staging manual, thickness levels of 1.0, 2.0, and 4.0 mm defined the T-classification thresholds and the absence or presence of ulceration defined a or b subcategories within each tumor stage. The presence of ulceration correlates with survival differences within a stage. Balch et al. [15] showed similar 5-year survival for T3a versus T2b penile melanoma (79 vs 82 %) and T4a versus T3b (71 vs 68 %). These results have not been validated in a prospective series of penile melanoma; however, complete resection of the primary tumor with negative margins is the goal of the surgical approach. In their series of nine patients with penile melanoma, Sanchez-Ortiz et al. [2] performed WLE or partial penectomy in eight patients, while the remaining patient with pT3bN1 disease underwent radical penectomy. The patients who remained free of disease at follow-up were all pT2 or less except for one patient who had a second primary melanoma of the trunk. In a retrospective study from Mayo Clinic, Stillwell et al. [16] treated 11 men with penile melanoma, the majority of whom had penile-preserving surgery. Four patients with known tumor thickness of ≤ 2.5 mm and N0 remained free of disease at 13 years of follow-up. Based on their experience, the MD Anderson group developed an algorithm for surgical treatment of penile melanoma based on the location of the tumor and achieving a margin of resection based on their previous report on SCC of the penis [2, 17].

The optimal approach to clinically positive lymph nodes in penile melanoma is not known; however, node positivity confers a poor prognosis. In a review of the literature describing node-positive patients with penile melanoma, all patients died of disease within 2 years, including one patient from the present series (Table 3). We performed inguinal and pelvic lymphadenectomy in one patient who presented with pT1a disease and palpable inguinal disease, and sentinel lymph node biopsy in one patient who presented with pT3b disease and a clinically negative groin examination. The first patient was pN3 and demonstrated early local recurrence and

distant metastasis and died of disease at 16.3 months despite salvage chemotherapy. The second patient was pN0 and remains NED at 105-month follow-up. The most significant predictors of outcome in all melanomas are the number of metastatic nodes, the microscopic vs. macroscopic tumor burden at the time of staging, and the absence or presence of ulceration within the primary tumor, with the number of metastatic nodes being the most significant factor [14]. Although we currently do not have guidelines for approaching lymphadenectomy in patients with penile melanoma, we believe that it is important that at minimum a sentinel lymph node sampling be performed.

Sarcoma

There were five patients with primary penile sarcomas: three with leiomyosarcoma, one with spindle cell sarcoma, and one with epithelioid sarcoma in this cohort. Dotan et al. [4] from MSKCC presented the largest experience with genitourinary sarcomas, where they identified 131 patients over a 25-year period. Three of these patients had primary penile sarcoma. The most common type of sarcoma was leiomyosarcoma (29 %), followed by liposarcoma (26 %), rhabdomyosarcoma (18 %), and other types (25 %). This distribution is distinct from nongenitourinary sarcomas, where the most common type is liposarcoma followed by malignant histiocytoma [18]. Seventy-eight percent of patients had high-grade disease, which is a higher proportion than is seen in nongenitourinary sarcomas. Tumor size, presence of metastasis, and gender were significantly associated with disease-specific survival, with a trend to significance for tumor grade. The authors noted that genitourinary sarcomas have a worse disease-specific survival compared with nongenitourinary sarcomas, likely due to a higher percentage of high-grade and metastatic disease. The best chance of cure was performing a complete surgical resection, with a 5-year overall survival of 65 %. However, as in all sarcomas, recurrence is common and an aggressive approach should be considered, particularly for deep-seated tumors [4, 19]. In a 30-year review of the

Table 3 Summary of literature of node-positive patients with penile melanoma

Reference	Number of patients	Age at presentation	TNM stage (2010 AJCC)	Lesion depth	Outcome (FU in months)
Stillwell et al. [4]	4	57	pT4aN+	5 mm	DOD (13)
		55	pTxN+ (with ulceration)	Unknown	DOD (6)
		67	pT2bN+	1.5 mm	DOD (24)
		52	pTxN+ (no ulceration)	Unknown	DOD (48)
Sanchez-Ortiz et al. [2]	1	67	pT3bN1M0	3.5 mm	DOD (20)
Present series	1	65	pT1aN3Mx	0.76 mm	DOD (16.3)

DOD dead of disease, FU time to follow-up

tissue registry of the Armed Forces Institute of Pathology, Fetsch et al. [20] identified 14 patients with primary penile leiomyosarcoma. As in our series, patients were young (mean age 51) and were managed with either local excision or partial penectomy. Nine patients had superficial tumors, of whom three were lost to follow-up, one died of unrelated causes, and the remaining five were NED (one of the five patients had two recurrences treated with local excisions). Three patients had deep-seated tumors, one of whom was lost to follow-up, one experienced multiple recurrences and metastasis and was then lost to follow-up, and the third patient had low-grade disease and was NED after WLE at 18 years of follow-up. As noted in the MSKCC series, the strongest predictors of outcome were tumor depth and size. The vascular tissue of the corporal bodies is likely the source of deep-seated tumors, which contributes to the aggressive behavior and poorer prognosis of these tumors and thus mandates complete resection of the tumor [20, 21]. Sarcoma patients typically have local recurrence and/or distant metastasis, and lymphatic metastasis is not commonly noted with genitourinary sarcomas; thus, inguinal lymphadenectomy is generally unnecessary in nonpalpable disease [4, 22].

Extramammary Paget's disease

Two patients in our series presented with EPD. Both patients underwent WLE for pT1 lesions, and one received adjuvant radiation because of a positive margin. One remains NED at nearly 10 years, and the other passed away from unrelated causes. In general, isolated EPD of the penis is extremely rare, with only a few reported cases in the literature [23–25]. More commonly seen is EPD of the penoscrotal region, which presents as an erythematous, well-demarcated area that may be pruritic or expresses a serosanguinous discharge. Paget's disease may herald a more deep-seated carcinoma in situ or malignancy of an adjacent organ; therefore, careful genitourinary physical examination and cystoscopy should be a part of the patient workup [26, 27]. Paget's disease arises from apocrine-gland-bearing regions, namely the axilla, perineum, vulva, penis, and scrotum. Immunohistochemical testing may be necessary to differentiate EPD from other malignancies such as Bowen's disease or melanoma [26]. Penoscrotal EPD is typically seen in men in the seventh to ninth decades, and complete surgical excision of the skin and subcutaneous tissue of the affected region is required with the occasional need for skin graft or flap coverage of the defect [25, 26, 28]. There is a paucity of data on men with penile EPD owing to the rarity of the disease; however, Karam et al. [29] identified 1,439 patients with invasive EPD of other organs from the SEER database. They reported a 5-year DSS of 94.9 % for localized disease, 84.9 % for regional disease, and 52.5 % for distant disease. In addition, they demonstrated that surgical resection

was associated with a significantly improved outcome when compared with patients who received radiation alone or in combination with surgery. Based on these findings and others, surgical resection remains the mainstay for the treatment of EPD regardless of the organ of origin.

Sebaceous carcinoma

One patient in our series had sebaceous carcinoma of the penis presenting at the age of 60 as a 2.4-cm nodular lesion at the base of the penis. To our knowledge, there have been five prior reports of primary penile sebaceous carcinoma [30, 31]. Sebaceous carcinoma is a rare malignancy that arises from the sebaceous glands of the skin. The eyelid is particularly rich in sebaceous glands and thus is the most common site for this malignancy [32]. Greater than 70 % of sebaceous carcinomas present in the head and neck region, and overall 5-year survival in patients is 71 % [33]. This tumor type has high metastatic potential, and treatment for tumors of the eyelid is typically multimodal, with local resection, topical chemotherapy, and radiation therapy being among the treatment choices [32].

Conclusion

We present our single-center, 15-year experience of non-SCC of the penis. We identified 12 patients with melanoma, sarcoma, EPD, or sebaceous carcinoma. Tumor and nodal stage, as well as tumor grade, are important in determining outcomes after treatment. In this unique population, many patients can be treated with penis sparing approaches, with achievement of negative margins being the primary goal. The approach to lymphadenectomy is dependent on clinical presentation, with the understanding that lymphatic spread may be less predictable, particularly in the case of melanoma. Sarcoma patients tend to be younger with worse outcomes, particularly for deep-seated tumors, and may benefit from a more aggressive approach. Meticulous follow-up and early use of adjuvant chemotherapy may be of benefit in these rare cases; however, small numbers preclude any definitive statements regarding optimal treatment.

Conflict of interest The authors declare that they have no conflict of interest.

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