Leiomyosarcoma of the Penis

A Clinicopathologic Study of 14 Cases With Review of the Literature and Discussion of the Differential Diagnosis

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Abstract: Primary leiomyosarcomas of the penis are very rare. To date, less than 30 have been documented in the English language literature. In this report, we describe the clinical, histopathologic, and immunohistochemical findings in 14 cases retrieved from our files. The patients ranged in age from 43 to 62 years (mean age, 51 years) at the time of initial surgical resection. The tumors involved the prepuce (n = 1), prepuce and distal shaft (n = 1), circumcision scar line (n = 2), circumcision scar line and distal shaft (n = 1), shaft (n = 5), base of the penis (n = 3), and penis, not otherwise specified (n = 1). The lesions ranged in size from 0.5 to 6.0 cm (median size, 1.5 cm) in greatest dimension. Nine tumors were superficially located, two were of indeterminate depth, and three were deep-seated. The superficial tumors were relatively asymptomatic, and seven were reportedly present for 1 year to more than 20 years (median duration, 5 years) before medical attention was sought. In contrast, one deep-seated lesion caused dysuria and difficulty voiding, prompting the patient to seek a clinical opinion within only a few months of the apparent onset. Histologically, all tumors contained smooth muscle cells with both cytologic atypia and mitotic activity. Immunohistochemical studies were available for nine tumors, and immunoreactivity for desmin was present in all instances. All patients were initially treated with a local procedure. Follow-up information is available for 9 of the 14 patients (64%), with a median follow-up interval of 12 years 11 months. Three patients had multiple (two to four) local recurrences. Two of these patients were ultimately treated with a wide local excision or partial penectomy, and both were alive and well at last follow-up. In contrast, one patient, who had four local recurrences and refused a penectomy, developed a distant metastasis 10 months after the fourth recurrence. The best predictors of outcome are tumor depth and tumor size. Superficial leiomyosarcomas of the penis are optimally managed by wide local excision whenever this is technically feasible. Tumors with a deep-seated component may require more aggressive intervention to ensure complete removal.

Key Words: genitourinary, Kaposi's sarcoma, leiomyoma, leiomyosarcoma, malignant fibrous histiocytoma, myointimoma, penis, sarcoma, smooth muscle, soft tissue tumor

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This report presents the clinical, histopathologic, and immunohistochemical findings associated with 14 primary leiomyosarcomas of the penis. It represents the largest series of cases from one referral center published to date. All previous publications have been case reports, adding only a single new case to the literature, except for one article that included two new cases. The medical literature is reviewed, and the differential diagnosis is discussed.

MATERIALS AND METHODS

All soft tissue tumors of the penis with available slides and clinical information, coded between 1970 and 1999, were retrieved from the Tissue Registry of the Armed Forces Institute of Pathology. Tumors were classified on the basis of hematoxylin and eosin morphology and histochemical and immunohistochemical findings. The initial study group consisted of 116 cases, and from this cohort, 14 (12%) leiomyosarcomas and 1 (<1%) leiomyoma were identified. All 14 leiomyosarcomas fulfilled accepted diagnostic criteria (ie, all tumors had smooth muscle morphology, and *both* nuclear atypia and mitotic activity).

The recorded tumor size is the largest tumor dimension based on clinical, gross, or microscopy slide measurement. The clinical size was given preference over gross size when the lesions were received in a fragmented state.

The tumors were classified as superficial or deep based on whether they were situated above or below the tunica albuginea (eg, tumors that involved the corpus cavernosum or cor-

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pus spongiosum of the shaft were considered deep). In the glans penis, which lacks a tunica albuginea, involvement of corpus spongiosum was considered deep. Tumors were scored and graded with the modified French Federation of Cancer Centers Sarcoma Group Grading System.[12]

Immunohistochemistry, using the avidin-biotin complex immunoperoxidase technique, was performed on nine tumors with appropriate formalin-fixed, paraffin-embedded material. Table 1 lists the immunohistochemical antibodies, their sources, and dilutions. Enzymatic digestion and heat-induced epitope retrieval steps to optimize antigen-antibody interaction are also noted in this table. Appropriate controls were tested simultaneously.

Follow-up information was obtained by reviewing submitted medical records or through telephonic or written communication with the patients or their clinicians.

RESULTS

Clinical Findings

The 14 patients with leiomyosarcoma of the penis ranged in age from 43 to 62 years (median and mean ages, 49 and 51 years, respectively) at the time of their initial surgical procedure (Table 2). The tumors involved the prepuce (n = 1), prepuce and distal shaft (n = 1), circumcision scar line (n = 2), circumcision scar line and distal shaft (n = 1), shaft (n = 5), base of the penis (n = 3), and penis, not otherwise specified (n =1).

Eight patients reported a relatively asymptomatic, slow-growing mass present for 1 year to more than 20 years before seeking medical attention. Seven of these patients had superficial tumors, and one had a tumor of unstated depth. Two of the patients were circumcised as adults and noted the development of a mass at the circumcision scar line at intervals ranging from almost immediately thereafter to approximately 7 years later.

One additional patient with a deep-seated tumor reported symptoms of dysuria and difficulty voiding for only a few months before seeking medical attention.

Treatment and Follow-up Data

Initial surgical intervention consisted of a biopsy (n = 2), incomplete local excision (n = 2), or local excision (n = 10). The two patients that were biopsied had a local excision shortly thereafter. Follow-up information is available for nine patients, with a median follow-up interval of 12 years 11 months. Two patients developed two local recurrences, each, and one patient developed four local recurrences followed by a distant metastasis. These three patients are briefly summarized below.

One patient (patient no. 5), initially managed by local excision, developed a local recurrence 2 years 4 months later. This was also managed by local excision. A second recurrence developed 3 months latter, and this was treated with a wide local excision. The individual has been free of disease for the past 10 years 4 months. A second patient (patient no. 7), initially managed with an incomplete local excision, developed a local recurrence at 12 months. This was again treated with an incomplete local excision. The patient developed a second recurrence 3 years later, and this was managed with a partial penectomy. The patient has now been free of disease for 5 years 8 months. The third patient (patient no. 14) was initially treated with a local excision and subsequently underwent four additional local procedures and an inguinal lymph node dissection at unspecified time intervals for recurrent disease. This individual was offered and refused a penectomy on multiple occasions. Ten months after the fourth local recurrence, the patient developed biopsy-confirmed, metastatic leiomyosarcoma to the left arm. The patient has since been lost to follow-up.

None of the remaining six patients, with follow-up intervals ranging from 5 years 2 months to 18 years 7 months (me-

TABLE 1. Immunoreagents Used in the Analysis of Leiomyosarcoma of the Penis

Reagent	Source	Dilution
Anti-desmin (D33)*	Dako Corporation (Carpinteria, CA)	1:320
Anti-desmin (DE-R-11)*	Dako Corporation	1:80
Anti-α-smooth muscle actin*	Enzo Diagnostics, Inc. (Syosset, NY)	1:160
Anti-muscle-specific actin (HHF35)†	Enzo Diagnostics, Inc.	1:160
Anti-CD117a‡	Dako Corporation	1:100
Anti-CD34 (QBEnd/10)§	Ventana Medical Systems (Tucson, AZ)	Predilute

*Tissue sections were microwaved in 10 mM sodium citrate buffer (pH 6.0) at or near boiling for 20 minutes and cooled for 25 minutes in the buffer before washing and incubation with the primary antibody.

†Tissue sections were pretreated with Protease Type XIV (Sigma Chemical Co., St. Louis, MO; concentration = 0.067 g/100 mL, 0.01 M phosphate-buffered saline, pH 7.4) for 7 minutes at 37°C.

‡Tissue sections were cooked in a vegetable steamer in EDTA buffer for 25 minutes.

§Tissue sections were processed in EDTA buffer on the Ventana Beckmark using heat-induced epitope retrieval for 32 minutes.

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TABLE 2. Clinicopathologic Features for 14 Primary Leiomyosarcomas of the Penis

Patient No.	Age* (yr)	Anatomic Location	Size (cm)	Depth/Tumor Grade	Procedure	Follow-up Interval	Clinical Course and Outcome
1	43	Circumcision scar	2	S/Gr 2	LE	LTF	
2	43	Periurethral (shaft)	Multiple pieces to 2†	D/Gr 1	LE	18 yr 7 mo	NED
3	45	Dorsolateral mid shaft	2.4 (Est)	S/Gr 2	ILE	LTF	
4‡	45	Prepuce	2	S/Gr 2	LE with circumcision	13 yr 6 mo	Dead of unrelated cause§
5	47	Shaft	1.5	I/Gr 2	LE, LE, WLE	12 yr 11 mo	Local recurrence × 2 (2 yr 4 mo and 3 mo later); NED for 10 yr 4 mo
6	48	Penis, NOS	1.5	I/Gr 2	LE	LTF	
7	49	Circumcision scar and distal shaft	1.5 (Est)	S/Gr 1	ILE, ILE, partial penectomy	10 yr	Local recurrence × 2 (1 yr and 3 yr later); NED for 5 yr 8 mo
8	53	Base of penis at junction with abdominal wall	0.5 (Est)	S/Gr 2	Bx followed by LE	5 yr 2 mo	NED
9	53	Lateral shaft near base	0.9	S/Gr 2	Bx followed by LE	11 yr	NED
10	58	Penile root	6	D/Gr 2	LE	LTF	
11	59	Prepuce and distal shaft	1.2	S/Gr 2	LE	LTF	
12	61	Shaft	2	S/Gr 2	LE	13 yr 11 mo	NED
13	62	Circumcision scar	0.7	S/Gr 2	LE	16 yr 1 mo	NED
14	NA	Shaft	NA	D/Gr 3	LE × 5 and lymph node dissection	years	Local recurrence × 4, followed 10 mo later by a metastasis to left arm, then LTF

*At time of first procedure.
†Tumor size considered >2 but <5 cm.
‡Previously reported in two separate publications,[19,30] now with extended follow-up information.
§Patient died of metastatic gastrointestinal stromal tumor of the stomach, diagnosed 9 years after the penile leiomyosarcoma.
NA, not available; NOS, not otherwise specified; Est, estimate based on microscopic slide measurement; S, superficial; I, indeterminate depth; D, deep; Gr, grade; LE, local excision; WLE, wide local excision; ILE, incomplete local excision; Bx, biopsy; LTF, lost to follow-up.

dian follow-up interval, 13 years 8.5 months), developed recurrent or metastatic disease. This includes one patient who had a deep periurethral tumor that was managed by complete local excision without partial penectomy.

Four patients were diagnosed with other malignant tumors after their primary leiomyosarcoma of the penis. One patient (patient no. 2) had an ameloblastoma of the maxilla, diagnosed 15 years after his penile lesion. Another patient (patient no. 9) had "skin cancer" of the face and a malignant melanoma of the shoulder at unspecified time intervals. A third patient (patient no. 12) was treated for colon cancer almost 14 years post-leiomyosarcoma, and finally, the fourth patient (patient no. 4) was diagnosed with a CD117a-positive malignant gastrointestinal stromal tumor of the stomach, 9 years after his penile tumor. This last patient subsequently developed liver metastases and died of complications of the gastrointestinal stromal tumor, 4 years 6 months after its diagnosis.

Pathologic Findings

The initial surgical resection specimens contained tumors ranging in size from 0.5 to 6.0 cm in maximum dimension (median size, 1.5 cm). The neoplasms had a white-tan, light gray, or pink-tan color, and almost always, a firm consistency. One example had a mucoid or gelatinous cut surface. Five examples were documented to form distinctly nodular masses. Three cases were received as multiple fragments.

Microscopically, all specimens contained a spindle cell neoplasm with morphologic features of leiomyosarcoma (Fig. 1). The neoplastic cells generally had abundant eosino-

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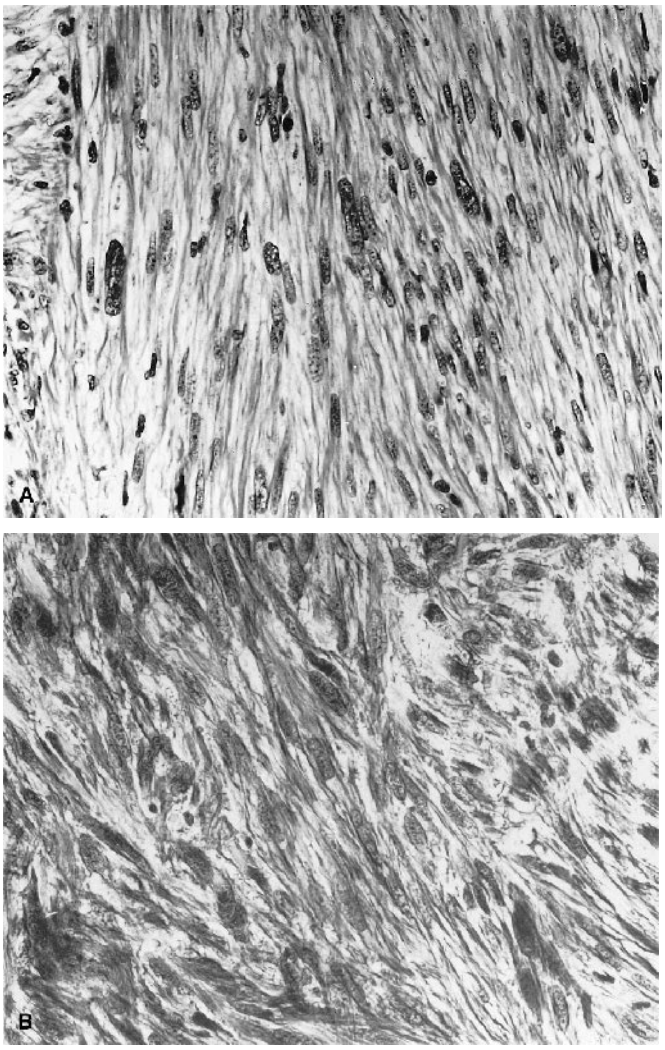

FIGURE 1. A, B: High-power views of leiomyosarcoma demonstrating classic morphologic features. **A:** The spindled tumor cells have abundant cytoplasm, focal juxtanuclear vacuoles, and blunt-ended nuclei with atypia. **B:** Masson's trichrome stain demonstrated fuchsinophilic cytoplasm and longitudinal cytoplasmic striations.

philic cytoplasm, and there was a tendency for the cells to be organized into fascicles. Blunt-ended nuclei and juxtanuclear vacuoles were identified at least focally in all but one case. A Masson's trichrome stain was available for eight tumors; this revealed fuchsinophilic neoplastic cells in all instances, and in seven of the eight cases, longitudinal cytoplasmic striations were demonstrated. A periodic acid-Schiff stain in two cases demonstrated focal cytoplasmic glycogen.

The one tumor that lacked juxtanuclear vacuoles and longitudinal cytoplasmic striations had loosely organized spindled cells and abundant intervening myxoid matrix (Fig. 2). This tumor was deep-seated and involved the base of the penis. It closely resembled myxoid leiomyosarcoma, as seen in the gynecologic tract.

Nuclear atypia was present in all cases (Fig. 3). The degree of atypia was mild in one case, moderate in eight cases, and severe in five cases. Nuclear pleomorphism was also usually present, and in four cases, it was very pronounced. The tumors had maximum mitotic counts ranging from 2 to 14 mitotic figures per 10 high power fields (HPFs). The mean and median mitotic counts were 6 mitotic figures/10 HPFs. Ten tumors had focal necrosis, representing <50% of the tumor area. The modified French Federation of Cancer Centers Sarcoma Group Grading System tumor scores ranged from 3 to 6. Two tumors were grade 1, 11 tumors were grade 2, and one tumor was grade 3.

Nine of the leiomyosarcomas were superficially located, and three were deep-seated, situated beneath the tunica albuginea (Fig. 4). The depth of the remaining two tumors could not be ascertained from the resection material. The superficial tumors were well demarcated with a circumscribed nodular configuration (n = 5), poorly marginated (n = 2), or both multilobular (or multinodular) and infiltrative (n = 2). The two tumors of uncertain depth had either a circumscribed, nodular or multilobular configuration. Two of the deep-seated tumors were nodular, and one was multilobular and infiltrative.

Immunohistochemical data are available for nine tumors (Fig. 5). The tumors had immunoreactivity for muscle-specific actin (7 of 7), α-smooth muscle actin (7 of 9), desmin (D33 clone) (9 of 9), and desmin (DE-R-11 clone) (9 of 9). Immunoreactivity ranged from moderately extensive to diffuse in all but one case, the myxoid leiomyosarcoma. This last tumor had reactivity for both desmin clones in <25% of the tumor cells and reactivity for muscle-specific actin in >25% but <50% of the cells.

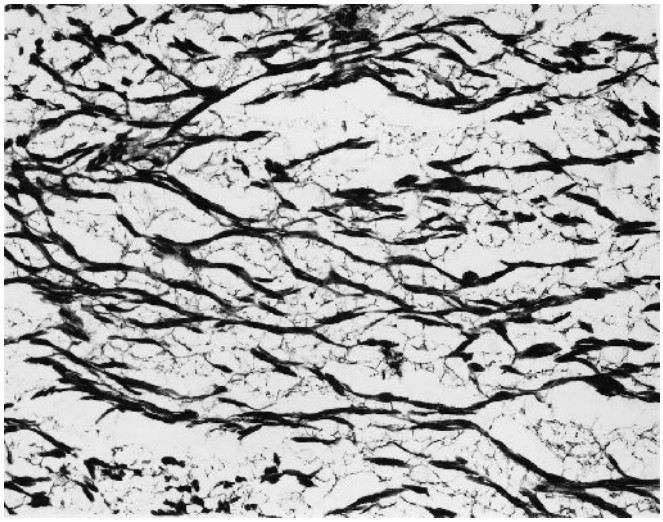

FIGURE 2. This myxoid leiomyosarcoma involved the root of the penis (case no. 10). The tumor had focal immunoreactivity for both muscle-specific actin and desmin. Note a resemblance to myxoid leiomyosarcomas as seen in the gynecologic tract.

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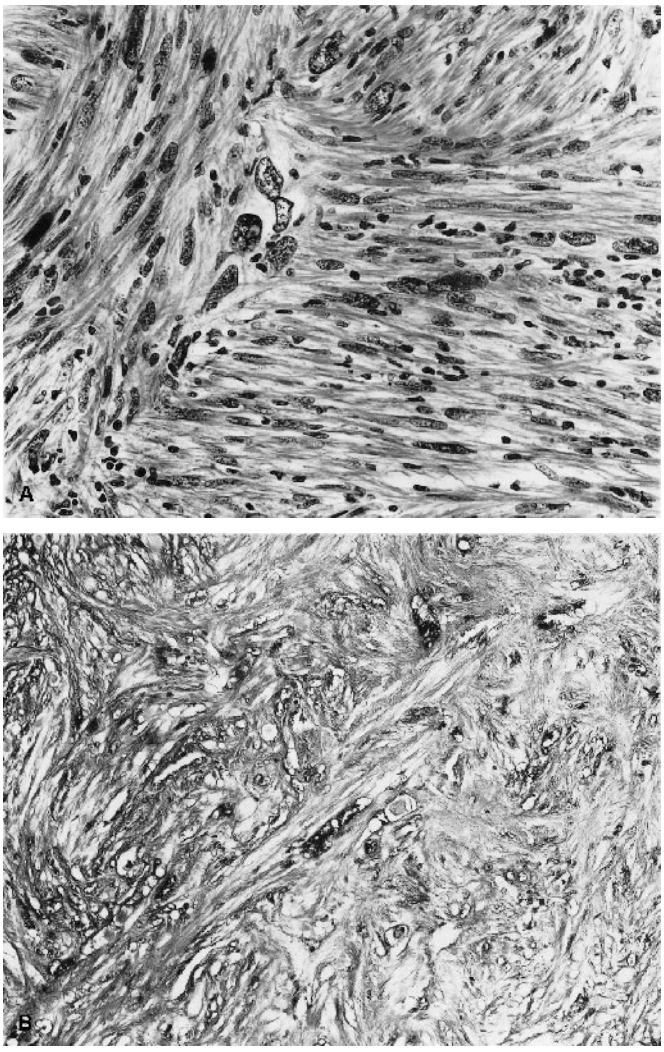

FIGURE 3. A, B: Nuclear pleomorphism was a common finding in penile leiomyosarcomas. In some instances, it was pronounced, resulting in a morphologic appearance reminiscent of malignant fibrous histiocytoma.

Muscle-specific actin was expressed in the absence of α-smooth muscle actin in two instances, and in two additional cases, a higher percentage of tumor cells expressed this marker than α-smooth muscle actin. However, in four cases, including one case with a lesser number of immunoreactive cells, the intensity of the reaction for α-smooth muscle actin was notably greater than for muscle-specific actin. The two desmin clones generally produced similar results, with no significant difference in the extent of immunoreactivity or intensity of the immunoreaction.

Two additional surgical specimens warrant comment. First, the presumed metastasis to the left arm of patient no. 14 was reviewed, and it was histologically similar to the primary leiomyosarcoma of the penis. Second, the malignant gastrointestinal stromal tumor of the stomach from patient no. 4 was also examined. This tumor was morphologically and immunohistochemically different from the patient's primary leiomyosarcoma of the penis. The gastric tumor was composed predominantly of small epithelioid cells with strong immunoreactivity for CD117a and focally strong reactivity for CD34. The gastric tumor was nonreactive for actins and desmin. The penile tumor from the same patient had strong diffuse reactivity for α-smooth muscle actin and desmin, only focal weak reactivity for CD117a, and no reactivity for CD34.

DISCUSSION

Leiomyosarcoma of the penis is very rare, with <30 cases documented in the English language literature over the past half century.[1–8,11,13,14,16–20,22–27,29,30,33] Nevertheless, this represents the second most common primary sarcoma type of this anatomic location (after Kaposi sarcoma) in the Armed Forces Institute of Pathology files.

There are a number of potential sources within the penis from which leiomyosarcoma can arise: 1) the dartos muscle layer of the prepuce and shaft, 2) the arrector pili muscles associated with lanugo hairs on the penile shaft, 3) the muscular walls of superficial vessels situated outside of the tunic albuginea, and 4) the muscular walls of the deep vascular complex that make up the corpus cavernosum and corpus spongiosum.

All 14 patients in our study group were adults, between the ages of 43 and 62 years, at the time of their initial surgical procedure. Nine patients had superficially located tumors, three had deep-seated tumors, and two had tumors of uncertain depth. The superficial tumors tended to be asymptomatic, and seven of these were reportedly present for intervals ranging from 1 year to >20 years (median duration, 5 years) before medical attention was sought. In contrast, one deep-seated tumor associated with the corpus spongiosum produced symptoms of dysuria and obstruction over a rather short period of several months.

We attempted to determine the site of origin for the leiomyosarcomas based on their depth, architectural growth patterns, and association with regional structures. All deep-seated tumors were presumed of vascular (corpora) origin. The two tumors of indeterminate depth were also judged to most likely be of vascular derivation, but it was unclear from which vessels they arose. The superficial leiomyosarcomas were divided into two groups: circumscribed nodular examples usually appeared to be derived from the superficial vasculature of the penis, whereas in most instances, infiltrative (poorly marginated) examples appeared to originated from dartos or arrector pili muscle.

We were able to obtain follow-up information for nine of the 14 patients (64%) included in this series, with a median follow-up interval of 12 years 11 months. All patients in our study were initially treated conservatively. Three patients experienced multiple local recurrences, and one of these developed a distant metastasis. This last patient had a deep-seated

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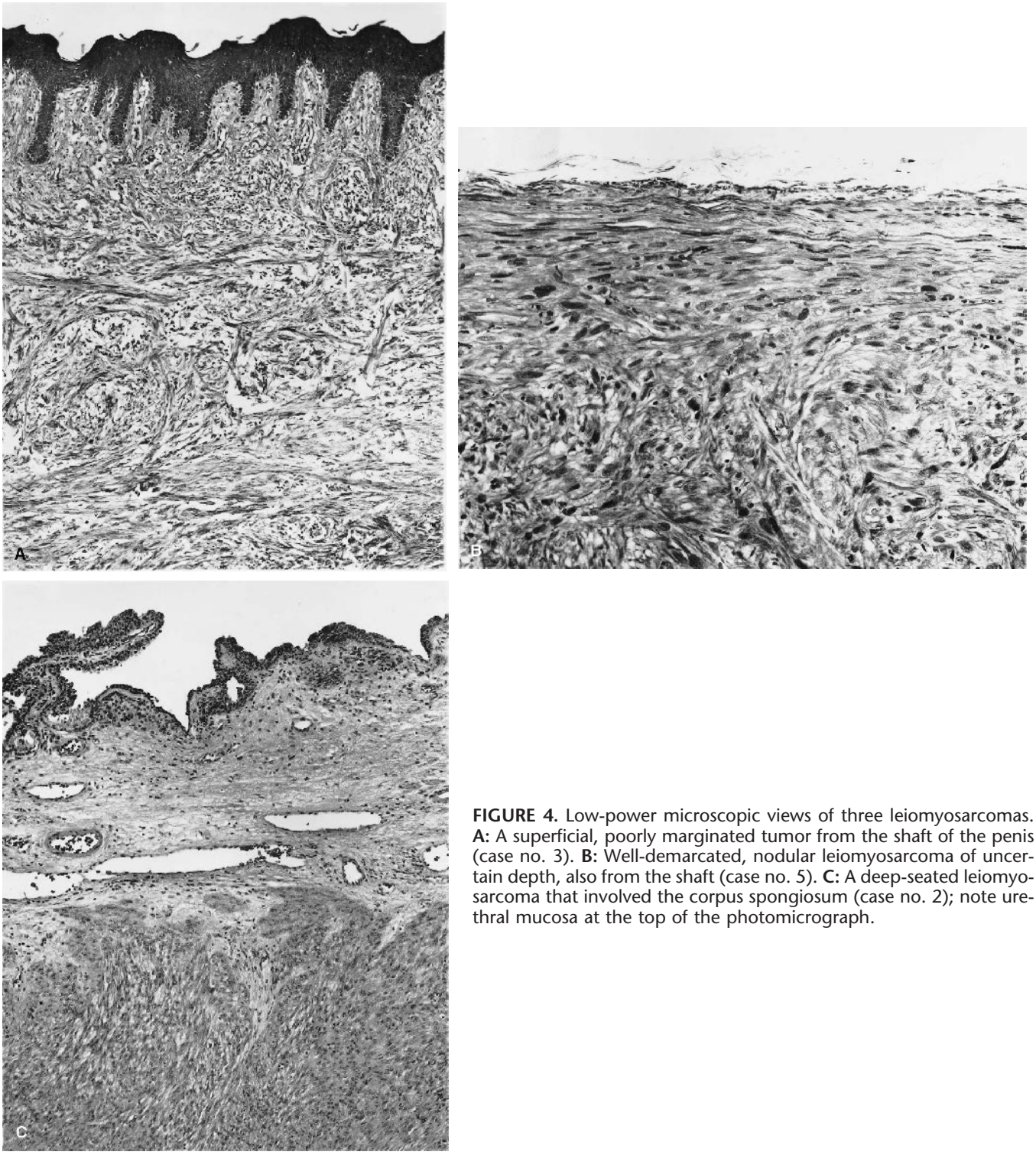

FIGURE 4. Low-power microscopic views of three leiomyosarcomas. **A:** A superficial, poorly marginated tumor from the shaft of the penis (case no. 3). **B:** Well-demarcated, nodular leiomyosarcoma of uncertain depth, also from the shaft (case no. 5). **C:** A deep-seated leiomyosarcoma that involved the corpus spongiosum (case no. 2); note urethral mucosa at the top of the photomicrograph.

tumor on the shaft with a multinodular/multilobular configuration. It was the only grade 3 tumor in our series, and it had the highest mitotic count (14 mitotic figures/10 HPFs). Of the remaining two patients with recurrences, one had a 1.5-cm grade 2 tumor of indeterminate depth with a circumscribed nodular configuration on the shaft, and the other had a superficial 1.5-cm grade 1 tumor with a multilobular and infiltrative configuration involving the circumcision scar line and distal shaft.

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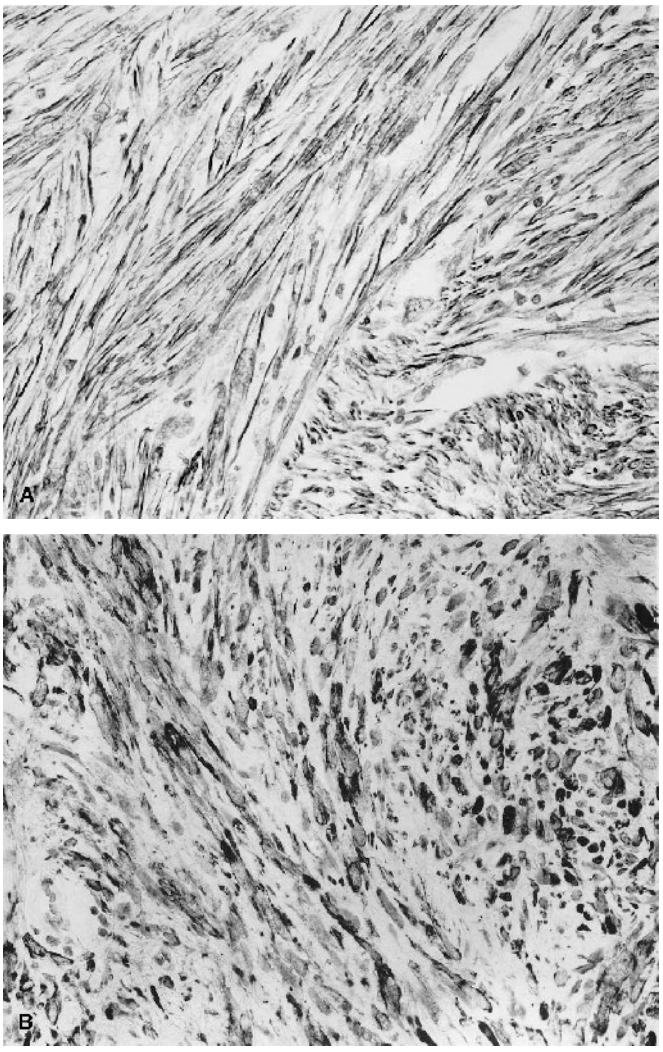

FIGURE 5. Muscle-specific actin (**A**) and desmin (**B**) were expressed in all of the leiomyosarcomas that were examined with immunohistochemistry.

It is difficult to draw a close comparison between our findings and that published in the literature. This is because past reports have often contained very limited histopathologic information, and in many instances, insufficient follow-up data. For comparative purposes, our analysis of the literature includes 25 of the 26 cases published in the English language (Table 3). It excludes one English language report that cannot be accepted without better documentation,[10] and it excludes all reports published in an alternate language. While there is reason to be skeptical of the diagnosis in a few instances, we have given all remaining authors benefit of the doubt and feel the few possible outliers probably minimally impact on the overall picture. We noted eight patients who presented with superficial tumors,[1,3–5,17,19,27,30,33] 12 patients with deep-seated tumors,[2,6–8,13,18,22–26,29] and five patients with tumors of uncertain depth.[5,11,14,16,20] The mean ages for these patient groups were 42 years, 56 years, and 66 years, respectively. The patients with superficial tumors usually lacked symptoms but reported a mass lesion had been present 1 to 12 years before seeking medical attention (median duration, 27 months). The superficial tumors involved the prepuce (n = 3), prepuce and shaft (n = 1), dorsal shaft (n = 1), and tissue just proximal to the coronal sulcus of the glans (n = 3). Three tumors of the prepuce (1.5–5 cm) were treated by circumcision or "wide" circumcision, and one tumor of the prepuce and distal shaft (6 cm) was treated by radical penectomy and regional lymph node dissection. All four patients were disease free with follow-up intervals of 1 to 3 years (mean follow-up, 23.5 months). The superficial tumor of the dorsal penile shaft was treated by local excision, and the patient was alive and well with 1-year follow-up. Tumors from the coronal sulcus region were initially treated by local excision (n = 2) or circumcision (n = 1). One patient from this group had a prophylactic wide local excision (no tumor was identified in the resection specimen) approximately 6 months after the initial procedure and was disease free with 9 months of follow-up. One patient developed a local recurrence, also managed by local excision (18 years after the initial procedure), and was free of disease for a follow-up period of 18 months, and the third patient[17] developed recurrent disease (with invasion of the corpus cavernosum in the third surgical specimen), and ultimately, an 18-cm regional groin metastasis. This last individual underwent three local procedures, a partial penectomy, and a groin dissection with adjuvant radiotherapy, all occurring over a period of approximately 40 years. Although the patient was stated to have 1-year of disease-free follow-up since his last procedure, his outcome remains in doubt.

The patients from our literature review with deep-seated tumors were often symptomatic and had more rapidly growing masses, present 1 month to 2 years before clinical consultation (median duration, 6 months). Seven of the patients had tumors involving the root of the penis, three had tumors of the glans and shaft, one had a tumor of the distal shaft, and one had a tumor involving the "entire length" of the corpus spongiosum. The majority of these patients had radical intervention (sometimes with adjuvant radiotherapy and chemotherapy). Despite treatment efforts, five patients were dead with metastases, one was alive with metastases, and two were dead of uncertain cause. Four patients were alive without clinical evidence of disease, but the longest follow-up interval after the last surgical procedure was only 2 years, and two patients had less than 1-year follow-up.

Five published reports contain tumors of uncertain initial depth. While some authors have considered one or more of these tumors to be superficial, others have viewed them as deep-seated. The point of contention has usually revolved around whether the tumor was confined to the skin or extended into the corpus spongiosum of the glans or corpus cavernosum

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TABLE 3. Clinicopathologic Features for 25 Previously Reported Primary Leiomyosarcomas of the Penis

Age* (yr)	Tumor Sizes (cm)	Anatomic Location	Depth	Treatment§	Outcome	Reference
19	NA ("small nodule") >1.8 >1.5 >18	Dorsal shaft near coronal sulcus	S, later D	Circ.¶ > LE(41) > LE followed by partial Amp (49) > Bx, groin dissection‖ and Rad (59)	Local recurrence (×1 or 2) and regional (18-cm groin) metastasis; alive without clinical evidence of disease, 1 yr after groin dissection	17
40	6	Prepuce and part of shaft	S	Radical Amp & LND**	AW, 3 yr	4
44	5 (multinodular)	Prepuce	S	Wide circ	AW, 1 yr	3
44	1.5	Prepuce	S	Wide circ.	AW, 2 yr 4 mo	27
45	3	Dorsal shaft	S‡	LE	AW, 1 yr	5
45†	2	Prepuce	S	Circ	AW, 1 yr 6 mo	19, 30
47	1	Shaft, proximal to coronal sulcus	S	LE followed ~6 mo later by a WLE that was negative for tumor	AW, 9 mo after last procedure	33
49	NA > 2	Shaft, proximal to coronal sulcus	S	LE > LE (67)	Recurrence (×1); AW, 1 yr 6 mo after last procedure	1
53	NA	Distal shaft	I	Bx followed by partial Amp, LND** & Chemo	AW, 1 yr	20‡‡
63	NA ("large proportions") >5 >4.5	Dorsal shaft	I, later D	Bx > LE (66) > radical Amp (69) > en bloc radical resection with LND** (74)	Recurrence (×2); alive with only 27 days follow-up after last procedure	16
64	2	Junction of glans and frenulum	I	Bx & Rad > partial Amp (~66)	AW, 11 mo	11
67	8	Dorsal shaft	I‡	LE	LTF	5
84	1.5	Glans and prepuce	I	Partial Amp	AW, 6 mo	14
38	3	Root of penis	D	Bx followed by radical Amp and Chemo	AW, 2 yr after surgery	23
38	2.5, 0.4, and 0.3	Distal shaft, 1 cm proximal to glans	D	Bx followed by radical Amp	Alive with widespread metastases, 6 mo after surgery	6
52	NA > ~4 ("size of a nut")	Root of penis	D	LE > LE and Rad (55) > urethrostomy (56) > Amp (57)	Recurrence (×2); AW, 10 mo after last procedure	8
52	NA	Root of penis	D	Bx followed by LE	DCU, 3 mo after LE	24
54	6	Glans and distal shaft	D	Bx followed within 1 mo by Amp	DCU, 1 day postoperative	26
55	5	Glans and shaft	D	Bx followed by radical Amp	AW, 1.5 yr	18
60	19	Root of penis	D	Bx followed by radical Amp	DOD with metastases, 6 mo after surgery	2
60	10.5	Glans and shaft	D	Amp	Local recurrence (postoperative) and DOD with metastases, 5 mo after surgery	13
60	NA (apparently large)	Corpus spongiosum (shaft ± glans)	D	Mass and spongy urethra excised	DOD with metastases, 1 mo	7
61	10 (4 inches)	Root of penis	D	Bx followed by radical Amp and LND,** Rad & Chemo	Alive without clinical evidence of disease but minimal follow-up	29
62	8	Root of penis	D	Bx followed by Chemo > radical Amp with scrotum and testes, then Rad and Chemo	Local recurrence (postoperative) and DOD with metastases within 7 mo of diagnosis	22
83	4	Root of penis	D	Bx followed by Rad > radical Amp > yttrium 90 (~84)	DOD with metastases within 2 yr of onset††	25

NA, not available; S, superficial; I, indeterminate depth; D, deep; Circ, circumcision; LE, local excision; Amp, amputation; Rad, radiation; LND, lymph node dissection; WLE, wide local excision; Chemo, chemotherapy; Bx, biopsy; AW, alive and well; LTF, lost to follow-up; DCU, dead cause unknown; DOD, dead of disease.

*Age at first treatment.

†Updated information on this patient is included in Table 2 (AFIP data).

‡Considered superficial in previous reviews. However, precise depth is not stated in the initial report. We find it difficult to accept the 8-cm mass as such.

§The patient's age (years) at the time of subsequent procedures is listed in parentheses, when available.

¶No histologic examination was performed. It is unclear to what extent the patient's "small nodule" was excised with the circumcision. If gross residual disease was left behind, then the number of actual local recurrences would be one.

‖Soft tissue versus lymph node metastasis.

**Lymph nodes negative for tumor.

††Updated in reference 23.

‡‡Patient also had an invasive well-differentiated squamous cell carcinoma.

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of the shaft. Tumors involving either of these structures are generally considered deep-seated. Three patients from this group were managed by partial amputation (n = 1), partial amputation with lymph node dissection and chemotherapy (n = 1), and biopsy followed by irradiation therapy and 2 years 3 months later by partial amputation (n = 1). All three individuals were alive without evidence of disease with 6 to 12 months of follow-up. A fourth patient from this group[16] had an initial biopsy procedure, followed 3 years later by a local excision. A recurrence 3 years after this (probably with a deep-seated component by this time) led to a penile amputation, and a regional recurrence 5 years later led to an en bloc dissection of the lower abdominal wall, groin, penile stump, and scrotum. This patient had minimal postoperative follow-up (27 days), and so, his outcome is in doubt. The fifth patient had a local excision of an 8-cm mass from the dorsal shaft, and then, was lost to follow-up.

Given the rarity of this disease and the limited long-term follow-up, it is difficult to make specific treatment recommendation. However, we cautiously support the following conclusions, based on our observations: 1) Tumor depth and tumor size (when stratified as follows: ≤2 cm *vs.* >2 cm and ≤5 cm *vs.* >5 cm) are currently the best predictors of outcome for primary leiomyosarcoma of the penis (Table 4). 2) Small (≤2 cm) superficial tumors are probably best managed, in most instances, by wide local excision with fully documented resection margins and long-term follow-up.[17,23,27,30] When the tumor is confined to the prepuce of an uncircumcised man, a "wide" circumcision may be adequate treatment.[3,19,27,30] 3) Large, deep-seated tumors, especially those located at the root of the penis, often have a poor prognosis despite aggressive surgical intervention.[17] However, small deep-seated tumors that are distally located in the shaft or glans may be salvageable, and some of these appear to be effectively treated by wide local excision or partial amputation. 4) Tumors that are inadequately excised, whether superficial or deep, can be expected to have a high local recurrence rate. However, superficial recurrences are much more likely to be salvageable (sometimes even with additional wide local excisions) because they often remain local for extended periods of time before giving rise to metastases.[27,30] 5) Adjuvant radiation[11,17,27] and chemotherapy[27] have no clear value as primary treatment of penile leiomyosarcoma. 6) Regional lymph node dissection is usually not indicated, as nodal metastases are uncommon and generally limited to the very late stages of disease when distant metastases are already evident.[14,16,17,27]

Observations in our referral-based study group suggest the following histologic parameters warrant additional investigation to better assess their prognostic significance: tumor growth pattern (circumscribed and uninodular vs. infiltrative or multinodular/multilobular), high mitotic count (≥10 mitotic figure/10 HPFs), and grade 3 histology. These parameters should be documented in all future case reports so their prognostic value can be more fully assessed.

The differential diagnosis for leiomyosarcoma of the penis includes leiomyoma, myointimoma, nodular Kaposi sarcoma, malignant fibrous histiocytoma, and sarcomatoid carcinoma. Leiomyomas of the penis are very rare, perhaps even rarer than leiomyosarcomas. These tumors tend to present as small, painless, slow-growing masses in mid adult life. Histologically, they are typically well demaracted, and in contrast with leiomyosarcomas, they should not have cytologic atypia and mitotic activity.

The recently described myointimoma is a highly distinctive soft tissue lesion with a strong predilection for the corpus spongiosum of the glans penis.[9] This benign process has been documented in individuals ranging from 2 to 61 years (mean age, 29 years). Histologic examination reveals a multinodular

TABLE 4. Outcome by Initial Tumor Depth and Tumor Size (n = 38)*

	Local Recurrence	Metastases	Dead of Disease	Dead of Uncertain Cause	No Follow-up Information
Initial tumor depth					
Superficial (n = 16)	3 (23%)	1‡ (8%)	0	0	3
Indeterminate (n = 7)	2 (40%)	0	0	0	2
Deep (n = 15)	4 (29%)	7 (50%)	5 (36%)	2 (14%)	1
Tumor size at first resection					
≤2 cm (n = 14)	2 (18%)	0	0	0	3
>2 and ≤5 cm (n = 8)	0	2 (29%)	1 (14%)	0	1
>5 cm (n = 8)	1 (17%)	3 (50%)	3 (50%)	1 (17%)	2
Not available† (n = 8)	5 (62.5%)	3 (37.5%)	1 (12.5%)	1 (12.5%)	0

*For a more complete summation of the clinical data, see Tables 2 and 3, and the Discussion.
†This category includes some large tumors, but a specific size was not recorded for the neoplasms at the surgical outset.
‡This tumor was initially superficial, but it invaded the corpus cavernosum in the second recurrence (see Table 3 and reference 17).

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or plexiform intravascular proliferation of relatively uniform myoid cells with extensive immunoreactivity for muscle-specific actin, α-smooth muscle actin, and calponin, but minimal reactivity for desmin. A derivation from myointimal cells has been postulated. A review of the literature suggests that examples of myointimoma have previously been published as leiomyoma,[28] intravascular leiomyoma,[5,15] solitary cutaneous myofibroma,[31] and localized fibrosis of the corpus cavernosum.[21] The strong predilection for the glans, characteristic growth pattern, minimal cytologic atypia, and scarcity of desmin immunoreactivity militate against a diagnosis of leiomyosarcoma. Myointimomas appear to be adequately managed by conservative local excision.

Kaposi sarcoma is the most common sarcoma of the penis, outnumbering leiomyosarcoma in the Armed Forces Institute of Pathology archives by a margin of more than 2:1. Nodular Kaposi sarcoma is sometimes confused with a superficial leiomyosarcoma because, histologically, it features atypical spindled cells that often exhibit fascicular architecture. However, clues to the diagnosis of Kaposi sarcoma include the presence of slit-like spaces with numerous red blood cells, intracytoplasmic grape-like clusters of periodic acid Schiff-positive, diastase-resistant hyaline globules, and a generally prominent lymphoplasmacytic inflammatory infiltrate. Early patch-plaque-like Kaposi changes are also often evident at the periphery of the nodular mass. Nodular Kaposi sarcoma differs immunohistochemically from leiomyosarcoma by exhibiting strong reactivity for CD34 and CD31 and by lacking desmin expression. Most patients with Kaposi sarcoma younger than 60 years will have clinical or laboratory evidence of an immunodeficiency disorder.[32]

Malignant fibrous histiocytoma is a diagnosis of exclusion, and in our experience, only rarely arises in the penis. While some leiomyosarcomas of this location contain pleomorphic areas that resemble a storiform-pleomorphic malignant fibrous histiocytoma, the identification of areas with fascicular architecture, tumor cells with blunt-ended, cigar-shaped nuclei, and immunoreactivity for actins and desmin help establish the correct diagnosis.

A sarcomatoid carcinoma should also be considered whenever a superficial spindle cell neoplasm of the penis is encountered. This is because carcinomas are vastly more common in this location, outnumbering sarcomas by a margin of >100:1. The distinction of sarcomatoid carcinoma from a true sarcoma is aided by careful evaluation of the patient's past medical history, review of the overlying surface epithelium for evidence of atypia, and immunohistochemical assessment of the tumor for the pattern and extent of keratin expression.

One final word of caution is warranted, and this is, whenever one encounters a leiomyosarcoma (especially when small, well demarcated, and not clearly arising from a vessel wall), the possibility of a metastasis should be considered. While it is our impression that the penis is a truly rare site for a leiomyosarcoma metastasis, malignant smooth muscle tumors are known for hematogenous spread and a tendency to secondarily involve the skin and subcutaneous tissues. Therefore, clinical correlation is required to rule out a metastasis whenever there is histopathologic uncertainty about the primary site of disease.

In summary, leiomyosarcoma of the penis is primarily a disease of mid and late adult life. These tumors are widely distributed and arise from both superficial and deep smooth muscle elements. Currently, the best predictors of outcome are tumor depth and tumor size. The extreme rarity of this disease makes it difficult to make specific treatment recommendations. However, management should be directed toward complete removal of the tumor to minimize the risk of local recurrence and distant metastases. Complete (wide) local excision with fully documented margins appears to be the optimal management for superficial tumors, especially when they are small (≤2 cm) and well demarcated. The local recurrence rate for these lesions appears to be relatively low, and recurrences are often still controlled with additional surgical intervention. Small, well-demarcated, deep-seated tumors may also be amenable to local intervention, assuming that adequately documented margins can be obtained. However, in instances where an adequate margin cannot be achieved via a local procedure, a partial or total penectomy may be required.

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REFERENCES

1. Ashley DJB, Edwards EC. Sarcoma of the penis. Leiomyosarcoma of the penis: report of a case with review of the literature on sarcoma of the penis. *Br J Surg*. 1957;45:170–179.
2. Bakken CL, Hanna EA, Seybold HM. Leiomyosarcoma of the penis. *J Urol*. 1968;99:769–771.
3. Blath RA, Manley CB. Leiomyosarcoma of the prepuce. *J Urol*. 1976; 115:220–221.
4. Chaudhuri S, Balasubrahmanyan M. Leiomyosarcoma of the penis: a case report. *Indian J Pathol Bacteriol*. 1966;9:278–284.
5. Dehner LP, Smith BH. Soft tissue tumors of the penis: a clinicopathologic study of 46 cases. *Cancer*. 1970;25:1431–1447.
6. Dobos N, Nisenbaum HL, Axel L, et al. Penile leiomyosarcoma: sonographic and magnetic resonance imaging findings. *J Ultrasound Med*. 2001;20:553–557.
7. Elem B, Nieslanik J. Leiomyosarcoma of the penis: case report. *Br J Urol*. 1979;51:46.
8. Fagundes LA, Hampe O, Brentano L, et al. Leiomyosarcoma of the penis: a case report. *J Urol*. 1962;88:803–804.
9. Fetsch JF, Brinsko RW, Davis CJ Jr, et al. A distinctive myointimal proliferation ('myointimoma') involving the corpus spongiosum of the glans penis: a clinicopathologic and immunohistochemical analysis of 10 cases. *Am J Surg Pathol*. 2000;24:1524–1530.
10. Glucker E, Hirshowitz B, Gellel B. Leiomyosarcoma of the glans penis: case report. *Plast Reconstr Surg*. 1972;50:406–408.
11. Greenwood N, Fox H, Edwards EC. Leiomyosarcoma of the penis. *Cancer*. 1972;29:481–483.

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12. Guillou L, Coindre J-M, Bonichon F, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. *J Clin Oncol*. 1997;15:350–362.
13. Gupta S, Gupta IM, Bhatnagar BNS. A rapidly fatal leiomyosarcoma of the penis with widespread metastasis. *Indian J Pathol Bacteriol*. 1973;16: 71–73.
14. Hamal PB. Leiomyosarcoma of penis: case report and review of the literature. *Br J Urol*. 1975;47:319–324.
15. Hey A. Beobachtung zweier seltener nichtepithelialer benigner tumoren des penis. *Pathologe*. 1984;5:286–288.
16. Hutcheson JB, Wittaker WW, Fronstin MH. Leiomyosarcoma of the penis: case report and review of literature. *J Urol*. 1969;101:874–875.
17. Isa SS, Almaraz R, Magovern J. Leiomyosarcoma of the penis: case report and review of the literature. *Cancer*. 1984;54:939–942.
18. Jain S, Vohra R, Kohli PK, et al. Leiomyosarcoma of penis: a case report. *J Postgrad Med*. 1982;28:121–122.
19. Kathuria S, Jablokow VR, Molnar Z. Leiomyosarcoma of penile prepuce with ultrastructural study. *Urology*. 1986;27:556–557.
20. Koizumi H, Nagano K, Kosaka S. A case of penile tumor: combination of leiomyosarcoma and squamous cell carcinoma. *Acta Urol Jpn*. 1987;33: 1489–1491.
21. Lopes M, Lanzafame S, Magro G. Localized fibrosis of the corpus cavernosum: an example of fibrosis arising from the vascular smooth muscle cells. Report of a case with histogenetic considerations. *Urol Int*. 2000; 64:173–179.
22. McDonald MW, O'Connell JR, Manning JT, et al. Leiomyosarcoma of the penis. *J Urol*. 1983;130:788–789.
23. McKenzie Pratt R, Ross RTA. Leiomyosarcoma of the penis: a report of a case. *Br J Surg*. 1969;56:870–872.
24. Nkposong EO, Osunkoya BO. Leiomyosarcoma of the penis: report of a case. *West Afr Med J*. 1972;21:34–36.
25. Pack GT, Trinidad SS, Humphreys GA. Primary leiomyosarcoma of the penis: report of a case. *J Urol*. 1963;89:839–840.
26. Prabhakar BR, Sethi RS, Singh H, et al. Leiomyosarcoma of penis. *Indian J Cancer*. 1975;12:103–106.
27. Pow-Sang MR, Orihuela E. Leiomyosarcoma of the penis. *J Urol*. 1994; 151:1643–1645.
28. Redman JF, Liang X, Ferguson MA, et al. Leiomyoma of the glans penis in a child. *J Urol*. 2000;164:791.
29. Smart RH. Leiomyosarcoma of the penis. *J Urol*. 1984;132:356–357.
30. Valadez RA, Waters WB. Leiomyosarcoma of penis. *Urology*. 1986;27: 265–267.
31. Val-Bernal JF, Garijo MF. Solitary cutaneous myofibroma of the glans penis. *Am J Dermatopathol*. 1996;18:317–321.
32. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. Council of state and territorial epidemiologists; AIDS program, Center for Infectious Diseases. *MMWR Morb Mortal Wkly Rep*. 1987;36(suppl 1):1–15.
33. Weinberger GI, Beckley S, Wajsman Z, et al. Primary sarcoma of penis. *Urology*. 1982;19:193–194.

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