AUCTORES
Globalize your Research

Clinical Medical Reviews and Reports

Anthony Kodzo-grey Venyo*

Open Access

Research Article

Primary Leiomyosarcoma of the Penis: Review and Update

Anthony Kodzo-grey Venyo

Department of Urology, North Manchester General Hospital, United Kingdom.

***Corresponding Author:** Anthony Kodzo-grey Venyo, Department of Urology, North Manchester General Hospital, Retired Clinician, United Kingdom.

Received Date: September 06, 2024; **Accepted Date:** September 13, 2024; **Published Date:** September 20, 2024

Citation: Anthony Kodzo-grey Venyo, (2024), Primary Leiomyosarcoma of the Penis: Review and Update, *Clinical Medical Reviews and Reports*, 6(8); **DOI:**10.31579/2690-8794/232

Abstract

Leiomyosarcoma of the penis is stated to arise from smooth muscles, which can be from dartos fascia, erector pili in the skin covering the shaft, or from tunica media of the superficial vessels and cavernosa. Prognosis of penile LMS is stated to be difficult to ascertain because reported cases of the tumour are rare. It has been pointed out that leiomyosarcoma of the penis could be classified as superficial tumour or deep tumour based upon the relation of the tumour to the tunica albuginea. It has been pointed out that deep tumours that measure greater 3 cm, high-grade lesions, and tumours that involve the corpora cavernosa, tend to spread locally and metastasize to distant areas and require more radical surgery with or without postoperative radiation therapy. In contrast, it has been stated that superficial lesions could be treated by the undertaking of local excision of the tumour only. It is known that carcinoma of the penis is not common with a worldwide incidence of 0.8 cases per 100,000 men. It is known that the commonest type of cancer of the penis squamous cell carcinoma (SCC) followed by soft tissue sarcoma (STS) and Kaposi sarcoma. Leiomyosarcoma (LMS) of the penis is stated to be the second most common STS subtype afflicting the penis. It has been iterated that about 50 cases of penile LMS had been reported in the English literature by 2022, most of these cases had been reported as isolated case reports while Fetsch and colleagues had reported 14 cases from a single institute. Considering that primary leiomyosarcoma of the penis is not common, it would be envisaged that many clinicians would not have encountered a case before and hence it is important for all clinicians globally to be updated on the manifestations, diagnosis, and treatment of LMS to enable them establish the diagnosis promptly in order to provide adequate and effective treatment for LMS of the penis.

Keywords: leiomyosarcoma of penis; biopsy; histopathology; immunohistochemistry; rare; local, superficial; deep; tunica albuginea; corpus cavernosum; excision; penectomy

Introduction

Malignant tumours of the penis are stated to be relatively uncommon, with an incidence of about 1 per 100,000 within developed countries such as North America and Europe; nevertheless, the incidence in less economically developed regions such as Asia, Africa, and South America is stated to be slightly higher in comparison with within the aforementioned developed regions. [1] The majority of penile malignant tumours amounting to 95% of the cases are iterated to be squamous cell carcinoma, while adenocarcinoma, malignant melanoma, and sarcoma are sporadic cases [1-2]. Malignant mesenchymal tissue tumours, including Kaposi's sarcoma, smooth muscle sarcoma, rhabdomyosarcoma, and malignant fibrous histiocytoma, are stated to account for less than 5%, among which primary leiomyosarcoma (LMS) of the penis is incredibly rare, mostly afflicting middle-aged and older males [1,3]. In 1969, Pratt and Ross [4] first classified LMS of the penis into deep and superficial types according to the site of the tumour. In view of the fact that deep LMS has tended to be associated with the development of early metastasis and poor prognosis, early diagnosis and correct identification of the type of leiomyosarcoma of the penis are crucial. [1]

Aim

To review and update the literature on leiomyosarcoma of the penis.

Method

Internet data bases were searched including: Google; Google scholar; Yahoo and PUBMED. The search words that were used included: Primary leiomyosarcoma of penis; and penile leiomyosarcoma. Eighty-one (81) references were identified which were used to write the article which has been divided into two parts: (A) Overview and (B) Miscellaneous narrations from some case reports, case series, and studies related to primary leiomyosarcoma of the penis.

Results

[A] Overview

Definition / general statement [5]

- It has been iterated that leiomyosarcoma (LMS) is a malignant mesenchymal tumour which exhibits smooth muscle differentiation [5-6]

Essential features

- It has been stated that leiomyosarcomas contain fascicles of eosinophilic spindled cells with blunt ended nuclei showing variable pleomorphism. [5,7-8]
- It has been pointed out that immunohistochemistry staining studies of specimens of leiomyosarcomas demonstrate positive staining for SMA, MSA, desmin or h-caldesmon. [5]
- It has been iterated that dedifferentiated areas of leiomyosarcoma lack expression of myogenic markers. [5,9]
- It has been iterated that primary leiomyosarcomas are clinically aggressive neoplasms with frequent local recurrences and distant metastases. [5]

Epidemiology

- It has been stated that leiomyosarcoma is one of the most common subtypes of malignant mesenchymal neoplasms and represents between 10% and 20% of all newly diagnosed soft tissue sarcomas [5-6]
- It has been pointed out that the overall incidence of leiomyosarcoma increases with age and peaks at the seventh decade of life. [5]
- It has been pointed out that sex predilection for the development of finding of leiomyosarcoma greatly depends upon the location of the tumour, with women comprising a clear majority of patients with retroperitoneal and inferior vena cava leiomyosarcoma and men demonstrating a slight predominance in non-cutaneous soft tissue sites. [5]

Sites

- It has been iterated that leiomyosarcoma most commonly afflicts extremities, retroperitoneum, abdomen / pelvis and trunk. [5,7,10]
- It has been pointed out that a distinctive sub-group of leiomyosarcoma originates in large blood vessels, most commonly the inferior vena cava. [5,8,11]

Pathophysiology

- With regard to pathophysiology, it has been iterated that leiomyosarcoma belongs to the group of soft tissue sarcomas with complex and unbalanced karyotypes, which results in severe genomic instability [5-6]
- It has been documented that some of the most common changes in leiomyosarcoma occur in the form of loss in chromosomes 10q(*PTEN*) and 13q (*RB1*) and gain at 17p (*TP53*) [5]

Aetiology

- With regard to aetiology, it has been pointed out that there is no definite, identifiable, causative factor for leiomyosarcoma [5]
- It has been iterated that previous history of radiotherapy, which is one of the most significant risk factors for development of soft tissue sarcomas, can also lead to the development of leiomyosarcoma [5,12]
- It has been documented that patients with genetic syndromes like hereditary retinoblastoma *(RB1* gene deletion) and Li-Fraumeni syndrome (mutation in the *TP53* gene) can develop leiomyosarcoma, amongst other soft tissue sarcomas [5-6]

Clinical features

- It has been iterated that clinical manifestation of leiomyosarcoma, as with other soft tissue sarcomas, is often associated with nonspecific symptoms caused by the displacement of structures, rather than invasion, in specific anatomic locations of the primary tumour and its metastases [5-6]

Diagnosis

- It has been iterated that radiology imaging approaches to the assessment of leiomyosarcoma include magnetic resonance imaging (MRI) in soft tissue extremity / truncal tumours and contrast enhanced computed tomography (CT) scan for retroperitoneal lesions. [5]
- It has been iterated that thorax and abdominal CT scans are required in the initial workup assessment of leiomyosarcoma, as hematogenous spread is a frequent event in leiomyosarcoma, with the lung and liver as two common sites of the development of metastases. [5,13]
- It has been iterated that the undertaking of pre-treatment biopsy is mandatory in extrauterine sites of leiomyosarcomas, with core biopsy as the preferred technique. [5] [6]
- It has been pointed out that the undertaking of detailed pathological evaluation is typically undertaken pursuant to complete resection of leiomyosarcoma. [5]
- It has been iterated that fine needle aspiration of leiomyosarcoma lesion has tended not to be adequate for the establishment of a diagnosis of leiomyosarcoma. [5-6]

Laboratory test

- It has been explained that there is no laboratory test that is diagnostic of leiomyosarcoma [5-6]

Radiology description

The ensuing summations had been made regarding the radiology image features of leiomyosarcoma: [5]

- CT findings [5,14]
    - CT scan imaging of leiomyosarcoma does demonstrate a generally heterogeneous lesion / mass.
    - CT scan imaging of leiomyosarcomas commonly demonstrate central low attenuation representing necrosis
    - Demonstration of calcification upon CT scan images in leiomyosarcomas are exceedingly rare
- MRI findings. [5,15]

- Upon MRI scan imaging of leiomyosarcoma there tends to be demonstration upon T1, of the lesion to be isointense to muscle. [5,15]
- Upon MRI scan imaging of leiomyosarcoma there tends to be demonstration upon T2 of the lesion to be non-fat suppressed: intermediate to hypointense to neighbouring fat. [5,15]
- Upon MRI scan imaging of leiomyosarcoma there tends to be demonstration upon T2 FS of the lesion to be: predominantly hyperintense. [5,15]

Prognostic factors

The factors of prognostication associated with leiomyosarcoma had been summated as follows: [5]

- Histological grade, tumour size and tumour depth are the 3 major clinicopathologic prognostic factors for soft tissue sarcomas, including leiomyosarcoma. [5,16-17]
- Leiomyosarcoma should be staged utilising the TNM staging for soft tissue tumours of the AJCC and UICC. [18-19]
- Leiomyosarcoma is stated to have substantial intrinsic aggressiveness and is one of the sarcoma sub-types with the highest risk of distant recurrence and decreased disease specific survival [5,16]
- Retroperitoneal leiomyosarcoma and leiomyosarcoma of large vessels tend to have a poor prognosis [5]
- Metastases most commonly occur in lung, liver and soft tissue [7,10]
- Leiomyosarcoma is the most common sarcoma to produce skin metastases. [5,20]
- The overall 5-year survival associated with leiomyosarcoma had been stated to be 68%. [5,21]

Treatment

The treatment of leiomyosarcoma has been summated as follows: [5]

- Staging of soft tissue sarcomas, including leiomyosarcoma, is important in guiding the treatment of leiomyosarcoma. [5]
  - Leiomyosarcoma should be staged utilising the TNM staging for soft tissue tumours of the AJCC and UICC [5,18-19]
- Treatment of leiomyosarcoma is best undertaken in a specialized centre with expertise in sarcoma care. [5,22]
- Treatment planning of leiomyosarcoma commences with a multidisciplinary review of the patient's history, all available radiographic images and the pathologic results from biopsy. [5]
- Treatment plan of leiomyosarcoma is formulated upon the input from orthopaedic and general surgeons, musculoskeletal radiologists, pathologists, medical oncologists and radiation oncologists (The multidisciplinary team). [5]
- The goal of treatment of leiomyosarcoma is stated to control the symptoms, decrease tumour bulk as well as to prolong survival. [5-6]
- Surgery is undertaken to excise / remove completely the lesion as the main plan. [5,23]
  - Local control of soft tissue leiomyosarcoma is usually achieved with the undertaking of surgical resection
  - Achieving wide tumour-free surgical margins is important in preventing local recurrence
- Radiotherapy
  - It has been iterated that radiotherapy is an important additional treatment for improving rates of local control of leiomyosarcoma [5]
  - Many leiomyosarcoma tumours involve or are directly adjacent to vital structures and in these cases achieving a wide surgical margin is impossible. [5]
  - It has been iterated with radiotherapy could be administered either preoperatively (neoadjuvant) or postoperatively (adjuvant) [5]
    - It has been pointed out that in the scenario of leiomyosarcoma, peri-operative radiotherapy for soft tissue sarcoma is the gold standard of treatment for localized disease in extremities, trunk and head / neck region [5-6]
    - It had also been pointed out that at this point, no consensus exists on the timing or benefit of perioperative radiotherapy for patients diagnosed with retroperitoneal soft tissue sarcoma
  - It has also been stated that radiotherapy could also be utilized as a means of palliative local control when extensive metastases have already occurred. [5]
- Chemotherapy

The ensuing summation had been made regarding chemotherapy in the treatment of leiomyosarcoma: [5]

- It has been iterated that leiomyosarcoma is typified by severe genomic instability, which emanates in multiple genetic aberrations; as a result, leiomyosarcoma is considered to be moderately sensitive to chemotherapy. [5,24]
- It has been pointed out that neoadjuvant chemotherapy could help shrink the tumour, thus, improving the resectability of the tumour, achieving tumour-negative resection margins and earlier control of metastatic disease. [5]
- It has been iterated that adjuvant chemotherapy pursuant to surgery significantly improves the time to local and distant recurrence and overall recurrence free survival [5,25]
- It has been iterated that chemotherapy is the first line treatment in metastatic or unresectable leiomyosarcoma. [5]

Gross description [5]

The macroscopy examination features of leiomyosarcoma had been summarised as follows: [5]

- Leiomyosarcoma typically forms a fleshy, grey to white to tan tumour mass. [5]
- In leiomyosarcoma, whorled appearance may be evident. [5]
- Large leiomyosarcoma tumours often display haemorrhage, necrosis and cystic change. [5]
- The border of leiomyosarcoma tumour frequently appears to be well-circumscribed. [5,26-28]

Frozen section description

Frozen section examination features of leiomyosarcoma specimens had been summarised as follows: [5]

- Frozen section examination of specimens of leiomyosarcoma demonstrates cellular neoplasm that is composed of intersecting fascicles of spindle cells with bright eosinophilic cytoplasm and elongated, blunt ended (cigar shaped) nuclei [5,29-30]
- Frozen section examination of specimens of leiomyosarcoma demonstrates nuclear pleomorphism, tumour necrosis and mitotic activity. [5]

Microscopic (histologic) description

Microscopy pathology examination features of leiomyosarcoma specimens had been summarised as follows: [5]

- Classic leiomyosarcoma. [5,29-30]
    - Microscopy pathology examination of specimens of leiomyosarcoma demonstrates spindle shaped cells with plump, blunt ended nuclei and moderate to abundant, pale to brightly eosinophilic fibrillary cytoplasm
    - Microscopy pathology examination of specimens of leiomyosarcoma demonstrates cells that are set in long intersecting fascicles parallel and perpendicular to the plane of section
    - Microscopy pathology examination of specimens of leiomyosarcoma demonstrates that some tumours show areas with storiform or palisaded patterns
    - Microscopy pathology examination of specimens of leiomyosarcoma demonstrates that moderate nuclear pleomorphism is usually noted, even though pleomorphism may be focal
    - In microscopy pathology examination of specimens of leiomyosarcoma mitotic figures, including atypical ones, tend to be easy to find
    - Microscopy examination of leiomyosarcoma specimen shows tumours that usually exhibit diffuse hypercellularity
    - Focal fibrosis, myxoid change and hyalinized hypocellular areas can be seen upon microscopy examination of leiomyosarcoma specimens.
    - Tumour cell necrosis is often present in specimens of leiomyosarcoma upon microscopy examination.
    - Unusual features in soft tissue leiomyosarcoma including multinucleated osteoclast-like giant cells, granular cytoplasmic change and epithelioid morphology could be visualised upon microscopy examination of specimen of leiomyosarcoma.
- Pleomorphic leiomyosarcoma.

Microscopy pathology examination findings of specimens of pleomorphic leiomyosarcoma had been summated as follows: [5,31]

    - The tumour is demonstrated to be composed of pleomorphic cells with or without abundant eosinophilic or fibrillary cytoplasm in > 66% of the maximum cut surface of the tumour, accompanied by an ordinary leiomyosarcoma fascicular area covering < 33%
    - There tends to be evidence in the tumour of storiform pattern in > 50% of cases
    - There tends to be evidence of stromal hyalinization in the tumour.
    - There tends to be evidence of chronic inflammatory infiltrate within the tumour.
    - There tends to be evidence of myxofibrosarcoma-like (myxoid malignant fibrous histiocytoma-like) areas in the tumour.
- Myxoid leiomyosarcoma

Microscopy pathology examination findings of specimens of pleomorphic leiomyosarcoma had been summated as follows: [5,32]

    - There tends to be evidence of extensively myxoid stroma (> 50% of the tissue examined)
    - There tends to be evidence of tumour cells that are predominantly spindled
    - 3 major histologic architectures: fascicular, reticular / microcystic and myxofibrosarcoma-like tend to be seen.
    - Areas of conventional leiomyosarcoma are usually present at least focally upon microscopy examination.
- Dedifferentiated leiomyosarcoma.

Microscopy pathology examination findings of specimens of dedifferentiated leiomyosarcoma had been summated as follows: [5,9]

- Microscopy pathology examination Tumour showing features of low grade leiomyosarcoma associated with a discrete undifferentiated component lacking morphological or immunophenotypic features of myogenic differentiation
- Diagnostic threshold for diagnosing low grade leiomyosarcoma is much lower outside the uterus than in the uterus
    - Diagnosis requires nuclear atypia and essentially any level of mitotic activity. [5,33]
    - Some authors recommend expert review by sarcoma pathologists for diagnosis of leiomyosarcoma at any site. [5,33]
- Histologic grade (French Federation of Cancer Centers Sarcoma Group [FNCLCC]) [5,34]
    - The majority of soft tissue leiomyosarcomas are high grade based upon their histopathology microscopy examination features.

Cytology description

The cytology examination features of leiomyosarcoma had been summated as follows:

- Leiomyosarcoma, classical variant [5,35]
    - Various proportions of spindle shaped, cohesive, small or large sized cells arranged in parallel alignment tend to be found upon cytology examination of the specimen.
    - Blunt ended nuclei, tend to be found on cytology examination of the specimen.
    - The cytoplasm has tended on cytology examination to vary from fibrillary to granular to vacuolar
- Leiomyosarcoma, epithelioid variant. [5]
    - Round or polygonal cells tend to be visualised upon cytology examination.
    - Eccentrically located nuclei, tend to be visualised upon cytology examination. [5,36]
    - Granular or clear cytoplasm tends to be seen on cytology examination. [5]
- Leiomyosarcoma, pleomorphic variant
    - Variably sized and shaped cells, often including multinucleated giant cells with atypical nuclei, tend to be visualised during cytology examination of the specimen. [5]
- Leiomyosarcoma, myxoid variant
    - Large amounts of background myxoid matrix containing large spindle shaped and giant cells, tend to be visualised during cytology examination of the specimen. [5]
- Intranuclear inclusions and mitotic figures are occasionally seen, as well as stromal fragments tend to be seen in cases of leiomyosarcoma. [5]

Positive stains

It has been iterated that immunohistochemistry staining studies of specimens of leiomyosarcoma demonstrate tumour cells that exhibit positive staining for the ensuing tumour markers: [5]

- **SMA, MSA, desmin, h-caldesmon**. [5,37-39]

Negative stains

It has been iterated that immunohistochemistry staining studies of specimens of leiomyosarcoma demonstrate tumour cells that exhibit negative staining for the ensuing tumour markers: [5]

- **ER, PR, WTI** [5,40]
- **CD117, S100, HMB45.** [5,37]
- Positive staining for **cytokeratin** and **EMA** in 38% and 44% of cases, respectively [5,41]

Molecular / cytogenetics description

The molecular / cytogenetics study features of leiomyosarcomas had been summated as follows: [5]

- Complex karyotypes with numerous chromosomal gains and losses are found [5,42]
- Losses involving tumour suppressors *TP53* (17p13.1), *RB1* (13q14.2) and *PTEN* (10q23.31) are found. [5,43]
- *TP53* is mutated in as many as 50% of sporadic leiomyosarcomas are found. [5]
- Homozygous copy loss of *CDKN2C* at chromosome 1p32.3b are found. [5,42]
    - *CDKN2C* null leiomyosarcoma defines a genomically distinct tumour that may have prognostic or therapeutic clinical implications, including the possible use of specific cyclin dependent kinase inhibitors [5]

Differential diagnoses [5]

The differential diagnoses of leiomyosarcomas had been summarised as follows:

- **Leiomyoma** [5,37,44]
    - Leiomyoma is stated to be well circumscribed
    - Leiomyoma lacks significant nuclear atypia upon microscopy examination.
    - Mitoses are rare to absent upon microscopy examination of leiomyoma.
    - Retroperitoneal leiomyomas resemble uterine leiomyomas by histology and are positive for hormone receptors
- **Malignant peripheral nerve sheath tumour**: [5,45]
    - This tumour may demonstrate clinical and histologic origin from nerve
    - This tumour can arise in association with benign nerve sheath tumour
    - Fascicles of spindle shaped cells, often with a hemangiopericytoma-like vascular pattern are seen upon pathology examination of the tumour specimen.
    - Alternating hypercellular and hypocellular areas (tapestry appearance) tend to be visualised upon pathology examination of this tumour.
    - **S100** and **SOX10** expression (often focal) are seen upon immunohistochemistry staining of the tumour.
    - Loss of **H3K27me3** is demonstrated in this tumour.
    - Negative for muscle markers
        - **Desmin** expression is seen in rhabdomyoblastic elements in malignant Triton tumour.
- **PECOMA**: [5] [46] [47]
    - PECOMA may show morphologic overlap with leiomyosarcoma
    - Nested architecture or sheet-like growth pattern tend to be visualised upon pathology examination of specimen of PECOMA.

- Spindled to epithelioid cells with abundant clear to granular eosinophilic cytoplasm tend to be visualised in PECOMA.
- Distinctive perivascular pattern of growth, with tumour cells radially arranged around vessels, tend to be seen in specimen of PECOMA.
- Characteristic myomelanocytic immunophenotype tend to be demonstrated in PECOMA as follows: [5]
  - Variable expression of **SMA, desmin, caldesmon, HMB45, MART1 / Melan A**
  - Minor subset shows nuclear **TFE3** expression

- **Synovial sarcoma (monophasic)**: [5,48,50]
  - Monomorphic blue spindle cells arranged in dense cellular sheets or vague fascicles are visualised in this tumour.
  - This tumour may contain strands of wiry or hyalinized collagen and calcifications
  - Many monophasic synovial sarcoma tumours focally display a staghorn shaped vascular pattern
  - Expression of **EMA, keratins, BCL2, CD99, and TLEI** tend to be demonstrated in this tumour.
  - Negative for muscle markers
  - Synovial sarcoma harbours a unique t(X;18)(p11;q11) translocation

- **Undifferentiated pleomorphic sarcoma**: [5,50]
  - Can be indistinguishable from pleomorphic leiomyosarcoma
  - Lacks areas of classic leiomyosarcoma
  - Pattern-less or fascicular architecture
  - Frequent bizarre multinucleated tumour giant cells
  - Negative for **desmin**, **MSA** and **caldesmon**

[B] Miscellaneous Narrations and Discussions From Some Case Reports, Case Series, And Studies Related To Leiomyosarcoma Of The Penis.

Ajmal et al. [51] reported a patient who was aged 70 years, and who had manifested with 1-year history of a slowly enlarging penile mass that was associated with phimosis. He did not report any pain, dysuria, or hesitancy. During his clinical examination, a 2 cm × 2-cm smooth, mobile, non-ulcerating mass was visualised upon the tip of his left glans without inguinal lymph node enlargement. He underwent circumcision and excision biopsy which revealed an encapsulated tan-white mass that measured 3 cm × 2.2 cm × 1.5 cm under the surface of his foreskin. Histopathology examination of the lesion showed a spindle cell tumour with areas of increased cellularity, prominent atypia, and pleomorphism, focal necrosis, as well as scattered mitoses, including atypical forms. The tumour upon immunohistochemistry studies stained positive for smooth muscle actin and desmin. Ki-67 staining showed foci with a very high proliferation index. The tumour resection margins were negative. The Final Fédération Nationale des Centres de Lutte Contre Le Cancer score of the tumour noted to be grade 2 (differentiation, 1; mitotic, 3; necrosis, 1). He had computed tomography of his chest, abdomen, and pelvis, which did not demonstrate any evidence of metastasis. The tumour was classified as superficial, stage IIA (pT1cN0cM0). The local excision of the tumour with negative margins was deemed to be an adequate treatment.

Ajmal et al. [51] made the ensuing educative discussions:

- Penile LMS is uncommon and arises from smooth muscles, which in the penis could be from dartos fascia, erector pili in the skin covering the shaft, or from tunica media of the superficial vessels and cavernosa. [52]
- It commonly manifests as a nodule or ulcer which might be ensued by paraphimosis, phimosis, erectile dysfunction, and lower urinary tract symptoms depending upon the extent of local tissue involvement.
- In their review of 31 cases, the age at manifestation had ranged between 38 years and 85 years, with 1 case report of LMS was in in a 6-year-old boy.
- The highest incidence was in the 6th decade.
- Tumour behaviour could be indolent or aggressive.
- Majority of the patients in their review had asymptomatic, slow-growing lesions for 6 months to 24 months before their manifestation including their patient, while other patients had an aggressive tumour with symptoms for a few weeks which was followed by rapid metastatic spread. [53-54]
- Diagnosis of LMS entails the undertaking of biopsy of the lesion followed by histopathology examination and immunohistochemistry examination of the lesion.
- Typically, upon pathology examination LMS demonstrates fascicles of spindle cells with various degrees of nuclear atypia, pleomorphisms, and necrotic regions.
- Mitotic rate is variable and usually higher than 5 mitoses per high power field.
- The cells stain positively upon immunohistochemistry studies for smooth muscle actin, desmin, and h-caldesmon. [55]
- TNM (tumour, nodes, metastasis) stage is determined by the American Joint Committee on Cancer guidelines for STS.
- Pratt and Ross. [56] were the first to categorize penile LMS as superficial or deep.[56]
- The former includes all lesions superficial to tunica albuginea while the latter run deep to this layer.
- Anatomical differentiation is an important factor in tumour behaviour, treatment selection, and prognosis.
- In their review, they found 14 cases of superficial and 17 cases of deep LMS.
- There are no established guidelines on optimum treatment of penile LMS. Nevertheless, they could extrapolate principles from current guidelines on penile cancer, cutaneous leiomyosarcoma, and limb sarcomas.
- At the time of publication of their article, the first-line treatment for superficial penile LMS has been wide local excision to achieve negative margins.

- The undertaking of circumcision alone might be sufficient for tumours of the distal prepuce, as in their reported case. [57]
- Radical resection generally is not required for these early-stage tumours.
- In their review, no patient in this category had developed recurrence or metastasis regardless of initial surgery type
- For deep lesions, partial, if functional penile stump and negative margins can be achieved— or total penectomy is required. [57]
- In their review, more conservative approaches to deep tumours were found to be associated with local recurrences. [54,58-59]
- Lymphatic spread is rare for LMS.
- Furthermore, involvement of local lymph nodes usually had coincided with distant spread.
- Inguinal lymph node dissection is not indicated if initial negative surgical margins are achieved.
- For STS at other sites within the body, radiotherapy has been recommended postoperatively for high-grade lesions, which could be extrapolated to penile LMS as well.
- The benefit of preoperative radiotherapy is less certain.
- In limb sarcomas, radiotherapy is associated with better local control for large-sized tumours and is utilised for patients who have initial unresectable tumours. [60]
- Similar recommendation could be extended to penile LMS that are associated with local spread to the inguinal lymph nodes, scrotum, or abdominal wall.
- In their review, they had found out that postoperative radiotherapy was used in 3 patients with deep tumours. [61-63] Of these, short-term relapse had occurred in 1 patient.
- Chemotherapy for LMS has remained controversial.
- The tumour generally has been noted to be resistant to chemotherapy and systemic therapy, if employed, it had been for palliative purpose.
- The most promising results for adjuvant chemotherapy for resectable STS was seen in limb and uterine sarcomas with high-grade, metastatic, or relapsed tumours; nevertheless, improvement in overall survival had been reported to be marginal. [64-65]
- Single and multidrug regimens based upon doxorubicin, ifosfamide, and gemcitabine had been studied with results demonstrating no efficacy or a slight benefit. [55,66]
- Immunotherapy and targeted therapy for penile STS had not been studied.
- In their review, postoperative chemotherapy was utilised for 2 patients with deep tumours and 1 patient with a superficial tumour whilst pre-operative chemotherapy was utilised for 1 patient. [61,63,67] Short-term relapse was demonstrated in 2 of 4 of these patients.
- LMS has tended to metastasize haematogenously and lymphatic spread has not been common.
- In their review, 7 patients had developed metastasis. These patients had deep tumours at their initial manifestation with tumour size greater than 3 cm. Five of 7 patients had involvement of corpora cavernosa at manifestation. The lung was the most common site of metastasis, followed by local extension to lower abdominal wall and scrotum. Out of the 7 patients, 3 were treated with initial limited excision or partial penectomy and then they experienced local recurrence or distant metastasis. [54,58-59,68] This finding has supported the use of radical surgery in large, deep tumours. Furthermore, in 4 cases, metastasis occurred despite initial treatment with total penectomy and utilisation of adjuvant chemoradiation therapy.
- In most cases penile LMS was noted to be a de novo tumour; however, on occasion it could be accompanied by another epithelial malignancy. Similarly, penile LMS might be a site of recurrence for a primary LMS at another site in the human body, as was seen in 3 of the reviewed cases. In the first, a patient had manifested with a nodule upon his glans penis which was suspicious for SCC, second with synchronous SCC and LMS, and a third case where a patient had manifested with penile LMS 9 years pursuant to his undergoing treatment for similar tumour within his epididymis. [62,69-70]
- The prognosis of penile LMS is difficult to ascertain because reported cases are rare.
- In their review, the longest documented disease-free survival was 3.5 years for a patient who had superficial LMS that was treated with local excision. [71]
- In cases of distant metastasis, the average survival was reported to be 4.6 months, while the longest survival since the initial manifestation and last documented local recurrence was 16 years. [59] Five-year survival had not been reported.

Ajmal et al. [51] made the ensuing conclusions:

- LMS of the penis is an uncommon and potentially aggressive neoplasm.
- LMS of the penis could be classified as superficial or deep based on tumour's relation to the tunica albuginea.
- Deep tumours, are tumours that measure more than 3 cm, high-grade lesions, and tumours with involvement of corpora cavernosa, tend to spread locally, metastasize to distant areas, and require more radical surgery with or without postoperative radiotherapy.
- In comparison, superficial lesions could be treated with local excision only. Both superficial and deep tumours require close follow-up.

Romero Gonzalez [71] reported a 39-year-old patient, smoker, who had frenuloplasty intervention in 1990, who attended the Urology clinic in December 2009 due to his manifestation with an enlarged tumour on the ventral area of his penis over the preceding one year that was associated with pruritus. His clinical examination demonstrated a palpable tumour of 1 cm in diameter in his preputial frenulum area, adjacent to the urethra, mobile, painless and without inguinal lymph node enlargement. He underwent excision of the lesion under local anaesthesia, respecting his urethra and aiming macroscopically that its indemnity was maintained. Pathology examination of the penile lesion demonstrated features based upon which a diagnosis of leiomyosarcoma of penis was made based upon

the finding of a proliferation of long spindle cells which had exhibited nuclear atypia and mitotic index of 2/10 with high power field. With Ac. Ki67 proliferation index of 25% (see figure 1 and figure 2).

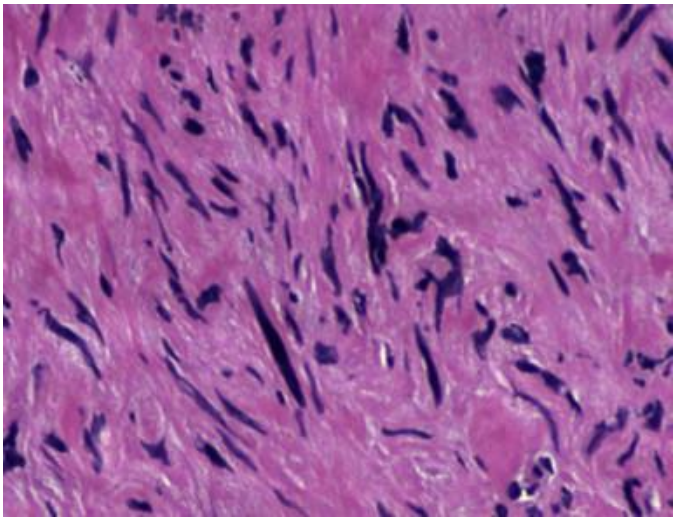

Figure 1: Spindle cells with clear nuclear pleomorphism and high mitotic index. Reproduced from: [71] Under the Creative Commons Attribution License.

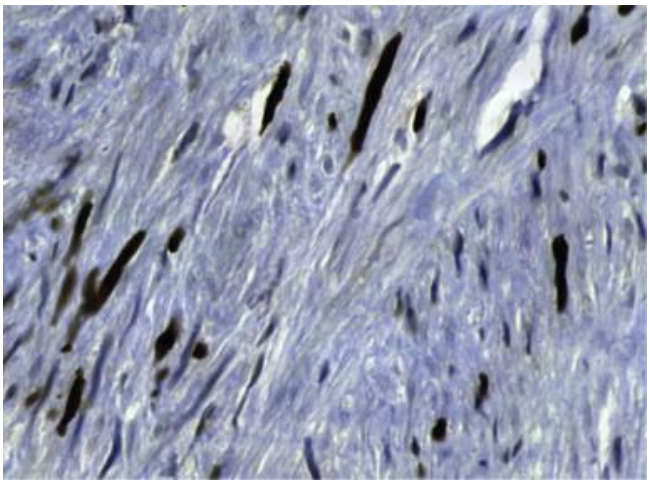

Figure 2: Immunohistochemistry Ac. Ki767 demonstrating the high proliferation index. Reproduced from: [71] Under the Creative Commons Attribution License.

He underwent CT scan of thorax, abdomen and pelvis, which did not demonstrate any residual tumour, lymph node enlargement or metastasis. Given this situation, it was decided to undertake reoperation with conservative intention, extending surgical margins of the lesion to ventral urethra and glans sending intraoperative sample which reported the absence of tumour cells. He had a good postoperative recovery without complications. At the time of the report of his case he had undergone follow-up assessments three and half years with no evidence of local recurrence or metastasis.

Hao et al. [1] made the ensuing iterations:

- Leiomyosarcoma (LMS) is a malignant spindle-cell mesenchymal tumor which originates from the smooth muscle cells, which mostly afflicts soft tissues and abdominopelvic organs over extremities.
- Primary LMS of the penis is a relatively uncommon mesenchymal tissue disease and a poorly understood neoplasm.

Hao et al. [1] reported a 69-year-old man, who had manifested with a growing, painless mass protruding from his penis. The irregularly lobulated

lump was measured to be roughly 3 cm × 2.5 cm, with a smooth surface, tough texture, distinct boundary, and no tenderness. The mass was

determined to be a penile tumor during his pre-operative radiology imaging assessment. The patient underwent resection of the penile mass, which was ensued by extended resection in the second operation. The diagnosis of LMS was verified by pathology examination of the specimen. During a 20-month follow-up, the patient made a smooth recovery and had remained disease-free. Hao et al. [1] made the ensuing conclusions:

- An immunohistochemical examination is essential for establishing this rare diagnosis.
- Radical excision of the tumour lesions with negative cut margins is guaranteed to be the best treatment for primary penile LMS.
- Close follow-up the patient should be undertaken due to the high rate of local recurrence.

Goyal et al. [72] stated made the ensuing iterations:

- Mesenchymal tumours arising within the penis are extremely uncommon.
- Sarcomas must be differentiated sarcomatoid squamous carcinomas, owing to their treatment and prognostic implications.

Goyal et al. [72] reported a rare case of leiomyosarcoma of the penis in a 70-year-old patient. Histopathology examination of the penile lesion demonstrated features of a high-grade spindle cell sarcoma, which was initially reported as sarcomatoid carcinoma on biopsy, but this was subsequently confirmed on partial penectomy as a leiomyosarcoma. Goyal et al. [72] made the ensuing conclusions:

- Penile LMS is a rare tumour and may mimic a sarcomatoid carcinoma.
- Careful morphology evaluation and ancillary immunohistochemistry (IHC) studies help in the accurate diagnosis of the tumour and in tailoring of the treatment.

Fetsch et al. [73] made the ensuing iterations:

- Primary leiomyosarcomas of the penis are very rare.
- Up to 2004, less than 30 had been documented in the English language literature.

Fetsch et al. [73] reported the clinical, histopathological, and immunohistochemical findings in 14 cases of primary leiomyosarcomas of the penis they had retrieved from their files. The patients had ranged in age from 43 years to 62 years, and their mean age was 51 years at the time of initial surgical resection. The tumours had involved the prepuce in 1 case, the prepuce and distal shaft in 1 case, circumcision scar line in 2 cases, circumcision scar line and distal shaft in 1 case, the shaft of the penis in 5 cases, base of the penis in 3 cases, and penis, not otherwise specified in 1 case. Fetsch et al. [73] summarised their results as follows:

- The lesions had ranged in size from 0.5 cm to 6.0 cm and their median size, was 1.5 cm, in greatest dimension.
- Nine tumours were superficially located, two were of indeterminate depth, and three were deep-seated.
- The superficial tumours were reported to be relatively asymptomatic, and seven were reportedly present for 1 year to more than 20 years with a median duration time of 5 years, before medical attention was sought.
- In contrast, one deep-seated lesion had caused dysuria and difficulty voiding, prompting the patient to seek a clinical opinion within only a few months of the apparent onset.
- Histologically, all of the tumours had contained smooth muscle cells with both cytological atypia and mitotic activity.
- Immunohistochemical studies were available for nine of the tumours, and immunoreactivity for desmin was present in all instances.
- All of the patients were initially treated with a local procedure.
- Follow-up information was available for 9 out of the 14 patients, which amounted to 64% of the patients, 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 was reported to have had four local recurrences and who had refused a penectomy, developed a distant metastasis 10 months after the fourth recurrence.

Fetsch et al. [73] made the ensuing conclusions:

- The best predictors of outcome are tumour depth and tumour size.
- Superficial leiomyosarcomas of the penis are optimally managed by wide local excision whenever this is technically feasible.
- Tumours that have a deep-seated component may require more aggressive intervention to ensure complete removal.

Khobragade et al. [74] stated the ensuing:

- Sarcomas represent about 1% of all malignant tumours. [75]
- Primary mesenchymal tumours of penis are uncommon.
- Majority of these tumours are of vascular origin.
- They were reporting two cases of primary leiomyosarcoma of penis.

Khobragade et al. [74] reported Case 1, a 26-year-old male patient, who had manifested with progressively increasing painless swelling at the base of his penis over the preceding 3 months. Upon examination, the swelling was found to have a 3cm × 3cm firm swelling at his penoscrotal junction, that was free from his underlying pubic bone and no evidence of groin lymphadenopathy. He had magnetic resonance imaging (MRI) scan which demonstrated a 4.7 cm × 3.7 cm × 5.4 cm lobulated soft-tissue mass which had involved his left corpus cavernosum without lymphadenopathy. Fine needle aspiration cytology was undertaken and the examination features of the aspirate had indicated a diagnosis of a spindle cell tumour. The penile mass was excised through an inguinoscrotal incision taking margin of left corpus cavernosum. No lymphadenectomy was undertaken due to N-0 status. The histopathology report was high grade leiomyosarcoma with immunohistochemistry positive staining of the tumour cells for (Desmin, smooth muscle antibody [SMA]), Calponin and negative for myoglobin and Myo-D1 (see figure 3). The surgical resection margins were reported to be tumour-free, and the closest tumour being 2 cm away from the resection margin. No adjuvant therapy was given. Patient was reported to be disease free at the time of publication of the article present which was after 2 years of his follow-up assessment.

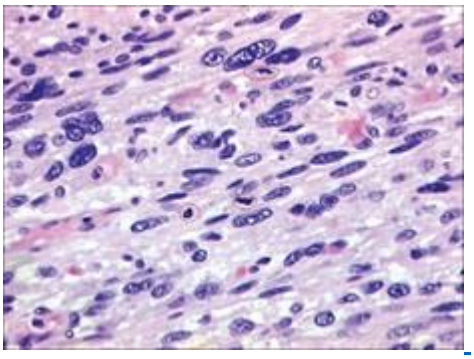

Figure 3: Leiomyosarcoma comprised of pleomorphic spindle cells with mitotic activity (encircled)

Reproduced from: [74] Under the Creative Commons Attribution License.

Khobragade et al. [74] reported case 2, a 38-year-old male patient, who had manifested with multiple lesions over his over the preceding 8 months. During his examination, he was found to have a fungating mass over his glans penis of 3 cm × 4 cm size which had involved his urethral meatus with three separate mobile nodules over proximal shaft of his penis [see figure 4]. There were no groin nodes. Pathology examination of his punch biopsy specimen of his penile lesion demonstrated a high-grade leiomyosarcoma with immunohistochemistry staining positivity for SMA and desmin and negative staining for S-100, CD34, and Myogenin. He underwent total penectomy with perineal urethrostomy. No lymph-node dissection was undertaken in view of his N-0 status. The patient was reported to be disease free at his 9 months of follow-up.

Figure 4. Clinical photograph. Reproduced from [74] under the Creative Commons Attribution License.

Khobragade et al. [74] made the ensuing educative discussions:

- Soft-tissue sarcomas (STS) of the genitourinary (GU) tract are relatively rare, and they are stated to account for of 2.1% of STS's and 1-2% of all malignant GU tumours. [76-78]
- Penile sarcomas represent less than 5% of malignancies of the penis.
- They comprise of endothelial cell sarcomas (Kaposi's sarcoma, epithelioid hemangioendothelioma, angiosarcoma) and less frequently rhabdomyosarcoma and leiomyosarcoma.
- Leiomyosarcoma represents about 5% to 6% of penile sarcomas. [2]
- The first case was described by Levi in 1930. [79]
- The age range at diagnosis for penile leiomyosarcoma has ranged from 6 years to the late 80s with the highest incidence within the fourth and fifth decade of life.
- Pratt and Ross [80] had classified penile leiomyosarcomas as superficial and deep depending upon invasion of the tunica albuginea.
- Histologically the two types of leiomyosarcoma of penis are stated to be identified including:

    (a) Superficial lesions which arise from the dartos muscle layer, the piloerector complex and the muscular walls of superficial vessels situated outside the albuginea. They manifest as a small tumour within the distal shaft or the penile prepuce, often in middle-aged men. These are slow growing tumours that are likely to recur locally with fewer propensities for metastases.

    (b) Deep lesions arise from the proximal portions of the corpora cavernosa or corpus spongiosum and they occur at a relatively later age. Clinically they tend to be poorly circumscribed, firm, non-tender masses that infiltrate surrounding tissues and can also cause urinary obstruction. Deep lesions show a greater propensity to metastasize and have a poorer prognosis. [81]

- Sarcomas usually spread by hematogenous route. Lymph node metastases is rare and seen in disseminated disease. [81]
- Upon gross section leiomyosarcomas are found to be well-circumscribed with rubbery consistency.
- Microscopically, spindle shaped smooth muscle bundles arranged into interlacing fascicles are visualised.
- Upon electron microscopy, myofibrils, dense bodies and abundant pinocytic vesicles are noted with a continuous basal lamina.

- The literature had iterated that mitotic rate and degree of differentiation are reliable in order to predict the tumour's propensity to infiltrate the adjacent structures or to metastasize.
- Treatment of this rare malignancy has been iterated to be predominantly surgical, either wide excision or amputation; nevertheless, the approach should be individualized. Complete resection of the tumour has been iterated to be associated with better survival. [81]
- Wide local excision of leiomyosarcoma of penis could be undertaken for small (<2 cm), superficial tumours in young males. Recurrences in superficial tumours are likely to be salvageable (sometimes even with additional wide excision) due to the fact that they often remain localized for a long time before giving rise to metastases.
- Deep-seated tumours are treated with amputation either partial or radical with perineal urethrostomy.
- Regional lymph node dissection is usually not indicated in the absence of clinic-radiologically apparent lymph-node metastases as nodal involvement is uncommon.
- Adjuvant radiotherapy and chemotherapy have no proven value in treatment of primary. Pre- or post-operative radiotherapy had not proven its value in reducing loco-regional recurrences or in increasing survival rates. Radiotherapy had been utilised for palliation, with chemotherapy being reserved for cases of disseminated disease. In the series by Russo et al. [76] of adult urological sarcomas, no patient with disseminated disease was fully responsive to the use of several chemotherapy regimens.
- Local recurrence had seemed to be a frequent phenomenon and leiomyosarcomas become more undifferentiated with each recurrence.
- The recurrence rate of leiomyosarcoma of the penis had been stated to be similar for superficial and deep lesions, 23% and 29% respectively, but the metastatic potential is stated to be higher in deep seated lesions (50%). [81]
- The metastatic potential of leiomyosarcoma of the penis is also stated to vary according to the size of lesions, 29% for <5 cm and 50% for >5 cm. The most frequent sites of distant metastases of leiomyosarcoma of the penis had been iterated to include: the lungs, liver and brain. Large tumours especially those located within the root of the penis, had been iterated to often portend a poor prognosis despite aggressive surgical intervention. [81]

Khobragade et al. [74] made the ensuing conclusions:

- Additional histopathology examination parameters such as tumour growth pattern (circumscribed and uninodular versus. infiltrative and/or multinodular), mitotic count (>10 mitotic Figure/10 high power fields) and grade three histology could be studied in the future in order to better prognosticate these tumours.
- Penile leiomyosarcomas are rare tumours and they portend a poor prognosis when deep-seated.
- The analysis of prognostic factors associated with primary leiomyosarcomas of the penis could help to identify patients at higher risk for disease progression.
- Surgical treatment of leiomyosarcoma of the penis provides the best chance of cure, with additional treatment options required in few patients.

Conclusions

- Primary leiomyosarcoma of the penis is an uncommon neoplasm which may simulate other lesions of the penis including sarcomatoid carcinoma of the penis.
- Careful morphology assessment and immunohistochemistry staining studies of the penile lesion helps with regard to the establishment of the correct diagnosis which would then enable the multi-disciplinary team recommend the most appropriate and effective treatment.

Conflict of Interest – NIL

Acknowledgements

Acknowledgements to:

- Urology Case Reports and Elsevier for granting permission for reproduction of figures and contents of their journal article under the Creative Commons Attribution License. Copyright © 2015 The Authors This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
- Indian Journal of Cancer and Wolters Kluwer – Medknow for granting permission for reproduction of figures and contents of their journal article under the Creative Commons Attribution License.

References

1. Hao Y, Xia L, Lu M, Liu C, Zhang F, (2023). Case report and literature review: Primary leiomyosarcoma of the penis. *Front Surg*. 2023 Jan 9;9:1068935.
2. Dehner LP, Smith BH (1970). Soft tissue tumors of the penis. A clinicopathologic study of 46 cases. *Cancer*. 1970 Jun;25(6):1431-47.
3. Cigna E, Maruccia M, Parisi P, Soda G, Nasca MR,(2013). Superficial leiomyosarcoma of the glans: report of a case and literature review. *Aesthetic Plast Surg*. 2013 Oct;37(5):1052-8.
4. Pratt RM, Ross RT (1969). Leiomyosarcoma of the penis. A report of a case. *Br J Surg*. 1969 Nov;56(11):870-2
5. Alexiev B. Leiomyosarcoma-general. PathologyOutlines.com website. Accessed August 29th, 2024.
6. George S, Serrano C, Hensley ML, Ray-Coquard I (2018). Soft Tissue and Uterine Leiomyosarcoma. *J Clin Oncol.* 2018 Jan 10;36(2):144-150.
7. Wile AG, Evans HL, Romsdahl MM (1981). Leiomyosarcoma of soft tissue: a clinicopathologic study. *Cancer*. 1981 Aug 15;48(4):1022-32.
8. Arshid G, Pradhan M, Goldblum J, Weiss SW (2002). Leiomyosarcoma of somatic soft tissues: a tumor of vascular origin with multivariate analysis of outcome in 42 cases. *Am J Surg Pathol*. 2002 Jan;26(1):14-24.
9. Chen E, O'Connell F, Fletcher CD (2011). Dedifferentiated leiomyosarcoma: clinicopathological analysis of 18 cases. *Histopathology*. 2011 Dec;59(6):1135-43.
10. Gladdy RA, Qin LX, Moraco N, Agaram NP, Brennan MF, Singer S (2013). Predictors of survival and recurrence in primary leiomyosarcoma. *Ann Surg Oncol.* 2013 Jun;20(6):1851-7.

11. Leu HJ, Makek M (1986). Intramural venous leiomyosarcomas. Cancer. 1986 Apr 1;57(7):1395-400.
12. Robinson E, Neugut AI, Wylie P (1988). Clinical aspects of postirradiation sarcomas. *J Natl Cancer Inst*. 1988 Apr 20;80(4):233-40.
13. Demas BE, Heelan RT, Lane J, Marcove R, Hajdu S, Brennan MF (1988). Soft-tissue sarcomas of the extremities: comparison of MR and CT in determining the extent of disease. *AJR Am J Roentgenol*. 1988 Mar;150(3):615-20.
14. McLeod AJ, Zornoza J, Shirkhoda A (1984). Leiomyosarcoma: computed tomographic findings. Radiology. 1984 Jul;152(1):133-6.
15. Santos P, Cunha TM (2015). Uterine sarcomas: clinical presentation and MRI features. *Diagn Interv Radiol*. 2015 Jan-Feb;21(1):4-9.
16. Coindre JM, Terrier P, Guillou L, Le Doussal V, Collin F (2001). Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. *Cancer*. 2001 May 15;91(10):1914-26.
17. Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF (1996). Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. *J Clin Oncol.* 1996 May;14(5):1679-89.
18. AJCC Cancer Staging Manual 8th ed. 2017, Corr. 3rd printing 2018 Edition by Mahul B. Amin (Editor), Stephen B. Edge (Editor), Frederick L. Greene (Editor), David R. Byrd (Editor), Robert K. Brookland (Editor), Mary Kay Washington (Editor), Jeffrey E. Gershenwald (Editor), Carolyn C. Compton (Editor), Kenneth R. Hess (Editor), Daniel C. Sullivan (Editor), J. Milburn Jessup (Editor), James D. Brierley (Editor), Lauri E. Gaspar (Editor), Richard L. Schilsky (Editor), Charles M. Balch (Editor), David P. Winchester (Editor), Elliot A. Asare (Editor), Martin Madera (Editor), Donna M. Gress (Editor), Laura R. Meyer (Editor)
19. Brierley J D, (Editor), Gospodarowicz M K, (Editor), Wittekind C. (Editor)TNM Classification of Malignant Tumours 8th Edition.
20. Wang WL, Bones-Valentin RA, Prieto VG, Pollock RE, Lev DC, Lazar AJ (2012). Sarcoma metastases to the skin: a clinicopathologic study of 65 patients. *Cancer*. 2012 Jun 1;118(11):2900-4.
21. Radkowski CA, Dodd LG, Johnson JL, Harrelson JM, Brigman BE (2012). Leiomyosarcoma of the somatic soft tissues. *J Surg Orthop Adv*. 2012 Summer;21(2):96-101
22. Devaud N, Vornicova O, Abdul Razak AR, Khalili K, Demicco EG, et.al (2022). Leiomyosarcoma: Current Clinical Management and Future Horizons. *Surg Oncol Clin N Am*. 2022 Jul;31(3):527-546.
23. Crago AM, Brennan MF (2015). Principles in Management of Soft Tissue Sarcoma. *Adv Surg*. 2015;49(1):107-22.
24. Grimer R, Judson I, Peake D, Seddon B (2010). Guidelines for the management of soft tissue sarcomas. *Sarcoma*;2010:506182.
25. Writing committee, study participating investigator, institutions and secretariate listed at end of paper Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration Lancet 1997 December 6; 350: 1647
26. Senol T, Kahramanoglu I, Muezzinoglu B, Yucesoy I (2016). Giant leiomyosarcoma: A case report. *Int J Surg Case Rep*. 2016;19:109-11.
27. Yamamoto T, Minami R, Ohbayashi C, Inaba M (2002). Epithelioid leiomyosarcoma of the external deep soft tissue. *Arch Pathol Lab Med*. 2002 Apr;126(4):468-70.
28. Moran CA, Suster S, Perino G, Kaneko M, Koss MN (1994). Malignant smooth muscle tumors presenting as mediastinal soft tissue masses. A clinicopathologic study of 10 cases. *Cancer*. 1994 Oct 15;74(8):2251-60.
29. Hauben EI, Weeden S, Pringle J, Van Marck EA, Hogendoorn PC (2002). Does the histological subtype of high-grade central osteosarcoma influence the response to treatment with chemotherapy and does it affect overall survival? A study on 570 patients of two consecutive trials of the European Osteosarcoma Intergroup. *Eur J Cancer*. 2002 Jun;38(9):1218-25
30. Klein MJ, Siegal GP (2006). Osteosarcoma: anatomic and histologic variants. *Am J Clin Pathol.* 2006 Apr;125(4):555-81.
31. Oda Y, Miyajima K, Kawaguchi K, Tamiya S, Oshiro Y, et.al (2001). Pleomorphic leiomyosarcoma: clinicopathologic and immunohistochemical study with special emphasis on its distinction from ordinary leiomyosarcoma and malignant fibrous histiocytoma. *Am J Surg Pathol*. 2001 Aug;25(8):1030-8.
32. Rubin BP, Fletcher CD (2000). Myxoid leiomyosarcoma of soft tissue, an underrecognized variant. *Am J Surg Pathol*. 2000 Jul;24(7):927-36.
33. Weiss SW (2002). Smooth muscle tumors of soft tissue. *Adv Anat Pathol*. 2002 Nov;9(6):351-9.
34. Guillou L, Coindre JM, Bonichon F, Nguyen BB, Terrier P,(1997). 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 Jan;15(1):350-62.
35. Klijanienko J, Caillaud JM, Lagacé R, Vielh P (2003). Fine-needle aspiration of leiomyosarcoma: a correlative cytohistopathological study of 96 tumors in 68 patients. *Diagn Cytopathol*. 2003 Mar;28(3):119-25.
36. Smith MB, Silverman JF, Raab SS, Towell BD, Geisinger KR (1994). Fine-needle aspiration cytology of hepatic leiomyosarcoma. *Diagn Cytopathol*. 1994 Dec;11(4):321-7.
37. Paal E, Miettinen M (2001). Retroperitoneal leiomyomas: a clinicopathologic and immunohistochemical study of 56 cases with a comparison to retroperitoneal leiomyosarcomas. *Am J Surg Pathol*. 2001 Nov;25(11):1355-63.
38. Rubin BP, Fletcher CD (2000). Myxoid leiomyosarcoma of soft tissue, an underrecognized variant. *Am J Surg Pathol*. 2000 Jul;24(7):927-36.
39. Watanabe K, Kusakabe T, Hoshi N, Saito A, Suzuki T (1999). h-Caldesmon in leiomyosarcoma and tumors with smooth muscle cell-like differentiation: its specific expression in the smooth muscle cell tumor. *Hum Pathol*. 1999 Apr;30(4):392-6.
40. Gupta S, Jimenez RE, Folpe AL, Cheville JC (2016). Renal Leiomyoma and Leiomyosarcoma: A Study of 57 Cases. *Am J Surg Pathol*. 2016 Nov;40(11):1557-1563.
41. Iwata J, Fletcher CD (2000). Immunohistochemical detection of cytokeratin and epithelial membrane antigen in leiomyosarcoma: a systematic study of 100 cases. *Pathol Int.* 2000 Jan;50(1):7-14.
42. Williams EA, Sharaf R, Decker B, Werth AJ, Toma H,(2020). CDKN2C-Null Leiomyosarcoma: A Novel, Genomically Distinct Class of TP53/RB1-Wild-Type Tumor With Frequent CIC Genomic Alterations and 1p/19q-Codeletion. *JCO Precis Oncol*. 2020 Sep 1;4:PO.20.00040.

43. Pérot G, Chibon F, Montero A, Lagarde P, de Thé H,(2010). Constant p53 pathway inactivation in a large series of soft tissue sarcomas with complex genetics. *Am J Pathol*. 2010 Oct;177(4):2080-90.
44. Kilpatrick SE, Mentzel T, Fletcher CD (1994). Leiomyoma of deep soft tissue. Clinicopathologic analysis of a series. *Am J Surg Pathol*. 1994 Jun;18(6):576-82.
45. Cleven AH, Sannaa GA, Briaire-de Bruijn I, Ingram DR, van de Rijn M, et.al (2016). Loss of H3K27 tri-methylation is a diagnostic marker for malignant peripheral nerve sheath tumors and an indicator for an inferior survival. *Mod Pathol*. 2016 Jun;29(6):582-90.
46. Folpe AL, Mentzel T, Lehr HA, Fisher C, Balzer BL(2005). Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. *Am J Surg Pathol*. 2005 Dec;29(12):1558-75.
47. Bao L, Shi Y, Zhong J, Zhao M, Wu J,et.al (2019). Histopathologic characteristics and immunotypes of perivascular epithelioid cell tumors (PEComa). *Int J Clin Exp Pathol*. 2019 Dec 1;12(12):4380-4389. PMID: 31933841; PMCID: PMC6949869.
48. Foo WC, Cruise MW, Wick MR, Hornick JL (2011). Immunohistochemical staining for TLE1 distinguishes synovial sarcoma from histologic mimics. *Am J Clin Pathol*. 2011 Jun;135(6):839-44.
49. Ladanyi M, Antonescu CR, Leung DH, Woodruff JM, Kawai A, (2002).Impact of SYT-SSX fusion type on the clinical behavior of synovial sarcoma: a multi-institutional retrospective study of 243 patients. *Cancer Res*. 2002 Jan 1;62(1):135-40.
50. Hornick JL (2018). Subclassification of pleomorphic sarcomas: How and why should we care? Ann Diagn Pathol. 2018 Dec; 37:118-124.
51. Ajmal Z, Khan AM, Zahra FT, McCarthy L, O'Malley R, et.al (2022). Leiomyosarcoma of the Penis: A Case Report and Re-Appraisal. *Fed Pract*. 2022 May;39(Suppl 2):S58-S61.
52. Sundersingh S, Majhi U, Narayanaswamy K, Balasubramanian S (2009). Primary leiomyosarcoma of the penis. *Indian J Pathol Microbiol*. 2009 Jul-Sep;52(3):447-8.
53. Mendis D, Bott SR, Davies JH (2005). Subcutaneous leiomyosarcoma of the frenulum. *Scientific World Journal*. 2005 Aug 1;5:571-5.
54. Elem B, Nieslanik J (1979). Leiomyosarcoma of the penis. *Br J Urol*. 1979 Feb;51(1):46.
55. Serrano C, George S (2013). Leiomyosarcoma. *Hematol Oncol Clin North Am*. 2013 Oct;27(5):957-74.
56. Pratt RM, Ross RT (1969). Leiomyosarcoma of the penis. A report of a case. *Br J Surg*. 1969 Nov;56(11):870-2.
57. National Comprehensive Cancer Network. Penile cancer. NCCN evidence blocks. Version 2, 2022. [Accessed March 16, 2022]. Updated January 26, 2022.
58. Isa SS, Almaraz R, Magovern J (1984). Leiomyosarcoma of the penis. Case report and review of the literature. *Cancer*. 1984 Sep 1;54(5):939-42.
59. Hutcheson JB, Wittaker WW, Fronstin MH (1969). Leiomyosarcoma of the penis: case report and review of literature. *J Urol*. 1969 Jun;101(6):874-5.
60. Grimer R, Judson I, Peake D, Seddon B (2010). Guidelines for the management of soft tissue sarcomas. *Sarcoma*. 2010;2010: 506182.
61. McDonald MW, O'Connell JR, Manning JT, Benjamin RS (1983). Leiomyosarcoma of the penis. *J Urol*. 1983 Oct;130(4):788-9.
62. Planz B, Brunner K, Kalem T, Schlick RW, Kind M (1998). Primary leiomyosarcoma of the epididymis and late recurrence on the penis. *J Urol*. 1998 Feb;159(2):508.
63. Smart RH (1984). Leiomyosarcoma of the penis. *J Urol*. 1984 Aug;132(2):356-7.
64. Patrikidou A, Domont J, Cioffi A, Le Cesne A (2011). Treating soft tissue sarcomas with adjuvant chemotherapy. *Curr Treat Options Oncol*. 2011 Mar;12(1):21-31.
65. Italiano A, Delva F, Mathoulin-Pelissier S, Le Cesne A, Bonvalot S,(2010). Effect of adjuvant chemotherapy on survival in FNCLCC grade 3 soft tissue sarcomas: a multivariate analysis of the French Sarcoma Group Database. *Ann Oncol*. 2010 Dec;21(12):2436-2441.
66. Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M (2008). A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer*. 2008 Aug 1;113(3):573-81.
67. Lacarrière E, Galliot I, Gobet F, Sibert L (2012). Leiomyosarcoma of the corpus cavernosum mimicking a Peyronie's plaque. *Urology*. 2012 Apr;79(4):e53-4.
68. Hamal PB (1975). Leiomyosarcoma of penis--case report and review of the literature. *Br J Urol*. 1975 Jun;47(3):319-24.
69. Greenwood N, Fox H, Edwards EC (1972). Leiomyosarcoma of the penis. *Cancer*. 1972 Feb;29(2):481-3.
70. Koizumi H, Nagano K, Kosaka S (1987). A case of penile tumor: combination of leiomyosarcoma and squamous cell carcinoma. *Hinyokika Kiyo*. 1987 Sep;33(9):1489-91.
71. Romero Gonzalez EJ, Marenco Jiménez JL, Mayorga Pineda MP, Martínez Morán A, Castiñeiras Fernández J (2015). Leiomyosarcoma of the Penis, an Exceptional Entity. *Urol. Case Rep*. 2015 Mar 12;3(3):63-4.
72. Goyal N, Menon S, Pal M (2022). Primary leiomyosarcoma of the penis: A rare penile neoplasm. *Med J Armed Forces India*. 2022 Jul;78(3):365-367.
73. Fetsch JF, Davis CJ Jr, Miettinen M, Sesterhenn IA (2004). Leiomyosarcoma of the penis: a clinicopathologic study of 14 cases with review of the literature and discussion of the differential diagnosis. *Am J Surg Pathol*. 2004 Jan;28(1):115-25
74. Khobragade K H, Tamhankar A S, Bakshi G K, Tongaonkar H B, Menon S. Leiomyosarcoma of penis. Indian Journal of Cancer
75. Hayes AJ, Thomas JM (1997). Soft tissue tumours. Postgrad Med J. 1997 Nov;73(865):705-9.
76. Russo P, Brady MS, Conlon K, Hajdu SI, Fair WR,(1992). Adult urological sarcoma. J Urol. 1992 Apr;147(4):1032-6; discussion 1036-7.
77. Mondaini N, Palli D, Saieva C, Nesi G, Franchi A,(2005). Clinical characteristics and overall survival in genitourinary sarcomas treated with curative intent: a multicenter study. Eur Urol. 2005 Apr;47(4):468-73.
78. Dotan ZA, Tal R, Golijanin D, Snyder ME, Antonescu C,(2006). Adult genitourinary sarcoma: the 25-year Memorial Sloan-Kettering experience. J Urol. 2006 Nov;176(5):2033-8; discussion 2038-9.
79. Levi I (1930). On a case of primary fibrosarcoma of the skin of the penis: Clinical and histological study G Ital Dermatol Venereol. 1930; 71:1559–74

80. Pratt RM, Ross RT (1969). Leiomyosarcoma of the penis. A report of a case. Br J Surg. 1969 Nov;56(11):870-2.
81. Fetsch JF, Davis CJ Jr, Miettinen M, Sesterhenn IA (2004). Leiomyosarcoma of the penis: a clinicopathologic study of 14 cases with review of the literature and discussion of the differential diagnosis. Am J Surg Pathol. 2004 Jan;28(1):115-25.

DOI:10.31579/2690-8794/232