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Original Article

Pathology Section

# Clinicopathological Features of Primary Renal Mesenchymal Neoplasms in Adults: A Cross-sectional Study

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## ABSTRACT

**Introduction:** Renal mesenchymal tumours are a subset of primary renal tumours arising from the mesenchymal tissue in the kidney. They are a heterogeneous group of mostly benign tumours that exhibit varied behaviours and molecular characteristics.

**Aim:** To analyse the wide spectrum of histological subtypes, their unique clinical presentation, and pathological features of primary renal mesenchymal neoplasms.

**Materials and Methods:** This was a retrospective cross-sectional observational clinicopathological study conducted in Department of General Pathology, Christian Medical College, tertiary care hospital, Vellore, Tamil Nadu, India, looking at data of adult Primary Renal Mesenchymal Tumours (PRMT) for a 15-year period between January 2006 and March 2021. Clinical details such as age, presenting symptoms, and tumour size were obtained from the hospital information system. Histopathology and immunohistochemical slides were reviewed for all the cases. Additional Immunohistochemistry (IHC) and molecular studies were performed for the undifferentiated sarcomas. The tumours were categorised into three groups as recommended by the World Health Organisation (WHO) 2020 classification of soft-tissue tumours based on biological behaviour: benign, intermediate, and malignant. Continuous variables are expressed as mean and Standard Deviation (SD). Comparison of categorical variables between groups was performed using the Chi-squared test. Continuous variables between groups were compared using the Student's t-test for significance. A p-value of less than 0.05 was considered statistically significant.

**Results:** Of the 2164 nephrectomies performed for neoplastic conditions, 97 (4.5%) were diagnosed as renal mesenchymal tumours. There were 59 (60.8%) benign, 10 (10.3%) with intermediate biologic behaviour and 28 (28.9%) malignant tumours. The mean ages at presentation were 40.5 years for benign, 43.4 years for intermediate, and 41 years for malignant tumours, respectively. Haematuria was seen in 11 of 38 (29%) intermediate grade and malignant tumours and in only 6 of 59 (10%) benign tumours, a difference that was statistically significant (p-value=0.017). Malignant tumours 24 of 28 (86%) were more likely to be larger (>7 cm) when compared to benign tumours 28 of 59 (47%) at the time of presentation (p-value=0.027). Classical angiomyolipomas constituted 53/59 (90%) of the benign tumours. Of the 10 intermediate grade tumours, epithelioid angiomyolipomas and solitary fibrous tumours were the most common, accounting for 50% and 30% of the intermediate group, respectively. Undifferentiated small round cell sarcoma was the most common malignant neoplasm, making up 12/28 (43%) of the malignant tumours.

**Conclusion:** The present study found that renal mesenchymal tumours constitute a small but unique group of renal tumours. They are predominantly benign, but up to a quarter are malignant. Malignant tumours tend to be larger and more often present with haematuria. The present study highlights the importance of IHC in the diagnosis of intermediate and malignant mesenchymal tumours and the requirement of exhaustive molecular studies individually tailored to the immuno-profile of malignant tumours.

**Keywords:** Angiomyolipomas, Malignant tumours, Mesenchymal tissue, Sarcoma

## INTRODUCTION

Renal parenchymal tumours arise from epithelial tissue, renal tubules, and collecting ducts, while stromal tumours are mesenchymal in origin and arise from connective tissue consisting of fat, vessels, nerves, juxtaglomerular bodies. Broadly, renal tumours in adults are classified as epithelial, neuroendocrine, or mesenchymal in origin, as well as metastatic tumours [1]. Renal Cell Carcinomas (RCC) are by far the most common, accounting for 85% of kidney tumours, while mesenchymal tumours are distinctly rare, with a prevalence of <5%, the majority of which are benign. Nevertheless, at least 15-20% of primary mesenchymal renal tumours are malignant [2]. In the 2022, World Health Organisation (WHO) classification of tumours of the urinary and male genital tract, mesenchymal tumours of the kidney are divided into those that occur in children and those that occur in adults [1].

Given that the majority of renal tumours are characterised by a lack of early-warning signs, a high proportion present with metastatic disease or are incidentally detected on routine abdominal imaging [3,4]. Autopsy studies have detected renal tumours in two- thirds of cases that had no clinical symptoms in their lifetime [4]. The WHO recently updated the classification of renal tumours, expanding on the subtypes based on tumour histology, chromosomal alterations, and molecular pathways [1]. There is limited published literature on mesenchymal renal tumours subsequent to this update [2,5]. As mesenchymal tumours are a rare subset with several new markers introduced to define each entity, the main objective was to reclassify the adult primary mesenchymal renal tumours using the new classification. The primary aim of the present, clinicopathological study was therefore, to determine the prevalence of surgically excised renal mesenchymal tumours in adults that presented to a tertiary care hospital in South India with the intention of understanding their clinical presentation, pathological features and spectrum of histological subtypes.

## MATERIALS AND METHODS

This retrospective cross-sectional observational clinicopathological study was conducted at the Department of General Pathology,

Christian Medical College, tertiary care hospital, Vellore, Tamil Nadu, India, examining data over a 15-year period from 2006 to 2021. The study received approval from the Institutional Review Board and Ethics Committee (Ref: IRB Min. No11762 dated 07.01.2019 and IRB Min. No. 12029 dated 24.04.2019). Written consent was waived as it was a retrospective study of data.

**Inclusion and exclusion criteria:** The Pathology database was scrutinised for renal tumours in adults (>18 years) received during the specified time frame, identifying 116 out of 2164 primary renal tumours as mesenchymal neoplasms were included. Total of 19 tumours originating from the inferior vena cava, adrenal glands, and retroperitoneal soft tissue were excluded, resulting in 97 cases categorised as primary adult renal mesenchymal tumours.

### Study Procedure

Clinical and intraoperative details including age, presenting symptoms, and tumour size were obtained from the hospital information system. Radiological imaging was not reviewed due to unavailability of images. Two experienced pathologists, who routinely sign out surgical urology cases, reviewed the cases. Haematoxylin and Eosin (H&E) stained slides and immunohistochemistry for cases categorised as primary adult renal mesenchymal tumours were reviewed, and the diagnosis was reached by consensus. Among the 12 undifferentiated sarcomas, additional immunohistochemical markers, namely NKX2.2, BCOR, SATB2, and Cyclin D1, were utilised. Additionally, these 12 tumours underwent Reverse Transcriptase- Polymerase Chain Reaction (RT-PCR) for Ewing Sarcoma-friend Leukaemia Integration (EWS-FLI) types 1 and 2 and EWS-ERG translocations.

The tumours were reclassified by consensus using the WHO 2020 classification of tumours of soft tissue [6] and were assigned to the three categories as recommended by the WHO, namely, benign, intermediate, and malignant.

## STATISTICAL ANALYSIS

Continuous variables are expressed as mean and Standard Deviation (SD). Student's t-tests were used for comparing the benign tumours with intermediate and malignant tumours, grouped together, to analyse the differences in continuous variables. The Chi-squared test was used to compare categorical variables between groups. A p-value of less than 0.05 was considered statistically significant. As the diagnosis was reached by consensus, there was no interobserver variability.

| Variables | Benign (n=59) | Intermediate (n=10) | Malignant (n=28) | p-value* |
|---|---|---|---|---|
| Mean±SD (years) | 40.5 (12.27) | 43.4 (12.45) | 41.14 (14.87) | 0.66 |
| Size of tumour | | | | |
| <7 cm<br>>7 cm | 31<br>28 | 7<br>3 | 4<br>24 | 0.022 |
| Haematuria | 6 | 1 | 10 | 0.017 |

**[Table/Fig-1]:** A comparison of the broad subgroups of Primary Renal Mesenchymal Tumours (PRMT).
*Benign vs Intermediate + Malignant

## RESULTS

The PRMTs constituted 97/2164 (4.5%) of all renal neoplasms. There were 59 (60.8%) benign tumours, 28 (28.9%) malignant tumours, and 10 (10.3%) classified as intermediate biologic behaviour. The mean age varied minimally across all categories. Haematuria was seen in 11 of 38 (29%) intermediate grade and malignant tumours and in only 6 of 59 (10%) benign tumours, a difference that was statistically significant (p=0.017). The malignant tumours were significantly larger than the benign and intermediate tumours (p-value<0.001) [Table/Fig-1]. Overall, 18 tumours were reported to have been detected incidentally on routine imaging, including 13 angiomyolipomas, and one each of a leiomyoma, solitary fibrous tumour, inflammatory myofibroblastic tumour, undifferentiated small round cell sarcoma, and rhabdomyosarcoma. [Table/Fig-2] shows the demographic, clinical, and pathology details of the 97 cases.

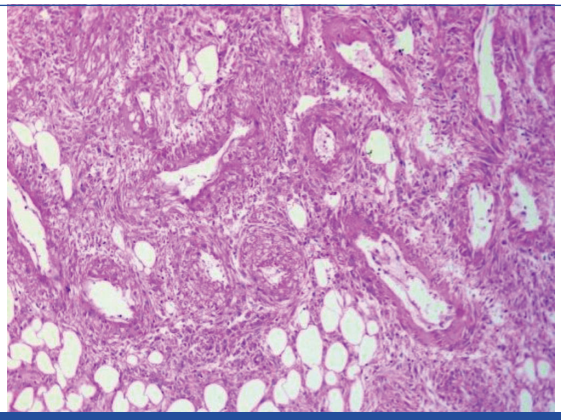
**Among 59 benign tumours:** Angiomyolipoma was the most common, constituting 53/97 (59.8%) of all mesenchymal tumours. Of these, 48 displayed the "classical" morphology, representing the most common benign mesenchymal tumours in this cohort. The remaining five cases showed "epithelioid" morphology, considered biologically aggressive, and were classified in the intermediate biological behaviour category. Classical angiomyolipoma was more common in women with a male to female ratio of 1:2.5. The mean age of presentation was 40.3±11.9 years, and loin pain was the typical presenting symptom. Notably, haematuria was present in only six benign tumours, all of which were angiomyolipomas. Smooth muscle, adipose tissue, and vascular channels were seen in 24 cases [Table/Fig-3], while in 29 cases, the adipocytic component was focal. Immunohistochemistry (IHC) was performed in these 29 cases and revealed immunopositivity for HMB45 and SMA in 28 cases. One case that showed extensive hyalinisation but had both vascular and adipocytic elements was negative for both HMB45 and SMA.

Leiomyoma represented the next common benign tumour seen in four patients with a mean age of 48.7±15.65 years. The single schwannoma seen in this series occurred in a 37-year-old male who presented with loin pain and a 3.9 cm tumour at the hilum of the right kidney. It displaced the renal pelvis anteriorly and extended up to, but did not transgress, the cortical margin. There was one benign angiomatous neoplasm, which was immuno-negative for HMB45, SMA, and EMA.

| Tumour category (N=96) | Diagnosis | No. | Mean±SD (years) | Gender | Presenting complaint | Mean±SD tumour size cm | IHC | Molecular tests positivity |
|---|---|---|---|---|---|---|---|---|
| Benign (N=59) | Classical angiomyolipomas | 53 | 40.3 (11.9) | 38 F<br>15 M | Mass 2, Loin pain 29; Haematuria 6, LUTS 4 Incidental 12 | 8.12 (4.5) | HMB45 (24/26)<br>SMA (9/9)<br>Melan A (5/5) | Nil |
| | Leiomyoma | 4 | 48.75 (15.65) | 4 F | Incidental1;Loin pain 1, Ascites1<br>Fever 1 | 5.2 (3.5) | SMA (2/2)<br>Desmin (1/1)<br>h-Caldesmon (1/1) | |
| | Schwannoma | 1 | 37 | M | Loin pain | 3.9 | nil | |
| | Benign angiomatous lesion | 1 | 22 | F | Loin pain | 8.5 | nil | |
| Intermediate (N=10) | Epithelioid angiomyolipoma | 5 | 44 (12.8) | 3 M 2 F | Loin pain 4<br>Incidental 1 | 3.56 (0.96) | SMA (4/4)<br>HMB45 (5/5) | Nil |
| | Solitary fibrous tumour | 3 | 43 (13.95) | 2 M 1 F | Haematuria/loin pain | 7.6 (4.48) | CD34 (3/3)<br>STAT6 (3/3) | |
| | Inflammatory myofibroblastic tumour | 1 | 34 | M | Incidental | 8 | MSA +; SMA and Alk-1 neg | |
| | Well-differentiated liposarcoma | 1 | 51 | M | Loin pain | 20 | nil | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Malignant (N=28) | Ewing's sarcoma | 12 | 29.6 (9.1) | 7 F 5 M | Haematuria 8, Loin pain 3, Lung metastasis 1 | 11.2 (3.2) | CD99 (11/11) FLI1 (5/5) NKX2.2 (6/6) BCOR (0/6) CDK4 (2/2) MDM2 (2/2) | PCR for translocations EWS-FLI types 1 and 2, EWS-ERG (3/8) |
| | Dedifferentiated liposarcoma | 6 | 51.1 (7.62) | 4 M 2F | 3 loin pain, 1 mass, 1 LUTS | 15.21 (5.58) | SMA (4/4) Desmin (2/2) | PCR for SYT-SSX1 (2/2) |
| | Leiomyosarcoma | 5 | 53.8 (11.75) | 3 M 2 F | Loin pain 3, Haematuria 1, incidental 1 | 11.5 (7.14) | h-Caldesmon (1/1) CD99 (2/2) TLE1 (1/2) EMA (1/2) | |
| | Synovial sarcoma | 2 | 27.5 (1.5) | 2 F | Loin pain 2 | 9.35 (3.65) | | |
| | Osteosarcoma | 1 | 52 | F | Loin pain | 6.6 | | |
| | Angiosarcoma | 1 | 67 | 1 M | Loin pain | 13 | CK;CAM5.2 and PAX8 neg | |
| | Rhabdomyosarcoma | 1 | 46 | 1 M | Loin pain | 14.5 | CD31, CD34 MyoD1, Desmin | |

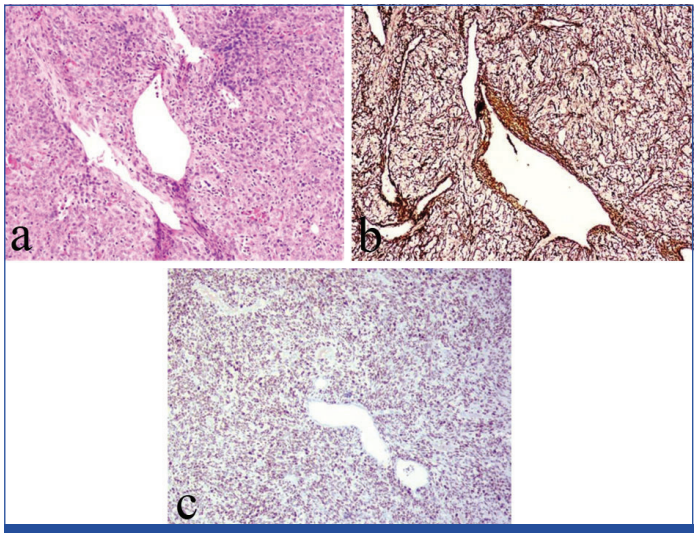
**[Table/Fig-2]:** Demographic, clinical, Immunohistochemistry (IHC) and molecular details of the pathological subtypes of 97 renal mesenchymal tumours.
CK=pancytokeratin



**[Table/Fig-3]:** Photomicrograph of an angiomyolipoma with the classic triphasic histology with the three components, the vasculature, smooth muscle and adipose tissue. (H&E x40).

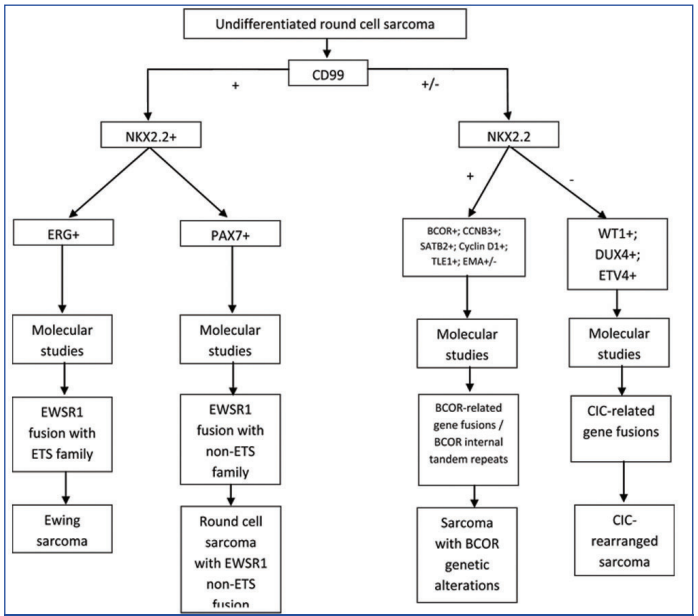
**Tumours with intermediate biologic behaviour:** The epitheloid angiomyolipoma represented the most common tumour in this subcategory, accounting for 5 out of 10 (50%) cases. The mean age of presentation of these tumours was 44±14.3 years. Macroscopically, these tumours ranged in size from 2.2 to 6 cm in dimension. Microscopically, these tumours were characterised by sheets of plump spindle-shaped to polygonal cells with abundant eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli. Immunohistochemistry (IHC) was performed in all five cases, showing positivity for HMB45 in all and immunopositivity for SMA in 4 out of 5 cases. [Table/Fig-2] Solitary fibrous tumour was diagnosed in three cases, ranging in age from 25 to 59 years; one was detected incidentally while the other two presented with loin pain. The tumours ranged in size from 4 to 14 cm. IHC showed consistent expression of CD34 and STAT6 in all three cases [Table/Fig-4a-c]. The tumours were categorised as low risk using the 4-variable model comprising age, mitoses per 10 high-power fields, tumour size, and tumour necrosis [7]. There was one well-differentiated liposarcoma diagnosed in a 51-year-old male who presented with flank pain and a large mass in the lower and interpole of the right kidney. The single case of inflammatory myofibroblastic tumour was incidentally detected in a 34-year-old male being investigated for chest pain.

**Malignant tumours:** There were 28 malignant tumours belonging to seven subtypes: undifferentiated small round cell sarcoma, dedifferentiated liposarcoma, leiomyosarcoma, synovial sarcoma, osteosarcoma, angiosarcoma, and rhabdomyosarcoma, in descending order of frequency. The mean age of presentation was 41.14±14.87 years. Among them, 24 (86%) malignant tumours were larger than 7 cm with a mean of 12 cm (SD 5.06). The details of the immunohistochemical features are provided in [Table/Fig-2]. There were 12 cases of undifferentiated small round cell sarcomas [Table/Fig-5]. The clinical presentations were haematuria in 8




**[Table/Fig-4]:** Photomicrograph of a solitary fibrous tumour illustrating: a) the cellular Neoplasm with prominent vascularity (H&E x100); b) Rich pericellular reticulin (Gordon Sweet's reticulin x100); and c) Diffuse strong nuclear positivity for STAT6 (Avidin peroxidase x40)

cases, loin pain in 3, and lung metastasis in one case. These patients presented at a younger age (mean age 29.67 ± 9.47) and showed no predilection for gender or laterality. The tumours were large (mean size 11.2±SD 3.2), with evidence of haemorrhage in a quarter of cases (4/13). Dedifferentiated liposarcoma was diagnosed in six cases (four males and two females). The mean




**[Table/Fig-5]:** Step-wise approach to diagnosis of undifferentiated round cell sarcomas using Immunohistochemistry (IHC) and molecular markers.

age at presentation was 51.1±7.62 years and most had loin pain. The tumours were very large with a mean maximum dimension of 15.21±5.58 cm. Leiomyosarcoma was diagnosed in five patients with a mean age of presentation at 54 years (range 33-66 years). Patients had loin pain and haematuria. These neoplasms ranged in size from 2.5 to 23 cm, with a mean size of 11.5 cm. Synovial sarcoma was diagnosed in two women, both in their twenties, who presented with loin pain.

The single angiosarcoma in this series was observed in a 67-year-old male who presented with left loin pain and a mass lesion involving the upper pole of the left kidney. The renal parenchyma was infiltrated by an extensively haemorrhagic and focally necrotic tumour. In the case diagnosed as osteosarcoma, the nephrectomy specimen showed a partially calcified mass involving the medullary region of the right kidney. The tumour infiltrated the wall of the renal pelvis, perinephric adipose tissue, sinus fat, and hilar vessel. The rhabdomyosarcoma was observed in a 46-year-old male presenting with a large right renal solid-cystic mass.

## DISCUSSION

The 2020 WHO classification of renal mesenchymal tumours stratifies them into benign, intermediate, and malignant categories [6]. In present series, which covers a 15-year period, there were 97 PRMTs out of 2164 (4.5%) nephrectomy specimens performed for tumours. The majority of these were benign (61%), while those belonging to the malignant and intermediate categories constituted 29% and 10%, respectively. This prevalence differs from other studies that report a higher proportion of benign tumours (85%) and a lower prevalence of intermediate and malignant tumours, at 3% and 12%, respectively [1]. One plausible reason for this difference could be a referral bias, as this was a tertiary care centre.

Although PRMTs are exceedingly rare, constituting only 4-5% of all renal tumours, they are diverse in their histopathology, and some are highly malignant, mandating a systematic approach to diagnosis.

As RCC accounts for the vast majority of kidney tumours (95%), the pathologist initially distinguishes between tumours of epithelial origin and those arising from the renal stroma, composed of fat, vessels, nerves, juxtaglomerular bodies that are mesenchymal in origin. The choice of specific immunomarkers in a panel for diagnosis depends entirely on the microscopic findings and the differential diagnoses being considered. On occasion, at least two to three immunohistochemical markers may be required to arrive at a diagnosis, while Fluorescence In-situ Hybridisation (FISH) and molecular genetics are necessary in select cases. A survey conducted among uropathologists revealed that the majority (87%) used IHC for the histologic subtyping of RCC; however, similar data is not available for other kidney tumours [4].

**Benign tumours:** Angiomyolipomas constituted 90% (53/59) of benign tumours, consistent with other studies. These tumours belong to the Perivascular Epithelioid Cell (PEC) tumour family and commonly occur sporadically, displaying a predilection for the female gender, as echoed by the findings in the present study showing a male-to-female ratio of 1:2.5. Some angiomyolipomas occur in association with familial conditions such as Tuberous Sclerosis, and these tumours tend to be larger, bilateral, and have no sex predilection [8]. Although angiomyolipomas are frequently asymptomatic in up to 75% of patients [8], larger tumours tend to present with loin pain and may be complicated by haemorrhage. In the present series, the mean size of the angiomyolipomas was 8.12 cm, explaining why nearly half presented with loin pain (29/53) and less than a quarter (12/53) were detected incidentally. While angiomyolipomas typically display a 'triphasic component' morphology of smooth muscle, adipose tissue, and vascular channels, even in the 29 cases where the adipocytic component was focal, IHC revealed immunopositivity for HMB45 and SMA in 28 cases.

Notably absent from this cohort of nearly 2164 nephrectomy specimens were the renomedullary interstitial cell tumours, also called "Medullary Fibromas". With a purported prevalence of up to 17% [2], these tumours are usually asymptomatic and frequently detected incidentally in nephrectomies performed for chronic non-functioning renal disease or during autopsy. This absence from the present data can be explained by the fact that the present data consisted of surgically excised tumour specimens, operated on if the tumour was large or symptomatic. The non functioning kidneys received in this laboratory inevitably show end-stage histology with significant paucity of renal parenchyma, probably explaining the absence of these medullary fibromas. Amongst the nephrectomy specimens, other benign tumours noted were leiomyomas, schwannomas, and a benign angiomatous lesion that posed no difficulty in diagnosis.

**Tumours with intermediate biologic behaviour:** The 2020 WHO classification of soft-tissue tumours separated those tumours that display features of benign tumours but tend to behave aggressively with local recurrence into a "borderline or uncertain behaviour" [6]. There were 10 out of 97 tumours that fit into this category, including Epithelioid Angiomyolipomas (5), Solitary Fibrous Tumours (3), and one each of Well-differentiated Liposarcoma and inflammatory myofibroblastic tumour. These tumours have histological features aiding in diagnosis; however, IHC is used for confirmation, particularly SMA, HMB45, and Melan A for epithelioid angiomyolipoma. Richly vascular tumours with dense intercellular collagen can be confirmed as solitary fibrous tumours using the specific marker STAT6. Well-differentiated liposarcomas are locally aggressive mesenchymal neoplasms that are easy to diagnose morphologically as they are composed of well-differentiated adipocytes, which are variably sized and have foci of nuclear atypia in the adipocytes and stromal cells [6]. When amenable to complete excision, they do not recur; however, when they extend deep into the retroperitoneal tissue, they are difficult to excise and recur repeatedly.

When one encounters a spindle-celled tumour with a prominent inflammatory component, an inflammatory myofibroblastic tumour should be considered. These tumours display variable staining for SMA, MSA, calponin, and desmin. An important differential diagnosis here is IgG4-related disease, which would be rich in plasma cells and have an IgG4:IgG ratio of >40%, together with serum elevation of IgG4 [9].

**Malignant tumours:** Malignant PRMTs are relatively uncommon, with a prevalence of less than 1% in nephrectomy specimens in a large retrospective study [3]. In the present study, these tumours were generally symptomatic and presented at a young age (41 years), consistent with other large studies [3]. Common presenting complaints were loin pain and haematuria, which were more likely to be present than in the benign tumour category (p=0.027). Malignant tumours tended to be larger, with a mean size of 12 cm. Tumours larger than 7 cm had a three times higher risk of being malignant. Changing clinical practices in the management of soft-tissue sarcomas have compelled pathologists to provide specific histological diagnoses for this group of tumours, directing the type of resection and the institution of adjuvant therapy, particularly for liposarcomas, leiomyosarcomas, synovial sarcomas, and Ewing sarcoma [10]. De-differentiated liposarcomas were the second most common malignant tumour in this series. These tumours were much larger than the other tumours (15 cm) and presented with loin pain or a palpable mass. These tumours have a variable histological appearance and often resemble undifferentiated pleomorphic sarcomas. A careful and extensive search must be made for well-differentiated lipogenic areas as there is often an abrupt transition between these two histologies. These tumours show diffuse nuclear expression of MDM2 and/or CDK4, confirming the diagnosis. Other malignant tumours in the present series included leiomyosarcoma, osteosarcoma, angiosarcoma,

and rhabdomyosarcoma, which were very rare. Each of these has histological features and immunohistochemical markers that aid in diagnosis.

In the present series, there were two synovial sarcomas, both in young women. Tumour cells in these cases were immunopositive for CD56, CD99, and vimentin, but negative for desmin, myogenin, EMA, cytokeratin, NKX2.2, and WT1. However, one of the cases was negative for TLE1. RT-PCR, however, showed a SYT-SSX2 translocation in both cases, confirming the diagnosis.

Synovial sarcoma could be monophasic, composed entirely of spindle cells; biphasic, composed of spindle cells and a population of cells with epithelial differentiation; or poorly-differentiated . Its defining characteristic is a t(X;18) chromosome translocation {t(X:18)(p11.2/q11.2)}, which results in a fusion between the SYT gene on chromosome 18 (SS18) and a member of the SSX gene family (SSX1, SSX2, SSX4, or SS18L) on the X chromosome. The most common fusion seen is that between the SYT gene on chromosome 18 (SS18) and SSX2 [11-17]. Both cases in the present series showed this fusion. Renal synovial sarcoma affects males and females equally; the two cases in the current series were female. These tumours occur predominantly in young to middle-aged adults (median age, ~ 37 years). The mean age in this series was 27.5 years. Tumours are typically large, ranging from 5 to 20 cm in diameter, with variegated cut surfaces. The mean size in the present series was 9.4 cm [11,12]. According to the WHO classification of soft-tissue tumours, an essential component of the diagnostic criteria is a monomorphic blue spindle cell sarcoma showing variable epithelial differentiation with diffuse and strong immunostaining for TLE1 [14]. Although TLE1 is a sensitive marker for the diagnosis of synovial sarcomas, the findings in the current study highlight the importance of confirmation with molecular studies.

Other malignant tumours in this series included leiomyosarcoma, osteosarcoma, angiosarcoma, and rhabdomyosarcoma, each having histological features and immunohistochemical markers that aid in diagnosis. Leiomyosarcomas are reported to be the most common primary renal sarcoma [18-21]; however, in the present series, they constituted only 18% of malignant mesenchymal tumours. The mean age of 54 years is similar to that reported in the literature [19]. In the present series, only tumours primarily arising in the kidney were included, and this may explain the lower prevalence as, in those reported in the literature, only 30% are primarily intrarenal [21]. Presenting symptoms in this series included loin pain and haematuria, similar to that reported in the literature [18,19]. While tumours can measure up to 23 cm, the mean tumour diameter is 13 cm [21]. In the present series, leiomyosarcomas ranged in size from 2.5 to 23 cm, with a mean size of 11.5 cm.

Leiomyosarcomas are composed of fascicles of spindle-shaped cells with blunt-ended nuclei. Necrosis, nuclear pleomorphism, and atypical mitoses help differentiate these from leiomyomas [20]. The differential diagnosis includes sarcomatoid Renal Cell Carcinoma (RCC), which will be immunopositive for epithelial and mesenchymal markers, and AML. The latter is typically positive for melanocytic markers and cathepsin, which are not seen in leiomyosarcoma [19].

**Osteosarcoma:** This is an extremely rare primary malignant mesenchymal tumour of the kidney [22-24]. Patients present in their fifth to ninth decade of life. The case in this series was of a 52-year-old male. Tumours can be as large as 28 cm [24]. The present case was 6.6 cm in size. Histological diagnosis requires the demonstration of osteoid formation in the setting of a tumour with malignant pleomorphic polygonal to spindle-shaped cells. IHC is helpful to exclude other neoplasms; in the present case, the tumour was immunonegative for cytokeratin, CAM5.2 and PAX8.

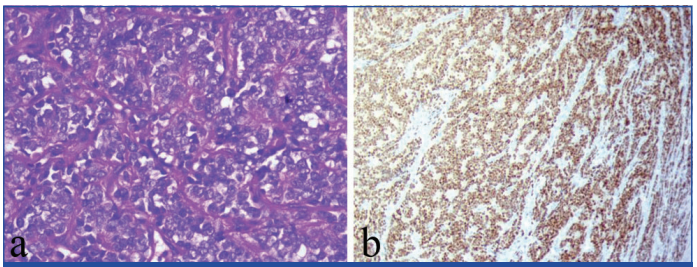
**Angiosarcoma:** There was one case of angiosarcoma in the present study. Angiosarcomas constitute only 2% of all soft-tissue tumours, so their prevalence in the kidney is low [25]. According to the literature, most patients are men with a mean age of 61 years at presentation, similar to the case in the present study [26].

Patients with angiosarcoma present with haematuria, weight loss, or symptoms related to metastatic cancer [25,27,28]. The case in this series was 13 cm, while tumours can vary in size and measure up to 23 cm. Angiosarcomas are histologically similar to those occurring at other sites with vasoformative architecture [25,27,28]. Tumour cells show positive immunostaining for CD31, CD34, ERG, FLI1, and factor VIII-RA. The solitary case in the present study was immunopositive for CD31, CD34, and ERG.

**Rhabdomyosarcoma:** This malignant neoplasm is composed of cells that demonstrate varied degrees of skeletal muscle differentiation. Only about 20 well-documented cases of primary renal rhabdomyosarcoma have been reported thus far, most occurring in children [29-31]. Diagnosis requires the gross appearance to show an origin in the kidney and the absence of a retroperitoneal primary. The histological picture and immunoprofile are similar to those at other sites. The present case occurred in a 46-year-old male and was 14.5 cm in size. The tumour was immunopositive for myoD1 and desmin.

**Undifferentiated small round cell sarcoma:** The most common malignant PRMTs in the present series were the group of undifferentiated small round cell sarcomas (12/28) that presented at a younger age (30 years). The median age reported for the Ewing's sarcoma tumours is ~27 years with a slight male preponderance [32]. Presenting symptoms include abdominal pain, haematuria, a palpable mass, and sometimes constitutional symptoms. In the present series, haematuria was the predominant presenting symptom.

These tumours have overlapping histological and immunohistochemical features and hence pose a diagnostic challenge. The high mitotic rate on histological examination identifies the malignant nature of this group; however, there are no cytological features that aid in further typing. The tumour consists of sheets of monotonous small cells with round hyperchromatic nuclei, high nuclear-to-cytoplasmic ratios, arranged in a vaguely lobular pattern [Table/Fig-6a,b]. On IHC, all the tumours showed either diffuse or patchy strong membranous positivity for CD99. While NKX2.2 was positive in 10/12 tumours, subsequent molecular studies for translocation in EWS FLI type 1 and 2 and EWS-ERG showed positive results in only 4/11 cases. BCOR was negative in all tumours, and WT1 was weakly positive in one case. The latter was negative for NKX2.2. In one case, the tissue was inadequate for subsequent immunohistochemical and molecular studies.




**[Table/Fig-6]:** Photomicrograph of an undifferentiated small round cell sarcoma illustrating: a) The cellular neoplasm with a high nuclear cytoplasmic ratio (H&E x400); b) Diffuse strong nuclear positivity for NKX2.2 (Avidin peroxidase x40).

Ewing sarcoma is the best-known prototype and has the signature gene fusion of the EWSR1 gene with a member of the ETS transcription factor family (ERG, FLI1, ETV1, ETV4, or FEV) [33]. The 2020 WHO classification of soft-tissue tumours recognises three more types of round cell sarcomas, each with characteristic molecular features. These include round cell sarcoma with EWSR1-non ETS fusions, CIC-rearranged sarcoma, and sarcoma with BCOR genetic alterations [6,34,35]. CD99 is frequently expressed immunohistochemically by these three groups of tumours. Sarcomas with EWSR1-non ETS fusions may also express PAX7 and NKX2.2

and co-express neurogenic and myogenic markers [36,37]. The CIC-rearranged sarcomas frequently immunoexpress WT1, DUX4, and ETV4 [38-40]. While IHC for BCOR lacks sensitivity and specificity for the diagnosis of sarcomas with BCOR genetic alterations, most cases also express CCNB3, SATB2, TLE1, EMA, and cyclin D1 [39,41-43]. IHC does play a role in screening, but molecular confirmation of the specific genetic alterations is necessary for validation of the diagnosis.

Molecular analysis for Ewing sarcoma was performed in the laboratory using RT-PCR with limited coverage of only EWS FLI types 1 and 2 and EWS-ERG translocations. In the current series, 4/12 cases were confirmed to be Ewing sarcoma; tissue was suboptimal for molecular testing in one case. A detailed coverage of other genetic alterations or a much more sensitive assay such as the break-apart FISH assay for the detection of EWS (22q12) gene rearrangement would be more specific for Ewing sarcoma. A total of 6 of the remaining 7 cases expressed NKX2.2 but not WT1 or BCOR. One case expressing WT1 was negative for NKX2.2, suggestive of a CIC-rearranged sarcoma. These findings suggest that the present cohort probably did not have cases of sarcomas with BCOR genetic alterations. The six tumours with NKX2.2 expression could possibly belong to the "sarcoma with EWSR1-non ETS fusions (including NFATC2, PATZ1, SMARCA5, and SP3)." As shown in the algorithm [Table/Fig-6], further confirmatory molecular tests can be individually tailored based on the immunoprofile of the tumour.

### Limitation(s)

The present study, being a retrospective study, had limitations related to the acquisition of radiological images, and the investigators had to rely on details provided in the clinical records. The classification of undifferentiated round cell tumours has evolved over the past few years, and although immunohistochemical markers and molecular tests were performed, this was handicapped by the archival and limited nature of material available. As the aim of the present study was to look at the prevalence of different mesenchymal tumours in the kidney, follow-up information was not obtained and may have shed some light on the behave of these tumours.

## CONCLUSION(S)

The PRMTs are a very rare spectrum of tumours, with the majority being benign. In malignant mesenchymal tumours, IHC is pivotal in the diagnostic armamentarium, and in cost-constrained countries, the histology should guide further immunohistochemical testing. The poorly-differentiated malignant tumours require an extensive immunohistochemical work-up. The present study highlights the limitations in the immunohistochemical workup of malignant round cell tumours and the requirement of exhaustive molecular studies individually tailored to the immuno-profile of the tumour. The spectrum of these neoplasms will continue to evolve as new genetic changes are recognised, and the therapeutic and prognostic implications of these findings are established.

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