Original Article

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Oncology Section

Oncological Outcomes of Primary Renal Malignancies other than Clear Cell Renal Carcinoma: A Retrospective Study from a Tertiary Centre in Southern India

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ABSTRACT

Introduction: A lot of research is available about clear cell Renal Carcinomas (ccRCC). But there are lesser known facts about other subtypes of renal malignancies. With advances in immunohistochemical and cytogenetic techniques, new variants of renal tumours are being increasingly reported. The treatment and prognosis of such rare malignancies is still an enigma.

Aim: To analyse the incidence, clinicopathological features, surgical treatment, and survival of non clear cell RCC at the tertiary care centre.

Materials and Methods: The present study was a retrospective study in which histopathological reports of 77 nephrectomy specimens, who underwent surgical treatment for suspected renal tumours from 2013-2018 were reviewed. Out of which, 19 (24%) patients had documented uncommon histologic variants of RCC. The clinical, demographic, and histologic characteristics of these patients were analysed, and survival was evaluated. The characteristic light microscopy and immunohistochemical features of these lesions were documented.

Results: The mean age of the study participants was 45 years (21-67 years). Out of 19 patients, 14 (73.6%) were males, and 5 (26.4%) were females. Mean tumour size was 8.8 cm (range 6-36) in the largest dimension. About 17 (22%) patients underwent radical nephrectomy, and 2 (2.5%) were treated with partial nephrectomy. Patients with collecting duct, synovial sarcoma, and Primitive Neuroectodermal Tumour (PNET) had associated inferior vena caval thrombus and underwent venous thrombectomy. Adjuvant treatment in the form of chemotherapy was instituted in collecting duct, adult Wilm's and pure sarcomas. There was no mortality in the papillary carcinoma, and the worst prognosis was encountered in collecting duct carcinoma.

Conclusion: Papillary variant had a good outcome as compared to other non clear cell carcinomas. RCC with sarcomatoid variant has a poor prognosis. Variants like renal sarcomas are rare but can be managed by nephron sparing surgeries with adjuvant therapies.

Keywords: Collecting duct carcinoma, Renal cell carcinoma, Renal sarcoma, Renal tumours, Uncommon nephrectomy, Uncommon renal tumours

INTRODUCTION

Renal tumours are a cause of significant morbidity and mortality worldwide. The advances in radiological imaging and its widespread adoption have translated into earlier detection leading to better outcomes. As per World Health Organisation (WHO) classification, renal tumours can be classified as renal cell tumours, metanephric tumours, mixed mesenchymal and epithelial tumours, nephroblastic tumours, neuroendocrine tumours, lymphomas, and metastatic lesions to the kidneys [1]. The incidence of histological classification of Renal Cell Carcinomas (RCC) include clear cell carcinoma 70%, papillary 10-15%, chromophobe 4-6%, collecting duct <1% and unclassified lesion 4-5% [2]. Sarcomatoid differentiation occurs in 1-5% of malignant renal tumours and portends a poorer prognosis [3]. Different histologic types have a different biologic and prognostic profile. Among these, clear cell RCC has a less favourable prognosis. Papillary and chromophobe variants have a preferably good prognosis. Still, others like angiosarcoma, collecting duct carcinoma, renal medullary carcinoma, and sarcomatoid variants have a poorer prognosis [4,5].

The aim of the present study was to analyse the incidence, clinicopathological features, surgical treatment, and survival of non clear cell RCC at our Institution.

MATERIALS AND METHODS

The present study was a retrospective study which included patients who underwent radical or partial nephrectomy from January 2013 to July 2018 in a tertiary care centre in Southern India. The analysis of the data was done from January 2019 till December 2019. The patients' records were retrospectively reviewed for demographic, radiologic, and pathologic data, surgical intervention, and adjuvant therapy if any. A total of 19 (24%) out of 77 patients had histopathology reported as uncommon non clear cell renal tumours.

Inclusion criteria: All patients who underwent radical or partial nephrectomy for renal tumour with malignant histopathology other than clear cell RCC, were included in the study.

Exclusion criteria: All patients who underwent radical nephrectomy or partial nephrectomy with histopathology as clear cell RCC or benign tumour, were excluded from the study.

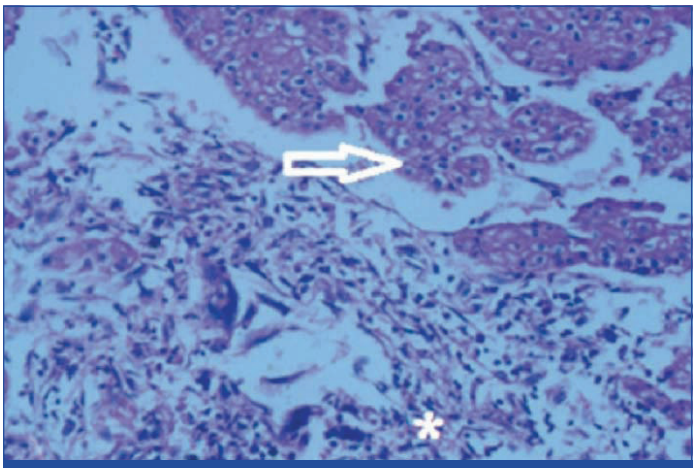
All the patients presented to the Department of Urology with the complaints of either abdominal or back pain. Besides, two patients had a history of haematuria, and one had significant weight loss and weakness. One patient presented with retroperitoneal haemorrhage (Wunderlich syndrome) and shock and underwent partial nephrectomy after stabilisation. All the patients initially underwent ultrasonography, which diagnosed renal tumours. Fifteen patients underwent a Contrast Enhanced Computed Tomography (CECT) abdomen, and three had an Magnetic Resonance Imaging (MRI) abdomen for accurate staging and surgical planning.

STATISTICAL ANALYSIS

All proportions were measured in percentages. The continuous variables were measured as median with range. The specific nominal parameters were described separately, where necessary.

RESULTS

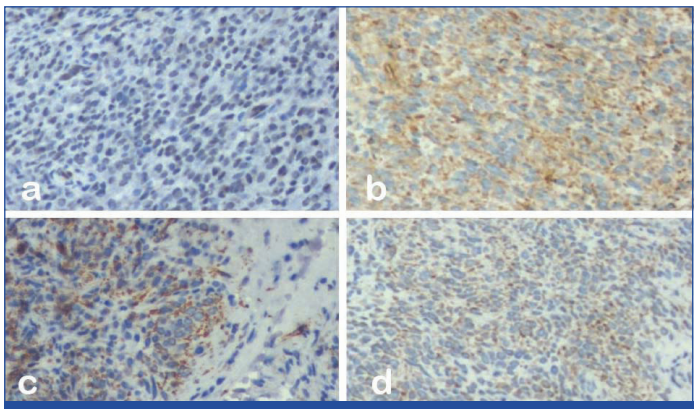
Tumour characteristics: Out of 19 patients, 14 (73.6%) were males, and 5 (26.4%) were females. The mean age was 45 (range 21-67) years. Abdominal Ultrasonography (USG) revealed the presence of a heterogeneous mass in the involved kidney in all the patients. On cross-sectional imaging, the mean tumour size was 8.8 cm (range 6-36) in the largest dimension. Three out of 19 had venous thrombosis (Collecting duct carcinoma, synovial sarcoma, and PNET) and underwent MRI to stage tumour thrombosis. Three patients had clinically significant lymph node enlargement. On histopathological evaluation, the following histologies were identified: Papillary carcinoma-5, chromophobe-3, Collecting duct carcinoma-3, clear cell with sarcomatoid differentiation-2, chromophobe with sarcomatoid differentiation-1 [Table/Fig-1] primary renal sarcoma-5 [primary biphasic synovial sarcoma-1, Angiosarcoma-1, unclassified sarcoma-1, Adult Wilm's tumour-1, Primitive Neuroectodermal Tumour (PNET)-1] [Table/Fig-2]. The light microscopy and immunohistochemical features of these lesions is shown in [Table/Fig-3]. Among these, 10 (53%) patients had T2 disease, 7 (37%) had T3, and 2 (10%) patients had T4 disease. Two patients had metastatic lymph nodes positive histopathologically (collecting duct carcinoma and synovial sarcoma), and the same patients had venous tumour thrombus. These findings were also diagnosed radiologically.



[Table/Fig-1]: Chromophobe renal cell carcinoma (arrow) with sarcomatoid transformation (asterix) (H&E 100x).

S. No.	Type of carcinoma	Type of cells	Immunohistochemistry
1	Papillary RCC	Pseudostratified cells with abundant cytoplasm having atypical nuclei with prominent nucleoli	CK7 and CD10 negative
2	Chromo-phobe RCC	Finely reticular pale cytoplasm, perinuclear halos, and wrinkled raisinoid nuclei.	CD117 positive. CK7 focally positive. Vimentin negative
3	Collecting duct RCC	Polygonal shaped cells with squamous differentiation and abundant keratin pearls	CK 5/6, Pancytokeratin, and Vimentin positive. CD10, CD117 Negative
4	Chrom-ophobe with sarco-matoid Variant	Abundant granular eosinophilic cytoplasm with admixed spindle cells. Bizarre cells present.	CD-117 positive in kidney chromophobic component. CK-7 focally positive. Vimentin and SMA positive in spindle cells.
5	Angios-arcoma	Polygonal/spindle-shaped cells. Moderate vesicular nuclei present eosinophilic cytoplasm.	CD34, factor 8, and CD31 positive. Integrase interactor (INI)-Negative
6	Biphasic synovial sarcoma	Spindle cells with marked nuclear atypia with mast cell infiltration. Marked pleomorphic nuclei.	Cytokeratin, CD99, S100, and Bcl-2 positive
7	Adult Wilm's tumour	Highly cellular with blastemal, stromal, and epithelial derivatives. Elongated, wedge-shaped nuclei with frequent mitoses.	Vimentin and PanCk positive. EMA and Bcl-2 focal positive. CD10, CD99, CD56, synaptophysin, CK7, WT 1, Desmin, and myoD1 negative.
8	Unclassified sarcoma	Tumour cells appeared small, round to oval-shaped, with scant cytoplasm vesicular chromatin and tiny nucleoli with extensive haemorrhagic areas with haemosoderin-laden macrophages.	Vimentin, Bcl-2 and FL1 positive. Pan CK, CK7, CD10, CD31, S100, HMB45, SMA, ER, PR, and WT-1 negative
9	PNET	Nests of cells intersected by fibrous septa present. Tumour cells show hyperchromatic	CD-99 positive. WT 1, CK, desmin, BCL-2, FLI 1 negative.

[Table/Fig-2]: Microscopic features of different subtypes of renal tumours.
CK: Cytokeratin; CD: Cluster of differentiation; SMA: Smooth muscle antigen



[Table/Fig-3]: Immunohistochemical markers for sarcoma. a) Tumour cells with strong diffuse nuclear expression for FLI1. Immunohistochemistry with DAB counterstain, DAKO monoclonal antibody, 400X; b) Strong diffuse staining of tumour cells for Vimentin.Immunohistochemistry with DAB counterstain, DAKO monoclonal antibody, 400X; c) Strong cytoplasmic and Golgi expression of WT1 and no nuclear expression in tumour cells. Immunohistochemistry with DAB counterstain, DAKO monoclonal antibody, 400X; d) Tumour cells showing strong cytoplasmic expression for Bcl-2. Immunohistochemistry with DAB counterstain, DAKO monoclonal antibody, 400X.

Treatment: Out of 19, 17 (89%) patients underwent radical nephrectomy, and 2 (11%) had partial nephrectomy. At the time of relapse, patients with RCC except collecting duct were given targeted therapy in the form of sorafenib. Collecting duct carcinoma, which relapsed, were given chemotherapy Gemcitabine and Cisplatin. Sarcoma patients were given adriamycin, cisplatin, ifosfamide based chemotherapy.

Survival: Among all non clear cell RCC, papillary cell carcinoma had a good outcome with all the patients alive. Among three patients of chromophobe RCC, 1 (33.3%) patient died. 2 out of 3 (66.6%) patients of collecting duct carcinoma died. Sarcomatoid differentiation also had the same mortality rate; 2 out of 3 (66.6%) succumbed to the disease. One patient of PNET died in the perioperative period. Among the four with primary renal cell sarcomas, patients with angiosarcoma and adult Wilm's tumour histology, died.

DISCUSSION

On reviewing literature, clear cell carcinoma, which is the most prevalent of all malignant tumours, has poorer survival as compared to papillary and chromophobe variants [6]. Chromophobe RCC tends to occur in the 6th decade of life and has a relatively better prognosis than other subtypes of RCC [2]. Choueiri TK et al., suggested that sunitinib and sorafenib are effective in metastatic chromophobe RCC as in their study, 75% of patients had stable disease for more than three months, and 25% reported a partial respons [7]. According to Shuch B et al., chromophobe RCC cells have overexpression of the CD117 marker. Hence, targeted agents like imatinib, dasatinib, and nilotinib may still have a role in their treatment as adjuvant agents. The sarcomatoid variant has been reported to have a median survival of 4-9 months after being diagnosed [8]. Cytoreductive nephrectomy has been an integral part of treatment for advanced conventional RCC. But in cases of sarcomatoid variants, it has a doubtful benefit in survival, with 60% of patients not able to proceed to the stage of targeted therapy after surgery [9,10]. Therefore Shuch B et al., suggested that upfront Tyrosine Kinase Inhibitor (TKI) therapy would be a better option for these patients and reserving

surgery for those patients with good performance status and who demonstrate good clinical response [8]. Collecting duct RCC is a sporadic tumour with a <1% incidence and has a poor survival. In a multicentre study, Kwon KA et al., studied 35 patients of collecting duct carcinoma and reported median Progression Free Survival (PFS) of 5.8 months and Overall Survival (OS) of 54.5 months [11]. In their study, 27 patients underwent nephrectomy, comprised of curative surgery in 17 cases, and 10 had palliative surgery. Three patients received upfront chemotherapy, and four received no treatment at all. Overall, 22 patient received different palliative chemotherapy regimen in the form of Methotrexate, Vinblastine, Adriamycin, and Cisplatin (MVAC), Interferon (IFN), 5-fluorouracil, Interleukin-2 (IL-2), Gemcitabine, Methotrexate, Adriamycin, and Cisplatin (GMAC), Gemcitabine and cisplatin (GP), gemcitabine and carboplatin (GC). They reported improved OS in patients on palliative chemotherapy (18.4 months) than those without treatment (4.5 months). Ciszewski S et al., in their study of 10 patients with collecting duct carcinoma, reported a median overall survival of 7.6 months after nephrectomy and chemotherapy or radiotherapy. Only two patients survived >2 years after the nephrectomy [12]. The primary renal sarcoma is a rare malignancy of kidney, constituting <1% of all malignant renal tumours [13]. Leiomyosarcoma is the most common histological type, followed by liposarcoma, spindle cell sarcoma, malignant fibrous histiocytoma, and fibrosarcoma. Other histological types are rarer like primary synovial sarcoma, adult Wilm's tumour, and angiosarcoma [14-16]. Due to fewer numbers of cases reported in the literature, the natural history and prognosis of such tumours are difficult to understand. Moreira DM et al., studied retrospectively, 322 non metastatic patients with primary renal sarcoma and evaluated the survival after surgical resection alone or in combination with radiation [13]. With these modalities, five-year cancer-specific survival was 58%. They attributed age, race, tumour size, and tumour grade to be independently associated with cancer death in non metastatic disease, while race and tumour histology had prognostic significance in only metastatic disease. Wang X et al., reported a high mortality rate of 62.2% at 24 months of follow-up in patients with primary renal sarcoma. Only 8% of patients were disease-free, suggesting the poor prognosis of the disease [17]. They reported a 1, 3, and 5-year survival rate as 86.3%, 40.7%, and 14.5%, respectively. It was similar to present study in which there was 50% mortality till the last follow-up. Different studies showing the incidence of uncommon renal tumours are shown in [Table/Fig-4] [2,14-16,18,19].

Type of cancer	Literature review	Present study (%)
Clear cell carcinoma [2]	70%	52 (67.5)
Papillary RCC [2]	10-15%,	5 (6.5)
Chromophobe RCC [2]	4-6%,	4 (5.2)
Collecting duct RCC [2]	<1%	3 (3.9)
Primary angiosarcoma [16]	<40 cases	1 (1.3)
Primary synovial sarcoma [14]	34 cases	1 (1.3)
Adult Wilm's tumour [15]	<1%	1 (1.3)
Unclassified renal sarcoma	-	1 (1.3)
Primitive Neuroectodermal tumour [18]	80 cases	1 (1.3)
Sarcomatoid differentiation of different renal tumours [19]	1-5 %	3 (3.9)

[Table/Fig-4]: Incidence of uncommon renal tumours [2,14-16,18,19].
RCC: Renal cell carcinoma

In the present study, rare subtypes of adenocarcinoma as well as primary renal sarcoma were included. Among adenocarcinoma, papillary tumours had a good prognosis with all patients alive at the end of the study period without relapse. Sarcomatoid variants and collecting duct carcinoma had a dismal prognosis, with patients dying within one year of surgery. Four patients of primary renal sarcoma had a varying course. Three patients received adjuvant chemotherapy, out of which two died within two years following surgery. One patient of primary renal sarcoma was managed by partial nephrectomy and is disease-free after 12 months of follow-up. In comparison to the similar studies, this study suggested the same outcomes of the non clear cell variant. Papillary variant had a good outcome as compared to other variants like the one with sarcomatoid differentiation, collecting duct carcinoma and chromophobe carcinoma. Different studies showing the prognosis of uncommon renal malignancies are shown in [Table/Fig-5] [11,20-22].

Subtype of renal tumours in the study	Study	Outcome	Treatment given
Metastatic non clear cell carcinoma	Agarwala V et al., [20] (n=40)	OS for :	Either of them as first-line therapy:
		1. Papillary 9.8 months,	1. Sorafenib
		2. Chromophobe 30.3±8.4 months	2. Sunitinib
		3. Sarcomatoid 4 months.	3. Pazopanib
		4. Others for 7.9 months.	4. Everolimus
			5. Supportive care
Chromophobe RCC	Klatte T et al., [21] (n=124)	1. 5-year DSS 78%	Nephrectomy± Immunotherapy
		2. OS- 6 months	
	Lee WK et al., [22] (n=148)	1. 5 year RFS 82.7%	Nephrectomy
		2. 5 year CSS 88.8%	
Collecting duct RCC	Kwon KA et al.,[11] (N=35)	1. PFS-5.8 months	Nephrectomy± Immunotherapy/ Chemotherapy/ Targeted therapy
		2. OS- 54.4 months	

[Table/Fig-5]: Different studies showing survival and prognosis in uncommon renal malignancies [11,20-22].
DSS: Disease specific survival; RFS: Relapse free survival; CSS: Cause specific survival; PFS: Progression free survival

Limitation(s)

The present study has several limitations. First, the sample size was small, and it is challenging to generalise disease outcomes and prognosis due to less number of cases. Second, it was a retrospective, descriptive study without comparison with the clear cell variant outcomes. Third, including all the non clear cell variant under one group cannot give the exact outcome as there is a great difference in natural history among all the histopathological subtypes.

CONCLUSION(S)

Different subtypes of renal malignancies give prognostic information. Papillary variant had a good outcome as compared to other non clear cell carcinomas. RCC with sarcomatoid variant has a poor prognosis. Variants like renal sarcomas are rare but can be managed by nephron sparing surgeries with adjuvant therapies. At present, aggressive surgical extirpation is the mainstay in the management of histologic variants of RCC. Adjuvant chemotherapy and TKI inhibitors have a limited role. Moreover, multicentric prospective trials with a large patient population are required to assess the impact of newer adjuvant therapies for such rare variants.

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