Original Article

Retrospective review of experience with sarcomatoid renal cell carcinoma: Multimodality treatment remains an unmet goal

Gowrinath Kondisetty, Pallavi Vijay Borkar[1], Sandeep Kondisetty[2], Appu Thomas[2]

Department of General Surgery, Medicity Institute of Medical Sciences, Medchal, Telangana,
Departments of [1]Pathology and [2]Urology, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India

Abstract

Background: Sarcomatoid change in Renal cell carcinoma(RCC) is associated with adverse outcomes with median survival of 6 months.

Settings and Design: This is a retrospective study of patients diagnosed of sarcomatoid RCC(sRCC) between 2007 and 2013 which were followed up till 2017.

Methods and Material: Patients ($n=22$) were grouped based on whether they received additional chemotherapy following nephrectomy. Two groups were followed up until 2017 and overall survival was record. Overall survival curves were estimated by Kaplan-Meier method and compared using Log Rank (Mantel-Cox) test between two groups.

Statistical analysis used: Kaplan-Meier method and Log Rank (Mantel-Cox) test.

Results: The patients who had chemotherapy had 13.4 cm of mean tumour size with a mean survival of 20.4 ± 8.3 months. The patients who did not undergo chemotherapy had mean tumour size of 11.7 cm with a mean survival of 21 ± 5.9 months. There was no much statistical difference between the two groups in OS with *P* value = 0.99.

Conclusion: The current adjuvant chemotherapy used in sRCC patients who develop metastasis gives no survival advantage.

Keywords: Adjuvant chemotherapy, metastatic renal cell carcinoma, sarcomatoid renal cell carcinoma, sunitinib

Address for correspondence: Dr. Pallavi Vijay Borkar, Department of Pathology, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Ponekkara, Kochi, Kerala, India.
E-mail: drpallaviborkar@gmail.com

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BACKGROUND

Cancers of the kidney is one of the top ten cancers affecting patients both male and female. Renal cell carcinoma (RCC) is the most common type of renal cancer which is further classified into subtypes. One in 20 cases of RCC is known to show a sarcomatoid transformation. Sarcomatoid transformation in RCC is an aggressive phenotype characterized by malignant spindle-shaped cells. Sarcomatoid RCC (sRCC) is no longer considered as separate entity, but sarcomatoid change can be noted in any variant of RCC. It is considered to have worst prognosis of all renal tumors with a median survival of 4–9 months.[1-3] The behavior of the sRCC could not be properly controlled by the conventional modalities which stresses upon better treatment requirement.

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As this is a very rare disease, there is a deficiency in data on the best modalities of the treatment. Nephrectomy is almost standard of care for all renal malignancies, and a lot of controversy surrounds over the further systemic therapy.

Pathology

One of the earliest descriptions of sRCC was by Farrow *et al*. in 1968, where it was described as carcinoma with pleomorphic component represented by malignant spindle cells along with rhabdoid cells or areas of metaplasia.[4] More recent ultrastructural and cytogenetic studies suggest that sRCC arises due to genetic rearrangements leading to dedifferentiation.[5] Molecular studies have shown that sRCC is not a single entity; however, it is discrete from RCC with upregulation of transforming growth factor – beta signaling.[6] In keeping with this current classification systems do not consider sRCC as distinct type, as sarcomatoid change can be seen in any subtype. In the International Society of Urological Pathology 2012 Consensus meeting, it was concluded that no minimum amount or percentage is required for diagnosis of sRCC.[7]

MATERIALS AND METHODS

This is a retrospective study of patients diagnosed of sRCC in tertiary referral hospital between 2007 and 2013 which were followed-up till 2017. All underwent nephrectomy initially followed by chemotherapy by tyrosine kinase inhibitors (TKIs) in case patient develops metastasis only. Hence, the patients who received TKIs were grouped in Group I and who did not were grouped in Group II. The total study had 22 patients, of which 10 patients who had chemotherapy were included in Group I and 12 patients who did not have chemotherapy were included in Group II. The study was conducted in accordance with the Dissertation Review Committee, and the protocol was approved by the Institutional Ethics Committee.

The diagnosis of sRCC was made by presence of any amount of carcinoma with pleomorphic component represented by malignant spindle cells along with rhabdoid cells or areas of metaplasia as per International Society of Urological Pathology 2012 Consensus meeting.

Systemic therapy was only offered after a documented metastasis which was done with TKIs either sorafenib or sunitinib. Overall survival of patients was taken into consideration. Overall survival curves were estimated by Kaplan–Meier method and compared using log-rank (Mantel–Cox) test. Of the 22 patients, four patients were alive during the statistical analysis. Patients who were alive at the time of study were censored from the statistical analysis.

RESULTS

The data from all the 22 patients were analyzed in Table 1. The mean age of patients at initial diagnosis is 53.6 with male a preponderance of 72.7%. All the patients were symptomatic at the diagnosis with abdominal pain in 54.6% and hematuria in 45.5% of patients as presenting symptom. The size of tumor ranges from 5 to 17 cm with a mean size of 12.5 cm.

Patients were divided into Group I who had chemotherapy and Group II who did not have chemotherapy. The patients who had chemotherapy had a mean tumor size of 13.4 cm with a mean survival of 20.4 ± 8.3 months. The patients who did not undergo chemotherapy had a mean tumor size of 11.7 cm with a mean survival of 21 ± 5.9 months. There was no much statistical difference between the two groups [Figure 1]. There was no improvement in Overall survival (OS) in Group I who had chemotherapy with TKI with $P = 0.99$. Actually there was a decreased survival of 18 days in patients who received chemotherapy [Table 2].

DISCUSSION

Systemic therapies for sRCC were grouped as targeted therapy, immunotherapy, and chemotherapy or combinations. Targeted therapy includes TKIs and mammalian target of rapamycin inhibitors, immunotherapy by interleukins or monoclonal antibodies, and chemotherapy with various agents such as cyclophosphamide, cisplatin, doxorubicin, gemcitabine, or combinations. Keskin *et al*. in 2017 published that the survival of sRCC has increased

Table 1: Clinicopathological characteristics

Feature	*n* (%)
Mean age at diagnosis yrs (range)	53.6 (40-65)
Number of female (%)	6 (27.3)
Number of male (%)	16 (72.7)
Number with symptoms (%)	
Hematuria	10 (45.5)
Abdominal pain	12 (54.6)
Abdominal mass	2 (9)
Mean tumor size in cm (range)	12.5 (5-17)
Number pathological tumor stage (%)	
T1 and T2	2 (9)
T3	14 (63.7)
T4	6 (27.3)

Table 2: Comparison of two groups in the study

	Mean size in cm (range)	Mean survival in months±SE	Mortality
Group I with Chemotherapy (*n*=10)	13.4 (6-17)	20.4±8.3	8/10
Group II without chemotherapy (*n*=12)	11.7 (7-16)	21±5.9	10/12
Overall	12.5 (6-17)	21.8±5.4	18/22

SE: Standard error

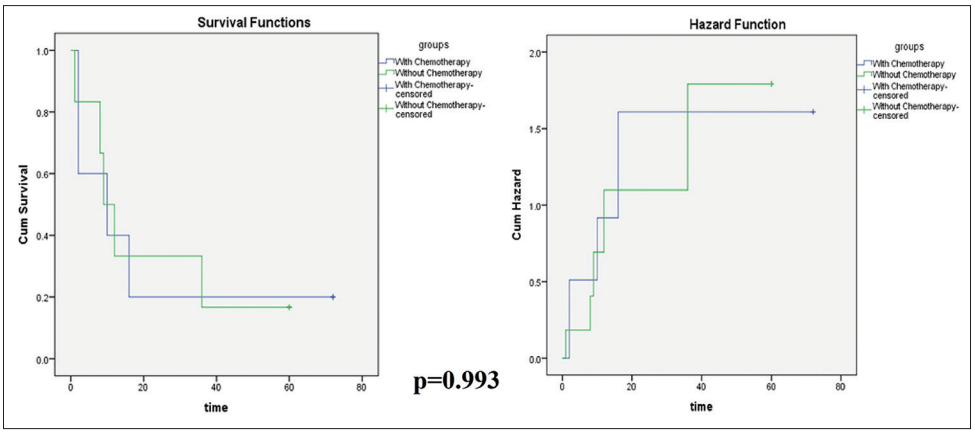

Figure 1: Kaplan–Meier curves using log-rank (Mantel–Cox) test

steadily from 2000 mainly because of the early diagnosis and better supportive care.[8] The overall survival does not go beyond 2 years. All the therapeutics showed varied results, but there was no single therapy which showed significant survival benefit.

Ravaud *et al*.[9] randomized double-blind trial including 615 high-risk RCC who were randomized to sunitinib 50 mg OD in an adjuvant setting and placebo. The group receiving sunitinib had a survival benefit of 1.2 years compared to other group. This was an important observation which made Food and Drug Administration to approve sunitinib in adjuvant setting for high-risk RCC.

In our study, the patients were offered the best available chemotherapy of that time period, and the survival advantage was compared with that of patients with metastasis not given any chemotherapy. Although many studies in RCC showed that survival advantage of our study could not replicate the survival advantage in patients with sRCC. Our study has an advantage of analyzing survival advantage in a single variant of RCC that is sRCC.

The newer therapy with monoclonal antibodies against programmed cell death-1 (PD-1) and PD ligand-1 (PD-L1) is being tried in many cancer types. Joseph *et al*.[10] has analyzed that RCC with sarcomatoid differentiation with Immunohistochemistry (IHC) found that PD-1/PD-L1 levels are high in sRCC compared to other types. The PD-1/PD-L1 inhibitors used in advanced renal cell carcinoma by Motzer *et al*.[11] showed promising results. They compared the effects of nivolumab plus ipilimumab with that of sunitinib among the intermediate-risk and poor-risk patients who were not previously treated. The results show that objective response and overall survival are much better with the combination of nivolumab plus ipilimumab which is a hope in sRCC, which has to be tried. This study is a part of checkmate 214 clinical trials.

As this is a rare type of tumor, randomized controlled trials are not possible, and we have to depend on other advanced RCC types and try that therapy in these cases. The results to replicate in these tumors are unpredictable. With many studies coming up saying that the pathogenesis of sRCC is different from other RCC tells us that we are nowhere near to a definite treatment plan for these type of tumors.

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Conflicts of interest
There are no conflicts of interest.

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