

Impact of COVID-19 on Treatment in Patients with Renal Cell Carcinoma

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The current pandemic has resulted in a significant reallocation of health-care resources, with the recommended treatment strategy advocating for oncology patients was to delay elective procedures. A retrospective analysis was conducted to evaluate the impact of COVID-19 on patients with renal cell carcinoma (RCC) and the associated treatment protocols. A retrospective review of the inpatient and outpatient records of all patients presenting with renal cell carcinoma during the period from March 2020 to the end of March 2021 was conducted. A total of 26 patients (21 males and 5 females) with a mean age of 55.46±9.44 years were diagnosed with an operable renal mass during the study period. The mean hospitalisation period (15.19±2.28) was found to be longer in patients who required surgical intervention. The delay was attributable to a number of factors, including the necessity for pre-operative testing using RT-PCR, a chest HR-CT, clearance from the chest physician, and preparation. The overall cost of hospitalization increased in these patients compared to the pre-pandemic period due to a number of factors, including prolonged hospitalization, an increased incidence of complications, the necessity for pre-operative testing for SARS-CoV-2, the use of personal protective equipment, and the provision of nursing care. During the same period, three out of eight patients who had metastatic disease with positive RT-PCR were initiated on targeted therapy, while the remaining underwent cytoreductive nephrectomy. The study concludes that patients with RCC seeking treatment during the current pandemic face significant challenges, including delays in treatment, increased hospitalization rates, and a rise in testing, which collectively contribute to elevated treatment costs. It is imperative to conduct a long-term follow-up to ascertain whether these factors have influenced the outcome of the patients in question.

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1. Introduction

The ongoing pandemic of coronavirus disease 2019 (COVID-19) in India is part of a larger global phenomenon caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The initial case of SARS-CoV-2 infection in India was documented on January 30, 2020 (1). At present, India has the highest number of confirmed cases in Asia. As of May 2021, India has the second-highest number of confirmed cases in the world (after the United States), with nearly 20 million reported cases of infection with the SARS-CoV-2 virus and 226,188 deaths as of May 5, 2021 (3,4). The pandemic resulted in a significant reallocation of healthcare resources to address the global public health emergency (5). The healthcare delivery system underwent a temporary restructuring to meet the demands of the pandemic while maintaining the provision of quality care for routine healthcare needs, including cancer therapy. On the evening of March 24, 2020, the Government of India enacted a nationwide lockdown for 21 days, imposing limitations on the movement of the entire 1.38 billion (138 crore) population of India as a preventive measure against the spread of the novel coronavirus (SARS-CoV-2) in India (6). The implementation of this lockdown resulted in the cessation of public transportation, interstate travel, the availability of medications, and access to healthcare services for patients with conditions other than those related to the novel coronavirus (7, 8). The recommended course of action for oncology patients was to postpone elective procedures, avoid superfluous testing, and consider deferring treatment until the risk of contracting and transmitting the novel coronavirus, SARS-CoV-2, had diminished. In response to the pandemic, cancer societies and national authorities issued guidelines on the provision of cancer care (9, 10). The objective of the treatment was to maintain favourable clinical outcomes while limiting exposure to SARS-CoV-2 and the potential adverse effects of infection, which could otherwise result in prolonged hospitalisations. This objective is particularly pertinent for patients with renal cell carcinoma. Patients with localized or locally advanced renal cell carcinoma (RCC) require upfront surgical resection, which has been the standard of care. However, in the context of the ongoing pandemic, surgical resection necessitates the extensive use of personal protective equipment and, in most cases, overnight hospitalisation, which carries an increased risk of exposure to SARS-CoV-2 for patients, healthcare professionals and hospital staff (11). In light of these considerations, experts from around the globe have advised that surgical intervention should be prioritized for those patients at the highest risk of disease progression or complications from the disease in the absence of treatment. Similarly, it was proposed that for patients with a high risk of postoperative complications or evidence of extensive localized disease (for example, inferior vena cava thrombus and extensive retroperitoneal lymphadenopathy), the immediate surgical intervention could be postponed. In such cases, surgical therapy (and the

subsequent utilization of valuable resources) may be deferred in favor of effective systemic therapy, which does not necessitate hospital admissions. The treatment of patients with metastatic renal cell carcinoma (RCC) has continued to evolve over the past few years. The results of the CARMENA and SURTIME trials have indicated that cytoreductive nephrectomy offers minimal benefits and that there is no evidence of harm associated with the use of upfront systemic therapy (12). At present, cytoreductive nephrectomy is only recommended for a select group of patients who do not present with extensive metastatic burden or poor-risk disease. In the context of the ongoing pandemic, however, a number of experts have put forth the proposition that upfront cytoreductive nephrectomy should be regarded as a non-essential surgical procedure, unless there are severe symptoms emanating from the primary tumor. They have also recommended that systemic therapy be considered for patients with intermediate-risk or poor-risk disease (13). Aeppli et al. (14) conducted an online survey of physicians engaged in the management of metastatic clear cell renal cell carcinoma (mccRCC). The vast majority of experts (73%) identified the combination of the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk category and patient fitness as two crucial factors influencing treatment decision-making. In patients with favorable risk profiles who were not affected by the pandemic, the primary treatment option was pembrolizumab/axitinib for 53% of experts, while avelumab/axitinib, sunitinib, or pazopanib were selected by 13% of experts each. During the pandemic, immune checkpoint inhibitors (ICIs) were selected less frequently than tyrosine kinase inhibitors (TKIs) as monotherapy, with sunitinib and pazopanib being the most common choice (35%). In patients with a favorable prognosis and intermediate/poor risk of progression outside the pandemic, over 80% of experts selected ipilimumab/nivolumab, in contrast to only 41% of physicians during the pandemic. Instead, more tyrosine kinase inhibitor monotherapies were administered. In this paper, we undertake a retrospective analysis of the impact of the SARS-CoV-2 pandemic on patients with renal cell carcinoma (RCC) and the associated treatment protocols.

2. Materials and Methods

A retrospective review of the inpatient and outpatient records of all patients presenting with renal cell carcinoma was conducted between March 2020 and the end of March 2021. This study was conducted in accordance with the approval of the institutional review board. The imaging records, histopathological findings, and treatment protocols were meticulously documented and subjected to rigorous analysis. In patients in whom the surgical procedure was postponed either due to a complete lockdown or due to a positive RT-PCR (real-time polymerase chain reaction) result, the volume of the renal tumor was calculated using the formula (15), with the assumption that the tumors were spheroidal in shape.

$$V = [4/3 \times \pi \times a \times b \times (a + b/2)] \times 1/8$$

in this context, the symbols "a" and "b" are used to indicate the maximum and minimum tumor diameters, respectively. The data were analyzed using the statistical software package SPSS version 20.

3. Results

A total of 26 patients (21 males and 5 females) with a mean age of 55.46 ± 9.44 years, presenting to the Uro-oncology outpatient department, were diagnosed with an operable renal mass during the study period. The majority of patients presented with a history of gross hematuria. Additional symptoms included abdominal discomfort, loss of appetite, and generalized weakness. Upon examination and imaging, the clinical staging of these patients was determined to be as shown in Table 1. In the initial period between March and June 2020, all scheduled surgical procedures were postponed in accordance with hospital regulations and guidelines set forth by the Indian Council for Medical Research (ICMR). In accordance with the guidelines issued by the hospital authorities, patients requiring admission for planned surgeries were required to have a negative RT-PCR (real-time polymerase chain reaction) test and high-resolution chest computed tomography (HR-CT) performed. This was effective from July 2020 onwards. Patients who tested positive for the RT-PCR test were referred for care for the novel coronavirus disease (Covid-19) and advised to return for surgery at a later date. Of the 26 patients, 11 (42.30%) required a subsequent partial

nephrectomy or radical nephrectomy due to the initial lockdown period, during which only emergency surgeries were permitted, or because they tested positive at the time of presentation to the hospital. (Please refer to Figures 1 and 2) The mean delay in surgery was as shown in Table 2. During this period, there was a statistically insignificant increase in the volume of the tumor masses. Four patients (15.38%) with IVC thrombus underwent thrombectomy in conjunction with radical nephrectomy. The mean length of hospitalization (15.19 ± 2.28 days) was also prolonged for patients who required surgical intervention. The delay was attributable to the necessity of pre-operative testing, including RT-PCR, chest HR-CT, and a fitness evaluation by a chest physician, in addition to the requisite preparation. The overall cost of hospitalization was also elevated in comparison to the pre-pandemic period. The elevated costs were attributable to prolonged hospitalization, augmented complications, preoperative SARS-CoV-2 testing, utilization of personal protective equipment, and augmented nursing care. Post-operative complications affecting the chest were observed in nine patients who had previously tested positive for the virus through RT-PCR. The chest complications observed included the need for prolonged postoperative oxygen therapy, cough, fever, and chest pain. No evidence of excessive bleeding was observed during the intraoperative or postoperative periods. During the same period, eight other patients exhibited evidence of metastatic disease (Figure 3).

Table 1. Stagewise number of patients and the number of patients postponed surgery.

No	Stage	n	Postponed	Volume 0 (cc)	Volume F (cc)	p value
1	T1N0M0	4 (15.38%)	2	169±0	242.6±37.9	0.115
2	T2N0M0	17 (65.38%)	7	461±164	628.9±194.9	0.107
3	T3N0M0	5 (19.23%)	2	724±455	883.8±439.9	0.755

V0: Volume of the tumour at clinical presentation. **VF:** Volume of the tumour at surgery.

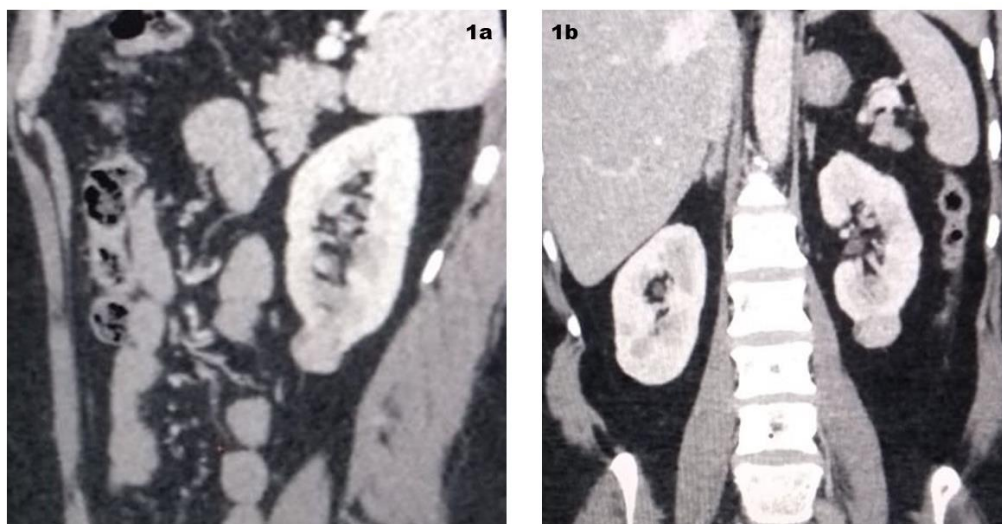


Figure 1a and 1b. CT scan in a 40-year-old female shows Lt. sided exophytic lower polar renal mass (T1a N0 M0).

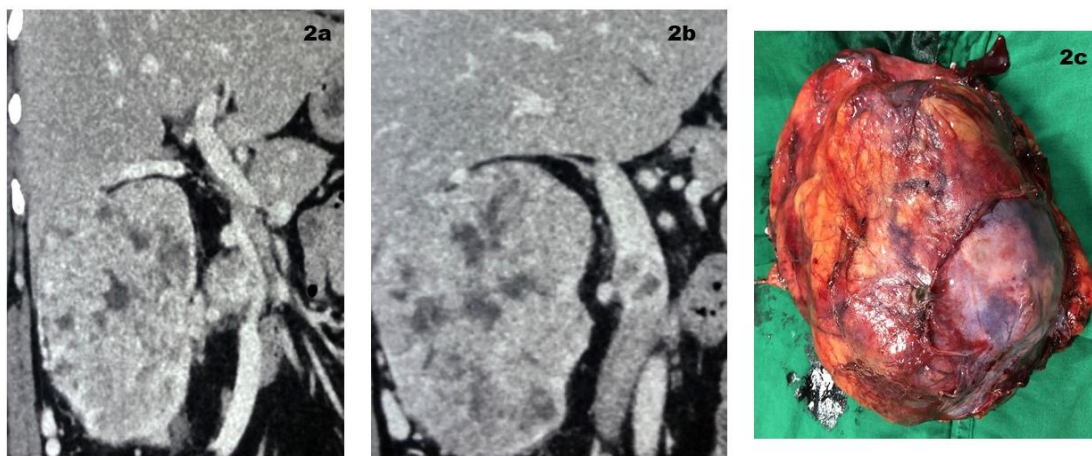


Figure 2a and 2b. A and B) CT scan of a 68-year-old male patient reveals a well-defined exophytic lobulated mass emerging from the right upper and mid-pole of the kidney. The lesion extends into the right renal vein and the infrahepatic portion of the inferior vena cava. **2C)** excised specimen showing kidney with IVC thrombus.

Table 2. Type of surgery, hospitalization duration and increase in hospitalization cost.

No	Surgery	N (%)	Mean Delay (days prior to surgery)	Hospitalization days (mean)	Increase in hospitalization cost compared to pre-Covid time
1	Partial Nephrectomy	10 (32.25%)	63.5±45.8	14±2.35	125%
2	Radical Nephrectomy Radical nephrectomy plus IVC thrombectomy	12 (38.70%) 4 (12.90%)	32.25±39.70	16.25±2.13	150%
3	Cytoreductive N	5 (16.12%)	55±48.51	15±0.81	125%
4	Total	31		15.19±2.28	



Figure 3a and 3b. CT scan of a 66-year-old male patient reveals an enlarged right kidney with a well-defined, heterogeneously enhancing mass measuring 7.3 x 8.2 x 7.5 cm. The lesion is extending into the right renal vein and the infra-diaphragmatic inferior vena cava. **3C.** Histopathological examination reveals renal cell carcinoma of clear cell variety.

Three of the subjects exhibited a positive result on the RT-PCR test and were subsequently initiated on a targeted therapeutic regimen. The remaining five patients underwent cytoreductive nephrectomy, followed by targeted therapy in accordance with the departmental policy. The targeted therapy was not administered consistently to all patients due to the unavailability of the requisite medications. No deaths were observed.

4. Discussion

Renal cell carcinoma represents 2% to 3% of all adult malignant neoplasms and is regarded as the most lethal of the common urologic cancers. (14) In general, approximately 16 new cases are diagnosed per 100,000 population per year, with a male-to-female predominance of 1.9 to 1 (14). This disease is primarily observed in older adults, with the typical age of presentation ranging from 55 to 75 years. (14,16) RCC is associated with a poor prognosis for patients with metastatic disease (17,18), as it has demonstrated only limited responses to cytotoxic chemotherapeutic agents. The study of renal cell carcinoma (RCC) tumor biology has yielded insights into the mechanisms underlying the disease's resistance to chemotherapy. Furthermore, the elucidation of the vascular endothelial growth factor (VEGF), mammalian target of rapamycin (mTOR), and relevant immunomodulatory pathways has led to the development of agents with clinical benefits for advanced RCC (18). In the opinion of Ged et al. (11), surgical intervention should be prioritized for patients who are at the greatest risk of disease progression or complications from the disease in the absence of treatment (Table 3). Furthermore, it was recommended that patients at high risk of postoperative complications or with evidence

of extensive localized disease (e.g., inferior vena cava thrombus and extensive retroperitoneal lymphadenopathy) should have their immediate surgical intervention deferred. Such patients could be initiated on systemic therapy, with a plan to address the surgical intervention in the subsequent few months. The scenario in which patients with RCC require initiation of systemic treatment during the course of the ongoing pandemic raises a number of questions. Two principal questions emerge: first, whether patients with RCC genuinely face an elevated risk of contracting the SARS-CoV-2 virus, and second, whether they are more susceptible to adverse outcomes from the viral infection. A nationwide analysis in China revealed that patients with cancer exhibited a significantly elevated risk of severe events in comparison to patients without cancer (39% vs. 8%; $p=0.0003$) (19). The systemic therapy of patients with treatment-naïve metastatic RCC has undergone a significant transformation in recent years, with immunotherapy-based combination treatments currently representing the standard of care. However, these patients are at risk of serious organ-specific irAEs (\geq grade 3), necessitating prolonged courses of immunosuppressive therapy. During the ongoing pandemic, there is a heightened concern for the development of immunotherapy-related pneumonitis, which can present in a manner similar to that of SARS-CoV-2-induced pneumonia. It is noteworthy that 27% and 29% of patients who received pembrolizumab plus axitinib in the KEYNOTE-426 trial (20) and nivolumab plus ipilimumab in the CheckMate 214 trial (21), respectively, received oral prednisone doses equivalent to ≥ 40 mg/day to manage select irAEs. Furthermore, the regimen of nivolumab plus ipilimumab was associated with a higher incidence of

Table 3. Risk based suggested approaches for RCC during COVID-19 times.

Stage/clinical presentation	Suggestion (s)	Alternative(s)
cT1aN0M0 (<4.0cm)	Active Surveillance and postponed Surgery	Thermal ablation Partial nephrectomy
complex renal cysts (BosniaK III/IV)	Active Surveillance and postponed Surgery	Laparoscopic/ Robotic surgery
cT1b-T2 N0M0	Partial/ Radical nephrectomy	Surveillance and delayed surgery (only for selected cT1b and cT2a <7.0 cm) CT/ MRI after 90 days in recommendable A renal biopsy could be discussed before decision between surgery or surveillance.
cT3 and or N+, venous thrombus	Upfront Surgery	Individualized discussion or tumor board discussion
Low Risk Metastatic	Systemic Therapy (TKI or TKI+ICI) and postponed cytoreduction	-
Intermediate and poor Risk Metastatic	Systemic Therapy (ICI+ICIC, or ICI+TKI)	Alternative drugs doses or scheduling intervals between applications.
Special conditions		
Local Recurrences (small asymptomatic lesion)	Surveillance	Thermal ablation
Local Recurrences (symptomatic or locally invasive lesion)	Wide surgery	Systemic Therapy and delayed postponed surgery. Individualized discussion or tumor board
Hereditary RCC	Follow usual guidelines (surgery if >3.0 cm, except for HLRCC syndrome (prompt resection)	Individualized discussion or tumor board discussion

irAEs than pembrolizumab plus axitinib, including a higher risk of immune-related pneumonitis (6% versus 2.8%, respectively). In light of the heightened risk of irAEs associated with treatment-naïve metastatic disease, Ged et al (11). Advocated for the preferential utilization of pembrolizumab plus axitinib as the frontline regimen during the ongoing pandemic. It is of the utmost importance to provide these patients with adequate support, as this is a crucial aspect to maintain throughout the ongoing pandemic. For patients with cancer, concerns about receiving inadequate care can outweigh the perceived risk of contracting the virus. In a survey conducted by the Kidney Cancer Research Alliance (KCCure) of over 500 patients with renal cell carcinoma (RCC) in the USA, 71% of the participants indicated that they perceived themselves to be at a high risk of contracting the novel coronavirus disease (COVID-19). However, 50% of the participants expressed reluctance or strong reluctance to forego an infusion of systemic therapy, and 64% reported feelings of anxiety regarding disease progression in the event of delayed systemic therapy (11). It is incumbent upon oncologists and urologists who are treating patients with RCC to reassure them that for a significant proportion of patients, deferring therapies and avoiding the risks associated with SARS-CoV-2 exposure represents the optimal course of action. (22). Patients with renal cell carcinoma (RCC) who are seeking treatment during the ongoing Coronavirus Disease 2019 (Covid-19) pandemic are encountering a number of challenges. These include delays in treatment, an increase in hospitalisations, and a rise in testing, which is leading to a higher cost of treatment. It is imperative to conduct long-term follow-up to ascertain whether these factors have influenced the outcomes of these patients. Further research is required to gain insight into the effects of the SARS-CoV-2 virus on cancer, particularly renal cell carcinoma. It is inevitable that the global public health crisis of the novel coronavirus disease 2019 (Covid-19) will have long-term implications. Consequently, it is imperative that the kidney cancer community develops updated guidelines to address these implications.

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Authors' Contribution

RBN and GS were involved in the design, intellectual content, and data acquisition of the study. SG conducted the literature search, performed the data analysis, and prepared the manuscript. The editing was performed by SR. RBN, GS, SG, and SR contributed to the review, with SG assuming responsibility as guarantor.

Ethics

The study was not funded. The requisite ethical formalities have been observed in accordance with the guidelines set forth by the KLES Kidney Foundation Institutional Ethics Committee.

Conflict of Interest

The authors have no conflicts of interest to declare.

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Data Availability

The data that substantiate the findings of this study are presented in the manuscript.

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