Impacts of the COVID-19 pandemic on diagnosis of renal cell carcinoma and disease stage at presentation

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ABSTRACT

Introduction: Renal cell carcinoma (RCC) is often associated with significant morbidity and mortality, with overall survival contingent on multiple factors — most importantly, disease stage at diagnosis. Disruptions in healthcare delivery during the COVID-19 pandemic have resulted in various reported diagnostic and treatment delays, which have had detrimental impacts on malignancies such as RCC.

Methods: Surgically managed cases of RCC at our center were identified using a retrospective chart review of all nephrectomies conducted from March 1, 2018, to February 28, 2023. Examination of disease characteristics in three time period cohorts (before, during, and following the COVID-19 pandemic) was undertaken. Timeframes were consistent with implementation and abolition of public health restrictions in the province of Newfoundland and Labrador.

Results: A total of 483 surgically managed RCC cases were identified during the study period. The median age was 65 years (interquartile range [IQR] 56–71), and 62.3% of patients

KEY MESSAGES

- RCC has high mortality rates heavily dependent on disease stage at diagnosis.
- Disruptions in healthcare delivery during COVID 19 resulted in diagnostic and treatment delays.
- With the ease of pandemic-induced restrictions, there has been a clinically significant stage migration in the proportion of pathologic stage 3 RCC, as surgical wait times have significantly increased.
- The impacts of COVID-19 on diagnostic and therapeutic outcomes for patients with RCC warrant greater consideration in the prevention of detrimental outcomes.

were male. Demographics did not vary across timeframes. Before and during the pandemic, pathologic stage 3 (pT3) disease was reported in 38.9% and 35.4% of cases, respectively, whereas the post-pandemic period saw this presentation in 50.0% of patients. Surgical wait times increased significantly across study timeframes (p=0.003).
Conclusions: The first year following the COVID-19 pandemic saw an 11.1% increase in patients presenting with pT3 RCC. These findings are suggestive of a clinically significant stage migration, which paired with prolonged wait times for surgery, provide critical consideration in the urgency of diagnostic and treatment decisions for RCC in the immediate future.

INTRODUCTION

Renal cancer involves a diverse variety of renal pathologies with variable patterns of aggressiveness and malignant potential.[1] Renal cell carcinoma (RCC) are insidious neoplasms frequently associated with high mortality rates despite only accounting for approximately 2% of all cancer diagnoses.[2] Current global age-standardized incidence of RCC has been reported at 4.4/100,000; however, incidence and mortality for these malignancies have been increasing over the past several years. The highest rates have been observed in North America, with an age-standardized incidence of approximately 12/100,000 compared with near negligible numbers in several Central African nations, representing discrepancies in risk factors between geographical locations.[2–5]

The pathogenesis of RCC has been linked to several risk factors, categorized relative to environmental and behavioral patterns, or inheritance of genetic mutation.[3–6] Smoking is a major predictor for development of RCC in multiple studies, with greater than half of diagnoses amongst current or former smokers.[7–9] Elevated risk is also associated with an increasing number of comorbidities, including obesity, hypertension, and type 2 diabetes mellitus.[5,10] Risk of RCC increases 25 – 35% for an approximate 5kg gain in bodyweight, and hypertension is associated with a doubled risk for development.[5,11–16] Genetic mutations, including Birt-Hogg-Dube and Vonn Hippel Lindau syndrome, have established predisposition for development of renal malignancies.[17–19]

Most cases of RCC are discovered incidentally on imaging. Prognosis is contingent on multiple factors, including tumour grade, histology and, more importantly disease stage at diagnosis.[20,21] Accordingly, patients presenting with localized disease amenable to surgical resection have a 5-year overall survival (OS) of 93%.[22,23] OS decreases to 72.5% in those with regional spread, and further declines to 12% among those with distant metastaties.[15,24,25] The decreased utility of surgical intervention in later stage disease prompts need for improved public health initiatives to promote early diagnosis of RCC.

Disruptions in healthcare delivery during the COVID 19 pandemic have resulted in various diagnostic and treatment delays, and subsequently detrimental impacts on management of

malignancies including RCC.[26–30] Pandemic-induced delays have consistently increased morbidity and mortality for oncology patients during this timeframe.[31–33] Urogenital malignancies have typically accounted for a small percentage of cancers and have seen significant advancement in management options over the past several decades. Such considerations have likely rendered these afflictions as low priority in access to resources throughout the COVID-19 pandemic.

To date, there has been limited research assessing pandemic-induced delays in diagnosis and treatment of urogenital malignancies. The province of Newfoundland and Labrador (NL) possesses the highest national rates of obesity, smoking, and hypertension, along with a propensity to act as a microcosm for rare genetic conditions which correlate with higher risk of renal malignancies.[34–36] The present study aimed to assess how the COVID-19 pandemic, and associated healthcare restrictions, affected the diagnosis, staging, and final surgical pathology of RCC at our institution. We hypothesized that a greater proportion of RCC diagnoses presented with late-stage disease during and following the pandemic compared to the pre-pandemic era. It was also predicted that individuals with a diagnosis of RCC during and following the pandemic would have experienced greater delays in treatment secondary to implemented healthcare restrictions.

METHODS

This study was approved by the provincial health research ethics board at Memorial University (St. Johns, Newfoundland and Labrador, Canada). A retrospective chart analysis was conducted of all surgically managed cases of RCC from March 1, 2018 – February 28, 2023. Patients undergoing radical or partial nephrectomy during this timeframe were identified utilizing operating room (OR) codes. Pathology reports for each identified case were examined to determine eligibility as RCC or separate pathology, with the latter being excluded. Tumour staging for all eligible charts was completed in accordance with American Joint Committee on Cancer guidelines. The assessed study timeframe was further sub-divided into pre-pandemic, pandemic, and post-pandemic periods, consistent with the implementation and abolition of COVID-19 public health restrictions in the province of NL. Timeframes were defined as follows:

- Pre-pandemic: March 1, 2018 – March 31, 2020 (25 months)
- Pandemic: April 1, 2020 – February 28, 2022 (23 months)
- Post-pandemic: March 1, 2022 – February 28, 2023 (12 months)

Each case was assessed for time from surgical booking to operative intervention along with further, relevant epidemiological and pathological variables. Differences across timeframes were calculated using the Kruskal-Wallis test for non-parametric samples with significance set at p=0.05. All demographic and comorbidity data were retrieved from pre-operative anesthetic assessment reports. Statistical analyses were conducted using SPSS version 27.0 (IBM Corporation, Armonk, NY). Continuous variables have been reported as means and standard deviations while descriptive analyses are summarized as absolute counts and percentages.

RESULTS

There were 608 identified nephrectomies in the study timeframe with 484 procedures in 477 individuals meeting the inclusion criteria. Given the goals of the present study, each undertaken surgical procedure was included as a separate case. One case was accidentally documented twice and subsequently excluded leaving a total of 483 analyzed cases. Breakdown of all identified nephrectomies is outlined in Figure 1.

Patient characteristics

Mean age across the study timeframe was 63.20 ± 11.22, while 301 (62.3%) members of the cohort were male. Incidental discovery of RCC on imaging was noted for 336 (69.6%) cases. Hypertension and type 2 diabetes were reported for 327 (67.7%) and 123 (25.5%) individuals, respectively. There were 239 (47.5%) participants reported as either current or former smokers. Predisposing genetic mutations were noted for 7 (1.8%) individuals and 277 (57.3%) patients were classified as obese. Demographics information and comorbidity status across pandemic timeframes is displayed in Table 1.

Tumor pathology

Stage pT3 disease accounted for 38.9% of cases in the pre-pandemic period, and 35.4% of cases throughout the pandemic, before increasing to 50.0% of individuals post-pandemic restrictions (p=0.07) (Figure 3).

The most utilized surgical procedure across all study time periods was laparoscopic radical nephrectomy which was employed in 212 (43.9%) cases. Laparoscopic approaches further accounted for 278 (57.6%) of total cases. A full breakdown of the utilized surgical procedures by pandemic timeframe is outlined in Table 2.

Several histopathological classifications of RCC were identified (Figure 2), with clear cell RCC (ccRCC) observed in 367 (76.0%) cases. Papillary RCC, which accounted for 77 (16.0%) cases, was subclassified during the study period.

Tumour necrosis was found on 115 (23.8%) pathology specimens, while sarcomatoid and rhabdoid features were seen in 14 (2.9%) and 56 (11.6%) cases, respectively. Table 3 details tumour pathology across the stratified time periods.

Outcomes

Two patients had malignancy discovered incidentally on pathology and were excluded from analysis of surgical wait times as these cases were not indicative of RCC-associated surgical delays. The average time from surgical booking to operative intervention prior to the pandemic was 44.5 (±35.1) days, increasing to 56.8 (±46.8) and 61.2 (±42.2) days during and following the abolition of public health restrictions. Surgical wait times increased significantly across the study period (p=0.003).

Following surgical intervention, metastatic disease was seen in 48 (9.9%) patients with 39 undergoing additional treatments. Pulmonary metastases represented the most common site of

spread in 24 (51.0%) cases. Characteristics and treatment of patients with metastatic disease stratified by pandemic timeframe are displayed in Table 4.

DISCUSSION

Our study is one of the few to date that attempts to assess the impacts of the COVID-19 pandemic on RCC diagnoses and outcomes. The most pertinent finding of the present study was an 11.1% increase in the proportion of pT3 disease in the post-pandemic period which, compared with the pre-pandemic era, is suggestive of a stage migration for RCC. Pathologic T3a RCC represents locally advanced disease with invasion of the vascular supply and/or perinephric fat and is associated with comparatively poorer oncologic outcomes.[37] RCC often presents with a variable clinical course which has led to the design of several prognostic models for this patient population dependent on multiple variables including disease extent, tumour size, grade and necrosis.[20,21,38] Unequivocally, these models depict worsening survival outcomes with increasing disease stage as previous reports have indicated 5-year cancer specific survival decreasing from 97% in those with T1a disease to 71% in individuals with T3a disease.[21,38,39] Further, likelihood of progression to metastatic disease increases for individuals with later stage disease on pathology, with 5-year OS in disseminated disease cited at 12%.[5,15]

There have been several studies to date that have attempted to assess the impact of the COVID-19 pandemic on cancer patients with notable increases in the percentage of patients presenting with inoperable or metastatic conditions compared with the pre-pandemic era.[40] Similarly, attempts to classify stage migration amongst various cancers during the pandemic have indicated increases in advanced stage disease at presentation for otolaryngologic, breast, and colorectal malignancies, however, there are notable discrepancies across studies.[26–30] A recent retrospective Canadian study documented similar findings with a 7.6% increase in stage III disease staging of testicular germ cell tumours throughout the pandemic without assessment of the post-pandemic period.[41] There has been limited reporting regarding pandemic impacts on RCC staging with one Italian study, conducting an annual comparison of RCC from 2018 – 2020 finding insignificant differences in staging across this timeframe. Interestingly, the present study showed a 3.5% decrease in the proportion of pT3 RCC diagnosed during the pandemic compared with the pre-pandemic period. Arguably, pandemic-induced healthcare restrictions at our center may have limited assessment to urgent presentations of various conditions with incidentally detected RCC that had yet to progress to later stage disease. Unlike the previous authors our timeframes were established based on the implementation and abolition of public health restrictions in our province. While our results did not achieve statistical significance, we have documented a clinically significant stage migration for RCC in the year following the pandemic at our center that may have important implications in future management.

We further identified a statistically significant increase in surgical wait times between the pre- and post-pandemic timeframes. Previous attempts have been made to classify the consequences of prolonged surgical wait times in management of RCC with conflicting results. Srivastava et al. (2021) assessed the implications of delaying surgery for stage T1b – T2b RCC

during the pandemic and found up to a 3-month delay in surgery did not significantly increase risk of tumour progression.[42] On the contrary, a recent meta-analysis found insufficient evidence to support delays in surgery for localized RCC, citing worsened cancer-specific survival in individuals with T1a disease over a mean observation period of approximately two years. Important to note is that this review reported considerable heterogeneity amongst analyzed studies and found no significant differences in OS. These authors further reported assessment of delayed surgery in malignancies beyond T1b was limited, contradictory and prone to selection bias.[43] Regardless of interpretation, our study demonstrated a clear stage migration which was likely multifactorial during pandemic-induced restrictions in healthcare delivery and unlikely to be due wholly to observed increases in surgical wait times.

The present study is the first to our knowledge that has assessed a timeframe beyond the peak pandemic period and presents with findings suggestive of delays in both diagnosis and management of RCC impact longitudinal outcomes for these patients. Those with surgically managed RCC had a greater occurrence of metastatic disease and cancer-specific mortality in the pandemic and pre-pandemic periods when compared to the post-pandemic era. These findings were inevitably the result of a length-time bias, however, given the pertinent findings of this study it will be important to conduct longitudinal follow-up in patients diagnosed with pT3 disease following the pandemic. It is also important to note that our cohort consisted of surgically managed cases of RCC and did not account for individuals who presented with metastatic disease and received non-operative interventions. Further examination of these patients may shed further light on the burden of pandemic-induced delays for those with RCC.

- Risk profile seen in our study did not differ significantly across defined timeframes and was, again, comparable to extant literature as RCC has consistently been causally associated with smoking, obesity, and hypertension.[3,5,44] Our results indicated 47.5% of patients had utilized tobacco products, consistent with previous studies stating increased risk for RCC in current and former smokers, whom account for approximately 50% of all RCC diagnoses.[7,45] Smoking has direct correlations with hypertension, which has frequently been recorded as an independent risk factor for RCC in a dose-dependent fashion, therefore, it is unsurprising that this variable was present in greater than two-thirds of our sample.[44,46] Alternatively, obesity, previously reported in 30% – 40% of RCC diagnosis, was seen in nearly 60% of our cohort which may have contributed to an increased risk among our population and may warrant greater examination.[4,44,46] Despite lack of consistent evidence for type 2 diabetes as a risk factor, this condition was still seen in one-quarter of our patients, supporting the likelihood of a previously proposed interplay with other chronic comorbid conditions in the development of RCC.[5]

The province of NL has traditionally possessed the highest national incidence of various malignancies paired with a unique risk factor profile for RCC. Considering the findings of the present study, additional research should aim to assess the epidemiology of these malignancies in this province Evidently, the events of the pandemic have negatively impacted staging for several malignancies, including RCC, which may have real-world implications for survival during the

continued recovery from this global catastrophe. Future research should aim to assess how these findings impact longitudinal outcomes and overall survival in this patient population in comparison to the pre-pandemic period and assess allocation of limited management resources.

Limitations

Several limitations must be considered when interpreting the findings of the present work. First and foremost is the retrospective nature of the project which presents a natural predisposition for inconsistent reporting or missing variables. Despite lack of omitted information in collected variables the possibility for inaccuracies in the data recorded still exist. Regardless, we are confident that the results reported are indicative of a true stage migration given the rigorous reporting procedures required in pathological interpretation. Further, our focus on proportion of cases rather than absolute counts provides further reassurance in the accuracy of study findings. A second limitation exists in the interpretation of surgical wait times as delayed timeframes may not be a true representation given the amenability of small renal masses (SRM) to active surveillance and do not represent emergent situations. In avoiding potential skews in data interpretation surgical delay was calculated from time of surgical booking rather than first presentation. Additionally, prolonged wait times may present if other necessitated and more immediate interventions are required, however, it is expected that the chance occurrence of these cases would have been equal across timeframes. We are confident that our results are indicative of increasing time from surgical booking to operative intervention resultant from the pandemic given the backlog of urgent operative oncologic cases at our institution paired with the observed stage migration. Further limitation exists in the unequal timeframes given the shorter post-pandemic time-period have inevitably subjected these results to a length-time bias such that future research should focus on assessing longitudinal outcomes for these patients. Finally, the island of Newfoundland has been documented as having significant potential to act as a microcosm for rare malignancies, including those with predisposition to RCC, which may limit applicability of these findings to other geographies. However, results of the present study demonstrated limited genetic influence paired with a risk factor profile consistent with extant literature on RCC such that we are confident the findings are applicable to other centers.

CONCLUSIONS

We identified a clinically significant stage migration for RCC paired with increasing wait times for surgical intervention during the immediate post-pandemic period. The impacts of the COVID-19 pandemic on diagnostic and therapeutic outcomes for patients with RCC cannot be ignored and warrant greater consideration in the prevention of detrimental outcomes.

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FIGURES AND TABLES

Figure 1.

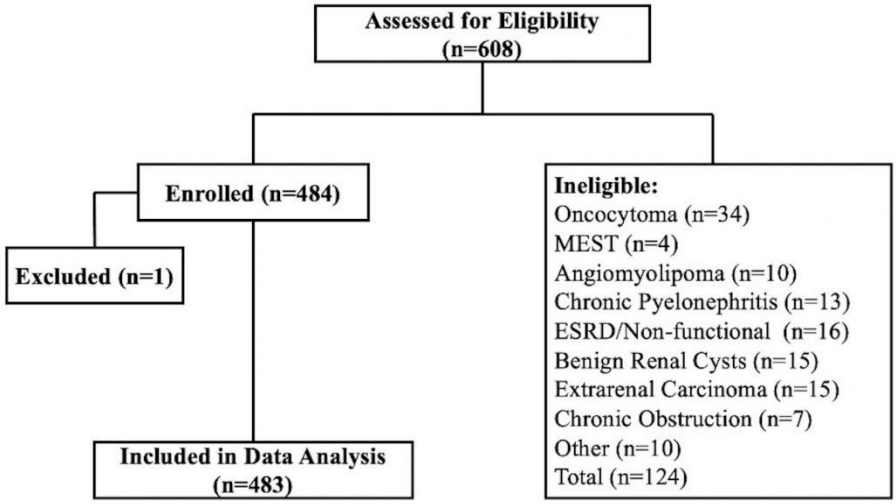

Figure 2.

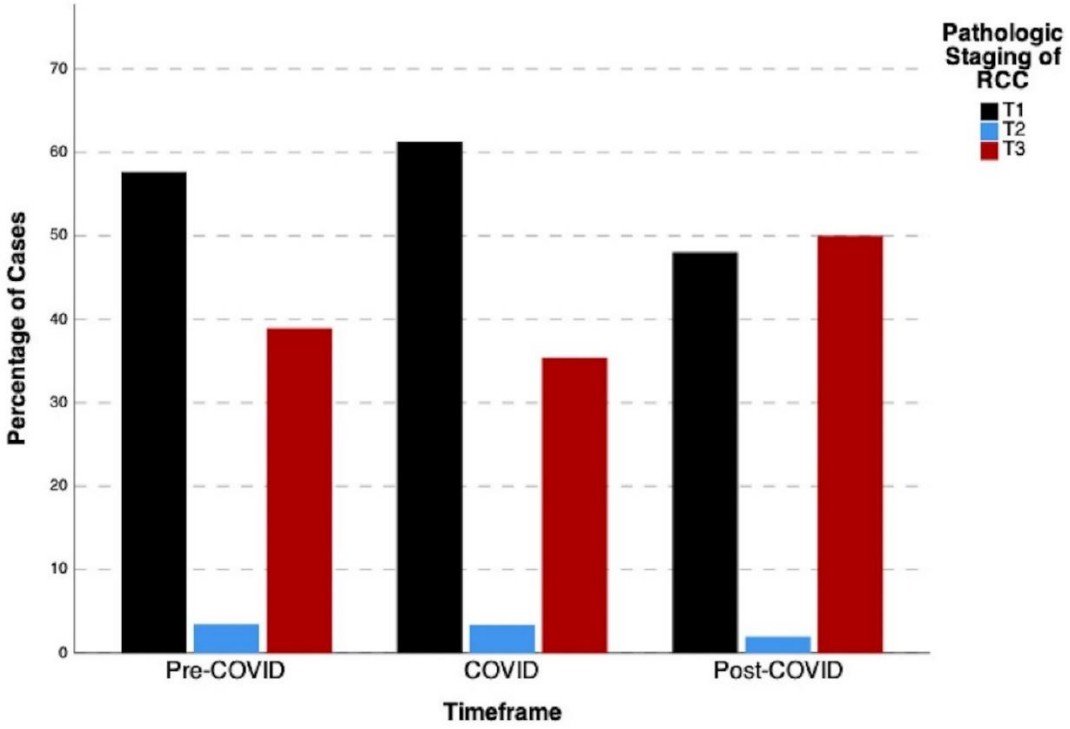

Figure 3.

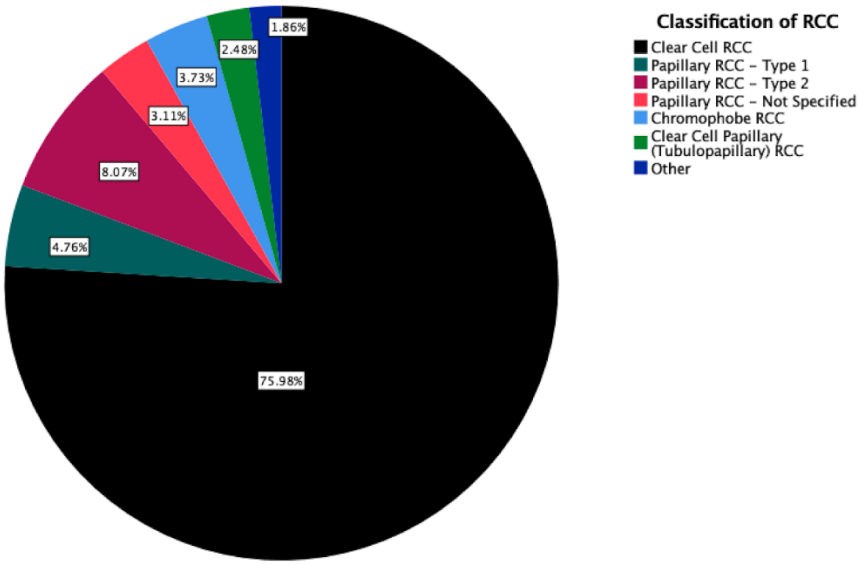

Table 1. Patient demographic and comorbidity status stratified by defined pandemic timeframes

Demographic Variables	**Pre-pandemic n=203**	**Pandemic n=178**	**Post-pandemic n=102**	**p**
Sex, n (%)				0.615
Male	123 (60.6%)	116 (65.2%)	62 (60.8%)	
Female	80 (39.4%)	62 (34.8%)	40 (39.2%)	
Age, $\bar{\bar{x}}$ ± SD	62.79±11.98	62.7 ±10.39	64.91±11.06	0.419
BMI, median (IQR)	31 (23–39)	30.5 (22.8–38.2)	31.9 (21.5 42.1)	0.830
BMI classification, n (%)				0.459
Non-obese	85 (41.9%)	81 (45.5%)	39 (38.2%)	
Obese (BMI ≥30)	118 (58.1%)	96 (54.5%)	63 (61.8%)	
Smoking status, n (%)				0.474
Never	103 (50.7%)	93 (52.2%)	58 (56.8%)	
Current	48 (23.6%)	42 (23.6%)	26 (25.5%)	
Former	52 (25.6%)	43 (24.2%)	18 (17.6%)	
Hypertension, n (%)				0.543
Yes	132 (65.0%)	125 (70.2%)	70 (68.6%)	
No	71 (35.0%)	53 (29.8%)	32 (31.4%)	
Type 2 diabetes, n (%)				0.829
Yes	52 (25.6%)	43 (24.2%)	28 (27.5%)	
No	151 (74.4%)	135 (75.8%)	74 (72.5%)	
Genetic condition, n (%)				0.893
Yes	3 (1.5%)	3 (1.7%)	1 (1.0%)	

No	200 (98.5%)	175 (98.3%)	101 (99.0%)	
Vital status, n (%)				0.077
Alive	193 (95.1%)	172 (96.6)	102 (100.0%)	
Deceased	10 (4.9%)	6 (3.4%)	0 (0.0%)	

BMI: body mass index.

Table 2. Employed surgical procedures presented by pandemic timeframe			
Surgical Procedure	**Pre-pandemic n (%)**	**Pandemic n (%)**	**Post-pandemic n (%)**
Open radical nephrectomy	24 (11.8%)	32 (18.0%)	16 (15.7%)
Open partial nephrectomy	58 (28.6%)	43 (24.2%)	32 (31.4%)
Laparoscopic radical nephrectomy	95 (46.8%)	71 (39.8%)	46 (45.1%)
Laparoscopic partial nephrectomy	26 (12.8%)	32 (18.0%)	8 (7.8%)
Total	203 (100.0%)	178 (100.0%)	102 (100.0%)

Table 3. Histopathological characteristics of patients with surgically managed RCC in Newfoundland and Labrador during the COVID pandemic timeframes			
Tumor characteristics	**Pre-pandemic n=203**	**Pandemic n=178**	**Post-pandemic n=102**
Tumor size (cm), median (IQR)	3.30 (0.20–6.40)	3.55 (0.09–7.01)	4.15 (1.55–6.75)
Pathologic staging, n (%)			
pT1a	102 (50.2%)	88 (49.4%)	35 (34.3%)
pT1b	14 (7.4%)	21 (11.8%)	14 (13.7%)
pT2a	4 (2.0%)	2 (1.1%)	2 (2.0%)
pT2b	3 (1.5%)	4 (2.2%)	0 (0.0%)
pT3a	77 (38.0%)	62 (34.8%)	51 (50.0%)
pT3b	2 (1.0%)	1 (0.6%)	0 (0.0%)
Nodal assessment, n (%)			
NX	187 (92.1%)	163 (91.6%	94 (92.2%)
N0	14 (6.9%)	13 (7.3%)	8 (7.8%)
N1	2 (1.0%)	2 (1.1%)	0 (0.0%)
Grade, n (%)			

N/A	14 (6.9%)	10 (5.6%)	7 (6.9%)
G1	12 (5.9%)	5 (2.8%)	0 (0.0%)
G2	85 (41.9%)	66 (37.1%)	39 (38.2%)
G3	55 (27.1%)	65 (36.5%)	41 (40.2%)
G4	37 (18.2%)	32 (18.0%)	15 (14.7%)
Sarcomatoid features, n (%)			
Present	7 (3.4%)	5 (2.8%)	2 (2.0%)
Absent	196 (96.6%)	173 (97.2%)	100 (98.0%)
Rhabdoid features, n (%)			
Present	31 (15.3%)	16 (9.0%)	9 (8.8%)
Absent	172 (84.7%)	162 (91.0%)	93 (91.2%)
Tumor necrosis, n (%)			
Absent	158 (77.8%)	132 (74.2%)	78 (76.5%)
1–25%	31 (15.3%)	29 (16.3%)	17 (16.7%)
26–50%	2 (1.0%)	2 (1.1%)	0 (0.0%)
51–75%	3 (1.5%)	2 (1.1%)	0 (0.0%)
76–100%	5 (2.7%)	4 (2.2%)	3 (2.9%)
Unknown %	4 (2.0%)	9 (5.1%)	4 (3.9%)
LVI, n (%)			
Positive	6 (3.0%)	4 (2.2%)	1 (0.9%)
Negative	197 (97.0%)	174 (97.8%)	101 (99.1%)

IQR: interquartile range; LVI: lymphovascular invasion; RCC: renal cell carcinoma.

Table 4. Characterization of patients with metastatic RCC stratified by defined COVID timeframes

Metastatic characteristics	**Pre-pandemic n=20**	**Pandemic N=22**	**Post-pandemic n=6**	**Total n=48**
Site of metastases, n (%)				
Retroperitoneal LN	3 (15.0%)	1 (4.5%)	3 (50.0%)	7 (14.9%)
Lungs	9 (45.0%)	15 (68.3%)	2 (33.3%)	26 (54.2%)
Bone	5 (25.0%)	4 (18.2%)	0 (0.0%)	9 (18.8%)
Thyroid	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (92.0%)
Adrenals	1 (5.0%)	1 (4.5%)	1 (16.7%)	3 (6.3%)
Multiple	1 (5.0%)	1 (4.5%)	0 (0.0%)	2 (4.2%)
Additional treatment, n (%)				
Immunotherapy				
Monotherapy	10 (50.0%)	10 (45.5%)	0 (0.0%)	20 (41.7%)
+ TKI	0 (0.0%)	3 (13.6%)	1 (16.7%)	4 (8.3%)
TKI monotherapy	11 (55.0%)	7 (31.8%)	2 (33.3%)	20 (41.7%)

Radiation	5 (25.0%)	2 (9.1%)	0 (0.0%)	7 (14.6%)
Surgery	0 (0.0%)	1 (4.5%)	0 (0.0%)	1 (2.1%)
None	4 (20.0%)	2 (13.6%)	2 (33.3%)	9 (18.8%)
Vital status, n (%)				
Alive	11 (55.0%)	18 (81.9%)	6 (100.0%)	35 (72.9%)
Deceased	9 (45.0%)	4 (18.1%)	0 (0.0%)	13 (27.1%)

Multiple sites of metastases indicates combined osseous and pulmonary metastatic deposits. LN: lymph nodes; RCC: renal cell carcinoma; TKI: tyrosine kinase inhibitor.