



Comparison of Renal Cell Cancer Surgery During the COVID-19 Pandemic with Prepandemic Period, Turkey Multicenter Study

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Abstract

Objective: Coronavirus disease-2019 (COVID-19) pandemic changed various priorities in health area. Many elective surgeries for renal cell cancers (RCC) have been postponed. We examined the influence of the COVID-19 pandemic on the surgical treatment of RCC in Turkey.

Materials and Methods: Surgically treated 457 patients for kidney tumor, from March 1, 2019 to February 28, 2021 in 9 centers in Turkey were analyzed retrospectively.

Results: The number of surgical treatments for RCC during the COVID-19 pandemic has decreased significantly, in contrast to the same period before COVID-19. Admission symptoms were similar in these two periods ($p=0.32$). However, although not statistically significant, the rate of admission to hospital due to hematuria was higher during the pandemic period compared to the prepandemic period (14.4% vs 9.8%, respectively). The two study periods differed significantly in terms of the rate of metastatic RCC detected in preoperative imaging (13.1% vs 6.1%, during COVID-19 and pre-COVID-19, respectively) ($p=0.01$). Moreover, the study periods differed significantly in terms of time between imaging and operation [35 (2-240) vs 30 (1-210) days, during COVID-19 and pre-COVID-19, respectively] ($p=0.01$). However, these two periods were similar in terms of tumor size, type of surgery, and pathological stage ($p\geq 0.05$). Although the pathological stages were similar among the groups, nephrectomies due to the metastatic disease were significantly higher in the pandemic period ($p=0.01$).

Conclusion: The number of RCC-related surgeries were significantly decreased during the pandemic period. However, the rate of surgery for metastatic disease has significantly increased.

Keywords: COVID-19 pandemic, RCC, treatment

Introduction

The prevalence of renal cell cancer (RCC) is incrementally rising worldwide. With the increasing use of imaging methods such as ultrasonography (USG) and computed tomography (CT), more than 60% of RCC can often be detected in the early stages when

patients are asymptomatic (1). RCC is the third most common urological cancer. Most of the cases are detected between the ages of 60-70. RCC is more common in men than in women (3:2). Only 10% of RCC patients present with characteristic clinical symptoms consisting of hematuria, palpable abdominal mass, and back or flank pain. Despite the increase in early

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diagnosis, metastatic RCC is detected in imaging methods in 20-30% of patients (2,3). Smoking, obesity, hypertension and/or medications have been implicated as risk factors, but the etiology of RCC is still unclear (4). RCC is divided into different histological types and the most common types are clear cell (70-90%) (5). Tumor-node-metastasis (TNM) classification can be used in RCC staging and surgery is the only viable option for non-metastatic RCC. Partial nephrectomy is the first choice for T1 tumors, while radical nephrectomy is the first choice for T2-4 tumors (6).

A viral syndrome-coronavirus-2 [coronavirus disease-2019 (COVID-19)] strain emerged in the Wuhan region of China in late 2019, initiating a pandemic that affected millions of people worldwide and caused a high number of deaths (7). Healthcare professionals were entrusted to deal with the pandemic, and intensive-care units were used to treat COVID-19 patients. A rapid working group has been formed by the European Association of Urology to establish convenient guidelines to deal with various circumstances and precedences following the COVID-19 outbreak. Within the scope of the COVID-19 pandemic, urological diseases were divided into 4 priority levels: low priority (can be delayed for 6 months), medium priority (can be delayed for 3-4 months), high priority (can't be delayed for more than 6 weeks), and emergency (can't be delayed for more than 24 h) (8).

In terms of RCC treatment, for Bosnian type III and IV cysts as well as T1 tumors it was recommended to postpone under monitoring and for T2 tumors to postpone and keep under close observation. It was suggested that surgery should be performed primarily for T3-T4 tumors. For metastatic RCC, it was recommended to be evaluated for surgery, follow-up, or chemotherapy, depending on the patient's condition (9).

In this study, we investigated whether there was a difference in the number of RCC operations, pathologies, and surgical preferences in 9 different centers in Turkey between the 1-year period before and during the COVID-19 pandemic. We also examined how the COVID-19 pandemic affected the diagnosis and treatment of RCC.

Materials and Methods

The study was conducted after approval from the Ethical Review Committee of Afyonkarahisar Health Science University, Afyonkarahisar, Turkey (date: 16.04.2021, reference code: 2011-KAEK-2 2021/292). Nine centers from various regions of Turkey were included in this study. The data of 457 patients who underwent surgery for kidney tumors between March 1, 2019 and February 28, 2021 were retrospectively analyzed. The period between March 1, 2019 and February 28, 2020 was defined as the 1-year period before COVID-19. The period between March 1, 2020 and February 28, 2021 was defined as a 1-year period during COVID-19. In the one-year period before COVID-19 and in the one-year period COVID-19, the number of operations for RCC, the age, gender of the patients, symptoms at presentation, tumor size and presence of distant metastases on imaging, time between imaging and operation, type of surgery, pathological tumor size and stages were evaluated and compared. 4 patients who were operated during the COVID-19 period and 8 patients

who were operated during the pre-COVID-19 period, whose pre-operative images and Histopathology could not be reached, were excluded.

Statistical Analysis

All the data was analysed using the Statistical Package for the Social Sciences, version 15.0 (SPSS Inc. Chicago, Illinois). Any $p < 0.05$ was accepted as significant. Kolmogorov-Smirnov test was used to assess the distribution of continuous variables. Since the variables were non-normally distributed, Mann-Whitney U test for continuous and Pearson's chi-square for categorical variables were preferred for comparing these two groups.

Results

Of the 457 patients included in the study, 290 (63.5%) were male and 167 (36.5%) were female. The median age of the patients was 61 (19-86). Ages for the 25-50-75 percentiles were 52-61-69 respectively. A renal mass was detected incidentally in 221 (48.4%) patients. It was observed that 184 (40.2%) patients applied with the complaint of pain, 52 (11.4%) patients applied with the complaint of hematuria and were operated due to the detection of a mass in the kidney. The median tumor size in preoperative imaging methods was calculated 50 mm (10-180). Tumor sizes for the 25-50-75 percentiles were 35-50-72 respectively. Distant metastasis was detected in 39 (8.5%) patients. The time elapsed between imaging and operation median was 31 days (1-240). The time between imaging and operation for the 25-50-75 percentiles were 15-31-62, respectively. Open partial nephrectomy was performed in 135 (29.5%) patients, open radical nephrectomy in 157 (34.4%) patients, laparoscopic partial nephrectomy in 31 (6.8%) patients, and laparoscopic radical nephrectomy in 134 (29.3%) patients. Tumor pathologies were as following: clear cell RCC in 294 (64.3%) patients, papillary RCC in 56 (12.3%) patients, chromophobic RCCs in 39 (8.5%) patients, and other types in 68 (14.9%) patients. The median tumor size of the pathological specimens was 50 mm (10-200). Tumor size of pathological spesmen for the 25-50-75 percentiles were 35-50-72 respectively. Staging was as follows: 249 (54.5%) patients were diagnosed with stage 1, 78 (17.1%) patients at stage 2, 75 (16.4%) patients at stage 3, and 55 (12%) patients with stage 4 kidney tumors. Table 1 shows the socio-demographic characteristics of the patients included in the study.

Among all patients, 160 (35.01%) were in group 1 (operated during 1-year period amid COVID-19) and 297 (64.99%) were in group 2 (operated during period of 1-year before COVID-19). The number of surgeries was significantly lower in the COVID-19 period ($p < 0.001$). Median age was statistically similar between the groups [60 (19-80) and 61 (21-86) respectively] ($p = 0.31$). Twenty-three (14.4%) patients who applied with the complaint of hematuria were in group 1 and 29 (9.8%) were in group 2. Although there was no statistical difference, the percentage of applications due to hematuria during the COVID period increased compared with the pre-COVID period. In the preoperative imaging, tumor median size was 45 (10-180) mm in group 1 and 50 (12-180) mm in group 2, and the difference was not statistically significant ($p = 0.21$). In the preoperative evaluation,

metastasis was significantly higher in group 1 [21 (13.1%) vs 18 (6.1%), $p=0.01$]. There was a significant difference among the groups in terms of time between imaging and operation [35 (2-240) days vs 30 (1-210) days, respectively] ($p=0.01$). However, the difference among these groups in terms of surgery type was not statistically significant ($p=0.13$). Moreover, no statistical difference was found between the groups in terms of the tumor median sizes measured in the pathology specimens [50 (10-200) mm vs 48 (12-200) mm, respectively] ($p=0.73$). Lastly, no significant difference was observed among the groups in terms of pathological stage ($p=0.16$). Metastasis was detected in preoperative imaging in 21 of 22 patients with stage 4 RCC during the period of COVID-19. In the pre-COVID-19 period, metastases were detected in 18 of 33 patients with stage 4 RCC on preoperative imaging. Although tumor size and stage did not change, an increase was observed in the number of

surgeries for metastatic disease. Table 2 compares the data of operations performed for RCC in the 1-year period during and pre-COVID-19.

Discussion

In this article, we found that the number of surgeries for RCC decreased significantly during the COVID-19 period, but the number of surgeries for metastatic disease increased.

RCC is more common in males than in females (1). In our study, 63.5% of the patients were male and 36.5% were female, which was consistent with the literature. RCC is especially common among the 60-70 age group (3). The median age of our patients was 61 (19-86) years, which was similar to the literature.

More than 50-60% of RCCs are detected incidentally in USG evaluation for other reasons (2,3). Incidental RCCs were detected in 48.4% of the patients in our study. The rate of stage 1 RCC according to TNM staging Chang et al. (10) found 54.9%, while Chen et al. (11) they found it to be 69.8%. Because of the increased use of USG and CT over the years, it is expected that the incidence of incidental diagnosis will increase, which in turn increases the incidence of early-stage RCC. In our study, since the number of patients diagnosed incidentally (48.4%) was lower than expected, the rate of stage 1 RCC (54.5%) was also lower compared to other stages.

During the pandemic, active monitoring was recommended at 6-12 months intervals for kidney tumor masses below 4 cm. Patients with more advanced renal tumors, such as T2, T3, or

Gender	Number %	
Male	290	63.5
Female	167	36.5
Group	Number %	
Group 1 (During COVID-19)	160	35.01
Group 2 (Pre-COVID-19)	297	64.99
Median age	61 (19-86)	
Admission symptom	Number %	
Incidental	221	48.4
Pain	184	40.2
Hematuria	52	11.4
Median tumor size on imaging (mm)	50 (10-180)	
Distant metastasis	Number %	
Absent	418	91.5
Present	39	8.5
Median time between imaging and operation (day)	31 (1-240)	
Type of renal surgery	Number %	
Open partial nephrectomy	135	29.5
Open radical nephrectomy	157	34.4
Laparoscopic partial nephrectomy	31	6.8
Laparoscopic radical nephrectomy	134	29.3
Pathological tumor type	Number %	
Clear Cell RCC	294	64.3
Papillary RCC	56	12.3
Chromophobic RCC	39	8.5
Other pathological types	68	14.9
Median pathological tumor size (mm)	50 (10-200)	
Pathological stage	Number %	
Stage 1	249	54.5
Stage 2	78	17.1
Stage 3	75	16.4
Stage 4	55	12

COVID-19: Coronavirus disease-2019, RCC: Renal cell cancers

	Group 1	Group 2	p-value
Number of patients	160	297	$p<0.001$
Median age	60 (19-80)	61 (21-86)	$p=0.31$
Admission symptom			
Incidental	76 (47.5%)	145 (48.8%)	$p=0.32$
Pain	61 (38.1%)	123 (41.4%)	
Hematuria	23 (14.4%)	29 (9.8%)	
Median tumor size on imaging (mm)	45 (10-180)	50 (12-180)	$p=0.21$
Metastasis	21 (13.1%)	18 (6.1%)	$p=0.01$
Median time between imaging and operation (day)	35 (2-240)	30 (1-210)	$p=0.01$
Type of renal surgery			
Open partial	49 (30.6%)	86 (29%)	$p=0.13$
Open radical	47 (29.4%)	110 (37%)	
Laparoscopic partial	16 (10%)	15 (5.1%)	
Laparoscopic radical	48 (30%)	86 (29%)	
Median pathological tumor size (mm)	50 (10-200)	48 (12-200)	$p=0.73$
Pathological stage			
Stage 1	76 (47.5%)	173 (58.2%)	$p=0.16$
Stage 2	30 (18.8%)	48 (16.2%)	
Stage 3	32 (20%)	43 (14.5%)	
Stage 4	22 (13.7%)	33 (11.1%)	

COVID-19: Coronavirus disease-2019

T4 should be evaluated carefully as they are at risk of metastasis. Early treatment should be preferred if there are imaging findings showing aggressive features and if renal biopsy has been performed and aggressive features were detected (12). Lei et al. (13) reported 20% mortality after surgery, among the patients whose tests were positive for COVID-19 and without symptoms. However, in another study conducted during the COVID-19 pandemic, it was reported that surgical procedures can be performed safely without the development of COVID-19-related mortality if adequate precautions are taken (14).

RCC consists of a heterogeneous group of diseases. While treatment of some RCC tumors that do not show aggressive features can be safely postponed, treatment of RCC with aggressive features should be given a priority. Therefore, a risk-based approach should be made for patients with RCC during the pandemic (15). In our study, 297 (65%) patients were operated for RCC in the 1-year period before COVID-19, and 160 (35%) were operated in the 1-year period during COVID-19. The number of surgeries for RCC during the COVID-19 period have decreased drastically.

The classic symptom triad, which presents as gross hematuria, palpable abdominal mass, and flank pain, is rarely seen in RCC. However, hematuria is an important finding in terms of diagnosis and treatment (3). Lee et al. (16) reported that patients with symptomatic symptoms such as pain and hematuria showed aggressive histology and a poor prognosis. In our study, although there was no significant difference in terms of admission complaints between the two study periods, the rate of patients presenting with hematuria was found to be higher in the COVID-19 period compared in the pre-COVID-19 period (14.4% vs. 9.8%). Although patients can neglect or delay seeking medical help pain, hematuria is a finding that is noticed by the patient and urges them to seek medical attention. Therefore, we found that the rate of admission due to hematuria was observed more frequently throughout the pandemic.

In the study that they compared the prepandemic and COVID-19 period, Srivastava et al. (17) reported that postponing surgery for 3 or more months after diagnosis did not increase the risk of tumor progression and tumor size in localized RCC. In our study, the median time between diagnosis and surgery was 30 (1-210) days in the pre-pandemic, and 35 (2-240) days during the COVID-19 period, and the difference among these groups was significant. However, the pathological tumor size and tumor stage were statistically similar in these two periods.

In the review by de Simone et al. (18), they suggested that open surgery should be preferred instead of laparoscopy if adequate precautions cannot be taken in terms of the risk of airborne transmission throughout the COVID-19 period. To our knowledge, there are no studies comparing open surgery to laparoscopic surgery in terms of the possibility of transmission of a virus during the operation. The recommendation for open surgery over laparoscopy is solely based on expert opinion (19). In our study, there was no difference in open and laparoscopic surgery rates between the two study periods.

Although there is an increase in the early diagnosis of RCC, metastasis may be detected at first diagnosis in almost one-third of patients (20). It should be kept in mind that as the RCC tumor

size increases, the possibilities of detecting metastases and the development of metastases in the future are higher (21). In localized RCC, after a surgical treatment, metastasis is detected in 30% of patients in the later stages (22). In our study, there was no significant difference between pre-COVID-19 period and the COVID-19 period in terms of tumor sizes in imaging. Metastasis was not detected in 418 (91.5%) patients in the imaging methods performed at the time of diagnosis. However, distant organ metastases were detected in 39 (8.5%) patients. There was a significant difference between the two study periods in terms of metastases detected in pre-operative imaging [21 (13.1%) vs 18 (6.1%) patients, in groups 1 and 2, respectively]. Although the number of metastatic patients was similar in both periods, the rate of metastatic patients was higher in the COVID-19 period due to the lower number of operated patients in that period. We think that this is due to the earlier admission due to metastatic disease symptoms.

In their study of RCCs smaller than 4 cm, Uzosike et al. (23) found that the mean tumor size increased by 0.09 cm per year during delayed treatment in RCC. They also reported that the increase was 0.54 cm in the group followed for less than 6 months, 0.07 cm in the group followed for more than 1 year. Moreover, no metastatic disease developed in any patient, no significant difference was found in growth rates, and the variability of tumor growth rates decreased over time (23). In Uzosike et al.'s (23) study, the tumor sizes increased more in the group of patients followed for less than 6 months, and therefore, earlier surgery was performed instead of follow-up in these rapidly growing tumors, therefore we believe that their grouping was not homogeneous. Daugherty et al. (24) found the rate of metastasis at the time of diagnosis to be 4% in RCC below 5 cm. They reported that tumor size is the main factor in decision making, but the risk of metastasis is different for each mass depending on the tumor histology. Kim et al. (25) compared waiting periods of less than 3 months and less than 1 month in RCC over 7 cm and concluded that there was no difference between the two groups in terms of overall survival and disease-related survival. Although it was not significant, they found the pathological upstage to be higher in the group with a longer waiting period. However, they excluded patients who waited longer than 3 months (25). In the literature, most studies were retrospective and clinicians seem to be more selective and turn to early surgery for RCC patients who appear to have more aggressive and fast-growing tumors. In our study, when the period between the COVID-19 period and the period before it is compared, there is an increase in the time between diagnosis and treatment, but it is seen that this increase is too short to increase tumor size and stage. This decrease in the number of surgeries for RCC is a situation that may increase the number of newly diagnosed patients, tumor sizes, advanced stage tumors and metastatic disease in the future.

Study Limitations

This study had some limitations. Due to the retrospective design of the study, all patients whose data were thought to be incomplete or inaccurate had to be excluded from this study. Another limitation is the unknown number of patients for whom follow-up is recommended because of low tumor size.

Conclusion

The COVID-19 pandemic has affected the practice of the diagnosis and management of RCC. There has been a decrease in the number of operations performed for RCC. The time between imaging and operation increased. There has been an increase in the rate of surgery for metastatic disease. An increase in the rate of advanced and metastatic diseases should be expected in the future.

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Ethics

Ethics Committee Approval: The study was conducted after approval from the Ethical Review Committee of Afyonkarahisar Health Science University, Afyonkarahisar, Turkey (date: 16.04.2021, reference code: 2011-KAEK-2 2021/292).

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