Comparison of renal cell cancer surgery during Covid-19 pandemic with prepandemic period, Turkey multicenter study

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Abstract

Aim COVID-19 pandemic changed the priorities in medical field. Many elective surgeries for renal cell cancers (RCC) have been postponed. In this study, we aimed to examine the effects of the COVID-19 pandemic on the surgical treatment of RCC in Turkey. Methods 457 patients that underwent surgery for kidney tumor in the 2-year period between March 1, 2019 and 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 compared to the same period before COVID-19. No significant differences were found between the two periods in terms of admission symptoms (p=0.32). However, while the rate of application due to hematuria was 6.1% in the pre-COVID-19 period, it was 13.1% during the COVID-19 period. Despite not being significant, this difference was still proportional. 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 (55.98±51.02 vs 40.30±34.9 days, during COVID-19 and pre-COVID-19, respectively) (p=0.01). However, there was no significant difference between the two periods in terms of tumor size, type of surgery, and pathological stage (p>0.05). Conclusion There was a significant decrease in the number of RCC-related surgeries over 1-year period during the pandemic. However, the rate of surgery for metastatic disease increased. Covid-19 is a pandemic that continues to affect the whole world. Oncological diseases are negative affected in this process in terms of early diagnosis and treatment.

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ABSTRACT

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Methods

457 patients that underwent surgery for kidney tumor in the 2-year period between March 1, 2019 and February 28, 2021 in 9 centers in Turkey were analyzed retrospectively.

Results

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Conclusion

There was a significant decrease in the number of RCC-related surgeries over 1-year period during the pandemic. However, the rate of surgery for metastatic disease increased.

What's Known?

Covid-19 is a pandemic that continues to affect the whole world. Oncological diseases are negative affected in this process in terms of early diagnosis and treatment.

What's New?

Due to the Covid-19 pandemic, the diagnosis of renal cell carcinoma incidentally diagnosed is decreasing. There are serious reductions in the number of surgeries performed for RCC. It is likely that there will be an increase in the rates of advanced and metastatic RCC in the following periods.

INTRODUCTİON

The incidence of renal cell cancer (RCC) is increasing 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. Nowadays, the incidence of RCC varies more than 10 times worldwide, and is higher in Western countries than in Asian countries.[1] The fact that more than 60% of the cases are seen in developed countries supports this notion.[2] RCC is the third most common urological cancer. Most of the cases are detected between the ages of 60-70.[3] RCC is more common in men than 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 diagnosis, metastatic RCC is detected in imaging methods in 20-30% of patients.[2]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. The most common types are clear cell (70-90%), papillary (10-15%), and chromophobe (3-5%) RCCs. Tumor type is known to have prognostic significance.[5] The tumor-node-metastasis (TNM) system is used in RCC staging and only curative treatment for localized RCC is surgery. Partial nephrectomy is the first choice for T1 tumors, while radical nephrectomy is the first choice for T2-4 tumors.[6]

A viral SARS-CoV-2 (COVID-19) strain emerged in the Wuhan region of China in late 2019, initiating a global pandemic that affected millions of people worldwide and caused a high number of deaths.[7] Healthcare professionals were deployed to combat the pandemic, and intensive care units and other units were used to treat COVID-19 patients. Rapid working group has been formed by the European Association of Urology (EAU) to develop adaptive guidelines for dealing with various situations and priorities 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 hours).[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 evaluate for surgery, follow-up, or chemotherapy, depending on the patient's condition.[9]

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

MATERIALS AND METHODS

Local ethics committee aproval was obtained before the study. Nine centers from various regions of Turkey were included in the study. The data of 457 patients that underwent surgery for kidney tumor in the 2-year period between March 1, 2019 and February 28, 2021 were retrospectively analyzed. The period between March 1, 2019 and February 28, 2020 was defined as 1-year period before COVID-19. The period between March 1, 2020 and February 28, 2021 was defined as 1-year period during COVID-19.

STATISTICAL ANALYSES

Statistical analyses were done with IBM SPSS (Statistical Package for the Social Sciences) version 15.0 program. The conformity of the variables to the normal distribution was examined using the Kolmogorov-Smirnov (K-S) test. It was observed that all parameters showed non-normal distribution and were analyzed by using non-parametric tests. The Mann-Whitney U test was used to compare paired groups. Pearson's Chi-square test was used for multivariate comparisons. Results were considered statistically significant when $p<0.05$.

RESULTS

Of the 457 patients included in the study, 290 (63.5%) were male and 167 (36.5%) were female. The mean age of the patients was 59.68±12.54 (19-86). 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 mean tumor size in preoperative imaging methods was calculated as 59.64±32.48 mm (10-180). Distant metastasis was detected in 39 (8.5%) patients.The time elapsed between imaging and operation was 45.79±41.89 days (1-240). 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 RCC in 39 (8.5%) patients, and other types in 68 (14.9%) patients. Tumor size of pathological specimens was 58.36±33.25 mm (10-200). Staging was as follows: 249 (54.5%) patients were diagnosed as stage 1, 78 (17.1%) patients as stage 2, 75 (16.4%) patients as stage 3, and 55 (12%) patients as 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). There was no significant

difference between the two groups in terms of mean age (59.05±11.81 years and 60.02±12.92, 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 to the pre-COVID period. In the preoperative imaging, tumor size was 58.21±33.16 mm in group 1 and 60.41±32.13 mm in group 2, and there was no significant difference between the two groups (p=0.21). Preoperative evaluation in terms of metastasis showed that it was detected in 21 (13.1%) patients in group 1 and in 18 (6.1%) patients in group 2, and this difference between the groups was significant (p=0.01). There was a significant difference between the groups in terms of time between imaging and operation (55.98±51.02 days vs 40.30±34.9 days, respectively) (p=0.01). However, no significant difference was found between the two groups in terms of the type of performed surgery (p=0.13). Moreover, no statistical difference was found between the groups in terms of the tumor sizes measured in the pathology specimens (57.86±31.52 mm vs 58.64±34.21 mm) (p=0.73). Lastly, no significant difference was found between the groups in terms of pathological stage (p=0.16). Table 2 compares the data of operations performed for RCC in the 1-year period during and pre-COVID-19.

DISCUSSION

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 mean age of our patients was 59.68±12.54 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 RCC was detected in 48.4% of the patients in our study. The rate of Stage 1 RCC according to TNM staging Chang et al. found 54.9%, while Chen et al. they found it to be 69.8%.[10,11] As a result 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%) were 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 month intervals for kidney tumors masses below 4 cm. Patients with more advanced renal tumors such as T2, T3, or 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 a renal biopsy has been performed and aggressive features were detected.[12] Lei et al. reported that the mortality rate of asymptomatic patients who tested positive for COVID-19 after surgery was 20%.[13] On the other hand, 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. reported that patients with symptomatic findings such as pain and hematuria showed aggressive histology and a worse prognosis.[16] In our study, although there was no significant difference in terms of admission complaints between two study periods, the rate of patients presenting with hematuria was found to be higher in the COVID-19 period compared to the pre-COVID-19 period (14.4% vs. 9.8%). Although patients can neglect or delay seeking medical help for 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 increased during the COVID-19 period.

In their study comparing the COVID-19 period to the same period before the pandemic, Srivastava et al. 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.[17] In our study, while the mean time between diagnosis and surgery was 40.3±34.9 days in the pre-COVID-19 period, it was 55.98±51.02 days during the COVID-19 period, and this difference between the two groups was significant. However, there was no significant difference in pathological tumor sizes and tumor stages between two periods.

In the review by Simone et al., 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 during the COVID-19 pandemic.[18] To our knowledge, there are no studies comparing open surgery to laparoscopic surgery in terms of possibility of transmission of a virus during the operation. The recommendation for open surgery over laparoscopy is based solely 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 early diagnosis of RCC, metastasis is detected at the time of initial 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, metastases are 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 the 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 two study periods in terms of metastases detected in the pre-operative imaging (21 (13.1%) vs 18 (6.1%) patients, in groups 1 and 2, respectively). Although the numerical values of metastatic patients were close to each other in both study periods, the rate of metastatic patients was higher in the COVID-19 study period due to the lower number of operated patients in that period. We think that this is because patients applied due to metastasis-related symptoms.

In their study of RCCs smaller than 4 cm Uzosike et al. 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 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. Doughtery et al. 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.[24] Kim et al. 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.

CONCLUSION

A temporary reduction in the incidence of RCC and especially early stage RCC should be expected as a result of the decrease in the frequency of incidentally detected RCC due to the decline in hospital admissions during the COVID-19 pandemic, stay-at-home orders, postponement of all non-emergency surgeries, and the fact that healthcare professionals were busy managing the pandemic. However, a proportional increase in the rate of symptomatic patients and metastatic patients should be expected in this period due to recommendations for patients experiencing concerning symptoms to continue applying to hospitals. After the COVID-19 pandemic, it is possible to encounter higher rates of advanced stage RCCs and metastatic RCCs. Since the COVID-19 pandemic is still ongoing and its end cannot be predicted, the importance of early surgical

treatment should be kept in mind by comparing the risk-benefit ratio in cancers such as RCC that have high metastasis rates at the time of diagnosis and after curative surgery.

Table 1: Patients' socio-demographic characteristics

Gender	**Number %**
Male Female	290 63.5 167 36.5
Group	**Number %**
Group 1 (During COVID-19) Group 2 (Pre-COVID-19)	160 35.01 297 64.99
Mean Age	59.68±12.54 (19-86)
Admission symptom	**Number %**
Incidental	221 48.4
Pain	184 40.2
Hematuria	52 11.4
Tumor Size on Imaging	59.64±32.48 mm (10-180)
Distant Metastasis	**Number %**
Absent	418 91.5
Present	39 8.5
Time between imaging and operation	45.79±41.89 days (1-240)
Type of Surgery Performed	**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 RHK	39 8.5
Other Pathological Types	68 14.9
Pathological Tumor Size	58.36±33.25 mm (10-200)
Pathological Stage	**Number %**
Stage 1	249 54.5
Stage 2	78 17.1
Stage 3	75 16.4
Stage 4	55 12

Table 2: Comparison of perioperative data between group 1 (during COVID-19) and group 2 (Pre-COVID-19)

	Group 1 (160)	Group 2 (297)	p
Age	59.05±11.81	60.02±12.92	p=0.31
Admission symtom	76 (%47.5) 61 (%38.1) 23 (%14.4)	145 (%48.8) 123 (%41.4) 29 (%9.8)	p=0.32
Incidental Pain Hematuria			
Tumor size on imaging	58.21±33.16	60.41±32.13	p=0.21
Metastasis	21 (%13.1)	18 (%6.1)	**p=0.01**
Time between imaging and operation	55.98±51.02	40.30±34.9	**p=0.01**
Operation type	49 (%30.6) 47 (%29.4) 16 (%10) 48 (%30)	86 (%29) 110 (%37) 15 (%5.1) 86 (%29)	p=0.13

Open partial Open radical Laparoscopic partial Laparoscopic radical			
Pathological Tumor Size	57.86±31.52	58.64±34.21	p=0.73
Pathological Stage	76 (%47.5) 30 (%18.8) 32(%20) 22 (%13.7)	173(%58.2) 48 (%16.2) 43 (%14.5) 33 (%11.1)	p=0.16
Stage 1 Stage 2 Stage 3 Stage 4			

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