Characteristics of renal cell carcinoma in Saudi patients below the age of 50 years

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Abstract

Background: The incidence of renal cell carcinoma (RCC) in young adults has started to increase in recent years.

Objectives: The objective of the study was to describe and compare the mode of presentation, incidence, risk factors, histopathological features, nephrectomy modalities used, and outcome in patients diagnosed with RCC below the age of 50.

Materials and Methods: A total of 139 confirmed RCC patients diagnosed below the age of 50 years who underwent nephrectomy from January 1990 to April 2019 were included in this retrospective review. We compared the characteristics of two age groups (≤40 years and 41–50 years) and evaluated incidentally discovered versus symptomatic tumors in patients below 50 years.

Results: Loin pain contributed to most symptomatic presentations in the older group (55%) (P = 0.014). Hypertension and diabetes were present in 24% of patients from 41 to 50 years of age versus 3.8% for hypertension and 5.7% for diabetes in the young group. (P = 0.001 and P = 0.004, respectively). Chromophobe was the second most common pathology (26.5%). Tumor size tended to be larger in the older group (P = 0.006). Fuhrman's grade was significantly lower in incidentally diagnosed patients (88.2%) (P = 0.006). The T stage was significantly lower in the incidental group (P = 0.005), but the mortality rate was higher in symptomatic patients (9.6%) (P = 0.013).

Conclusion: RCC increases after the age of 40–50 years in the presence of other risk factors. Chromophobe represented almost a quarter percentage of the pathology, while partial nephrectomy yielded a better outcome.

Keywords: Incidence, partial nephrectomy, radical nephrectomy, renal cell carcinoma, young adults

INTRODUCTION

In Saudi Arabia, kidney tumor incidence and its associated mortality account for 3.4% and 2.4% of the population, respectively, favoring male gender and elderly individuals. Approximately 85% of kidney tumors are renal cell carcinoma (RCC). RCC can be histologically subdivided into the clear cell, papillary, and chromophobe, representing more than 90% of all RCC cases.
The average age for RCC incidence is 61 years, with only a minor percentage (5%) in the younger age group. Variations of causes, risk factors, clinical and pathological presentations, recurrence, and prognosis among the young group require clarification.

This study aims to determine the incidence, characteristics, and prognosis of RCC among patients below 50 years in Saudi Arabia.

MATERIALS AND METHODS

This study was conducted in a tertiary hospital in Riyadh, Saudi Arabia. We retrospectively reviewed the data records of all RCC patients between the ages of 20 and 50 years who were pathologically diagnosed with RCC and underwent open, laparoscopic, or robotic-assisted partial or radical nephrectomy surgery from January 1990 to April 2019. We included adult patients with primary RCC between the ages of 18 and 50 years. Any patient who did not have a confirmed pathological report of RCC was excluded.

Data, including age, sex, body mass index, nephrectomy type and date, mode of presentation, past medical history, histological, and pathological characteristics, were collected. Histopathology report based on biopsy obtained after performing the nephrectomy by any surgical mean included Fuhrman grade; primary tumor, nodal involvement, and metastatic involvement (TNM) stage of the lesion; and tumor size, which was recorded as the longest dimension of the lesion measured on pathologic examination. All RCCs were staged according to the American Joint Commission on Cancer 1997 TNM staging system and graded using the Fuhrman grading system. The patient follow-up for recurrence, site of recurrence, and death rate were obtained from medical charts.

Descriptive data are presented as mean (standard deviation) or median (interquartile range) for continuous variables and n (%) for categorical variables. \( P < 0.05 \) was considered statistically significant. Statistical analysis was performed using the IBM Corp., Released 2016, IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.

RESULTS

Table 1 shows the demographic data of the patients along with a comparison of the younger age group (≤40 years) and older age group (41–50). A total of 139 patients were included in the study, with a male-to-female ratio of almost 2:1. The mean age at diagnosis was 42 ± 7 and ranged from 20 to 50 years. The age group ≤40 was 53 patients (38.1%), and age group from 41 to 50 was 86 patients (61.9%) of the included population. The majority of patients were male (59.7%).

The RCC cases were divided into six groups, each representing 5 years, from 1990 to 2019. The distribution of RCC cases was as follows: 1990–1994, 7 cases (5%); 1995–1999, 11 cases (7.9%); 2000–2004, 14 cases (10.1%); 2005–2009, 19 cases (13.7%); 2010–2014, 45 cases (32.4%); and 2015–2019, 43 cases (30.9%). RCC incidence was found to be significantly increased over the years, particularly in the older group (41–50) \( (P < 0.031) \).

Nearly 50% of the patients were obese, and 35.4% were overweight. Regarding risk factors, 24 (17.3%) of the total patient population had diabetes, 23 (16.5%) had hypertension, and 12 were smokers (15%). In an age comparison, diabetes was significantly associated with the older age group between 40 and 50 years (24.4%), while it was present in only 5.7% of the younger patients \( \leq 40 \) years \( (P < 0.004) \). Furthermore, the incidence of hypertension was significantly increased in the older group, representing 24.4%, while only observed in 3.8% of the younger patients \( (P < 0.006) \).

About 93 (71%) underwent radical nephrectomy, and 75 (55.1%) were symptomatic, with an increase in symptomatic presentation in the older group. Symptomatic patients presented with loin pain (44.1%), followed by hematuria (18.6%). Comparing the symptoms at presentation between the two groups, loin pain was significantly associated with patients over the age of 41–50, representing 55% \( (P < 0.014) \). However, hematuria was more prevalent in younger patients (31.6%), while in the older age group, it was only (12.5%).

The histopathology report revealed that 25% of patients had tumors invading the renal sinus, and 12% had lymphovascular invasion, while only 1.7% of the patients had tumors reaching the collecting system. Furthermore, RCC histology subtypes were mostly clear cell carcinoma (66.2%), followed by chromophobe (26.5%), papillary carcinoma (6.6%), and unclassified RCC was 0.7%. Patients were mostly diagnosed as pT1 stage (56.4%), followed by T3 (23.3%). Only 2.4% of patients had metastasis to the lymph node and nodal metastasis (42.7%). Metastasis was not identified in the vast majority of patients (67.5%), while M0 accounted for 28.9%, and M1 accounted for 3.6% of all patients. The Fuhrman grade was low in 75.7% of patients, and 10.5% had a positive surgical margin.
Table 1: Demographic data and comparison between younger group (≤40) and older group (41-50)

| Variables                          | n (%): ≤40, n (%): 41-50 | P       |
|------------------------------------|--------------------------|---------|
| Gender                             |                          |         |
| Female                             | 56 (40.3)                | 24 (45.3) | 32 (37.2) | 0.346 |
| Male                               | 83 (59.7)                | 29 (54.7) | 54 (62.8) |       |
| RCC cases in 5 years interval      |                          |         |
| 1990-1994                          | 7 (5.0)                  | 2 (3.8)  | 5 (5.8)  | 0.031* |
| 1995-1999                          | 11 (7.9)                 | 9 (17.0) | 2 (2.3)  |       |
| 2000-2004                          | 14 (10.1)                | 7 (13.2) | 7 (8.1)  |       |
| 2005-2009                          | 19 (13.7)                | 5 (9.4)  | 14 (16.3)|       |
| 2010-2014                          | 45 (32.4)                | 17 (32.1)| 28 (32.6)|       |
| 2015-2019                          | 43 (30.9)                | 13 (24.5)| 30 (34.9)|       |
| Smoking                            |                          |         |
| No                                 | 68 (85.0)                | 27 (79.4)| 41 (89.1)| 0.229 |
| Yes                                | 12 (15.0)                | 7 (20.6) | 5 (10.9) |       |
| BMI                                |                          |         |
| Underweight                        | 0                        | 0        | 0        | 0.179 |
| Normal                             | 12 (14.6)                | 7 (24.1) | 5 (9.4)  |       |
| Overweight                         | 29 (35.4)                | 10 (34.5)| 19 (35.8)|       |
| Obese                              | 41 (50.0)                | 12 (41.4)| 29 (54.7)|       |
| Nephrectomy type                   |                          |         |
| Radical                            | 93 (71.0)                | 35 (71.4)| 58 (70.7)| 0.932 |
| Partial                            | 38 (29.0)                | 14 (28.6)| 24 (29.3)|       |
| Procedure type                     |                          |         |
| Open                               | 69 (51.5)                | 28 (54.9)| 41 (49.4)| 0.688 |
| Laparoscopy                        | 56 (41.8)                | 19 (37.3)| 37 (44.6)|       |
| Robotic                            | 9 (6.7)                  | 4 (7.8)  | 5 (6.0)  |       |
| Clinical presentation              |                          |         |
| Symptomatic                        | 75 (55.1)                | 23 (45.1)| 52 (61.2)| 0.068 |
| Incidental                         | 61 (44.9)                | 28 (54.9)| 33 (38.8)|       |
| Hematuria                          |                          |         |
| No                                 | 48 (81.4)                | 13 (68.4)| 35 (87.5)| 0.079 |
| Yes                                | 11 (18.6)                | 6 (31.6) | 5 (12.5) |       |
| Loin pain                          |                          |         |
| No                                 | 33 (55.9)                | 15 (78.9)| 18 (45.0)| 0.014*|
| Yes                                | 26 (44.1)                | 4 (21.1) | 22 (55.0)|       |
| Hypertension                       |                          |         |
| No                                 | 116 (83.5)               | 51 (96.2)| 65 (75.6)| 0.001*|
| Yes                                | 23 (16.5)                | 2 (3.8)  | 21 (24.4)|       |
| Diabetes                           |                          |         |
| No                                 | 115 (82.7)               | 50 (94.3)| 65 (75.6)| 0.004*|
| Yes                                | 24 (17.3)                | 3 (5.7)  | 21 (24.4)|       |
| Histology                          |                          |         |
| Lymphovascular invasion            | 7 (11.9)                 | 2 (10.5) | 5 (12.5) | 0.827 |
| Renal sinus invasion               | 15 (25.4)                | 3 (15.8) | 12 (30.0)| 0.241 |
| Collecting system                  | 117 (1.7)                | 0        | 1 (2.5)  | 0.487 |
| Nature of lesion                   |                          |         |
| Clear cell                         | 90 (66.2)                | 36 (67.9)| 54 (65.1)| 0.822 |
| Papillary                          | 9 (6.6)                  | 4 (7.5)  | 5 (6.0)  |       |
| Chromophobe                        | 36 (26.5)                | 13 (24.5)| 23 (27.7)|       |
| Unclassified RCC                   | 1 (0.7)                  | 0 (0.0)  | 1 (1.2)  |       |
| Surgical margin                    |                          |         |
| Negative                           | 51 (89.5)                | 19 (100.0)| 32 (84.2)| 0.067 |
| Positive                           | 6 (10.5)                 | 0        | 6 (15.8) |       |
| Furhman grade                      |                          |         |
| Low                                | 81 (75.7)                | 33 (84.6)| 48 (70.6)| 0.103 |
| High                               | 26 (24.3)                | 6 (15.4) | 20 (29.4)|       |
| Tumor size (cm)                    |                          |         |
| ≤4                                 | 28 (33.3)                | 14 (48.3)| 14 (25.5)| 0.006*|
| >4 and≤7                           | 27 (32.1)                | 11 (37.9)| 16 (29.1)|       |
| >7 and<10                          | 12 (14.3)                | 4 (13.8) | 8 (14.5) |       |
| ≥10                                | 17 (20.2)                | 0 (0.0)  | 17 (30.9)|       |
| Mortality                          |                          |         |
| No                                 | 130 (94.9)               | 50 (96.2)| 80 (94.1)| 0.599 |
| Yes                                | 7 (5.1)                  | 2 (3.8)  | 5 (5.9)  |       |

Continued...
Regarding tumor size, tumors equal to or <4 cm were present in 33.3% of the cases, followed by >4 to ≤7 cm (32.1%), ≥10 cm (20.2%), and >7 to < 10 cm (14.3%). There was no significant difference in tumor diameter between the young group and the older group, although the younger age group tended to present with smaller tumor size. Tumors sized ≤ 4 cm, >4 to ≤ 7 cm, >7 to <10 cm, and  ≥10 cm were present in 48.3%, 37.9%, 13.8%, and 0% of the younger cases, respectively. However, the majority of the older age group tended to have tumors ≥10 cm at the time of diagnosis (30.9%), followed by tumors sized 4 to ≤7 (29.1%), ≤4 (25.5%), and >7 to <10 (14.5%) \( (P < 0.006) \).

Other variables were not statically significant in the comparison between the two age groups such as nephrectomy type, nature of the lesion, surgical margin, Furman grade, invasion of lymphovascular tissue, renal sinuses, the collecting system, recurrence, mortality, and TNM stage.

In Table 2, we compared incidental versus symptomatic presentation in patients diagnosed with RCC below the age of 50. Most patients (79.4%) presented with symptoms that were managed by radical nephrectomy \( (P < 0.016) \). In comparison to symptomatic patients, incidentally discovered tumors were found to have a low Furhman grade at the time of diagnosis \( (P = 0.006) \). In addition, around 70% of incidentally discovered tumors presented with lower T stage \( (P < 0.005) \). The average mean diameter of incidentally discovered tumors was 5.62 (±3 cm), while the average mean size of symptomatic tumors was 7.50 (±4 cm) \( (P = 0.0178) \). Mortality in incidentally discovered tumors after surgical treatment was \( (90\%) \), whereas, in symptomatic tumors, it was around 10% \( (P < 0.013) \). There were no significant differences in the nature of the lesion between symptomatic and incidental findings.

**DISCUSSION**

This study is the first local study to define the presentation and histopathological features and outcomes of surgical modalities in patients diagnosed with RCC below the age of 50 years.

The incidence of RCC is trending up both globally and locally in recent years, especially in younger age groups.\[1\,7\,9\] One study linked the rise of RCC cases to an increase in the incidence of low risk cancers such as pT1a tumors that can be explained on the basis of ascertainment bias due to the overdiagnosis of small renal masses.\[10\] Other risk factors may be specific genetic and environmental factors along with obesity, smoking, and occupational exposure.\[11\] In addition, the use of advanced radiological modalities in detecting renal masses has contributed to an increased level of incidental findings of RCC, which increases the overall incidence of RCC, especially for tumors measuring 4 cm or less.\[12\,13\] In our study, we found that there was a significant increase in RCC in young patients below the age of 50 years over the past 30 years, especially between the years 2010 and 2019.
There are conflicting reports regarding the presentation of RCC in the literature. Several studies have reported that younger patients are more likely to present symptomatically.\(^{[11,14]}\) In contrast, others study noticed more incidental presentation in the younger group.\(^{[11,14]}\) In our study, approximately 55% of patients in the older group presented with symptoms. There was no statistically significant variation in the presentation in comparison with the younger group. In addition, we found that the older group had a high tendency to present with loin pain, which was reported in another study.\(^{[13]}\) While several studies reported that loin pain was the most common presentation in the young group,\(^{[13]}\) we found hematuria accounted for a higher percentage. This finding is in line with a previous study as well.\(^{[3]}\)

Our study showed an increase in diabetes and hypertension in patients in the 41–50-year age group. A recent meta-analysis and closer scrutiny of the cancer type revealed a close association of RCC with hypertension, which increased to around 20%–30%. In another study, about 500,000 Korean men participated, and it proved hypertension to be a strong and independent risk factor for kidney cancer mortality.\(^{[18]}\) A meta-analysis of 18 studies showed a positive association between diabetes and kidney cancer.\(^{[19]}\) A recent study suggested a significant increase in the risk of RCC among diabetic women. In fact, RCC in patients with Type 2 diabetes shows more DNA alterations when compared with RCC inpatients without Type 2 diabetes.\(^{[20]}\)

Young patients diagnosed with RCC tended to present with low Fuhrman grade tumors. In a study conducted in patients younger than 45 years of age with RCC, tumors with low Fuhrman grade represented almost 75% of the total cases.\(^{[10]}\) Similarly, in our study, most RCC patients below the age of 50 had a low Fuhrman grade (76%). Moreover, in patients below the age of 40 years, approximately 85% of cases had a low Fuhrman grade. In addition, a study reported that younger patients had significantly lower Fuhrman grades than those aged 40–60 years.\(^{[21]}\)

The clear cell subtype was dominant in our study, and no significant difference was found when comparing the two age groups (67.9% vs. 65.1%). This is in line with other studies but with different percentages.\(^{[13,22]}\) The second most common RCC subtype in our study was the chromophobe subtype, accounting for 26%. This was also observed in other studies.\(^{[14,21,23]}\) This is an advantage with regard to prognosis, given that chromophobe has a less aggressive nature and a favorable prognosis.\(^{[24]}\) However, other studies reported that papillary is the second most common histology subtype.\(^{[25,26]}\) Racial variation in the histology subtypes of renal RCC has been addressed in several studies, probably because of differences in multiple RCC prognostic factors.\(^{[45,10]}\)

Based on our results, we observed that the mode of presentation had an impact on the surgical modality that was used to manage the tumor. We found that incidentally diagnosed patients were managed more with partial nephrectomy compared to the group who presented with symptoms. This may be explained by the incidental group in our study presented with low Fuhrman grade, small tumor diameter, and low T stage. Furthermore, the mortality rate was significantly lower in the incidental group than in the symptomatic group [Table 2]. This finding was supported by a meta-analysis conducted in 2016. In this meta-analysis, a total of 21 reviews were included, and a comparison between partial and radical nephrectomy in T1b and T2 was performed. It was found that partial nephrectomy had a better prognosis in terms of renal function and a lower probability of chronic kidney disease. Moreover, they had a lower recurrence rate and lower mortality than their peers who underwent radical nephrectomy.\(^{[27]}\)

**CONCLUSION**

We concluded that RCC surges simultaneously with
hypertension and diabetes after the age of 40 years. Around 27% of young patients with RCC tend to present with chromophobe subtypes, which are less aggressive and have a favorable prognosis. However, clear cell carcinoma still accounts for most RCC cases. Surgical management with partial nephrectomy when feasible yields a lower recurrence rate and increase overall survival.

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Conflicts of interest
There are no conflicts of interest.

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