# The Effect of Female Gender in Renal Cell Carcinomas

**Selahattin Çalışkan, Orhan Koca, Mehmet Akyüz, Metin İshak Öztürk, Muzaffer Oğuz Keleş, and Muhammet İhsan Karaman**

*Department of Urology, Haydarpaşa Numune Training and Research Hospital, Istanbul, Turkey*

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**Abstract-** Renal cell carcinoma accounts 85% of all renal tumors. In this study, we aimed to investigate the clinical and pathological results of female patients with RCCs and compare with male patients. The patients who underwent radical or partial nephrectomy were reviewed retrospectively. The clinical characteristics of male and female patients were analyzed and compared with age, tumor size, histological subtype, Fuhrman nuclear grade, and pathological T stage. There were 266 patients in the study. Of these patients; 181 patients (68.05%) were male and 85 patients (31.95%) were female. The female patients' and male patients' mean ages were 57.09±13.36 and 60.24±10.44 years (*P*=0.007), respectively. Tumor size was smaller in female patients than male patients with statistically significant association (5.69±3.20 and 6.97±3.67, *P*=0.046). According to the histological subtypes, female patients had a greater proportion of chromophobe RCC with 18.82% of the patients. Interestingly, papillary (12.56%) and sarcomatoid differentiation (6.01%) subtypes were predominantly seen in male patients. The proportion of localized disease (pT1-2) was 80% and 74.3% in female and male patients, grade 1 and 2 consist 61.16% and 48.63% of the female and male patients. The female patients with RCC had smaller tumors and presented at younger age than male patients. Further research and epidemiologic studies are needed to define the effect of gender in renal cell carcinomas.

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**Keywords:** Renal cell; Carcinoma; Gender

## Introduction

Renal cell carcinoma (RCC) is the most common malignancy of the kidney that accounts 85% of all renal tumors (1) and 2-3% of all adult malignancies (2). Although the etiology of RCC is not clear, smoking is the most generally accepted environmental risk factor (3). Other factors including obesity, anti-hypertensive therapy, coffee and tea, Western diet (high fat and protein and low fruits and vegetables) may be related to the RCC pathogenesis. However, the detection of small renal masses has been increased because of widespread use of sonography, computed tomography and magnetic resonance imaging techniques in recent years, (4) but one-third of the patients with RCC still present with large, locally advanced or metastatic disease (1).

Renal cell carcinoma is approximately twice as common in men than in women (1). The ratio of male to female is 1.7 in the United States of America (1), 1.37 in Europe (5) and 1.90 in China (3). There are some studies that indicate some reproductive and hormonal factors may be associated with risk of RCC (6,7). An international, multicenter, population-based, case-control study showed an 80% excess risk for six or more birth compared with one birth, and decreasing risk for increasing age at first birth and a suggestive reduction of risk for increasing age at menarche (6). Another cohort study that was included 89835 women showed that parous women had increased risk when compared with nulliparous women and this risk increases with levels of parity (7). The aim of this study was to investigate the clinical and pathological results of female patients with RCCs and compare with male patients.

## Materials and Methods

From January 2004 through November 2015, 307 patients who underwent open radical or partial nephrectomy were reviewed retrospectively. Patients with benign lesions, urothelial carcinoma, metastatic tumor, von Hippel-Lindau syndrome and Birt-Hogg-Dube syndrome were excluded. The patients who were treated with laparoscopic surgery and focal therapies were excluded from the study. Partial nephrectomy was

**Corresponding Author:** S. Çalışkan
Department of Urology, Haydarpaşa Numune Training and Research Hospital, Istanbul, Turkey
Tel: + 90 55 47846552, Fax: +90 36 42230300, E-mail address: dr.selahattin@gmail.com

performed in patients with tumor size ≤7 cm in maximal diameter, exophytic and peripheral localization. After the operation, specimens were examined for tumor size, histological subtype according to 2004 World Health Organization classification (8). Pathological TNM classification, which defines tumor (T), involvement of lymph node (N) and distant metastasis (M) was examined according to the 2009 TNM classification(9),and Furhman nuclear classification (Grade 1, 2, 3 and 4) system was used (10).

The clinical characteristics of male and female patients were analyzed and compared with age, tumor size, histological subtype, Fuhrman nuclear grade, pathological T stage. At our hospital, extended lymphadenectomy is not generally included in routine nephrectomy operations, so comparison of groups with nodal staging did not performed, because of it would not be objective.

The Mann Whitney U and student *t*-tests were used to comparing the groups and $P<0.05$ was considered as a significant difference.

## Results

There were 266 patients in the study. Of these patients; 181 patients (68.05%) were male and 85 patients (31.95%) were female. Two of the male patients had bilateral renal tumors, and nephrectomy specimens were increased to 268. Partial nephrectomy was performed in 51 patients. Of these 51 patients; 19 patients (22.35% of the women) were female and 32 patients (17.67% of the men) were male. The female patients' and male patients' mean ages were 57.09±13.36 and 60.24±10.44 years ($P$=0.007), respectively. Tumor size was smaller in female patients than male patients with statistically significant ($P$=0.046). Comparison of the clinicopathological characteristics by gender is shown in table 1.

**Table 1. Clinicopathological results of the patients**

| | Total | Male | Female | *p* |
|---|---|---|---|---|
| **Patients, n (%)** | 266(100) | 181(68.05) | 85(31.95) | |
| **Mean Age±SD (years)** | 59.24±11.50 | 60.24±10.44 | 57.09±13.36 | *0.007 |
| **Mean Tumor size±SD(cm)** | 6.57±3.57 | 6.97±3.67 | 5.69±3.20 | *0.046 |
| **T stage** | | | | 0.538 |
| **T1** | 154(57.4) | 95(51.9) | 59(69.4) | |
| **T2** | 50(18.6) | 41(22.4) | 9(10.6) | |
| **T3** | 61(22.8) | 45(24.59) | 16(18.8) | |
| **T4** | 3(1.1) | 2(1.1) | 1(1.2) | |
| **Fuhrman Grade** | | | | 0.108 |
| **G1** | 23(8.58) | 11(6.01) | 12(14.11) | |
| **G2** | 118(44.02) | 78(42.62) | 40(47.05) | |
| **G3** | 99(36.94) | 71(38.80) | 28(32.94) | |
| **G4** | 28(10.44) | 23(12.56) | 5(5.9) | |

*$P<0.05$ statistically significant

Histological subtype of the patients is shown in table 2. Female patients had a greater proportion of chromophobe RCC with 18.82% of the patients. Interestingly, papillary (12.56%) and sarcomatoid differentiation (6.01%) subtypes are predominantly seen in male patients. Comparison of the clinicopathological features in female patients with studies was presented in Table 3.

According to the Fuhrman nuclear grade and T stage classification; the proportion of localized disease (pT1-2) is 80% and 74.3% in female and male patients, grade 1 and 2 consist 61.16% and 48.63% of the female and male patients. More than 50% of the male patients had high-grade renal cell carcinoma (Grade 3-4).

**Table 2. Histologic subtypes of the patients with renal cell carcinoma**

| | Total n(%) | Male n(%) | Female n(%) |
|---|---|---|---|
| **Clear cell** | 189 (70.52) | 129 (70.49) | 60 (70.58) |
| **Chromophobe** | 31 (11.56) | 15 (8.19) | 16 (18.82) |
| **Papillary** | 29 (10.82) | 23 (12.56) | 6 (7.05) |
| **Sarcomatoid differantiation** | 12 (4.47) | 11 (6.01) | 1 (1.17) |
| **Others** | 7 (2.44) | 5 (2.73) | 2 (2.35) |

**Table 3. Comparison of the pathological results with the studies**

| | | Studies | | |
|---|---|---|---|---|
| | **Gender** | **Aron *et al* (1)** | **Lee *et al* (11)** | **Present study** |
| **Patients n (%)** | **Male** | 22288 (63.1) | 1069 (70.9) | 181 (68.05) |
| | **Female** | 13048 (36.9) | 439 (29.1) | 85 (31.95) |
| **Tumor size cm ±SD** | **Male** | 6.1±3.8 | 5.2 | 6.97±3.67 |
| | **Female** | 5.9±3.6 | 5.4 | 5.69±3.20 |
| **Clear cell ,%** | **Male** | 85.3 | 84.3 | 70.49 |
| | **Female** | 88.4 | 72 | 70.58 |
| **Chromophobe, %** | **Male** | 2 | 5.2 | 8.19 |
| | **Female** | 2.1 | 12.5 | 18.82 |
| **Papillary, %** | **Male** | 5.6 | 5.6 | 12.56 |
| | **Female** | 3 | 7.1 | 7.05 |
| **Sarcomatoid diff., %** | **Male** | 1 | 3.2 | 6.01 |
| | **Female** | 0.8 | 2.5 | 1.17 |

## Discussion

We found that the female patients consist 31.95% of the patients and male to female ratio was 2.13. This ratio is lower than the study of Lee *et al*., (11) and higher than Chen *et al.*, (3) Pichler *et al*., (5) and Aron *et al*., (1). The authors reported that male to female ratio was 2.44 in the study from Korea (11). There is not enough evidence to explain the gender-specific differences in the incidence of RCC. The age-adjusted incidence rates of RCC in Korean women and men in 2007 were 7.1 and 2.8 per 100000 person-year according to the Korean cancer registry system. Some studies have suggested that some hormonal and reproductive factors such as decreased maternal age at first birth and low parity might be associated decreased risk of RCC (7,12). Additionally, Gago-Dominguez *et al*., (13) reported that women who had undergone hysterectomy were at higher risk for RCC, parity and hormone replacement were not risk factors when adjusted for hysterectomy.

The age at diagnosis in female patients was 62.4, 64.3 and 55.3 years in the study of Aron *et al*., (1) Woldrich *et al*., (14) and Lee *et al*., (11) We found that the age of female patients at diagnosis was 57.09 years which was younger than males. Tumor size is one of the well-known prognostic factors for RCC (8). Comparison of the clinicopathological features in female patients with studies is presented in Table-3. Aron *et al*., (1) reported that female patients were presented with smaller tumors compared to men. Explanation of this situation is not clear, but women are more likely to have incidental detection of tumors during imaging for abdominal or pelvic pathology (1). Additionally, Woldrich *et al*., (14) reported that tumor size among stage I cases was smaller in females than males without significant difference. Chen *et al*., (3) reported that tumor size was 5.69 and 5.77 cm in females and males. On the contrary, in the study by Lee *et al*., (11) female patients were presented with bigger tumor size than male patients (5.4 and 5.2). In the present study, tumor size was significantly smaller in female patients than male patients (5.69 and 6.97).

The other prognostic factors for RCC are anatomical (TNM classification) and histological (Fuhrman grade and histological subtype) characteristics (11).Tumor stage and grade has been frequently re-evaluated, and these factors are considered to be the most important prognostic factors (15). Grade I and II lesions were accounted for 72%, 53.1% and 73% of female patients in the study of Aron *et al*., (1), Lee *et al*., (11) and Woldrich *et al*., (14). This ratio of grade I and II are much more in female patients than in male patients. In our study the 61.16% of the female patients were grade I and II tumors, the proportion of grade I and II tumors is 48.63% of the male patients. Pathological T stages of the female patients are different in the studies. While Chen *et al*., (3) reported that 76.7% and 68.4% of the female and male patients were T1 and 2. Lee *et al*., (11) reported that the ratio of T1 and 2 was much more in male patients with 82% than female patients (81.5%). In the analysis of SEER database for renal cell carcinoma, the localized disease was seen in 71.7% of the female patients and 66% of the male patients (1). We found the proportion of localized disease was 80% and 74.3% in female and male patients.

The histological subtype is another prognostic factor for RCC. There are different results about histological subtype in the literature. Nason *et al*., (16) found that clear cell is the most common RCC with 83% of the patients. Papillary and chromophobe RCC follows the clear cell carcinoma with the proportion of 9.3% and

5.9%. In another study from USA, clear cell RCC is more common in females than males and papillary RCC is seen much more in males (1). Lee *et al*., (11) reported that clear cell and sarcomatoid RCC were much more in male patients and chromophobe and papillary RCC were much more in female patients. The proportion of clear cell RCC was similar in both males and females, while chromophobe RCC is much more in female patients, papillary and sarcomatoid RCC was predominantly seen in males in the present study. Interestingly, the proportion of the clear cell histology is lower in two sexes than the studies. Turkish female patients had a greater chromophobe (18.82%) histology than Western (2.1%) and Korean (12.5%) studies. Chromophobe histology is a good prognostic factor RCC (11), and presence of sarcomatoid differentiation or other histology have been considered as a worse factor for cancer-specific and overall survival (1).

There are some studies examined the gender differences in RCC. The clinicopathological results might be different in the studies. Genetics, lifestyle, smoking, diet, racial and other risk factors with known and unknown may contribute the differences.

The limitations of this study; retrospective design and single-center study, number of the patients are relatively small and there is no data about the survival of the patients. Additionally, we could not access the patients who were diagnosed with RCC but not treated surgical management.

In conclusion, the female patients with RCC have smaller tumors and present at younger age than male patients. The histological subtype is more favorable in female patients. The proportion of organ confined disease is much more in female patients than males. Gender differences in RCC pathology and epidemiology are not fully understood. Further research is needed to define the effect of gender in renal cell carcinoma pathogenesis.

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