# Renal cell carcinoma: Associations between tumor imaging features and epidemiological risk factors

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## ARTICLE INFO

## ABSTRACT

*Purpose:* To investigate associations between imaging features of tumors and age, gender and body mass index (BMI) in patients with renal cell carcinoma.

*Method:* This IRB-approved, HIPAA-compliant study included 1348 patients with histopathologically confirmed renal cell carcinoma of the clear cell subtype (ccRCC, $n = 904$) or non-clear cell subtype ($n = 444$), who underwent pre-treatment CT imaging less than 180 days before nephrectomy between 1999 and 2011. Two radiologists independently, retrospectively analyzed all imaging studies and identified features (necrosis, renal vein invasion, contact with renal sinus fat, multicystic appearance and nodular enhancement), which were then correlated with patient age, gender and BMI at time of surgery.

*Results:* Inter-reader agreement on imaging features ranged from substantial to excellent (kappa: 0.688 to 0.982). In the ccRCC group, multicystic tumor appearance was significantly associated with lower patient age ($p < 0.05$) and lower BMI ($p < 0.05$); the presence of renal vein invasion was significantly associated with lower BMI in males ($p < 0.05$); and both tumor contact with the renal sinus and nodular enhancement were significantly associated with greater patient age ($p < 0.05$). In the non-clear cell RCC group, necrosis was associated with lower BMI for females ($p < 0.05$).

*Conclusions:* This study demonstrated significant associations between imaging features of RCC and patient age and BMI, hinting an influence of these factors on tumor biology and genomic make-up. These findings could aid future studies in selecting patients while investigating genomic, molecular and metabolic variables in RCC and might potentially impact on future stratification and therapy of patients.

## 1. Introduction

Several risk factors have been identified that are potentially responsible for the increasing number of newly-diagnosed renal cell carcinomas [1], among them smoking [2], hypertension [3], age [4], male gender [5] and, especially with regard to the clear cell histopathologic subtype, obesity [6–10]. Though an elevated BMI is considered a major risk factor for the development of kidney cancer and is thought to be the cause of up to 27–40% of all RCCs in the United States [11,12], several independent reports have indicated that outcomes are better in obese patients than in patients of normal weight [13–16]. However, recent studies [17,18] indicate that the protective effect of

obesity extended only to men and not to women. The causes of the paradoxical nature of obesity as both a risk factor and a protective characteristic in men are still unknown but may lie in the genomic make-up of the tumor [19,9].

This underscores that even within individual RCC subtypes, prognosis and clinical behavior vary strongly, and imaging features are similarly diverse: Whereas some tumors show extensive necrosis, cystic components or strong peripheral enhancement, others have a rather homogeneous enhancement pattern and appear solid on imaging. To our knowledge, no studies have yet investigated whether these 'imaging phenotypes' are also associated with specific risk factors (i.e., age, gender and BMI) that could themselves influence tumor biology and

explain the heterogeneous collection of tumor subtypes that is still subsumed as RCC as of today. The discovery of such associations is of high interest especially as some imaging features (like renal vein invasion or nodular enhancement) have already been found to be associated with specific mutations [20].

Therefore, the purpose of our study was to correlate imaging features of RCC on CT with patient age, gender and BMI and identify associations that might lead to further insights regarding the heterogeneous clinical behavior of RCC.

## 2. Materials and methods

### 2.1. Patients

This retrospective study was HIPAA compliant and was approved by our institutional review board, which waived the requirement for informed consent. Our institution's radiology and urology databases were searched for the years 1999 through 2011 to identify all patients in whom a histopathologically proven RCC had been resected and who had undergone contrast-enhanced CT imaging of the abdomen that included at least a nephrographic phase less than 180 days before surgery. The search yielded a total of 1348 patients. The patient characteristics (age and BMI at time of surgery, gender, RCC subtype and Fuhrman grade in clear cell RCC) were retrieved from our institution's electronic medical records system.

### 2.2. Imaging

Of the 1348 CT imaging examinations included in this study, 980 (73%) were performed at our institution and 368 (27%) were performed elsewhere. The mean time interval between CT examination and surgery was 42 days (range: 0–169 days).

All imaging studies were evaluated independently by two radiologists (CAK and PLDP, blinded for review) with fellowship- and resident-level experience in the interpretation of genitourinary imaging, respectively, on commercial PACS software (Centricity, GE Healthcare, Waukesha, WI, USA). Both readers were partaking in a dedicated program for genitourinary research and had each read > 300 CT examinations of renal cell carcinoma previously. To facilitate consistent interpretation, both readers underwent training, in which they evaluated a set of cases ($n = 90$) not included in the patient cohort. The readers were blinded to all clinical, histopathological and epidemiological data.

The readers assessed the presence or absence of the following imaging features: intratumoral necrosis (defined as a non-enhancing tumor region on nephrographic and/or delayed phases), gross renal vein invasion by the tumor, direct contact of the tumor with the renal sinus fat, multicystic (as opposed to solid) appearance and nodular (as opposed to homogeneous) tumor enhancement (see Fig. 1a–c for examples of these features). The selection of these imaging features before the start of the readings was based on their prior use in the literature [20] and their ability to be easily assessed on routine imaging, so that a reliable assessment could be expected. In addition, reader 1 measured the longest tumor diameter in the axial plane.

### 2.3. Statistical methods

Mean and standard deviation (SD) for age and BMI, and percentages for gender, grade and imaging features were summarized separately for patients with clear cell RCC and those with other malignant RCCs.

Agreement between the two readers was assessed using the kappa statistic, which was interpreted as proposed by Landis and Koch [21].

We first examined associations between clinical characteristics and imaging features by using (1) the Chi-squared test to examine the associations between gender and Fuhrman grade and between gender and imaging features; (2) linear regression to examine the association

between age and BMI (which was approximately normally distributed in our study population, with a mean of 29.9 kg/m$^2$ and a median of 28.9 kg/m$^2$); and (3) the *t*-test to compare age as well as BMI between patients with and without specific imaging features. To further examine if each imaging feature was independently associated with BMI in patients with clear cell RCC, we performed linear regression controlling for age and Fuhrman grade and applied a likelihood ratio test. In patients with non-clear cell RCC, similar tests controlling for age were applied. Associations between imaging features and BMI were also assessed separately in males and females. No adjustment for multiple testing was made, given the hypothesis-generating purpose of the study.

A test with a *p*-value < 0.05 was considered statistically significant. All statistical analysis was performed in SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

## 3. Results

### 3.1. Patient and tumor characteristics

Of the 1348 patients included in the study, 904 (67%) patients (mean age 59.8 years; 316 [35%] female and 588 [65%] male) had clear cell RCC and 444 (33%) patients (mean age 60.5 years; 161 [36%] female and 283 [64%] male) had non-clear cell RCC. Of the patients with non-clear cell RCC, 167 (38%) had chromophobe RCC, 201 (45%) had papillary RCC, and 76 (17%) had unclassified RCC. Additional patient and tumor characteristics are listed in Tables 1 and 2.

Among patients with clear cell RCC, females had a significantly higher mean BMI than males (31.1 kg/m$^2$ vs 30.0 kg/m$^2$; $p = 0.0221$; Table 2), and BMI was significantly associated with age for males but not for females ($p = 0.0318$; females: $p = 0.6476$; both genders: $p = 0.0988$).

Fuhrman grade was also distributed unequally: Females tended to have lower-grade tumors (mostly Fuhrman grade 2) compared to male patients, a majority of whom had tumors of grade 2 or 3; this trend was statistically significant ($p < 0.001$, Table 2). Male patients with clear cell RCC also tended to be slightly younger than female patients ($p = 0.0166$, Table 2).

Tumor size did not differ significantly between genders (Table 2) for patients with clear cell RCC or those with non-clear cell RCC, and there was no difference in age or BMI between female and male patients in the non-clear cell RCC group. However, a significant association between BMI and age was found for all patients with non-clear cell RCC ($p = 0.009$); when the patients were stratified by gender, this association was only significant for males (females: $p = 0.1205$; males: $p = 0.0298$).

### 3.2. Inter-reader agreement

Inter-reader agreement on imaging features was mostly excellent (kappa: 0.934–0.980 in clear cell RCC, 0.863–0.982 in non-clear cell RCC), except with regard to renal vein invasion, regarding which agreement was substantial (kappa: 0.688 in clear cell RCC and 0.694 in non-clear cell RCC).

### 3.3. Associations between imaging features and age, gender and BMI

Detailed results regarding associations between imaging features and patient characteristics can be found in Table 3a (clear cell RCC) and Table 3b (non-clear cell RCC).

In the clear cell RCC group, patients with tumors of multicystic appearance were significantly younger (57.2/57.4 vs 60.2/60.1 years; $p = 0.0084$ and $p = 0.0149$, for the two readers) and also had significantly lower BMI (28.7/28.9 kg/m$^2$ vs 30.8/30.7 kg/m$^2$; $p < 0.0001$ and $p = 0.0007$) than those with solid tumors. These associations remained statistically significant for both males and females with clear cell RCC when adjusting for Fuhrman grade and age and
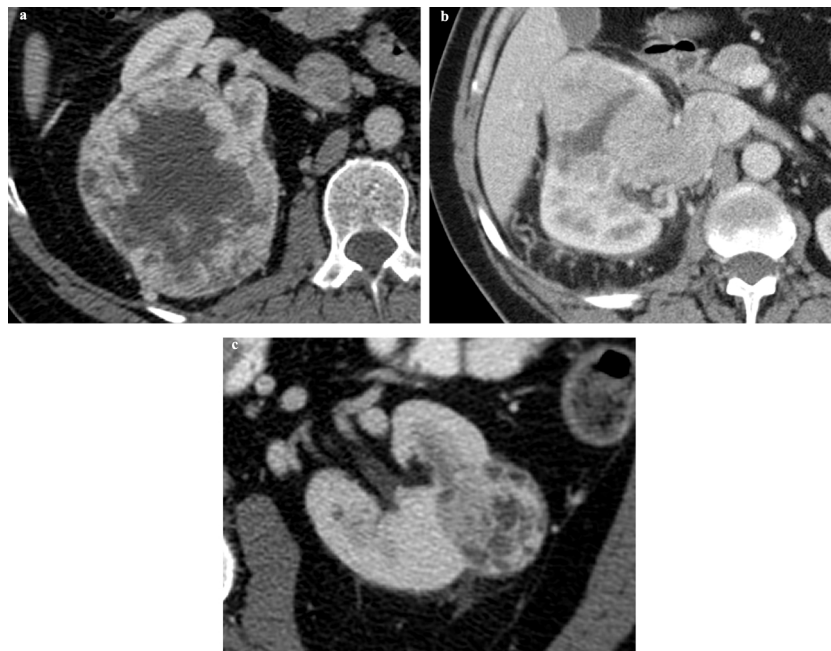
**Fig. 1.** (a–c) Examples of imaging features measured on CT. (a) Large, centrally necrotic clear cell RCC, demonstrating contact with the renal sinus fat and nodular enhancement; (b) clear cell RCC in the right kidney with renal vein invasion; and (c) multicystic tumor appearance.

**Table 1**
Patient characteristics for clear cell RCC ($n = 904$) and non-clear cell RCC ($n = 444$) groups. * as indicated by histopathological report.

| Gender | | Clear cell RCC N (%) | Non-clear cell RCC N (%) |
|---|---|---|---|
| | F | 316 (35%) | 161 (36%) |
| | M | 588 (65%) | 283 (64%) |
| T stage* | | | |
| | T1a | 449 (49.7%) | 227 (51.1%) |
| | T1b | 137 (15.2%) | 84 (18.9%) |
| | T2a | 29 (3.2%) | 22 (5.0%) |
| | T2b | 10 (1.1%) | 18 (4.1%) |
| | T3a | 94 (10.4%) | 61 (13.7%) |
| | T3b | 174 (19.2%) | 32 (7.2%) |
| | T3c | 2 (0.2%) | 0 (0%) |
| | T4 | 9 (1.0%) | 0 (0%) |
| N stage* | | | |
| | N− | 282 (31.2%) | 77 (17.3%) |
| | N+ | 14 (1.5%) | 22 (5%) |
| | Nx | 608 (67.3% | 345 (77.7%) |
| M stage* | | | |
| | M− | 827 (91.5%) | 430 (96.8%) |
| | M+ | 77 (8.5%) | 14 (3.2%) |

**Table 2**
Comparison of BMI (kg/m$^2$), Fuhrman grade (only applicable in clear cell RCC), age (years) and tumor size on CT (cm) between genders for patients with clear cell RCC and non-clear cell RCC. *p-value for the comparison between male and female patients.

Clear cell RCC

| | Both genders | Female | Male | p-value* |
|---|---|---|---|---|
| BMI, mean (SD) | 30.4 (6.4) | 31.1 (7.5) | 30.0 (5.8) | 0.0221 |
| Fuhrman grade | | | | |
| 1, n (%) | 25 (3%) | 8 (3%) | 17 (3%) | < .001 |
| 2, n (%) | 449 (50%) | 202 (64%) | 247 (42%) | |
| 3, n (%) | 363 (40%) | 86 (27%) | 277 (47%) | |
| 4, n (%) | 66 (7%) | 19 (6%) | 47 (8%) | |
| Age, mean (SD) | 59.8 (11.9) | 61.0 (12.1) | 59.0 (11.6) | 0.0166 |
| Tumor size (cm), mean (SD) | 4.8 (2.8) | 4.6 (2.9) | 4.9 (2.8) | 0.1305 |

Non-clear cell RCC

| | Both genders | Female | Male | p-value* |
|---|---|---|---|---|
| BMI, mean (SD) | 28.9 (5.5) | 28.7 (6.8) | 29.0 (4.7) | 0.7087 |
| Age, mean (SD) | 60.5 (11.3) | 60 (12) | 61 (12) | 0.3483 |
| Tumor size (cm), mean (SD) | 4.4 (3.0) | 4.2 (3.0) | 4.6 (3.0) | 0.1674 |

including gender as an additional distinction. An association between multicystic tumor appearance and lower BMI was also found in the non-clear cell RCC group, but it did not remain statistically significant after adjusting for age (except for reader 2 when looking at both genders, Table 3b).

Renal vein invasion was associated with significantly lower BMI in males with clear cell RCC (28.7/28.0 kg/m$^2$ vs 30.2/30.2 kg/m$^2$, $p = 0.0441$ and 0.0067); this association was not seen in females with clear cell RCC or in patients with non-clear cell RCC. In addition, nodular enhancement (60.5/60.5 vs 58.3/58.3 years; $p = 0.0068$ and $p = 0.0069$) and contact between the tumor and the renal sinus fat (60.4/60.3 vs 57.3/57.3 years; $p = 0.002$ and 0.0026) were significantly associated with greater age in the group of patients with clear cell RCC.

In the non-clear cell RCC group, a higher rate of necrosis was associated with a lower BMI (28.0/27.9 vs 29.6/29.6 kg/m$^2$; $p = 0.0047$

and $p = 0.0029$, Table 3b), but after adjusting for age, this association only remained statistically significant for females ($p = 0.0328$ and $p = 0.0184$).

## 4. Discussion

Age, gender and BMI are long-established risk factors for cancer development that influence cancer-specific morbidity and mortality, and their influence extends to renal cancer [8,22]. Though obesity in particular is known to significantly increase the risk of developing clear cell RCC [6–8,11,12], several independent groups have shown that patients with clear cell RCC who have a higher BMI paradoxically have a better prognosis than those of normal weight [23,14,15]. This "obesity paradox" was most recently described in two studies [17,18],

**Table 3a**

Association between patient characteristics and CT features in clear cell RCC (BMI: kg/m², age: years, R1 = reader 1, R2 = reader 2. * p-value adjusted for Fuhrman grade and age.

| CT Features | | Age Mean (SD) | p-value | Gender Female | Male | p-value | BMI Mean (SD) | p-value | Adjusted p-value* | BMI in females Mean (SD) | p-value | Adjusted p-value* | BMI in Males Mean (SD) | p-value | Adjusted p-value* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Necrosis (R1) | No | 58.2 (12.2) | 0.1792 | 38 (12%) | 76 (13%) | 0.6976 | 31.0 (7.3) | 0.3271 | 0.3412 | 31.3 (8.7) | 0.8841 | 0.9569 | 30.9 (6.5) | 0.2133 | 0.2390 |
| | Yes | 59.9 (11.8) | | 278 (88%) | 512 (87%) | | 30.3 (6.3) | | | 31.1 (7.3) | | | 29.9 (5.6) | | |
| Necrosis (R2) | No | 58.4 (12.2) | 0.2177 | 39 (12%) | 79 (13%) | 0.6416 | 30.9 (7.2) | 0.3961 | 0.4263 | 31.2 (8.6) | 0.9681 | 0.9491 | 30.8 (6.4) | 0.2423 | 0.2798 |
| | Yes | 59.9 (11.8) | | 277 (88%) | 509 (87%) | | 30.3 (6.3) | | | 31.1 (7.3) | | | 29.9 (5.6) | | |
| Renal vein invasion (R1) | No | 59.5 (12.0) | 0.3657 | 275 (87%) | 505 (86%) | 0.6344 | 30.5 (6.4) | 0.0649 | 0.1924 | 31.2 (7.4) | 0.8068 | 0.7962 | 30.2 (5.8) | 0.0190 | 0.0441 |
| | Yes | 60.5 (10.8) | | 41 (13%) | 83 (14%) | | 29.4 (6.3) | | | 30.8 (7.9) | | | 28.7 (5.3) | | |
| Renal vein invasion (R2) | No | 59.7 (12.0) | 0.9160 | 288 (91%) | 523 (89%) | 0.3006 | 30.5 (6.5) | 0.0203 | 0.1108 | 31.1 (7.5) | 0.8764 | 0.3636 | 30.2 (5.8) | 0.0012 | 0.0067 |
| | Yes | 59.8 (9.8) | | 28 (9%) | 65 (11%) | | 29.0 (5.8) | | | 31.3 (7.1) | | | 28.0 (4.9) | | |
| Contact renal sinus fat (R1) | No | 57.3 (12.4) | 0.0020 | 75 (24%) | 130 (22%) | 0.5779 | 30.3 (5.8) | 0.7213 | 0.2857 | 29.9 (5.9) | 0.0663 | 0.0521 | 30.5 (5.7) | 0.3033 | 0.6348 |
| | Yes | 60.4 (11.6) | | 241 (76%) | 458 (78%) | | 30.4 (6.6) | | | 31.5 (7.9) | | | 29.9 (5.8) | | |
| Contact renal sinus fat (R2) | No | 57.3 (12.4) | 0.0026 | 71 (22%) | 124 (21%) | 0.6305 | 30.3 (5.8) | 0.8926 | 0.4035 | 30.1 (6.0) | 0.1195 | 0.0909 | 30.5 (5.7) | 0.2801 | 0.5729 |
| | Yes | 60.3 (11.6) | | 245 (78%) | 464 (79%) | | 30.4 (6.6) | | | 31.4 (7.8) | | | 29.9 (5.8) | | |
| Multicystic (R1) | No | 60.2 (11.4) | 0.0084 | 258 (82%) | 478 (81%) | 0.8965 | 30.8 (6.6) | <.0001 | <.0001 | 31.7 (7.6) | 0.0011 | 0.0027 | 30.3 (6.0) | 0.0035 | 0.0060 |
| | Yes | 57.2 (13.5) | | 58 (18%) | 110 (19%) | | 28.7 (5.2) | | | 28.5 (6.2) | | | 28.8 (4.6) | | |
| Multicystic (R2) | No | 60.1 (11.6) | 0.0149 | 263 (83%) | 490 (83%) | 0.9677 | 30.7 (6.6) | 0.0002 | 0.0007 | 31.6 (7.7) | 0.0070 | 0.0169 | 30.2 (5.9) | 0.0115 | 0.0180 |
| | Yes | 57.4 (12.9) | | 53 (17%) | 98 (17%) | | 28.9 (5.2) | | | 28.9 (6.1) | | | 28.9 (4.6) | | |
| Nodular enhancement (R1) | No | 58.3 (12.0) | 0.0068 | 107 (34%) | 227 (39%) | 0.1587 | 30.6 (6.5) | 0.4003 | 0.5315 | 31.8 (8.1) | 0.2846 | 0.3304 | 30.1 (5.5) | 0.7763 | 0.9290 |
| | Yes | 60.5 (11.7) | | 209 (66%) | 361 (61%) | | 30.3 (6.4) | | | 30.8 (7.1) | | | 29.9 (5.9) | | |
| Nodular enhancement (R2) | No | 58.3 (12.0) | 0.0069 | 112 (35%) | 246 (42%) | 0.0609 | 30.5 (6.4) | 0.6956 | 0.8963 | 31.7 (8.0) | 0.3446 | 0.4116 | 30.0 (5.4) | 0.8732 | 0.7034 |
| | Yes | 60.5 (11.6) | | 204 (65%) | 342 (58%) | | 30.3 (6.5) | | | 30.8 (7.2) | | | 30.0 (6.0) | | |

**Table 3b**

Association between patient characteristics and CT features in non-clear cell RCC (BMI: kg/m², age: years, R1 = reader 1, R2 = reader 2. * p-value adjusted for age.

| CT features | | Age Mean (SD) | p-value | Gender Female | Male | p-value | BMI Mean (SD) | p-value | Adjusted p-value* | BMI in females Mean (SD) | p-value | Adjusted p-value* | BMI in Males Mean (SD) | p-value | Adjusted p-value* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Necrosis (R1) | No | 59.5 (10.9) | 0.0563 | 89 (55%) | 166 (59%) | 0.5537 | 29.6 (5.7) | 0.0021 | 0.0047 | 29.8 (7.3) | 0.0226 | 0.0328 | 29.4 (4.7) | 0.0431 | 0.0669 |
| | Yes | 61.6 (11.6) | | 72 (45%) | 117 (41%) | | 28.0 (5.1) | | | 27.4 (6.0) | | | 28.3 (4.5) | | |
| Necrosis (R2) | No | 59.7 (10.9) | 0.1602 | 90 (56%) | 167 (59%) | 0.5905 | 29.6 (5.7) | 0.0015 | 0.0029 | 29.9 (7.2) | 0.0148 | 0.0184 | 29.4 (4.7) | 0.0467 | 0.0683 |
| | Yes | 61.3 (11.6) | | 71 (44%) | 116 (41%) | | 27.9 (5.2) | | | 27.3 (6.1) | | | 28.3 (4.6) | | |
| Renal vein invasion (R1) | No | 60.4 (11.3) | 0.8025 | 155 (96%) | 272 (96%) | 0.8629 | 28.9 (5.6) | 0.778 | 0.8126 | 28.8 (6.9) | 0.3902 | 0.4909 | 28.9 (4.7) | 0.7098 | 0.6955 |
| | Yes | 61.0 (9.4) | | 6 (4%) | 11 (4%) | | 28.5 (5.0) | | | 26.7 (5.3) | | | 29.5 (4.9) | | |
| Renal vein invasion (R2) | No | 60.4 (11.3) | 0.7983 | 156 (97%) | 271 (96%) | 0.6237 | 28.8 (5.5) | 0.3122 | 0.2386 | 28.7 (6.8) | 0.4904 | 0.4447 | 28.9 (4.6) | 0.4957 | 0.3527 |
| | Yes | 61.0 (9.7) | | 5 (3%) | 12 (4%) | | 30.4 (6.1) | | | 30.8 (6.3) | | | 30.2 (6.3) | | |
| Contact renal sinus fat (R1) | No | 61.5 (11.1) | 0.0769 | 60 (37%) | 117 (41%) | 0.4578 | 28.8 (5.0) | 0.815 | 0.9915 | 28.7 (6.4) | 0.9141 | 0.8891 | 28.9 (4.2) | 0.8016 | 0.8619 |
| | Yes | 59.6 (11.3) | | 101 (63%) | 166 (59%) | | 28.9 (5.9) | | | 28.8 (7.1) | | | 29.0 (5.0) | | |
| Contact renal sinus fat (R2) | No | 61.5 (11.1) | 0.0821 | 62 (39%) | 119 (42%) | 0.5291 | 28.9 (5.0) | 0.9557 | 0.7868 | 28.9 (6.4) | 0.7798 | 0.5842 | 28.9 (4.2) | 0.8074 | 0.8515 |
| | Yes | 59.6 (11.3) | | 99 (61%) | 164 (58%) | | 28.9 (5.9) | | | 28.6 (7.1) | | | 29.0 (5.0) | | |
| Multicystic (R1) | No | 60.3 (11.3) | 0.3529 | 151 (94%) | 267 (94%) | 0.9758 | 29.0 (5.6) | 0.0057 | 0.0582 | 28.9 (7.0) | 0.0016 | 0.1988 | 29.1 (4.7) | 0.1242 | 0.1669 |
| | Yes | 62.2 (9.8) | | 10 (6%) | 16 (6%) | | 26.8 (3.5) | | | 26.0 (1.9) | | | 27.3 (4.3) | | |
| Multicystic (R2) | No | 60.4 (11.4) | 0.5782 | 153 (95%) | 271 (96%) | 0.9061 | 29.0 (5.6) | 0.0001 | 0.0260 | 28.9 (6.9) | 0.0056 | 0.2217 | 29.1 (4.7) | 0.0092 | 0.0508 |
| | Yes | 59.3 (8.6) | | 8 (5%) | 12 (4%) | | 26.3 (2.5) | | | 26.1 (2.9) | | | 26.4 (2.9) | | |
| Nodular enhancement (R1) | No | 60.2 (11.1) | 0.5654 | 124 (77%) | 230 (81%) | 0.3426 | 29.1 (5.4) | 0.2212 | 0.2195 | 29.1 (6.7) | 0.2748 | 0.3363 | 29.0 (4.6) | 0.5711 | 0.4956 |
| | Yes | 61.0 (11.8) | | 37 (23%) | 53 (19%) | | 28.2 (5.9) | | | 27.6 (7.2) | | | 28.6 (4.9) | | |
| Nodular enhancement (R2) | No | 60.1 (11.2) | 0.3622 | 126 (78%) | 232 (82%) | 0.4076 | 29.1 (5.4) | 0.1715 | 0.1767 | 29.1 (6.7) | 0.2250 | 0.2673 | 29.1 (4.6) | 0.5156 | 0.4796 |
| | Yes | 61.4 (11.5) | | 35 (22%) | 51 (18%) | | 28.1 (5.9) | | | 27.4 (7.2) | | | 28.6 (5.0) | | |

which found that the benefits of an elevated BMI were restricted to the male study population.

While the underlying causes of the obesity paradox are still unknown, the results of these recent studies add to the mounting evidence that even a histopathological subtype such as clear cell RCC does not represent a single entity [24,19,25], but rather constitutes a heterogeneous family of tumors with varying levels of aggressiveness and differing genomic, molecular and metabolic characteristics that are affected by epidemiological factors. For example, there is growing evidence that the expression of certain genes in the fatty acid metabolism of clear cell RCC is influenced by epidemiological factors, especially by obesity [19]. Ongoing research is therefore focused on further exploring the genomic, molecular, metabolic and epidemiologic variables that could potentially explain the observed clinical heterogeneity in RCC. However, the heterogeneity of the imaging features of RCC has not yet been incorporated into these investigations. Given the established associations between imaging features of RCC and certain mutations [20], we aimed to investigate potential associations between distinctive imaging features and patient age, gender and BMI.

One of our most interesting findings was that a multicystic tumor appearance was significantly associated with younger age as well as lower BMI in patients (both men and women) with clear cell RCC. This is of importance, as it has recently been demonstrated that in clear cell RCCs of multicystic appearance, mutations of SETD2, KDM5C and BAP1 are not seen and mutations of VHL and PBRM1 are significantly less common than in solid clear cell RCCs [20]. A fraction of these multicystic tumors might represent multilocular cystic clear cell RCC of low malignant potential, a rare entity and low-grade subtype of clear cell RCC with a favorable prognosis [26,27]; such a circumstance would align well with findings linking the mutations mentioned above with poor outcome in patients with solid tumors [19,28]. However, the association between a multicystic tumor appearance and lower BMI also reached statistical significance in the non-clear cell RCC group, though only for one reader after adjusting for age, and not when patients were differentiated by gender. The reasons for the findings in this group require further investigation in a larger cohort of patients with non-clear cell RCC who could be stratified by histological subtype. In perspective, molecular alterations specific for an individual imaging phenotype might even allow for the personalization of therapies based on CT imaging.

Our finding that renal vein invasion, which is a known sign of poor prognosis [29], was significantly associated with a lower BMI in males with clear cell RCC might provide an explanation for the so-called "protective effect" of a higher BMI [13,14] in males [17,18]. The fact that this association remained statistically significant even after adjusting for age and Fuhrman grade suggests the presence of a distinct and more aggressive subtype in these patients, influenced by epidemiological features. Interestingly, the association between renal vein invasion and lower BMI might be unique to clear cell RCC, as it was not found in the patients with non-clear cell RCC. In this context, the differentiation between visceral and retroperitoneal fat could be of interest in future studies, as recent investigations indicate a distinct influence of the fat distribution on survival in patients with RCC [30].

The fact that patients with clear cell RCC whose tumors were in direct contact with the renal sinus fat were slightly but significantly older might also reflect the presence of a more aggressive tumor type in older patients. However, the differences between the patient groups assessed in this comparison were small in absolute numbers, which limits the applicability of this finding to routine clinical care. Nodular contrast enhancement, which was also associated with greater age in patients with clear cell RCC in our analysis, has been found to be associated with a mutation of the VHL gene in clear cell RCC [20]. Thus, taken together, these findings align well with prior findings of a higher rate of VHL mutations in older patients [31].

The presence of necrosis at histopathology is another established poor prognostic factor [32]. Although microscopic necrosis is not evident on clinical imaging, gross necrosis can be appreciated on contrast-enhanced CT as a non-enhancing area of tumor. In our study, necrosis on CT was associated with significantly lower BMI in females with non-clear cell RCC though not in males with non-clear cell RCC after adjusting for age. The molecular reasons for this association are unknown and might represent a motif for future studies.

In our study, we were not able to correlate certain entities (e.g., a multicystic tumor appearance on imaging and an actual histopathological diagnosis of multilocular cystic RCC) due to the long patient inclusion period of 12 years and the fact that the international histopathological classification of renal cell carcinoma was revised during this period. Even though our study population as a whole was large, the low number of patients with less common RCC subtypes forced us to analyze the data for all patients with non-clear cell RCC as a group and not stratified by RCC subtype. Also, our investigation was designed as an exploratory study to find correlations between imaging features and epidemiological factors only, and it did not include genomic or detailed histopathological assessment of the tumor specimens. As such, the interpretation of our findings is complicated by the fact that the exact biochemical/genomic pathways for the influence of epidemiological factors we were able to demonstrate are still unknown. Further studies will be needed to investigate the exact molecular causes, possibly in relation to other known epidemiological risk factors. In addition, due to the hypothesis-generating purpose of this study, we did not perform adjustment for multiple testing and therefore our results require verification in a separate cohort.

Finally, though the interval between CT examination and surgery was relatively short (averaging 42 days), it was not possible to account for potential changes in patients' BMI during that interval. Additionally, we required all CT examinations to include an intravenous contrast agent, which greatly increases image quality and helps in the assessment of qualitative imaging features. As a result of this decision, patients with renal impairment, in whom the injection of an intravenous contrast agent would have been contra-indicated, could not be included into our study.

In conclusion, this study identified associations of imaging features with age and BMI in patients with RCC that are known to affect outcome and therefore suggest the existence of additional subtypes of RCC with differing levels of aggressiveness and prognoses, influenced by these epidemiological factors. These findings could potentially impact on future stratification and therapy of patients, maybe even allowing personalization of therapies based on imaging features. Future genomic, molecular and metabolic studies of RCC that incorporate our findings – for example, by including subset analyses of solid vs cystic tumors or of tumors from male patients with clear cell RCC and lower BMI – might provide new insights into the causes of the heterogeneous clinical appearance and behavior of RCC.

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## Contribution author(s)

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