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Composition of Perinephric Fat and Fuhrman Grade in Clear Cell Renal Cell Carcinoma: The Role of Peritumoral Collateral Vessels

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Abstract: Background: The aim of this study was to investigate whether the presence of peritumoral collateral vessels could be indicative of a high Fuhrman grade (e.g., III and IV) in clear cell renal cell carcinoma (ccRCC). Methods: Between November 2019 and February 2020, a total of 267 ccRCC patients with histology-proven diagnoses were retrospectively analyzed and screened. Imaging analysis was performed on computed tomography (CT) images to assess the presence of peritumoral collateral vessels and understand the potential association with high Fuhrman grades. These vessels are defined as dilated and macroscopically visible peritumoral renal capsular veins. Results: A total of 190 ccRCC patients were included in the study, considering the exclusion criteria. In patients with peritumoral collateral vessels, there was a statistically significant greater presence of ccRCC with a high Fuhrman grade both among the total cohort of patients regardless gender (n = 190) ($p < 0.001$) as well as among ccRCC male patients only (n = 127) ($p < 0.005$). Conclusion: Here, we show a novel association between peritumoral collateral vessels and ccRCC with high Fuhrman grades in male patients. The presence of peritumoral collateral vessels in perinephric adipose tissue can be indicative of more aggressive ccRCC.

Keywords: body composition; clear cell renal cell carcinoma; collateral vessels; computed tomography; imaging; Fuhrman grade; kidney cancer; perinephric adipose tissue

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1. Introduction

Collateral vessels can be found around renal cell carcinoma (RCC). These vessels are enlarged renal capsular veins, which become macroscopically visible in computed tomography (CT) or magnetic resonance imaging (MRI) studies (Figure 1).

Collateral vessels adjacent to RCC are poorly investigated, and the significance of this finding is not fully understood.

Gonadal vein recruitment is more frequently associated with RCC located at the lower renal pole [1]. On the other hand, tumors of the upper renal pole usually have a different drainage route, flowing into the adrenal and lower phrenic veins [1].

A CT study performed on 58 RCC patients showed that 26 patients had peritumoral collateral vessels, of which 18 had outflow through the gonadal vein [1]. This finding was present in tumors greater than 5 cm in diameter (18/18), more frequently in males (15/18), in tumors of the right kidney (12/18) and at the lower pole (15/18) [1].

Moreover, collateral vessels were found to be associated with greater blood loss during surgery for RCC (mean volume of 1078 mL vs. 304 mL) [1] and have been linked to

cancer staging in RCC patients, possibly reflecting a sign of locally advanced disease (i.e., T stage > T3a) [2].

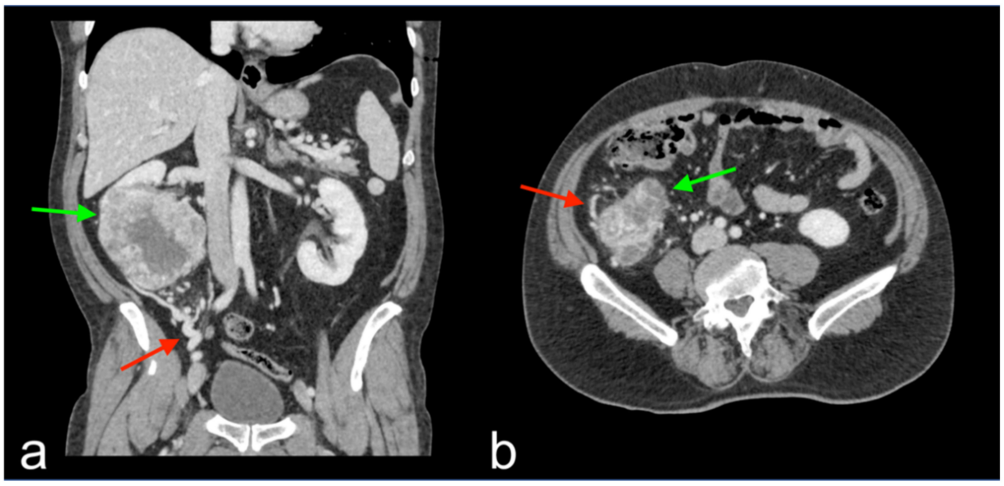

Figure 1. CT images in the coronal (**a**) and axial (**b**) planes of the abdomen in the venous phase, showing the presence of collateral vessels (red arrows) adjacent to clear cell renal cell carcinoma with a high Fuhrman grade (IV) (green arrow), with the characteristic tortuous course within the perinephric adipose tissue.

The most frequent grading system in clear cell RCC (ccRCC) and papillary RCC is the four-tiered Fuhrman system (I, II, III and IV) [3]. A simplified two-tiered Fuhrman grade system has been proposed by dividing the ranks into low grade (I and II) and high grade (III and IV) [4]. It has been shown to have the same specificity in predicting mortality as the traditional four-tiered Fuhrman grade system but with greater reproducibility and less variability for pathologists [4]. High-grade tumors have a greater risk of post-operative recurrence [5].

The possible association between peritumoral collateral vessels adjacent to RCC and the Furman grade has never been explored to date.

Herein, we test the hypothesis that the presence of peritumoral collateral vessels in perinephric adipose tissue adjacent to ccRCC is indicative of a high Furman grade (i.e., III and IV).

2. Materials and Methods

The study design was cross-sectional observational. All the procedures were retrospective and were in agreementagreed with the Declaration of Helsinki.

CT images and data of ccRCC patients were acquired at multiple centers and re-trieved from The Cancer Imaging Archive (TCIA) [6–8]. The TCIA project received approval of the Institutional Review Board. This subsequent retrospective analysis was on the publicly available, anonymized data and did not require further review due to previous protections implemented by TCIA. All the subjects enrolled signed a written informed consent.

Between November 2019 and February 2020, a total of 267 patients with histological diagnoses of ccRCC were retrospectively analyzed and selected based on medical history, CT images and the exclusion criteria. The cohort was selected among consecutive patients with kidney cancer undergoing CT for disease staging.

Exclusion criteria for the ccRCC patients were as follows: patients with previous renal ablation, heminephrectomized and nephrectomized patients and patients with congenital solitary kidney. These categories of patients were excluded because previous interventions, procedures or congenital anatomical variants could change the macroscopic vascular architecture, making the anatomy difficult to compare. Moreover, we also excluded cirrhotic patients with collateral vessels due to the macroscopically abnormal vascular architecture. Finally, we excluded patients who had undergone chest CT only and patients who had undergone MRI examination only. Specifically, the latter patients were excluded to

consistently and systematically investigate peritumoral vessels using the same imaging technique, given the well-known greater spatial resolution for the CT images.

3. CT Analysis

All ccRCC selected patients underwent CT examination. All CT images were evaluated and analyzed by a consensus of two radiologists (F.G. and C.A.M., with 5 years and 9 years of experience, respectively) blinded to the clinical data. Imaging analysis, performed on the venous phase in all the cases, was aimed at assessing the presence or absence of peritumoral collateral vessels. These vessels are defined as dilated and macroscopically visible peritumoral renal capsular veins.

4. Statistical Analysis

Data distribution was verified using the Kolmogorov–Smirnov (KS) test. Then, the Mann–Whitney U test was used to assess differences in tumor size between the low (i.e., I and II) and high (i.e., III and IV) Fuhrman grade groups.

A chi-squared test with Yates correction was used to detect whether the distribution of ccRCC patients showed a statistically significant difference. Particularly, we focused on presence or absence of collateral vessels and low or high Fuhrman grades.

A subanalysis was carried out, dividing the groups according to gender.

Then, to assess the impact of tumor size and peritumoral collateral vessels on the Fuhrman grade, we performed a subanalysis grouping the patients with peritumoral collateral vessels according to the median value of the tumor size (i.e., above or below).

Finally, we verified the distribution of patients with or without peritumoral collateral vessels with respect to the low (i.e., T1 and T2) or high (i.e., T3 and T4) staging.

5. Results

A total of 190 ccRCC patients were included in the study, following the exclusion criteria. The descriptive data of the patients are summarized in Table 1.

Table 1. Descriptive data of the enrolled patients.

Gender (Number)	**Male (129)** **Female (61)**
Age of Total Patients (mean; median; range; standard deviation)	60; 59; 26–88; 12.4
Age of Male Patients (mean; median; range; standard deviation)	58.7; 58; 26–84; 12.4
Age of Female Patients (mean; median; range; standard deviation)	62.8; 63; 40–88; 12
Ethnicity of Male Patients (number)	Caucasian (122) Black or African American (5) Hispanic (1) Asian (1)
Ethnicity of Female Patients (number)	Caucasian (53) Black or African American (7) Asian (1)
Histology of Male and Female Patients (number)	ccRCC (190)
Tumor Size (mean; median; range; standard deviation)	61; 52.5; 14–144; 30.3
Fuhrman Grade of Male Patients (number)	Low Grade (46) High Grade (83)
Fuhrman Grade of Female Patients (number)	Low Grade (33) High Grade (28)

There was a statistically significant ($p < 0.0001$) greater tumor size in the high Fuhrman grade group ($n = 112$) compared with the low Fuhrman grade group ($n = 78$).

Among the ccRCC patients, 47 showed an absence of collateral vessels and low Fuhrman grades (ccRCCal), 31 had the presence of collateral vessels and low Fuhrman grades (ccRCCpl), 39 had an absence of collateral vessels and high Fuhrman grades (ccRCCah) and, lastly, the presence of collateral vessels and high Fuhrman grades were found in 73 patients (ccRCCph). The chi-squared statistic with Yates correction showed statistically significant different distribution due to greater number of patients with high Fuhrman grades in the group with collateral vessels ($p < 0.001$) (Figure 2).

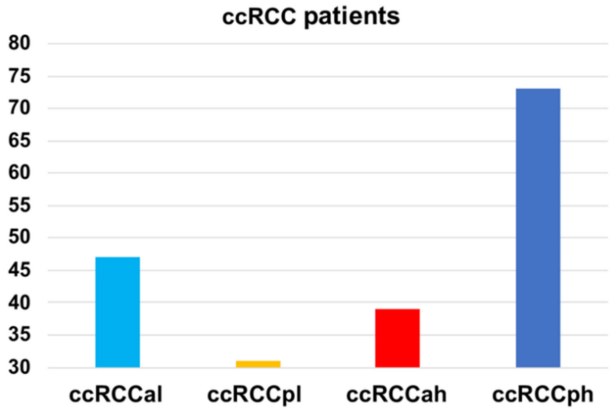

Figure 2. Bar charts showing the distribution of ccRCC patients in the four categories. Note the greater number of patients with collateral vessels and high Fuhrman grades. Shown are patients with an absence of collateral vessels and low Fuhrman grades (ccRCCal); the presence of collateral vessels and low Fuhrman grades (ccRCCpl); an absence of collateral vessels and high Fuhrman grades (ccRCCah); and the presence of collateral vessels and high Fuhrman grades (ccRCCph).

Similar results were found with male patients (MccRCCal $n = 33$; MccRCCpl $n = 18$; MccRCCah $n = 27$ and MccRCCph $n = 49$) with statistically significant different distribution ($p < 0.005$) (Figure 3). Conversely, no statistically significant differences ($p = 0.31$) were detected in the subanalysis performed with the female patient ccRCC subgroups (FccRCCal $n = 14$; FccRCCpl $n = 14$; FccRCCah $n = 12$ and FccRCCph $n = 23$).

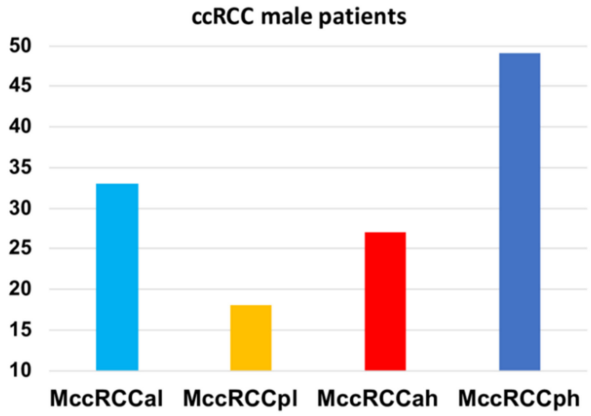

Figure 3. Bar charts showing the distribution of ccRCC male patients in the four categories. Note the greater number of male patients with collateral vessels and high Fuhrman grades. Shown are patients with an absence of collateral vessels and low Fuhrman grades (ccRCCal); the presence of collateral vessels and low Fuhrman grades (ccRCCpl); an absence of collateral vessels and high Fuhrman grades (ccRCCah); and the presence of collateral vessels and high Fuhrman grades (ccRCCph).

Non-significant results ($p = 0.13$) were found by sub-grouping patients with ccRCC and peritumoral collateral vessels according to the median value (i.e., 7.2 cm) of tumor size (low Furhman grade and size < median $n = 20$; low Furhman grade and size > me-

dian $n = 12$; high Furhman grade and size < median $n = 32$; high Furhman grade and size > median $n = 40$).

Lastly, there was a statistically significant ($p < 0.0001$) different distribution of collateral vessels according to disease staging, mainly due to the lower presence of patients with high staging (i.e., T3 and T4) and lack of peritumoral collateral vessels (ccRCCa and low stage $n = 79$; ccRCCp and low stage $n = 49$; ccRCCa and high stage $n = 7$; and ccRCCp and high stage $n = 55$).

6. Discussion

This is a large series study showing a novel association between collateral vessels in ccRCC male patients and high Fuhrman grades.

The Fuhrman grade is the most widely used histological grading system for ccRCC [3]. Several studies investigated signs that could predict Fuhrman grades in ccRCC using a non-invasive imaging-based approach [9–19].

Zhu YH et al., measured the portion of the lesion that exhibited greater contrast enhancement and found that low contrast enhancement during the corticomedullary phase correlated with a high Fuhrman grade [14]. Vargas HA et al., reported that the correlation between the Fuhrman grade and contrast enhancement was significant only when measured in the entire lesion, compared with the portion with greater contrast enhancement on a single slice [15].

A further radiomics study showed that data obtained in the corticomedullary and nephrographic phases, separate or combined, could predict the Fuhrman grade in ccRCC [16]. Regarding small ccRCCs (<4 cm), no correlation was found between lesion contrast enhancement and the histological grade [17].

Birnbaum et al., reported that the majority of low-grade RCCs showed sharp or slightly irregular margins [18]. Furthermore, a study conducted by Ro et al., showed that defined margins are associated with less aggressive RCCs due to less infiltrative behavior [19]. On the other hand, no significant correlations were found between the morphological characteristics of the lesion and the Fuhrman grades in the small RCCs, probably due to the sample being comprised by tumors smaller than 4 cm [17].

Unenhanced CT found that low lesion attenuation was a predictor of a low Fuhrman grade. This low attenuation probably reflects the intracellular lipids content [17]. In fact, histological ccRCC can be rich in intracytoplasmic lipids and glycogen; the presence of intracytoplasmic lipids gives the characteristic "clear" appearance of ccRCC [15]. It has been shown that there is an inverse relationship between the histological grade and intra-cellular lipid droplets [20,21].

Additionally, Yao et al., showed that low-grade ccRCCs exhibited greater expression of adipose differentiation-related protein (ADFP), a protein involved in the uptake of fatty acids and the formation of intracellular lipid droplets, compared with high-grade ccRCCs. Increased ADFP expression correlates with increased intracytoplasmic lipid accumulation in low-grade ccRCC compared with high-grade ccRCC [22,23].

The non-invasive imaging approach with CT allows a correct qualitative and quantitative assessment of the tissues [24]. An interesting paradigm is based on the analysis of peritumoral tissues, such as local composition changes of perinephric fat with collateral vessels, or the assessment of whole-body imaging composition [25–31].

Here, we confirm the known association between greater ccRCC tumor size and a high Fuhrman grade [13]. Moreover, in the present study, we demonstrated for the first time a link between peritumoral collateral vessels and high Fuhrman grades in patients with ccRCC. The presence of collateral vessels can be explained as inability of the renal vein to drain venous blood also due to a tumor-related unbalance caused by an increase total size, cellularity and blood demand. These findings might cause dilation of the renal capsular veins, becoming macroscopically evident as collateral vessels in CT or MRI studies. Furthermore, the abnormal cellular architecture of the tumor due to hypercellularity diverts the blood flow toward "alternative routes" (e.g., dilated and macroscopically visible renal

capsular veins). Taken together, these mechanisms might explain the presence of collateral vessels in RCCs with high Fuhrman grades.

CcRCC can harbor inactivating mutations (or less commonly by ipermethylation) of the maternal or paternal copies of the Von Hippel Lindau (VHL) gene. When the VHL gene is inactive, the accumulated HIFα upregulates the transcription of genes that respond to tumorigenic hypoxia, including vascular endothelial growth factor A (VEGFA) and encoding VEGF, which stimulates the formation of blood vessels [32,33]. With respect to the change of vascular architecture due to the activity of VEGF, further studies will have to evaluate the relationship between perinephric fat collateral vessels and VEGF expression in ccRCC patients. Moreover, it would be interesting to assess whether hybrid genes formed by two previously independent genes (i.e., fusion genes) might play a role in the development of peritumoral collateral vessels adjacent to ccRCC.

The limit of this study is relying on the low number of ccRCC female patients, which does not allow for providing definitive answers on the possible association of peritumoral collateral vessels and high histological grades in this category of patients. Moreover, clinical variables such as the body mass index (BMI), data on R0/R1 resection and survival outcomes were not available due to the retrospective nature of the study.

Further studies will be conducted involving a larger sample of ccRCC female patients and with multiple clinical variables to increase the generalizability of the results.

7. Conclusions

This study shows a novel association between peritumoral collateral vessels in perinephric adipose tissue and high Fuhrman grades (i.e., III and IV) in male patients with ccRCC. Thus, peritumoral collateral vessels adjacent to ccRCC can be considered a diagnostic clue, suggestive of a more aggressive disease.

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Institutional Review Board Statement: All the procedures were retrospective and agreed with the Declaration of Helsinki. CT images and data of ccRCC patients were retrieved from The Cancer Imaging Archive (TCIA). The TCIA project received approval of the Institutional Review Board. This subsequent retrospective analysis was on the publicly available, anonymized data and did not require further review due to previous protections implemented by TCIA.

Informed Consent Statement: All the subjects enrolled signed a written informed consent.

Data Availability Statement: The data presented in this study are openly available in The Cancer Imaging Archive (https://wiki.cancerimagingarchive.net/display/Public/TCGA-KIRC, accessed on 1 November 2019).

Conflicts of Interest: The authors declare that they have no conflict of interest.

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