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The Relationship Between Hounsfield Unit Fuhrman Grades and Subtypes of Renal Cancers: Descriptive Research

Hounsfield Ünitesi Fuhrman Gradeleri ve Renal Kanserlerin Subtipleri Arasındaki İlişki: Tanımlayıcı Araştırma

Muharrem BATURU[a], Ahmet METE[b], Asaf DEMİRBAĞ[c], Ömer BAYRAK[a], Sakıp Mehmet ERTURHAN[a], Haluk ŞEN[a], İlker SEÇKİNER[a]

[a]Department of Urology, Gaziantep University Faculty of Medicine, Gaziantep, Türkiye
[b]Department of Radiology, Gaziantep University Faculty of Medicine, Gaziantep, Türkiye
[c]Clinic of Urology, Gaziantep Ersin Arslan Training and Research Hospital, Gaziantep, Türkiye

ABSTRACT Objective: To determine whether predicting tumor pathology and Fuhrman grade with Hounsfield Unit (HU) increase in computed tomography (CT) is possible. **Material and Methods:** The study was based on a retrospective evaluation of 71 patients who underwent radical nephrectomy or nephron-sparing surgery due to kidney tumors between May 2013 and May 2016. The patients were divided into 2 groups based on the HU change in the unenhanced and contrast-enhanced CT tumor images, namely the "0-30 HU" group and the ">30 HU" group. Pathological grading was performed in line with the 2010 American Joint Committee on Cancer TNM system, based on the phase of the tumor, size of the tumor, necrosis, and fat invasion. **Results:** Evaluation of the tumors' histological type revealed that 31 (43.7%) patients had non-clear cell renal cell carcinoma (RCC), while 40 (56.3%) had clear cell RCC. Twenty-two (61.1%) of the 36 patients with a 0-30 increase in HU had non-clear cell RCC, while 14 (38.9%) had clear cell RCC. Of the 35 patients who had >30 HU increase following the administration of the contrast agent, 9 (25.7%) patients were diagnosed with non-clear cell RCC, versus 26 patients (74.3%) were diagnosed with clear cell RCC (p=0.003). Values above 30 HU, which were considered as the threshold value, pointed out to clear cell RCC with 88.4% sensitivity, 89.3% specificity. **Conclusion:** The study's results suggested that a HU value greater than 30 indicated Fuhrman Grade 2-4 pathology and a clear-cell RCC pathology in a ratio of approximately 3:4.

Keywords: Computed tomography; renal tumors; pathological conditions; signs and symptoms

ÖZET Amaç: Bu çalışmanın amacı, bilgisayarlı tomografide (BT) Hounsfield Ünitesi (HU) artışı ile tümör patolojisini ve Fuhrman derecesini öngörmenin mümkün olup olmadığını belirlemektir. **Gereç ve Yöntemler:** Çalışma, Mayıs 2013 ile Mayıs 2016 tarihleri arasında böbrek tümörü nedeniyle radikal nefrektomi veya nefron koruyucu cerrahi uygulanan 71 hastanın retrospektif olarak değerlendirilmesine dayanmaktadır. Hastalar, kontrastsız ve kontrastlı BT tümör görüntülerindeki HU değişimine göre "0-30 HU" grubu ve ">30HU" grubu olmak üzere 2 gruba ayrılmıştır. Patolojik derecelendirme, 2010 Amerikan Kanser Ortak Komitesi TNM sistemi ile uyumlu olarak, tümörün fazı, tümörün boyutu, nekroz ve yağ invazyonu temelinde yapıldı. **Bulgular:** Tümörlerin histolojik tipi değerlendirildiğinde, 31 (%43,7) hastada berrak hücreli olmayan renal hücreli karsinom (RHK), 40 (%56,3) hastada ise berrak hücreli RHK olduğu görüldü. HU'da 0-30 artış olan 36 hastanın 22'sinde (%61,1) berrak hücreli olmayan RHK, 14'ünde (%38,9) berrak hücreli RHK vardı. Kontrast madde verilmesini takiben >30HU artışı olan 35 hastadan 9'na (%25,7) berrak hücreli olmayan RHK tanısı konurken, 26 hastaya (%74,3) berrak hücreli RHK tanısı konmuştur (p=0,003). Eşik değer olarak kabul edilen 30 HU üzerindeki değerler %88,4 duyarlılık, %89,3 özgüllük ile berrak hücreli RHK'ye işaret etmiştir. **Sonuç:** Çalışmanın sonuçları, 30'dan büyük HU değerinin yaklaşık 3:4 oranında Fuhrman Grade 2-4 patolojisine ve berrak hücreli RHK patolojisine işaret ettiğini göstermiştir.

Anahtar Kelimeler: Bilgisayarlı tomografi; böbrek tümörleri; patolojik durumlar; belirti ve semptomlar

Renal cell carcinoma (RCC) is the third most common type of urogenital cancer, after prostate and bladder cancers. In recent years, there has been a constant increase in renal cancer rates, mostly RCCs.[1] This issue is partly explained by the common use of ultrasound, computed tomography (CT), and magnetic resonance imaging for early diagnosis of asymptomatic cancers and other purposes.[2]

Correspondence: Asaf DEMİRBAĞ
Clinic of Urology, Gaziantep Ersin Arslan Training and Research Hospital, Gaziantep, Türkiye
E-mail: dr.asafdemirbag@gmail.com

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CT has high diagnostic performance for diagnosing renal cancer and evaluating the morphology and function of the contralateral kidney. Furthermore, CT helps to evaluate extrarenal extension and venous involvement of the primary tumor, as well as the status of lymph nodes and surrenal glands. In many publications, RCC subtypes were presented using dynamic multiphasic CT, where CT attenuation (density) measurements of renal masses in non-contrast imaging were used as a baseline. Other studies suggest that RCC subtyping can be performed using single-phase arterial/corticomedullary phase-contrast CT.[3-7] However, a recent study showed no significant differences in the attenuation values between pathologically proven RCC subtypes on non-contrast CT.[8]

This study aimed to evaluate the correlation between the changes in attenuation values predicted by CT on the Fuhrman grade and the histologic subgroup of renal cancer. In addition, Hounsfield Unit (HU) changes were analyzed to determine whether the tumor-adjacent renal parenchyma was also affected.

MATERIAL AND METHODS

STUDY PARTICIPANTS

The study was based on a retrospective evaluation of 71 patients who underwent radical nephrectomy (RN) or nephron-sparing surgery (NSS) for kidney tumors between May 2013 and May 2016.

Age, sex, urinalysis results, CT findings, and pathological results of the patients were recorded. Regarding surgical treatment, NSS was performed in 22 (30.9%) patients with tumor size ≤4 cm (T1a) and ≤7 cm (T1b), and if the operation was possible with respect to mass localization. In addition, RN was performed for tumors >4 cm (69.1%).

Ethics committee approval was received for this study from the Clinical Research ethics committee of Gaziantep University (date: November 28, 2016; no: 2016/314) and was performed following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

CT EXAMINATION PROTOCOL

The CT examination was conducted while the patient was in a supine position and held his/her breath. The 71 patients were examined using 64-section multidetector CT (Lightspeed VCT-XTe, General Electric, Milwukee, USA). The following parameters were used during the CT examination: 100 kV, 650 mAs, 5 mm slice thickness, 5 mm reconstruction interval, 0.8 sec rotation time, and 512×512 matrix. Using a 19-20-gauge catheter, a 100 mL contrast agent with a 300-320 mg/mL content was administered as an intravenous bolus into the antecubital vein. In all CT examinations, full non-contrast and contrast (arterial phase, 25-30 sec delay) images were obtained for both the kidneys.

ATTENUATION (HU) MEASUREMENT

Regarding HU measurements (attenuation values) of renal tumors, three separate measurements were performed for the non-contrast and contrast phases, and the average of these values was recorded. The region of interest (ROI) cursor was placed in matching positions in the non-contrast and contrast phases, and the same radiologist identified the highest density area. Calcification, cystic degeneration, or necrotic zones were left outside the areas where the ROI cursor was placed. The ROI was placed in the best possible extensive position (to cover the solid part of the tumor), close to the diameter of the tumor. HU measurements of the adjacent tumor parenchyma were made three times in the kidney with the tumor, and the average of these values was recorded (Figure 1).

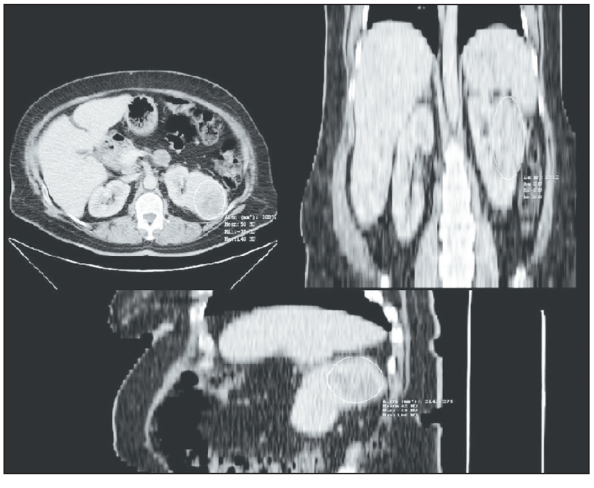


FIGURE 1: Calculation of Hounsfield Unit

PATHOLOGICAL EVALUATION

Pathological grading was performed in accordance with the 2010 American Joint Committee on Cancer (AJCC) TNM system, based on tumor phase, tumor size, necrosis, and fat invasion. A single urologic pathologist examined all specimens. No biopsies were obtained for pathological diagnosis before the patients underwent surgery.

THE FUHRMAN GRADING SYSTEM

Over the years, many systems have been suggested for grading RCCs. Among them, the one suggested by Fuhrman et al. has been the most acknowledged.[9] What differentiates the Fuhrman Grade from other grading systems is that the prominence of the nucleoli and nucleus size are evaluated under a microscope. In addition, the system has a 4-group classification based on the structure of the nucleus.[10]

STATISTICAL ANALYSIS

The SPSS 22 for Windows (IBM Corporotion, USA) statistical package was used for statistical analysis, and data were expressed as arithmetic average and standard deviation. The chi-square distribution test was conducted to calculate categorical variables, and Mann-Whitney U test was to compare averages. A reliability interval of 95% ($p<0.05$) was considered to be statistically significant.

RESULTS

NSS was performed in 22 (30.9%) patients and RN was performed in 49 (69.1%) patients. The mean age was 55.8 (18-79) years (Table 1).

According to the AJCC on cancer classification system, 31 (43.7%) patients had non-clear cell RCC and 40 (56.3%) patients had clear cell RCC. In the non-clear and clear cell RCC patient groups, the average HU increases in the contralateral kidney, tumor-adjacent parenchyma, and tumor tissues were compared based on the pre-contrast phase. Mean values were calculated as 26.4±5.3, 30.9±9.7 and 32.7±15.4 in the non-clear cell RCC group, and 29.2±6.3, 29.8±7.8 and 32.8±9.8 in the clear-cell RCC group (p=0.85, p=0.70 and p=0.80, respectively).

TABLE 1: The demographic data of the patients.

Variable	Value
Age (years)	55.8 (18-79)
Sex	
Male	48 (67.6%)
Female	23 (32.4%)
Localization	
Right	31 (43.7%)
Left	40 (56.3%)
Bilateral	0 (0%)
Tumor placements	
Upper pole	20 (28.1%)
Middle zone	31 (47.8%)
Lower pole	20 (28.1%)
Pathological stage	
T1a	29 (40.8%)
T1b	18 (25.3%)
T2	10 (14%)
T3	8 (11.2%)
T4	6 (8.4%)
Surgery	
NSS	22 (30.9%)
RN	49 (69.1%)

NSS: Nephron sparing surgery; RN: Radical nephrectomy.

The difference between the average HU values of the tumor and tumor-adjacent parenchyma was compared in the pre-contrast phase. The values were measured as 1.8 HU in non-clear cell RCC and 3 HU in clear cell RCC (p=0.72). While the average HU values of the parenchyma neighboring the tumor and parenchyma of the contralateral healthy kidney were 30.3±8.7 and 28±6 in the non-contrast phase, the values were measured as 114±33.3 and 114.4±31.2 in the contrast phase (p=0.55, p=0.55 respectively) (Table 2).

In the present study, the average increase in HU after administration of the contrast agent was 30 HU for all lesions. The values below and above 30 were compared with histological types. Since the result was statistically significant, 30 HU was considered a threshold value. On radiological examination, 22 of 36 (61.1%) patients with a 0-30 increase in HU were diagnosed with non-clear cell RCC. In comparison, 14 (38.9%) patients were diagnosed with clear cell

TABLE 2: The HU values of the tumor contiguous parenchyma and contralateral healthy kidney parenchyma.

	Non-contrast phase	Contrast phase	p value
HU values of the tumor contiguous parenchyma	30.3±8.7	114±33.3	0.55
HU values of the contralateral healthy kidney parenchyma	28±6	114.4±31.2	0.55

HU: Hounsfield Unit.

TABLE 3: The HU threshold, RCC subtype and Fuhrman grade correlation.

Fuhrman grade	HU increase between 0-30	>30 HU increase	Average HU increase	Tumor pathology
Fuhrman Grade 1 n, (%)	10 (100)	0 (0)	11.1±5.1	Non-clearcell 6 (60) Clear cell 4 (40)
Fuhrman Grade 2 n, (%)	11 (36.6)	19 (63.4)	28.26±22.5	Non-clearcell 15, (50) Clear cell 15, (50)
Fuhrman Grade 3 n, (%)	6 (20.6)	23 (79.4)	52.96±24.2	Non-clearcell 7, (24.1) Clear cell 22, (75.9)
Fuhrman Grade 4 n, (%)	0 (0)	2 (100)	85±7	Clear cell 2 (100)

HU: Hounsfield Unit; RCC: Renal cell carcinoma.

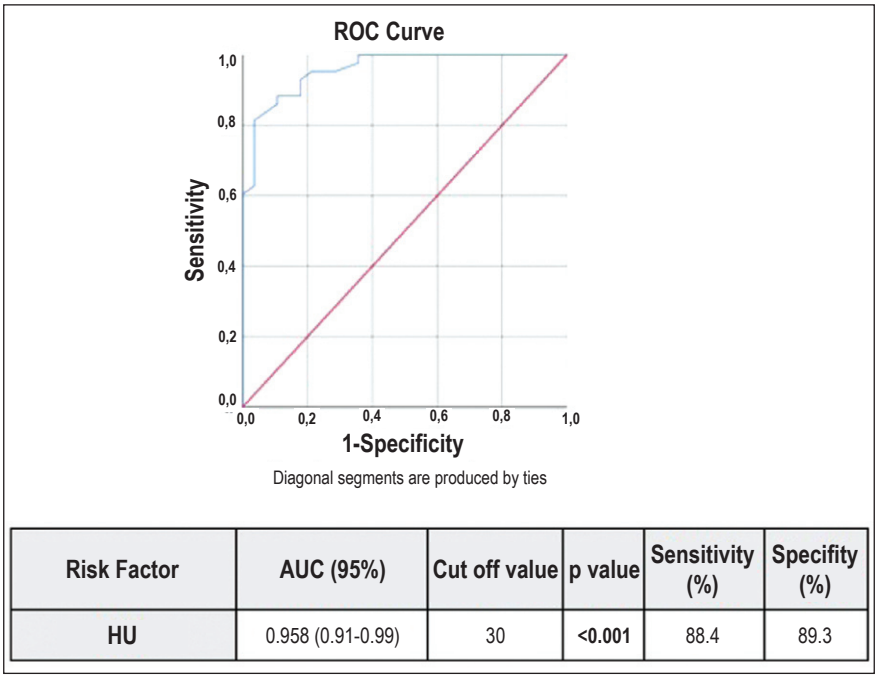
RCC, suggesting that non-clear cell RCC is more common in patients with lower HU values (p<0.001). Among the 35 patients who had a >30 HU increase following the administration of the contrast agent, 9 (25.7%) patients were diagnosed with non-clear cell RCC, while 26 (74.3%) patients were diagnosed with clear cell RCC (p=0.003). Values above 30 HU, which were considered the threshold value, indicated clear cell RCC with 88.4% sensitivity, 89.3% specificity (p<0.001) (Figure 2).

There was a statistically significant correlation between the changes in HU, RCC subtype, and Fuhrman grade (p<0.001 and p<0.001, respectively) (Table 3). In 31 patients diagnosed with non-clear cell RCC, the average HU increase was 25.6±18.8, and 21 patients (67.6%) had Fuhrman Grade 1-2. In 40 patients diagnosed with clear cell RCC, the average HU increase was 42.44±25.6, among whom 36 (90%) patients had Fuhrman Grade 2 and above (p<0.003) (Table 4).

DISCUSSION

Several retrospective studies have identified different contrast changes in different RCC subtypes. Herts et al. compared papillary-RCC (PRCC) with other subtypes in 90 (12 PRCC, 66 non-papillary RCC, and 12 benign lesions) patients, and lower levels of contrast agent involvement were interpreted in favor of PRCC since it was hypovascular and homogenous.[11] PRCC and clear cell RCC were compared in another study, and a lower change was observed with contrast agents in PRCC.[12] This study suggests that such differences result from differences in intratumoral vascularization. Similarly, Zhang et al. compared 198 patients with kidney tumors [108 (55%) with clear cell RCC, 90 (45%) with non-clear cell RCC]. They observed a higher contrast change in clear cell RCC due to hypervascularity.[13] Young et al. observed the highest level of contrast agent involvement in clear-cell RCC. Clear cell RCC has a higher level of contrast agent involvement because it has a rich vein network.[14] In our study, the highest increase in the HU values of the masses was also observed in clear cell RCC. We found an average HU increase in non-clear cell RCC 25.6±18.8 and clear cell RCC 42.44±25.6, respectively (p<0.003).

Zokalj et al. suggested that in RCC patients who required minimal invasive treatments and/or targeted treatments instead of biopsy, contrasting measurements in arterial phase CT examinations might be used as an auxiliary method to distinguish the most common solid forms of RCC subtypes.[15] Different



Risk Factor	AUC (95%)	Cut off value	p value	Sensitivity (%)	Specifity (%)
HU	0.958 (0.91-0.99)	30	<0.001	88.4	89.3

FIGURE 2: ROC analysis of HU according to tumor histology.
HU: Hounsfield Unit; AUC: Area under the curve.

TABLE 4: The HU values of the tumor pathology, average HU increase and Fuhrman grade.

	Non-contrast HU	Contrast HU	Average HU increase	Fuhrman Grade (n, %)
Non-clearcell RCC	32.70±15.4	58.35±20	25.6±18.8	Grade 1: 6 (19.3) Grade 2: 15 (48.3) Grade 3: 10 (32.2) Grade 4: 0 (0)
Clear cell RCC	32.85±9.8	75.4±28.4	42.44±25.6	Grade 1: 4 (10) Grade 2: 13 (32.5) Grade 3: 21 (52.5) Grade 4: 2 (5)

HU: Hounsfield Unit; RCC: Renal cell carcinoma.

studies have indicated that the utilization of arterial phase CT in surgical treatment planning provides better imaging of arterial vascularization in both kidneys and tumors.[16,17] In the present study, we used the arterial phase to distinguish kidney tumor subtypes. Furthermore, our results showed that the arterial phase was effective for RCC subtyping.

In their study on small renal masses of 4 cm, Mancini et al. evaluated the difference between the average HU values in the tumor-adjacent parenchyma. The difference was highest in clear cell RCC with 10 HU, whereas it was 4 HU in chromophobe RCC, 5 HU in papillary RCC, and 4.5 HU in oncocytoma.[18] In our study, these values were 1.8 HU and 3 HU for non-clear and clear cell RCC, respectively. In our study, the value was also higher in clear cell RCC, but the difference was not statistically significant, which can be explained by the hypervascularity in clear cell RCC.

In the literature, there are few publications on Fuhrman Grade and the level of HU changes in the kidney. Young et al. analyzed 65 cases of clear cell

RCC and divided them into 2 groups according to Fuhrman grading: low-grade (Fuhrman Grade 1-2) and high-grade (Fuhrman Grade 3-4), according to Fuhrman grading. The rates of change in contrast enhancement were calculated using the formula HU/aorta HU.[14] The changes in HU according to the Fuhrman Grade were more significant in the low-grade groups; conversely, more HU changes in tumors and higher Fuhrman Grades were observed in contrast-enhanced images in our study. In a recent study, Choi et al. evaluated 101 patients with small clear cell RCC. They emphasized that low-grade tumors had homogenous or relatively homogenous enhancement patterns, high-grade tumors had heterogeneous enhancement patterns, and low-grade tumors had lower attenuation on unenhanced scan.[19] Zhu et al. stated that high-grade tumors had significantly lower enhancement in patients with clear cell RCC. Their study used cutoff value in the corticomedullary phase 84 HU and in the excretory phase 44 HU.[20]

The most significant factors limiting our study were its retrospective nature and small number of patients. Additional studies that involve detecting the level of HU change in both the tumor-adjacent renal parenchyma and tumor lesion with a larger sample size may be advantageous for obtaining more precise RCC subtyping.

In conclusion, the 0-30 HU increases suggests the possibility of Fuhrman Grade 1-2 and approximately 67% non-clear cell RCC pathology. Increases in HU above 30 suggest the possibility of Fuhrman Grade 2 and above, and approximately 72% clear cell RCC pathology in the contrasting series. While this value may vary in studies that can be performed with a broader series, the 30 HU value in our study may be a practical threshold value for RCC subtyping. Furthermore, to our knowledge, we have yet to come across a similar threshold value that can be used in RCC subtyping in the literature.

CONCLUSION

In conclusion, the 0-30 HU increases suggest the possibility of Fuhrman Grade 1-2 and approximately 67% non-clear cell RCC pathology. Increases of HU above 30 suggest the possibility of Fuhrman Grade 2 and above and approximately 72% clear cell RCC pathology in contrasting series. While this value may vary in studies that can be performed with broader series, the 30 HU value, we found in our study, maybe a practical threshold value for RCC subtyping. Furthermore, to our knowledge, we have yet to come across a similar threshold value that can be used in RCC subtyping in the literature.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Asaf Demirbağ, Ahmet Mete, Ömer Bayrak;* ***Design:*** *Muharrem Baturu, Sakıp Mehmet Erturhan;* ***Control/Supervision:*** *İlker Seçkiner, Haluk Şen;* ***Data Collection and/or Processing:*** *Asaf Demirbağ, Muharrem Baturu;* ***Analysis and/or Interpretation:*** *Ömer Bayrak, Ahmet Mete;* ***Literature Review:*** *Muharrem Baturu;* ***Writing the Article:*** *Muharrem Baturu, Asaf Demirbağ;* ***Critical Review:*** *Sakıp Mehmet Erturhan;* ***References and Fundings:*** *Ömer Bayrak;* ***Materials:*** *Muharrem Baturu, Haluk Şen.*

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