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Comparison of Three-dimensional Calculated Tumor Size, Radiologic Tumor Size, and Pathologic Tumor Size in Renal Cell Carcinoma

Renal Hücre Karsinomunda Üç Boyutlu Yöntemle Hesaplanmış Tümör Boyutu, Radyolojik Tümör Boyutu ve Patolojik Tümör Boyutunun Karşılaştırılması

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ABSTRACT Objective: The aim of the study was to investigate the correlation between tumor sizes of surgical specimens and tumor sizes obtained preoperatively by radiology and three-dimensional (3D) segmentation in our series. **Material and Methods:** All patients underwent an intravenous contrast-enhanced abdominal computed tomography (CT) within 4 weeks before surgery. The size of the tumor on CT was measured in coronal, sagittal and transverse axes. The radiologic tumor size (RTS) was defined as the largest of these three measurements. Tomography data were uploaded to 3D segmentation software (Dornheim Segmenter?). The largest diameter of the tumor was measured and defined as 3D-calculated tumor size (3DTS).The largest diameter of the tumor in the pathologic specimen was defined as the pathologic tumor size (PTS). Afterward, the mean measurements of RTS, PTS, and 3DTS were calculated and compared. **Results:** A total of 113 patients were included in the study. Mean age was 64.2±13.1 years. There were 61 (54%) men and 52 (46%) women. While 65 (57.5%) patients underwent radical nephrectomy (RN), 48 (42.5%) underwent partial nephrectomy (PN). The most common histology was clear cell 93 (82.3%) while the most common pathologic stage was T2a 40 (35.4%). The mean 3DTS was 7.5±3.2, the mean RTS was 7.1±3.1 cm and the mean PTS was 6.8±2.8 (p <0.001). Comparison of 3 DTS, PTS, and PTS according to the grade revealed that high-grade tumors seem to be larger than low-grade tumors with all of 3 measurement methods. **Conclusion:** Our study found that RTS was overestimated compared to PTS. Similarly, 3DTS of a tumor was overestimated compared to PTS. Additionally, we found that high-grade tumors were larger than low-grade tumors. Three-dimensional measurement of tumor size could be utilized preoperatively for assessment of tumor. However, it should be kept in mind that three-dimensional imaging modalities could overestimate the tumor size compared to pathologic specimens.

Keywords: Kidney; carcinoma, renal cell; imaging, three-dimensional; neoplasm staging

ÖZET Amaç: Çalışmamızın amacı, serimizdeki operasyon öncesi radyoloji ve 3 boyutlu (3D) segmentasyon analizi ile elde edilen tümör boyutlarını cerrahi örneklerden elde ile tümör boyutları ile karşılaştırmak idi. **Gereç ve Yöntemler:** Tüm hastalara ameliyattan önceki 4 hafta içinde intravenöz kontrastlı abdominal bilgisayarlı tomografi (BT) çekildi. Tomografide tümör boyutu koronal, sagital ve enine eksenlerde ölçüldü. Radyolojik tümör boyutu (RTS) bu üç ölçümün en büyüğü olarak tanımlandı. Tomografi verileri 3D segmentasyon yazılımına (Dornheim Segmenter?) yüklendi. Tümörün en büyük çapı ölçüldü ve 3D- hesaplanmış tümör büyüklüğü (3DTS) olarak tanımlandı. Patolojik örnekteki tümörün en büyük çapı patolojik tümör büyüklüğü (PTS) olarak tanımlandı. Daha sonra, ortalama RTS, PTS ve 3DTS ölçümleri hesaplandı ve karşılaştırıldı. **Bulgular:** Toplamda 113 hasta bu çalışmaya dahil edildi. Yaş ortalaması 64.2±13.1 idi. Altmış bir (%54) erkek ve 52 (%46) kadın vardı. Bu hastalardan 65'ine (%57,5) radikal nefrektomi (RN), 48'ine (%42,5) parsiyel nefrektomi (PN) uygulandı. En sık görülen histoloji, berrak hücreli 93 (%82,3) iken, en yaygın patolojik evre T2a 40 (%35,4) idi. Ortalama 3DTS 7,5 ±3,2, ortalama RTS 7,1±3,1 cm ve ortalama PTS 6,8±2,8 idi (p <0,001). 3 DTS, PTS ve PTS' nin tümör derecesine göre karşılaştırıldığında, yüksek dereceli tümörlerin, üç ölçüm yönteminin hepsinde düşük dereceli tümörlerden daha büyük ölçülmesiyle sonuçlanmıştır. **Sonuç:** Çalışmamız RTS'nin PTS ile karşılaştırıldığında fazla hesaplandığını buldu. Benzer şekilde, bir tümörün 3DTS'si PTS'ye kıyasla fazla hesaplandı. Ek olarak, yüksek dereceli tümörlerin düşük dereceli tümörlerden daha büyük olduğunu bulduk. Tümörün değerlendirilmesinde preoperatif olarak tümör boyutunun üç boyutlu ölçümü kullanılabilir. Bununla birlikte, üç boyutlu görüntüleme yöntemlerinin, patolojik örneklerle karşılaştırıldığında tümör boyutunu abartabileceği akılda tutulmalıdır.

Anahtar Kelimeler: Böbrek; karsinom, renal hücreli; görüntüleme, üç-boyutlu; tümör evrelemesi

Renal cell cancer (RCC) accounts for 2–3 % of whole cancers. The increased usage of modern imaging techniques leads to a rising of incidentally diagnosed kidney tumors.[1-3] Tumor size is a crucial factor for the staging and treatment of RCC. Prognosis of RCC is straight connected to the spread of the disease, and staging is the most significant prognostic agent for survival.[4] Size of RCC differs in possible metastatic potential and responsiveness to the surgical or immunotherapeutic or antiangiogenic therapies.[5] Accurate staging is important for selecting the optimum treatment, especially, when choosing between radical nephrectomy (RN) and partial nephrectomy (PN). The decision of PN is generally made by the radiographic size of the renal masses on preoperative intravenous contrast-enhanced abdominal computed tomography (CT). Consequently, the correlation of the radiographic size of renal tumors to the pathologic size is significant. There are several studies in the literature searching this relationship. Generally, the RTS of the tumor was seen overestimated up to 1 cm compared to PTS.[6-8] Three-dimensional (3D) volume segmentation is a new method obtaining detailed anatomy of the soft tissue. Recently some studies were conducted both to measure the radiologic tumor volume (RTV) via this novel method and make a comparison with pathologic tumor volume (PTV).[9-12]

In this study, we investigated for a relationship between tumor sizes in surgical specimens and tumor sizes, obtained preoperatively by radiology and 3D segmentation.

MATERIAL AND METHOD

STUDY POPULATION

In this study, charts of 113 patients who underwent RN or PN for non-metastatic RCC at our institute between 2010 and 2019 were reviewed. Selection of patients for analysis was based on surgical treatment for a unilateral kidney tumor. We excluded the patients with a solitary kidney and patients with incomplete data from this study. The study has been approved by the Ethics Committee of the institution and that it conforms to the provisions of the Declaration of Helsinki (T.C Health Sciences University Okmeydanı Training and Research Hospital, Date: 24.09.2018, Number: 48670771-514.10/981).

All patients underwent an intravenous contrast-enhanced abdominal CT within 4 weeks before surgery. The size of the tumor on CT was measured in coronal, sagittal and transverse axes. The radiologic tumor size (RTS) was defined as the largest of these three measurements. Tomography data were uploaded to 3D segmentation software (Dornheim Segmenter™). Segmentation of kidney parenchyma and tumor were done by a semiautomatic tool of the segmentation software. Subsequently, the largest diameter of the tumor was measured and defined as 3D- calculated tumor size (3DTS), (Figure 1). The largest diameter of the tumor in the pathologic specimen was defined as the pathologic tumor size (PTS). Afterward, the mean measurements of RTS, PTS, and 3DTS were calculated. Age, gender, tumor sizes, TNM stage, histological subtype, and Fuhrman grade were collected from patients records. The staging was done clinically separately for 3DTS and RTS and pathologically (PTS) according to the American Joint Committee on Cancer.[13] Downstaging or upstaging of tumors were determined by comparing these stage among them.

STATISTICAL ANALYSIS

The study was conducted as a retrospective case-control series. Continuous variables were expressed as mean and compared using the Student's t-test, whereas, categorical variables were expressed as the percentages and compared using the Chi-square test. The analyses of repeated measures were compared with Friedman test. The data were analyzed with the Statistical Package for Social Sciences (SPSS) version 22.0™ (IBM Corporation, California). All p values were two-tailed and a p-value of <0.05 was considered statistically significant.

RESULTS

A total of 113 patients were included in the study. Mean age was 64.2±13.1 years. The patient demo-

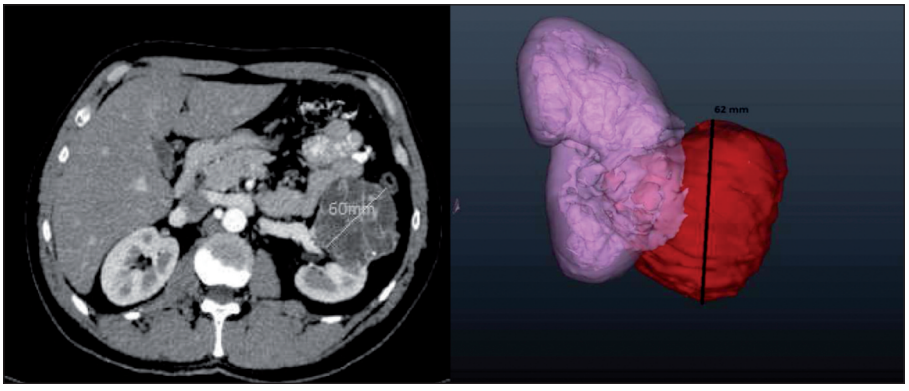

FIGURE 1: Measurement of RTS and 3-DTS.

graphics are listed in Table 1. There were 61 (54%) men and 52 (46%) women. Among these patients, 65 (57.5%) underwent RN, and 48 (42.5%) underwent PN. The most common histology was clear cell 93 (82.3%) while the most common pathologic T stage was T2a 40 (35.4%). The mean 3DTS was 7.5±3.2, the mean RTS was 7.1±3.1 cm and the mean PTS was 6.8±2.8 ($p < 0.001$). Three-Dimensional scatter-dot graphic of 3DTS, RTS, and PTS is depicted in Figure 2.

Mean measurements of 3DTS, RTS, and PTS according to the pT stages is summarized in Table 2. Inconsistency between 3DTS and PTS resulted in clinical under or over staging depicted in Table 3. Likewise, the distribution of up-staging and down-staging according to the RTS and PTS is shown in Table 4. Comparison of 3DTS and PTS as stratified by pT stages is demonstrated in Table 5. 3DTS overestimates the tumor size in all stages. Comparison of RTS and PTS as stratified by pT stages is summarized in Table 6. It is obvious that when RTS is greater than 7 cm, radiology statistically overestimates the tumor size. Comparison of 3DTS, RTS, and PTS according to the grade is demonstrated in Table 7. High-grade tumors seem to be larger than low-grade tumors with all of 3 measurement methods.

TABLE 1: Patient characteristics.

	Patients Mean±S.D. (n%)
Age	64.2±13.1
3-D calculated tumor size (3DTS)	7.5±3.2
Radiologic tumor size (RTS)	7.1±3.1
Pathologic tumor size (PTS)	6.8±2.8
Sex Male	61 (54%)
Female	52 (46%)
Pathologic stage	
T1a	23 (20.4%)
T1b	35 (31.0%)
T2a	40 (35.4%)
T2b	15 (13.3%)
Histology	
Clear cell	93 (82.3%)
Chromofob	11 (9.7%)
Sarcomatoid	1 (0.9%)
Papillary	8 (7.1%)
Grade	
1	15 (13.3%)
2	59 (52.2%)
3	28 (24.8%)
4	8 (7.1%)
Operation type	
Radical nephrectomy	65 (57.5%)
Partial nephrectomy	48 (42.5%)

DISCUSSION

We investigated a relationship between surgical specimens and tumor sizes obtained by pre-operative CT and 3D segmentation in the current study. In our study, the mean 3DTS was 7.5±3.2, the mean RTS was 7.1±3.1 cm and the mean PTS was 6.8±2.8 ($p < 0.001$). We found that RTS was overestimated compared with PTS. Similarly, 3DTS of a tumor was overestimated compared with PTS. These re-

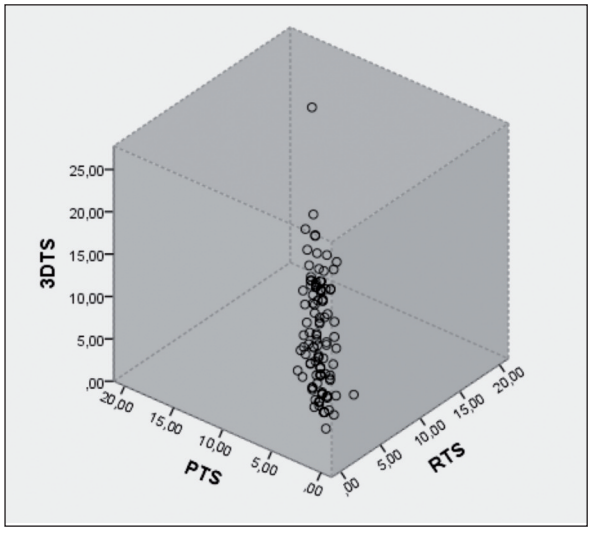

FIGURE 2: Three-Dimensional Scatter-Dot Graphic of 3-DTS, RTS, and PTS.

sults support the results of the previous studies.[7,8,14] Although, some studies are also available reporting no significant difference between RTS and PTS.[15,16] They are limited in their evaluation because of one-dimensional measurement. However, renal tumors have a variable three-dimensional shape. Therefore, our study emphasizes the importance of utilizing a three-dimensional volumetric method to measure.

Seçil et al., measured the radiologic tumor volume (RTV) with the help of a View-Forum workstation that can process 3D images.[17] In another study, RTV was measured with the help of a medical imaging processing system for measurements of volumetric.[18] Choi et al., measured the RTV using Xelis software.[9] They found that the mean RTS was 5.00 cm and the mean PTS was 4.84 cm ($p<0.001$). In their study, the RTV importantly overestimated PTV, especially, when PTS less than 7 cm. They claim that this new method might suggest a more precise measurement of volume irrespective of tumor shape.[9] In the current study, similarly, 3DTS of a tumor was overestimated compared to PTS. This phenomenon may explain by tumor shrinkage secondary to vasoconstriction after surgery.[16] After surgical resection, because of a loss of blood in the mass, renal tumor size is generally reduced.[7] Also, it should be kept in mind that formalin fixation might cause shrinkage of the tumor to some degree.[14,19]

Tumor size is a significant factor in the staging of organ-confined renal masses. Discrimination up to stage T2 is done concerning the size of a tumor. In our study, clinical under or over-staging occurred in 23 of 113 patients in the comparison between 3DTS and PTS. Likewise, clinical under or over-staging occurred in 30 of 113 patients in the comparison between RTS and PTS. Ateş et al., reported that the comparison between radiographic and pathologic tumor sizes has resulted in clinical under and over-staging in 19 of 86 individuals in their study.[15] Kurta et al., reported that pathologic tumor stage was found to be pT1a in 30 of 258 patients with stage cT1b and higher.[20] They concluded that the shift in stage might have implications on choosing the treatment method, which occurred only in a few patients and which is not a clinically significant problem.[15,20]

Our study revealed that high-grade tumors were larger than low-grade tumors. Similarly, Seçil et al., reported that when RTV rises, the Fuhrman grade also rises for whole patients.[17] Choi et al., found that RTV correlated with pathologic grade.[9]

Our study had some limitations. First is the retropsective and single-center design of the study. Secondly, a sub-analysis was not performed for

TABLE 2: Averages as stratified by pT stages.

Stage	n	3DTS	RTS	PTS	p-value
T1a (<4)	23	3.9±1.0	3.6±1.1	3.5±1.0	**<0.001**
T1b (4-7)	35	5.8±1.1	5.4±0.9	5.3±1.1	**<0.001**
T2a (7-10)	40	9.4±1.7	8.8±1.8	8.3±1.3	**<0.001**
T2b (>10)	15	12.2±2.6	11.8±2.6	11.1±2.3	**<0.001**
All Cohort	113	8.2±3.2	7.7±3.3	7.4±2.8	**<0.001**

TABLE 3: Distribution of up-staging and down-staging according to the 3DTS and PTS.

3D-cT	pT	n	Change in status
T1b	T1a	4	Down-staging
T2a	T1b	3	Down-staging
T2b	T2a	13	Down-staging
T1a	T1b	2	Up-staging
T2a	T2b	1	Up-staging

TABLE 4: Distribution of up-staging and down-staging according to the RTS and PTS.

RTS-cT	pT	N	Change in status
T1b	T1a	8	Down-staging
T2a	T1b	7	Down-staging
T2b	T2a	6	Down-staging
T1a	T1b	4	Up-staging
T1b	T2a	2	Up-staging
T2a	T2b	3	Up-staging

non-clear cell histology due to the relatively small number of cases.

CONCLUSION

Three-dimensional tumor size can be measured using a 3D rendering program. To the best of our knowledge, this is the first study which compares three- dimensional calculated tumor size with pathologic size in renal cell carcinoma. Our study found that RTS was overestimated compared to PTS. Similarly, 3DTS of a tumor was overestimated compared to PTS. Additionally, we found that high-grade tumors were larger than low-grade tumors. Three-dimensional measurement of tumor size could be utilized preoperatively for assessment of tumor. However, it should be kept in mind that three-dimensional imaging modalities could overestimate the tumor size compared to pathologic specimens.

TABLE 5: Comparison of 3DTS and PTS as stratified by pT stages.

Stage	n	3-DTS	PTS	p-value
T1a (<4)	23	3.9±1.0	3.5±1.0	**0.006**
T1b (4-7)	35	5.8±1.1	5.3±1.1	**0.003**
T2a (7-10)	40	9.4±1.7	8.3±1.3	**<0.001**
T2b (>10)	15	12.2±2.6	11.1±2.3	**0.001**
All Cohort	113	8.2±3.2	7.4±2.8	**<0.001**

TABLE 6: Comparison of RTS and PTS as stratified by pT stages.

Stage	n	RTS	PTS	p-value
T1a (<4)	23	3.6±1.1	3.5±1.0	0.590
T1b (4-7)	35	5.4±0.9	5.3±1.1	0.903
T2a (7-10)	40	8.8±1.8	8.3±1.3	**0.011**
T2b (>10)	15	11.8±2.6	11.1±2.3	**0.005**
All Cohort	113	7.7±3.3	7.4±2.8	**0.004**

TABLE 7: Comparison of 3DTS, RTS, and PTS according to the grade.

Grade	3DTS	RTS	PTS	p-value
1	6.6±3.2	6.1±3.1	5.7±2.7	**<0.001**
2	7.9±3.1	7.2±3.2	7.2±2.7	**<0.001**
3	8.5±2.8	8.1±2.9	7.6±2.6	**<0.001**
4	10.2±3.7	9.9±3.6	9.4±3.0	**<0.001**

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: *Sait Özbir;* ***Design:*** *Sait Özbir, Hasan Anıl Atalay;* ***Control/Supervision:*** *Sait Özbir, Hasan Anıl Atalay;* ***Data Collection and/or Processing:*** *Hasan Anıl Atalay;* ***Analysis and/or Interpretation:*** *Sait Özbir;* ***Literature Review:*** *Sait Özbir;* ***Writing the Article:*** *Sait Özbir;* ***Critical Review:*** *Sait Özbir, Hasan Anıl Atalay.*

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