ORGINAL ARTICLE

INVESTIGATION OF THE RATE OF BENIGN HISTOLOGY AND RELATED FACTORS IN CLINICAL STAGE T1 KIDNEY TUMORS

Klinik Evre T1 Böbrek Tümörlerinde Benign Histoloji Sıklığı ve İlişkili Faktörlerin İncelenmesi

Serkan YILDIZ[1], Muhammet Sahin YILMAZ[2], Alihan KOKURCAN[3], Idris Kıvanc CAVILDAK[4], Burhan BAYLAN[5], Alper GOK[6]

[1]Istinye State Hospital, Clinic of Urology, İstanbul, Türkiye.

[2]Samsun University Faculty of Medicine, Department of Urology, Samsun, Türkiye.

[3]Hitit University Çorum Erol Olçok Training and Research Hospital, Clinic of Urology, Çorum, Türkiye.

[4]Liv Hospital Samsun, Clinic of Urology, Samsun, Türkiye.

[5]Afyonkarahisar University of Health Sciences Faculty of Medicine, Department of Urology, Afyonkarahisar, Türkiye.

[6]Ankara Etlik City Hospital, Clinic of Urology, Ankara, Türkiye.

Serkan YILDIZ, MD. (https://orcid.org/0000-0001-6717-5743) ✉ s_yildiz55@yahoo.com

Muhammet Şahin YILMAZ, Assist. Prof. Dr. (https://orcid.org/0000-0001-8713-8675) ✉ mardarli_sahin@hotmail.com

Alihan KOKURCAN, MD. (https://orcid.org/0000-0003-3486-108X) ✉ alihankokurcan@gmail.com

İdris Kıvanç CAVILDAK, MD. (https://orcid.org/0000-0003-0149-7146) ✉ icavildak@gmail.com

Burhan BAYLAN, Assoc. Prof. (https://orcid.org/0000-0002-5509-7140) ✉ baylanburhan@gmail.com

Alper GÖK, Prof. Dr. (https://orcid.org/0000-0001-6874-4151) ✉ alper_gok@hotmail.com

Contact:
Muhammet Şahin YILMAZ, Samsun University Faculty of Medicine, Department of Urology, Samsun, Türkiye.

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ABSTRACT

Objectives: To compare the relationship between a benign pathology of preoperative parameters of renal masses <7cm (T1) in diameter. To evaluate the prevalence and identify predictors of benign histopathology in renal masses smaller than 7 cm (T1 stage).

Materials and Methods: Patients who underwent radical nephrectomy (RN) or partial nephrectomy (PN) for renal masses < 7 cm (T1) at Ankara City Etlik Hospital, between January 2007 and June 2016 were evaluated retrospectively. Data including age, gender, smoking history, comorbidities (diabetes mellitus, hypertension, dyslipidemia, obesity), presentation symptoms or signs (hematuria, weight loss, hypertension), tumor size, location, laterality, the pattern of growth (endophytic/exophytic) and character (cystic/ solid) were collected.

Results: Overall, 243 patients underwent surgery for a renal tumor. Among these, 58 (23.8%) had benign, and 185 (76.2%) had malignant tumor histopathology. Female sex (63.8%) was significantly higher in the benign tumor group (p=0.004). There was no significant difference between the groups regarding age, tumor size, smoking history and comorbidities, laterality (left/right), presentation symptoms, tumor location (upper/middle/lower pole), the pattern of growth (endophytic/exophytic) and character (cystic/ solid) were observed pathological results to impact not significantly (p>0.05). No significant differences were observed between the groups in terms of age, tumor size, smoking history, comorbidities, laterality, presentation symptoms, tumor location, growth pattern, or tumor characteristics (p>0.05).

Conclusion: In our study, the female gender was associated with benign histopathology in small renal tumors. As a result, predictors before surgery may be considered due to the high rate of benign pathology of small renal masses.

Keywords: *Renal Cell Carcinoma; Cancer of Kidney; Nephrectomy; Benign Neoplasms*

ÖZET

Amaç: Çapı <7 cm (T1) olan renal kitlelerde preoperatif parametrelerin benign patoloji ile ilişkisini karşılaştırmak.

Gereç ve Yöntemler: Ocak 2007 ile Haziran 2016 arasında Ankara Şehir Etlik Hastanesi'nde çapı <7 cm (T1) olan renal kitleler nedeniyle radikal nefrektomi (RN) veya parsiyel nefrektomi (PN) uygulanan hastalar retrospektif olarak değerlendirildi. Yaş, cinsiyet, sigara öyküsü, komorbiditeler (diabetes mellitus, hipertansiyon, dislipidemi, obezite), başvuru semptom veya bulguları (hematüri, kilo kaybı, hipertansiyon), tümör boyutu, yerleşimi, tarafı, büyüme paterni (endofitik/ekzofitik) ve karakteri (kistik/solid) dahil olmak üzere veriler toplandı.

Bulgular: Toplamda 243 hastaya renal tümör nedeniyle cerrahi uygulandı. Bunların 58'inde (%23,8) benign, 185'inde (%76,2) malign tümör histopatolojisi vardı. Benign tümör grubunda kadın cinsiyet (%63,8) anlamlı olarak daha yüksekti (p=0,004). Yaş, tümör boyutu, sigara öyküsü ve komorbiditeler, taraf (sol/sağ), başvuru semptomları, tümör yerleşimi (üst/orta/alt pol), büyüme paterni (endofitik/ekzofitik) ve karakteri (kistik/solid) açısından gruplar arasında anlamlı fark gözlenmedi ve patolojik sonuçlar üzerinde anlamlı bir etkisi olmadığı görüldü (p>0,05).

Sonuç: Çalışmamızda küçük renal tümörlerde kadın cinsiyet benign histopatoloji ile ilişkili bulundu. Sonuç olarak, küçük renal kitlelerde benign patoloji oranının yüksek olması nedeniyle cerrahi öncesi prediktörler dikkate alınabilir.

Anahtar Kelimeler: *Renal Hücreli Karsinom; Böbrek Kanseri; Nefrektomi; Benign Neoplazmlar*

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INTRODUCTION

Some patients undergoing surgery for renal tumors with the preliminary diagnosis of renal cell carcinoma (RCC) have benign histology (1-4). One of the reasons for this finding is that benign tumors such as oncocytoma or angiomyolipoma cannot be fully differentiated from malign malignant tumors using imaging methods, including ultrasonography (USG), computerized tomography (CT), and magnetic resonance imaging (MRI).

Therefore, some researchers worked on the demographic and clinical factors related to the histopathological features of renal tumors (2-10). They investigated the association of factors including patient age, gender, chief complaints, tumor size, and tumor structure (i.e., cystic or solid) with tumor histopathology. In one of these studies, Frank et al. reported that smaller tumors were more likely to be benign benign (5). In another report, Jeon et al. noted that young age, female gender, and earlier surgery were associated with benign histology (3). Some studies focused on geographical factors and reported that the rate of benign renal tumors significantly varied between countries (2,4,8,9,11-14). According to these studies, this rate was between 13% and 25% in Western countries, while it was in the range of 7.1-13.5% in Asian countries. It was also stated that oncocytoma was the most common benign renal tumor in Western countries and angiomyolipoma was more prevalent in Asia (3,7,10,11,15). Some authors reported that the difference in the rates of benign renal tumors could be due to the differences between genetic features, environmental factors, and lifestyles of the patients (3,10).

This study aimed to determine the prevalence of benign histopathology in a group of Turkish patients who underwent surgery with the suspicion of renal cell cancer and were determined to have a renal mass smaller than 7 cm during radiological investigations in order to find the factors associated with benign renal tumors. This study aimed to determine the prevalence of benign histopathology and to identify preoperative predictive factors associated with benign renal tumors in Turkish patients with renal masses smaller than 7 cm.

MATERIAL AND METHODS

Study design, Setting, Participants

Adult (age>18) patients who underwent radical nephrectomy (RN) or partial nephrectomy (PN) in Ankara City Etlik Hospital, Department of Urology, between January 2007 and June 2016 constituted the target population of this study. Data of these patients were retrospectively reviewed. Among these patients, those with a renal mass smaller than 7 cm (clinical stage T1) without distant metastasis or local invasion findings were included. In contrast, those who underwent surgery with the preliminary diagnosis of renal angiomyolipoma and those with incomplete data were excluded. Patients with incomplete or missing data were excluded from the analysis.

Variables, Data Sources

Data including age, gender, smoking history, comorbidities (diabetes mellitus, hypertension, dyslipidemia, obesity), presentation symptoms or signs (hematuria, weight loss, hypertension), tumor size, location, laterality, the pattern of growth (endophytic/ exophytic) and character (cystic/ solid) were collected. All patients had pre-operative test results such as complete blood count, blood biochemistry, coagulation profile, and a chest X-ray. Also, patients with normal serum creatinine levels underwent contrast-enhanced computerized tomography (CT), while those with high levels were scanned by magnetic resonance imaging (MRI). Patients were categorized as ≤ 2 cm, 2-3 cm, 3-4 cm ve and 4-7 cm according to radiologically measured tumor size.

Quantitative Variables

Surgical resection was performed in cases with

enhanced renal masses and Bosniak type 3 or 4 renal cysts. The histopathological assessments were performed based on the classification reported by World Health Organization (WHO) in 2004. In addition, the histopathological classification and nuclear grading of the malign malignant tumors were performed according to the Union Internationale Contre le Cancer (UICC), American Joint Committee on Cancer (AJCC), and Fuhrman grading system.

Statistical Analyses

All statistical analyses were performed using IBM SPSS Statistics 17.0 (IBM Corporation, Armonk, NY, USA). The normal distribution of the continuous numerical data was tested by the Kolmogorov-Smirnov test. Descriptive data were given as means±standard deviations (SDs) or medians [min-max] for continuous numerical data and numbers (n) and percentages (%) for categorical data. The significance of the differences between the means was tested by the Student`s t test, while the Mann-Whitney U test was performed to analyze the differences between the medians. The categorical data were analyzed by Pearson`s chi-square, continuity correction chi-square, and Fisher`s exact probability tests. Multivariate logistic regression analysis was performed to assess the impact of all potential factors on benign histopathology. A difference was considered significant when the p value was lower than 0.05.

RESULTS

Overall, 243 patients underwent surgery for a renal tumor between January 2007- June 2016. Among these, 58 (23.8%) had benign, and 185 (76.2%) had malignant tumor histopathology. Mean patient age was 57.8±12.9, 58.0±13.9, and 57.7±12.5 for all patients and those with benign and malignant tumors, respectively. There was no significant difference between the groups regarding mean patient age (p=0.877). Mean tumor sizes were 4.9 (1.2-7) median tumor size was 4.9 cm (range: 1.2–7) and 4.5 (1.6-7.0) 4.5 cm (range 1.6-7) for the patient groups with benign or malignant tumors, respectively, and the difference was not statistically significant (p=0.642).

The comparison of the two groups regarding the rates of smoking history and comorbidities, including diabetes mellitus (DM), hypertension (HT), dyslipidemia, and obesity, did not reveal a significant difference (p>0.05). Also, the two groups were similar concerning laterality and presentation symptoms (p>0.05). However, the rate of female patients was significantly higher in the benign tumor group than in the malignant tumor group (p=0.004) (Table 1). There was no significant difference between the patient groups concerning tumor location, the pattern of growth (endophytic/exophytic), and character (cystic/solid) (p>0.05) (Table 2). Our analysis revealed that tumor size was not significantly associated with benign or malignant histopathology (p=0.148) (Table 3). There was no statistically significant association between tumor size categories and histopathological outcomes (p=0.148, Pearson's chi-square test) (Table 3). The impact of potential factors was analyzed by univariate analysis and subsequently confirmed by multivariate analysis. All variables leading to a p value lower than 0.25 were considered potential risk factors and included in the multivariate logistic regression model. Variables with a p value <0.25 in univariate analysis were considered potential predictors and entered into the multivariate logistic regression model, in line with established recommendations to avoid excluding potentially important variables (16). Our analysis showed that the male gender was associated with malignant histopathology irrespective of the tumor size (Table 4). There was a 2.39-fold increase in the risk of malignancy in male patients (95% CI:1.275-4.487, p=0.007) (Table 4). Adjustment according to the risk factors revealed no statistically significant impact of tumor size on the risk of malignancy (p>0.05) (Table 4).

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Table 1. Demographic and clinical features

Variables	Total (n=243)	Benign (n=58)	Malignant (n=185)	p value
Age (year)	57.8±12.9	58.0±13.9	57.7±12.5	0.877†
Gender				0.004‡
Male	128 (52.7%)	21 (36.2%)	107 (57.8%)	
Female	115 (47.3%)	37 (63.8%)	78 (42.2%)	
DM	58 (23.9%)	12 (20.7%)	46 (24.9%)	0.635¶
HT	96 (39.5%)	23 (39.7%)	73 (39.5%)	1.000¶
Dyslipidemia	32 (13.2%)	6 (10.3%)	26 (14.1%)	0.613¶
Obesity	55 (22.6%)	13 (22.4%)	42 (22.7%)	1.000¶
Smoking	129 (53.1%)	27 (46.6%)	102 (55.1%)	0.253‡
Laterality				0.478‡
Right	123 (50.6%)	27 (46.6%)	96 (51.9%)	
Left	120 (49.4%)	31 (53.4%)	89 (48.1%)	
Symptoms or signs				
Hematuria	31 (12.8%)	6 (10.3%)	25 (13.5%)	0.685¶
Weight loss	2 (0.8%)	0 (0.0%)	2 (1.1%)	1.000$
HT	2 (0.8%)	0 (0.0%)	2 (1.1%)	1.000$

† Student's t test, ‡ Pearson's Chi-square testi, ¶ Continuity correction chi square test, $ Fisher's exact probability test.
DM: Diabetes mellitus, HT: Hipertansion

Table 2. Other clinical features of the patients

Variables	Total (n=243)	Benign (n=58)	Malignant (n=185)	p value
Tumor location				0.694‡
Upper pole	86 (35.4%)	23 (39.7%)	63 (34.1%)	
Middle pole	67 (27.6%)	14 (24.1%)	53 (28.6%)	
Lower pole	90 (37.0%)	21 (36.2%)	69 (37.3%)	
Endophytic/exophytic				0.301¶
Endophytic	23 (9.5%)	3 (5.2%)	20 (10.9%)	
Exophytic	219 (90.5%)	55 (94.8%)	164 (89.1%)	
Cystic/solid				0.325¶
Cystic	42 (17.3%)	13 (22.4%)	29 (15.7%)	
Solid	201 (82.7%)	45 (77.6%)	156 (84.3%)	

† Mann Whitney U test, ‡ Pearson's Chi-Square test, ¶ Continuity correction chi-square test

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Table 3. Results of the analysis based on tumor sizes

	Benign (n=58)	Malign (n=185)	p value
Tumor size			0.148‡
0-2.0 cm	5 (33.3%)	10 (66.7%)	
2.1-3.0 cm	7 (20.6%)	27 (79.4%)	
3.1-4.0 cm	6 (12.5%)	42 (87.5%)	
4.1-7.0 cm	40 (27.4%)	106 (72.6%)	

† Pearson's Chi-square test

Table 4. Results of the multivariate analysis of potential risk factors performed for distinguishing malign from benign histopathology in renal tumors

	Odds ratio	95% Confidence interval		Wald	p value
		Lower limit	Upper limit		
Male gender	2.391	1.275	4.487	7.377	0.007
Tumor size 0-2.0 cm	1.000	-	-	-	-
Tumor size 2.1-3.0 cm	2.119	0.516	8.703	1.085	0.298
Tumor size 3.1-4.0 cm	3.815	0.918	15.847	3.395	0.065
Tumor size 4.1-7.0 cm	1.337	0.405	4.407	0.227	0.634

DİSCUSSİON

The incidence of renal tumors has increased during the last decades due to the increasing use of imaging modalities (8,17,18). In the interim, the detection rate of relatively small and low-stage renal tumors has also increased 6. It is known that a significant proportion of small renal tumors have benign histopathology (1-4,11,19,20). In the literature, this rate was reported to be in the range of 11-30%. According to these studies, the most common benign renal tumors are oncocytomas and angiomyolipomas. Today, modern cross-sectional imaging techniques can differentiate most renal angiomyolipomas from malignant tumors with the help of their fat content (6). However, some angiomyolipomas lack a sufficient amount of fat, and it is challenging to distinguish them from other tumors.

On the other hand, one-third of renal oncocytomas have a central scar and regular contours on computerized tomography scans (14). Of note, this appearance is not specific to oncocytomas: it can also be detected in renal cell cancers (RCC). Unfortunately, molecular biology and renal biopsy methods can also be insufficient in discriminating benign from malignant renal tumors.

Some studies worked on the impact of gender, age, tumor size, cystic component content, obesity, smoking history, presentation symptoms, and time of surgery on renal tumor histopathology. Lane et al. analyzed the histopathological assessment results in patients who underwent surgery for renal tumors smaller than 7 cm (9). In this cohort, benign tumors represented 33%, 26%, and 24% of the tumors in women younger than 40, those between 40 and 60, and those older than 60, respectively. Jeon and coworkers also investigated the relationship between age and histopathology in 376 patients (3). In this cohort, the mean age of patients with benign tumors was 49.2±13.3, while the mean age of patients with malignant tumors was 54.7±12.9. The

difference was statistically significant (p<0.001). In the study of Murphy et al., the median age was 65.5 and 63.7 in patients with benign and malignant tumors, respectively(8). These researchers reported that age was not a predictive factor for benign histopathology in renal tumors (p=0.705). In our study, there was no statistically significant difference between the mean age of the patients with benign and malignant renal tumors (p=0.877).

Murphy et al. found a significant difference between patients with benign and malignant renal tumors concerning body mass index (BMI). They noted that patients with a normal BMI (BMI <25 kg/m^2) had the lowest risk of developing malignant tumors (p=0.01). However, in the multivariate analysis, BMI did not emerge as an independent predictive factor for benign histopathology (p>0.05). In our study, 22.6% of the patients were obese (BMI >30 kg/m^2). The rate of obesity was 22.4% and 22.7% in patients with benign and malignant tumors, respectively. The difference was not statistically significant (p=1.00). Sekito et al. investigated pre-operative factors for predicting whether renal masses are benign (21). Their study included 278 patients with renal masses who had undergone a partial or radical nephrectomy for clinically suspected T1 or T2 renal cell carcinoma. They noted that relatively high pre-operative serum albumin levels might predict benign tumors, particularly when they are associated with female sex and smaller tumor size. In line with this, Pierorazio et al. increased tumor size and male sex associated with malignancy (22). These findings are consistent with ours.

While previous studies have explored various demographic and clinical predictors of histopathological outcomes in renal tumors, our study provides additional evidence from a Turkish cohort, demonstrating that female gender is significantly associated with benign histopathology in small renal masses.

Study Limitations

There were some limitations of this study that should be put forward for discussion to guide follow-up research. Our study found that the female gender was associated with benign histopathology in small renal tumors. However, further studies, including larger samples, are needed to reveal the predictive factors for benign renal histopathology with a higher certainty.

CONCLUSION

As a conclusion, radiological imaging is critical in the pre-operative diagnosis of renal masses. Since the rate of benign histopathology is relatively high in patients with small renal masses, pre-surgical diagnosis of these tumors is crucial. Some researchers analyzed demographic and clinical data to predict the histopathological diagnosis considering that renal biopsy is often inconclusive. Our study found that the female gender was associated with benign histopathology in small renal tumors. However, further studies, including larger samples, are needed to reveal the predictive factors for benign renal histopathology with a higher certainty.

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