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Original Research / Özgün Araştırma

Could Renal Tumour Scoring Systems Predict Tumour Aggressivity?

Böbrek Tümör Skorlama Sistemleri Tümör Agresivitesini Tahmin Edebilir Mi?

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Özet

Amaç: Bu çalışmanın amacı, T1 böbrek tümörlerinde R.E.N.A.L. nefrometri skoru (RNS), Padua skoru (PS), C-indeks ile tümör agresivitesi arasındaki ilişkiyi incelemek ve bu skorlama sistemlerinin, tümörün anatomisine ek olarak patolojisi hakkında klinik değerlendirmeyi yönlendirmek için bilgi sağlayıp sağlamadığını sorgulamaktır.

Gereç ve Yöntemler: Preoperatif klinik evrelendirmeye göre evre 1 (T1N0M0) 83 berrak hücreli renal hücreli karsinom (cRCC) hastası değerlendirildi. Patolojik sonuçlarına göre hastalar iki gruba ayrıldı: Fuhrman derecesi 1 veya 2 (FG1-2) olan hastalar (Non-agresif grup (NAG)) ve FG3-4 ve/veya TNM Evre 3 olan hastalar (Agresif grup (AG)). Her hastanın RNS, PS ve C-indeks puanları hesaplandı. Son olarak, nefrometri skorları ile patolojik agresivite arasındaki ilişki karşılaştırıldı.

Bulgular: Ortalama RNS, 7.3±2.4 olarak hesaplandı. Toplam RNS, AG'de (9.2±1.2) NAG'den (6±2.2) anlamlı derecede yüksekti (p<0.001). RNS, patolojik agresif hastalığın bağımsız bir öngörücüsüydü (p<0.001). En yüksek eğri altı alan için RNS' nin eşik değeri 8 olarak bulundu (p<0.001). Ortalama PS, 8.1±1.6 olarak hesaplandı. PS ayrıca patolojik agresif hastalığın bağımsız bir öngörücüsüydü (p<0.001). En yüksek eğri altı alan için PS'nin eşik değeri 8 olarak bulundu (p<0.001). AG›nin ortalama C-indeks puanı (1.4 ± 0.4), NAG› den (2.7±2.0)

Abstract

Objective: The aim of this study is to investigate the relationship between R.E.N.A.L. nephrometry score (RNS), Padua score (PS), Centrality (C)-index and tumour aggressivity in T1 renal tumours and to question whether these scoring systems would provide information about the pathology of renal tumours to manage clinical judgement rather than the anatomy of tumour.

Material and Methods: We evaluated 83 patients with stage 1 (T1N0M0) clear cell renal cell carcinoma (cRCC) according to preoperative radiological and pathological staging. Patients were divided according to pathological results of cRCC into two groups: Patients with Fuhrman grade 1 or 2 (FG1-2) (Non-aggresive group (NAG)) and patients with FG3-4 and/or TNM Stage 3 (Aggressive group (AG)). RNS, PS and C-index scores were calculated for each patient. Finally,the relationship between nephrometry scores and pathological aggressivity were compared.

Results: The mean RNS was calculated as 7.3±2.4. Total RNS was significantly higher in AG (9.2±1.2) than in NAG (6±2.2) (p<0.001). RNS was an independent predictor of pathological aggressive disease (p<0.001). The cut off value of RNS at the highest area under curve was 8 (p<0.001). The mean PS was calculated as 8.1±1.6. PS was also an independent predictor of pathological aggressive disease (p<0.001). The cut off value of PS at the highest area under

This study was reviewed and approved by the Taksim Education Hospital Ethical Committee (No:23/23.03.2016).
All research was performed in accordance with relevant guidelines/regulations, and informed consent was obtained from all participants.

anlamlı derecede düşüktü (p<0.001). C-indeks, patolojik agresiviteyi tahmin etmede anlamlıdır (p<0.001).

Sonuçlar: Daha yüksek RNS ve PS puanları ile düşük C-indeks puanlarının böbrek tümörlerinin tümör agresivitesi ile ilişkilendirildiğini sonucuna varılmıştır.

Anahtar Kelimeler: Böbrek hücreli karsinom, Padua, C-indeks, R.E.N.A.L. nefrometri, tümör agresivitesi, Fuhrman Derecesi

curve was 8 (p<0.001). The mean C-index score of AG (1.4 ± 0.4) was significantly lower (p<0.001) than NAG (2.7±2.0). C-index is significant in predicting pathological aggressiveness (p<0.001).

Conclusions: Our results suggested that higher RNS and PS scores, lower C-index scores were associated with tumour aggressivity of renal tumours.

Keywords: Renal cell carcinoma, Padua, C-index, R.E.N.A.L. nephrometry, tumour aggressivity, Fuhrman Grade

INTRODUCTION

The number of patients diagnosed with renal masses is increasing with the widespread use of cross-sectional imaging methods (1). Pathological uncertainty exists when an incidental renal mass is identified. Preoperative counselling and treatment planning are often made in the context of this uncertainty, even though 20-30% of these lesions ultimately prove benign, and only 10-30% are found to be potentially aggressive (2–5). Preoperative variables, including percutaneous biopsy and pathologic predictive models, have been developed to address this uncertainty, while kidney biopsies, involving the extraction of a small tissue sample from the renal mass, have emerged as valuable tools in this diagnostic puzzle, providing critical insights into the histological nature of the renal mass to aid clinicians in making more informed treatment decisions, albeit with associated complications such as the risk of bleeding, infection, and injury to adjacent structures (6–8).

Evidence of the relationship between the pathology and anatomy of the renal mass began to emerge in various publications in the literature (9–11). Objective anatomical scoring systems, including R.E.N.A.L. Nephrometry Score (RNS), Padua Score (PS), and C-index, have been developed to identify renal mass anatomy (12–14). Radiographic anatomical attributes are used in these systems.Preoperative determination of tumour aggressivity is essential for treatment planning. In our study, we aimed to explore the relationship between RNS, PS, and C-index with tumour aggressivity in T1 renal tumours. We aim to demonstrate that these scoring systems can provide not only anatomical but also pathological information, aiding in treatment management.

MATERIAL AND METHODS

The records of patients who underwent renal surgery due to T1 renal masses from February 2008 to February 2016 were collected from the electronic medical database after obtaining ethical approval (Ethical Approval Number:23, Date:23.03.2016). Radical nephrectomy (RN) (62.6%) or partial nephrectomy (PN) (37.4%) was performed in 102 patients. Among them, 83 (81.4%) patients had clear cell pathology. Fuhrman Grade (FG) is of prognostic value only in clear cell pathology; therefore, 19 (18.6%) patients with other pathological diagnoses were excluded, including 4 with papillary RCC (3.9%), 5 (4.9%) with chromophobe RCC, 5 (4.9%) with angiomyolipoma, and 5 (4.9%) with oncocytoma. Clinical characteristics, pathological slides, and computed tomography (CT) images were retrieved for all patients. All specimens were reviewed by a pathologist. Only patients with clear cell carcinoma (cRCC) were included, and those with other renal cell carcinoma subtypes (19 patients) were excluded. Preoperative CT images were reviewed by a urologic surgeon (AÖ); RNS, PS, and C-index were calculated as previously described (12–14).

Patients were divided according to postoperative pathological results of cRCC into two groups: Patients with FG1-2 were considered as the non-aggressive group (NAG), and those with FG3-4 and/or TNM Stage 3 were considered as the aggressive group (AG). RNS, PS, and C-index scores and components were compared between patients with AG vs. NAG.

Descriptive statistics for the data encompassed mean, standard deviation, median, interquartile range, frequency, and ratio values. To assess the distribution of variables, the Kolmogorov-Smirnov

test was employed. If the variables were not normally distributed, quantitative data were analysed using the Mann-Whitney U test. In contrast, if the variables were normally distributed, an independent sample t-test was used. Qualitative data were subjected to analysis using the Chi-square test, with the Fischer exact test being applied when the conditions for the Chi-square test were not met. The determination of effect level and cut-off values was carried out through the utilization of the ROC curve. Statistical analyses were conducted using SPSS 22.0 software.

RESULTS

Among the included 83 patients, the median patient age was 58.7 years (IQR: 50-64.9) with a male predominance (54.2%). The ages were divided into AG (n = 48, 58%) and NAG (n=35, 42%) according to the pathology results as described. Age and gender distribution of patients were similar ($p > 0.05$). The RCCs were removed by radical nephrectomy in 52 (62.7%) and partial nephrectomy in 31 (37.3%) patients. Table 1 presents a comprehensive overview of the detailed pathological examinations. Collecting system and/or renal sinus invasion were observed in 2 (2.4%) cases; In 3 (3.7%) cases, lymph node positivity was observed; 11 cases (13.3%) were pathological stage 3; 9 patients were pathologically diagnosed as T3A (10.8%). Two of stage 3 tumours were pathologic stage 3 due to lymph node positivity, and the other 9 cases were stage 3 due to extracapsular spread and/or collecting system and/or renal sinus invasion.

The mean RNS for all patients was 7.3 ± 2.4. According to the components of the RNS: Tumours with increased diameter (R) ($p < 0.05$), endophytic nature (EII-III) ($p < 0.05$), distance to the collecting system or sinus < 4 mm (N III), posterior location of the tumor (P) ($p < 0.05$), and a central location within the polar lines of the kidney (LII-III) ($p < 0.05$) were significantly higher in AG than in NAG. The total RNS was significantly higher in AG (9.2 ± 1.2) than in NAG (6 ± 2.2) ($p < 0.05$) (Table 2). RNS was an independent predictor of pathological aggressive disease [0.863 (0.785-0.940)] ($p < 0.001$). The cutoff value of RNS at the highest area under the curve was 8 [0.807 (0.710-0.905)] ($p < 0.001$). Sensitivity was 88.6%, the positive predictive value was 70.5%, specificity was 72.9%, negative predictive value was 89.7% (Figure).

The mean PS for all patients was 8.1 ± 1.6. According to the components of the PS: Tumour with medial localization (M), polar localization, and tumour size between 4-7 cm were significantly higher in AG than in NAG ($p < 0.05$); Collector system and renal sinus involvement were although higher in AG than in NAG but not statistically significant ($p > 0.05$); The rate of exophyticity (Exophyticity II-III) was significantly higher than that of NAG ($p < 0.05$). PS AG (9.2 ± 1.1) was significantly higher than NAG (7.3 ± 1.4) ($p < 0.05$). PS is significant in predicting pathological aggressiveness [0.846 (0.762-0.929)] ($p < 0.001$) (Table 2). The cutoff value of PS at the highest area under the curve was 8 [0.761 (0.653-0.868)] ($p < 0.001$). Sensitivity was 77.1%, the positive predictive value was 69.2%, specificity was 75.0%, negative predictive value was 81.8% (Figure).

The C-index value was calculated for each patient. All patients had a mean age of 39.8 ± 10.7 mm, a mean r (mm) of 22.9 ± 9.1mm, and a mean C-index of 2.2 ± 1.7. When parameters are considered separately, c (mm) in AG was not significantly different from NAG ($p > 0.05$), r (mm) in AG was significantly higher than NAG ($p < 0.05$). The C-index in AG (1.4 ± 0.4) was significantly lower ($p < 0.05$) than in NAG (2.7 ± 2.0) (Table 2). C-index is significant in predicting pathological aggressiveness [0.787 (0.690-0.883)] ($p < 0.001$). The highest cutoff value for the sub-curve area was 1.55. Sensitivity was 77.1%, the positive predictive value was 77.1%, specificity was 68.6%, and the negative predictive value was 68.6% (Figure).

DISCUSSION

The diverse nature of enhancing renal masses presents a multifaceted clinical challenge, with varying biological characteristics. Achieving the alignment of renal mass biology with an optimal treatment approach continues to be a challenging objective in contemporary urologic oncology (15).

For patients in good health with T1 tumours suitable for nephron-sparing surgery, partial nephrectomy is presently considered the established standard of care. Nevertheless, the American Urological Association includes thermal ablation and active surveillance as potential choices for patients with tumours measuring 7 cm or smaller (16). The prevalence of small tumours, particularly in elderly or comorbid patients, is on the rise. The utilization of observation/surveillance approaches and ablative treatments that could be deemed safer for less aggressive cancers has gained prominence, primarily due to the limited availability of short- to medium-term oncological outcomes (17). The widespread hesitance surrounding the adoption of percutaneous biopsy, driven by concerns over potential complications or its inherent limitations in accurately determining grading, further underscores the potential applicability of a system capable of precisely predicting malignancy or aggressiveness (18). Because of these purposes, various systems were designed using nomograms (7,8). RNS, PS, and C-index have been used to predict warm ischemia time, urine leak, blood loss, urine leakage hospital length stay, and patient recovery time for PN previously. Recently, there have been some studies to correlate nephrometry scores, especially RNS, with tumour biology and pathology.

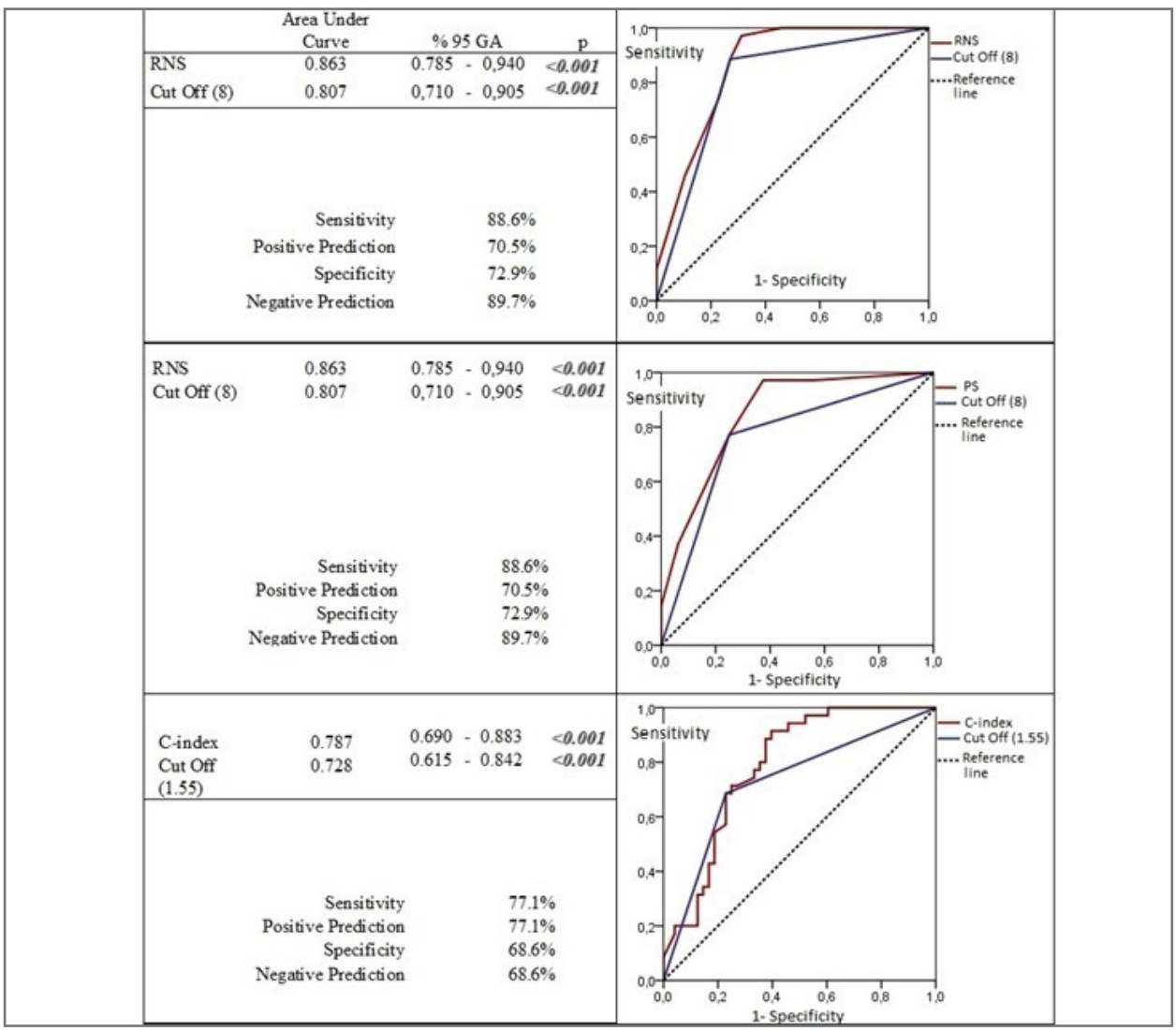

Figure: ROC curve, area under curve and Cut off value of RNS, PS, and C-index

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Table 1. Demographic and pathological features of the cases.

		Non-aggressive group (NAG) (n=48)		Aggressive group (AG) (n=35)		Total	P
		Mean ± sd / n%	Median (IQR)	Mean ± sd / n%	Median (IQR)		
Age, year		57.5 ± 10.3		57.2 ± 14.0		57.4±11.9	0.896
Gender, n (%)	Male	22 (45.8%)		23 (65.7%)		45 (54.2%)	0.073
	Female	26 (54.2%)		12 (34.3%)		38 (45.8%)	
Tumour size (mm)		35.4 ± 16.9	32.0 (24-50)	55.9 ± 11.7	55.0 (48-70)		***<0.001***
Surgical modality, n (%)	RN	20 (41.6%)		32 (91.4%)		52 (62.6%)	
	PN	28 (58.4%)		3 (8.6%)		31 (37.4%)	
Fuhrman Grade, n (%)	I	15 (31.2%)		-		15(18.1%)	
	II	33 (68.8%)		8 (22.8%)		41 (49.4%)	
	III	-		25 (71.4%)		25 (30.1%)	
	IV	-		2 (5.8%)		2 (2.4%)	
Collector system /renal sinus involvement, n (%)		-		2 (5.7%)		2 (2.4%)	
Pathological (T) Stage	T1A	34 70.8%		8 21%		42 (50.6%)	
	T1B	14 29.2%		18 51.4%		32(38.5%)	
	T3A	- -		9 27.6%		9(10.8%)	
Pathological (N) Stage	N0	48 100%		32 91.4%		80 (96.3%)	
	N1	- -		3 8.6%		3 (3.7%)	

Abbreviations: RN: Radical Nephrectomy; PN: Partial Nephrectomy.

Table 2. Nephrometries and features

		Non-aggressive group (NAG)		Aggressive group (AG)		P
		Mean ± sd / n%	Median (IQR)	Mean ± sd / n%	Median (IQR)	
(R)adius	I	32 66.7%		6 17.1%		<***0.001***
	II	16 33.3%		29 82.9%		
(E)xophytic/ endophytic	I	32 66.7%		4 11.4%		<***0.001***
	II	15 31.3%		19 54.3%		
	III	1 2.1%		12 34.3%		
(N)earness	I	28 58.3%		2 5.7%		<***0.001***
	II	7 14.6%		4 11.4%		
	III	13 27.1%		29 82.9%		
(A)nt/Post	A	17 35.4%		4 11.4%		<***0.001***
	P	31 64.6%		31 88.6%		
(L)ocalisation	I	27 56.3%		4 11.4%		<***0.001***
	II	12 25.0%		15 42.9%		
	III	9 18.8%		16 45.7%		
R.E.N.A.L Score		6.0 ± 2.2	5.0 (4-8)	9.2 ± 1.2	9.0 (8-10)	<***0.001***
Renal Rim Lateral Medial	 1 2	 41 85.4% 7 14.6%		 23 65.7% 12 34.3%		***0.035***
Tumour size (cm) ≤4 4.1-7 >7	 1 2 3	 32 66.7% 16 33.3% -		 6 17.1% 29 82.9% -		<***0.001***
Renal sinus Not involved Involved	 1 2	 48 100.0% 0 0.0%		 32 91.4% 3 8.6%		0.071
Polar Location Superior/Inferior Middle	 1 2	 30 62.5% 18 37.5%		 8 22.9% 27 77.1%		<***0.001***
Collecting system Not involved Dislocated/infiltrated	 1 2	 46 95.8% 2 4.2%		 33 94.3% 2 5.7%		1.000
Exophytic rate ≥50% <50 Endophytic	 1 2 3	 32 66.7% 15 31.3% 1 2.1%		 5 14.3% 20 57.1% 10 28.6%		<***0.001***
Padua Score		7.3 ± 1.4	7.0 (6.0-8.75)	9.2 ± 1.1	9.0 (9-10)	<***0.001***
C (mm)		40.2 ± 10.3	40.0 (30.5-50.0)	39.2 ± 11.3	40.0 (30.0-47.0)	0.691
r (mm)		19.0 ± 8.7	17.5 (12.0-25.0)	28.4 ± 6.5	30.0 (24.0-35.0)	<***0.001***
C-index		2.7 ± 2.0	2.2 (1.6-3.1)	1.4 ± 0.4	1.3 (1.1-16)	<***0.001***

Kutikov et al (19), based on some results that correlated the anatomical features of the tumour with pathological findings, have created a nomogram that integrates age and sex with some elements of RS with high predictive ability. However, the patients taken into this study had a high proportion of advanced and/or large tumours (>25 cm), and the malignancy or aggressiveness of such tumours were not required to be predicted, because of the high grade in nearly all the cases, and that was the flaw of the study. Whereas in our case, all patients had T1 and clear-cell pathology tumours. Wang et al. (20) affirmed a robust predictive capability for high-grade tumours when analysing an exclusively malignant tumour cohort that exhibited similarities to the Kutikov cohort. Conversely, Bagrodia et al. (21) reported a weak predictive performance for malignancy but an exceptionally high predictive accuracy for tumor grading in a small patient cohort with tumours up to 8 cm who underwent partial nephrectomy. In contrast, Koo et al. (22) examined an extensive cohort of clinically T1 renal tumours and found an acceptable predictive performance for malignancy but a notably poor performance in predicting high-grade tumours. On the other hand, Antonelli et al. (23) and Mullin et al. (24) failed to identify any correlations between malignancy or high-grade pathology in large cohorts of cT1a patients (506 patients and 754 patients), possibly due to the lower nephrometry scores of the tumours. A limitation of these studies lies in the heterogeneity of the patient groups included in their analyses.

Pathological aggressiveness is not only due to nuclear grading; there are also some prognostic parameters according to pathological results. We should use not only nuclear grading but also add upstaging (from stage 1 to stage 3) to make pathological aggressiveness; from this point of view, our study is different from the others (25–27).

Kutikov et al. (19) and Chen et al. (28) compared individual components of the RNS with nuclear grade, and their results showed that R score, E score, and L score were strongly associated with high-grade pathology. It has also been reported that a high percentage of endophytic tumours were associated with clear-cell histology and higher-grade tumours (29,30). That is consistent with our study. We demonstrated that in RNS, tumours with increased diameter (R) ($p < 0.05$), endophytic nature (EII-III) ($p < 0.05$), distance to the collecting system or sinus < 4mm (N III), posterior location of the tumour (P) ($p < 0.05$), and with a central location within the polar lines of the kidney (LII-III) are associated with aggressive pathology. The components of the PS demonstrated that larger tumours (4-7 cm) ($p < 0.05$), location relative to the polar lines, and endophytic tumours (Exophyticity II-III) ($p < 0.05$) were more likely to be classified as aggressive pathology diagnosed with cRCC. In previous studies, there is not any cut-off point about RNS, PS, and C-index for predicting aggressivity of RCC. We demonstrated that when RNS and PS are higher than 8, and the C-index is lower than 1.55, aggressivity risk is rising.

CONCLUSION

Overall, this study uncovered that there is a relationship between nephrometry scores (RNS, PS, and C-index) and final aggressive tumoral pathology. The prediction of malignant and metastatic potential of the tumour alters the management of T1 renal tumors. This is of great practical importance for preoperatively predicting renal mass aggressivity. Using these data, which will help urologists choose appropriate therapies for patients. RNS, PS, and C-index represent a novel tool that can help preoperatively predict the aggressivity of renal masses and make therapeutic decisions. However, well-designed randomized controlled trials are needed to produce comparable results.

Ethics Committee

Our study was approved by Taksim Education Hospital Ethical Committee (No:23/23.03.2016).

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