

Impact of renal capsular infiltration on disease specific survival in patients with localized renal cell carcinoma ($\leq pT2$)

Lokalize renal hücreli kanserlerde ($pT \leq 2$) renal kapsül infiltrasyonunun hastalık spesifik sağkalım üzerine etkisi

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Abstract

Objective: To investigate the impact of renal capsular infiltration on disease specific survival in pathologically localized renal cell carcinoma.

Materials and methods: The medical records of 89 patients with pT1-3aN0M0 renal cell carcinoma who underwent open radical nephrectomy in our institution between 2000-2009 were evaluated retrospectively. The prognostic value of renal capsular involvement was investigated with univariate and multivariate survival analyses in patients with pT1-2N0M0 disease.

Results: Capsular involvement was present in 26 of 79 (32.9%) pT1-2N0M0 patients. The 3-year disease specific survival rates for patients with and without capsular infiltration were 75.4% and 97.7%, respectively ($p < 0.001$). Similarly, capsular involvement worsened disease specific survival in pT1 patients (80% vs. 100%, $p = 0.002$), although it had had no impact on survival of pT2 patients (72.9% vs 93.3%, $p = 0.168$). Multivariate survival analysis revealed that capsular involvement was an independent prognostic factor (HR=13.213, $p = 0.021$). Three-year disease specific survival for capsule positive pT1-2 patients were similar with that of pT3 patients (75.4% vs. 72%, $p = 0.544$).

Conclusion: Capsular infiltration is an independent prognostic factor in localized renal cell carcinoma. The presence of capsular infiltration significantly reduces disease specific survival rates in pT1 renal cell carcinoma. Capsular infiltration in pT1-2 renal cell carcinoma decreases prognosis to levels similar to those of pT3a patients.

Key words: Renal capsule; renal cell carcinoma; survival.

Özet

Amaç: Patolojik lokalize renal hücreli kanserlerde renal kapsül infiltrasyonunun, hastalık spesifik sağkalım üzerine etkisini araştırmak.

Gereç ve yöntem: Kliniğimizde 2000-2009 yılları arasında renal kitle nedeni ile açık radikal nefrektomi uygulanmış ve patolojik evresi pT1-3aN0M0 olan 89 hastanın kayıtları retrospektif olarak tarandı. Patolojik evresi pT1-2N0M0 olan hastalarda renal kapsül infiltrasyonunun tek ve çok değişkenli sağkalım analizleri ile prognostik değeri araştırıldı.

Bulgular: Patolojik evresi pT1-2N0M0 olan 79 hastanın 26'sında (%32.9) kapsül infiltrasyonu mevcuttu. Kapsül infiltrasyonu olan ve olmayan hastalarda 3 yıllık hastalık spesifik sağkalım oranları sırası ile %75.4 ve %97.7 idi ($p < 0.001$). Benzer olarak kapsül infiltrasyonu pT1 hastalarda hastalık spesifik sağkalımı düşürür (%80 ve %100, $p = 0.002$), ancak pT2 hastalarında sağkalım üzerine etkisi yoktur (%72.9 ve %93.3, $p = 0.168$). Çok değişkenli sağkalım analizi kapsül infiltrasyonunun bağımsız bir prognostik faktör olduğunu göstermiştir (hazard ratio=13.213, $p = 0.021$). Kapsül pozitif pT1-2 hastalarda 3 yıllık hastalık spesifik sağkalım pT3 ile benzerdir (%75.4 ve %72, $p = 0.544$).

Sonuç: Lokalize renal hücreli kanserlerde kapsül infiltrasyonu bağımsız bir prognostik göstergedir. Evre pT1 renal hücreli kanserde kapsül infiltrasyonu olması hastalık spesifik sağkalımı kısaltmaktadır. pT1-2 renal hücreli kanserde kapsül infiltrasyonu prognozu pT3a ile benzer hale getirmektedir.

Anahtar sözcükler: Renal hücreli kanser; renal kapsül; sağkalım.

Incidence of localized renal cell carcinoma (RCC) has been continuously increasing during the last two decades as a result of the frequent use of abdominal imaging.^[1-3] The standard treatment for clinically localized RCC remains to be surgery, including nephron-sparing surgery and radical nephrectomy performed either open or laparoscopically, which may provide 5-year survival rates of 75-95% and 87%, respectively.^[4,5] However, 20-40% of the patients develop local recurrence or distant metastases after surgery.^[6,7] Although pathological stage according to the currently used 2002 TNM staging system for RCC is accepted to be the major prognostic predictor, it has a well-known drawback for localized tumors of being solely based on tumor size, ignoring other known prognostic factors. Therefore, tumors of the same stage would exhibit diverse clinical behaviours and different levels of aggression after definitive treatment. In an effort for a better prediction of prognosis after surgery for RCC, numerous clinical and pathological parameters were evaluated regarding their prognostic values such as collecting system involvement and body mass index. Renal capsular involvement in localized (\leq pT2) disease was also a subject of interest resulting in few retrospective studies with conflicting conclusions.^[8-11]

In this study, we aimed to determine the impact of renal capsular involvement on disease specific survival (DSS) in pathologically localized RCC.

Material and methods

Medical records of patients who underwent open radical nephrectomy for a renal mass and who were diagnosed as pathological stage pT1-3aN0M0 RCC were evaluated retrospectively. Patients who had had preoperative ultrasound and computed tomography (CT) scans and who were followed-up regularly to date were included in the analysis. Node (+) and metastasis (+) patients were excluded. Eighty-nine pT1-3aN0M0 patients were eligible for analysis. Pathological evaluations included tumor size, histological subtype, and nuclear grading. Grading and staging were done according to Fuhrman nuclear grading and 2002 TNM classification systems, respectively.^[12,13]

Patients were followed with abdominal CT and chest X-rays every 6 months for the first year, and

yearly afterwards. The time interval from nephrectomy to disease-related death or the last recorded follow-up visit was used for survival analysis.

Impact of renal capsular infiltration on survival was investigated with univariate and multivariate survival analyses in 79 patients with pT1-2N0M0 RCC. Capsular infiltration was defined as the presence of cancer cells within the capsular fibrous tissue without perinephric fat invasion.

The mean values of continuous variables were compared using t test, categorical data were evaluated using chi square or Fisher's exact tests. Survival estimates and comparisons were calculated using Kaplan-Meier, log rank tests and Cox proportional hazards method. P values <0.05 were accepted to be statistically significant.

Results

Mean age of the patients was 56.59 ± 13.30 years. Of the 79 patients with pT1-2N0M0 disease, 39 (49.4%) and 40 (50.6%) were male and female, respectively. Patient distribution according to stage was as follows: 16 (17.9%) pT1a, 32 (35.9%) pT1b, 31 (34.8%) pT2, and 10 (11.2%) pT3a. Twenty-six of 79 patients (35.9%) had had capsular involvement. Median follow-up was 31 (range 3-66) months. Capsular infiltration was more common in male patients (43.5% vs. 22.5%, $p=0.046$). Table 1 shows the characteristics of capsule (+) and (-) patients.

At the time of analysis, disease recurrence was present in 10 (12.7%) of the 79 pT1-2 patients, and 6 (7.6%) were dead due to cancer-specific causes.

Three-year DSS of patients with and without capsular involvement regarding the entire cohort were 75.4% and 97.7%, respectively ($p<0.001$). (Table 2, Fig. 1). Similarly, capsular involvement worsened DSS in pT1 patients (80% vs 100%, $p=0.002$), although it had had no impact on survival of pT2 patients (72.9% vs 93.3%, $p=0.168$) (Table 2). Multivariate survival analysis revealed that capsular involvement was an independent prognostic factor (HR=13.213, $p=0.021$).

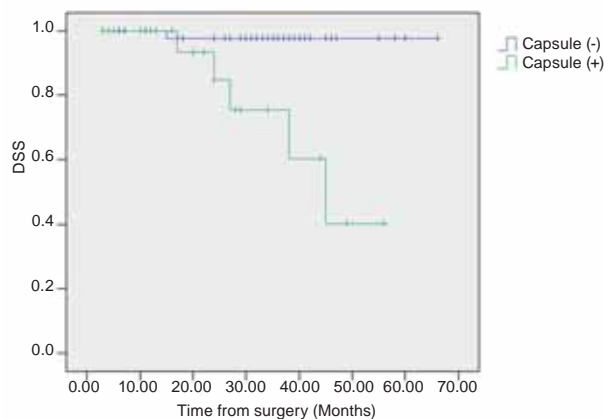
Three-year DSS for capsule positive pT1-2 patients were similar with that of pT3 patients (75.4% vs. 72%, $p=0.544$).

Table 1. Patient characteristics in capsular involvement (+) and (-) groups [mean±standard deviation or n (%)]

	Capsule (+)	Capsule (-)	Total	p value
Age (years)	58.60±13.40	55.60±13.26	-	0.348
Gender				
Male	17 (43.5)	22 (56.5)	39 (100)	0.046
Female	9 (22.5)	31 (77.5)	40 (100)	
Stage				
pT1	14 (29.1)	34 (70.9)	48 (100)	0.378
pT2	12 (38.7)	19 (61.3)	31 (100)	
Histological type				
Clear cell	19 (29.7)	45 (70.3)	64 (100)	0.233
Other	7 (46.7)	8 (53.3)	15 (100)	
Fuhrman grade				
1, 2	15 (29.5)	36 (70.5)	51 (100)	0.532
3, 4	6 (40)	9 (60)	15 (100)	

Table 2. Impact of capsular involvement on disease specific survival (DSS)

Stage	3-Year DSS		p value
	Capsule (-)	Capsule (+)	
pT1-2 (n=79)	97.7%	75.4%	<0.001
pT1 (n=48)	100%	80%	0.002
pT2 (n=31)	93.3%	72.9%	0.168

**Figure 1** Survival plots for capsular involvement (+) and (-) patients. DSS: Disease specific survival.

Discussion

The incidence of localized RCC has been increasing due to the increased and widespread use of imaging modalities. Surgery (nephron-sparing or radical nephrectomy performed either open or laparoscopically) remains to be the standard therapeutic approach

to clinically localized RCC. Although efficient disease control could be achieved by surgery in 70-80% of the clinically localized tumors, 20-30% of them eventually develop disease recurrence and metastasis.^[14] The main prognostic predictor used for RCC is the updated 2002 version of TNM classification system which is based on size and anatomical extent of the tumor.^[12] Although the prognostic value of pT stage is well-established in a vast number of studies, it is also known that tumors with similar pathological stage do not always exhibit similar biological behaviour and aggression. Debate is going on with the coverage and classification of the risk factors by the TNM system regarding issues like invasion of adrenal gland or parapelvic renal sinus fat. Therefore, numerous clinical, anatomical, histological, and molecular risk factors were defined and categorized in a search for better predictors of treatment outcome for localized and advanced RCC; some of which are patient age, Fuhrman nuclear grade, histological subtype, microvascular infiltration, and collecting system involvement.^[15-17]

Renal capsular involvement is another factor which has been evaluated in 4 studies in the literature, which (except one), showed significant negative impact of capsular infiltration on patient survival.^[8-11] Although 3 of the studies found a correlation between capsular involvement and survival, a similarly designed one with adequate number of patients and follow-up failed to demonstrate the relation. Our study aimed to question, and if confirmed, reinforce

the present evidence suggesting a possible role for capsular involvement as a risk factor for pathologically localized RCC (Table 3).

To our knowledge, Jeong et al.^[8] were the first to evaluate the impact of capsular involvement on patient survival in pT1-2N0M0 RCC patients. Of the 288 patients, 108 (37.5%) had had capsular involvement which was associated with a worse pT stage, but not with grade. They also stated that, pT1 tumors infiltrating renal capsule are significantly larger than the ones those do not, although the same correlation between tumor size and capsular involvement could not be demonstrated for pT2 patients and the entire cohort. Capsular infiltration had no significant prognostic effect on patient survival regarding the overall cohort and pT1 patients, but significantly worsened 5-year DSS of pT2 patients. Cox regression analysis revealed that capsular involvement was a prognostic predictor for pT2 stage disease, independent of tumor size, grade and patient age. Klatter et al.^[9] examined 519 patients and defined capsular involvement as a risk factor for recurrence independent of tumor size, Fuhrman grade, ECOG performance status, and collecting system invasion. Capsular infiltration was associated with pT stage, tumor size, and Fuhrman grade. All <pT3a patients were included in the survival analysis, without further sub-group calculations

according to pT stage. They reported similar survival for capsule positive pT1-2 and pT3a patients which is an interesting finding. They also claimed that including capsular involvement in TNM system may improve its validity. This study confirmed some of the findings of Jeong et al.^[8] and added some additional information especially in its Cox proportional hazards model, owing to its higher statistical power due to the higher number of patients included. Süer et al.^[10] on the other hand, could not demonstrate prognostic significance of renal capsular involvement in their study of 249 patients, neither in the overall cohort, nor according to the pT stage, and not even in univariate analysis. They found that capsular involvement was associated with tumor stage and grade. Discordance with the previous studies may be due to inter-institutional variations regarding the extent, and definitions and technique used in pathological evaluations of the specimens, as all these three studies have similar retrospective design and patient characteristics (i.e. male/female ratio, stage distribution). In a more recent study of 299 patients, Cho et al.^[11] evaluated prognostic implications of additional factors along with capsular involvement, including body mass index, clinical presentation, collecting system and microvascular invasion in a pathological subset of clear cell RCC. They demonstrated significant impact of capsular involvement on both 5- and

Table 3. Studies evaluating renal capsular involvement in renal cell carcinoma

	Number of patients	Follow-up (Months)	Capsular infiltration [n (%)]	Prognostic implication	
				DSS	RFS
Present study	79	31 (median)	26 (32.9) pT1: 14 (29.1) pT2: 12 (38.7)	3 years	
Cho et al. ^[11]	299	52.3 (median)	106 (35.5) pT1: 77 (30.5) pT2: 29 (61.7)	5-10 years	5-10 years
Süer et al. ^[10]	249	40.7 (mean)	79 (31.7) pT1: 45 (24.5) pT2: 34 (51.5)	- 5 years	-
Klatte et al. ^[9]	519	49 (median)	112 (21.6) - -	-	5-10 years
Jeong et al. ^[8]	288	61 (mean)	108 (37.5) pT1: 78 (33.9) pT2: 30 (51.7)	5 years	-

DSS: Disease specific survival, RFS: Recurrence free survival.

10-year recurrence free and disease specific survival rates. Capsular involvement was associated with age, symptomatic presentation, tumor size, pT stage, collecting system invasion and microvascular invasion. Body mass index and stage, and body mass index and tumor size were other independent risk factors according to multivariate analysis for recurrence-free survival and cause-specific survival, respectively.

Similarly, our study also demonstrated a significant negative impact of capsular involvement on patient survival in pT1-2N0M0 patients. Although this correlation was significant for the overall cohort and pT1 patients, it lacked significance for pT2 patients. This may be partly due to the relatively difficult pathological evaluation, as a tumor >7 cm would probably have a direct contact with a larger area of the renal capsule increasing the probability of missing small areas of infiltration. However, despite the lack of significance in pT2 tumors, our study confirmed the negative prognostic effect of capsular involvement in the overall cohort and pT1 tumors, supporting a possible role of capsular involvement in the risk assessment or even staging of RCC's.

The present study provides useful information regarding the effects of capsular infiltration on treatment outcome as studies with conflicting conclusions are present in the literature, and a consensus is yet to be achieved.

As a conclusion, capsular infiltration is an independent prognostic factor in localized RCC. The presence of capsular infiltration significantly reduces DSS rates to levels similar to those of pT3a patients. However, findings of our study should be further supported with prospective studies including higher number of patients.

Conflict of interest

No conflict of interest was declared by the authors.

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Prostat kanserinde iğne biyopsi ve radikal prostatektomi örneklerinin Gleason skorları arasındaki uyum üzerine modifiye Gleason derecelendirme sisteminin etkisi

The effect of modified Gleason grading on the score concordance between the Gleason scores of needle biopsy and radical prostatectomy specimens in prostatic carcinoma

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Özet

Amaç: Bu çalışmanın amacı, 2005 Uluslararası Ürolojik Patoloji Grubu Prostat Karsinomu Gleason Derecelendirmesi Uzlaşma Toplantısı'nda önerilen modifiye Gleason derecelendirme sisteminin, prostat iğne biyopsi ve radikal prostatektomi örneklerinin Gleason skorları arasındaki uyumun başarısına etkilerini araştırmaktır.

Gereç ve yöntem: Hastanemizde 2005 ile 2008 arasında radikal prostatektomi yapılmış 71 hastanın prostat iğne biyopsi ve radikal prostatektomi örnekleri konvansiyonel ve modifiye Gleason derecelendirme sistemiyle yeniden derecelendirildi. Hem prostat iğne biyopsi hem de radikal prostatektomi örneklerinin konvansiyonel Gleason derecelendirme sistemiyle elde edilen Gleason skorları, modifiye Gleason derecelendirme sistemiyle elde edilen Gleason skorları ile istatistiksel olarak karşılaştırıldı. Daha sonra, prostat iğne biyopsi ve radikal prostatektomi örnekleri arasındaki uyum konvansiyonel ve modifiye Gleason derecelendirme sistemlerine göre ayrı ayrı hesaplanarak istatistiksel olarak karşılaştırıldı.

Bulgular: Konvansiyonel ve modifiye Gleason derecelendirmesiyle değerlendirildiğinde, 71 iğne biyopsisinin 30'unda (%42.3) ($p<0.001$), 71 radikal prostatektomi örneğinin ise 10'unda (%14.1) ($p=0.019$) yeni bir Gleason skoru elde edildi. Konvansiyonel Gleason derecelendirme sisteminde iğne biyopsi ve radikal prostatektomi örnekleri arasındaki uyum %32.4 iken, modifiye Gleason derecelendirme sistemiyle bunun %46.5'e çıktığı gözlemlendi ($p=0.021$). Konvansiyonel Gleason derecelendirme sistemiyle %52.1 (37/71) olguda radikal prostatektomi örneklerinde daha yüksek bir skor rapor edilirken, %15.5 (11/71) olguda ise daha düşük bir skor rapor edilmiştir. Modifiye Gleason derecelendirme sisteminde ise radikal prostatektomi örneklerinde, yüksek skorlama oranı %42.2 (30/71) ve düşük skorlama oranı %11.3 (8/71) bulunmuştur.

Sonuç: Modifiye Gleason derecelendirme sistemiyle prostat iğne biyopsisi ve radikal prostatektomi örnekleri arasındaki uyum artmakta, düşük skorlama ve yüksek skorlama oranları azalmaktadır.

Anahtar sözcükler: Biyopsi; Gleason derecesi; prostat kanseri; radikal prostatektomi.

Abstract

Objective: The aim of this study was to evaluate the effect of modified Gleason grading, recommended at International Society of Urological Pathology Consensus Conference in 2005, on the concordance of Gleason scores between prostatic needle biopsy and radical prostatectomy specimens.

Materials and methods: A total of 71 needle biopsy and radical prostatectomy specimens obtained from patients who underwent prostatectomy in our hospital between 2005 and 2008 were regraded with conventional and modified Gleason grading. The Gleason scores of the prostatic needle biopsy and radical prostatectomy specimens, which were achieved by conventional Gleason grading, were statistically compared with those of modified Gleason grading. Then, the concordance between the Gleason scores of needle biopsy and radical prostatectomy specimens were estimated separately by conventional and modified Gleason grading, and compared statistically.

Results: When the conventional and modified Gleason scores of 71 patients were compared, a new Gleason score was achieved in 30 out of 71 needle biopsies (42.3%) ($p<0.001$) and in 10 out of 71 radical prostatectomy specimens (14.1%) ($p=0.019$). The concordance between needle biopsy and radical prostatectomy specimens improved from 32.4% to 46.5% ($p=0.021$). While a higher score was reported in 52.1% (37/71) of the cases in radical prostatectomy specimens, a lower score was reported in 15.5% (11/71) of the cases with conventional Gleason grading. The rates of overgrading and undergrading were respectively 42.2% (30/71) and 11.3% (8/71) in radical prostatectomy specimens with modified Gleason grading.

Conclusion: The concordance between Gleason scores of prostatic needle biopsy and radical prostatectomy specimens improves, and the rate of undergrading and overgrading decreases with modified Gleason grading.

Key words: Biopsy; Gleason grade; prostate cancer; radical prostatectomy.