의학석사 학위논문

임상병기 T1 신세포암의 수술 후 병리학적 병기 T3a 로 악화 시 예후 및 그와 관련된 인자 분석

Pathological T3a upstaging of clinical T1 renal cell carcinoma: outcomes according to surgical technique and predictors of upstaging

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Abstract

Purpose: To evaluate the prognosis of pT3a upstaging from cT1 renal cell carcinoma, and to compare the outcomes of partial or radical nephrectomy in cases of pT3a upstaging.

Materials and Methods: We reviewed the records of patients who underwent partial or radical nephrectomy for cT1 at our center between January 2001 and October 2013. We compared the 2-year recurrence-free survivals for cases with pT1 or pT3a upstaging, and for partial or radical nephrectomy in cases with pT3a upstaging. Clinicopathological parameters were analyzed in univariate and multivariate analyses to evaluate their associations with upstaging.

Results: Among the 1,009 eligible patients, 987 patients were included in the analysis. The mean follow-up was 48.5 months. The 2-year recurrence-free survival was worse in the pT3a upstaging group, compared to the pT1 group (87.3% vs. 99.3%; $p < 0.001$). Partial nephrectomy and radical nephrectomy provided comparable 2-year recurrence-free survivals (88.2% vs. 83.7%; $p = 0.251$). The multivariate analysis revealed that upstaging was associated with old age, cT1b stage, clinical symptoms, and a high Fuhrman grade.

Conclusions: Pathological T3a upstaging of cT1 renal cell carcinoma was associated with a poorer prognosis, compared to pT1 disease. However, the surgical technique (radical or partial nephrectomy) did not affect the recurrence rate. Therefore, clinicians should select the treatment method based on the clinical stage, and consider the pathological stage during the follow-up.

Keywords: renal cell carcinoma, nephrectomy, recurrence

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Introduction

Partial nephrectomy is recommended for the treatment of T1 renal cell carcinoma (RCC), as it preserves renal function and provides oncological outcomes that are comparable to those of radical nephrectomy [1–3]. In cases of surgically–treatable T2 RCC, partial nephrectomy can be properly performed, although it is not generally used for T3 RCC [4,5].

Thus, clinical T stage is considered important for selecting the surgical technique (partial vs. radical nephrectomy), and is typically determined using computed tomography (CT). In this context, T1 and T2 tumors are limited to the kidney and are classified according to the tumor's size (≤7 cm or >7 cm, respectively). In contrast, the American Joint Committee on Cancer (AJCC) seventh TNM staging system defines T3a disease as exhibiting perirenal fat invasion, renal sinus fat infiltration, or renal vein thrombosis, regardless of the tumor's size [6].

However microscopic perirenal invasion, renal sinus fat infiltration, and renal vein thrombosis can be missed during CT, and pT3a upstaging occasionally occurs in cases of cT1 RCC [7–9]. Furthermore, there has been discordance in previous studies regarding the prognoses and risk factors for T3a upstaging [10–13].

Therefore, the present study aimed to define the effect of pT3a upstaging from cT1 on recurrence–free survival, to evaluate the outcomes of pT3a upstaging according to surgical technique (partial or radical nephrectomy), and to identify the clinical factors that were associated with upstaging.

Materials and Methods

This study's retrospective design was approved by the institutional review board of the Seoul National University Hospital. We included consecutive patients who underwent partial nephrectomy for clinical T1N0M0 disease or radical nephrectomy exhibited pT3a up staging from clinical T1N0M0 disease between January 2001 and October 2013 at our institution. All surgical techniques were included, such as open, laparoscopic, and robotic surgeries

However, we excluded cases with non-RCC pathology, bilateral or multiple renal tumors, lymph node metastasis, or von Hippel-Lindau disease. Clinical T stage was assessed using contrast-enhanced CT, according to the AJCC seventh TNM staging system.

Patients were classified into three groups: pT3a upstaging after partial nephrectomy (group A, n = 37), pT3a upstaging after radical nephrectomy (group B, n = 54), and no pT3a upstaging after partial nephrectomy (group C, n = 896)

The clinicopathological characteristics that we evaluated included age, sex, body mass index (BMI), cT stage, clinical symptoms, tumor histology, Fuhrman grade, positive surgical margins, and pseudosarcomatous components. Postoperative follow-up was performed using enhanced kidney CT and chest radiography at 6 months, and then annually thereafter.

The 2-year recurrence-free survivals in all groups were analyzed using the Kaplan-Meier method and the log rank test. Clinicopathological characteristics were compared using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Multivariate analyses were performed using logistic regression. All analyses were

performed using SPSS software (version 19.0; SPSS Inc., Chicago, IL, USA), and differences were considered statistically significant at a two-sided p-value of <0.05.

Results

A total of 987 patients were analyzed, and their clinicopathological characteristics are shown in Table 1. The mean follow-ups were 50.8 ± 32.4 months for groups A and B (upstaging) and 48.2 ± 27.2 months for group C (no upstaging). The upstaging groups were significantly older, compared to the no upstaging group (58.6 ± 13.9 years vs. 54.9 ± 12.6 years; p = 0.006). The upstaging groups also exhibited a higher proportion of cT1b stage, compared to the no upstaging group (47.3% vs. 10.9%; p < 0.001). Clinical symptoms (e.g., hematuria, flank pain, and a palpable mass) were significantly more common in the upstaging groups, compared to the no upstaging group (21.8% vs. 0.8%; p = 0.002). High-grade tumors (Fuhrman grade 3- 4) were significantly more frequent in the upstaging groups (63.7% vs. 28.2%; p < 0.001). The upstaging groups exhibited a higher frequency of pseudosarcomatous components, compared to the no upstaging group (4.4% vs. 0.2%; p = 0.001). There were no significant differences in the tumor histology distributions or rates of positive surgical margins between the two groups.

The results of the multivariate analyses are shown in Table 2. Upstaging was associated with old age (odds ratio [OR]: 1.026, 95% confidence interval [95% CI]: 1.007- 1.046, p = 0.009), cT1b stage (OR: 5.882, 95% CI: 3.585- 9.651, p < 0.001), clinical symptoms (OR: 2.330, 95% CI: 1.282- 4.234, p = 0.006) and a high Fuhrman grade (grade 2, OR: 4.008, 95% CI: 0.535-30.027, p = 0.177; grade 3, OR: 12.206, 95% CI: 1.640-90.875, p = 0.015; grade 4, OR: 33.911, 95% CI: 3.520-327.647, p = 0.002). The presence of pseudosarcomatous components was not significantly associated with upstaging.

The no upstaging group exhibited a higher estimated 2-year recurrence-free survival, compared to the upstaging groups (99.3% vs. 87.3%; $p < 0.001$) (Figure 1). In the upstaging groups, 14 patients experienced distant metastasis and 1 patient experienced local recurrence. In the no upstaging group, 19 patients experienced distant metastasis and 6 patients experienced local recurrence. The estimated 2-year recurrence-free survivals were similar for groups A and B (88.2% vs. 83.7%, respectively; $p = 0.251$). Group B had a significantly higher proportion of cT1b stage, compared to group A (63.0% vs. 24.3%; $p < 0.001$), although clinical symptoms were similar in groups A and B (16.2% vs. 27.7%; $p = 0.218$).

Discussion

Partial nephrectomy has been the standard treatment for T1 RCC, because it provides extended overall survival that is related to preserved renal function and reduced cardiovascular risk [2,5,3]. Furthermore, given that it provides oncological outcomes that are equivalent to those of radical nephrectomy, attempts have been made to use partial nephrectomy for T2 RCC [5,14]. However, in locally advanced RCC, violation of the Gerota's fascia and dissection of the perirenal fat during partial nephrectomy can increase the risk of recurrence [5].

The TNM stage mainly determines the treatment option, follow-up protocol, and prognosis [15,16]. Clinical stage is typically assessed using contrast-enhanced CT, although there is a risk of missing renal sinus fat invasion, perirenal fat invasion, or renal vein thrombosis during CT, which can lead to pT3a upstaging [7,17,9].

In the present study, the estimated 2-year recurrence-free survival rate was lower for pT3a upstaging, compared to pT1 disease (99.3% vs. 87.3%; $p < 0.001$). This finding agrees with the findings of Groin et al., who found a lower 24-month recurrence-free survival rate after robotic partial nephrectomy for cT1 in cases with pT3a upstaging, compared to cases with pT1 or pT2 disease (91.8% vs. 99.2%) [10].

In contrast, Roberts et al. found that there was no difference in the 5-year recurrence-free survival rates in cases of pT3a upstaging or pT1 disease (90.6% vs. 97.5%, $p = 0.08$) [12]. Furthermore, Ramaswamy et al. reported that the oncological outcomes of pT3a upstaging from cT1 were good, because they did not observe recurrence in 66 patients with pT3a upstaging during a median follow-up of 50 months [11].

In the present study, the estimated 2-year recurrence-free survivals were similar in groups A and B (88.2% vs. 83.7%; p = 0.251). Weight et al. analyzed the cancer-specific survivals among patients who underwent radical or partial nephrectomy with cT1 and pT3 upstaging, and also found equivalent survivals in the radical and partial nephrectomy groups [18]. Moreover, Hansen et al. found that partial and radical nephrectomy provided similar cancer-specific survivals among patients with pT3a disease [19].

In the cases with pT3a upstaging, we observed distant metastasis in 14 patients (93.3%) and local recurrence in 1 patient (6.7%). In the pT1 group, we observed distant metastasis in 19 patients (76%) and local recurrence in 6 patients (24%). Moreover, the rates of positive surgical margins were 2.2% in the pT3a group and 3.7% in the pT1 group. These findings suggest that tumors with pT3a upstaging tend to progress as distant metastasis, rather than local recurrence, and that progression is not typically related to failed local control. Thus, the trend towards distant metastasis in cases of pT3a upstaging reflects its aggressiveness, and accounts for its higher recurrence rate, compared to cases of pT1 disease.

In the multivariate analyses, pT3a upstaging was associated with old age, cT1b stage, clinical symptoms, and a high Fuhrman grade. In addition, Ramaswamy et al. demonstrated that upstaging was associated with clear cell histology, a tumor size of >4 cm, and positive surgical margins [11]. Moreover, Melissa et al. found that high RENAL nephrometry scores were a risk factor of upstaging, although age and Fuhrman grade were not significant risk factors [20].

The important implications of our findings are that tumors with pT3a upstaging have aggressive features (vs. pT1 tumors), and that the surgical technique (radical or partial nephrectomy)

does not alter the prognosis. Therefore, clinicians do not have to avoid partial nephrectomy based on concerns regarding upstaging, although cautious follow-up is warranted in cases with upstaging. Furthermore, upstaging should be considered in cases that involve old age, cT1b stage, or clinical symptoms.

There are several limitations in the present study. First, this study used a single-center retrospective design, which is associated with a well-known risk of bias. Second, this study had a small sample size, which is also associated with a risk of bias. Third, we only evaluated the 2-year recurrence-free survivals, and did not analyze long-term outcomes. Therefore, large prospective multicenter randomized cohort studies are needed to validate our findings.

Conclusions

The postoperative recurrence-free survival in cases of cT1 RCC was worse in cases with pT3a upstaging, compared to cases with pT1 disease. Furthermore, old age, cT1b stage, clinical symptoms, and a high Fuhrman grade were associated with pT3a upstaging. Therefore, because partial nephrectomy and radical nephrectomy provide similar recurrence-free survivals, the treatment plan should be determined based on clinical stage and operability.

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Table 1. Clinical and pathological parameters

Variable	No upstaging N = 896	Upstaging N = 91	P-value
Age (years), mean ± SD	54.9 ± 12.6	58.6 ± 13.9	0.006
Sex, no. (%)			0.712
Men	647 (72.2)	68 (74.7)	
Women	249 (27.8)	23 (25.3)	
BMI (kg/m^2), mean ± SD	24.6 ± 3.2	24.7 ± 3.1	0.651
Clinical stage			< 0.001
T1a	798 (89.1)	48 (52.7)	
T1b	98 (10.9)	43 (47.3)	
Symptoms (%)	97 (10.8)	21 (21.8)	0.002
Follow-up (months), mean ± SD	48.2 ± 27.2	50.8 ± 32.4	0.752
Pathological T stage (%)		N.A.	
T1a	499 (89.2)		
T1b	97 (10.8)		
Histology (%)			0.134
Clear cell	721 (80.5)	69 (75.8)	
Papillary	81 (9.0)	7 (7.7)	
Chromophobe	69 (7.7)	11 (12.1)	
Other	25 (2.8)	4 (4.4)	
Fuhrman grade (%)			< 0.001
1	88 (9.8)	1 (1.1)	
2	553 (61.7)	32 (35.2)	
3	242 (27.0)	50 (54.9)	
4	11 (1.2)	8 (8.8)	
Positive surgical margin, no. (%)	33 (3.7)	2 (2.2)	0.764
Pseudosarcomatous component, no. (%)	2 (0.2)	4 (4.4)	0.001

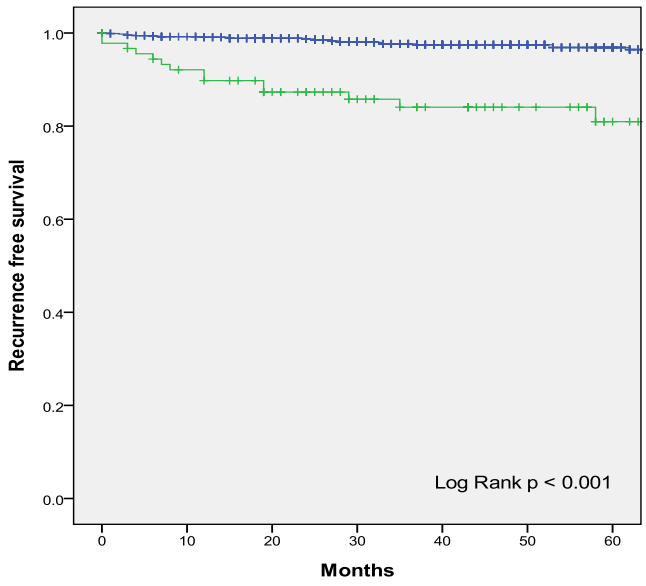
SD: standard deviation; BMI: body mass index.

Table 2. Multivariate analyses of clinicopathological parameters that were associated with pT3a upstaging.

Variable	Odds ratio	95% CI	P-value
Age	1.026	1.007 – 1.046	0.009
Clinical stage			
T1a	1		
T1b	5.882	3.585 – 9.651	< 0.001
Symptoms	2.330	1.282 – 4.234	0.006
Fuhrman grade (%)			
1	1		
2	4.008	0.535 – 30.027	0.177
3	12.206	1.640 – 90.875	0.015
4	33.911	3.520 – 327.647	0.002
Pseudosarcomatous component	2.679	0.373 – 19.230	0.327

CI: confidence interval

(A)



(B)

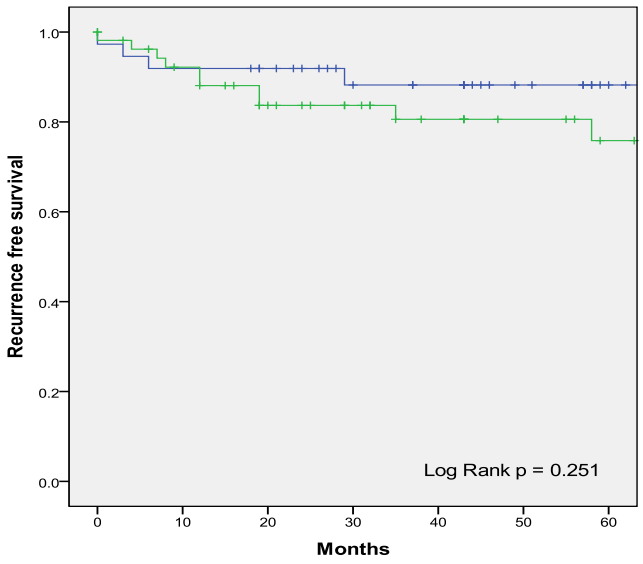


Figure 1. Recurrence-free survivals in (A) the pT1 (blue curve) and pT3a upstaging groups (green curve), and (B) the partial nephrectomy (blue curve) and radical nephrectomy (green curve) subgroups of the pT3a upstaging group.

국 문 초 록

서론: 본 연구의 목적은 임상병기 T1 신세포암 환자에서 수술 후 병리학적 병기 T3a 로 악화된 경우 예후 및 병기상승과 관련된 인자를 평가하는데 있다.

대상 및 방법: 2001년 1월부터 2013년 10월까지 서울대학교병원에서 cT1 신세포암으로 부분 신절제술 혹은 근치적 신절제술을 시행 받은 환자의 의무기록을 분석하였다. pT1 과 pT3a의 2년 무재발 생존율을 비교하였으며, pT3a 로 병기상승 된 경우 부분 신절제술과 근치적 신절제술의 무재발 생존율을 함께 분석 하였다. 병기상승과 관련된 임상적, 병리학적 인자들을 단변량 및 다변량 분석하였다.

결과: 1009명의 대상환자 중 987명을 최종 분석하였다. 평균 추적관찰기간은 48.5개월 이었다. 2년 무재발 생존율은 pT1 에 비해 pT3a 가 낮았다 (87.3%vs. 99.3%; $p < 0.001$). pT3a로 병기상승 된 환자에서 부분 신절제술과 근치적 신절제술 간의 2년 무재발 생존율은 통계적으로 유의한 차이가 없었다 (88.2% vs. 83.7%; $p = 0.251$). 다변량 분석에서 고령, cT1b 병기, 임상증상 동반, 고등급 Fuhrman grade 등이 병기상승과 연관이 있었다.

결론: 임상병기 T1의 수술 후 병리학적 병기 T3a 로의 병기상승은 그렇지 않은 경우에 비해 불량한 예후를 나타낸다. 하지만 부분 신절제술 혹은 근치적 신절제술등의 수술방법에 따른 예후의 차이는 유의하지 않았다. 그러므로 임상병기에 기반하여 수술방법을 선택하는 것이 합당하며 병기상승이 있을 경우 더욱 면밀한 추적관찰이 필요하다.

주요어: 신장암, 신절제술, 재발