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Original Article

Stage T1N0M0 renal cell carcinoma: the prognosis in Asian patients

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Abstract

The prognostic features of T1N0M0 renal cell carcinoma (RCC) in Asian patients have not been well explored in large sample studies. In this study, we retrospectively analyzed the records of 713 patients undergoing nephrectomy for T1N0M0 RCC between 1991 and 2009 in three Asian hospitals. Univariate and multivariate analysis were performed to identify the independent predictive factors for T1N0M0 RCC prognosis among a series of clinicopathological parameters, including age, gender, tumor size, Fuhrman grade, and histological classification. Our results showed that 388 of 713 patients had tumors 4.0 cm or smaller (stage T1a) and 325 of 713 patients had tumors 4.0–7.0 cm in size (stage T1b). Five-year cancer-specific survival (CSS) and recurrence-free survival (RFS) rates for this group of patients were 96.0% and 93.5%, respectively. The patients with T1b RCC had a significantly lower 5-year CSS and RFS rates than did those with T1a RCC (CSS, 93.1% vs. 98.6%, $P = 0.026$; RFS, 90.0% vs. 96.5%, $P < 0.001$). Patients with low grade (grades I–II) tumors had a higher 5-year CSS (97.8% vs. 91.2%, $P = 0.001$) and RFS (95.5% vs. 85.5%, $P < 0.001$) rate than did those with high grade (grades I–II) tumors. More interestingly, when stratifying patients to T1a and T1b groups, the role of grade in distinguishing prognosis could be only observed in patients with T1b disease. Cox regression showed tumor size and Fuhrman grade were significant in predicting CSS and RFS. Our study suggests that the prognosis of patients with T1N0M0 RCC is excellent, and these results are comparable to previously reported studies in Western patients. Furthermore, our data indicates that patients with T1b disease and high Fuhrman grade have high risk of tumor recurrence and death, thus requiring more frequent follow-up.

Key words Renal cell carcinoma, tumor size, Fuhrman grade, prognosis

Renal cancer is the third most common malignancy of the urinary system. Approximately 90% of malignant renal tumors are renal cell carcinomas (RCCs)[1]. The incidence of RCC in the USA has increased by an average of 3% per year for whites and 4% per year for African-Americans since the 1970s[2]. In 2010, the cancer statistical data revealed that there were 58 240 new RCC cases and 13 040 RCC-related deaths in the USA[3]. Although the prognosis of RCC has improved greatly because of early detection and advanced technology, some patients will still suffer cancer recurrence and even death. Several studies from Europe and America reported a 10-year survival rate around 90% for stage T1 RCC[4,5]. However, there are few large-scale studies focusing on stage T1 RCC in the Asian population. In 2004, Srivastava *et al.*[6] reported findings from a group of 178 RCC patients who underwent nephrectomy in an Indian center. In 2001, Igarashi *et al.*[7] studied the prognosis of 333 patients with T1 RCC in a single Japanese hospital. Last year, we reviewed the oncological outcome of 336 Chinese RCC patients treated with nephrectomy, and this review included 211 T1 stage tumors[8]. In summary, the prognostic features

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of T1N0M0 RCC in Asian patients have not been well explored in large sample multi-center studies.

To study the prognosis of stage T1N0M0 RCC in Asian patients, we retrospectively analyzed a large cohort of T1N0M0 RCC patients from three Asian hospitals: the Sun Yat-sen University Cancer Center, the First Affiliated Hospital of Sun Yat-sen University, and the National Cancer Center of Singapore. We used univariate and multivariate analysis to identify the independent predictive factors for prognosis of patients with T1N0M0 RCC among a panel of clinicopathological features, including age, sex, tumor size, Fuhrman grade, and histological classification. The patients were stratified according to T stage to find the predictive efficacy of grade in different T subgroups.

Patients and Methods

Patient information

Between January 1991 and July 2009, 713 patients diagnosed with T1N0M0 RCC according to the 2010 American Joint Committee on Cancer (AJCC) TNM staging system[9] underwent nephrectomy in three Asian hospitals. We retrospectively analyzed the clinicopathological records of this cohort, including age, sex, tumor size, Fuhrman grade, and histological classification. Tumor histology was classified according to the 2004 WHO classification[10], and tumors were graded according to the Fuhrman grading scheme[11]. No patients received synchronic postoperative adjuvant therapy and/or new adjuvant therapy preoperatively. All patients had negative margins, and tumor residuals did not exist in this cohort.

Follow-up

The prognosis of these patients was determined from information from hospital charts and telephone follow-up. All patients were followed up every 3-6 months in the first three years after surgery and every year thereafter by physical examination, blood chemistry analysis, chest X-ray, and abdominal ultrasound. If there were any abnormalities detected by chest X-ray and/or abdominal ultrasound, enhanced computed tomography (CT) of the chest and/or abdomen was performed. Tumor recurrence included local relapse in the renal fossa or/and remnant kidney tissues and distal metastasis. Cancer-specific survival (CSS) was the main endpoint of this study and was computed from the date of surgery to the date of death from cancer or last follow-up. Death from RCC was considered an event, whereas deaths from causes other than RCC were censored at the date of death. Another endpoint was recurrence-free survival (RFS), which was computed from the date of surgery to the date of recurrence or last follow-up. Death from other causes was regarded as a censored event.

Statistic methods

Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Multivariate Cox analysis was used to determine the clinicopathological features that were independently associated with CSS and RFS. All P values were determined from two-tailed tests, and $P < 0.05$ was considered statistically significant. Data were analyzed using the statistical software SPSS, version 13.0 (SPSS Inc, Chicago, IL, USA).

Results

Clinical findings

Clinicopathological characteristics of the patients are summarized in Table 1. There were 481 men and 232 women included in this study. The median patient age at surgery was 54 years (range, 14-89 years), and the median follow-up was 37 months (range, 3-300 months). The median tumor size was 4 cm (range, 1.2–7.0 cm).

Prognosis information

Of the 713 patients, 40 (5.6%) had tumor recurrence, 15 of whom were alive at the time of last follow-up, and 25 (3.5%) of whom died of RCC. The time from nephrectomy to tumor recurrence ranged from 3 to 161 months (median, 27 months). The time from nephrectomy to death from RCC ranged from 3 to 132 months (median, 30 months). Estimated 5-year CSS and RFS rate were 96.0% and 93.5%, respectively (Figures 1A and B).

Univariate and multivariate analysis for CSS and RFS

Univariate survival analysis was performed using the Kaplan-Meier method, and results were compared using the log-rank test. As shown in Table 2, tumor size and Fuhrman grade were associated with CSS and RFS. The patients with T1b RCC had significant lower 5-year CSS and RFS rates than did the patients with T1a RCC (CSS, 93.1% vs. 98.6%, $P = 0.026$; RFS, 90.0% vs. 96.5%, $P < 0.001$) (Figures 1C and D). The 5-year CSS was 97.8% for low Fuhrman grade patients and 91.2% for high Fuhrman grade patients ($P = 0.001$). The 5-year

Table 1. Clinicopathological characteristics of 713 patients with renal cell cancer

Characteristic	Number of patients (%)
Gender	
Male	481 (67.5)
Female	232 (32.5)
Age (years)	
Median	54
Range	14–89
Tumor size (cm)	
Median	4
Range	1.2–7.0
T stage	
T1a	388 (54.4)
T1b	325 (45.6)
Fuhrman grade	
I	165 (24.0)
II	387 (56.3)
III	113 (16.4)
IV	22 (3.2)
Histological classification	
Clear cell	598 (83.9)
Papillary	68 (9.5)
Chromophobe	30 (4.2)
Multilocular cystic	17 (2.4)
Prognosis	
Cancer death	25 (3.5)
Cancer recurrence	40 (5.6)

Table 2. Univariate analysis of factors for the prediction of survival outcome in patients with T1N0M0 renal cell cancer

Clinicopathological factor	5-year CSS rate (%)	Log-rank value	*P*	5-year RFS rate (%)	Log-rank value	*P*
Gender		0.153	0.696		0.013	0.909
Male	96.2			93.7		
Female	95.8			93.0		
Age (years)		1.117	0.291		0.826	0.363
⩽54	96.2			92.3		
>54	95.8			94.8		
Tumor size (cm)		4.937	0.026		12.344	<0.001
⩽4	98.6			96.5		
>4	93.1			90.0		
Fuhrman grade		10.787	0.001		17.199	<0.001
Low grade (I + II)	97.8			95.5		
High grade (III + IV)	91.2			85.5		
Histological classification		1.490	0.222		1.147	0.284
Clear	96.5			94.3		
Non-clear	93.3			89.0		

CSS, cancer-specific survival; RFS, recurrence-free survival.

RFS was 95.5% for low Fuhrman grade patients and 85.5% for high Fuhrman grade patients (P < 0.001) (Figures 1E and F). The differences in CSS (P = 0.222) and RFS (P = 0.284) were not significant between clear cell RCC (ccRCC) and other subtypes. Interestingly, when patients were stratified according to T stage, the role of grade in distinguishing prognosis was only observed in patients with T1b disease. As shown in Figure 2, T1b patients with low grade tumors had a 5-year CSS of 96.4% and RFS of 94.3% compared to 83.1% and 75.3% , respectively, in patients with high grade tumors (both P < 0.001). However, the 5-year CSS and RFS were similar between T1a patients with low and high grade tumors (CSS, 98.9% vs. 100%, P = 0.899; RFS, 96.5% vs.95.8%, P = 0.797) (Figure 2).

Multivariate Cox regression showed tumor size [CSS, hazard ratio (HR) = 3.130, P = 0.019; RFS, HR = 3.284, P = 0.002] and Fuhrman grade (CSS, HR = 3.377, P = 0.005; RFS, HR = 3.398, P < 0.001) were independently associated with CSS and RFS (Table 3).

Discussion

To our knowledge, the present study represents the largest sample size with which the prognosis of T1 RCC has been investigated in the Asian population. As shown in the results, this patient cohort had an excellent prognosis with 5-year CSS and RFS of 96.0% and 93.5%, respectively, which is comparable to reports from the West in the world's top medical centers. Lau *et al.*[4] from Mayo Clinic reported a group of 840 patients with T1 RCC. Although the CSS and RFS were not reported for the whole group, the 10-year CSS and RFS for ccRCC was 89.1% and 88.6%, respectively. Tsui *et al.*[12] from the University of California Los Angeles School of Medicine reported a 5-year CSS rate of 91% for patients with stage I RCC. Similarly, another study on stage I RCC from the Japan Chiba University [7] showed a 10-year CSS rate of 89% and RFS rate of 82% . Our previous study from the Sun Yat-sen University Cancer Center [8] indicated a 5-year CSS rate of 94.7% for patients with T1N0M0 RCC who underwent nephrectomy. These above mentioned studies suggest that the disease control effect and long-term survival rate for stage I RCC is satisfactory.

As for the prognostic factors of T1N0M0 RCC, no consensus has been reached. Many studies suggest different prognostic factors for early stage renal tumor. However, only tumor size and Fuhrman grade are widely accepted as prognostic factors for stage I RCC. Lau *et al.* [4] used multivariate Cox analysis to identify the independent prognostic factors for a large group of patients with T1 ccRCC. Their results showed that both tumor size and Fuhrman grade were independently associated with CSS and RFS. The adjusted risk of death from RCC or suffering from cancer recurrence was much higher in patients with high Fuhrman grade (HR, 4.38 and 1.59) or large size tumor (HR, 4.18 and 1.50). Cheville *et al.*[5] revealed that tumor size, Fuhrman grade, and necrosis were jointly and significantly associated with CSS of T1 ccRCC. Patients with tumors larger than 5 cm in diameter had a 4.7-fold higher risk of cancer death than did those with tumors smaller than 5 cm diameter. In our study, we found tumor size and Fuhrman grade were associated with CSS and RFS. Patients with T1b RCC had a significant lower CSS and RFS rate than did those with T1a RCC. The 5-year CSS was 97.8% for patients with low Fuhrman grade RCC compared to 91.2% for those with high Fuhrman grade RCC (P = 0.001). The 5-year RFS was 95.5% for patients with low Fuhrman grade RCC compared to 85.5% for those with high Fuhrman grade RCC (P < 0.001). Multivariate Cox regression showed tumor size and Fuhrman grade were independently associated with CSS and RFS.

Although both in the 6th and 7th editions of the AJCC Cancer Staging Manual, T1 tumors were subdivided into T1a and T1b using 4 cm as a cutoff[9,13], the T classification of RCC has consistently been the focus of controversy. Many studies indicate that sub-staging T1 patients into T1a and T1b groups may not differentiate the prognosis of the two groups. Bedke *et al.*[14] found the 4 cm cutoff point that is used to distinguish between stage T1a and T1b did not affect the prognosis between the two groups. Srivastava *et al.* [6] studied a group of 178 patients with RCC and found that sub-classifying stage I RCC into tumors smaller than and equal to 4 cm and larger than 4 cm did not reveal any statistically significant difference (P = 0.32) in prognosis. Klatte *et al.*[15] focused their study in a group of patients with small RCC and reported the incidence of metastatic disease is similar in patients with different tumor sizes. Thus, some investigators sought to find a more practical cutoff for T1 RCC subgroups. Elmore *et al.* [16] studied 233 patients with T1N0M0 RCC and reported that after separating patients using various size cutoffs, survivals were most different using a 5 cm cutoff. Lau *et al.*[4] revealed that 5 cm, other than 4 cm, had the highest concordance index for predicting metastasis-free survival (MFS) and CSS for T1N0M0 ccRCC. More recently, in 7th edition AJCC Cancer Staging Manual renal tumors with a diameter between 7 and 10 cm were subgrouped to T2a category and tumors larger than 10 cm to T2b category [9]. With more population-based studies across the world focusing on sub-grouping T1 RCC, the cutoff of T1a and T1b renal tumor may be renewed in the future.

Notably, when we stratified patients according to tumor size, the role of grade in distinguishing prognosis

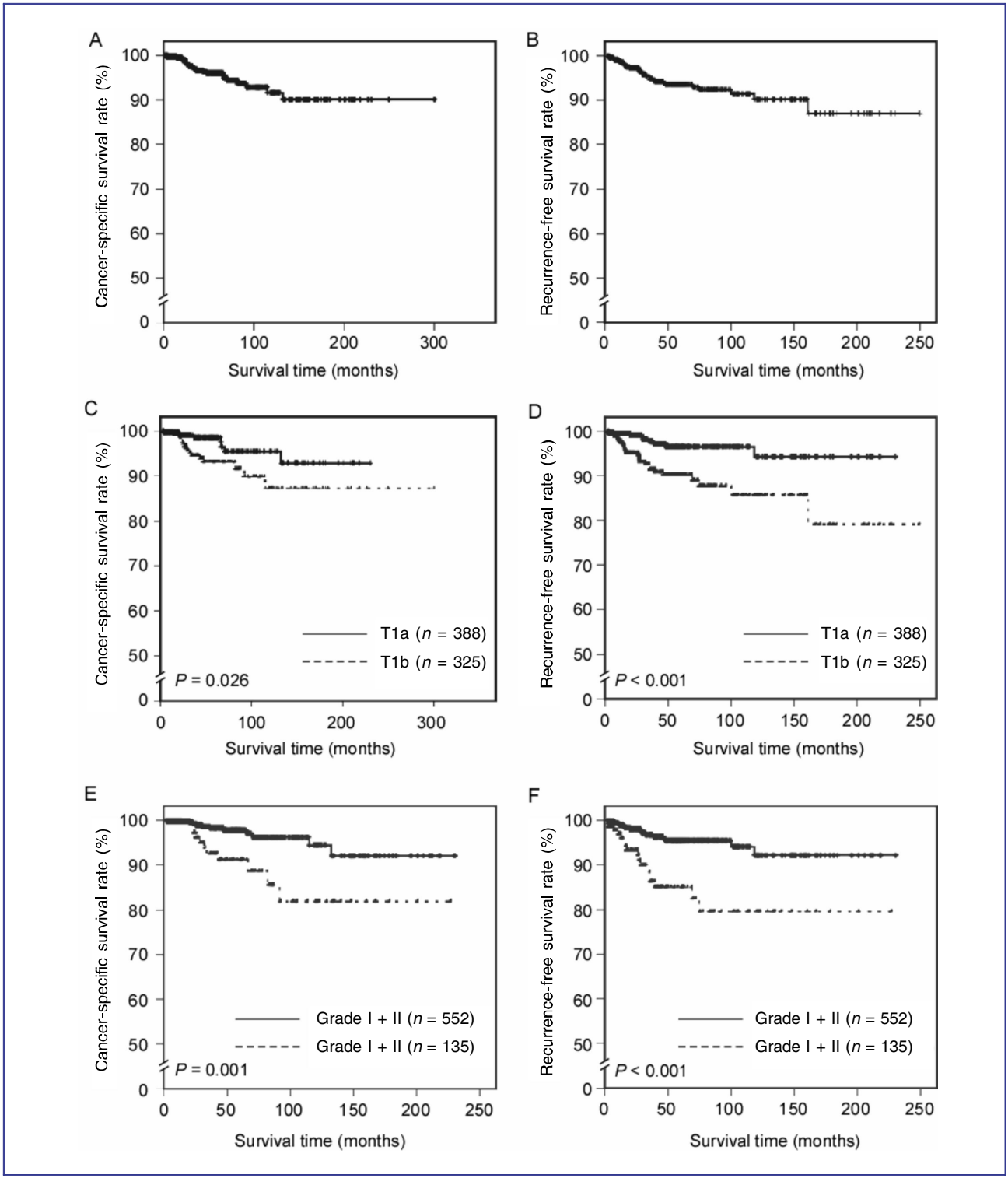

Figure 1. **Survival curves with univariate analyses (log-rank).** A and B, overall cancer-specific survival (CSS) and recurrence-free survival (RFS) curves for the whole group, respectively. C, T1aN0M0 patients (bold line) had a cumulative 5-year CSS rate of 98.6% compared to 93.1% for T1bN0M0 patients (dotted line). D, 5-year RFS in patients with T1aN0M0 and T1bN0M0 RCC patients (96.5% vs. 90.0%, $P < 0.001$). E, CSS curves of patients with high grade (dotted line) and low grade (bold line) tumors (91.2% vs. 97.8%, $P < 0.001$). F, patients with low grade tumors had a longer RFS than did those with high grade tumors (85.5% vs. 95.5%, $P < 0.001$).

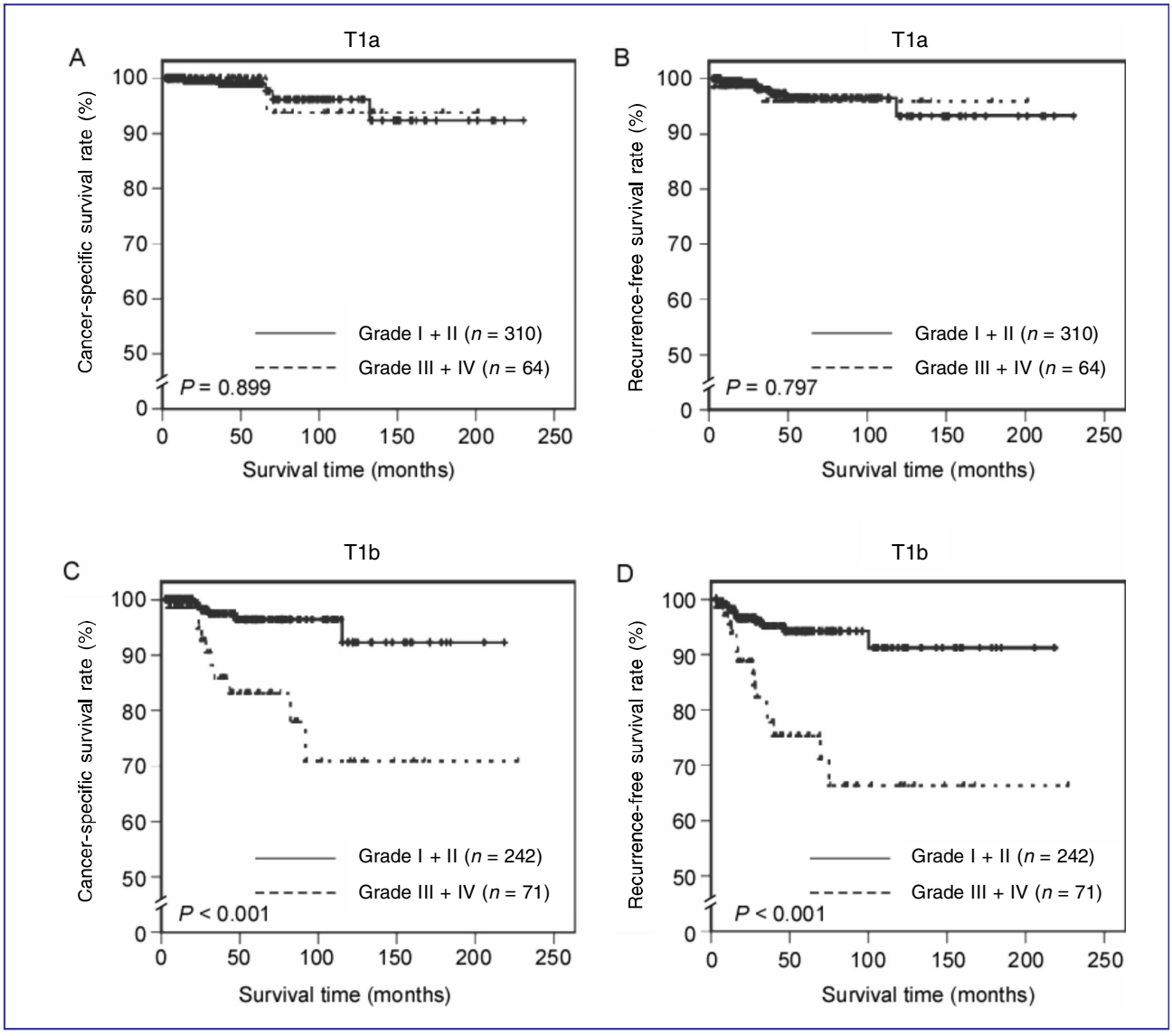

Figure 2. **The role of Fuhrman grade in distinguishing prognosis can be only observed in T1b patients.** A, in T1a patients, the 5-year CSS for patients with low and high Fuhrman grade tumor was 98.9% and 100%, respectively (P = 0.899). B, 5-year RFS rate was not significantly different between T1a patients with low and high Fuhrman grade tumor (96.5% vs. 95.8%, P = 0.797). C and D, T1b patients with low grade tumor had a 5-year CSS of 96.4% and a 5-year RFS of 94.3% compared to 83.1% and 75.3% in high grade patients, respectively (both P < 0.001).

Table 3. Multivariate analysis with Cox regression model for risk factors predictive for CSS and RSS

Item	Category	CSS			CSS		
		Relative risk	95% CI	*P*	Relative risk	95% CI	*P*
Age (years)	≤54 vs. >54	0.468	0.190–1.150	0.098	0.761	0.389–1.488	0.425
Gender	Male vs. female	0.771	0.311–1.911	0.595	1.013	0.507–2.024	0.971
Histological classification	Clear vs. non-clear	2.029	0.789–5.221	0.142	1.599	0.723–3.536	0.247
Fuhrman grade	I+II vs. III+IV	3.377	1.458–7.825	0.005	3.398	1.744–6.623	<0.001
Tumor size (cm)	≤4 vs. >4	3.130	1.211–8.091	0.019	3.284	1.528–7.058	0.002

CI, confidence interval. Other abbreviations as in Table 2.

can be only observed in patients with T1b RCC. As shown in Figure 2, patients with low grade tumors had a 5-year CSS of 96.4% and RFS of 94.3% compared to 83.1% and 75.3% in high grade tumors, respectively, suggesting that patients with T1b RCC had significantly better prognosis than did the patients with T1a RCC. The 2009 National Comprehensive Cancer Network (NCCN) guidelines for kidney cancer do not recommend adjuvant treatment for organ-confined RCC but, instead, recommend the same follow-up schedule for all T1–2 N0M0 RCC[17]. We found patients with the risk factors of T1b category and high Fuhrman grade tumor had high recurrence risk, suggesting that follow-up in these patients should be performed more often. Forty patients had cancer recurrence in our cohort, 28 of whom had at least one of the aforementioned risk factors. The time from nephrectomy to tumor recurrence ranged from 3 to 161 months (median, 27 months). For patients with more than one recurrence risk factor, it is more advisable that follow-up be performed at 3-month intervals in the first three years and annually thereafter. For those with only one risk factor, follow-up should begin three months after surgery and continue at 6-month intervals for 2 years, then annually for 5 years. However, this is only a preliminary follow-up plan for patients with T1N0M0 RCC. A more reasonable and convincing follow-up schedule must be verified by further large-scale and long-term studies.

Conclusions

For T1N0M0 RCC, the prognosis is excellent. The long-term survival of this Asian cohort is comparable to that in Western reports. Patients with T1b and high Fuhrman grade disease have high risk of tumor recurrence and death, thus need more frequent follow-up.

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