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Oncological outcome of surgical treatment in 336 patients with renal cell carcinoma

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[**Abstract**] **Background and Objective:** The most effective therapy against renal cell carcinoma (RCC) is surgical treatment; however, there have been few large-scale studies that focused on the oncological outcome of this disease in China. The aim of the current study was to report the clinicopathological results and cancer-specific survival (CSS) rate in RCC patients after surgical treatment in our center. **Methods:** We retrospectively analyzed the clinicopathological data of 336 RCC patients who underwent radical or partial nephrectomy between 1999 and 2006. Of the 336 patients, 226 were male and 110 were female; the median age was 51 years. Univariate and multivariate analyses were conducted to identify the independent prognostic predictors for this cohort of RCC patients. **Results:** During follow-up, the overall 5-year CSS rate was 81.4%. The 5-year CSS rates for patients with stage-I, -II, -III, and -IV RCC were 94.7%, 88.9%, 68.8%, and 19.3%, respectively. The patients with T1N0M0 (T1) and T2N0M0 (T2) tumors had similar survival curves. For patients with T1 category tumor, the survival rate did not differ significantly between the radical nephrectomy and nephron-sparing surgery groups. For the 21 patients with metastasis confined to the local lymph nodes, the 5-year survival rate was 31.6% after radical nephrectomy and lymph node dissection. For the 15 patients with vena caval tumor thrombus, the 5-year survival rate was 52.5% after radical nephrectomy and tumor thrombus extirpation. Multivariate Cox regression showed that stage was an independent predictor for CSS (hazard ratio, 3.359; $P < 0.001$). **Conclusions:** For localized RCC, the oncological outcome of this cohort is comparable to that reported in the Western literature. For some patients with locally advanced RCC, aggressive surgical treatment can lead to better long-term survival. However, the prognosis of the patients with metastasis still needs to be improved.

Key words: Kidney, renal cell carcinoma, radical nephrectomy, nephron-sparing surgery, prognosis

Renal cell carcinoma (RCC) accounts for approximately 3% of all adult malignancies and is the most lethal genitourinary tumors. More than 40% of RCC patients die of the disease, whereas the mortality rates for other urologic cancers, such as prostate cancer and bladder cancer, are approximately 20%[1,2]. Although there are many types of emerging treatment, including radiofrequency ablation, interventional therapy, immunological therapy, and targeted therapy, surgery is still the most effective treatment for this disease. Fortunately, the efficacy of surgery for RCC has increased in recent years due to the standardization of the operation. However, there are few large-scale reports focusing on the oncological outcome of RCC in China; hence, we still lack long-term prognostic information. Herein, we report on a group of 336 surgically treated RCC patients in order to determine the survival details of this cohort of Chinese patients.

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Materials and Methods

This study included 226 men and 110 women. The median age of patients at surgery was 51 years (range,

4–83 years) and the median tumor size was 5 cm (range, 1.2–19 cm). Of the 336 patients, 169 (50.3%) were asymptomatic and 167 (49.7%) were symptomatic. Lymph node dissection and tumor thrombus extirpation in combination with radical nephreceomy were performed in 245 and 15 patients respectively. TNM staging was performed according to the system outlined by the American Joint Committee on Cancer (AJCC, 2002) [3]. Tumor histology was classified according to the 2004 WHO classification system [4]. The operations were performed as described by Hinman[5].

All patients were followed at 3-month intervals during the first 2 years after operation and at 6-month intervals thereafter. Follow-ups consisted of a physical examination, blood chemistry analysis, and functional evaluation. Chest X-ray and abdominal ultrasound examination were performed every half a year. The first follow-up abdominal computer tomography (CT) was performed 3 months after surgery and once a year thereafter. A complete checkup was performed for patients with any evidence of recurrence or metastasis.

Tumor recurrence, including local relapse and distal metastasis, was confirmed by CT scan or magnetic resonance imaging (MRI). The primary endpoint of this study was cancer-specific survival (CSS), which was computed from the date of operation to the date of death or last follow-up. Death from RCC was considered as the event, whereas death from causes other than RCC was censored at the date of death. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. All *P* values were two-tailed, and $P < 0.05$ was considered as statistically significant. Data were analyzed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Recurrence and metastasis

During the follow-up ranging from 3 to 122 months (median, 42 months), 44 patients developed recurrence and 51 died of RCC. The local relapse rate and distal metastasis rate were 3.0% and 10.9%, respectively.

Five-year survival rate in different subgroups

The detailed 5-year CSS rates are listed in Table 1. The 5-year CSS rate for the whole group was 81.4% (Figure 1A). For the patients with stage-I, -II, -III, and -IV diseases, the 5-year CSS rates were 94.7%, 88.9%, 68.8%, and 19.3%, respectively (Figure 1B). The survival rate of patients with T2N0M0 (T2) RCC was not significantly different from that of patients with T1N0M0 (T1) RCC ($P = 0.298$); however, patients with localized disease (T1 and T2) showed better survival rates than did patients T3N0M0 (T3) with RCC (5-year CSS rate: 93.3% vs. 77.2%, $P < 0.001$) (Figure 1C,1D). For stage-I RCC, survival rate in patients undergoing partial nephrectomy was similar to that in patients with radical nephrectomy (93.7% vs. 97.6%, $P = 0.332$) (Figure 1E). After lymph node dissection, 21 patients were found to have metastasis confined to the local lymph nodes and their 5-year survival rate was 31.6% after radical nephrectomy and lymph node dissection (Figure 1F). For the 15 patients with vena cava tumor thrombus, the 5-year survival rate was 52.5% after radical nephrectomy and tumor thrombus extirpation (Figure 1G).

Multivariate analysis results

To find the independent predictors for CSS, Cox regression analysis were performed. Multivariate Cox regression analysis showed that stage was an independent predictor for CSS (hazard ratio, 3.359; $P < 0.001$).

Discussion

Recently some Western studies have reported an encouraging outcome for RCC patients, with 5-year survival rates of 85%–96%[6] and 87.8%–88.7%[7] for stage-I and -II diseases, respectively. However, the 5-year survival rates for patients with stage-III and -IV diseases are still disappointed (40%–80% and 0–20%, respectively)[8]. In the present Chinese study, patients underwent radical or partial nephrectomy during the last 10 years and the 5-year CSS rate was comparable to that reported in the Western literature. As shown in Table 1, the patients with stage-I and -II diseases had 5-year CSS rates of 94.7% and 88.9%, respectively, whereas the 5-year CSS rates of patients with stage-III and -IV diseases were only 68.8% and 19.3%, respectively. Some of the patients with advanced-stage diseases developed tumor recurrence or metastasis after surgery and eventually died of disease progression. For these patients, it is a global priority to find a way to improve RCC prognosis. In view of those above mentioned, three international multicenter prospective clinical trials (SORCE, S-TRAC, ECOG 2805), using sunitinib or sorafenib to prevent recurrence of high risk recurrent RCC, are in progress. However, accurate N staging, an important factor of high risk recurrent RCC[9], can only be achieved by lymph node dissection. Moreover, our results suggest that lymph node dissection may improve the prognosis of RCC patients with metastasis confined to local lymph nodes. Although the European Organization for Research and Treatment of

Table 1 Cancer specific 5-year survival rate of 336 patients with renal cell carcinoma

Characteristic	Number of cases	5-year survival rate	*P*
Gender			0.704
Male	226	80.5%	
Female	110	83.1%	
Age (years)			0.874
> 51	162	79.7%	
⩽ 51	174	83.4%	
Laterality			0.441
Left	167	78.1%	
Right	166	85.2%	
T classification			< 0.001
1	211	90.1%	
2	62	81.6%	
3	57	57.3%	
4	6	16.7%[a]	
N classification			< 0.001
0	308	85.5%	
1 + 2	28	34.1%	
M classification			< 0.001
0	309	86.7%	
1	27	24.4%	
Stage			< 0.001
I	200	94.7%	
II	49	88.9%	
III	50	68.8%	
IV	37	19.3%	
Histological classification			0.846
CCRCC	312	81.7%	
Others	24	76.0%	

[a] The data were analyzed by using Cox regression analysis. [b] This is 3-year survival rate. CCRCC, clear cell renal cell carcinoma.

Cancer (EORTC) designed a randomized trial[10] comparing radical nephrectomy combined with a complete lymphadenectomy to radical nephrectomy alone in clinical localized RCC and after long-term follow-up they concluded that no survival advantage was observed in the group received a complete lymph-node dissection, we still lack the prospective data to make sure whether lymph-node dissection can benefit the patients with clinical positive lymph-node disease. Hence, we think that for the patients with locally advanced RCC, it is still necessary to perform lymph node dissection.

In 2002, the AJCC renewed the TNM staging system for RCC, in which organ-confined RCC was divided into T1 and T2 subgroups based on a tumor diameter cutoff of 7 cm[11]. However, there are still controversy about setting 7 cm as the tumor diameter cutoff and even the necessity of subgrouping localized renal cancer. Kinouchi *et al.* [12] reported that there was no significant difference in the survival curves between T1 and T2 patients. They believed that a 5.5-cm tumor diameter cutoff for T1 and T2 disease has more predictive value. Srivastava *et al.*[13] studied 233 patients with T1 disease and found that a 5-cm cutoff value could maximize the differences in patient survival. They pointed out that subgrouping T1 into T1a and T1b by a cutoff value of 4 cm may not be accurate. Some researchers have found that tumor size does affect the prognosis of localized RCC, however, it is not an independent prognostic factor. Usually, tumor size is associated with the Fuhrman grade and histological classification, thus affecting survival indirectly [14]. In our study, patients with T1- and T2- stage tumors had similar survival curves, but the patients with localized RCC (T1 and T2) had a markedly higher 5-year CSS rate than did some locally advanced patients (T3). In view of the results of our study and the literature, we considered that for organ-confined RCC, tumor size may not be an independent prognostic factor. However, larger sample size trials are required to shed light on this controversial issue.

For stage I RCC, many scholars are interested in knowing which surgical procedures are associated with improved long-term survival. In 1995, Butler *et al.*[15] reported that partial nephrectomy and radical nephrectomy had similar oncological outcomes for patients with solitary small renal cancer (5-year survival rate, 97% vs. 100%, *P* >

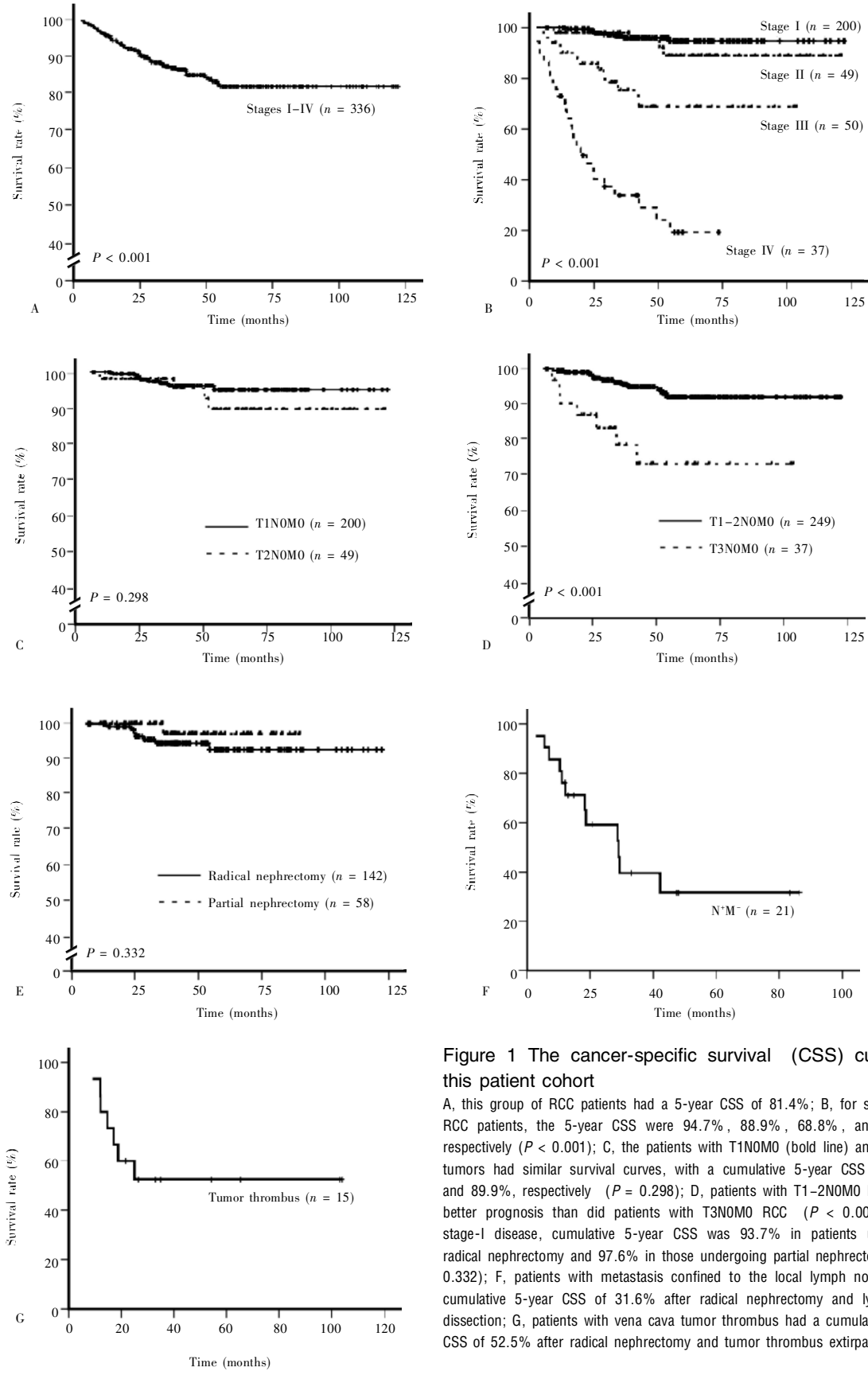

Figure 1 The cancer-specific survival (CSS) curve for this patient cohort

A, this group of RCC patients had a 5-year CSS of 81.4%; B, for stages I–IV RCC patients, the 5-year CSS were 94.7%, 88.9%, 68.8%, and 19.3%, respectively ($P < 0.001$); C, the patients with T1N0M0 (bold line) and T2N0M0 tumors had similar survival curves, with a cumulative 5-year CSS of 94.7% and 89.9%, respectively ($P = 0.298$); D, patients with T1–2N0M0 RCC had a better prognosis than did patients with T3N0M0 RCC ($P < 0.001$); E, for stage-I disease, cumulative 5-year CSS was 93.7% in patients undergoing radical nephrectomy and 97.6% in those undergoing partial nephrectomy ($P = 0.332$); F, patients with metastasis confined to the local lymph nodes had a cumulative 5-year CSS of 31.6% after radical nephrectomy and lymph-node dissection; G, patients with vena cava tumor thrombus had a cumulative 5-year CSS of 52.5% after radical nephrectomy and tumor thrombus extirpation.

0.05). The study results by Patard *et al.*[16] showed there were no significant differences in local or distant recurrence rates between patients undergoing partial nephrectomy and those undergoing radical nephrectomy for either T1a or T1b tumors. This international study suggested that it is safe to expand the indications of partial nephrectomy to patients with T1 tumors up to 7 cm in diameter. Similarly, our data confirmed that for T1 RCC, there was no significant difference between the radical nephrectomy and nephron-sparing surgery groups in survival curves (5-year survival rate, 93.7% vs. 97.6%, $P > 0.05$). However, careful patient selection remains necessary.

Skinner *et al.*[17] reported a group of 56 RCC patients with vena caval thrombus. The overall 1-, 3-, and 5-year survival rates after surgery were 56%, 34%, and 25%, respectively. Seventy-five percent of patients in their series received successful extirpation of all apparent tumors, accompanied by an expected 5-year survival rate of 57% for those without metastatic disease to other organs. They claimed that complete surgical excision was crucial for survival. In China, Cai *et al.*[18] reported 21 RCC patients with vena caval thrombus. Two patients died of cancer without surgery shortly after diagnosis. In the 19 patients who underwent tumor thrombus extirpation, 8 patients died and 11 survived (8 alive disease-free and 3 alive with tumor). In our cohort, 15 patients underwent vena caval thrombus extirpation, with a 5-year survival rate of 52.5%. Taken together, this suggests that it is reasonable to advocate an aggressive optimistic approach for patients with kidney cancer vena caval thrombus if there is no preoperative evidence of metastatic disease.

Although we reported a group of 336 Chinese RCC patients, there are still a lot of problems. First, it is a retrospective study and the sample is not very large. Second, some unavoidable bias does exist. Third, some useful nomograms and scoring system for the predicting of prognosis have not been tried in this study. Further prospective study focusing on the prognosis of RCC is warranted.

Conclusion

For localized RCC, the oncological outcome of this cohort is comparable to that reported in the Western literature. For some patients with locally advanced disease, such as those with vena caval thrombus or metastasis confined to local lymph nodes, aggressive surgical treatment can bring long-term survival. However, the prognosis of patients with metastasis still needs to be improved.

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