Survival Analysis of Pathological T3a Upstaging in Clinical T1 Renal Cell Carcinoma

GU-SHUN LAI1, JIAN-RI LI2,3,4, SHIAN-SHIANG WANG2,3,5, CHUAN-SHU CHEN2,3, CHUN-KUANG YANG2, SHENG-CHUN HUNG2,3, CHEN-LI CHENG2,3, YEN-CHUAN OU3,6 and KUN-YUAN CHIU2,5

1Division of Urology, Department of Surgery, Chiayi Branch, Taichung Veterans General Hospital, Chiayi, Taiwan, R.O.C.;
2Division of Urology, Department of Surgery, Taichung Veterans General Hospital, Taichung, Taiwan, R.O.C.;
3Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan, R.O.C.;
4Department of Medicine and Nursing, Hungkuang University, Taichung, Taiwan, R.O.C.;
5Department of Applied Chemistry, National Chi Nan University, Nantou, Taiwan, R.O.C.;
6Department of Urology, Tung’s Taichung MetroHarbor Hospital, Taichung, Taiwan, R.O.C.

Abstract. Aim: To evaluate the oncological outcomes of pathological T3a upstaging from clinical T1 renal cell carcinoma. Patients and Methods: We retrospectively studied patients who underwent radical or partial nephrectomy for clinical T1 renal tumors. Results: The median follow-up period was 44 months. At three and five years, the respective overall survival rate was 88.7% and 82.4% in pT3a disease, 95.7% and 93.4% in pT1 (p=0.008), the cancer-specific survival rate, 93.9% and 90.8% in pT3a, 99% and 97.7% in pT1 (p=0.001), and the recurrence-free survival rate, 79.7% and 71.0% in pT3a, and 95.5 and 94.3% in pT1 (p<0.001). Conclusion: Patients with pathological T3a upstaging tumors were associated with a significantly decreased survival rate, along with a higher recurrence rate when compared to those with pathological T1 disease.

With the increased use of cross-sectional imaging modalities, the recognition of renal cell carcinoma (RCC) is increasing. Most new cases are detected incidentally as small renal masses in asymptomatic patients (1-3). The majority of masses are ≤7 cm in size, or at clinical stage T1 (cT1), and confined to the kidney (3). Patients with these small renal masses are generally given a favorable prognosis. Current guidelines recommend nephron-sparing surgery, such as a partial nephrectomy, for the treatment of these masses with the advantages of offering renal function preservation and equivalent oncologic outcomes when compared to traditional radical nephrectomy (4-6). However, after surgery for these small renal masses, a number of tumors are found to have pathologically upstaged to T3a (pT3a). Unfortunately, current imaging modalities have a limited ability in detecting the adverse pathologic features associated with pT3a upstaging, such as renal sinus extension, perinephric fat invasion or renal vein thrombosis, which in turn will lead to under-staging of the tumors and underestimate its seriousness if preoperatively based solely upon the size criteria.

Previous literature offers conflicting results regarding the prognosis and associated factors for pT3a upstaging (6-10). Therefore, the objective of the present study was to evaluate the oncologic outcomes of the patients with pT3a upstaging tumors, and also to identify the clinicopathological features associated with upstaging.

Patients and Methods

The present study was approved by the Institutional Review Board. We retrospectively reviewed the charts of consecutive patients who underwent radical or partial nephrectomy for the treatment of clinical T1N0M0 renal tumors in our Institute during the period from January 2002 to June 2018. All types of surgical approaches (open, laparoscopic and robotic surgeries) were included. Clinical stages were determined by the surgeon according to the patients’ documents and confirmed with preoperative Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). All renal tumors were diagnosed pathologically as RCC. Patients with a diagnosis of non-RCC renal tumors on their pathologic reports, bilateral renal tumors, loss of follow-up or insufficient data for analysis were excluded.
Patients included in the present study were divided into pathologic T1 (pT1) and T3a (pT3a) groups. Patient demographics and tumor characteristics, including age, gender, tumor size, clinical stage, Fuhrman grade, histology type, margin status and pathologic features, were evaluated and compared between the two groups using the Mann-Whitney U-test and Fisher’s exact test for continuous variables, and the Pearson’s Chi-Square test for categorical variables analysis. Kaplan-Meier survival curves and the log rank test were used to investigate overall survival (OS), recurrence-free survival (RFC) and cancer-specific survival (CSS). In order to determine the clinicopathological features associated with pT3a upstaging, multivariate analyses were conducted using logistic regression. Univariate and multivariate Cox proportional hazards regression models were used to investigate the features related to disease recurrence. A p-value<0.05 was considered statistically significant, and all analyses were performed using SPSS software (version 19.0; SPSS Inc., Chicago, IL, USA).

Results

Charts were reviewed from a database of Taichung Veteran’s General Hospital after approval by the Institutional Review Board. From January 2002 to June 2018, a total number of 476 patients who had underwent partial or radical nephrectomy for the treatment of clinical stage T1M0N0 renal tumors were evaluated. After excluding patients with pathological non-RCC lesions or insufficient information for analysis, 429 patients were included in the final study, of which 55 (12.8%) were found to have renal tumors upstaged to pT3a, while 374 (87.2%) were not upstaged. Patients’ demographics and the clinicopathological characteristics between the two groups are shown and compared in Table I.

### Table I. Patients’ demographics and pathological characteristics.

|                          | T1 (n=374, 87.2%) | T3a (n=55, 12.8%) | p-Value   |
|--------------------------|------------------|------------------|-----------|
| Age, years (IQR)         | 59 (49-68)       | 64 (56-75)       | 0.011*    |
| Gender, n (%)            |                  |                  | 0.214     |
| Male                     | 256              | 68               | 33        |
| Female                   | 118              | 32               | 22        |
| Follow up, months (IQR)  | 43 (20-96)       | 44.5 (24-70)     | 0.439     |
| Clinical stage, n (%)    |                  |                  | <0.001*   |
| T1a                      | 196              | 52               | 15        |
| T1b                      | 178              | 48               | 40        |
| Tumor size, cm           | 3.9              | 2.6-5            | 5         |
|                         |                  |                  | 3.5-6.5   |
| Etiology of T3, n (%)    |                  |                  | <0.001*   |
| Sinus fat invasion       | 12               | 22               |           |
| Perinephric invasion     | 26               | 47               |           |
| Vein thrombosis          | 7                | 13               |           |
| Sinus fat invasion+vein thrombosis | 5  | 9  | |
| Perinephric invasion+vein thrombosis | 2  | 4  | |
| Collecting system invasion | 3  | 5  | |
| Fuhrman grade, n (%)     |                  |                  | 0.002*    |
| 1                        | 24               | 6                | 1         |
|                         | 200              | 54               | 22        |
| 3                        | 90               | 24               | 22        |
|                         | 4                | 1                | 4         |
|                         | 56               | 15               | 6         |
|                         |                  |                  | 11        |
| Histology, n (%)         |                  |                  | 0.277     |
| Clear                    | 264              | 71               | 44        |
| Papillary                | 34               | 9                | 4         |
| Chromophobe              | 31               | 8                | 2         |
| Others                   | 45               | 12               | 5         |
| Necrosis, n (%)          | 37               | 10               | 14        |
|                         | 9                | 2                | 15        |
|                         | 2                | 0.5              | 4         |
|                         | 9                | 2                | 3         |
| Method                   |                  |                  | <0.01*    |
| Radical                  | 234              | 63               | 48        |
| Partial                  | 140              | 37               | 7         |
| Recurrence, n (%)        |                  |                  | <0.001*   |
| Local recurrence         | 23               | 6.1              | 13        |
|                         | 7                | 1.9              | 2         |
| Distant metastasis       | 16               | 4.2              | 11        |
|                         |                  |                  | 20        |

IQR, Interquartile range; LVI, lymphovascular invasion.
Patients in the upstaged group were older than those in the non-upstage group (64 years vs. 59 years, \( p=0.011 \)). The majority of patients were male in both groups, though there was no significant difference between the groups. When compared with the non-upstage group, the upstaged group had a greater proportion of patients with clinical T1b tumors (73\% vs. 48\%, \( p<0.001 \)), and their tumor size was larger (5 cm vs. 3.9 cm, \( p=0.001 \)). The upstaged group tended to have a higher Fuhrman grade disease level (Grade 3 and 4) than the non-upstaged group (47\% vs. 25\%, \( p=0.002 \)). Additionally, histopathological features related to poor prognosis, including tumor necrosis (25\% vs. 10\%, \( p=0.03 \)), lymphovascular invasion (27\% vs. 2\%, \( p<0.001 \)), sarcomatoid change (7\% vs. 0.5\%, \( p<0.001 \)), were significantly more common in the upstaged group when compared to the non-upstage group. With regards to surgical methods, radical nephrectomy was performed significantly more frequently in the upstaged group than in the non-upstage group (87\% vs. 63\%, \( p<0.001 \)). During a median follow-up period of
44.5 months (interquartile range=24-70) after surgery, 13 (23.6%) patients with pT3a upstaging tumors experienced tumor recurrence, of which 2 (3.6%) patients had local recurrence and 11 (20%) developed distant metastasis. For the non-upstage group, median follow-up was 43 months (interquartile range=20-96) and disease recurrence occurred in 23 (6.1%) patients, including local recurrence in 7 (1.9%) and distant metastasis in 16 (4.2%). Disease recurrence was significantly more common in the pT3a upstaging group compared to the non-upstage group (23.6% vs. 6.1%, \( p < 0.001 \)). There was no significant difference in positive surgical margin and RCC histological type between the two groups.

For patients with pT3a upstaging disease, the 3- and 5-year OS rate was 88.7% and 82.4%, compared to 95.7% and 93.4% in the non-upstage group (\( p=0.008 \)) respectively. The 3- and 5-year CSS rate was 93.9% and 90.8% in the pT3a upstaging group, and 99% and 97.7% in the non-upstage group (\( p=0.001 \)) respectively. RFS at 3 and 5 years was 79.7% and 71.0% in the pT3a upstaging group, while it was 95.5 and 94.3% in the non-upstage group (\( p<0.001 \)) respectively. Figure 1 demonstrates the Kaplan-Meier survival curves to compare the OS, CSS and RFS between the two groups.

In the subgroup analysis for patients with pT3a upstaging renal tumors, patients treated with radical nephrectomy seemed to experience poor RFS when compared to those who underwent partial nephrectomy, but it did not reach a statistical significance (\( p=0.192 \)). Figure 2 shows the comparison of RFS between a radical and partial nephrectomy in the pT3a upstaging group.

Based upon multivariate analysis, pT3a upstaging was associated with old age [odds ratio (OR)=1.03, 95% confidence interval (95% CI)=1.005-1.056, \( p=0.021 \)], large tumor size (OR=1.328, 95% CI=1.046-1.687, \( p=0.02 \)), high Fuhrman grade (OR=2.63, 95% CI=1.313-5.270, \( p=0.006 \)), lymphovascular invasion (LVI) (OR=8.527, 95% CI=3.053-23.817, \( p<0.001 \)) and sarcomatoid change (OR=8.716, 95% CI=1.33-57.141, \( p=0.024 \)). Table II demonstrates the multivariate analysis of clinicopathologic factors associated with pathological upstaging.

Based on univariate analysis, high Fuhrman grade (OR=3.74, 95% CI=1.931-7.243, \( p<0.001 \)), upstaging disease (OR=4.75, 95% CI=2.385-9.464, \( p<0.004 \)), tumor necrosis (OR=3.812, 95% CI=1.818-7.885, \( p<0.001 \)) and larger tumor size (OR=1.444, 95% CI=1.168-1.785, \( p=0.001 \)) were related to a decreased RFS. Further multivariate analysis showed that high Fuhrman grade (OR=2.494, 95% CI=1.239-5.019, \( p=0.01 \)), upstaging disease (OR=2.579, 95% CI=1.212-5.488, \( p=0.014 \)) and larger tumor size (OR=1.297, 95% CI=1.033-1.63, \( p=0.025 \)) were significantly associated with tumor recurrence. Table III lists the univariate and multivariate Cox proportional hazards regression models for disease recurrence.

In the subgroup analysis of the pT3a upstaging group, there was no clinical or histopathological features significantly associated with tumor recurrence based upon the univariate analysis (Table IV).

Discussion

We herein report our analysis of incidental pT3a upstaging from cT1 RCC in our institution, and found that pT3 upstaging was associated with inferior oncological outcomes in terms of OS, RFS and CSS when compared to the non-upstaged pT1 group. Upon multivariate analysis, clinicopathological characteristics

---

Table II. Multivariate analysis of clinicopathological features associated with pathological upstaging.

| Variables          | OR   | 95% CI        | \( p \)-Value |
|--------------------|------|---------------|---------------|
| Age                | 1.03 | 1.005-1.056   | 0.021*        |
| Gender             |      |               |               |
| Female             | REF  |               |               |
| Male               | 0.616| 0.303-1.254   | 0.182         |
| Size               | 1.328| 1.046-1.687   | 0.02*         |
| Fuhrman grade      |      |               |               |
| I/II               | REF  |               |               |
| III/IV             | 2.63 | 1.313-5.270   | 0.006*        |
| Histology          |      |               |               |
| Nonclear           | REF  |               |               |
| Clear              | 2.328| 0.964-5.624   | 0.06          |
| Necrosis           | 1.701| 0.705-4.107   | 0.237         |
| LVI                | 8.527| 3.053-23.817  | \( p<0.001 \)*|
| Sarcomatoid features| 8.716| 1.33-57.141   | 0.024*        |

LVI, Lymphovascular invasion.
related to pT3a upstaging included old age, large tumor size, LVI and sarcomatoid change. We also found a positive relationship between pathological features (high Fuhrman grade, large tumor size and upstaged tumor) and a higher tumor recurrence rate based upon the multivariate analysis. For patients with pT3a upstaging disease, there were no significant factors identified that were related to tumor recurrence.

Several pieces of literature have reported on the impact of pT3a upstaging on prognosis, but results are conflicting. Some studies (8, 10) demonstrated that there was no significant difference regarding the oncologic outcomes, while the others showed inferior RFS (7, 9, 11), CSS (12) and OS (12) within the pT3a upstaging group. Our study also found that patients with pT3a upstaging disease experienced reduced 3- and 5-year OS, CSS and RFS rates. Given the inferior survival outcomes due to pT3a upstaging, counseling each patient regarding the severity of the disease, along with providing an intense follow-up protocol after surgery is warranted.

The prognosis for pT3a upstaging disease in our study was inferior to previously published literature that demonstrated a RFS rate between 86% and 98% with follow-up periods up to 5 years (7-8, 10). In contrast, the present study showed that the RFS at 3 and 5 years was 79.7% and 71.0%, respectively, for the pT3a upstaging group, that was similar to the studies conducted by Nayak et al. (9) and Russell et al. (12), which reported that the 3-year RFS was 76% and 81%, respectively.

The incidence rate of pT3a upstaging in the present study was 12.8%, which was consistent with previous studies that demonstrated the upstaging rate to be approximately 4.8-13% (7-9), with one study conducted by Robert et al. even reporting a higher incidence rate of up to 31% (10). Given the fact that incidence rate was not uncommon and survival outcomes were reduced, identifying factors related to upstaging is helpful for a surgeon when considering risk stratification and preoperatively determining the optimal treatment plan.

Regarding the multivariate analysis, pathological upstaging was associated with old age, larger tumor size, high Fuhrman grade, LVI and sarcomatoid change. Clear cell type RCC was related to upstaging, but did not reach statistical significance. (OR=2.328, 95% CI=0.964-5.624, p=0.06). Larger tumor size

### Table III. Univariate and multivariate Cox proportional hazards regression models of the factors associated with disease recurrence.

| Variables               | OR  | 95% CI       | p-Value | OR  | 95% CI       | p-Value |
|-------------------------|-----|--------------|---------|-----|--------------|---------|
| Age                     | 1.012 | 0.987-1.037 | 0.342   |     |              |         |
| Gender (M/F)            | 0.736 | 0.377-0.736 | 0.37    |     |              |         |
| Histology               |     |              |         |     |              |         |
| Non clear               | REF |              |         |     |              |         |
| Clear                   | 0.952 | 0.468-1.935 | 0.892   |     |              |         |
| Fuhrman grade           |     |              |         |     |              |         |
| I/II                    | 3.74 | 1.931-7.243 | <0.001* | 2.494 | 1.239-5.019 | 0.01*   |
| Method                  |     |              |         |     |              |         |
| Partial                 | REF |              |         |     |              |         |
| Radical                 | 2.281 | 0.946-5.502 | 0.066   |     |              |         |
| Margin                  | 0.047 | 0.022-0.716 | 0.481   |     |              |         |
| Upstaging               | 4.75 | 2.385-9.464 | <0.001* | 2.579 | 1.212-5.488 | 0.014*  |
| LVI                     | 2.519 | 0.889-7.136 | 0.082   |     |              |         |
| Sarcomatoid features    | 2.76 | 0.374-20.374 | 0.32    |     |              |         |
| Necrosis                | 3.812 | 1.818-7.991 | <0.001* | 1.953 | 0.88-4.331 | 0.1     |
| Size                    | 1.444 | 1.168-1.785 | <0.001* | 1.297 | 1.033-1.63 | 0.025*  |

LVI, Lymphovascular invasion.

### Table IV. Univariate analysis of factors related to tumor recurrence in pT3a upstaging group.

| Variables               | OR  | 95% CI       | p-Value |
|-------------------------|-----|--------------|---------|
| Age                     | 0.989 | 0.951-1.03  | 0.596   |
| Gender (M/F)            | 0.725 | 0.242-2.168 | 0.565   |
| Histology               |     |              |         |
| Non clear               | REF |              |         |
| Clear                   | 0.723 | 0.198-2.639 | 0.624   |
| Fuhrman Grade           |     |              |         |
| I/II                    | 1.885 | 0.61-5.826  | 0.271   |
| Method                  |     |              |         |
| Partial                 | REF |              |         |
| Radical                 | 25.102 | 0.012-50432 | 0.406   |
| Margin                  | 0.045 | 0.3586-5.371 | 0.591  |
| LVI                     | 1.327 | 0.408-4.314 | 0.638   |
| Sarcomatoid features    | 0.043 | 0.495-347   | 0.51    |
| Necrosis                | 1.056 | 0.285-3.912 | 0.935   |
| Size                    | 1.416 | 0.965-2.079 | 0.075   |

LVI, Lymphovascular invasion.
either partial or radical nephrectomy (11). Our series also demonstrated that there was no difference in RFS between patients with positive surgical margin (3 treated with radical nephrectomy, and these would be confounding factors. Third, the present study had a small sample size, with a difference in the case numbers between the two groups. Despite these limitations, we believe that our study may provide useful information regarding renal tumors with pT3a upstaging.

In conclusion, we demonstrated that renal tumors with pathological upstaging to T3a were related to significantly decreased RFS, CSS and OS rates when compared with pT1 renal tumors. Several clinicopathological characteristics associated with upstaging disease and RCC recurrence were identified, all of which could help clinicians in risk stratification, decision making, and arranging an appropriate follow-up schedule.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors’ Contributions

Study design and conception: Gu-Shun Lai and Jian-Ri Li. Interpretation of data and drafting of the manuscript: Gu-Shun Lai. Acquisition of data: Shian-Shiang Wang, Chuan-Shu Chen, Chun-Kuang Yang, Sheng-Chun Hung, Chen-Li Cheng, yen-Chuan Ou and Kun-Yuan Chiu.

References

1. Nini A, Muttin F, Cianflone F, Dehò F, Matloob R, DI Trapani D, Freschi M, Salonia A, Briganti A, Montorsi F, Bertini R and Capitanio U: Pathological high-risk renal cell carcinoma: Trends in clinical characteristics over 25 years. Anticancer Res 38(7): 4123-4130, 2018. PMID: 29970539. DOI: 10.21873/anticanres. 12703

(7-10) and high Fuhrman grade (9) have been reported to be predictors for pathological upstaging. Additional predictive factors previously described include a tumor’s central location (7), clear cell type (8), positive surgical margin (8) and a high R.E.N.A.L. nephrometry score (13). Current NCCN guidelines recommend partial nephrectomy, radical nephrectomy, active surveillance, or ablation therapy for the management of small renal tumors (14). Using preoperative cross-section image or tumor biopsy results, all of these predictive factors associated with upstaging can provide useful information during the decision-making process with regards to treatment plans and operation methods.

Several histopathological characteristics, including high Fuhrman grade, positive surgical margin, LVI, sarcomatoid change, tumor necrosis, preoperative anemia and lymph nodes involvement have been proven to be associated with inferior survival outcomes for RCC (15-18). The present study demonstrated that there was no factor associated with tumor recurrence in the pT3a upstaging group, which is similar to the study conducted by Russel et al. (12). This can be attributed to the fact that pT3a upstaging itself is associated with locally advanced disease, with a tendency for local recurrence or distant metastasis. Therefore, RCC recurrence tended to occur due to the aggressive nature of pathological upstaging, rather than any other clinical or histopathological factors.

The present study revealed that high Fuhrman grade, pathological upstaging and large tumor size were predictive factors of tumor recurrence upon the multivariate analysis. A previous study by Nayak et al. (9) reported that old age, high Fuhrman grade, positive surgical margin, pathological upstaging and large tumor size were all related to RCC recurrence. They also found that positive surgical margin was a strong predictor of tumor recurrence in their cohort (OR=3.08, 95% CI=1.51-6.03, p=0.02). The association between positive surgical margin and tumor recurrence has been controversial. Previous literature revealed that positive surgical margin or adjacent renal tissue were associated with higher recurrence (19-21), while some studies have shown that it was not related to tumor recurrence (22, 23). In the present study, positive surgical margin was not associated with tumor recurrence. In fact, all of the 12 patients with positive surgical margin (3 treated with radical nephrectomy and 8 with partial nephrectomy) did not receive adjuvant therapy and none of them experienced disease recurrence during the follow-up period, however, cautious surveillance remains necessary for these patients.

Whether the surgical approaches (radical or partial nephrectomy) have an impact on the survival outcomes for upstaging disease remains unclear. A previously published series by Shah et al. showed that partial nephrectomy was associated with inferior RFS, when compared with radical nephrectomy for pT3a upstaging renal tumors (18). However, Jeong et al. demonstrated that there was no difference in RFS between either partial or radical nephrectomy (11). Our series also discovered that there was no difference between the two surgical approaches. Interestingly, patients in the present study with upstaging disease treated with radical nephrectomy seemed to have a higher risk of recurrence, although it did not reach statistical significance (OR=25.102, 95% CI=0.012-50432, p=0.406). In fact, all patients with upstaging disease and RCC recurrence in the present study were treated with radical nephrectomy, and the vast majority involved distant metastasis (96.4%). Selection biases existed because the operating surgeon would prefer performing radical nephrectomy over partial nephrectomy for the larger or more technically challenging renal tumors, resulting inferior outcomes. Therefore, for patients with upstaging disease, radical nephrectomy appears not to provide survival benefits over partial nephrectomy, and as such adjuvant systemic therapy may be considered for these patients given the fact that most recurrence arises from distant metastasis other than local recurrence.

There were several limitations in the present study. First, this was a retrospective, non-randomized study from a single institution, which will result in several biases. Second, the current series included various surgical methods, such as open vs. minimally invasive approaches, or partial vs. radical nephrectomy, and these would be confounding factors. Third, the present study had a small sample size, with a difference in the case numbers between the two groups. Despite these limitations, we believe that our study may provide useful information regarding renal tumors with pT3a upstaging.

Several histopathological characteristics, including high Fuhrman grade, positive surgical margin, LVI, sarcomatoid change, tumor necrosis, preoperative anemia and lymph nodes involvement have been proven to be associated with inferior survival outcomes for RCC (15-18). The present study demonstrated that there was no factor associated with tumor recurrence in the pT3a upstaging group, which is similar to the study conducted by Russel et al. (12). This can be attributed to the fact that pT3a upstaging itself is associated with locally advanced disease, with a tendency for local recurrence or distant metastasis. Therefore, RCC recurrence tended to occur due to the aggressive nature of pathological upstaging, rather than any other clinical or histopathological factors.

The present study revealed that high Fuhrman grade, pathological upstaging and large tumor size were predictive factors of tumor recurrence upon the multivariate analysis. A previous study by Nayak et al. (9) reported that old age, high Fuhrman grade, positive surgical margin, pathological upstaging and large tumor size were all related to RCC recurrence. They also found that positive surgical margin was a strong predictor of tumor recurrence in their cohort (OR=3.08, 95% CI=1.51-6.03, p=0.02). The association between positive surgical margin and tumor recurrence has been controversial. Previous literature revealed that positive surgical margin or adjacent renal tissue were associated with higher recurrence (19-21), while some studies have shown that it was not related to tumor recurrence (22, 23). In the present study, positive surgical margin was not associated with tumor recurrence. In fact, all of the 12 patients with positive surgical margin (3 treated with radical nephrectomy and 8 with partial nephrectomy) did not receive adjuvant therapy and none of them experienced disease recurrence during the follow-up period, however, cautious surveillance remains necessary for these patients.

Whether the surgical approaches (radical or partial nephrectomy) have an impact on the survival outcomes for upstaging disease remains unclear. A previously published series by Shah et al. showed that partial nephrectomy was associated with inferior RFS, when compared with radical nephrectomy for pT3a upstaging renal tumors (18). However, Jeong et al. demonstrated that there was no difference in RFS between either partial or radical nephrectomy (11). Our series also discovered that there was no difference between the two surgical approaches. Interestingly, patients in the present study with upstaging disease treated with radical nephrectomy seemed to have a higher risk of recurrence, although it did not reach statistical significance (OR=25.102, 95% CI=0.012-50432, p=0.406). In fact, all patients with upstaging disease and RCC recurrence in the present study were treated with radical nephrectomy, and the vast majority involved distant metastasis (96.4%). Selection biases existed because the operating surgeon would prefer performing radical nephrectomy over partial nephrectomy for the larger or more technically challenging renal tumors, resulting inferior outcomes. Therefore, for patients with upstaging disease, radical nephrectomy appears not to provide survival benefits over partial nephrectomy, and as such adjuvant systemic therapy may be considered for these patients given the fact that most recurrence arises from distant metastasis other than local recurrence.

There were several limitations in the present study. First, this was a retrospective, non-randomized study from a single institution, which will result in several biases. Second, the current series included various surgical methods, such as open vs. minimally invasive approaches, or partial vs. radical nephrectomy, and these would be confounding factors. Third, the present study had a small sample size, with a difference in the case numbers between the two groups. Despite these limitations, we believe that our study may provide useful information regarding renal tumors with pT3a upstaging.

In conclusion, we demonstrated that renal tumors with pathological upstaging to T3a were related to significantly decreased RFS, CSS and OS rates when compared with pT1 renal tumors. Several clinicopathological characteristics associated with upstaging disease and RCC recurrence were identified, all of which could help clinicians in risk stratification, decision making, and arranging an appropriate follow-up schedule.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors’ Contributions

Study design and conception: Gu-Shun Lai and Jian-Ri Li. Interpretation of data and drafting of the manuscript: Gu-Shun Lai. Acquisition of data: Shian-Shiang Wang, Chuan-Shu Chen, Chun-Kuang Yang, Sheng-Chun Hung, Chen-Li Cheng, yen-Chuan Ou and Kun-Yuan Chiu.

References

1. Nini A, Muttin F, Cianflone F, Dehò F, Matloob R, DI Trapani D, Freschi M, Salonia A, Briganti A, Montorsi F, Bertini R and Capitanio U: Pathological high-risk renal cell carcinoma: Trends in clinical characteristics over 25 years. Anticancer Res 38(7): 4123-4130, 2018. PMID: 29970539. DOI: 10.21873/anticanres. 12703

804
2 Hollingsworth JM, Miller DC, Daignault S and Hollebeck BK: Rising incidence of small renal masses: a need to reassess treatment effect. J Natl Cancer Inst 98(18): 1331-1334, 2006. PMID: 16985252. DOI: 10.1093/jnci/djI362

3 Laguna MP, Algbare F, Cadeddu J, Clayman R Gill I, Guglio G, Hohenfellner M, Joyce A, Landman J, Lee B and van Poppel H: Current patterns of presentation and treatment of renal masses: a clinical research office of the endourological society prospective study. J Endourol 28: 861-870, 2014. PMID: 24555480. DOI: 10.1089/end.2013.0724

4 Campbell SC, Novick AC, Belldegrun A, Blute ML, Chow GK, Campbell SC, Novick AC, Belldegrun A, Blute ML, Chow GK, Morgan TM, Miller DC, Palapattu GS, Hafez KS, Sexton WJ, Russo P and Uzzo RG: Guideline for management of the clinical T1 renal mass. J Urol 182: 1271-1279, 2009. PMID: 19683266. DOI: 10.1016/j.juro.2009.07.004

5 Rendon RA, Kapoor A, Breau R, Leveridge M, Feifer A, Black PC and So A: Surgical management of renal cell carcinoma: Canadian Kidney Cancer Forum Consensus. Can Urol Assoc J 8: E398-E412, 2014. PMID: 25024794. DOI: 10.5489/cuaj.1894

6 Ljungberg B, Bansalash K, Cantfield S, Dabestani S, Hofmann F, Hora M, Kuczyn MA, Lam T, Marconi L, Merseburger AS, Mulders P, Powles T, Staevelh M, Volpe A and Bex A: EUA guidelines on renal cell carcinoma: 2014 update. Eur Urol 67: 913-924, 2015. PMID: 25616710. DOI: 10.1016/j.euro.2015.01.005

7 Gorin MA, Ball MW, Pierrozio PM, Tanagho YS, Bhayani SB, Kaouk JH, Rogers CG, Stifelman MD, Khalifeh A, Kumar R, Sivarajan G and Allaf ME: Outcomes and predictors of clinical T1 to pathological T3a tumor up-staging after robotic partial nephrectomy: a multi-institutional analysis. J Urol 190: 1907-1911, 2013. PMID: 23764083. DOI: 10.1016/j.juro.2013.06.014

8 Ramaswamy K, Khetari M, Pham H, Pham H, Mohan S, Stifelman M, Taneda S and Huang WC: Significance of pathological T3a upstaging in clinical T1 renal masses undergoing nephrectomy. Clin Genitourin Cancer 13: 344-349, 2015. PMID: 25680295. DOI: 10.1016/j.clgc.2015.01.001

9 Nayak JG, Patel P, Saarello O, Liu Z, Kapoor A, Finelli A, Tanguay S, Rendon R, Moore R, Black PC, Lacombe L, Breau RH, Kawakami J, Drachenberg DE: Pathological upstaging of clinical T1 to pathological T3a renal cell carcinoma: A multi-institutional analysis of short-term outcomes. Urology 94: 154-160, 2016. PMID: 27044717. DOI: 10.1016/j.urology.2016.03.029

10 Roberts WW, Bhayani SB, Allaf ME, Chan TY, Kawoussi LR and Jarrett TW: Pathological stage does not alter the prognosis for renal lesions determined to be stage T1 by computed tomography. J Urol 173: 713-715, 2005. PMID: 15711249. DOI: 10.1016/j.juro.2015.01.001

11 Jeong SH, Kim JK, Park J, Jeon HJ, Yoon MY, Jeong CW, Ku JH, Kim HH and Kwak C: Pathological T3a upstaging of clinical T1 renal cell carcinoma: Outcomes according to surgical technique and predictors of upstaging. PLoS One 11: e0166183, 2016. PMID: 27861519. DOI: 10.1371/journal.pone.0166183

12 Russell CM, Lebatschi AH, Choplin J, Niemann A, Mehra R, Morgan TM, Miller DC, Palapattu GS, Hafez KS, Sexton WJ, Spiess PE and Weizer AZ: Multi-institutional survival analysis of incidental pathologic T3a upstaging in clinical T1 renal cell carcinoma following partial nephrectomy. Urology 117: 95-100, 2018. PMID: 29678662. DOI: 10.1016/j.urology.2018.04.002

13 Tay Mh, Thamboo TP, Wu FM, Zhaojin C, Choo TB, Ramaan L and Tiong HY: High R.E.N.A.L. Nephrometry scores are associated with pathologic upstaging of clinical T1 renal-cell carcinomas in radical nephrectomy specimens: implications for nephron-sparing surgery. J Endourol 28(9): 1138-1142, 2014. PMID: 24810993. DOI: 10.1089/end.2014.0123

14 Motzer RJ, Jonasch E, Agarwal N, Bhayani S, Bro WP, Chang SS, Choueiri TK, Costello BA, Derwees IH, Fishman M, Gallagher TH, Gore JL, Hancock SL, Harrison MR, Kim W, Kyriakopolous C, LaGrance C, Lam ET, Lau C, Michaelson MD, Olencki T, Pierorazio PM, Pimlak ER, Redman BG, Shuch B, Sonner B, Sonpavde G, Solman J, Dwyer M and Kumar R: NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer, Version 2.2017. J Natl Compr Canc Netw 15(5): 804-834, 2017. PMID: 28596261. DOI: 10.6004/jnccn.2017.0100

15 Dall’Oglio MF, Arap MA, Antunes AA, Cury J, Leite KR and Srougi M: Impact of clinicopathological parameters in patients treated for renal cell carcinoma. J Urol 177: 1687-1691, 2007. PMID: 17437783. DOI: 10.1016/j.juro.2007.01.065

16 Kontak JA and Campbell SC: Prognostic factors in renal cell carcinoma. Urol Clin North Am 30: 467-480, 2003. PMID: 12953749. DOI: 10.1016/s0091-6749(03)00020-x

17 Xia L, Hu G and Guzzo TJ: Prognostic significance of preoperative anemia in patients undergoing surgery for renal cell carcinoma: A meta-analysis. Anticancer Res 37(6): 3175-3181, 2017. PMID: 28551661. DOI: 10.21873/anticancer.11677

18 Shah PH, Moreira DM, Okhunov Z, Patel VR, Chopra S, Razmara AA, Alom M, George AK, Yaskiv O, Schwartz MJ, Desai M, Vira MA, Richstone L, Landman J, Shallav AL, Gill I and Kawoussi LR: Positive surgical margins increase risk of recurrence after partial nephrectomy for high risk renal tumors. J Urol 196: 327-334, 2016. PMID: 26907508. DOI: 10.1016/j.juro.2016.02.075

19 Kryvenko ON: Positive surgical margins increase risk of recurrence after partial nephrectomy for high risk renal tumors. Urol Oncol 35(6): 449-450, 2017. PMID: 28416109. DOI: 10.1016/j.urolonc.2017.03.013

20 Marchinena PG, Tirapegui S, Gonzalez IT, Jurado A and Guglio G: Positive surgical margins are predictors of local recurrence in conservative kidney surgery for pT1 tumors. Int Braz J Urol 44(3): 475-482, 2018. PMID: 29368873. DOI: 10.1590/1674-5538.IBJU.2017.0039

21 Aufderklamm S, Hennenlotter J, Todenhöfer T, Senghaas N, Scharpf M, Gakis G, Rausch S, Mischinger J, Bier S, Stenzl A, Schwentner C and Bedke J: Oncologic impact of renal tissue for renal lesions determined to be stage T1 by computed tomography. J Urol 173: 713-715, 2005. PMID: 15711249. DOI: 10.1097/01.ju.0000153638.15018.58

22 Auferklamm S, Hennenlotter J, Todenhöfer T, Senghaas N, Scharpf M, Gakis G, Rausch S, Mischinger J, Bier S, Stenzl A, Schwentner C and Bedke J: Oncologic impact of renal tissue for renal lesions determined to be stage T1 by computed tomography. J Urol 173: 713-715, 2005. PMID: 15711249. DOI: 10.1097/01.ju.0000153638.15018.58

23 Sundaram V, Figenshau RS, Roytman TM, Kibel AS, Grubb RL 3rd, Bullock A, Benway BM and Bhayani SB: Positive margin during partial nephrectomy: does cancer remain in the renal remnant? Urology 77(6): 1400-1403, 2011. PMID: 21411126. DOI: 10.1016/j.juro.2010.12.016

Received December 7, 2019
Revised December 20, 2019
Accepted January 4, 2020